



**TITLE:** Computed Tomographic Colonography (Virtual Colonoscopy) for Screening of Colorectal Cancer

**AUTHOR:** Mitchell D. Feldman, MD, M.Phil.  
Professor of Medicine  
Division of General Internal Medicine  
Department of Medicine  
University of CA, San Francisco

**PUBLISHER NAME:** California Technology Assessment Forum

**DATE OF PUBLICATION:** June 9, 2004

**PLACE OF PUBLICATION:** San Francisco, CA



## COMPUTED TOMOGRAPHIC COLONOGRAPHY (VIRTUAL COLONOSCOPY) FOR SCREENING OF COLORECTAL CANCER

### INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of computed Tomographic Colonography (virtual colonoscopy) for screening of colorectal cancer.

### BACKGROUND

Colorectal cancer is the third most common cancer and the second leading cause of cancer death in the United States. In 2001, colorectal cancer was diagnosed in 138,900 Americans and was responsible for approximately 57,000 deaths. Men and women have similar incidence and mortality (Pignone 2002).

Death from colorectal cancer is largely preventable. When colorectal cancer is diagnosed at an early, localized stage, five-year survival is 90%; however, only 37% of cases are diagnosed while still localized (Smith *et al* 2001). More than 95% of colorectal cancers arise from colorectal adenomas. Adenomas are very common with a prevalence of 25-50% in persons over 50 years of age (Winawer *et al* 1997). However, most colorectal adenomas are small (less than 1cm) and therefore are likely to have a long “dwell time” (i.e. the time it takes an adenoma to progress to a carcinoma). An average dwell time for most colorectal polyps is thought to be on the order of ten years (Winawer *et al* 1997).

The two major types of colonic polyps are hyperplastic and adenomatous. Hyperplastic polyps, generally found in the rectosigmoid colon, are composed of non-neoplastic epithelial proliferation. About 50% of polyps smaller than 5mm, and 30% of polyps 6-9mm are hyperplastic; these polyps virtually never undergo malignant transformation. The majority of adenomatous polyps are tubular (85-90%); the rest are tubulovillous or villous. All may undergo malignant transformation, though 90% of adenomas remain benign (Atkin 2003). In general, the larger the polyp, the more likely it is to develop into invasive cancer (Geenen 2003). There is good evidence from multiple studies that over 95% of colorectal cancers arise in adenomatous polyps and that screening for colorectal cancer saves lives (Lieberman and Atkin 2004).

Safe and effective methods of screening for colorectal adenomas have been available for many years. The most common currently available tests include fecal occult blood testing (FOBT), flexible sigmoidoscopy, colonoscopy and double contrast barium enema. Ten years ago, the National Polyp Study demonstrated that endoscopic screening with removal of pre-cancerous adenomatous polyps decreased the incidence of colorectal cancer by 76-90% compared with an unscreened population (Winawer *et al* 1993). Since that time, there have been numerous studies

that have attempted to show the optimal means of screening for colorectal cancer. However, a recent comprehensive evidence-based review of colorectal screening concluded that the available evidence does not support choosing one test over another (Walsh and Terdiman, 2003).

Individuals at average risk have no known risk factors other than age. At least 75% of colorectal cancers occur in individuals at average risk (Helm *et al.* 2003). It is clear that all average-risk men and women over the age of 50 should undergo screening for colorectal cancer (Winawer *et al.* 2003). Most Americans do not adhere to this recommendation for screening. One study reported that only 44% of Americans eligible for colorectal screening reported ever having had FOBT, sigmoidoscopy or colonoscopy (MMWR 2001). There are several possible explanations for this low rate of adherence with screening, including physicians' poor adherence with guidelines, poor patient adherence with physician recommendations, and patients dislike of the available screening options. New screening methods such as CT colonography and fecal DNA testing eventually may help to address this important public health problem.

### CT Colonography

Virtual colonoscopy is a term that has been used to describe two different radiologic procedures, CT colonography (CTC) and magnetic resonance (MR) colonography, both of which can generate two and three-dimensional images of the colon. When these images are displayed at a fast rate, they allow the operator to view and "fly-through" the colon in either direction. While most of the experience with virtual colonoscopy has come using spiral CT scanners, there is a growing body of literature, primarily from Europe, describing MR colonography for the detection of colorectal polyps (Geenen *et al.* 2003, Pappalardo *et al.* 2000, Morin *et al.* 2001, Luboldt *et al.* 2001).

CT colonography is a non-invasive radiological technique that permits visualization of the entire colon. With current technology, the patient must undergo bowel preparation similar to that needed prior to a conventional colonoscopy. (An area of significant current research interest is the development of virtual colonoscopy techniques that do not require bowel cleansing [Zalis and Hahn 2001, Morrin *et al.* 2001].) The standard barium enema preparation (Fleet Prep; Fleet Pharmaceutical) produces a drier mucosal surface and is the agent generally preferred by radiologists, as retained fluid may obscure smaller polyps.

The colon must be distended throughout its length with air or carbon dioxide via a small rectal tube to enhance imaging (Johnson 2000). The patient is then scanned in both the supine and prone positions. Patients must be able to hold their breath during the scan for 20 – 50 seconds depending on whether a multi- or single-detector CT scanner is used. The radiation dose is no more than that of a conventional barium enema and considerably less than a standard abdominal or pelvic CT scan (Geenen 2003; Kay 1996). Once images are acquired, the data is transferred to a computer workstation for interpretation. Current software packages allow the radiologist to display axial, coronal

and sagittal images of a given point and can display a three-dimensional endoluminal view that simulates colonoscopy. Generally, 2D images are used for lesion identification and 3D views can be used when a suspicious area is identified. Using 2D and 3D images together allows for the differentiation between complex haustral folds, retained stool and polyps (Levin *et al.* 2003). Review of the images is reported to take anywhere from 15 to 40 minutes depending on the technique used and the experience of the radiologist (Yee *et al.* 2001). Exactly how much experience is required for optimal performance is not known. According to a recent review: "While it is generally accepted that CT colonography is a difficult examination to interpret, and has a steep learning curve, the slope of this curve is unknown" (Burling *et al.* 2004).

As with conventional colonoscopy, CTC allows visualization of the entire colon. Unlike colonoscopy, however, it requires no sedation and there is considerably less risk to the patient of adverse events such as bleeding or perforation. Another potential advantage is that there is a possibility of extra-colonic findings such as solid renal masses and pulmonary nodules (Edwards *et al.* 2002). In one study, 11% of patients had significant extra-colonic pathology detected as a result of the study (Hara *et al.* 2000). Another study of 681 patients found extracolonic findings of "high clinical importance" (e.g. liver masses) in 10% of patients; 50% had findings classified as of "low clinical importance" (e.g. renal cysts) (Gluecker 2003). CTC requires the patient to undergo bowel preparation similar to that used for colonoscopy. In addition, insufflation of the colon is required, often contributing to patient discomfort. For this reason, CTC has not consistently been shown to be preferred by patients over conventional colonoscopy (Akerkar 2001) and in its current form may not improve adherence with screening.

## TECHNOLOGY ASSESSMENT (TA)

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

The CT Colonography option (K023943) is substantially equivalent to the CT Colonography/Navigator 2 (General Electric Medical Systems, Milwaukee, WI).    FDA 510(k) clearance was awarded on May 6, 2003. The CT Colonography option is an image analysis software package that allows the user to study the inside, wall, and outside of the colon using CT-acquired helical images.

TA Criterion 1 is met.

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

Outcomes assessed in clinical trials of colorectal cancer screening methods include sensitivity and specificity of polyp detection, reduction in colorectal cancer mortality, and patient satisfaction and acceptance of the screening method. To date, there have been no prospective or retrospective studies of CTC on colorectal cancer mortality, and these

studies are unlikely to be conducted in the foreseeable future. Since colorectal screening is clearly effective on the basis of results from randomized controlled trials of FOBT (Mandel *et al* 1993 and 1999) and case-control studies of sigmoidoscopy (Selby *et al* 1992), it has been recommended that new tests such as CTC only need to demonstrate that they have equal or superior performance characteristics to be recommended for colorectal cancer screening (Winawer *et al* 1997). As a result, there is a growing body of literature comparing the sensitivity and specificity of CTC with conventional colonoscopy. Many of these studies were undertaken in populations with a high risk of colorectal polyps or cancer. More well designed studies comparing CTC to other accepted screening methods in average risk populations are needed before we can fully assess the effectiveness of this technology on health outcomes.

