Health Technology Assessment

Computed Tomographic Colonography (CTC)

Date: February 1, 2008

Presented by:

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

ICER

Health Technology Assessment Program

676 Woodland Square Loop SE

P.O. Box 42712

Olympia, WA 98504-2712

http://www.hta.hca.wa.gov

Computed Tomographic Colonography

Provided by:

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW
ICER

Prepared by:

Roberta Scherer, PhD
Amy Knudsen, PhD
Steven D. Pearson, MD, MSc

This technology assessment report is based on research conducted by ICER, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability

EXECUTIVE SUMMARY

Introduction

Computed tomography colonography (CT colonography or CTC) is a minimally invasive radiological technique used to provide images of the colon and rectum. CTC has been suggested as an alternative or as complementary to conventional colonoscopy and other population-based screening methods for colorectal cancer. Given that only 40%-60% of eligible patients undergo recommended screening for colorectal cancer, some commentators have suggested that the speed and relative ease of CTC compared to conventional colonoscopy might enhance patient compliance with screening recommendations. After more than a decade of research on CTC, however, questions remain about several important issues:

1) The sensitivity and specificity of CTC compared to conventional colonoscopy
2) Variation in performance across different providers and imaging modalities
3) Likely impact of CTC on population screening rates
4) Linkages between CTC and colonoscopy for removal of identified polyps
5) The impact on outcomes and costs of incidental "extracolonic" findings
6) Cost and cost-effectiveness of CTC

Given the possible benefits of introducing a widely available minimally-invasive option for colorectal cancer screening, there is considerable interest in CTC. That interest is colored by uncertainty over the evidence on the accuracy of CTC, and by questions about the potential impact broad adoption of CTC would have on systems of care and on health care costs. With these issues and questions in mind, ICER selected CTC as an important technology for which decision-makers would benefit from a thorough review of its clinical effectiveness and value compared to colonoscopy and other accepted screening methods for colorectal cancer.

Colorectal Cancer Screening and Polyp Size

Colorectal cancers most commonly develop from adenomatous polyps which arise from the mucosal lining of the large bowel. The interval from the development of an adenomatous polyp to transformation into cancer is estimated to be approximately 10 years (Winawer, 2003), although only a minority of all polyps progress to cancer (Stryker, 1987). The probability of progression to cancer is related to the size of the polyp. It has been estimated that 1% of polyps greater than or equal to 10mm will progress to cancer each year (Stryker, 1987; Van Dam, 2004). For polyps 5mm or less in size the risk of 10-year progression to cancer is considerably less than 1%, and may be as low as 0.25%. (Tsai, 1995). Guidelines for colorectal cancer screening programs and for the management of colorectal polyps have recommended that patients with polyps greater than or equal to 10mm and all patients with three or more smaller polyps should have the polyp(s) removed for histological examination. Although the natural history of smaller polyps is not known with certainty, and despite the fact that many clinicians in practice remove polyps of any size, the consensus among experts in this field is that the identification and biopsy of lesions ≤5mm are generally unnecessary unless the patient has three or more lesions.

Following the guidance of the ICER Evidence Review Group (see section on Evidence Review Group starting on page 17) the clinical effectiveness of CTC for this review was evaluated by examining data separately on its test characteristics for polyps ≥10mm and for polyps 6-9mm, since some policy makers will want to assign differential importance to CTC performance in these two categories. This review did not evaluate the performance of CTC for polyps ≤5mm as the clinical community does not assign significant importance to identification of these lesions and, in fact, recent articles have argued that greater harm than good arises from the biopsy of such "diminutive" lesions (Pickhardt, 2007).

Summary of Literature Review on Comparative Clinical Effectiveness

The accuracy of CTC has varied significantly in published studies over the years. In particular, the wide range of sensitivities (50%-90%) for medium and large polyps has led many commentators and previous health technology assessment bodies to judge the evidence base for CTC inadequate to support broad adoption of CTC for population-based screening. The best results in the literature have been those reported in a large study by Pickhardt in 2003, in which CTC was found to have comparable sensitivity with colonoscopy in the detection of both large and medium-sized polyps. Inferior results, however, were subsequently published by Cotton (2004), whose study reported that CTC detected only 23% of medium-sized lesions and 52% of larger polyps. Relatively poor results were also described by Rockey in 2005. The two latter studies, however, although published after Pickhardt, were actually performed prior to the Pickhardt study, and significant questions have been raised among clinical experts and in published commentaries regarding the adequacy of radiologist training and the quality of the CTC protocol used in these studies. For example, in the Cotton study radiologists reading the CTC in 8 of 9 centers were only required to have read 10 prior CTC studies, and the CTC results from the one center where radiologists had better training were significantly better than all others. Pickhardt's study required a minimum of 25 prior readings, whereas more recent guidelines suggest a minimum of 50-75. The deficiencies in many studies related to radiologist training and in other technical standards of CTC led our clinical experts to assert that Pickhardt's data are more representative of the performance of CTC as it would be practiced in the community today.

The ICER systematic review, guided by input from clinical experts, established minimum criteria for radiologist training and CTC technical specifications that had to be met for inclusion in our review. We identified four components of CT colonoscopy that we used to score studies using current best technology and performance standards versus studies using outdated technology or including sub-standard performance attributes. The four items include the following:

1. Multi-detector CT scanners with collimation < 5 mm;
2. Scan acquired within a single breath hold of ≤ 30 seconds;
3. Reference standard of combined CT colonoscopy and colonoscopy results (i.e., segmental unblinded colonoscopy or second look colonoscopy)
4. Trained readers by virtue of having read least 30 CT scans or undergone training before study start.

As shown in Tables 5-8 in the Tables section of this review, the data from our pooled analysis of studies that met these criteria demonstrated that the sensitivity and specificity of CTC for polyps ≥ 10mm was over 90%, very similar to that of colonoscopy. Pooled estimates of CTC sensitivity and specificity for all lesions ≥ 6mm are lower (86% and 81% respectively), but a judgment of these numbers must be made in light of the uncertainty among clinicians over the clinical significance of and best management strategies for these medium-sized polyps, and the proposed CTC screening strategy of rescreening every five years instead of every ten years, as is generally recommended for colonoscopy.

Using our pooled data on test characteristics from studies of "high-quality" CTC, the following estimates are obtained if one assumes that optical colonoscopy is a perfect reference standard:

- For every 1,000 patients screened by CTC and referred for colonoscopy for a finding of a lesion ≥ 6mm there will be:
  - 855 patients who have a true negative test
  - 15 patients who have a false negative test
  - 85 patients who have a true positive CTC (confirmed on colonoscopy)
  - 45 patients who have a false positive CTC (no polyp found on colonoscopy)

Potential Harms

Review of the evidence confirmed clinical expert opinion that CTC is a very safe procedure, with a far lower rate of complications than colonoscopy due to the virtual absence of risk for perforation when delivered in modern protocols. The potential for harm from radiation is more difficult to assess given the uncertainty of true risks of low levels of radiation exposure, but in the best empirical attempts to quantify the risk, it appears very low, less than the estimated attributable death rate from a colonoscopy with polypectomy, and clinically acceptable given the age of patients undergoing screening (>50) and the countervailing benefit of reducing the risk of cancer death conferred by screening for colorectal cancer.

The relative benefits and harms of extracolonic findings on CTC are also difficult to judge empirically. Studies suggest that approximately 6-8% of asymptomatic adults will have an extracolonic finding with a recommendation for follow-up of some kind. Were CTC to be adopted broadly, this rate of extracolonic findings would generate significant numbers of patients requiring further investigation. Upon further investigation some of these findings will be judged to have brought clinical benefit to the patient, most often either by early detection of a repairable

abdominal aortic aneurysm, or by detection of an early stage cancer. However, previous total body CT screening experience suggests that most abnormalities found among asymptomatic adults will be proven clinically insignificant, while additional risks, anxieties, and costs are generated by follow-up investigations. The additional cost per patient for these follow-up investigations has been found to be in the range of $2-$34, but these estimates are based on relatively small samples and further study will be required to arrive at a greater understanding of the net health benefit and costs of CTC extracolonic findings. From both a clinical and a health systems' perspective, this is one of the most important uncertainties regarding CTC. The determination of net health benefit for CTC may hinge on decision-makers interpretation of the boundaries of risk, benefit, and cost of extracolonic findings. As with judgments of all the potential benefits and harms of CTC, a decision on net health benefit may depend on whether CTC is viewed as an intervention among patients who otherwise would not receive colorectal cancer screening, or as an option for patients who would otherwise receive colonoscopy or some other accepted form of screening.

Patient Acceptance

The literature is somewhat inconsistent due to variations in the protocols for CTC and colonoscopy, but the preponderance of the data suggests that among patients who experienced both CTC and colonoscopy, a small majority preferred CT colonoscopy.

Impact on Population Screening Rates

It is unclear whether the preference elicited among some patients for CTC would result in a larger number of unscreened individuals in a population becoming screened. No study to date has examined whether the availability of CT colonography results in increased numbers of individuals being screened within a population.

Comparing CTC to screening modalities other than optical colonoscopy

This review did not undertake a formal systematic review of the literature on all colorectal screening methods, but the scoping committee expressed the desire to view the performance of CTC in relation to other accepted modalities such as fecal occult blood tests (FOBT), fecal immunochemical tests (FIT), and flexible sigmoidoscopy (SIG). In the Table on the following page we present a comparison based on single source estimates of test characteristics. In this simplistic comparison of sensitivities and specificities, in which major assumptions are made regarding the relationship of test characteristics for adenomas and those for cancer, CTC is estimated to have superior sensitivity and similar specificity compared to other non-invasive approaches.

Test characteristics of CTC in comparison to other accepted modalities

Test	Sensitivity for Adenomas, by Size			Sensitivity for Cancer	Specificity	Reach	Source
	≤ 5 mm	6-9 mm	10+ mm				
FOBT[1]	0.046	0.063	0.107	0.129	0.954	Whole colorectum	Imperiale

							2004
FIT[2]	0.045	0.11	0.224	0.658	0.955	Whole colorectum	Morikawa 2005
COL*	0.74	0.85	0.95	0.95†	0.9	98% to end of cecum	van Rijn 2006
SIG*	0.74	0.85	0.95	0.95†	0.92	80% to end of sigmoid colon; 40% to end of descending colon	Frazier, 2000, Expert opinion
CTCL	--	--	0.938	0.96†	0.92‡	Whole colorectum	ICER pooled estimate

[1]FOBT: Fecal occult blood test (Hemoccult II®)
[2]FIT: Fecal immunochemical test
COL: Colonoscopy
SIG: Flexible sigmoidoscopy
CTCL: Computed tomographic colonography with a positivity criterion of a large lesion (i.e., 10+mm)
*Sensitivity estimates are per lesion and are defined within reach of the scope
†Sensitivity for cancer assumed to equal that for large adenomas
‡Probability that CTC correctly finds a person to be free of an adenoma larger than the positivity criterion

Summary of Findings of Comparative Value:

CTC vs. no screening for population screening for colorectal cancer
The following numbers represent the base case analysis and compare *no screening* to a strategy of screening with CTC every five years and referring for colonoscopy all lesions ≥ 6mm.

- Cost of CTC = $523
- CTC cost to prevent one case of cancer *vs. no screening* = $19,000
- CTC cost to prevent one death *vs. no screening* = $37,000
- CTC cost per life-year gained *vs. no screening* = $1,500

CTC vs. colonoscopy for population screening for colorectal cancer
In direct comparison to colonoscopy, CTC every ten years is more expensive and marginally less effective in preventing cases of cancer (47 vs. 52 in a lifetime cohort of 1,000 individuals) and cancer deaths (24 vs. 26). Only one CTC screening strategy is more effective than colonoscopy every ten years, and that strategy is to perform CTC every five years with colonoscopy referral for polyps ≥ 6mm. For this strategy the cost-effectiveness is:

- Cost of CTC = $523
- Cost of colonoscopy = $522
- The cost per life-year gained for CTC *vs. colonoscopy* = $630,700

We also performed threshold analyses on the reimbursed price of CTC within the five-year strategy (the only CTC strategy we evaluated that was more effective than colonoscopy) to determine the CTC-to-colonoscopy-without-polypectomy cost ratio (i.e., "procedure cost ratio") that would produce incremental cost per life-year-saved at boundaries familiar to policy-makers.

- **To achieve Cost/Life-Year Saved = $150,000**
  Cost ratio CTC/colonoscopy = 0.52
  If colonoscopy cost = $522, CTC cost must = $272

- **To achieve Cost/Life-Year Saved = $100,000**
  Cost ratio CTC/colonoscopy = 0.47
  If colonoscopy cost = $522, CTC cost must = $246

- **To achieve Cost/Life-Year Saved = $50,000**
  Cost ratio CTC/colonoscopy = 0.42
  If colonoscopy cost = $522, CTC cost must = $219

Evidence Review Group Deliberation

The Evidence Review Group deliberation (see section starting on page 18 for membership and details) focused on many important issues regarding the evidence provided by the ICER review. Major points of discussion are shown in the numbered points below.

1) *Criteria for selection of relevant articles judged critical to review findings and was considered appropriate.*
   Like many diagnostic technologies, CTC has evolved in two aspects: technical, as the CT scanners, scanning software, bowel preps, and other technical aspects change; and interpretation, as the experience and standards for training of clinicians interpreting the results change. The ERG acknowledged that CTC remains in evolution, and that the criteria set for inclusion in our set of evaluated studies may not be applicable everywhere in the US. Nonetheless, the input of our clinical experts and health plan representatives suggested that the criteria selected were reasonable and that these standards could be widely achieved in the general community.

2) *Data on alternative colorectal cancer screening methods come from studies of their sensitivity/specificity for cancer detection, not polyp detection, so it is difficult to compare the evidence on FOBT and FIT to colonoscopy and CTC.*

3) *Colonoscopy is often considered the "gold standard," especially in comparison to CTC, but evidence demonstrates that colonoscopy also misses a fair number of medium and even large-sized polyps.*

4) *A key issue influencing the review of evidence is whether the benefits and harms of CTC should be viewed in comparison to optical colonoscopy, to other accepted modalities of colorectal cancer screening, or to no screening at all.*
   From a population perspective there are not nearly enough gastroenterologists available to perform needed colonoscopies, and if CTC can increase population-based screening its benefits and its cost-effectiveness are likely to be judged quite favorably. Others argued that there is no hard evidence to suggest that CTC would increase screening among those who would not have received screening another way; in addition, there are other non-invasive methods, such as FIT, that might be preferred by some systems of care. Some voiced concern that an increase in screening through CTC would only exacerbate the difficulty in obtaining timely gastroenterologist follow-up, and that broad considerations of capacity and professional training need to be done when considering adoption of CTC.

5) *On the horizon there is a new method of bowel prep for CTC that is non-cathartic, and if this method is demonstrated to provide the same sensitivity/specificity as current CTC, patient acceptance of CTC is likely to be much higher than for colonoscopy.*
   Our clinical experts estimated that evidence on the performance of non-cathartic prep would be available within the next 9-12 months.

6) *Judgments of the comparative clinical effectiveness and value of CTC may hinge on better understanding of the impact of extracolonic findings and the radiation risk.*
   Several ERG members expressed the opinion that extracolonic finding rates near 8% would drive a large number of follow-up investigations of highly dubious clinical value. Other

members of the ERG were more sanguine about the potential clinical benefits of early detection of significant extracolonic lesions, particularly if reporting of these lesions is guided by recently published ACR standards. The appraisal document has been revised to include significantly expanded examination of the evidence on radiation risk and on the published data on extracolonic findings.

7) *The economic model has several limitations but overall was viewed as a very useful tool for providing evidence on the clinical and cost-effectiveness of CTC.*
Some of the ERG participants would have liked the modeling to have included other possible CTC screening options, particularly one in which patients with medium-sized polyps are offered the option of immediate referral for colonoscopy vs. repeat CTC in 1-2 years. The decision model used for this appraisal could not evaluate this CTC surveillance strategy because the model does not explicitly simulate hyperplastic polyps. Data from the University of Wisconsin Medical School on the outcomes of individuals opting for CTC surveillance of medium-sized polyps are likely to be available in coming years and may help inform whether this is a reasonable strategy.

The specific discussion of the assignment of ICER ratings for comparative clinical effectiveness and for comparative value was preceded by the presentation of ICER's draft recommendations for ratings in two frameworks: 1) CTC vs. no screening; and 2) CTC vs. optical colonoscopy. There was unanimous consensus that, compared to no screening, CTC should be rated "Superior" in comparative clinical effectiveness, and "High Value" in comparative value. When rating CTC vs. colonoscopy there was some concern that the uncertainty regarding the impact of extracolonic findings made it difficult to have high confidence in any degree of net health benefit for CTC, but a majority (8/11) voters recommended a rating of "Comparable;" two voters recommended "Insufficient," and one voter recommended that CTC be rated as having "Incremental" comparative clinical effectiveness compared to colonoscopy.

Given that CTC is not covered by insurers for screening, the comparative value of CTC vs. colonoscopy was presented in draft form to the ERG in three versions according to three different possible scenarios of the potential reimbursement ratio between CTC and colonoscopy. A majority of voting ERG members (7/11) felt this was the best way to present the comparative value, but 4/11 felt that it would be preferable to label CTC only as "low value" according to the base case estimates of reimbursed price for CTC (equal to that of colonoscopy). The final ICER ratings are shown on the following pages, with background on the rating methodology immediately afterward.