In the first published study to examine CTC to detect colorectal polyps, Hara *et al* (1996) concluded that this “novel technique” was feasible for detecting polyps  $\geq 0.5$ cm in diameter. Since that time, there have been at least 14 additional studies published in peer-reviewed journals that have examined the sensitivity and specificity of CTC in detecting colorectal polyps. In all of these studies, the sensitivity and specificity of CTC is significantly better for polyps  $\geq 1.0$ cm. For screening purposes, some authorities recommend that 1 cm or larger should be the target lesion size (Winawer *et al* 1997), although some experts assert that flat adenomas, which are usually smaller, are more likely to have high grade dysplasia for a given size. Conventional colonoscopy is used as the standard of reference (the “gold standard”) for detected polyps in all studies to date.

Many studies distinguish in their analyses between “per-polyp” and “per-patient” sensitivity and specificity. For example, in Yee *et al.* (2001), a polyp noted at CTC was considered to have matched with a polyp identified at colonoscopy if it was in the same or in an adjacent segment of the colon and had a difference in size less than 4mm in diameter. In the per-patient analysis, the findings at CTC and conventional colonoscopy were considered to match if both studies showed at least one polyp or if neither test showed a polyp. The size, number or location of polyps was not considered. Although this type of analysis (i.e. per-patient) is a less rigorous standard by which to evaluate CTC, it may be more clinically relevant since any finding of a polyp on CTC should lead to a referral for a complete colonoscopy for the patient in question.

Many of the studies discussed below also consider a number of secondary outcomes having to do with the optimization of data acquisition and data interpretation. These outcomes are not directly relevant to this review so are discussed only when they directly impact the primary outcomes.

TA criterion 2 is met

Level of evidence 3,5

**TA Criterion 3:** The technology must improve the net health outcomes. For diagnostic tests, there is evidence that use of the test would result in improved medical management in a way that will benefit the patient.

There have been more than 20 studies in which the accuracy of CT colonography has been compared with conventional colonoscopy. However, in only five studies to date are at least some of the patients drawn from an average-risk population who present for routine screening (Pickhardt *et al.* 2003; Edwards *et al.* 2003; Yee *et al.* 2001; Rex *et al.* 1999; Macari *et al.* 2000).

### Effectiveness in Average-risk Screening Population

Pickhardt *et al.* (2003) evaluated the performance of CTC for the detection of colorectal neoplasia in an average-risk screening population. A total of 1233 adults underwent same day CTC and conventional colonoscopy. Patients underwent a 24-hour colonic preparation and consumed 500 ml of barium for solid stool tagging and Gastrografin for the opacification of luminal fluid. Image processing and interpretation was performed with the use of a three-dimensional approach. All radiologists received training involving the reading of 25 CTC's; two of the six radiologists had interpreted more than 100 prior studies. The final results on colonoscopy, including findings on repeat colonoscopy after unblinding to the results of CTC, served as the reference standard by which initial colonoscopy and CTC were compared. Of the 1233 patients, 97.4% were considered to be of average risk. The prevalence of adenomatous polyps 6 mm or more in diameter was 13.6%. In an analysis according to the patient, sensitivity of CTC for adenomatous polyps was 93.8% for polyps at least 10 mm, 93.9% for polyps at least 8 mm and 88.7% for polyps at least 6 mm. The corresponding specificity was 96%, 92.2% and 79% respectively. The sensitivity of conventional colonoscopy (prior to unblinding to results of CTC) was 87.5%, 91.5% and 92.3% for  $\leq 10$  mm,  $\leq 8$  mm and  $\leq 6$  mm polyps. If a threshold polyp size of 10 mm had been used, 7.5% of patients who underwent CTC would have required referral for polypectomy; at a threshold of 6 mm 29.7% of patients would have required referral. The mean time spent by patients in the CT suite was 14.1 minutes, and the meant time required for interpretation was 19.6 minutes. Overall, more patients recalled greater discomfort associated with CTC, but most patients found CTC more acceptable in terms of overall convenience. In an accompanying editorial, Morrin and LaMont (2003) discuss a number of factors that help to explain the impressive results of this study. For example, the colonic preparation used differed from prior studies. Their use of Gastrografin and barium allowed the imaging software to digitally remove all opacified fluid and stool from the image. In addition, they calculated sensitivity of CTC based on adenomatous polyps only; hyperplastic polyps were classified as false positives since they were not the targets for screening. Since hyperplastic polyps may be missed more frequently by CTC than adenomas are missed, this would have resulted in higher estimates of sensitivity for CTC than reported previously. Pickhardt and colleagues attribute the disparity between their and others' results to their use of a three dimensional fly-through view, even for the initial detection of polyps.

In a study conducted in Australia, Edwards *et al.* (2003) evaluated CTC as a screening tool for average risk asymptomatic subjects in a community with regard to participation, acceptability and safety. They mailed 2,000 letters inviting participation and found 1,452 persons eligible for screening; 340 eventually agreed to undergo screening. Of these, 93 (27.4%) had findings that triggered a referral for colonoscopy; 92 of them complied with the recommendation, 89 on the same day and 3 at subsequent dates. Seventy-three percent of these subjects had at least one lesion also seen at colonoscopy (55% had an adenoma or carcinoma). All the polyps larger than 9mm were also seen at CTC; 30 of 43 (70%) of polyps 6-9 mm and 31 of 84 (37%) of polyps smaller than 6mm detected by colonoscopy were also seen at CTC. This study was not able to accurately assess the sensitivity of CTC as only patients with positive CTC went on for colonoscopy. It does demonstrate that persons offered same day colonoscopy for positive CTC findings are likely to comply and that the acceptability of CTC was good. Almost 1/3 of patients required both procedures. This could be decreased by altering the size of polyp that would trigger a referral for colonoscopy. It is also likely that the availability of same day colonoscopy in this study significantly increased the adherence.

In the first blinded prospective study, Hara *et al* (1997) examined the sensitivity and specificity of CTC in 70 consecutive patients, half with known colorectal polyps and half from a surveillance population of individuals who were being followed up after removal of polyps 1-5 years earlier. All patients underwent colonoscopy, which served as the standard of reference, and supine position only CTC. The sensitivity and specificity for the two observers with CTC was 75% and 90% in patients  $\geq 1.0$  cm, 66% and 63% in patients with adenomas  $\geq 5$  mm and 45% and 80% for patients with adenomas less than 5 mm in diameter.

In a blind trial, Rex *et al* (1999) performed helical CT followed by same day colonoscopy on 46 asymptomatic patients, 60 years of age or older with no history of colonic neoplasia. The CT scans reported in the study were performed in 1995 and 1996, in an early phase of the technology. They found that CTC failed to identify a significant number of large polyps and most small adenomas (sensitivity = 50% for polyps  $\geq 10$  mm, sensitivity = 43% for polyps  $\geq 5$  and  $\leq 10$  mm, and 11% for those  $\leq 5$  mm).

Macari *et al* (2000) compared the findings of 2D, 3D and time-efficient CTC with conventional colonoscopy for detecting colorectal polyps in 42 asymptomatic patients. Twelve patients had a family history of colon cancer. Colonoscopy detected 16 polyps in 13 patients. Of these, 6 were prospectively visible on CTC and 10 polyps were overlooked. Sensitivity for polyps measuring 7 mm or more was 100% (4/4), 6 mm or more 67% (4/6). Overall sensitivity for polyp detection was 38%.

In the largest prospective, blind study to date, Yee *et al* (2001) evaluated the sensitivity and specificity of CTC in 300 asymptomatic (n=96) and symptomatic (n=204) patients recruited from a Veterans Affairs hospital. Patients were predominantly male with a mean age of 62.6 years (a population with an expected higher prevalence of colorectal

polyps and cancer). The overall sensitivity and specificity of CTC for polyp detection were 90.1% and 72% respectively. By direct polyp matching, the overall sensitivity was 69.7%. The sensitivity was 94% for the detection of adenomas 10 mm or larger, 82% for adenomas 5 - 9 mm and 66.9% for adenomas smaller than 5 mm. As the authors point out, however, specificity was not optimal. Thirty-three patients with normal colonoscopies, had polyps on CTC and would most likely be referred for colonoscopy in clinical practice. Overall specificity for adenoma detection was 57%. No statistically significant differences were found between symptomatic and asymptomatic patients in the sensitivity of CTC. The median interpretation times for the two radiologists in the study were 31 and 27 minutes with a range of 15 to 45 minutes.

### Clinical Trials in Symptomatic and/or High-risk Population

Fenlon *et al* (1999) prospectively studied 100 patients at high risk for colorectal cancer. Patients were considered high risk if they were 50 years of age or older plus had one of the following risk factors: a history of adenomatous polyps, recent sigmoidoscopy positive for polyps, a positive FOBT, or a history of colon cancer in a first degree relative. CT colonography was immediately followed by colonoscopy. The entire colon was clearly seen by CTC in 87 patients and by conventional colonoscopy in 89 patients. CTC identified 91% of polyps that were 10 mm or more, 82% of those 6-9 mm and 55% of those 5 mm or smaller. Of the 33 polyps that were not detected by CTC, 73% were between 1 and 5 mm in diameter. Retrospective analysis of the images did not significantly improve detection. Of the adenomatous polyps, CTC identified 90% of those 6 mm or more and 67% of those 5 mm or smaller. All three cancers were correctly identified by CTC. The diagnostic accuracy of CTC in this study of high-risk persons may be an overestimation of its performance in persons with average risk.

McFarland *et al* (2001) performed spiral CT colonography and conventional colonoscopy on 70 patients suspected of having or known to have a polyp. Analysis per polyp demonstrated a pooled sensitivity of 68% for polyps 10 mm or larger (n=40) and 36 % for 6-9 mm polyps. Analysis per patient was 88% for patients with polyps or cancers 10 mm or larger and 71% for patients with polyps 6-9 mm. Dachman *et al* (1998) prospectively performed CTC in 44 patients referred for colonoscopy. Sensitivity for polyps larger than 8 mm was 83% (5/6) and specificity was 100%. Overall sensitivity was approximately 44%.

Macari *et al* (2002) prospectively examined 105 patients with two CTC techniques compared with colonoscopy. Patients either had positive FOBT, iron deficiency anemia, hematochezia, or a history of polyps. 132 polyps in 59 patients were identified at colonoscopy. Sensitivities for detection of polyps smaller than 5 mm, 6-9 mm and larger than 10 mm in diameter were 12% (11/91), 70% (19/27), and 93% (13/14) respectively. Median CTC data interpretation time was 12 minutes. Fletcher *et al* (2000) report on 180 patients most with known or suspected colorectal neoplasms. The sensitivity and specificity for the identification of patients with polyps 10 mm or greater

were 85% (82/96 patients) and 93% (78/ 84 patients). In an unblinded study, Kay *et al* (2000) reported that CTC identified 5/13 polyps 5-9 mm in size and 10/11 larger than 10 mm.

Pedersen *et al* (2003) report on 148 patients who were examined with both multidetector-array CTC and colonoscopy. All patients had a history of colorectal polyps, colorectal cancer or were symptomatic (i.e. rectal bleeding, abdominal pain etc.). Complete colonoscopy was obtained in 91% of the patients and in 76% of the patients undergoing CTC, mainly due to suboptimal air distention of the sigmoid colon. Overall, detection rates between CTC and colonoscopy were quite similar; CTC detected 81% of polyps 6mm or larger compared with 87% detection by colonoscopy. For polyps 6-9mm in size, colonoscopy was superior to CTC. If a lesion 6mm or larger in size is accepted as an indication for colonoscopy, CTC would have correctly prompted a follow-up colonoscopy in 39/46 (85%) of patients. Of these, four had false negative and three false positive findings. If CTC alone were used as a screening test in this population, 25% of patients would have been sent for colonoscopy and 15% additionally would have needed sigmoidoscopy to complete the examination of the sigmoid colon.

Munikrishnan *et al.* (2003) prospectively studied 80 patients with symptoms of colo-rectal disease with CTC and colonoscopy. They found a sensitivity of CTC of 100% for polyps > 10 mm, 83% for polyps 6-9 mm and 53% for polyps  $\leq$  5 mm (overall sensitivity 74% and specificity 96%).

Pineau *et al.* (2003) studied 203 high and average-risk patients with CTC using oral iodinated contrast preceding conventional colonoscopy. They found an overall sensitivity and specificity of 61.8% and 70.7% respectively. As with other studies, sensitivity improved with lesion size; they found an 84.4% sensitivity for patients with lesions  $\geq$  6 mm.

larinaccone *et al.* (2003) report on a study of lower dose multidetector row CTC followed by conventional colonoscopy. They examined 158 mainly high-risk consecutive patients and compared lesions found at CTC with those identified at colonoscopy, and? considered the reference standard. CTC depicted all 22 carcinomas and 52 of 74 polyps (overall per polyp sensitivity, 70.3%). Sensitivity was 100% in all 13 polyps 10 mm or larger, 83.3% in polyps 6-9 mm and 51.3% in lesions 5 mm or smaller. The authors conclude that lower-dose multi-detector row helical CTC ensures a substantial reduction in the radiation dose while maintaining excellent sensitivity for carcinoma and polyps larger than 6 mm in diameter.

Johnson *et al.* (2003) conducted a multi-institutional retrospective study of 117 randomly selected patients, most of whom were high risk for CRC. These patients had previously undergone conventional colonoscopy +/- biopsy that provided the standard. Radiologists blinded to the standard reviewed the CTC for each patient. The average per-polyp sensitivity (for polyps  $\geq$  10 mm) was 75%. A trend was observed for better performance with more experience.

Several studies report significantly lower sensitivity for CTC than discussed above. Spinzi *et al* (2001) report on a study of 99 patients randomly selected among those attending an open-access endoscopy unit. Patients presented a

variety of gastrointestinal complaints. Overall sensitivity of CTC was 57.8%; specificity 92.6%. Unlike most other studies, they found no significant difference in sensitivity between large and small polyps. Inadequate bowel prep in several patients probably accounts for this discrepancy. Pescatore *et al* (2000) conducted a prospective study of 50 patients successively undergoing CTC and conventional colonoscopy. For patients with polyps  $\geq 10$  mm, their two observer teams found sensitivities of 38% and 63% and specificity of 74%. Mendelson *et al* (2000) studied 100 patients referred for colonoscopy because of symptoms or a family history of colorectal cancer. Sensitivity of CTC for detecting polyps  $\geq 10$  mm was 73% and only 19% for smaller polyps. Of note, two of the six cancers found with conventional colonoscopy were not detected by CTC (diameters 10 mm and 15 mm respectively). Miao (2000) found a combined sensitivity of 73% and specificity of 94% for detection of invasive carcinoma and/or  $\geq 10$  mm polyps in 201 patients with colorectal symptoms.

Johnson, Harmsen, Wilson *et al.* (2003) report on a prospective blinded study of 703 asymptomatic persons at higher than average risk for colorectal cancer who underwent CTC followed by same day colonoscopy. Overall lesion prevalence for lesions  $\geq 10$  mm was 5%. The sensitivity for detecting patients with at least 1 polyp 5-9 mm ranged from 41% to 69% (reviewer 1-3). For polyps  $> 10$  mm the sensitivity on a per patient basis ranged from 35% to 72%. The mean sensitivity for adenomas  $\geq 10$  mm of the three experienced radiologists in the study was 46%. The authors concluded that: "Based on observations in this screening-like setting of an asymptomatic population with a low prevalence of colorectal neoplasia, the accuracy of CT colonography for polyp detection may not be as high as suggested in earlier reports from smaller selected patient groups enriched with pathology".