ICER Integrated Evidence Rating™

ICER Integrated Evidence Rating™: CTC vs. NO SCREENING

The Comparative Clinical Effectiveness of CT colonography for colorectal cancer screening vs. NO SCREENING is rated as:

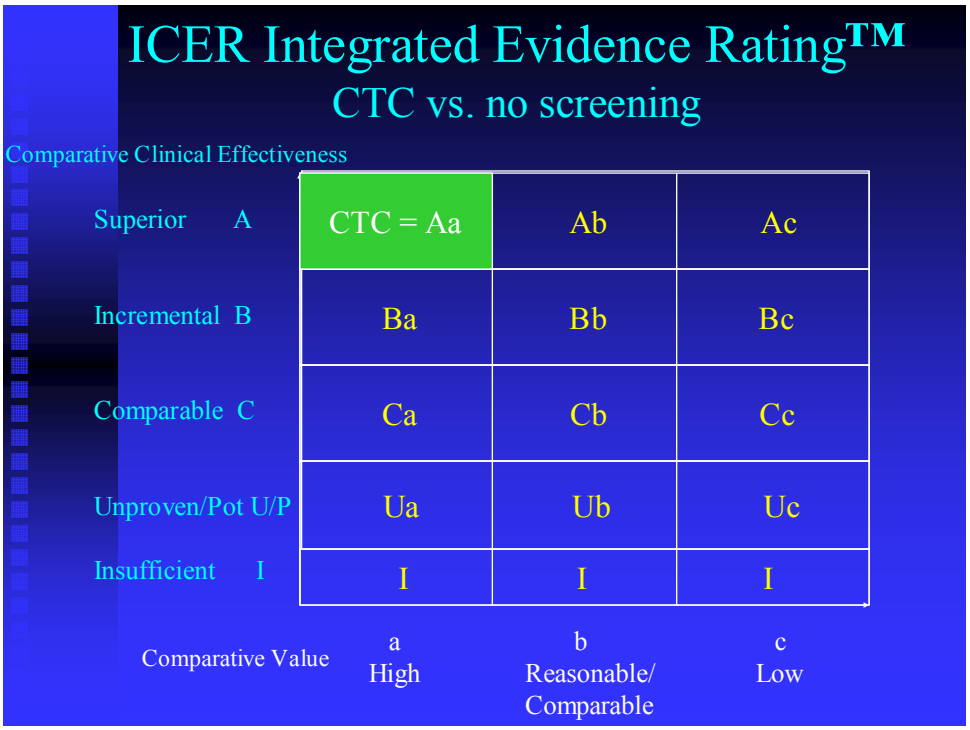
- **A --- Superior.**

The Comparative Value of CT colonography for colorectal cancer screening vs. no screening is rated as:

- **a --- High***

The Integrated Evidence Rating = Aa*

*** Reimbursed price of CTC assumed to = approximately $523**



ICER Integrated Evidence Rating™: CTC vs. OPTICAL COLONOSCOPY

The Comparative Clinical Effectiveness of CT colonography for colorectal cancer screening vs. OPTICAL COLONOSCOPY is rated as:

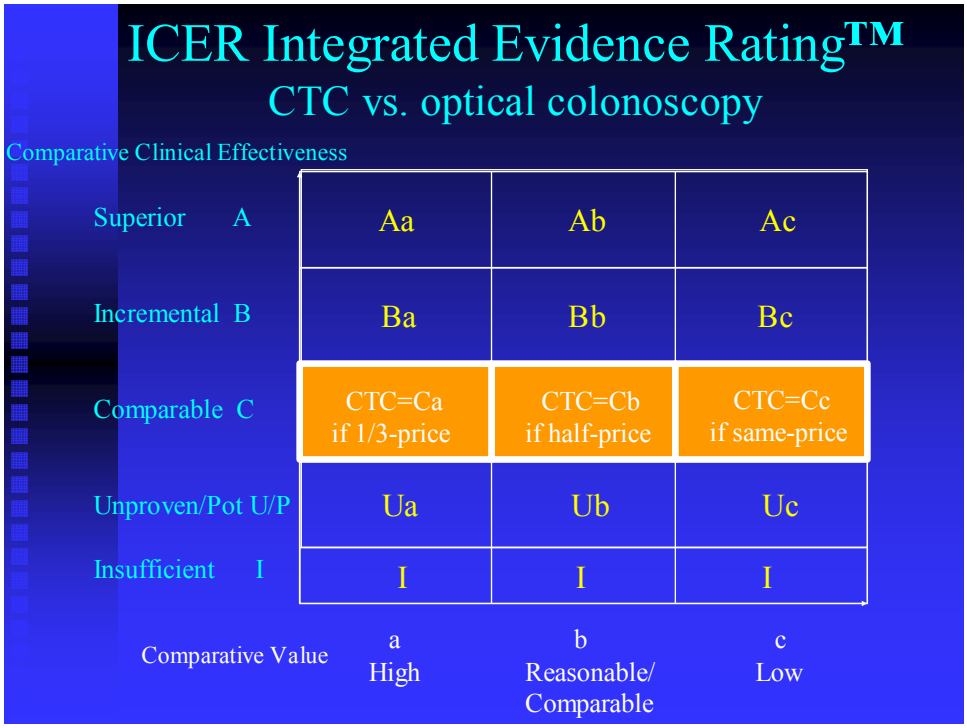
- **C --- Comparable**

The Comparative Value of CT colonography for colorectal cancer screening vs. optical colonoscopy screening is rated as:

- **c, b, or a --- low, comparable, or high, depending on reimbursed price ratio***

The Integrated Evidence Rating = Cc, Cb, or Ca*

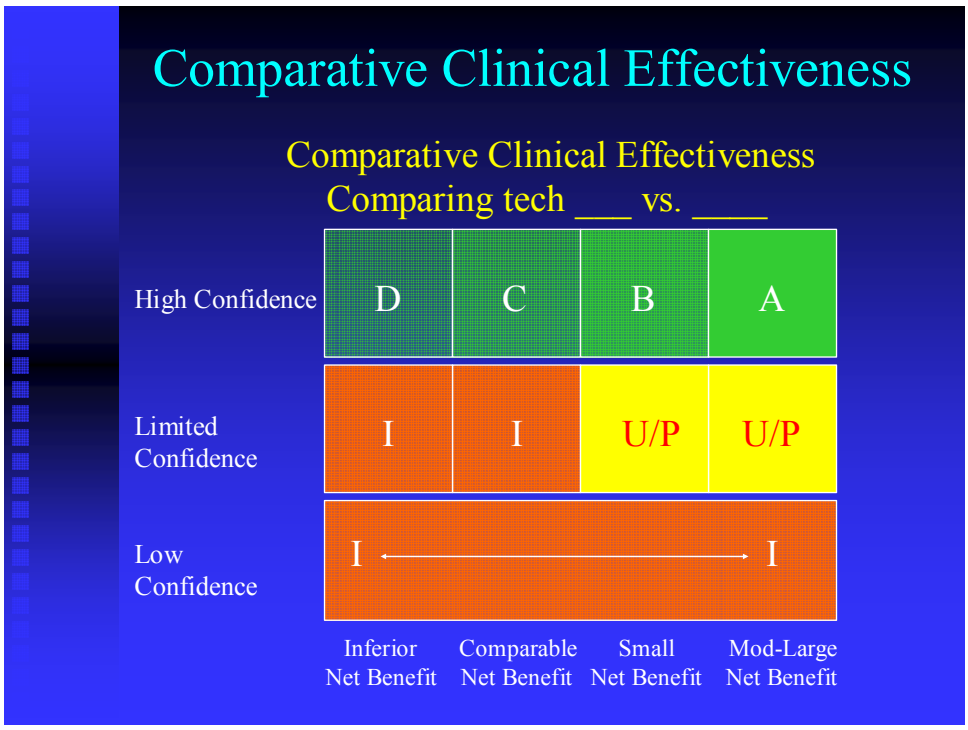
***If reimbursed price of CTC = same price as optical colonoscopy, comparative value = c**
If reimbursed price of CTC = half the price of optical colonoscopy, comparative value = b
If reimbursed price of CTC = one-third that of optical colonoscopy, comparative value = a



Methodology: ICER Integrated Evidence Rating™

Comparative Clinical Effectiveness

The ICER Integrated Evidence Rating™ combines a rating for comparative clinical effectiveness and a rating for comparative value. The clinical effectiveness rating arises from a joint judgment of the level of confidence provided by the body of evidence and the magnitude of the net health benefit -- the overall balance between benefits and harms. This method for rating the clinical effectiveness is modeled on the "Evidence- Based Medicine (EBM) matrix" developed by a multi-stakeholder group convened by America's Health Insurance Plans. This matrix is depicted below:



A = "Superior" [High confidence of a moderate-large net health benefit]
B = "Incremental" [High confidence of a small net health benefit]
C = "Comparable" [High confidence of a comparable net health benefit]
D = "Inferior" [High confidence of an inferior net health benefit]
U/P = "Unproven with Potential " [Limited confidence of a small or moderate-large net health benefit
This category is meant to reflect technologies whose evidence provides:

1) High confidence of *at least* comparable net health benefit
2) Limited confidence suggesting a small or moderate-large net health benefit

I = "Insufficient" The evidence does not provide high confidence that the net health benefit of the technology is at least comparable to that provided by the comparator(s).

Confidence

The vertical axis of the matrix is labeled as a degree of confidence with which the magnitude of a technology's comparative net health benefit can be determined. This operational definition of confidence thus is linked to but is not synonymous with the overall validity, consistency, and directness of the body of evidence available for the assessment. ICER establishes its rating of level of confidence after deliberation by the Evidence Review Group, and throughout ICER follows closely the considerations of evidentiary strength suggested by the Effective Health Care program of the Agency for Health Research and Quality (AHRQ) (www.effectivehealthcare.org) and the GRADE working group (www.gradeworkinggroup.org).

High Confidence:

An assessment of the evidence provides high confidence in the relative magnitude of the net health benefit of the technology compared to its comparator(s).

Limited Confidence:

There is limited confidence in the assessment the net health benefit of the technology. Limited confidence implies that the evidence is limited in one or more ways so that it is difficult to estimate the net health benefit with precision. ICER's approach considers two qualitatively different types of limited confidence. First, there may be limited confidence in the magnitude of any net health benefit, but there is high confidence that the technology is *at least* as effective as its comparator(s). The second kind of limited confidence applies to those technologies whose evidence may suggest comparable or inferior net health benefit and for which there is not nigh confidence that the technology is at least comparable. These two different situations related to "limited confidence" are reflected in the matrix by the different labels of "Unproven with Potential" and "Insufficient."

Limitations to evidence should be explicitly categorized and discussed. Often the quality and consistency varies between the evidence available on benefits and that on harms. Among the most important types of limitations to evidence we follow the GRADE and AHRQ approaches in highlighting:

1. Type of limitation(s) to confidence
    a. Internal validity
        i. Study design
        ii. Study quality
    b. Generalizability of patients (directness of patients)
    c. Generalizability of intervention (directness of intervention)
    d. Indirect comparisons across trials (directness of comparison)
    e. Surrogate outcomes only (directness of outcomes)
    f. Lack of longer-term outcomes (directness of outcomes)
    g. Conflicting results within body of evidence (consistency)

Low Confidence:

There is low confidence in the assessment of net health benefit and the evidence is insufficient to determine whether the technology provides an inferior, comparable, or better net health benefit.

Net Health Benefit

The horizontal axis of the comparative clinical effectiveness matrix is "net health benefit." This term is defined as the balance between benefits and harms, and can either be judged on the basis of an empiric weighing of harms and benefits through a common metric (e.g. Quality Adjusted Life-Years, or "QALYs"), or through more qualitative, implicit weightings of harms and benefits identified in the ICER appraisal. Either approach should seek to make the weightings as explicit as possible in order to enhance the transparency of the ultimate judgment of the magnitude of net health benefit.

Whether judged quantitatively or qualitatively, there are two general situations that decision-making groups face in judging the balance of benefits and harms between two alternative interventions. The first situation arises when both interventions have the same types of benefits and harms. For example, two blood pressure medications may both act to control high blood pressure and may have the same profile of side effects such as dizziness, impotence, or edema. In such cases a comparison of benefits and harms is relatively straightforward. However, a second situation in comparative effectiveness is much more common: two interventions present a set of trade-offs between overlapping but different benefits and harms. An example of this second situation is the comparison of net health benefit between medical treatment and angioplasty for chronic stable angina. Possible benefits on which these interventions may vary include improved mortality, improved functional capacity, and less chest pain; in addition, both short and long-term potential harms differ between these interventions. It is possible that one intervention may be superior in certain benefits (e.g. survival) while also presenting greater risks for particular harms (e.g. drug side effects). Thus the judgment of "net" health benefit of one intervention vs. another often requires the qualitative or quantitative comparison of different types of health outcomes.

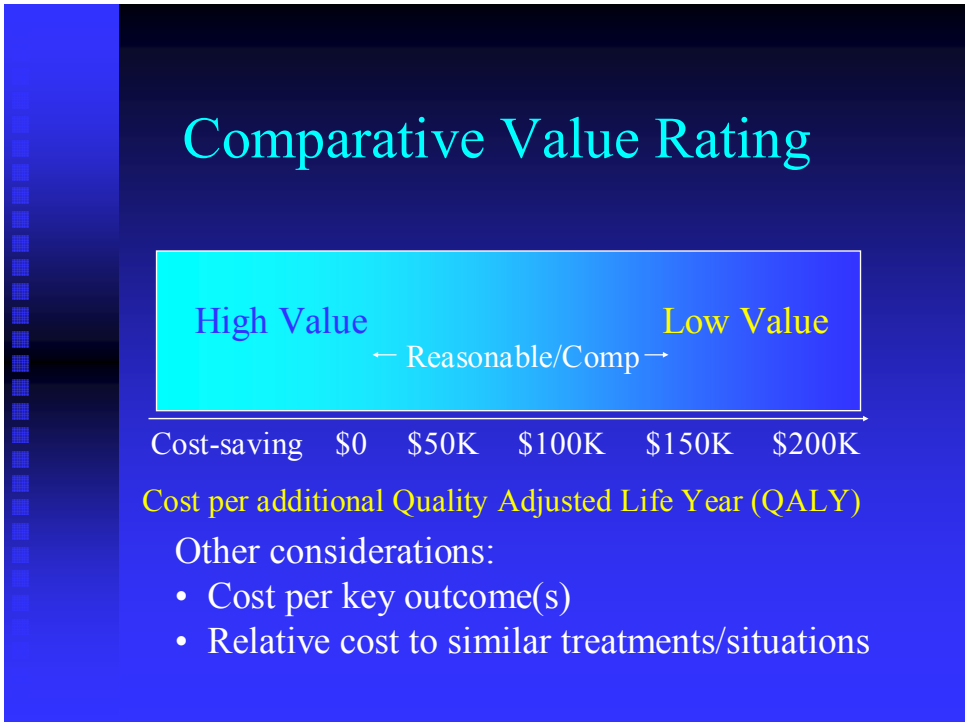
Since net health benefit may be sensitive to individual patient clinical characteristics or preferences there is a natural tension between the clinical decision-making for an individual and an assessment of the evidence for comparative clinical effectiveness at a population level. ICER approaches this problem by seeking, through the guidance of its scoping committee, to identify a priori key patient subpopulations who may have distinctly different net health benefits with alternative interventions. In addition, the ICER appraisal will also seek to use decision analytic modeling to identify patient groups of particular clinical characteristics and/or utilities which would lead them to have a distinctly different rating of comparative clinical effectiveness.

The exact boundary between small and moderate-large net benefit is subjective and ICER does not have a quantitative threshold. The rating judgment between these two categories is guided by the deliberation of the Evidence Review Group.

Comparative Value

The ICER rating for comparative value arises from a judgment largely based on the incremental cost-effectiveness of the technology being appraised. There are three categories of value: high, reasonable or comparable, and low. These categories, as shown in the figure below, are separated by general boundaries established by health care researchers and policy makers. The most commonly used metric for an assessment of comparative value is the quality adjusted life year, or QALY. This measure adjusts any improvement in survival provided by a technology by its corresponding impact on the quality of life as measured by the "utilities" or patients or the public for various health states. Details on the methodology underpinning the design and presentation of cost-effectiveness analyses within ICER appraisals is available on the ICER website at www.icer-review.org.

Although the cost per QALY is the most common way to judge the cost-effectiveness and comparative value of alternative medical interventions, ICER also presents the sub-component parts of the QALY, including the cost per key clinical benefits. Sensitivity analyses examining the robustness of results is also performed and presented in detail to the Evidence Review Group for deliberation.



Integrated Ratings

The ICER Integrated Evidence Rating™ combines the individual ratings given for comparative clinical effectiveness and comparative value. The overall purpose of the integrated ratings is to highlight the separate considerations that go into each element but to combine them for the purposes of conveying that clinical benefits provided by technologies come at varying relative values based on their cost and their impact on the outcomes of care and the health care system.

Evidence Review Group members

The Evidence Review Group (ERG) is an independent group brought together by ICER and composed of academic experts, patients, clinicians, epidemiologists, ethicists, and medical policy representatives of stakeholder groups including health plans and manufacturers.

The purpose of the ERG is to guide and help interpret the entire appraisal process. Members of the ERG are first convened to function as a "scoping committee" for the appraisal. During this phase the key questions for the appraisal are outlined, including elements such as the appropriate comparator technologies, patient outcomes of interest, patient subpopulations for which clinical and cost-effectiveness may vary systematically, time horizon for outcomes, and key aspects of the existing data that must be taken into account during the appraisal. The ERG may be divided into sub-committees that advise the ICER appraisal team at the mid-point of the appraisal on the early findings and challenges encountered.

At the final ERG meeting, members are asked to declare any interests in the technology or its comparator(s). The ERG meeting allows for in-depth deliberation on the findings of the ICER appraisal document and provides an opportunity for comment on the determination of the ICER integrated evidence rating. Although the ERG helps guide the final determination of the ICER Integrated Evidence Rating™, the final rating is ultimately a judgment made by ICER, and individual members of the ERG should not be viewed in any way as having endorsed this appraisal.

ERG Participant Name	**Conflict of interest**
John Ayanian, MD Professor of Medicine Harvard Medical School Brigham & Women's Hospital	None declared
Marc Berger, MD Vice President, Global Health Outcomes Eli Lilly and Company	None declared
William Corwin, MD Medical Director, Medical Management & Policy Harvard Pilgrim Health Care	None declared
Wendy Everett, ScD President, New England Healthcare Institute	Philips Medical is a member of her organization, New England Healthcare Institute
Robert Fletcher, MD, MSc Prof. of Ambulatory Care & Prevention Harvard Medical School	Scientific Advisory Board, Exact Sciences (developed DNA stool test for colorectal cancer screening)

G. Scott Gazelle Director, Institute for Technology Assessment, Massachusetts General Hospital and Prof. of Radiology, Harvard Medical School	None declared
Robert McDonough, MD Senior Medical Director, Clinical Research and Policy Development Aetna, Inc.	None declared
Peter J. Neumann, ScD Director, Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research & Health Policy Studies Tufts-New England Medical Center	None declared
Lisa Prosser, Ph.D. Assistant Prof., Dept of Ambulatory Care & Prevention Harvard Medical School	None declared
Paul C. Schroy, MD, MPH Prof. of Medicine, Boston University School of Medicine & gastroenterologist, Boston Medical Center	Exact Sciences, Inc. grant support and speaker's bureau; AmberGen, Inc. scientific advisory board and grant support
William C. Taylor, MD Associate Prof. of Medicine Harvard Medical School	Expert witness in medico-legal cases
Sunny Virmani Research Scientist Philips Medical Systems, Cleveland	Employee of manufacturer of CTC systems
Jed Weissberg, MD Associate Executive Director, Quality and Performance Improvement The Permanente Federation	Involved with purchasing of capital equipment at Kaiser Permanente
Michael Zalis, MD Radiologist, Massachusetts General Hospital	Investigator of CT colonography in academic setting

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

APPRAISAL OVERVIEW

CT COLONOGRAPHY
FOR COLORECTAL CANCER SCREENING

The overview is written by members of ICER's research team. It represents the information received by the Evidence Review Group members prior to the committee meeting. The overview summarizes the evidence and views that have been considered by ICER and highlights key issues and uncertainties.

Final Scope

Rationale for the Appraisal

Computed tomography colonography (CTC) is a minimally invasive radiological technique used to provide images of the colon and rectum. CTC has been suggested as an alternative or as complementary to conventional colonoscopy and other population-based screening methods for colorectal cancer. Given that only 40%-60% of eligible patients undergo recommended screening for colorectal cancer, some commentators have suggested that the speed and relative ease of CTC compared to conventional colonoscopy might enhance patient compliance with screening recommendations. After more than a decade of research on CTC, however, questions remain about several important issues:

1) The sensitivity and specificity of CTC compared to conventional colonoscopy
2) Variation in performance across different providers and imaging modalities
3) Likely impact of CTC on population screening rates
4) Linkages between CTC and colonoscopy for removal of identified polyps
5) Management of incidental findings in lung, liver, and kidney
6) Cost and cost-effectiveness of CTC

Given the possible benefits of introducing a widely available non-invasive option for colorectal cancer screening, the potential impact broad adoption of CTC would have on systems of care and on health care costs, and the uncertainty over the evidence on the accuracy of CTC, patients, clinicians, and payers will benefit from a formal appraisal of the comparative clinical effectiveness and comparative value of CTC as a modality for colorectal cancer screening.

Objective:
To appraise the comparative clinical effectiveness and comparative value of CTC versus optical colonoscopy and to place the performance of CTC in context with other accepted modes of colorectal cancer screening.

Key questions:

1) What is the sensitivity, specificity, and other key test characteristics of CTC compared primarily to optical colonoscopy but also in context with the test characteristics of accepted modalities of colorectal cancer screening?

2) How do the test characteristics of CTC vary according to the type of scanning machine and software, bowel prep, reader training, and other operational factors?

3) How do patient attitudes and acceptance of screening compare between CTC and colonoscopy?

Key considerations highlighted by scoping committee:

1) Interventions: This technology has been in constant evolution and it is now widely believed that "high quality" CTC requires several key features of the machine itself and of reader training in interpretation. Among the other potential non-invasive screening options, iFOBT (FIT) is being considered as the most promising by many groups and comparison of CTC to FIT would be helpful to decision-makers.

2) Individual vs. Population-based impact: A relevant question is to explore the impact on outcomes and costs on an entire screening population given the hypothesis that introduction of CTC would increase the total proportion of eligible adults who obtain colorectal screening of any kind.

3) Costs: Anesthesia and pathology costs should be incorporated in modeling of the costs of colonoscopy.

4) Professional considerations: Note was made that there have been differing interpretations of the existing literature and differing opinions on the relevance of identifying various types of polyps, some of which reflects differences among gastroenterologists and radiologists.

5) Ethical considerations: There appear to be no specific ethical concerns.

1. Background

1.1 The Condition

Colorectal cancer is the second leading cause of cancer death in the United States, with over 130,000 new cases diagnosed each year. More than 52,000 Americans will die from colorectal cancer in 2007.

Colorectal cancers most commonly develop from the mucosal lining of the large bowel. The underlying mechanism is believed to be an accumulation of genetic alternations that progressively alter the normal structure and function of the bowel wall lining. The earliest anatomical change known to be a precursor to colorectal cancer is called an aberrant crypt focus. Later pre-malignant changes include adenomatous polyps. These polyps can be detected by direct visualization of the bowel wall at colonoscopy or sigmoidoscopy. The interval from the development of an adenomatous polyp to transformation into cancer is estimated to be around 10 years (Winawer, 2003), although only a minority of all polyps progress to cancer (Stryker, 1987).

The probability of progression to cancer is related to the size of the polyp. Guidelines for colorectal cancer screening programs and for the management of colorectal polyps have recommended that patients with polyps greater than or equal to 10mm, or patients with three or more smaller polyps should have the polyp(s) removed for histological examination. It has been estimated that 1% of polyps greater than or equal to 10mm will progress to cancer each year (Stryker, 1987; Van Dam, 2004). For polyps 5mm or less in size the risk of 10-year progression to cancer is considerably less than 1%, and may be as low as 0.25%. (Tsai, 1995). It appears that the consensus in current practice is that the identification or biopsy of these small lesions is generally unnecessary unless the patient has three or more lesions. Some clinicians, however, argue that "it is a major paradigm shift to institute a policy of leaving most colorectal neoplasms in place considering that these polyps are so common" (Heresbach, 2007).

Guidelines for the management of polyps 6-9mm are less well defined. In polyps of this size, studies have indicated that 2-7% will contain high grade dysplasia and 0.9% will show invasive cancer (Van Dam 2004). A recently published decision analysis suggests that leaving these polyps in place results in 10-fold more cancers and 8-fold more deaths at 3 years, but investigators with Pickhardt's group in Wisconsin suggest that for patients with one or two polyps between 6-9mm it is reasonable to offer them the option of repeat CTC at 2-3 year intervals.

Varying opinions are also expressed in the literature regarding the significance of "flat" polyps. In European populations, up to 36% of adenomas removed were found to be flat or depressed. Studies indicate that flat or depressed lesions may be present in uip to 22.7% of patients undergoing screening colonoscopy in the United States (Saitoh, 2001). Flat polyps have been reported to be significantly more likely to contain high-grade dysplasia that protuberant polyps (Tsuda, 2002). However, this remains controversial for U.S. populations. A reclassification of sessile adenomas identified at baseline in the National Polyp Study cobort into flat or polypoid adenomas, indicated that flat polyps were not associated with a higher risk for high-grade dysplasia initially or for advanced adenomas at surveillance (O'Brien, 2004). The importance of flat polyps in western populations, therefore, remains unclear.

1.2 The Technology and its Comparator(s)

CT Colonography
CTC is a technique in which a spiral CT scanner is used to acquire multiple simultaneous tomographic sections ("slices") of the colon and rectum during one rotation of the x-ray source. Software programs are used to reformat these data and display two-dimensional images or three-dimensional reconstructions of the bowel (also referred to as "virtual colonoscopy"). Patients must take a cathartic bowel preparation regimen to empty the bowel the day before the procedure. At the time of the procedure, the patient is positioned on the CT scanner and a catheter is placed in the rectum to inflate the colon with air or carbon dioxide ("insufflation"). Two scans of the abdomen are then performed, one with the patient lying on their back, and one with the patient lying on their stomach. The patient does not require sedation, and the entire procedure usually takes less than 30 minutes for set-up and scanning.

After the publication of studies indicating that flexible sigmoidoscopy can miss over 50% of proximal neoplastic lesions, complete colonic examination with colonoscopy has become viewed by many as the single most effective and desirable screening option. However, the choice of colonoscopy as the principal screening modality for colorectal cancer is limited by several factors. Colonoscopy is an invasive test and thus carries a (small) risk for potential complications. For some patients there are also negative perceptions of colonoscopy based on poor acceptability of the bowel-preparation process, fear of discomfort during the procedure, and fear of the sedation required.

Colorectal Cancer Screening Alternatives
The major alternative screening methods in current use include several types of fecal occult blood testing (FOBT), immunochemical FOBT (iFOBT or FIT), flexible sigmoidoscopy, and double contrast barium enema. Current screening guidelines of the U.S. Preventive Services Task Force suggest the following with an "A" rating based on the strength of evidence:

Beginning at age 50, both men and women should follow 1 of these 5 testing schedules:

- yearly fecal occult blood test (FOBT)* or fecal immunochemical test (FIT)
- flexible sigmoidoscopy every 5 years
- yearly FOBT* or FIT, plus flexible sigmoidoscopy every 5 years**
- double-contrast barium enema every 5 years
- colonoscopy every 10 years

*For FOBT, the take-home multiple sample method should be used. **The combination of yearly FOBT or FIT flexible sigmoidoscopy every 5 years is preferred over either of these options alone.

All positive tests should be followed up with colonoscopy.

Guaiac-based FOBT tests measure the peroxidase activity of hemoglobin. Its advantages include privacy, noninvasiveness, and low cost. Drawbacks include limited sensitivity for detecting cancer (and worse sensitivity for detecting advanced polyps), the need for periodic testing, and

low patient adherence. Another disadvantage is poor specificity (or high false-positive rate); guaiac-based FOBT reacts with nonhuman heme in food and blood from the upper gastrointestinal tract. iFOBT tests have been developed in an effort to improve specificity and eliminate the need for dietary restriction. They use one or more monoclonal antibodies or polyclonal antibodies to detect human hemoglobin.

All of these screening options, both invasive and non-invasive, convey different advantages and disadvantages, and all have been found to be relatively cost-effective compared to no screening. Because population screening for colorectal cancer continues to be under-performed on both a regional and national basis, and because of wide variability in available resources, patient preferences, and program adherence, authorities such as the U.S. Preventive Services Task Force and the American Cancer Society have long advocated that clinicians and patients choose from a menu of accepted screening strategies the test that best matches the particular setting and with which the patient is most likely to be adherent.

1.3. Clinical Guidelines

United States Preventive Services Task Force (2002):
The USPSTF is currently conducting another evaluation of modalities for CRC screening. Its most recent statement is from 2002, when it found "insufficient evidence that newer screening technologies (for example, computed tomographic colography) are effective in improving health outcomes."

National Comprehensive Cancer Network (NCCN):
The NCCN has within their CTC screening guidelines the following statement: "Virtual colonoscopy is evolving as a very promising technique for CTC screening. Data regarding virtual colonoscopy are too premature to warrant its use in screening."

National Cancer Institute (NCI):
According to the NCI, "there are a number of hurdles that have to be overcome before virtual colonoscopy becomes widely used. Technical improvements involving both the interpretation methodology and bowel preparation are being studied. Current sensitivity and specificity variances are attributable to a number of factors, including characteristics of the CT scanner and detector, width of collimation, mode of imaging as well as variability in expertise of the radiologists."

American College of Radiology (2002):
Regarding CT colonography: "Early data suggest that these targeted examinations may be clinically valid. Large, prospective, multicenter trials are currently under way or in the planning phase to evaluate whether these screening exams reduce the rate of mortality." In 2005 the ACR published indications for the use of CTC and included "as a screening examination in individuals who are at average or elevated risk for CTC or who have a first-degree relative with a history of CTC."

American Gastroenterological Association (2003): Virtual colonoscopy is not yet ready for widespread screening outside the research setting pending improvements in the technology, clinical studies of performance in average-risk patients and a better understanding of associated costs.

America College of Gastroenterology (2002): The ACG has concluded that virtual colonoscopy based on CT or MRI is still in development, has not been established as a reliable screening test, and therefore is not endorsed for colorectal cancer screening.

American Cancer Society (2003):
The ACS Colorectal Cancer Advisory Group concluded that "CT colonography is a compelling, emerging technology that shows considerable promise, but it has not yet been studied in a typical screening population; therefore, whether or not it has comparable or superior performance compared with conventional tests is unknown."

1.4. Previous Systematic Reviews/Tech Assessments

- National Institute for Health and Clinical Excellence (NICE) (2005)
  Current evidence on the safety and efficacy of CTC appears adequate to support the use of this procedure.

- California Technology Assessment Forum (CTAF) (2004)
  Virtual colonoscopy did not meet TEC criteria.

- BCBSA TEC (2004)
  Failed criteria. The current evidence does not allow conclusions as to the comparative efficacy of CTC and colonoscopy.

- Canadian Agency for Drugs and Technologies in Health (CADTH)
  CADTH has not reviewed this topic.

- MSAC (2006):
  Evidence indicates that CTC is less effective and should not be proposed as a substitute for colonoscopy

- ICSI (2006):
  Due to the high number of extracolonic findings that require additional evaluation, additional studies are needed to determine if CTC can be an alternative to colonoscopy.

1.5. Medicare and Representative Private Insurer Coverage Policies

- There is a Medicare National Coverage Decision on CTC. CTC is not reimbursable when used for screening.

- In April, 2004 three private health plans in Wisconsin initiated coverage for CT colonography screening only at the University of Wisconsin by Pickhardt and his practice group. These health plans are Physicians Plus Insurance, Unity Health Insurance, and Group Health Cooperative.

- All other private health plans evaluated for this overview cover CTC only for specific situations in which conventional colonoscopy is contra-indicated or has failed. Screening CTC is not covered by Aetna, Tufts, Regence, CIGNA, Harvard Pilgrim, Wellpoint, United Healthcare.

1.6. Ongoing Clinical Trials

The American College of Radiology Imaging Network (ACRIN) has recently concluded a large multicenter study to compare the effectiveness of CTC to conventional colonoscopy. The ACRIN trial was projected to enroll more than 2,300 patients at 15 sites nationwide during a 1-year accrual period. Study participants were at least 50 years old, scheduled for a screening colonoscopy, and had not had a colonoscopy in the past 5 years. Each study participant had a CT colonography followed by a colonoscopy on the same day. Preliminary results were announced on September 28, 2007. This trial has been viewed as potentially definitive by some investigators and commentators in the field. A website report of the preliminary findings is enclosed as an attachment to this report.

2. The Evidence

2.1 Systematic Literature Review

Objectives

The primary objective of the systematic review was to compare the sensitivity and specificity of computed tomography (CT) colonography with that of optical colonoscopy for detection of polyps and colorectal neoplasia. Evidence regarding safety, extracolonic findings, patient acceptance, and impact on population screening rates were sought within the literature on test characteristics, supplemented with evidence obtained from review articles and expert guidance.

2.2 Methods

We included studies in this review which had a study population of adults who agreed to undergo colorectal screening by CT colonography. Populations were not restricted by risk status or demographic characteristic. Studies examining use of CT colonography for individuals with Crohn's disease, irritable bowel syndrome, or current or previous diagnosis of a gastrointestinal disease were excluded.

Eligible studies prospectively compared CT colonography with optical colonoscopy by evaluating the sensitivity and specificity of CT colonography using optical colonography or a combination of CT colonography and optical colonography (i.e.,segmental unblinded colonoscopy or second look colonoscopy) as the reference standard. We required investigators performing and evaluating screening tests to be unaware of patient risk status or results of the comparator screening test. Studies were not restricted by CT colonography instrumentation or imaging technology.

Electronic databases searched included PubMed, EMBASE, *The Cochrane Library*, and Science Citation Index for eligible studies, including health technology assessments (HTAs), systematic reviews, and primary studies. Reference lists of all eligible studies were also searched. The search strategies used for PubMed, EMBASE, and *The Cochrane Library* are shown in Appendix A.

Figure 1 on the next page shows a flow chart of the results of all searches for included primary studies. In addition to 52 primary studies, searches identified four systematic reviews and ten HTAs.

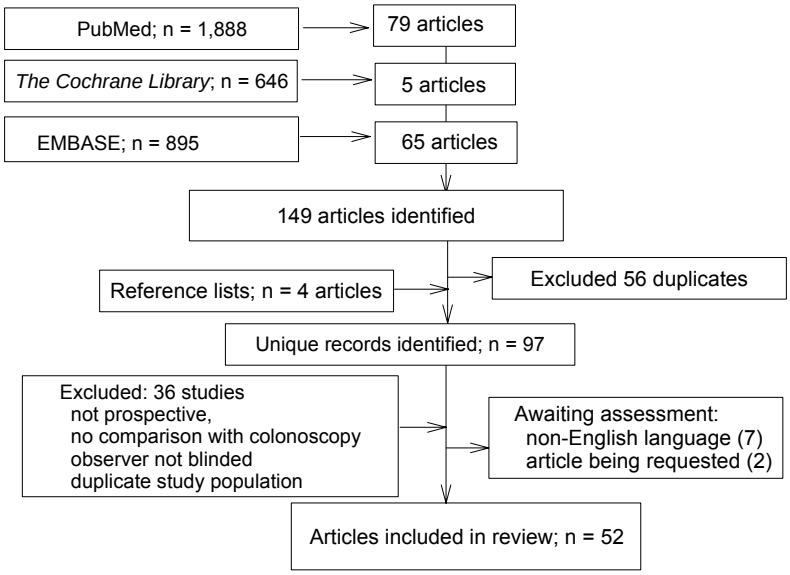


Figure 1. QUORUM flow chart showing results of literature search
Data abstracted from each primary study included inclusion and exclusion criteria, patient demographics and risk status, methods used for patient preparation, use of intravenous contrast media and/or oral fecal tagging agent, scanner and imaging parameters, number of procedures completed, sensitivity and specificity for detection of lesions $\geq$ 10 mm, $\geq$ 6 mm, and 6 to 9 mm by patient and by lesion, complications, extracolonic findings, and patient outcomes of preference and satisfaction.

Sensitivity and Specificity Data

If sensitivity or specificity was not reported, we calculated these values. We calculated sensitivities whenever true positive and false negatives values were reported using the formula "true positive/ (true positive + false negative). Specificity was calculated using the formula "true negative/(false positive + true negative), and positive predictive value as "true positive/ (true positive + false positive). If findings were reported separately for more than one observer, we calculated average true positive, false negative, and false positive values. Whenever possible, we calculated values for lesions of a particular size by subtracting or adding numbers of lesions reported. We did not attempt to calculate values for lesions sized 6 to 9 mm if values were reported only by size thresholds (e.g., $\geq$ 6 mm, $\geq$ 7 mm, etc.) for the per patient analysis, because it is not possible to account for any patient who may have had more than one lesion, with one lesion $\geq$ 10 mm ad the second between 6 and 9 mm.

Study quality of diagnostic accuracy studies is typically assessed using the QUADAS tool, an 8-item instrument evaluating the internal validity of a study developed by Whiting *et al* (2003). Since CT colonography is a rapidly evolving technology, we believed that while studies could very well be equally valid using the QUADAS tool, not all studies would be equally representative of current technology. Thus, we chose to begin the assessment of study quality not by using items in QUADAS, but rather by evaluating studies for characteristics that indicated use of current best technology and performance standards. CT colonoscopy instrumentation, image resolution, and procedure techniques have improved significantly in the last ten years and

so we chose to follow the recommendations of the CT Colonography Scoping and Evidence Review Committee as to the characteristics that characterize state-of-the-art in CT colonoscopy examination performance.

We identified four components of CT colonoscopy that we used to score studies using current best technology and performance standards versus studies using outdated technology or including sub-standard performance attributes. The four items include the following:

5. Multi-detector CT scanners with collimation < 5 mm;
6. Scan acquired within a single breath hold of ≤ 30 seconds;
7. Reference standard of combined CT colonoscopy and colonoscopy results (i.e., segmental unblinded colonoscopy or second look colonoscopy)
8. Trained readers by virtue of having read least 30 CT scans or undergone training before study start.

The choice of a breath hold threshold of 30 seconds was somewhat arbitrary but was within the breath hold time of a "normal" individual (36.2 ± 12 sec; mean ± SD) as reported by Taskar *et al* (1995). The choice of threshold for the amount of training for criterion 4 was based on Halligan's definition of an "experienced" CT reader as one who had interpreted 30 or more scans (Halligan 2005).

We considered including adequate colonic preparation as a criterion because many instances of false negatives appear to be due to residual stool or fluid or inadequate colonic distension. However, colonic preparation is dependent on patient compliance. Visualization of the colon appears to be optimal using combined supine and prone positioning, allowing for redistribution of fluid and stool. Since few studies used single supine positioning and all used approximately the same procedure for distension, we did not include any criteria related to bowel cleansing or insufflation as criteria. We also did not include any criteria related to the use of oral or intravenous contrast materials. Although use of contrast material may be considered an important component of current CT technology, it appears not to be routinely used as yet, with few studies reported using either type of contrast media.

Using the four criteria described above, we identified nine studies fulfilling these criteria, i.e., using current best CT colonographic performance standards, for further analysis. These studies are described in Table 1. Studies not included for analyses are shown in Table 2 (multi-detectors) and Table 3 (single detectors), with characteristics scored as present, not reported, or unclear.

Description of study objective and quality

Most investigators of the nine studies included for analysis designed their studies to compare the accuracy of CT colonography with optical colonoscopy. All investigators used optical colonoscopy to develop the reference standard. Many investigators also compared some technical or performance aspect of CT colonography. Iannaccone (2004) compared the accuracy of CT colonography in patients who had used non-cathartic bowel preparation versus those undergoing the usual cathartic preparation. Johnson (2007) compared CT colonoscopy accuracy using CT parameters of slice width (2.5 versus 1.25 mm) and imaging reconstruction (2-D versus 3-D). Iannaccone (2005) examined the accuracy of low dose CT colonography and Hoppe (2004a) evaluated CT colonography with the use of contrast agents versus optical colonoscopy.

The technical aspects of CT colonography for each of the nine studies are described in detail in Table 1. All studies used multi-detectors, but varied slightly in the collimation beam size, acquisition time, and amount of observer training or experience reported.

Each included study was further evaluated for validity using the QUADAS Tool (see Table 4.) Overall, five studies were scored as "high' quality and four as "fair." Items considered adequate for all studies included a representative patient population with clearly described selection criteria, and who were all tested within a short time period with an adequate reference standard. Almost all investigators described CT colonography in sufficient detail to permit replication, but fewer described optical colonoscopy as well. Because segmental unblinded colonoscopy uses the results of CT colonography for development of the reference standard, no study can be considered adequate in scoring QUADAS Item 7.

Description of study population

The nine included studies included two studies with only asymptomatic (Johnson 2007) or almost all asymptomatic (Pickhardt 2003) patients; three had combinations of asymptomatic and symptomatic patients (Ginnerup 2003, Iannaccone 2004, Iannaccone 2005); and four had almost all or all symptomatic patients (Hoppe 2004a, Rockey 2005, Taylor 2003, van Gelder 2004). Reported symptoms included abdominal pain, hematochezia, melana, altered bowel habits, family history of polyps or cancer, surveillance because of a history of polyps or cancer, etc.

The average age of study participants ranged from 56 to 69 years, and included a preponderance of men (1,907 men; 1,234 women). Iannaccone and colleagues investigated the use of a non-cathartic preparation for CT colonoscopsy (2004). Reported cathartic agents included phosphate-or magenesium-based agents, methylcellulose, and polyethylene glycol. Some investigators also used bisocodyl to enhance bowel cleansing. A relaxing agent, either 1 mg intravenous glucagon or 20 mg intravenous hyoscine butylscopolaminebromide (Buscopan) were used in eight studies, and three studies routinely used contrast material, either isopromide (Hoppe 2004a) or diatrizoate meglumine and diatrizoate sodium (Pickhardt 2003, Iannaccone 2004). Taylor and colleagues (2003) allowed the use of Niopam at the discretion of a radiologist if a lesion was suspected.

Although all studies reconstructed and used both 2-dimensional and 3-dimensional images in interpretation of CT scans, the method used for interpretation varied across studies. The majority of investigators used reconstructed axial or multiplanar 2-dimensional images for detection of an abnormality with 3-dimensional endoluminal views used for confirmation of an abnormality or for "problem-solving" (Ginnerup 2003, Iannaccone 2004 and 2005, Rockey 2005). Observers also used simultaneous axial and multiplanar images for the initial detection of abnormalities (Taylor 2003) or used 2-dimensional axial images in a high-contrast window for initial review with confirmation using both a different window setting and 3-dimensional endoluminal views (Hoppe 2004a). In contrast, Van Gelder used an initial 3-dimensional image for detection of abnormalities with 2-dimensional confirmation (2004), and Johnson (2007) compared interpretation of examinations using 2-dimensional views for initial detection and 3-dimensional views for problem solving versus initial 3-dimensional endoluminal images and 360^0 virtual dissection images for confirmation or problem solving. Yet another modification was the

computer subtraction of residual fluid opacified by contrast media in the Pickhardt study (Pickhardt 2003); in this study observers used 3-dimensional images for initial detection of abnormalities with 2-dimensional views for verification.