Cotton *et al.* (2004) report on a nonrandomized evaluator blinded study of 615 participants aged 50 years and older referred for colonoscopy in 9 centers in the United States and England between April 2000 and October 2001. The study did not include a screening population. Each participant underwent CTC followed by conventional colonoscopy within 2 hours. The technique of "segmental unblinding" was used in this, as in other studies. Patients received a standard prep and were not given oral contrast media or smooth muscle relaxants. Scans were read in 2-dimensional slices and when necessary by focal 3-D snapshot reconstructions. One hundred four participants had at least one lesion 6 mm or larger; CTC identified 41 of these participants (sensitivity, 39%; 95% CI, 29.6% - 48.4%) as compared with 99% sensitivity for colonoscopy. The sensitivity of CTC for detecting patients with lesions of at least 10 mm was 55% (95% CI, 39.9%-70%). In the per polyp analysis, CTC correctly identified 55 of 173 lesions at least 6 mm (sensitivity=32%) while conventional colonoscopy identified 170 lesions (sensitivity 98%). For lesions of at least 10 mm, sensitivities were 52% for CTC and 96% for conventional colonoscopy. Fly through data were analyzed separately in a blinded fashion and improved sensitivity to 45%. Of the 84% of patients who returned preference questionnaires, 46% preferred CTC and 41% preferred colonoscopy. Overall, as the authors report, the results of this study were surprising and disappointing. As they state, this study lends evidence to the conclusion that it remains to be proven that CTC technology can be reliably taught and implemented in routine practice.

## Patient Acceptance of CT Colonography

One of the potential benefits of CTC is greater acceptance of the procedure. Although *potential* patients favor virtual colonoscopy over conventional colonoscopy (Angtuaco *et al* 2001), this question has been empirically examined in only a few studies and the results so far are mixed. In a follow up to the large VA based study discussed above (Yee *et al* 2001), Akerkar *et al* (2001) report on the results of a patient survey questionnaire completed immediately after the procedures (colonoscopy and CTC) and 24 hours later. Two hundred ninety-five patients completed the questionnaire comparing their experiences with CTC and conventional colonoscopy. They found that 63.7% of patients preferred colonoscopy to CTC and would wait longer to undergo conventional colonoscopy than undergo CTC. Overall, patients reported more pain, discomfort, and less respect after CTC than conventional colonoscopy. Svensson *et al* (2002) also evaluated patient acceptance of CTC as compared with conventional colonoscopy. In a study of 111 patients who underwent CTC followed immediately by colonoscopy, they found that of the 68 patients who favored one examination over the other, 82% preferred CTC. In addition, CTC was regarded as “not painful” by 62 of 108 patients (57%) compared with 26% for colonoscopy. Discomfort from air filling of the colon was the major complaint about CTC. Taylor *et al.* (2003) compared patient experiences with CTC, barium enema, flexible sigmoidoscopy and colonoscopy with respect to discomfort, worry and overall satisfaction. They found that patients reported less discomfort with CTC but overall satisfaction was greater with colonoscopy than with all of the other procedures.

Another potentially significant barrier to patient acceptance of CTC is the fact that patients with abnormal tests must then undergo colonoscopy for polyp removal.

In addition to its performance as a screening method, greater patient acceptance of CTC may be key to its adoption in the wider medical community. Although the sedation that is required for colonoscopy is often seen as a disadvantage, it may account in part for the overall good tolerability of the procedure by patients compared with CTC. Patient acceptance of CTC may increase as strides are made to eliminate the need for pre-procedure prep (Zalis and Huhn 2001, Callstrom *et al* 2001, and Lauenstein *et al* 2001) and other technical innovations that will lead to increased patient comfort.

## Patient Safety

There are no reported complications from CTC. Potential complications include those related to the pre-procedure colonic preparation, radiation exposure and insufflation of the colon.

## Other indications for CTC

CT colonography has been studied for use in patients after incomplete colonoscopy (Macari *et al.* 1999; Neri *et al.* 2002), in the follow-up of colorectal cancer patients (Laghi *et al.* 2003), for evaluation of Crohns colitis (Matsui *et al.* 2003) and stricturing postoperative recurrence in Crohn’s disease (Biancone *et al.* 2003), for preoperative staging of

colorectal cancer (Blomqvist 2003) and for examining frail, elderly and disabled patients (Ng *et al.* 2002). A recent study compared minimal preparation CT (MPCT) with barium enema/colonoscopy for suspected colon cancer in frail elderly patients and found that those patients with a high pre-test probability of colorectal carcinoma and a negative MPCT still needed further evaluation (Kealey *et al.* 2004).

The best available evidence supports CTC for the preoperative assessment of the colon proximal to an occlusive cancer and for failed whole colon examinations. One study reported that 78% of surveyed gastrointestinal radiology departments in the UK employ it for incomplete colonoscopy (Burling *et al.* 2004). Two studies have evaluated CTC after incomplete colonoscopy (Macari *et al.* 1999 and Neri *et al.* 2002); both concluded that it is safe and effective when used for this indication. Morrin *et al.* (2000) and Fenlon *et al.* (1999) both found that CTC was superior to barium enema to assess the colon proximal to an occlusive tumor (i.e. a tumor that cannot be traversed endoscopically).

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 commonly used for the detection of colorectal polyps and cancer: Fecal Occult Blood Testing (FOBT), flexible sigmoidoscopy and colonoscopy. Double-contrast (air-contrast) barium enema also has been advocated as a screening method for colorectal cancer; there is no evidence from controlled studies examining efficacy, and it is now rarely used in clinical practice solely for screening (Halligan *et al.* 2003). The digital rectal examination is of limited value as a screening test for colorectal cancer. The examining finger, which is only 7-8 cm long, has limited access even to the rectal mucosa, which is 11 cm in length. A negative digital rectal examination provides little reassurance that the patient is free of colorectal cancer.

#### Fecal Occult Blood Testing (FOBT)

The reported sensitivity and specificity of FOBT for detecting colorectal cancer in asymptomatic persons are 26-92% and 90-99%, respectively, with the widely varying estimates reflecting differences in study designs. However, randomized control trials of serial FOBT have demonstrated that it reduces mortality from colorectal cancer (Winawer *et al.* 1993, Mandel *et al.* 1993, Mandel *et al.* 1999, Hardcastle *et al.* 1996, Kronborg *et al.* 1996). It is thought that key to the success of FOBT in reducing mortality is that a positive test is evaluated with colonoscopy, and it is with colonoscopy that pre-cancerous adenomas and early cancers are detected and removed. (Walsh and Terdiman 2003) FOBT is a safe test, but false positive results may lead to unnecessary invasive procedures such as colonoscopy.

## Flexible Sigmoidoscopy

Sigmoidoscopic screening in asymptomatic persons detects 1-4 cancers per 1,000 examinations (Bolt 1971, Frame 1987). Unlike FOBT, however, there are no large RCT's demonstrating efficacy of sigmoidoscopy in the prevention of colorectal cancer death. The major evidence supporting the efficacy of sigmoidoscopy comes from retrospective case-control studies (Selby *et al* 1992, Newcomb *et al* 1992, Muller *et al* 1995).

Flexible sigmoidoscopy is usually performed using the long (60 cm) flexible fiberoptic sigmoidoscope. It can be performed in an office setting, and sedation is not required. The test is safe with almost no risk of perforation. Expert recommendation is to repeat a normal exam in five years and to refer patients with advanced or multiple polyps for complete colonoscopy.

A disadvantage of sigmoidoscopy is that it examines only a portion of the colon so it may miss important findings. Only 20-30% of proximal colon cancers are associated with adenomas in reach of the sigmoidoscope (Lemmel *et al* 1996), and sigmoidoscopy alone may miss half of all cancers in the colon (Imperiale *et al* 2000). It has therefore become common clinical practice to combine FOBT and sigmoidoscopy into one screening regimen. However, there are no RCT's or other well-conducted retrospective studies that support this practice (Walsh and Terdiman, 2003).