Sensitivity, Specificity, and Positive Predictive Value of CT Colonoscopy

Analyses per patient

Table 5 and the accompanying Figure show the "per patient" sensitivity, specificity, and positive predictive value of CT colonography for the nine included studies for lesions ≥ 10 mm. Table 6 and its Figure show the same information for lesions ≥ 6 mm. Following clinical guidelines and the consensus of our own clinical experts we did not focus our review on test characteristics for detection of polyps 1-5mm in size that are felt to present negligible risk for progression to cancer within 10 years.

Johnson and colleagues (2007) reported values separately for slice size and imaging (2-dimemsional versus 3-dimensional). We chose to use the values reported for 2.5 mm slice and that reported for "double review," an averaged result of combined 2-dimensional and 3-dimensional imaging. As a result, the findings for only about half of the patient population are shown here. We pooled results for sensitivity and specificity, but not for positive predictive values, since sensitivity and specificity are measures of the accuracy of a test. Positive predictive value is sensitive to the prevalence of a condition in the tested population in that an increased prevalence usually results in a higher positive predictive value. Since the populations included in this review vary substantively by number and type of symptoms, a pooled positive predictive value would be difficult to interpret. Pooled values represent simple addition of true positives, false positives, etc. to obtain overall values, i.e., weighted by sample size.

Observation of the data suggests that the study by Rockey (2005) may be an outlier in that the remaining studies show per patient sensitivities with lesions ≥ 10 mm ranging from 84 to 100% compared with a sensitivity of 59% as reported by Rockey. Similarly, that for lesions ≥ 6 mm ranges from 76 to 92% while that reported by Rockey is 55%. One possible reason for the difference may lie in the experience or training of the observers: about half the readers in the original Rockey study had experience reading more than 50 CT colonography scans, but the remainder did not and were trained via a "training module" Directly measuring sensitivity by experienced versus inexperienced observers did not show any important differences (Rockey 2005), but a re-analysis of the data from the Rockey study with two experienced readers (having previously read 350 and 799 scans) re-reading the scans suggest that most of the false negatives were due to observer error (Doshi 2007). The second read was analyzed by calculating possible sensitivity taking into account observer error. This maneuver resulted in a hypothetical sensitivity of 87% (95% CI, 78-95%) to detect a lesion ≥ 10 mm per patient and 78% (95% CI, 71-84%) for a lesion ≥ 6 mm per patient. In interpreting these data, one must keep in mind however, the possible bias present in that the readers knew they were looking for potentially missed lesions. Nevertheless, because of the possibility that training was insufficient and that this is one of our inclusion criteria, we analyzed the data with and without including the results from the Rockey study, with results shown as an additional line in Tables 5 and 6.

Only three investigators reported per patient sensitivity for polyps between 6 and 9 mm as shown in Table 7.

Table 7. Sensitivity and specificity for detection of a lesion 6-9 mm per patient

Author	True positive	False positive	True negative	False negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value
Johnson 2007	9	21	194	5	64% (35-87%)	90% (85-94%)	30%
Rockey 2005	59	NR	NR	57	51% (41-60%)	N/A	N/A
Taylor 2003	1	NR	NR	1	50%	N/A	N/A

Per lesion analyses

Authors reported lesions as all lesions and/or as adenomatous or neoplastic lesions. We calculated pooled sensitivities separately for adenomatous/neoplastic lesions classified by size category. If findings were reported separately for more than one observer, all values were averaged. Similarly to the per patient analysis, we used the values reported for 2.5 mm slice and reported for "double review" for the study by Johnson (2007). Raw pooled results represent simple addition of true positives, false negatives, etc. to obtain overall values.

There were no important differences in the sensitivity or specificity of CT colonography in detecting adenomatous lesions compared to lesions of any histologic type. The sensitivity for detecting an adenomatous or neoplastic lesion of any size was slightly higher than that reported for lesions of any histology in four of the five studies reporting both values (Ginnerup 2003, Hoppe 2004a, Iannaccone 2004, Rockey 2005), and slightly lower in the remaining study (Iannaccone 2005).

Sensitivity by size lesion was quite similar to those found in the per-patient analyses. For lesions $\geq$10 mm, $\geq$ 6 mm, and between 6 to 9 mm, the pooled CT colonography sensitivities are 83% (95% CI, 77-87%), 76% (95% CI, 73-80%), and 73% (95% CI, 68-77%), respectively. As was found in the per patient analyses, detection by lesion is less sensitive for smaller sized lesions.

Direct comparison of CT colonography with optical colonoscopy

The use of segmental unblinded colonoscopy or a second look colonoscopy provided an opportunity to compare the sensitivity and specificity of CT colonography directly with that of optical colonoscopy. Table 8 and the accompanying Figure show this comparison on a per patient basis for lesions $\geq$ 10 mm.

Similar results were obtained for analyses comparing CT colonography with colonoscopy for sensitivity for detection of adenomatous lesions. For lesions ≥10 mm, combining the results from five studies (Ginnerup 2003, Hoppe 2004a, Pickhardt 2005, Rockey 2005, Van Gelder 2004) resulted in a pooled sensitivity of 81% (95% CI, 75-86%) for CT colonoscopy compared with 91% (85-94%) for colonoscopy. Although not a direct comparison, Iannaccone reported that colonoscopy missed 5 of 162 polyps, 4 to 8 mm in size (2004), and in a subsequent study colonoscopy failed to detect 16 of 94 polyps, 4 to 14 mm in size (Iannaccone 2005).

Extracolonic Findings

A controversial feature of CTC is its concurrent ability to image and to detect abnormalities in extracolonic abdominal tissues. Particularly among otherwise healthy adults undergoing screening examination, incidental lesions present a clinical and policy challenge because of the possible benefits of early detection of some significant lesions in the face of the overall likelihood that detection of such lesions will not prove clinically valuable but will instead engender unnecessary costs and risks that come with further investigation.

We reviewed the current literature for studies that reported extracolonic findings, comparing reports from investigators that looked at average risk (asymptomatic) populations with those of symptomatic populations. In Table 9 we have summarized the literature on extracolonic findings in asymptomatic populations. Any summary of this literature is complicated by differing definitions of "clinically important" lesions, and by the lack until 2005 of any published standard approach to formal reading of extracolonic findings (Zalis, 2005). The rate of patients with any lesion ranges from 19% to 69%; "clinically important" lesions have been found, on average, in 6% of patients screened. While it can be presumed that further investigation will be needed for most if not all of the "clinically important" lesions, it is not possible to gauge how many of the other lesions, once reported, would lead to further investigation. In the largest series reported to date (Kim, 2007), 241/3120 (7.7%) of asymptomatic patients screened with CTC had an extracolonic finding that led to a recommendation for an additional test or procedure. Among these patients eight extracolonic cancers were seen, accounting for a prevalence of 0.3%.

The most common lesions deemed "clinically important" include extracolonic cancers, abdominal aortic aneurysms, adrenal adenomas, lung nodules, and renal, ovarian, hepatic, and splenic cysts. The only published article that attempted to designate the percentage of patients benefiting from detection of these lesions estimated that 2.1% of all patients screened derived clinical benefit from early detection of their extracolonic lesions. However, no systematic report has looked at the clinical outcomes of patients with extracolonic findings, and it is difficult to arrive at an evidence-based assessment of the balance of clinical benefit and harms from extracolonic findings of CTC screening.

In the three published studies that have assessed the costs of investigation of extracolonic findings, the additional cost per CTC examination has ranged from $2.34 (Kim, 2007) to $34.33 per CTC (Gluecker, 2003). The Kim article is the most recent and largest US experience, but it also reflects the experience of a single institution that is the acknowledged leader in the field in the US, raising questions about the generalizability of its findings. However, if other centers were to follow their approach of low-dose CT, avoidance of IV contrast, and adherence to the recent radiological guidelines for reporting extracolonic findings (Zalis, 2005), very low average, per-patient additional costs may be required for evaluation of extracolonic findings.

Harms

Eleven investigators reported specifically on harms including adverse events and complications of treatment as well as level of radiation (Arneson 2005, Cotton 2004, Fenlon 1999, Iannaccone 2003a, Iannaccone 2004, Iannaccone 2005, Laghi 2002a, Lefere 2002, Miao 2000, Pickhardt 2003, Rockey 2005). No adverse events were reported related to the CT colonoscopy itself in the studies included in this review. Three investigators reported on events and on complications related to the cathartic colonic preparation (e.g., headache, nausea, vomiting) (Arneson 2005, Iannaccone 2004, Lefere 2002) and one investigator reported glucagon-induced nausea (Fenlon 1999). The remaining seven investigators specifically stated that no complications or adverse events were noted.

Harms associated with CT colonography have been reported, however. In a survey by Burling and colleagues of 50 institutions, nine cases of colonic perforation were reported in 17,067 CT colonographic examinations, a rate of 0.08% (Burling 2006). Similarly, in a survey of 11 medical centers, Sosna (2006) reported seven cases in 11,870 examinations (0.06%). It is important to point out that of the 16 instances of perforation, twelve occurred in patients with an existing colonic condition or disease (i.e.., irritable bowel syndrome, inguinal hernia, diverticulosis, etc.). By comparison, the rate of colonic perforation for optical colonoscopy is reported to be 0.13% (Burling 2006), significantly higher than that reported for CT colonography. No evidence was sought to document the rate of anesthesia-related adverse events experienced by patients undergoing optical colonoscopy, but our clinical experts advised that minor residual nausea and dizziness is not uncommon.

Radiation Exposure and Future Cancer Risk

Potential adverse health effects associated with radiation exposure are an important factor to consider in the evaluation of CTC as a potential adjunct to population screening for colorectal cancer. Radiation dose is a measure of ionizing energy absorbed per unit masss and has units of Gy (Gray) or mGy; it often is quoted as an equivalent dose, in units of Sv (Sievert) or mSv. For x-rays, which is the radiation produced by CT scanners, 1 mSv = 1 mGy. Some typical doses of radiation exposure are shown in the Table below:

Typical Mean Doses (From Brenner, 2005; FDA [www.fda.gov/cdrh/ct/risks.html])

Radiation exposure scenario	Approximate mean individual dose (mSv)
Chest x ray	0.02
Round-trip flight, New York-Seattle	0.06
Low-dose CT colonography (Van Gelder, 2004)	**0.5**
Lumbar spine x-ray	1.3
Head CT	2.0
Single-screening mammogram (breast dose)	3
Background dose caused by natural radiation	3 per year
Adult abdominal CT scan	10
Typical dose to A-bomb survivor at 2.3 km distance from ground zero Hiroshima	13
Radiation worker annual exposure limit	20 per year
Exposure on international space station	170 per year

The primary risk associated with exposure to ionizing radiation is cancer. According to the FDA, estimates based on the experience of A-bomb survivors suggests that a dose of 10 mSv may be associated with an increase in the possibility of fatal cancer of approximately 1 chance in 2000. This risk level is relatively small in comparison to the approximately 400 out of 2,000 individuals expected to develop cancer from all other causes combined.

There is considerable controversy on extrapolating cancer death risks from those experienced by adults with high radiation exposure at Hiroshima to the potential risks at much lower radiation doses. However, linear extrapolation has been the approach generally used, although the uncertainties inherent in this extrapolation become progressively greater at lower doses.

Our evidence review found eleven articles in which the radiation dosage was estimated. Estimated radiation dosages for CTC ranged from 0.7 to 12 mSv. In a study designed to estimate the amount of radiation risk from current scanners and protocols, Jensch and colleagues (2006) obtained surveys from 28 of 36 institutions from which CT colonography studies had been reported in the literature. They requested information on current CT scanning protocols and calculated the effective dose for each protocol, finding a median effective dose of 5.1 mSv (range 1.2 to 11.7 mSv) per scan (doubled when both supine and prone positioning is used). Using a linear non-threshold model, the authors calculated that this dose level equates to a radiation risk likely to result in one fatal cancer in 4,000 individuals when applied to a population over 50 years of age. Another paper evaluating this question used the ImPACT CT Dosimetry Calculator, which is available online, to calculate generic doses to the organs of a simplified anthropomorphic phantom (Brenner, 2005). This article found that "typical" current scanner techniques result in approximately 0.14% increased lifetime cancer risk for CTC for a 50-year old. This article also concludes that this value probably could be reduced by factors of 5 or 10 with optimized (ie low-dose) CTC protocols. Such lower-dosage approaches (about 0.5 mSv), reported in more recent studies, appear to be equally sensitive for screening purposes (Van Gelder 2004, Iannaccone 2003b).

Patient Acceptance

Four investigators examined patient-oriented outcomes, usually asking the patients after having experienced both procedures, which one – CT colonoscopy or optical colonoscopy - was preferred (Cotton 2004, Iannaccone 2004, Miao 2000, Pickhardt 2003). Generally, about half the participants preferred CT colonoscopy, about 40% preferred colonoscopy, and the remaining 10% were undecided (see Table 10). However, it must be kept in mind while looking at these data that the scores reflect the experience of the patients who have undergone both procedures and may not reflect the preferences of unscreened individuals.

Table 9. Patient preference for CTC vs. optical colonoscopy

Author	Preferred CT colonography	Preferred optical colonoscopy	Undecided or no preference
	n/N (%)	n/N (%)	n/N (%)
Cotton 2004	238/518 (45%)	213/518 (41%)	67/518(13%)
Iannaccone 2004	99/162 (61%)	57/162 (35%)	6/162(4%)
Miao 2000	83/198 (42%)	94/198 (47%)	21/198(11%)

Pickhardt 2003	500/1005 (50%)	413/1005(41%)	92/1005(9%)

Studies examining unscreened patients for preference of a screening method find that patients fall into two groups – those that consider accuracy as the most important factor in their choice of screening modality and those that consider the invasiveness of a test as the most important factor. In a study by Schroy (2007), among currently available screening options, colonoscopy was clearly the preferred screening option (133/263; 52%), with patients citing accuracy as the most important reason for choosing colonoscopy. Importantly, remaining patients who did not choose colonoscopy still considered accuracy a an important factor in their choice of a screening option, suggesting that there is a group of patients who are adverse to the invasiveness of optical colonoscopy who might be amenable to screening using CT colonography should its accuracy be deemed comparable.

Impact on Population Screening and Systems of Care

There are no published articles with evidence to address the question of how introduction of CTC screening would affect the overall proportion of eligible adults who are screened or the broader system of care. The best available evidence comes from the experience of Pickhardt and his practice group in Wisconsin (Pickhardt, 2006). Reporting on the initial experience from their first year following coverage of CTC screening by local private insurers, they found that 43 (3.9%) of 1110 screened patients had large (≥10mm) polyps. Medium-sized lesions were identified in 77 (6.9%) of patients, 31 (40%) of whom chose to undergo subsequent colonoscopy and 46 (60%) of whom chose to have CTC surveillance at 2-3 years instead. Of the total of 71 patients who underwent subsequent colonoscopy, 65 had concordant lesions, suggesting a false positive rate of approximately 8%. 86% of subsequent colonoscopies were performed the same day, obviating the need for a repeat bowel preparation.

The actual referral rate for positive findings was 6.4% (71 of 1110 patients). Pickhardt notes that with their protocol more than 90% of patients who underwent primary CTC were not referred for subsequent optical colonoscopy., and the likelihood of confirming a lesion that was at CTC was more than 90%. He also noted that the total number of patients who underwent optical colonoscopy did not decrease at his institution after CTC screening began, suggesting that more patients were being screened overall and that the CTC screening did not simply draw patients away from optical colonoscopy. Without true population-based evidence, however, this suggestion cannot be fairly evaluated.

Implications

In order to be effective as a screening tool for colorectal cancer, CT colonography must be accurate in detecting cancerous and precancerous lesions, must provide benefits in terms of short and long-term positive patient outcomes, have few or no harms associated with its use, and must be accepted by patients and clinicians.

CT colonography appears to be accurate. It approaches and, in our pooled analysis excluding the Rockey 2005 data, fully equals the sensitivity of optical colonoscopy for detecting lesions $\geq$ 10 mm. This conclusion requires that certain standards must be met, however. The conditions we set for describing a well-conducted CT colonography examination included a multi-detector scanner with collimation < 5 mm and acquisition of the scan within a single breath hold of $\leq$ 30

seconds. These two conditions allow for increased resolution of the image through use of multi-detectors and precise collimation, and with a reduced chance of motion artifact through reduced acquisition time. Positive predictive values varied across studies as was expected due to the different patient populations, and prevalence of expected positive results. To be used as an effective screening tool, i.e., in a population with a low prevalence of the condition, it is important for the screening test to have a high positive predictive value. Looking at studies with asymptomatic patients (Pickhardt 2003, Johnson 2007), the positive predictive values are 49% and 76%, respectively, for detection of a lesion $\geq$ 10 mm by patient – but it must be kept in mind that the positive predictive value by Pickhardt may be unrealistically low; he and his colleagues defined nonadenomatous lesions as a false positive finding, consequently reducing the measured positive predictive value. In the latest data from Pickhardt's group (Pickhardt, 2006), the positive predictive value per patient for lesions measuring 6mm or larger was 93.8%, an improvement over previous results that Pickhardt attributes to continued improvements in software, colonic preparation, and colonic distention.

CT colonography was not as sensitive is detecting a patient with a lesion when all lesions $\geq$ 6 mm were considered (77% for data with Rockey 2005; 86% if Rockey 2005 excluded). The importance of this result must be considered in light of the presumed clinical importance of lesions of this size. If it is critical that lesions larger than 6 mm, but less than 10 mm, be identified, then the sensitivity of CT colonography may not be viewed as acceptable in direct comparison to optical colonoscopy. CTC's sensitivity for lesions of this size is, however, far superior to that of other non-invasive screening modalities. And, if lesions of this size are not critically important for screening purposes, then the decrement in sensitivity between CTC and optical colonoscopy may not play a large role in decision-making.

Although the data are pooled to calculate overall sensitivity and specificity, caution must be taken in interpreting these data as such. The studies vary by study quality, patient population, use of fecal tagging or oral contrast media, interpretation of images, and observer experience. In fact, we chose not to pool the data to calculate an overall positive predictive value because of the differences in the patient populations. Formal tests of heterogeneity would have provided us with an estimate of statistical heterogeneity, but these tests tend to be difficult to interpret. In addition, the sources of heterogeneity described are likely to exist in the clinical (rather than academic) setting, and so we combined data to provide a reasonable estimate of the diagnostic accuracy of CT colonography as a screening tool.

Although not collected systematically for this review, many investigators revealed that the reason for observer error, especially in the size range of 6 to 9 mm, was because of inadequate colonic distension or residual fluid or stool. These technical errors can potentially be overcome in the future. Using both prone and supine positioning improves visualization in that residual fluid and stool may be re-positioned as well and that areas not distended in one position may be more readily seen in the alternate position. In addition, use of a "scout" scan before the actual CT scan to evaluate distension has resulted in improved imaging. Newer techniques such as use of oral fecal tagging materials and increased use of intravenous contrast materials may also improve the visualization of images when residual fluid or stool is present. Lefere (2002) examined the use of fecal tagging agents, but found no difference in sensitivity to detect lesions 6 to 9 mm with or without tagging agent (92% versus 89%), possibly due to the high sensitivity without use of the tagging agent. He does report an increase in specificity, however. Fecal

tagging was also used by Iannaccone (2004) in conjunction with a non-cathartic preparation, while Pickhardt (2003) used computer aided subtraction of opacified fluid and stool following use of fecal tagging and intravenous contrast material. These data suggest that fecal tagging, especially with the use of computer aided subtraction of fluid and stool, could remove the source of error caused by incomplete bowel cleansing.

Perceptual error is a more difficult issue and most likely arises from inadequate training or experience in interpreting CT scans. Readers for CT colonography must be trained, as in any other medical imaging discipline, to produce a reliable and valid interpretation of a given image. For this review, readers were required to have been trained by interpreting at least 30 CT scans before the study began. Given the wide range of training or experience reported (or not reported) in the included studies, the reliability of image interpretation is open to question. A steep learning curve for recognizing abnormalities has been reported (Spinzi 2001) but others have shown no difference in sensitivity between experienced and inexperienced readers (Rockey 2005). Given that high sensitivity is achievable with highly experienced readers (e.g., Pickhardt 2003), it would appear that sufficient training by readers in the clinical setting must be attained before CT colonography can reliably be used as a screening tool. While we used a threshold of 30 previous CT scans, the ACR Practice Guidelines recommend that supervising and interpreting clinicians should be trained by having read at least 50 CT colonography cases (ACR Practice Guidelines, 2007). Recommended methods for training include the use of formal hand-on interactive training, supervision with a CT colonography-trained physician acting as a second reader, or by correlation of CT colonography and endoscopy findings in patients undergoing both procedures.