## Colonoscopy

All of the current studies of CT colonography compare its performance to conventional colonoscopy. Surprisingly, the efficacy of colonoscopy for the prevention of colorectal cancer death has not been studied in RCT's or case-control studies. Indirect evidence does support its use as a screening method and many experts consider it the "gold standard" for detecting colorectal polyps and cancer (Walsh and Terdiman 2003). Colonoscopy is not a perfect screening test, however. Rex *et al* (1997) found that in back-to-back colonoscopic exams performed by experts, miss rates for adenomas 10 mm or larger was 6%, for adenomas 6-9 mm was 13%, and 27% for adenomas 5 mm or smaller.

Like CT colonography, conventional colonoscopy requires that the patient undergo a bowel preparation the day prior to the examination. The test takes approximately 30 minutes, but since sedation is required, the patient will generally spend several hours in the endoscopy suite in recovery. Colonoscopy is generally a safe procedure, but not as safe as sigmoidoscopy or CT colonography. In one study, 1-2% of patients had complications that required a visit to the emergency department (Zubarik *et al* 1999) and the risk of perforation has been reported to be around 0.1% (Nelson *et al* 2002).

Most of the current studies of CT colonography do not demonstrate sensitivity comparable to colonoscopy, and none demonstrate a reduction in mortality seen with flexible sigmoidoscopy or FOBT. Few of these studies have been

conducted in the population of interest, which is made up of average risk individuals referred for colorectal cancer screening. The shortcomings of current screening methods are not yet adequately addressed by CT colonography.

TA criterion 4 is not met.

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

There has not yet been adequate standardization and dissemination of the techniques and skills of CTC to confidently expect that the best results seen in clinical trials (e.g Pickhardt *et al.* 2003) can be replicated outside of investigational settings.

TA Criterion 5 is not met

## RECOMMENDATIONS OF OTHERS

### Blue Cross Blue Shield Association (BCBSA)

The Blue Cross Blue Shield Association Technology Evaluation Center reviewed CT Colonography in June, 2004, and has indicated that it does not meet TEC criteria.

### Centers for Medicare and Medicaid Services

*“Colorectal Cancer: As of January 1, 1998, Medicare will cover colorectal cancer screening. This coverage includes fecal-occult blood tests, flexible sigmoidoscopy, colonoscopy (for people at high risk for colorectal cancer), and in certain cases, barium enemas. Each of these tests are covered under different circumstances, so patients should check with their physician to determine what is best for them.*

*In the past, these tests were covered only when a physician already suspected the patient had cancer or other disease, and was using them for diagnostic, rather than screening, purposes.”*

A policy specific to CT Colonography was not found on either the national or local level.

### American Cancer Society Guidelines

The American Cancer Society does not endorse CT Colonography as a method of screening for colorectal neoplasms. (Last update: Levin *et al.* 2003)

### California Radiological Society

The California Radiological Society provided representation at the meeting and testimony in support of the use of virtual colonoscopy.

### American Gastroenterological Association

The American Gastroenterological Society recently concluded that “virtual colonoscopy” is not yet ready for widespread screening outside the research setting (Winawer *et al.* 2003). An AGA representative attended the meeting and provided testimony.

### U.S. Preventive Services Task Force

The USPSTF 2002 Recommendations and Rationale – The USPSTF found insufficient evidence that newer screening technologies (for example, computed tomographic colonography) are effective in improving health outcomes (Am Family Phys).

## CONCLUSION

### Advantages of CTC

There are several potential advantages to CT colonography over existing methods for screening for colorectal polyps and cancer. The procedure is shorter than colonoscopy and requires no sedation. Patients who are dissuaded from colorectal cancer screening with colonoscopy because of the time required may be more attracted to this test. In addition, some patients avoid screening because they fear the rare complications associated with colonoscopy. Although the risk with colonoscopy is low, CTC has even less risk to the patient. CT colonography also offers the advantage of potentially identifying cancers in the colon that may not be adequately assessed by colonoscopy, such as those located near complex haustral folds (Levin *et al.* 2003). In addition, it offers patients a choice regarding polypectomy; patients may elect not to remove small polyps as they are less likely to progress to cancer in the near time. Finally, if the tests currently in development ameliorate the need for bowel prep, this will also prove to be a significant advantage of CTC over colonoscopy. However, current research has failed to demonstrate that CTC is more acceptable to patients than current methods.

Some experts point to the fact that a possible advantage of CTC is the ability to screen other organs in the abdomen and pelvis for cancer and other disease. However, no prior study has ever demonstrated any benefit from routine “total body scanning” and the ability of CTC to elucidate extracolonic findings could lead to additional testing to evaluate clinically silent abnormalities and therefore is likely to be more a disadvantage than an advantage.

Finally, the need to screen more Americans for colorectal cancer is huge and may outstrip the ability of gastroenterologists to provide sufficient numbers of screening colonoscopy (Rex 2002). Adoption of CTC could help to fill this void.

### Limitations of CTC

#### 1. Inconsistent Results

While Pickhardt *et al.* (2003) raises the possibility that CTC can perform equally to colonoscopy in an average risk population, when taken as a whole, the CTC literature demonstrates inconsistent results. In the Pickhardt *et al.* (2003) study, CTC had a sensitivity of 88.7% for polyps larger than 6 mm, comparing favorably to conventional colonoscopy. A recently published meta-analysis of 14 “high quality” studies (of mainly high-risk patients) (Sosna *et al.* 2003) found a pooled per patient sensitivity for polyps 10 mm or larger 88% (95% CI; 0.84-0.93), for polyps 6-9 mm was 84% (0.80-0.89) and for polyps 5 mm or smaller it was 43% (0.39-0.47). In contrast, Cotton *et al.* (2004) found that of 104 participants who had at least one lesion 6 mm or larger, CTC identified 41 of these participants (sensitivity, 39%; 95% CI, 29.6% - 48.4%) as compared with 99% sensitivity for colonoscopy. Later analysis of the same data with a more sophisticated fly-through technique did not improve the sensitivity of CTC. Similarly, Johnson

*et al.* (2000) report on a prospective blinded study of 703 asymptomatic persons at higher than average risk for colorectal cancer who underwent CTC followed by same day colonoscopy. The sensitivity for detecting patients with at least 1 polyp 5-9 mm ranged from 41% to 69% (reviewer 1-3). For polyps > 10 mm the sensitivity on a per patient basis ranged from 35% to 72%. The mean sensitivity for adenomas  $\geq$  10 mm of the three experienced radiologists in the study was 46%. Overall, it remains to be proven that CTC technology can provide consistent and reproducible results outside of selected research settings.

## 2. No clear standards regarding polyp size

Standards will have to be established that guide physicians and patients as to what size polyp should trigger referral for colonoscopy. Since even the most diminutive polyp theoretically may harbor cancerous cells, it is difficult to imagine in practice that physicians will not encourage their patients to undergo colonoscopy to evaluate any abnormality on CTC. While this may not be the true evidence-based approach, the liability would be too great to imagine PCP's acting otherwise. With colonoscopy, no decision is needed whether or not to biopsy and remove a polyp. If it is seen, it will be removed. Currently with CTC however, there is debate as to which lesions should trigger a referral for colonoscopy and to what extent the patient can participate in this decision. This debate must be clarified with an evidence-based approach to decision making for patients and physicians before CTC can be embraced as a screening tool for average risk patients.

While there is considerable debate among radiologists and gastroenterologists as to what constitutes a clinically significant colorectal polyp, many CTC studies have yielded unacceptably low sensitivities for polyps of intermediate size (6-9 mm). Some experts recommend using 10 mm as the cut-off as these are more likely to undergo malignant transformation. Others argue that lesions 6 mm and larger detected by CTC (and judged not to be fecal residue, a fold, a lipoma, an extrinsic defect, or a foreign body) should be referred to colonoscopy for removal (Macari *et al.* 2003). The performance of CTC for small and flat polyps is poor. There is much discussion in the literature about the clinical importance of flat lesions and the inability of CTC to adequately detect them (Galdino and Yee 2003). Some experts report that flat lesions have a high malignant potential (Wolber and Owen 1991); others dispute this conclusion (Fidler *et al.* 2002). It remains to be determined how significant this is from a clinical perspective.

## 3. Applicability as a screening tool

The true test of the CTC as a useful screening tool is its ability to accurately diagnose and treat adenomatous polyps and early stage colorectal cancer in an average risk population. Unlike colonoscopy, CTC provides no means to remove polyps detected during the exam. Outside of research settings, few if any institutions are equipped to schedule immediate colonoscopy for patients with an abnormal CTC. Since for many patients the main barrier to colonoscopy is the requirement for colonic preparation, a barrier that also exists for CTC, many patients may be unwilling to undergo two preparations in a relatively short period of time. We have accomplished little if these patients

are unwilling to follow-up or encounter other barriers to colonoscopy. While an abnormal CTC may motivate some patients to pursue colonoscopy, this remains to be proven. As one recent review states: "In the long term, we must develop guidelines to link CTC results to recommendations for patient care. . . . In collaboration with our colleagues in gastroenterology, we need to determine what threshold of size constitutes a clinically relevant lesion for reporting and resection, and we need to collaborate in the development of an approach to the description and identification of lesions." (Dachman and Zallis 2004).

#### 4. Lack of standards for performance, training and reading of scans

While Pickhardt (2003) clearly raises the bar for subsequent CTC screening studies, several experts point out that the field overall is still working out quality and consistency issues in CTC. Exactly how much experience is required for optimal performance is not known. According to a recent review: "While it is generally accepted that CT colonography is a difficult examination to interpret, and has a steep learning curve, the slope of this curve is unknown" (Burling *et al.* 2004). Many other experts point out that accurate interpretation of CTC requires a steep learning curve (Ji *et al.* 2003, Iarinaccone *et al.* 2003, Taylor *et al.* 2003). In a recent review, Taylor *et al.* (2003) state that ". . . it is clear that CTC requires meticulous technique and the interpretation requires overcoming a considerable learning curve".

In spite of the promise, the problems and barriers to the use of CTC as a screening tool for colorectal cancer outweigh the possible advantages. Clinical trials conducted over the past 5-6 years reviewed above have shown mixed results. In some of the largest and best done trials, the sensitivity and specificity of CTC for polyps 10 mm or larger is comparable to that seen with colonoscopy (Pickhardt *et al.* 2003; Yee *et al.* 2001; Fenlon 1999). Other trials have had unacceptably low sensitivity of 50% to 70% for polyps, and in some cases cancer, of 10 mm or larger (e.g. Rex 1999; Spinzi 2001, Pescatore 2000, Miao 2000, Johnson 2003). Variable results in clinical trials are likely to lead to even greater variability in clinical practice (Rex 2002). Continued refinement of the technology coupled with more widespread training of radiologists is needed before widespread adoption of CTC as a screening tool can be advocated.

Promoting more widespread screening for colorectal cancer is a public health imperative. Current screening rates are tragically low and as a result lives are being needlessly lost. Current screening options; FOBT, flexible sigmoidoscopy and colonoscopy, are powerful tools but are far from perfect. Colonoscopy, the metric by which CT colonography is measured, requires bowel prep, sedation and carries with it a small but real risk of complications. It is also not clear if we will have enough trained professionals in the coming years to undertake the massive screening needs of the US population. New screening methods such as CT colonography may eventually help to address this important public health problem. More and better studies are needed, however, before CTC should be endorsed as a first line screening method for colorectal polyps and cancer.

## RECOMMENDATION

It is recommended that CT Colonography does not meet California Technology Assessment Forum TA criteria as a first-line screening test for colorectal cancer in persons at average risk.

*The California Technology Assessment Forum approved the recommendation as presented.*

June 9, 2004

## REFERENCES

- Akerkar GA, Yee J, Hung R, McQuaid K. Patient experience and preferences toward colon cancer screening. *Gastrointest Endosc.* 2001;54:310-315.
- Angtuaco TL, Banaad-Omiotek GD, Howden CW. Differing attitudes toward virtual and conventional colonoscopy for colorectal cancer Screening: surveys among primary care physicians and potential patients. *Am J Gastroenterol.* 2001;96:887-893.
- Atkin W. Options for screening for colorectal cancer. *Scand J Gastroenterol Suppl.* 2003;(237):13-6.
- Bolt RJ. Sigmoidoscopy in detection and diagnosis in the asymptomatic individual. *Cancer* 1971;28:121-122.
- Biancone L, Fiori R, Tosti C, Marinetti A, Catarinacci M, De Nigris F, Simonetti G, Pallone F. Virtual colonoscopy compared with conventional colonoscopy for stricturing postoperative recurrence in Crohn's disease. *Inflamm Bowel Dis.* 2003 Nov;9(6):343-50.
- Blomqvist L. Preoperative staging of colorectal cancer--computed tomography and magnetic resonance imaging. *Scand J Surg.* 2003;92(1):35-43.
- Burling D, Halligan S, Taylor SA, Usiskin S, Bartram CI. CT colonography practice in the UK: a national survey. *Clin Radiol.* 2004 Jan;59(1):39-43.
- Callstrom MR, Johnson CD, Fletcher JG, Reed JE, Ahlquist DA, *et al.* CT Colonography without Cathartic Preparation: Feasibility Study<sup>1</sup>. *Radiology.* June 2001;219:693-8.
- Citarda F, Tomaselli G, Capocaccia R, *et al.* The Italian multicenter study group. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. 2001;48:812-815.
- Cotton PB; Durkalski VL; Pineau BC; Palesch YY; Mauldin PD; Hoffman B; Vining DJ; Small WC; Affronti J; Rex D; Kopecky KK; Ackerman S; Burdick JS; Brewington C; Turner MA; Zfass A; Wright AR; Iyer RB; Lynch P; Sivak MV; Butler H. Computed Tomographic Colonography (Virtual Colonoscopy): A Multicenter Companion With Standard Colonoscopy for Detection of Colorectal Neoplasia. *JAMA.* 2004;291:1713-1719.
- Dachman AH, Kuniyoshi JK, Boyle CM, Samara Y, Hoffmann KR, Rubin DT, Hanan I. CT colonography with three-dimensional problem solving for detection of colonic polyps. *AJR Am J Roentgenol* 1998 Oct;171(4):989-95.
- Dachman AH, Zalis ME. Quality and consistency in CT colonography and research reporting. *Radiology.* 2004 Feb;230(2):319-23.
- Edwards JT, Mendelson RM, Fritschi L, Foster NM, Wood C, Murray D, Forbes GM. Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community-based study. *Radiology.* 2004 Feb;230(2):459-64. Epub 2003 Dec 19.
- Edwards JT, Wood CJ, Mendelson RM, Forbes GM. Extracolonic findings at virtual colonoscopy: Implications for screening programs. *Am J Gastroenterol.* 2002;96:3009-3012.
- Fenlon, HM, Ferrucci, JT. Virtual colonoscopy: What will the issues be? *AJR Am J Roentgenol* 1997; 169:453.
- Fenlon, HM, McAneny, DB, Nunes, DP, *et al.* Occlusive colon carcinoma: Virtual colonoscopy in the preoperative evaluation of the proximal colon. *Radiology* 1999; 210:423.
- Fenlon, HM, Nunes, DP, Schroy III, PC, *et al.* A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. *N Engl J Med* 1999; 341:1496-1503.

Ferrucci JT. Colon cancer screening with virtual colonoscopy: promise, polyps, politics. *AJR Am J Roentgenol*. 2001;177:975-978.

Fidler JL, Johnson CD, MacCarthy RL, Welch TJ, Hara AK, Harmsen WS. Detection of flat lesions in the colon with CT Colonography. *Abdom Imaging*. 2002 May-Jun;27(3):292-300.

Fletcher JG, Johnson CD, Welch TJ, *et al*. Optimization of CT colonography technique: prospective trial in 180 patients. *Radiology*. 2000;216:704-711.

Frame PS. Screening flexible sigmoidoscopy: is it worthwhile? An opposing view. *J Fam Pract* 1987;25: 604-607.

Galdino GM, Yee J. Carpet lesion on CT colonography: a potential pitfall. *AJR Am J Roentgenol*. 2003 May;180(5):1332-4.

Geenen RW, Hussain SM, Cademartiri F, Poley JW, Siersema PD, Krestin GP. CT and MR colonography: scanning techniques, postprocessing, and emphasis on polyp detection. *Radiographics*. 2004 Jan-Feb;24(1):e18. Epub 2003 Oct 03.