We also required that the reference standard combine the results of optical colonoscopy (the comparator) with the results of the CT colonography. It could be argued that this requirement produces a certain amount of bias in favor of CT colonography in that one is using the results from the index test to produce the reference standard. On the other hand, colonoscopy itself has been shown not to be a completely reliable gold standard, so the set of findings found using both optical and CT colonoscopy approaches a more accurate gold standard that that for either procedure alone. By using this reference standard, investigators reduce the possibility of incorrectly scoring CT colonography findings as false positive.

CT colonography is a very safe procedure, with only rare reports of colonic perforation found outside the body of literature reviewed for this report. The potential for harm from radiation also appears to be minimal and promises to become even lower with newer scanners delivering lower doses of radiation.

With CT colonography the radiologist has the benefit of, but also potential harm from, extracolonic findings. Clinically significant findings found during colonography provide for early detection of a serious condition for some patients. On the other hand, less clinically serious findings, in some cases reported in a majority of patients, may result in unnecessary expenses in following up on findings, and unneeded worry on the part of the patient.

In patients who experienced both tests, a small majority preferred CT colonoscopy to optical colonoscopy. It is unclear whether this preference would result in a larger number of unscreened

individuals becoming screened. No study to date has examined whether the availability of CT colonography has resulted in increased numbers of individuals being screened.

As reported by Gollub (2006) three large studies on diagnostic accuracy of CT colonography are currently being conducted, including those by the American College of Radiology Imaging Network, the Special Interest Group in Gastrointestinal and Abdominal Radiology Group in the United Kingdom, and the Italian Multicenter Study on Accuracy of CT Colonography. If the results of these studies show that CT colonography has adequate sensitivity, specificity, positive and negative predictive values, then the next step is to conduct randomized controlled trials using CT colonography as a screening tool. Trials are necessary to ascertain whether CT colonography is an adequate screen for colorectal cancer by measuring short and long-term patient outcomes following screening with CT colonography compared with those using no or an alternative screening option.

2.3 Summary

In conclusion, given the current standard for performance, CT colonography is nearly as or equally sensitive as optical colonoscopy for detection of lesions $\geq$ 10 mm on a per patient basis. It is somewhat less sensitive on a per patient basis for smaller lesions or for detecting individual lesions. It seems likely that the majority of current sources of observer error can be overcome through use of standardized and stringent methods for bowel cleansing, use of fecal tagging and contrast media, and use of computer assisted methods for scan interpretation. Observer training is a critical component for reducing perceptual errors. CT colonography is relatively safe and existing data suggest that CT colonography is acceptable to patients, although it is unclear whether implementation of CT colonography to the colorectal screening armamentarium would result in increased rates of colorectal screening and overall earlier detection of colorectal cancer in the general population.

Comparative Clinical Effectiveness References

Abdel Razek A. A., Zeid M. M., Bilal M., Adbel Wahab N. M. 2005. Virtual CT colonoscopy versus conventional colonoscopy: A prospective study. Hepato-gastroenterology 52:1698-1702.

ACR Practice Guidelines. ACR Practice Guideline for the performance of computed tomography (CT) colonography in adults. In: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/gastro/ct_colonography.aspx [Accessed 26 September 2007].

Arnesen, R. B., Adamsen, S., Svendsen, L. B., Raaschou, H. O., von Benzon, E., and Hansen, O. H. 2005. Missed lesions and false-positive findings on computed-tomographic colonography: a controlled prospective analysis. Endoscopy. 37(10):937-44).

Brenner DJ, Georgsson MA. Mass screening with CT colonography: Should the radiation exposure be of concern? Gastroenterology 2005;129:328-337.

Burling D., Halligan S., Slater A., Noades M. J., Taylor S. A. 2006. Potentially serious adverse events at CT colonography in symptomatic patients: National survey of the United Kingdom. Radiology 239(2): 464-71.

Chung, D. J., Huh, K. C., Choi, W. J., and Kim, J. K. 2005. CT colonography using 16-MDCT in the evaluation of colorectal cancer. AJR Am J Roentgenol 184(1):98-103.

Cohnen, M., Vogt, C., Aurich, V., Beck, A., Haussinger, D., and Modder, U. 2002. Multi-Slice CT-colonography in low-dose technique-preliminary results. RoFo Fortschr. Geb. Rontgenstr. Bildgebenden Verfahren 174(7):835-838.

Cohnen, M., Vogt, C., Beck, A., Andersen, K., Heinen, W., vom Dahl, S., Aurich, V., Haeussinger, D., and Moedder, U. 2004. Feasibility of MDCT Colonography in ultra-low-dose technique in the detection of colorectal lesions: comparison with high-resolution video colonoscopy. AJR Am J Roentgenol. 183(5):1355-1359.

Cotton, P. B., Durkalski, V. L., Pineau, B. C., Palesch, Y. Y., Mauldin, P. D., Hoffman, B., Vining, D. J., Small, W. C., Affronti, J., Rex, D., Kopecky, K. K., Ackerman, S., Burdick, J. S., Brewington, C., Turner, M. A., Zfass, A., Wright, A. R., Iyer, R. B., Lynch, P., Sivak, M. V., and Butler, H. 2004. Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. JAMA. 291(14):1713-9.

Dachman, A. H., Kuniyoshi, J. K., Boyle, C. M., Samara, Y., Hoffmann, K. R., Rubin, D. T., and Hanan, I. 1998. CT colonography with three-dimensional problem solving for detection of colonic polyps. Am. J. Roentgenol. (4):989-995.

Doshi T., Rusinak D., Halvorsen R. A., Rockey D. C., Suzuki K., Dachman A. H. 2007. CT colonography": false-megative interpretations. Radiology 244:165-73.

Fenlon, H. M., Nunes, D. P., Schroy, P. C. 3rd, Barish, M. A., Clarke, P. D., and Ferrucci, J. T. 1999. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. N Engl J Med. 1999 Nov 11; 341(20).

Fletcher, J. G., Johnson, C. D., Welch, T. J., MacCarty, R. L., Ahlquist, D. A., Reed, J. E., Harmsen, W. S., and Wilson, L. A. 2000. Optimization of CT colonography technique: Prospective trial in 180 patients. Radiology . 216(3):704-711.

Ginnerup Pedersen, B., Christiansen, T. E., Bjerregaard, N. C., Ljungmann, K., and Laurberg, S. 2003. Colonoscopy and multidetector-array computed-tomographic colonography: detection rates and feasibility. Endoscopy. 35(9):736-42.

Gluecker, T., Dorta, G., Keller, W., Jornod, P., Meuli, R., and Schnyder, P. 2002. Performance of multidetector computed tomography colonography compared with conventional colonoscopy. Gut. 51(2):207-11.

Gollub M. J., Schwartz L. H., Akhurst T. 2007. Update on colorectal cancer imaging. Radiol. Clin. North Am. 45:85-118.

Halligan S., Altman D. G., Taylor S. A., Mallett S., Deeks J. J., Bartram C. I. 2005. CT colonography in the detection of colorectal polyps and cancer: Systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 237:898-904.

Hara, A. K., Johnson, C. D., Reed, J. E., Ahlquist, D. A., Nelson, H., Maccarty, R. L., Scott Harmsen, W., and Ilstrup, D. M. 1997. Detection of colorectal polyps with CT colography: Initial assessment of sensitivity and specificity. RADIOLOGY. 205(1):59-65.

Hoppe, H., Netzer, P., Spreng, A., Quattropani, C., Mattich, J., and Dinkel, H.-P. 2004a. Prospective comparison of contrast enhanced CT colonography and conventional colonoscopy for detection of colorectal neoplasms in a single institutional study using second-look colonoscopy with discrepant results. Am. J. Gastroenterol. 99(10):1924-1935.

Hoppe, H., Quattropani, C., Spreng, A., Mattich, J., Netzer, P., and Dinkel, H.-P. 2004b. Virtual Colon Dissection with CT Colonography Compared with Axial Interpretation and Conventional Colonoscopy: Preliminary Results. Am. J. Roentgenol. 182(5):1151-1158.

Iannaccone, R., Catalano, C., Mangiapane, F., Murakami, T., Lamazza, A., Fiori, E., Schillaci, A., Marin, D., Nofroni, I., Hori, M., and Passariello, R. 2005. Colorectal polyps: Detection with low-dose multi-detector row helical CT colonography versus two sequential colonoscopies. Radiology. 237(3):927-937.

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

Iannaccone, R., Laghi, A., Catalano, C., Mangiapane, F., Lamazza, A., Schillaci, A., Sinibaldi, G., Murakami, T., Sammartino, P., Hori, M., Piacentini, F., Nofroni, I., Stipa, V., and Passariello, R. 2004. Computed tomographic colonography without cathartic preparation for the detection of colorectal polyps. Gastroenterology. 2004 Nov; 127(5):1300-11.

Iannaccone, R., Laghi, A., Catalano, C., Mangiapane, F., Piacentini, F., and Passariello, R. 2003b. Feasibility of ultra-low-dose multislice CT colonography for the detection of colorectal lesions: preliminary experience. Eur Radiol. 13(6):1297-302.

Jensch, S., van Gelder R.E., Venema H.w., Reitsma H. W., Bossuyt P. M. M., Lameris J. S., Stoker J. 2006 Effective radiation doses in CT colonography: results of an inventory among research institutions. Eur. Radiol. 16:981-7.

Johnson, C. D., Harmsen, W. S., Wilson, L. A., Maccarty, R. L., Welch, T. J., Ilstrup, D. M., and Ahlquist, D. A. 2003 Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. Gastroenterology. 125(2):311-9.

Johnson CD, Fletcher JG, MacCarty RL, Mandrekar JN, Harmsen WS, Limburg PJ, and Wilson LA. 2007. Effect of slice thickness and primary 2D versus 3D virtual dissection on colorectal lesion detection at CT colonography in 452 asymptomatic adults. Am. J. Roentgenol. 188:672-80.

Kalra, N., Suri, S., Bhasin, D. K., Sinha, S. K., Saravanan, N., Kour, T., Vaiphei, K., and Wig, J. D. 2006. Comparison of multidetector computed tomographic colonography and conventional colonoscopy for detection of colorectal polyps and cancer. Indian J Gastroenterol. 25(5):229-232.

Kay, C. L., Kulling, D., Hawes, R. H., Young, J. W. R., and Cotton, P. B. 2000. Virtual endoscopy - Comparison with colonoscopy in the detection of space-occupying lesions of the colon. Endoscopy. 32(3):226-232.

Kwan, W. H., Chau, W. K., Yeung, W. H., Wong, K. P., Kwok, W. K., Chan, T. M., and Khoo, J. 2004. Computed tomography colonoscopy with faecal tagging in the detection of colorectal tumours: Report of local experience. J. HK Coll. Radiol. 7(4):199-205.

Laghi, A., Iannaccone, R., Carbone, I., Catalano, C., Panebianco, V., Di Giulio, E., Schillaci, A., and Passariello, R. 2002a. Computed tomographic colonography (virtual colonoscopy): 2002a. Blinded prospective comparison with conventional colonoscopy for the detection of colorectal neoplasia. Endoscopy. 34(6):441-446.

Laghi, A., Iannaccone, R., Carbone, I., Catalano, C., Di Giulio, E., Schillaci, A., and Passariello, R. 2002b. Detection of colorectal lesions with virtual computed tomographic colonography. Am. J. Surg. 2002; 183(2):124-131.

Lefere, P. A., Gryspeerdt, S. S., Dewyspelaere, J., Baekelandt, M., and Van Holsbeeck, B. G. 2002. Dietary fecal tagging as a cleansing method before CT colonography: Initial results - Polyp detection and patient acceptance. Radiology. 224(2):393-403.

Macari, M.. Bini, E. J., Jacobs, S. L., Naik, S., Lui, Y. W., Milano, A., Rajapaksa, R., Megibow, A. J., and Babb, J. 2004a. Colorectal polyps and cancers in asymptomatic average-risk patients: evaluation with CT colonography. Radiology. 230(3):629-36.

Macari, M., Bini, E. J., Jacobs, S. L., Lui, Y. W., Laks, S., Milano, A., and Babb, J. 2004b. Significance of missed polyps at CT colonography. AJR Am J Roentgenol. 183(1):127-34.

Macari, M., Bini, E. J., Xue, X., Milano, A., Katz, S. S., Resnick, D., Chandarana, H., Krinsky, G., Klingenbeck, K., Marshall, C. H., and Megibow, A. J. 2002. Colorectal neoplasms: prospective comparison of thin-section low-dose multi-detector row CT colonography and conventional colonoscopy for detection. Radiology. 224(2):383-92.

Macari, M., Milano, A., Lavelle, M., Berman, P., and Megibow, A. J. 2000. Comparison of time-efficient CT colonography with two- and three-dimensional colonic evaluation for detecting colorectal polyps. AJR Am J Roentgenol. 174(6):1543-9.

McFarland, E. G., Pilgram, T. K., Brink, J. A., McDermott, R. A., Santillan, C. V., Brady, P. W., Heiken, J. P., Balfe, D. M., Weinstock, L. B., Thyssen, E. P., and Littenberg, B. 2002. CT colonography: Multiobserver diagnostic performance. Radiology. 225(2):380-390.

Miao, Y. M., Amin, Z., Healy, J., Burn, P., Murugan, N., Westaby, D., and Allen-Mersh, T. G. 2000. A prospective single centre study comparing computed tomography pneumocolon against colonoscopy in the detection of colorectal neoplasms. Gut. 47(6):832-837.

Park, S. H., Ha, H. K., Kim, M. J., Kim, K. W., Kim, A. Y., Yang, D. H., Lee, M. G., Kim, P. N., Shin, Y. M., Yang, S. K., Myung, S. J., and Min, Y. I. 2005. False-negative results at multi-detector row CT colonography: multivariate analysis of causes for missed lesions. Radiology. 235(2):495-502.

Pescatore, P., Glucker, T., Delarive, J., Meuli, R., Pantoflickova, D., Duvoisin, B., Schnyder, P., Blum, A. L., and Dorta, G. 2000. Diagnostic accuracy and interobserver agreement of CT colonography (virtual colonoscopy). Gut. 47(1):126-30.

Pickhardt PJ. The incidence of colonic perforation at CT colonography: review of the existing data and the implications for screening of asymptomatic adults. Radiology 2006;239:313-316

Pickhardt, P. J., Choi, J. R., Hwang, I., Butler, J. A., Puckett, M. L., Hildebrandt, H. A., Wong, R. K., Nugent, P. A., Mysliwiec, P. A., and Schindler, W. R. 2003. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med. 349(23):2191-200.

Pineau, B. C., Paskett, E. D., Chen, G. J., Espeland, M. A., Phillips, K., Han, J. P., Mikulaninec, C., and Vining, D. J. 2003. Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. Gastroenterology. 125(2):304-10.

Reuterskiold, M. H., Lasson, A., Svensson, E., Kilander, A., Stotzer, P. O., and Hellstrom, M. 2006. Diagnostic performance of computed tomography colonography in symptomatic patients and in patients with increased risk for colorectal disease. Acta Radiol. 47(9):888-98.

Rex, D. K., Vining, D., and Kopecky, K. K. 1999. An initial experience with screening for colon polyps using spiral CT with and without CT colography (virtual colonoscopy). Gastrointest Endosc. 50(3):309-13.

Rockey, D. C., Paulson, E., Niedzwiecki, D., Davis, W., Bosworth, H. B., Sanders, L., Yee, J., Henderson, J., Hatten, P., Burdick, S., Sanyal, A., Rubin, D. T., Sterling, M., Akerkar, G., Bhutani, M. S., Binmoeller, K., Garvie, J., Bini, E. J., McQuaid, K., Foster, W. L., Thompson, W. M., Dachman, A., and Halvorsen, R. 2005. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. Lancet. 365(9456):305-11.

Sanford, M. F. and Pickhardt, P. J. 2006. Diagnostic performance of primary 3-dimensional computed tomography colonography in the setting of colonic diverticular disease. Clin Gastroenterol Hepatol. 4(8):1039-47.

Schroy P. C. III, Lai S., Glick J. T., Robinson P. A., Zamor P., Heeren T. C. 2007. Patient preference for colorectal cancer screening: How does stool DNA testing fare? Amer. J. Managed Care 13:393-400.

Selcuk, D., Demirel, K., Ozer, H., Baca, B., Hatemi, I., Mihmanli, I., Korman, U., and Ogut, G. 2006. Comparison of virtual colonoscopy with conventional colonoscopy in detection of colorectal polyps. Turk J Gastroenterol. 17(4):288-93.

Spinzi, G., Belloni, G., Martegani, A., Sangiovanni, A., Del Favero, C., and Minoli, G. 2001. Computed tomographic colonography and conventional colonoscopy for colon diseases: a prospective, blinded study. Am J Gastroenterol. 96(2):394-400.

Sosna J., Blachar A. Amitai M., Barmeir E., Peled N., Goldberg S. N. 2006. Colonic perforation at CT colonography: Assessment of risk in a mulitcetner large cohort. Radiology 239 (2): 457-63.

Taylor, S. A., Halligan, S., Saunders, B. P., Morley, S., Riesewyk, C., Atkin, W., and Bartram, C. I. 2003. Use of multidetector-row CT colonography for detection of colorectal neoplasia in patients referred via the Department of Health "2-Week-wait" initiative. Clin Radiol. 58(11):855-61).

Van Gelder, R. E., Nio, C. Y., Florie, J., Bartelsman, J. F., Snel, P., De Jager, S. W., Van Deventer, S. J., Lameris, J. S., Bossuyt, P. M., and Stoker, J. 2004. Computed tomographic colonography compared with colonoscopy in patients at increased risk for colorectal cancer. Gastroenterology. 127(1):41-8.

Van Gelder, R. E., Venema, H. W., Serlie, I. W., Nio, C. Y., Determann, R. M., Tipker, C. A., Vos, F. M., Glas, A. S., Bartelsman, J. F., Bossuyt, P. M., Lameris, J. S., and Stoker, J. 2002. onography at different radiation dose levels: feasibility of dose reduction. Radiology. 224(1):25-33.

Vogt, C., Cohnen, M., Beck, A., vom Dahl, S., Aurich, V., Modder, U., and Haussinger, D. 2004. Detection of colorectal polyps by multislice CT colonography with ultra-low-dose technique: comparison with high-resolution videocolonoscopy. Gastrointest Endosc. 60(2):201-9.

Wessling, J., Domagk, D., Lugering, N., Schierhorn, S., Heindel, W., Domschke, W., and Fischbach, R. 2005. Virtual colonography: identification and differentiation of colorectal lesions using multi-detector computed tomography. Scand J Gastroenterol. 40(4):468-76.

Wessling, J., Fischbach, R., Domagk, D., Lugering, N., Neumann, E., and Heindel, W. 2001. Colorectal polyps: Detection with multi-slice CT colonography. Rofo. 173(12):1069-71.

Whiting P., Rutjes A. W., Reitsma J.B., Glas A. S., Bossuyt P. M., and Kleijnen J. 2003. The development of QUADAS; A tool for the quality assessment of studies of diagnostic accuracy included in systematic review BMC Medical Research Methodology 3:25. Available at http://www.biomedcentral.com/1471-228/3/25 [Accessed on 17 September 2007].

Wong, B. C., Wong, W. M., Chan, J. K., Lai, K. C., Hu, W. H., Chan, C. K., Lam, S. K., and Carr-Locke, D. L. 2002. Virtual colonoscopy for the detection of colorectal polyps and cancers in a Chinese population. J Gastroenterol Hepatol. 17(12):1323-7.

Xiong T., Richardson M., Woodroffe R., Halligan S., Morton D., Lilford R. J., 2005 incidental lesions found on CT clonography: their nature and frequency. British J. Radiol. 78:22-9.

Yasumoto T., Murakami T., Yamamoto H., Hori M., Iannaccone R., Kim T., Abe H., Kuwabara M., Yamasaki K., Kikkawa N., Arimoto H., Passariello R., and Nakamura H. 2006. Assessment of two 3D MDCT colonography protocols for observation of colorectal polyps. AJR Am J Roentgenol. 186:85-9.