Gluecker TM, Johnson CD, Wilson LA, Maccarty RL, Welch TJ, Vanness DJ, Ahlquist DA. Extracolonic findings at CT colonography: evaluation of prevalence and cost in a screening population. *Gastroenterology*. 2003 Apr;124(4):911-6.

Halligan S, Marshall M, Taylor S, Bartram C, Bassett P, Cardwell C, Atkin W. Observer variation in the detection of colorectal neoplasia on double-contrast barium enema: implications for colorectal cancer screening and training. *Clin Radiol*. 2003 Dec;58(12):948-54; discussion 945-7.

Hara AK, Johnson CD, MacCarty RI, Welch TJ. Incidental extracolonic findings at CT colonography. *Radiology*. 2000;215:353-357.

Hara, AK, Johnson, CD, Reed, JE, *et al*. Colorectal polyp detection with CT colography: Two-versus three-dimensional techniques work in progress. *Radiology* 1996; 200-40.

Hara A, Johnson CD, Reed JF, *et al*. Colorectal polyp detection using CT colonography: Initial assessment of sensitivity and specificity. *Radiology*. 1997;205:59-65.

Hara, AK, Johnson, CD, Reed, JE, *et al*. Detection of colorectal polyps by computed tomographic colography: Feasibility of a novel technique. *Gastroenterology* 1996; 110:284.

Hardcastle JD, Chamberlain JO, Robinson MH, *et al*. Randomized controlled trial of fecal-occult-blood screening for colorectal cancer. *Lancet*. 1996;348:1472-7.

Helm J, Choi J, Sutphen R, Barthel JS, Albrecht TL, Chirikos TN. Current and evolving strategies for colorectal cancer screening. *Cancer Control*. 2003 May-Jun;10(3):193-204.

Iannaccone R, Laghi A, Catalano C, Brink JA, Mangiapane F, Trenna S, Piacentini F, Passariello R. Detection of colorectal lesions: lower-dose multi-detector row helical CT colonography compared with conventional colonoscopy. *Radiology*. 2003 Dec;229(3):775-81.

Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med*. 2000;343:169-74.

Ji H, Rolnick JA, Haker S, Barish MA. Multislice CT colonography: current status and limitations. *Eur J Radiol*. 2003 Aug;47(2):123-34.

Johnson CD, Toledano AY, Herman BA, Dachman AH, McFarland EG, Barish MA, Brink JA, Ernst RD, Fletcher JG, Halvorsen RA Jr, Hara AK, Hopper KD, Koehler RE, Lu DS, Macari M, Maccarty RL, Miller FH, Morrin M, Paulson EK, Yee J, Zalis M; American College of Radiology Imaging Network A6656. Computerized tomographic colonography: performance evaluation in a retrospective multicenter setting. *Gastroenterology*. 2003 Sep;125(3):688-95.

Johnson CD, Harmsen WS, Wilson LA, Maccarty RL, Welch TJ, Ilstrup DM, Ahlquist DA. Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. *Gastroenterology*. 2003 Aug;125(2):311-9.

Johnson CD, Dachman AH. CT colonography: the next colon screening examination? *Radiology*. 2000;216:331-341.

Kay, CL, Evangelou, HA. A review of the technical and clinical aspects of virtual endoscopy. *Endoscopy* 1996; 28:768.

Kay, CL, Kulling, D, Hawes, RH *et al*. Virtual endoscopy—comparison with colonoscopy in the detection of space-occupying lesions of the colon. *Endoscopy* 2000; 32:226-232.

Kealey SM, Dodd JD, MacEneaney PM, Gibney RG, Malone DE. Minimal preparation computed tomography instead of barium enema/colonoscopy for suspected colon cancer in frail elderly patients: an outcome analysis study. *Clin Radiol*. 2004 Jan;59(1):44-52.

Knopp MV, Giesel FL, Radeleff J, Von Tengg-Kobligh H. Bile-Tagged 3D Magnetic Resonance Colonography After Exclusive Intravenous Administration of Gadobenate Dimeglumine, a Contrast Agent with Partial Hepatobiliary Excretion. *Investigative Radiology*. 2001;36:10:619-623.

Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomized study of screening for colorectal cancer with fecal-occult-blood test. *Lancet*. 1996;348:1467-71.

Levin B, Brooks D, Smith RA, Stone A. Emerging technologies in screening for colorectal cancer: CT colonography, immunochemical fecal occult blood tests, and stool screening using molecular markers. *CA Cancer J Clin*. 2003 Jan-Feb;53(1):44-55.

Lieberman DA, Atkin W. Balancing the ideal versus the practical-considerations of colorectal cancer prevention and screening. *Aliment Pharmacol Ther*. 2004 Feb;19 Suppl 1:71-6.

Lauenstein T, Holtmann G, Shoenfelder D, Bosk S, Ruehm SG, Debatin, JF. MR Colonography Without Colonic Cleansing: A New Strategy to Improve Patient Acceptance. *AJR. Am J Roentgenol* Oct. 2001;177:823-827.

Laghi A, Iannaccone R, Bria E, Carbone I, Trasatti L, Piacentini F, Lauro S, Vecchione A, Passariello R. Contrast-enhanced computed tomographic colonography in the follow-up of colorectal cancer patients: a feasibility study *Eur Radiol*. 2003 Apr;13(4):883-9. Epub 2002 Sep 25.

Lemmel GT, Haseman JH, Rex DK, Rahmani E. Neoplasia distal to the splenic flexure in patients with proximal colon cancer. *Gastrointest Endosc*. 1996;44:109-11.

Luboldt W, Luz O, Vonthein R, Heuschmid M, Seemann M, *et al*. Three-Dimensional Double-Contrast MR Colonography: A Display Method Simulating Double-Contrast Barium Enema. *AJR. Am J Roentgenol*, April 2000;176:930-932.

Luboldt W, Bauerfeind P, Wildermuth S, Marincek B, Fried M, Debatin JF. Colonic Masses: Detection with MR Colonography<sup>1</sup>. *Radiology*. August 2000;216:383-8.

Macari M, Berman P, Dicker M, *et al*. Usefulness of CT colonography in patients with incomplete colonoscopy. *AJR Am J Roentgenol*. 1999;173:561-564.

- Macari M, Bini EJ, Jacobs SL, Lange N, Lui YW. Filling defects at CT colonography: pseudo- and diminutive lesions (the good), polyps (the bad), flat lesions, masses, and carcinomas (the ugly). *Radiographics*. 2003 Sep-Oct;23(5):1073-91.
- Macari M, Milano A, Lavelle M, *et al*. Comparison of time-efficient CT colonography with two-and three-dimensional colonic evaluation for detecting colorectal polyps. *AJR Am J Roentgenol*. 2000;174:1543-1549.
- Macari M, Bini EJ, Xue X, Milano A, *et al*. Colorectal Neoplasms: Prospective Comparison of Thin-section Low-Dose Multi-Detector Row CT Colonography and Conventional Colonoscopy for Detection. *Radiology*. 2002;224(2):383.
- Mandel JS, Bond JH, Church TR, *et al*. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med*. 1993;328:1365-71.
- Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality; effectiveness of biennial screening for fecal occult blood. *J Natl Cancer Inst*. 1999;91:434-7.
- Martinez E, Stoffel, Syngal S. Colon Cancer Screening Strategies. *Gastroenterol* 2002;18(5); 595-601.
- Matsutani Y, Yoshida H, MacEaney PM, Dachman AH. Automated Segmentation of Colonic Walls for Computerized Detection of Polyps in CT Colonography. *Jour Comp Asst Tomography*. 2001;25(4):629-638.
- Matsui T, Kotake K, Koyama Y. Treatment for recurrent colorectal cancer. *Nippon Rinsho*. 2003 Sep;61 Suppl 7:589-92. Review.
- McFarland EG, Brink JA, Pilgrim TK, Heiken JP, Balfe DM, *et al*. Spiral CT Colonography: Reader Agreement and Diagnostic Performance with Two- and Three-dimensional Image-Display Techniques. *Radiology*. February 2001;218:375-383.
- Mendelson RM, Foster NM, Edwards JT, *et al*. Virtual colonoscopy compared with conventional colonoscopy: a developing technology. *Med J Aust*. 2000;173:472-475.
- Miao YM, Amin A, Healy J, *et al*. A prospective single center study comparing computed tomography pneumocolon against colonoscopy in the detection of colorectal neoplasms. *Gut*. 2000;47:832-837.
- Morrin MM, Kruskal JB, Farrell RJ, Goldberg SN, McGee JB, Raptopoulos V. Endoluminal CT Colonography After an Incomplete Endoscopic Colonoscopy. *AJR. Am J Roentgenol* April 1999;172:913-918. Morrin and Lumont 2003.
- Morrin MM, Farrell FJ, Raptopoulos V, McGee JB, Bleday R, Kruskal. Role of Virtual Computed Tomographic Colonography in Patients with Colorectal Cancers and Obstructing Colorectal Lesions. *Dis Colon Rectum*. March 2000;43(3):303-311.
- Morrin MM, Hochman MG, Farrell RJ, Marquesuzaa H, Rosenberg S, Edelman RR. MR Colonography Using Colonic Distention with Air as the Contrast Material: Work in Progress. *AJR. Am J Roentgenol*. January 2001;176:144-6.
- Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. *Ann Intern Med*. 1995;123:904-10.
- Munikrishnan V, Gillams AR, Lees WR, Vaizey CJ, Boulos PB. Prospective study comparing multislice CT colonography with colonoscopy in the detection of colorectal cancer and polyps. *Dis Colon Rectum*. 2003 Oct;46(10):1384-90
- Nelson DB, McQuaid KR, Bond JH, Lieberman DA, Weiss DG, Johnston TK. Procedural success and complications of large-scale screening colonoscopy. *Gastrointest Endosc*. 2002;55:307-14

Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst.* 1992;84:1572-5.

Neri E, Giusti P, Battolla L, Vagli P, Boraschi P, Lencioni R, Caramella D, Bartolozzi C. Colorectal cancer: role of CT Colonography in preoperative evaluation after incomplete colonoscopy. *Radiology.* 2002 Jun;223(3):615-9.

Ng CS, Doyle TC, Pinto EM, *et al.* Evaluation of CT in identifying colorectal carcinoma in the frail and disabled patient *Eur Radiol.* 2002; 12:2988-97.

Paik DS, Beaulieu CF, Jeffrey B, Jr., Karadi CA, Napel S. Visualization Modes for CT Colonography Using Cylindrical and Planar Map Projections. *Jour Comp Asst Tomography.* 2002;24(2):179-188.

Pappalardo G, Poletini E, Frattaroli FM, *et al.* Magnetic resonance colonography versus conventional colonoscopy for the detection of colonic endoluminal lesions. *Gastroenterology.* 2000;119:300-304.

Pescatore P, Glucker T, Delarive J, *et al.* Diagnostic accuracy and inter-observer agreement of CT colonography (virtual colonoscopy). *Gut.* 2000;47:126-130.

Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, Wong RK, Nugent PA, Mysliwiec PA, Schindler WR. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med.* 2003 Dec 4;349(23):2191-200. Epub 2003 Dec 01.

Pickhardt PJ. Three-dimensional endoluminal CT colonography (virtual colonoscopy): comparison of three commercially available systems. *AJR Am J Roentgenol.* 2003 Dec;181(6):1599-606.

Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;137:132-41.

Pineau BC, Paskett ED, Chen GJ, Espeland MA, Phillips K, Han JP, Mikulaninec C, Vining DF. Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. *Gastroenterology.* 2003 Aug;125(2):304-10.

Rex DK, Cutler CS, Lemmel GT, *et al.* Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology.* 1997;112:24-8.

Rex DK, Vining D, Kopecky KK. An initial experience with screening for colon polyps using spiral CT with and without CT colonography (virtual colonoscopy). *Gastrintest Endosc.* 1999;50:309-313.

Rex DK. Considering Virtual Colonoscopy. *Reviews in Gastroenterological Disorders.* 2002;2(3):97-105.

Royster, AP, Fenlon, HM, Clark, PD, *et al.* CT colonoscopy of colorectal neoplasms: Two-dimensional and three-dimensional virtual reality techniques with colonoscopic correlation. *AJR Am J Roentgenol* 1997;169:1237-1242

Royster, AP, Gupta, AK, Fenlon, HM, Ferrucci, JT. Virtual colonoscopy: Current status and future implication. *Acad Radiol* 1998; 5:282.

Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med.* 1992;326:653-7.

Smith RA, von Eschenbach AC, Wender R, Levin B, Byers T, *et al.* American Cancer Society Guidelines for the Early Detection of Cancer: Update of Early Detection Guidelines for Prostate, Colorectal, and Endometrial Cancers. *CA Cancer J Clin.* 2001;51:38-75.

Sonnenberg A, Delco F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. *Ann Intern Med.* 2000;133:573-584.

- Sosna J, Morrin MM, Kruskal JB, Lawin PT, Rosen MP, Raptopoulos V. CT colonography of colorectal polyps: a metaanalysis. *AJR Am J Roentgenol*. 2003 Dec; 181(6):1593-8.
- Spinzi, G, Belloni, G, Martegani, A, *et al*. Computed tomographic colonography and conventional colonoscopy for colon diseases: A prospective, blinded study. *Am J Gastroenterol* 2001; 96:394-400.
- Summers RM, Beaulieu CF, Pusanik LM, Malley JD, Jeffrey RB, Glazer DI, Napel S. Automated Polyp Detector for CT Colonography: Feasibility Study<sup>1</sup>. *Radiology*. July 2000;216(1):284-290.
- Summers RM, Johnson CD, Pusanik LM, Malley JD, Youssef AM, Reed JE. Automated Polyp Detection at CT Colonography: Feasibility Assessment in a Human Population<sup>1</sup>. *Radiology*. 2001;219:51-59.
- Svensson MH, Svensson E, Lasson A, Hellstrom M. Patient acceptance of CT colonography and conventional colonoscopy: prospective comparative study in patients with or suspected of having colorectal disease. *Radiology*. 2002;222:337-345.
- Taylor SA, Halligan S, Bartram CI. CT Colonography: methods, pathology and pitfalls. *Clin Radiol*. 2003 Mar;58(3):170-90. Review.
- Trends in screening for colorectal cancer-United States, 1997 and 1999. *MMWR Morb Mortal Wkly Rep* 2001, 50:162-166
- USPSTF. Screening for Colorectal Cancer: Recommendation and Rationale. *Am Fam Phys* 2002;66(12):2287-2290.
- Vining, DJ. Virtual endoscopy: Is it a reality? *Radiology* 1996; 200-30.
- Walsh JM, Terdiman JP. Colorectal cancer screening: scientific review. *JAMA*. 2003 Mar 12;289(10):1288-96.
- Wolber RA, Owen DA. Flat adenomas of the colon. *Hum Pathol*. 1991 Jan;22(1):70-4.
- Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C; Gastrointestinal Consortium Panel. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. *Gastroenterology*. 2003 Feb;124(2):544-60.
- Winawer SJ, Zauber AG, Ho MN, *et al*. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study workgroup. *N Engl J Med*. 1993;329:1977-1981.
- Winawer SF, Zauber AG, O'Brien MJ, *et al*. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. *N Engl J Med*. 1993;328:901-6.
- Winawer SJ, Flehinger BJ, Schottenfeld D, Miller DG. Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy. *J Natl Cancer Inst* 1993;85:1311-1318.
- Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, Woolf SH, *et al*. Colorectal Cancer Screening: Clinical Guidelines and Rationale. *Gastroenterology*. 1997;112:594-642.
- Yee J, Akerkar GA, Hung RK, *et al*. Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. *Radiology*. 2001;219:685-692.
- Zalis ME and Hahn PF. Digital Subtraction Bowel Cleansing in CT Colonography. *AJR Am J Roentgen*. March 2001;176:646-8.
- Zubarik R, Fleischer DE, Mastropietro C, *et al*. Prospective analysis of complications 30 days after outpatient colonoscopy. *Gastrointest Endosc*. 1999;50:322-8.