Yee, J., Akerkar, G. A., Hung, R. K., Steinauer-Gebauer, A. M., Wall, S. D., and McQuaid, K. R. 2001. Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. Radiology. 219(3):685-92.

Yee, J., Kumar, N. N., Hung, R. K., Akerkar, G. A., Kumar, P. R., and Wall, S. D. 2003. Comparison of supine and prone scanning separately and in combination at CT colonography. Radiology. 226(3):653-61.

Zalis ME, BArish MA, Choi JR, et al. (Working Group on Virtual Colonoscopy). Ct colonoscopy reporting and data systems: a consensus proposal. Radiology 2005;236:3-9.

Search Strategies

The search strategy for PubMed was:

1. colon [MeSH Terms]
2. colonic neoplasms[MeSH Terms]
3. colonic polyps[MeSH Terms]
4. colorectal neoplasms"[MeSH Terms]
5. 1 OR 2 OR 3 OR 4
6. colonography, computed tomographic[MeSH Terms]
7. colonoscopy[MeSH Terms]
8. image processing, computer assisted[MeSH Terms]
9. tomography, x ray computed[MeSH Terms])
10. 6 OR 7 OR 8 OR 9
11. sensitivity and specificity[MeSH Terms]
12. predictive value of tests[MeSH Terms]
13. prospective studies[MeSH Terms]
14. 11 OR 12 OR 13
15. 5 AND 10 AND 14

The search strategy for EMBASE was:
1. polyps
2. colorectal neoplasms
3. 1 OR 2
4. colonoscopy
5. sensitivity
6. predictive
7. 5 OR 6
8.[1990-2007]/py
9. 3 AND 4 AND 7 AND 8

The Cochrane Library was searched using the terms “colonography” or “colonoscopy.”

CT Colonography Clinical Effectiveness Review

TABLES

Table 1. Studies scored as fulfilling quality criteria

Author, year	Reference Standard	Scanner	Collimation < 5 mm	Acquisition in ≤ 30 sec	No. readers and amount of training
Ginnerup 2003	segmental unblinded colonoscopy	Marconi M x 8000, Marconi Medical Systems	NR*	2 x 17 sec	1; "experience of approximately 100 CTCs"
Hoppe 2004a	segmental unblinded colonoscopy	Asterion 4- channel multidetector	4 x 2 mm	single breath hold, ~ 30 sec	3; "had read 30-60 studies"
Iannaccone 2004	segmental unblinded colonoscopy	Somatom Plus 4 Volume Zoom, Siemens Medical Solutions	2.5 mm	12-18 sec	3; previously had read 300, 200, 100 CTC exams
Iannaccone 2005	colonoscopy with 2nd (unblinded) colonoscopy	Somatom Plus 4 Volume Zoom, Siemens Medical Solutions	4 x 2.5 mm	14-20 sec	3; previously had read 400, 200, 100 CTC exams
Johnson 2007	colonoscopy, 2nd look at videotaped colonoscopy	Lightspeed Ultra, GE Healthcare	1.25 mm	28 sec breath hold	3; "had interpreted more than 1,000 … CTC examinations"
Pickhardt 2003	segmental unblinded colonoscopy	GE Lightspeed or LightSpeed Ultra, GE Medical Systems	1.25 - 2.5 mm	NR**	2 per center; training by reading 25 scans; 2 had previously interpreted > 1,000 scans
Rockey 2005	segmental unblended colonoscopy	either 4- or 8-slice multidetector CT scanners; manufacturer NR	NR*	NR**	about half had experience reading more than 50 CTC scans; remainder required to undergo training module
Taylor 2003	segmental unblinded colonoscopy	Lightspeed Plus, GE Medical Systems	1.25 mm (90%); 2.5 mm (10%)	NR**	1; training NR
Van Gelder 2004	videotaped colonoscopy plus second look	Mx8000, Philips	4 x 2.5 mm	22 sec	2 readers; "had evaluated more than 50 cases before start of study"

* Assumed that collimation was < 5 mm.

** Assumed that scan was acquired in ≤ 30 sec within a single breath hold.

Table 2. Excluded studies using multi-detector scanners

Items not checked did not fulfill criteria. Items checked "**X**" fulfilled criteria; items checked "NR" were not reported, and items checked "?" were reported only as "experienced" with no description of specific experience or training.

Author	Reference Standard	Collimation < 5 mm	Acquisition in ≤ 30 sec	Adequate reader training
Chung 2005		X	X	X
Cohnen 2002		X	NR	?
Cohnen 2004		X	X	?
Cotton 2004	X	NR	NR	
Gluecker 2002				X
Hoppe 2004b		X	X	?
Iannaccone 2003a		X	X	X
Iannaccone 2003b		X	X	NR
Johnson 2003			X	X
Kalra 2006			NR	?
Kwan 2004		X	NR	NR
Laghi 2002a		X	X	NR
Laghi 2002b		X		?
Lefere 2002	X			NR
Macari 2002		X	X	?
Macari 2004a		X	X	X
Macari 2004b		X	X	X
Park 2005		X	X	X
Rex 1999				NR
Selcuk 2006		X	X	NR
Van Gelder 2002		X	NR	X
Vogt 2004		X	X	NR
Wessling 2001		X	NR	NR
Wessling 2005		X	NR	X
Yasumoto 2006		X	NR	X

Table 3. Excluded studies using single detector scanners

Items not checked did not fulfill criteria. Items checked "**X**" fulfilled criteria; items checked "NR" were not reported, and items checked "?" were reported only as "experienced" with no description of specific experience or training.

Author	Reference Standard	Collimation < 5 mm	Acquisition in ≤ 30 sec	Adequate reader training
Abdel Razek 2005				NR
Arneson 2005	**X**			
Dachman 1998				NR
Fenlon 1999			NR	?
Fletcher 2000				?
Hara 1997				**X**
Kay 2000				
Macari 2000			**X**	?
McFarland 2002				**X**
Mendelson 2000				NR
Miao 2000			NR	**X**
Pescatore 2000				NR
Pineau 2003	**X**			NR
Reuterskiold 2006	**X**		NR	NR
Spinzi 2001			NR	NR
Wong 2002		***X***		?
Yee 2001		***X***		NR
Yee 2003		***X***	NR	NR

Table 4. Evaluation of study quality using the QUADAS Tool

QUADAS Item	Author Year								
	Ginnerup 2003	Hoppe 2004a	Iannaccone 2004	Iannaccone 2005	Johnson 2007	Pickhardt 2003	Rockey 2005	Taylor 2003	Van Gelder 2004
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Were selection criteria clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Y	Y	Y	Y	Y	Y	Y	Y	Y
6. Did patients receive the same reference standard regardless of the index test result?	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the reference standard independent of the index test (ie the index test did not form part of the reference standard)?	N	N	N	N	N	N	N	N	N
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Y	Y	Y	Y	Y	Y	N	Y	Y
9. Was the execution of the reference standard described in sufficient detail to permit replication of the test?	Y	N	Y	Y	N	Y	N	Y	Y
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y
11. Were the reference standard results interpreted without knowledge of the index test?	Y	Y	Y	Y	Y	Y	Y	Y	U
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Y	N	N	N	U	U	U	Y	U
13. Were uninterpretable intermediate test results reported?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
14. Were withdrawals from the study explained?	Y	Y	Y	Y	U	Y	Y	N/A	Y
Overall quality (H, high; or F, fair)	H	F	H	H	F	H	F	H	F

Table 5. Sensitivity and specificity for CTC detection of a lesion ≥ 10 mm per patient

Author No. Patients	True positive	False positive	True negative	False negative	Sensitivity (95% CI)	Specificity (95% CI)
Ginnerup 2003 n = 148	NR	NR	NR	NR	NR	NR
Hoppe 2004a n = 86	19	1	65	1	95% (75, 99%)	98% (92-100%)
Iannaccone 2004 n = 203	17	0	186	0	100% (81-100%)	100% (98-100%)
Iannaccone 2005 n = 88	10	0	78	0	100% (72-10%)	100% (95-100%)
Johnson 2007 n = 452	16	5	205	3	84% (60-97%)	98% (95-99%)
Pickhardt 2003* n = 1233	45	47	1138	3	94% (83-99%)	96% (95-97%)
Rockey 2005 n = 614	37	22	529	26	59% (45-71%)	96% (94-98%)
Taylor 2003 n = 54	9	0	44	1	90% (59-98%)	100% (92-100%)
Van Gelder 2004 n = 249	26	18	200	5	84% (67-93%)	92% (87-95%)
Pooled (95% CI)	**179**	**93**	**2445**	**39**	**82% (76-87%)**	**96% (95-97%)**
Pooled** **(95% CI)**	**142**	**71**	**1916**	**13**	**92% (86-95%)**	**96% (95-97%)**

* Nonadenomatous polyps were considered to be false positive findings.
** Pooled values do not include results from Rockey (2005).

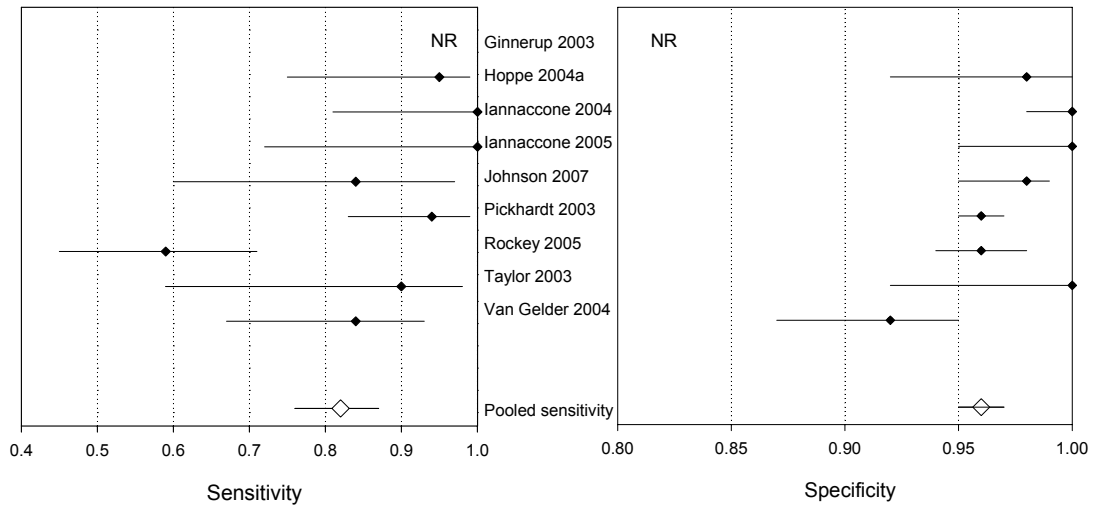


Figure. Pooled sensitivity and specificity per patient for lesions ≥ 10 mm
Each horizontal line represents the results from a single study with the point estimate shown as a circle and the length of the line representing the 95% confidence interval (CI). The pooled value is represented by the open diamond with 95% CI by the length of the horizontal line. NR, not reported.

Table 6. Sensitivity and specificity for CTC detection of a lesion ≥ 6 mm per patient

Author No. patients	True positive	False positive	True negative	False negative	Sensitivity (95% CI)	Specificity (95% CI)
Ginnerup 2003 n = 148	40	5	99	4	91% (79-96%)	95% (89-98%)
Hoppe 2004a n = 86	26	7	51	8	76% (59-89%)	88% (77-95%)
Iannaccone 2004 n = 203	44	8	130	4	92% (80-98%)	94% (89-98%)
Iannaccone 2005 n = 88	24	11	48	5	83% (66-92%)	81% (70-89%)
Johnson 2007 n = 452	NR	NR	NR	NR	NR	NR
Pickhardt 2003* n = 1233	149	217	848	19	89% (83-98%)	80% (77-82%)
Rockey 2005 n = 614	85	50	409	70	55% (47-63%)	89% (86-92%)
Taylor 2003 n = 54	NR	NR	NR	NR	NR	NR
Van Gelder 2004 n = 249	35	62	142	10	78% (61-87%)	70% (64-76%)
Pooled **(95% CI)**	**403**	**360**	**1727**	**120**	**77% (73-80%)**	**83% (81-84%)**
Pooled** **(95% CI)**	**318**	**310**	**1318**	**50**	**86% (83-90%)**	**81% (79-83%)**

* Nonadenomatous polyps were considered to be false positive findings.
** Pooled values do not include results from Rockey (2005).

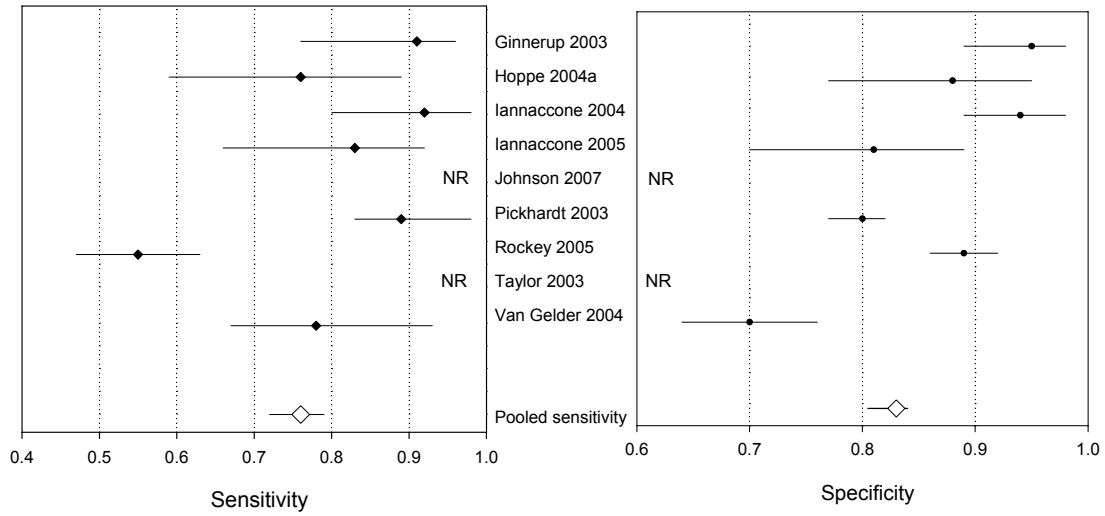


Figure. Pooled sensitivity and specificity per patient for lesions ≥ 6 mm
Each horizontal line represents the results from a single study with the point estimate shown as a circle and the length of the line representing the 95% confidence interval (CI). The pooled value is represented by the open diamond with 95% CI by the length of the horizontal line. NR, not reported.

Table 7. Sensitivity and specificity for CTC detection of a lesion 6-9 mm per patient

Author	True positive	False positive	True negative	False negative	Sensitivity (95% CI)	Specificity (95% CI)
Johnson 2007	9	21	194	5	64% (35-87%)	90% (85-94%)
Rockey 2005	59	NR	NR	57	51% (41-60%)	N/A
Taylor 2003	1	NR	NR	1	50%	N/A

Table 8. Comparison sensitivity and specificity for detection of a lesion ≥10 mm per patient using CTC versus colonoscopy

Author No. patients	Prevalence of lesions ≥ 10 mm (%)	CTC		Colonoscopy	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95%)
Hoppe 2004a n = 86	20/86 23.2%	95% (75-99%)	98% (92-100%)	100% (84-100%)	100% (95-100%)
Iannaccone 2004 n = 203	17/203 8.4%	100% (81-100%)	100% (98-100%)	100% (81-100%)	100% (98-100%)
Iannaccone 2005 n = 88	10/88 11.4%	100% (72-100%)	100% (95-100%)	90% (60-98%)	100% (95-100%)
Pickhardt 2003* n = 1233	48/1233 3.8%	94% (83-99%)	96% (95-97%)	87.5% (75-95%)	99% (98-99%)
Rockey 2005 n = 614	63/614 10.3%	59% (45-71%)	96% (94-98%)	98% (91-100%)	100% (99-100%)
Taylor 2007 n = 54	10/54 18.5%	90% (59-98%)	100% (92-100%)	100% (72-100%)	100% (92-100%)
Van Gelder 2004 n = 249	31/249 12.4%	84% (67-95%)	92% (87-95%)	81% (63-93%)	100% (98-100%)
Pooled (95% CI)		163/199 82% (76-87%)	**2240/2328 96% (95-97%)**	**185/199 93% (89-96%)**	**2316/23189 99.9% (99.7-100%)**
Pooled **(95% CI)**		**126/136 93% (87-96%)**	**1711/1777 96% (95-97%)**	**123/136 90% (84-94%)**	**1765-1767 99.9% (99.6-100%)**

* Nonadenomatous polyps were considered to be false positive findings.
** Pooled values do not include results from Rockey (2005).

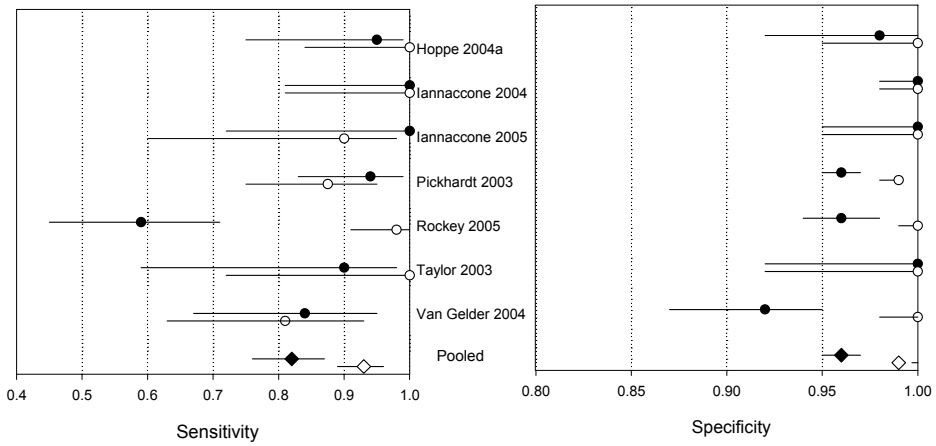


Figure. Comparison of sensitivity and specificity of CT colonography with optical colonoscopy for lesions ≥ 10 mm per patient . Each horizontal line represents the results from a single study with the point estimate shown as a black (CTC) or white (colonoscopy) circle and the length of the line representing the 95% confidence interval (CI). The pooled value is represented by the open diamond with 95% CI by the length of the horizontal line

Table 9 Extracolonic findings in asymptomatic populations

Study	Total No.	Total Lesions	Patients with lesions	Patients with clinically important lesions	Definition of "clinically important"
		No.	No. (%)	No. (%)	
Chin 2005	438	146	118 (27)	32 (7)	"required medical or surgical attention, or further hematological, biochemical, and/or radiological investigation.."
Gluecker 2003	681	858	469 (69)	71 (10)	"required immediate surgical treatment, medical intervention, and/or further investigation during that patient visit"
Kim 2007	2230	2186	1484 (66)	115 (5)	"required immediate further diagnostic studies or medical and/or surgical treatment
Pickhardt 2003	1233	223	223 (19)	56 (5)	"potentially high clinical importance"
Yee 2005	194	NR	116 (60)	12 (6)	"lesions that necessitated further diagnostic studies or medical or surgical intervention."
Average n/N	**4776**		**50.5% 2410/4776**	**5.9% 286/4776**	

* average risk subset

Table 9 (continued) Extracolonic findings in asymptomatic populations

Study	Clinically important findings as defined by author								Patients requiring additional care or benefit from finding	Additional cost per CTC exam
	Cancer	Aortic Aneurysm	Adrenal adenoma	Lung nodule	Other mass	Cyst*	Heman-gioma	Other		
	No.	No.	No.	No.	No.	No.	No.	No.	No. (%)	
Chin 2005	1	8	3	3	3	12	1	4	8 (1.9)	$24.37
Gluecker 2003	5	7	1	26	31	14	0	3	9 (1.3)	$34.33
Kim 2007	12	3	2	1	57	7	2	31	NR	$2.34
Pickhardt 2003	5	25	NR	NR	NR	NR	NR	49	NR	NR
Average n/N	**0.5% 23/4582**	**0.4% 20/4582**	**0.2% 6/3349**	**0.9% 30/3349**	**2.7% 91/3349**	**1.0% 33/3349**	**0.09% 3/3349**	**1.9% 87/3349**	**1.5% 17/1119**	

*renal, hepatic, or ovarian

Table 10. Patient preference for type colonoscopy

Author	Preferred CT colonoscopy	Preferred optical colonoscopy	Undecided or no preference
	n/N (%)	n/N (%)	n/N (%)
Cotton 2004	238/518 (45%)	213/518 (41%)	67/518(13%)
Iannaccone 2004	99/162 (61%)	57/162 (35%)	6/162(4%)
Miao 2000	83/198 (42%)	94/198 (47%)	21/198(11%)
Pickhardt 2003	500/1005 (50%)	413/1005(41%)	92/1005(9%)

ECONOMIC MODEL OVERVIEW

1. OBJECTIVES

The objectives of the economic evaluation were to evaluate the clinical and cost-effectiveness of CTC screening for colorectal cancer compared with optical colonoscopy, with other currently recommended CRC screening modalities, and with no screening.

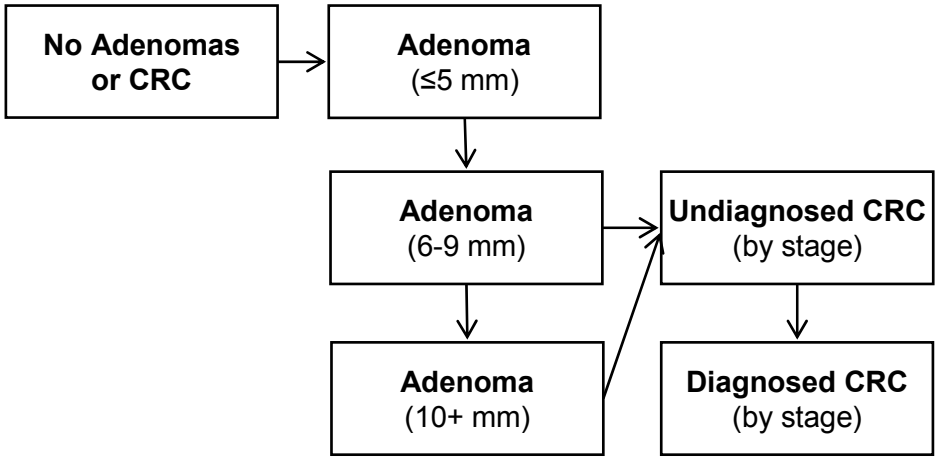
2. METHODS

2.1 Overview of Model

We used an existing microsimulation model of colorectal cancer, SimCRC, to evaluate the effectiveness and cost-effectiveness of CTC screening of individuals at average risk of colorectal cancer. The model tracks the natural history process (the adenoma-carcinoma sequence) and incorporates the effect of screening interventions on colorectal cancer incidence and mortality. The model was developed through a Cancer Intervention and Surveillance Modeling Network (CISNET) grant from the National Cancer Institute (PI Karen M. Kuntz, U01 CA 088204) and is an extension of a simpler model that has been used to evaluate the cost-effectiveness of cancer screening programs.[1]

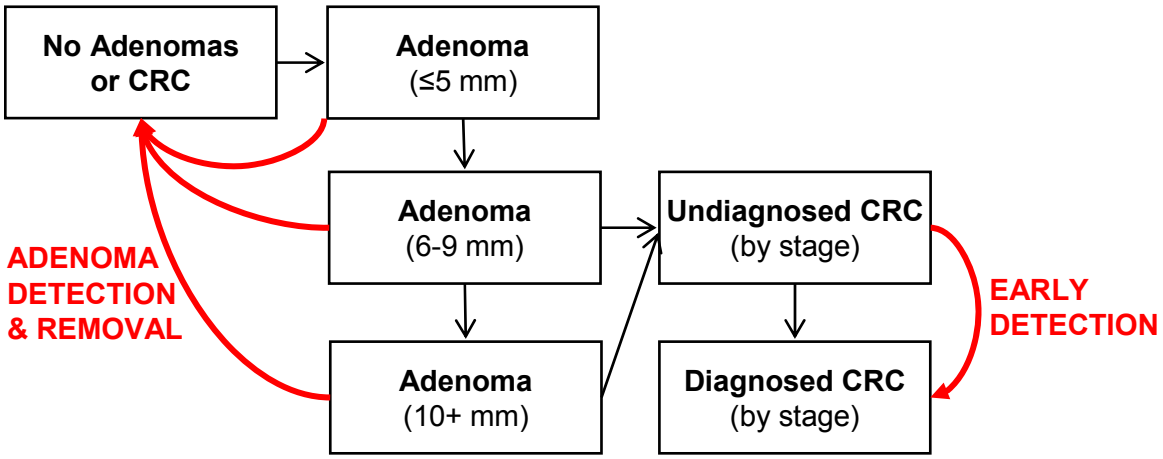
The SimCRC model consists of two components: a natural history model and a screening mechanism. The **natural history model** (Figure 1) simulates the life histories of a large cohort of individuals from birth to death. As an individual ages, he or she faces the risk of developing one or more adenomatous polyps (adenomas). Over time, each adenoma may grow and some may ultimately develop into a preclinical stage I (i.e., undiagnosed) colorectal cancer. Preclinical cancers may progress in stage and may be detected by symptoms, becoming a clinically-diagnosed case.

Figure 1. Schematic overview of the natural history component of the SimCRC model.



The **screening mechanism** is superimposed over the natural history model (Figure 2) and captures the ability of a given screening test to detect adenomas or preclinical cancer. In a screening year, a person with an underlying (i.e., undiagnosed) adenoma or cancer faces the chance that the lesion is detected based on the sensitivity of the test for that lesion and the reach of the test. Individuals who do not have an underlying adenoma or preclinical cancer also face the risk of having a positive screening test (and undergoing unnecessary follow-up procedures) due to the imperfect specificity of the test. While the SimCRC model does not explicitly simulate non-adenomatous polyps, they are accounted for through the specificity of the test. Additionally, individuals with false-negative screening tests (i.e., individuals with an adenoma or preclinical cancer that was missed by the screening test) may be referred for follow-up due to the detection of a non-adenomatous polyp.

Figure 2. Schematic overview of the SimCRC screening mechanism.



2.2 Model estimation

Because the natural history of colorectal cancer is an unobservable process, there are limited data with which to directly estimate the model parameters. As a result, the values of the model parameters were inferred by simultaneously calibrating the model-predicted outcomes with data on: (1) the prevalence, location, size, and multiplicity of adenomas by gender and age from autopsy studies;[2-11] (2) the prevalence of preclinical cancer by gender and age from autopsy studies;[2, 4-11] and (3) the stage-, location-, and age-specific incidence of colorectal cancer by gender and race from the Surveillance, Epidemiology, and End-Results (SEER) program.[12] The goodness of fit of the model predictions was assessed using a likelihood-based metric[13] and the parameter space was explored using the simulated annealing algorithm.[14]

2.3 Screening strategies

In the base-case analysis, we evaluated eleven strategies for screening average-risk individuals for colorectal cancer. These strategies included a no-screening scenario, as well as six of the seven strategies recommended by the American Cancer Society[15] (N.B., we did not consider double-contrast barium enema screening due to its limited use in clinical practice):

1. No screening
2. Annual fecal occult blood testing (FOBT 1y)
3. Annual fecal immunochemical testing (FIT 1y)
4. Sigmoidoscopy every five years (SIG 5y)
5. Annual FOBT + sigmoidoscopy every five years (FOBT 1y + SIG 5y)
6. Annual FIT + sigmoidoscopy every five years (FIT 1y + SIG 5y)
7. Colonoscopy every ten years (COL 10y)

Since the optimal CTC screening interval and polyp size threshold triggering referral for colonoscopy for polypectomy has not yet been established, we evaluated four possible strategies:

8. CTC every five years with a 6 mm referral threshold (CTCM 5y)
9. CTC every five years with a 10 mm referral threshold (CTCL 5y)
10. CTC every ten years with a 6 mm referral threshold (CTCM 10y)
11. CTC every ten years with a 10 mm referral threshold (CTCL 10y)

2.4 Follow-up, surveillance, and adherence

We assumed that individuals with a positive FOBT, FIT, or sigmoidoscopy are referred for a follow-up colonoscopy for polypectomy. If no adenomas or colorectal cancers are detected on the follow-up colonoscopy, individuals change to a strategy of colonoscopy screening every ten years. If the follow-up colonoscopy yields an adenoma, the individual begins colonoscopy surveillance. Surveillance was modeled according to the US Multi-Society Task Force and American Cancer Society guidelines.[16] These guidelines suggest that individuals with one or more large (10+ mm) adenomas or three or more smaller adenomas detected on the last colonoscopy should have a repeat colonoscopy in three years; all others should have a repeat colonoscopy in five to ten years (we used the approximate mid-point of this range, seven years).

Individuals with a CTC finding larger than the referral threshold are also assumed to be referred for colonoscopy for polypectomy. However, if the follow-up colonoscopy does not detect any adenomas or cancer, the individual is assumed to return to CTC screening. Individuals with adenomas detected on the follow-up colonoscopy are assumed to undergo colonoscopy surveillance as specified above.

For all strategies, screening is assumed to begin at age 50.[17, 18] Screening and surveillance are assumed to end when the individual has a ten-year life expectancy based on the US Multi-Society Task Force and American Cancer Society surveillance guidelines;[16] this corresponds with age 79.[19] We assumed that all individuals are perfectly adherent with screening, follow-up, and surveillance.

2.5 Test characteristics

Data on the sensitivity for adenomas by size, sensitivity for cancer, specificity, and reach of the screening tests are reported in Table 1.

Table 1. Sensitivity, specificity, and reach, by screening test.

	Sensitivity, by Adenoma Size and for Cancer						
Test	**Small**	**Medium**	**Large**	**Cancer**	**Specificity**	**Reach**	**Source**
FOBT	0.046	0.063	0.107	0.129	0.954	Whole colorectum	(26)
FIT	0.045	0.11	0.224	0.658	0.955	Whole colorectum	(23)
COL*	0.74	0.85	0.95	0.95†	0.9	98% to end of cecum	(22)
SIG*	0.74	0.85	0.95	0.95†	0.92	80% to end of sigmoid colon; 40% to end of descending colon	See text
CTCM	--	0.867	0.938	0.938†	0.796‡	Whole colorectum	(20)
CTCL	--	--	0.938	0.938†	0.96‡	Whole colorectum	(20)

FOBT: Fecal occult blood test (Hemoccult II)
FIT: Fecal immunochemical test
COL: Colonoscopy
SIG: Sigmoidoscopy
CTCM: CTC with a referral threshold of a medium lesion (i.e., 6+ mm)
CTCL: CTC with a referral threshold of a large lesion (i.e., 10+ mm)
*Sensitivity estimates are per lesion and are defined within the reach of the scope
†Sensitivity for cancer assumed to equal that for large adenomas
‡Probability that CTC correctly finds a person to be free of an adenoma larger than the referral threshold. For example, a specificity of 0.96 for the CTCL strategy implies that 4% of individuals without a large adenoma will be referred for follow-up colonoscopy

CTC

Neither CTC nor colonoscopy can reliably distinguish adenomatous polyps from benign non-adenomatous polyps, such as hyperplastic and mucosal polyps. While polyps detected by colonoscopy can be biopsied or resected for histological analysis, this information is unavailable with CTC due to its non-invasive nature. Given the inability to distinguish adenomas from other polyps, many studies (including most of the studies included in the clinical review) report the person-based sensitivity and specificity for all polyps, while others, namely the Department of Defense (DOD) study[20] report person-based estimates for adenomatous polyps only. This

difference is important because it impacts the value for the specificity of the test, and accordingly, the false positive fraction (i.e., 1-specificity). In the DOD study, a person with a single 6-9 mm non-adenomatous polyp detected by CTC was counted as a false positive, because the person does not have an adenoma. In a study that reports sensitivity and specificity for all polyps, this person would be counted a true positive.

The SimCRC model does not explicitly simulate non-adenomatous polyps. Accordingly, the model requires that sensitivity estimates are defined as the likelihood of a positive CTC given that the subject has an *adenomatous* polyp greater than or equal to the threshold size for referral; individuals with only non-adenomatous polyps detected on CTC must be included in the numbers of subjects with a false-positive CTC result. For our base-case analysis, we therefore used the CTC sensitivity and specificity reported in the DOD study,[20] the only study within those considered high-quality that defined sensitivity and specificity in this manner. These estimates are shown in Table 1. The sensitivity estimates are slightly higher than the pooled estimates from the review of comparative clinical effectiveness at each reporting threshold, but the specificity estimates are similar. In a sensitivity analysis, we use the pooled rates.

We assumed that there is no risk of perforation with CTC screening procedures based on a survey of over 11,000 screening CTCs.[21] We did not incorporate the rates of extracolonic findings (or the associated costs) because the data on these findings are variable and the net effect of detecting and managing these findings on a patient's life expectancy is unclear.

Colonoscopy

We used the results of a meta-analysis of miss rates on tandem colonoscopy studies to inform its sensitivity estimates and reach. van Rijn and colleagues[22] pooled the results of six tandem colonoscopy studies and found miss rates of 26%, 13%, and 2% for small, medium, and large adenomas respectively. Because back-to-back colonoscopy studies are likely to underestimate miss rates, we adjusted these numbers up slightly and assumed that the sensitivity is 74% for small adenomas, 85% for medium adenomas, and 95% for large adenomas. We further assumed that the sensitivity for cancer is equal to that for a large adenoma. In the pooled analysis, 98% of colonoscopies were complete to the cecum, which is equal to that observed in the Morikawa study[23] of FIT and colonoscopy in 21,805 subjects. We did not model the likelihood that a colonoscopy would have to be repeated due to inadequate preparation. However, we inflated the costs of a colonoscopy by 5% to account for repeated procedures. We assumed that 10% of subjects without adenomas or colorectal cancer incur the costs associated with the removal and histology assessment of non-adenomatous polyps, for a specificity of 90%. We also assumed that 10% of subjects with adenomas or cancer that were missed by colonoscopy incur these costs.

We included the risk of complications from colonoscopy, including perforations (0.7/1000), serosal burns (0.3/1000), bleeds requiring transfusion (0.4/1000), and bleeds not requiring transfusion (1.1/1000).[24] We assumed the risk of death from a colonoscopy with polypectomy is 1 per 10,000.[25]

FOBT

There are several versions of the guaiac-based FOBT available (e.g., Hemoccult II, Hemoccult SENSA, HemoQuant) that differ in terms of their sensitivity and specificity for adenomas and cancer. None of the current screening guidelines specify which guaiac-based FOBT is preferred. We focused on the Hemoccult II since it was the only FOBT for which a study assessed the sensitivity and specificity among average-risk individuals by performing a colonoscopy on all subjects regardless of the FOBT test result;[26] studies of Hemoccult Sensa used populations at above average risk[27-29] or used sigmoidoscopy as a reference standard.[30, 31]

Imperiale et al.[26] reported the number of individuals with positive Hemoccult II tests according to whether the most advanced finding at colonoscopy was cancer, an advanced adenoma (adenoma with high-grade dysplasia, villous features, or large tubular adenoma), a non-advanced adenoma <10 mm, or no adenoma. We assumed that the sensitivity for large adenomas was equal to that of advanced adenomas. The sensitivity for small and medium adenomas were not reported separately; the combined sensitivity for adenomas less than 10mm was reported to be 5.2%. We derived estimates of the sensitivity of Hemoccult II for small adenomas and for medium adenomas by assuming that: (1) small adenomas do not bleed so the rate of positive screening tests for small adenomas is approximated by the difference between perfect specificity and the measured specificity of the test (i.e., 100% - 95.4% = 4.6%) and (2) 61% of small and medium-sized adenomas are small based on data from the National Colonoscopy Study (personal communication, Ann G. Zauber). This approach yielded a sensitivity for small adenomas of 4.6% and of medium-sized adenomas of 6.3%.

FIT

While several studies have evaluated the performance of FIT,[27-30, 32-34] these studies suffer from many of the same problems as the FOBT studies. We used the sensitivity and specificity estimates reported by Morikawa and colleagues[23] comparing FIT and colonoscopy among 21,805 asymptomatic Japanese subjects. As with the Imperiale study of Hemoccult II, this study did not report the sensitivity for small and medium adenomas separately; the combined sensitivity of FIT for these groups was 7.0%. As with our estimations for FOBT, we assumed that small adenomas are detected at the rate suggested by the imperfect specificity (100% - 95.5% = 4.5%) and that 61% of small and medium adenomas are small (personal communication, Ann G. Zauber), yielding a sensitivity for small adenomas of 4.5% and for medium-sized adenomas of 11.0%. Note that in the Morikawa study the study subjects only completed one FIT test card instead of the recommended three.[15]

Sigmoidoscopy

We assumed that within the reach of the scope, the sensitivity of sigmoidoscopy is equal to that of colonoscopy. Based on data on the depth of insertion (in cm)[35, 36] and the approximate size of each colonic segment,[11] we assumed that 80% of sigmoidoscopies reach the junction of the sigmoid and descending colon and that 40% reach the splenic flexure. We assumed that sigmoidoscopy will detect a non-adenomatous polyp in 8% of individuals without an adenoma or cancer within the reach of the simoidoscope, for a specificity of 92%. Individuals undergoing sigmoidoscopy were assumed to face a small risk of perforation (0.02/1000). We assumed there were no sigmoidoscopy-related deaths.

2.6 Costs

With the exception of the cost of a CTC screening test, all of the cost estimates used in the analyses were obtained from a report to the Centers for Medicare and Medicaid Services and the Agency for Healthcare Research and Quality on the cost-effectiveness of DNA stool testing for colorectal cancer screening.[24] These cost estimates are described below.

Screening Costs

The costs of the screening tests are based on Medicare reimbursement rates for the relevant set of CPT codes for each procedure. The costs were adjusted for the point of service of the procedure but were not adjusted for geographic location in order to yield a national average reimbursement rate. The details of the costs included in each test are presented in Table 2.

Table 2. Costs of screening procedures.

Test/Procedure	Cost	Description
FOBT	$4.54	Medicare reimbursement rate for guaiac-based tests
FIT	$22.22	Medicare reimbursement rate for immunochemical tests
Colonoscopy without polypectomy	$522.47	Weighted national average CMS reimbursement rate for CPT codes 45378 (diagnostic colonoscopy), G0105 (colon screen in high risk individual) & G0121 (colon cancer screening for non high risk individual), adjusted for point of service. Includes costs of sedation, assuming it is not administered by an anesthesiologist. Average cost was inflated by 5% to account for colonoscopies that need to be repeated due to inadequate preparation ($25).
Colonoscopy with polypectomy	$673.40	Weighted national average CMS reimbursement rate for CPT codes 45380 (colonoscopy & biopsy), 45381 (colonoscopy, submucous injection), 45382 (colonoscopy/control bleeding), 45383 (lesion removal colonoscopy-fulguration), 45384 (lesion removal colonoscopy-hot biopsy) & 45385 (lesion removal colonoscopy-snare polypectomy), adjusted for point of service. Includes costs of sedation, assuming it is not provided by an anesthesiologist. Includes reimbursement for pathology costs (88305), assuming 1.38 jars per colonoscopy with polypectomy. To account for repeated procedures due to inadequate preparation, average cost was inflated by the same absolute amount as for colonoscopy without polypectomy ($25).
Sigmoidoscopy	$160.78	National average CMS reimbursement rate for CPT codes 45330 (diagnostic sigmoidoscopy) & G0104 (CA screen; flexi sigmoidoscope), adjusted for point of service. Assume no polypectomy/biopsy performed.
CTC	$523.40	CMS reimbursement rates for CPT codes 74150 (CT, abdomen; without contrast material), 72192 (CT, pelvis; without contrast material), & 76377 (3D rendering with interpretation & reporting of CT requiring image postprocessing on an independent workstation). The technical component of the reimbursement for a pelvic CT was reduced by 25% based on the Multiple Procedure Reduction for imaging procedures performed on contiguous body parts in one imaging session.

Sources: CTC https://catalog.ama-assn.org/Catalog/cpt/cpt_search.jsp, all others from (24)

Cost of complications

The costs of endoscopy complications are presented in Table 3.

Table 3. Costs of endoscopy complications.

Complication	Cost	Description
Colonoscopy		
Perforation	$12,446	National average Medicare reimbursement rate for DRG 442 (other OR procedures for injuries with colon cancer)
Bleed with transfusion	$5,208	National average Medicare reimbursement rate for DRG 452 (complications with treatments of colon cancer)
Bleed without transfusion	$320	Emergency room visit
Serosal burn	$5,208	Assumed to equal the cost of a bleed with transfusion
Sigmoidoscopy		
Perforation	$12,446	National average Medicare reimbursement rate for DRG 442 (other OR procedures for injuries with colon cancer)

Source: (24)

Cancer-related costs

The costs of colorectal cancer treatment were obtained from a comparison of the costs of colorectal cancer patients relative to matched controls in the SEER-Medicare files.[24] The methods used to estimate these costs were described in a previous analysis by Brown and colleagues,[37] although the analysis was updated using data from the period 1998 to 2003. As the expensive biologics Avastin® and Erbitux® were not approved for colorectal cancer treatment during this time-period,[38] these costs may underestimate the costs of cancer treatment.

The cost estimates are stratified by stage at diagnosis and phase of treatment (Table 4) and include the Medicare payments for Part A (inpatient services) and Part B (outpatient services). Costs were updated to 2007 U.S. dollars using the Medical Care component of the Consumer Price Index.

Table 4. Annual costs of cancer care, by phase of treatment and stage at diagnosis.

	Annual Cost, by Stage at Diagnosis			
Phase	**I**	**II**	**III**	**IV**
Initial	$25,487	$35,173	$42,885	$56,000
Continuing	$2,028	$1,890	$2,702	$8,375
Terminal, given died from colorectal cancer	$45,689	$45,560	$48,006	$64,428
Terminal, given died from other causes	$11,257	$9,846	$13,026	$34,975

Initial: Costs incurred in the initial 12 months following diagnosis
Continuing: Costs incurred in the months between the initial and final phases, converted to annual estimates
Terminal: Costs incurred in the final 12 months of life

2.7 Analyses

We used the SimCRC model to predict the number of colorectal cancer cases and deaths, as well as the discounted lifetime costs and the discounted number of years of life per 1,000 50-year-olds in each of the eleven screening scenarios. Costs are expressed in 2007 U.S. dollars and are tallied from the payer perspective (i.e., patient time costs and co-payments are not included). Our primary outcomes are the cost per life-year saved (C/LYS) for screening strategies compared with no screening and compared with colonoscopy screening every ten years.

We performed a number of sensitivity analyses. First, we explored the relationship between CTC test cost and the C/LYS of the CTC strategies compared with colonoscopy screening every ten years and identified the CTC cost thresholds that would yield a C/LYS of CTC vs. colonoscopy of $50K, $100K, and $150K. We also determined the CTC cost threshold below which is would be cost-saving vs. no screening. Next, we considered an alternative base-case estimate of CTC sensitivity and specificity, namely the pooled estimates from the clinical review. Finally, we assessed the number of colorectal cancer cases and deaths and cancer-related costs under alternative scenarios for the increase in screening penetrance (i.e., the percent of the population ever screened for colorectal cancer) associated with the addition of CTC to the menu of screening options.

3.1 Base-Case Results

All Strategies

The numbers (per 1,000) of colorectal cancer cases, deaths from colorectal cancer, cases and deaths prevented compared with no screening, and number of colonoscopies are presented in Table 5 by screening scenario. In the absence of screening, approximately 64 of 1,000 50-year olds will be diagnosed with colorectal cancer over their lifetimes and approximately 30 will die from the disease. CTC screening every 10 years with a colonoscopy referral threshold of a large lesion (CTCL 10y) prevents the fewest number of cases and deaths, while CTC screening every 5 years with a colonoscopy referral threshold of a medium-sized lesion (CTCM 5y) is the most effective strategy at preventing colorectal cancer and death. As expected, colonoscopy every ten years has the highest number of colonoscopies. Annual FIT with sigmoidoscopy every five years has the next highest number of colonoscopies (1,882 per 1,000 patients) and CTC every ten years with a colonoscopy referral threshold of a large lesion has the fewest (446 per 1,000).

Table 5. Number* of colorectal cancer cases and deaths, cases and deaths prevented through screening, and colonoscopies, by screening strategy.

Strategy	Cases	Cases Prevented	Deaths†	Deaths Prevented	Colonoscopies‡
No Screening	64.1	--	29.9	--	--
CTCL 10y	31.4	32.7	12.1	17.8	446
SIG 5y	25.8	38.3	11.0	18.8	653
FOBT 1y	25.6	38.5	10.2	19.7	1,720
CTCL 5y	22.5	41.6	7.7	22.2	644
CTCM 10y	17.2	46.9	6.4	23.4	1,274
FOBT 1y + SIG 5y	15.1	49.0	5.7	24.2	1,809
FIT 1y	17.8	46.3	5.3	24.6	1,839
COL 10y	11.8	52.3	4.4	25.5	3,159
FIT 1y + SIG 5y	12.4	51.7	4.0	25.8	1,882
CTCM 5y	11.2	52.9	4.0	25.9	1,813

*per 1,000 individuals; strategies are ranked in ascending order of deaths prevented
†Including deaths from colonoscopy
‡Including colonoscopies for screening, follow-up, and surveillance. For strategies involving FOBT, FIT, and/or SIG, individuals with a false-positive screening test are assumed to switch to screening with COL 10y rather than return to their original screening strategy

The total costs, life-years saved, and C/LYS compared with no screening are presented in Table 6. All of the strategies recommended by most major organizations are cost-saving compared with no screening; with our base-case estimates for CTC cost and performance, all of the CTC strategies are more costly than no screening. CTC every ten years with a colonoscopy referral threshold of a medium-sized lesion (CTCM 10y) is the least costly of the CTC strategies evaluated with a C/LYS compared with no screening of approximately $1,500. CTC every five years with a colonoscopy referral threshold of a large lesion (CTCL 5y) is the most expensive strategy, with a C/LYS compared with no screening of approximately $8,700.

Table 6. Costs, life-years saved, and cost per life-year saved compared with no screening, by screening strategy.

Strategy	Costs*	LYS*	Cost/LYS vs. No Screening
No Screening	$2,070,300	0	--
FOBT 1y	$1,747,865	76.4	more effective, less costly
SIG 5y	$1,787,669	83.4	more effective, less costly
FOBT 1y + SIG 5y	$1,820,082	106.8	more effective, less costly
FIT 1y	$1,701,037	108.4	more effective, less costly
COL 10y	$1,862,013	116.8	more effective, less costly
FIT 1y + SIG 5y	$1,932,805	118.1	more effective, less costly
CTCM 10y	$2,227,220	107.3	$1,500
CTCL 10y	$2,341,521	84.2	$3,200
CTCM 5y	$2,948,350	118.5	$7,400
CTCL 5y	$2,967,926	103.7	$8,700

LYS: life-years saved compared with no screening
*per 1,000 individuals, costs and life-years discounted at 3% annual rate

CTC vs. Colonoscopy

Table 7 focuses on the five CTC strategies compared directly with colonoscopy screening every ten years. Colonoscopy every ten years is less costly and more effective than three of the four CTC screening strategies, while CTC every five years with a colonoscopy referral threshold of a medium-sized lesion (CTCM 5y) provides an additional year of life at a cost of $630,700.

Table 7. Costs, life-years saved, and cost per life-year saved compared with colonoscopy screening every ten years, by screening strategy.

Strategy	Costs*	LYS*	Cost/LYS vs. COL 10y
COL 10y	$1,862,013	116.8	--
CTCM 10y	$2,227,220	107.3	less effective, more expensive
CTCL 10y	$2,341,521	84.2	less effective, more expensive
CTCL 5y	$2,967,926	103.7	less effective, more expensive
CTCM 5y	$2,948,350	118.5	$630,700

LYS: life-years saved compared with no screening

*per 1,000 individuals, costs and life-years discounted at 3% annual rate

3.2 Sensitivity and Threshold Analyses

CTC Cost

Because Medicare has not set a reimbursement rate for CTC screening for colorectal cancer, and coverage by private insurers is very rare, we performed sensitivity analyses on the cost of a CTC screening test. Our base-case estimate of the cost of CTC ($523.40) was approximately equal to the cost of a colonoscopy screening exam without polypectomy ($522.47). However, information from the University of Wisconsin Medical School, where CTC screening has been covered by several third-party payers since April 2004,[39] suggests that the cost of a CTC screening test in that setting is 0.36 times the cost of a colonoscopy without polypectomy (personal communication, P. Pickhardt). We applied this ratio to our estimate of the cost of a colonoscopy without polypectomy and arrived at a CTC cost of $186.59 (0.36 * $522.47). At this cost ratio, all four CTC screening strategies are cost-saving compared with no screening and are less costly than colonoscopy screening every ten years (Table 8).

Table 8. Costs and life-years saved, by screening strategy assuming the ratio of the cost of a CTC to the cost of a colonoscopy without polypectomy is 0.36.

Strategy	Costs*	LYS*
No Screening	$2,070,300	0
FOBT 1y	$1,747,865	76.4
SIG 5y	$1,787,669	83.4
FOBT 1y + SIG 5y	$1,820,082	106.8
FIT 1y	$1,701,037	108.4
COL 10y	$1,862,013	116.8
FIT 1y + SIG 5y	$1,932,805	118.1
CTCM 10y	$1,565,217	107.3
CTCL 10y	$1,645,992	84.2
CTCL 5y	$1,748,578	103.7
CTCM 5y	$1,840,353	118.5

LYS: life-years saved compared with no screening

*per 1,000 individuals, costs and life-years discounted at 3% annual rate

We also performed threshold analyses on the cost of CTC within the CTCM 5y strategy (the only CTC strategy we evaluated that was more effective than colonoscopy) to determine the CTC-to-colonoscopy-without-polypectomy cost ratio (i.e., "procedure cost ratio") that would produce incremental C/LYS comparing CTCM 5y with colonoscopy every 10 years at boundaries familiar to policy-makers. The procedure cost ratio would have to equal 0.52 to achieve an incremental C/LYS of $150,000; 0.47 to produce $100,000/LYS; and 0.42 to produce $50,000/LYS. At a cost for colonoscopy without polypectomy of $522 these procedure cost ratios translate into costs for CTC of $272, $246, and $219, respectively. In order for CTCM 5y to be cost-saving compared with no screening, the CTC cost per test must be less than $256, for a procedure cost ratio of 0.49.

CTC Sensitivity and Specificity

We performed a sensitivity analysis on CTC sensitivity and specificity. The base-case estimates were derived from Pickhardt et al.[20] When we instead used the pooled person-based sensitivity and specificity estimates (0.82 and 0.96 respectively for 10+ mm lesions and 0.76 and 0.83 respectively for 6+ mm lesions), all four CTC screening strategies are less effective and more costly than colonoscopy screening every ten years. The cost per life-year saved compared with no screening increases slightly (Table 9).

Table 9. Costs, life-years saved, and cost per life-year saved compared with no screening, by screening strategy using the pooled estimates of CTC sensitivity and specificity from the clinical review.

Strategy	Costs*	LYS*	Cost/LYS vs. No Screening
No Screening	$2,070,300	0	--
FOBT 1y	$1,747,865	76.4	more effective, less costly
SIG 5y	$1,787,669	83.4	more effective, less costly
FOBT 1y + SIG 5y	$1,820,082	106.8	more effective, less costly
FIT 1y	$1,701,037	108.4	more effective, less costly
COL 10y	$1,862,013	116.8	more effective, less costly
FIT 1y + SIG 5y	$1,932,805	118.1	more effective, less costly
CTCM 10y	$2,295,130	97.9	$2,300
CTCL 10y	$2,425,087	75.9	$4,700
CTCM 5y	$2,967,833	112.8	$8,000
CTCL 5y	$3,042,052	96.9	$10,000

LYS: life-years saved compared with no screening
*per 1,000 individuals, costs and life-years discounted at 3% annual rate

Effect of CTC on Screening Penetrance

Data from the 2005 National Health Information Survey[40] indicate that approximately 60% of U.S. adults aged 50 years and older have ever been screened for colorectal cancer. We evaluated the changes in the cancer-related costs and the number of additional colorectal cancer cases and deaths that could be prevented if the availability of CTC screening were to increase the percent of the population ever screened to 65, 70, 75, and 80%. We assumed that CTC would be performed every five years with a colonoscopy referral threshold of a medium-sized lesion (CTCM 5y) and that there would be no switching to CTC screening from other modalities. The changes in the number of colorectal cancer cases and deaths, life-years saved, and costs are presented in Table 10 by screening penetrance. If the availability of CTC increases the screening penetrance from 60 to 70%, the number of colorectal cancer cases and deaths per 1,000 would fall by 5.3 and 2.6 respectively and 11.9 discounted life-years would be saved. Discounted screening costs per 1,000 would increase by $247,600 and cancer-related costs would fall by $159,800, for a net increase in costs of $87,800 per 1,000. Note that the capital expenditures and programmatic costs required to increase screening penetrance are not included.

Table 10. Changes in outcomes and costs if the availability of CTC screening increases screening penetrance from a baseline of 60%

	Changes per 1,000 by Screening Penetrance*			
Outcome	**65%**	**70%**	**75%**	**80%**
Cases	-2.6	-5.3	-7.9	-10.6
Deaths	-1.3	-2.6	-3.9	-5.2
Life-years saved	5.9	11.9	17.8	23.7
Screening costs	$123,800	$247,600	$371,300	$495,100
Cancer costs	-$79,900	-$159,800	-$239,700	-$319,600
Total costs	$43,900	$87,800	$131,600	$175,500

*Assuming no switching to CTC from other screening modalities and that CTC would be performed every five years with a referral threshold of a medium adenoma (i.e., CTCM 5y)

4. SUMMARY

Strong clinical evidence supports the notion that CTC sensitivity and specificity are roughly comparable to those of colonoscopy. We evaluated the effectiveness and cost-effectiveness of CTC screening compared with no screening, compared with colonoscopy, and compared with other recommended colorectal cancer screening modalities using an existing model of the natural history of colorectal cancer. We considered four CTC screening strategies defined by the polyp size threshold triggering referral for colonoscopy for polypectomy (i.e., 6 mm and 10 mm) and the screening interval (i.e., every 5 years and every 10 years). Assuming a CTC cost of $523.40, we found that CTC screening is more costly than no screening, with a C/LYS ranging from $1,500 for CTC screening every ten years with a referral threshold of a medium-sized (CTCM 10y) to $8,700 for CTC screening every five years with a referral threshold of a large lesion (CTCL 5y). Of the four CTC strategies evaluated, only CTC screening every five years with a

referral threshold of a medium-sized (CTCM 5y) is more effective than colonoscopy screening every ten years; the other three strategies are both less effective and more costly than colonoscopy screening every ten years.

The C/LYS of CTCM 5y compared to colonoscopy every ten years is highly sensitive to the procedure cost ratio (i.e., the ratio of the costs of a CTC and of a colonoscopy without polypectomy). In our base-case analysis with the costs of CTC and colonoscopy nearly identical ($523.40 for CTC vs. $522.47 for colonoscopy without polypectomy), the C/LYS vs. colonoscopy is over $600,000. However, if the procedure cost ratios are 0.52, 0.47, and 0.42 then the C/LYS of CTCM 5y vs. colonoscopy are $150,000, $100,000, and $50,000 respectively. Procedure cost ratios of this magnitude may be reasonable, given that the cost ratio at the University of Wisconsin Medical School, where CTC has been covered by several third-party payers since 2004,[39] is 0.36.

We also found that all strategies other than the four CTC strategies were cost-saving compared with no screening. This is due to the high costs associated with cancer treatment (Table 4). These cost estimates were obtained from an analysis of the SEER-Medicare database and were based on data from 1998 to 2003. Since several expensive biologic cancer treatments had not yet been approved for colorectal cancer treatment during this timeframe, the costs used in this model may still underestimate the current costs of cancer treatment. The inclusion of the costs of these newer treatments would result in even greater cost-savings from screening with the other modalities and would lower the C/LYS for the CTC strategies, if not make them cost-saving as well compared with no screening.

Our study has a number of limitations. We did not consider all of the relevant CTC screening options. While there is consensus that individuals with only small lesions detected on CTC do not need to be referred for colonoscopy and that individuals with large lesions detected do need to be referred,[41] there is debate over the appropriate management of medium-sized lesions detected on CTC.[42] Some argue that the risk of invasive disease in such lesions could be high enough to warrant their immediate removal,[43] while others believe that it would be reasonable for an individual with one or two medium-sized lesions detected on CTC to undergo CTC surveillance every one to three years to monitor its growth.[41, 44] However, we could not evaluate the CTC surveillance strategy with the SimCRC model because it does not explicitly simulate hyperplastic polyps. SimCRC can be used to evaluate screening strategies that vary the screening interval based on the number and size category of *adenomas* detected by CTC (an unrealistic strategy since CTC cannot reliably distinguish adenomas from non-adenomatous lesions), but not the number and size of *polyps* detected by CTC. However, the results of our analysis suggest that strategies in which individuals with a lesion 6 mm or larger detected on CTC are referred for colonoscopy (the CTCM strategies) are less costly and save more lives than strategies in which only individuals with larger lesions detected on CTC are referred (CTCL strategies). This finding holds for both the five-year and the ten-year screening interval. Whether CTC surveillance of medium-size adenomas every one-to-three years is a reasonable approach is yet-to-be-determined. Data from the University of Wisconsin Medical School on the outcomes of individuals opting for CTC surveillance of medium-sized polyps are likely to be available in coming years and may help inform whether this is a reasonable strategy.[45]

Another limitation is that the analysis was performed from a payer perspective rather than from the societal perspective; quality of life weights for the health states, patient time costs, and co-payments were not incorporated.[46] It is unclear how our findings would change if we had used a societal perspective. While the disutility associated with a cancer screening test may be substantial, the effect on the number of quality-adjusted life-years and thus the cost-effectiveness ratio may be small due to the relatively short amount of time (days) spent in those health states. The inclusion of quality of life weights for the cancer health states would likely yield lower (i.e., more favorable) values of the cost-effectiveness ratio, since the number of quality-adjusted life-years saved by preventing a cancer should exceed the number of life-years saved. In contrast, the inclusion of patient time costs and co-payments would cause all screening strategies to be more costly (particularly those with more frequent screening intervals) and could potentially result in some strategies that are cost-saving in the current analysis to be more costly than no screening. The net effect of the inclusion of quality of life weights, patient time costs, and co-payments on our findings is unclear.

Finally, we assumed 100% adherence with all screening, follow-up, and surveillance procedures. While in practice adherence is much lower than 100% and varies by type of test, this assumption allowed us to directly compare the screening strategies under ideal conditions with differences solely based on the sensitivity and specificity of the tests.

5. COMPARISON WITH PRIOR ECONOMIC ANALYSES OF CTC

Several studies have evaluated the C/LYS of CTC screening compared with no screening and with colonoscopy screening every ten years. The models differ in terms of their structure, strategies evaluated, and assumptions about test characteristics and costs. Accordingly, direct comparison of the findings is difficult.

Vijan and colleagues[47] evaluated four CTC screening scenarios: 2D CTC screening every five years, 2D every ten years, 3D every five years and 3D every ten years. We focus on the 3D strategies for comparison with our findings. They found that the C/LYS vs. no screening was $8,150 and $13,460 for CTC every ten years and five years respectively. The C/LYS for CTC vs. colonoscopy screening every ten years was $6,600 for CTC every ten years and $156,000 with CTC every five years. They found that compared with no screening, colonoscopy every ten years had a C/LYS of $8,090.

Vijan et al. assumed that individuals with a lesion of any size detected on CTC would be referred for colonoscopy. Referring individuals with only small lesions exposes them to the small risk of mortality from colonoscopy and increases the number of individuals undergoing two screening procedures; the net effect on costs and life-years depends upon how many additional cancers are prevented by the immediate removal of small lesions.

Hassan and colleagues[48] also evaluated CTC (in an Italian population) assuming that individuals with a lesion of any size detected on CTC will be referred for colonoscopy. They found that CTC screening every ten years and colonoscopy every ten years are both cost-saving compared to no screening; they did not evaluate CTC screening every five years. Colonoscopy screening was more costly and more effective than CTC, with a C/LYS (in Euros) of colonoscopy vs. CTC of 15,100.

In a recent paper, Pickhardt and colleagues[49] performed additional analyses with the Hassan model assuming that individuals with only small lesions detected on CTC are not referred for colonoscopy. They recalibrated the model to data on the risk of colorectal cancer in the U.S. and used U.S. cost estimates, thus the results for a given scenario differ from those reported in the original analysis with the Hassan model. They found that CTC every ten years with a 6 mm referral threshold is less costly and more effective than CTC every ten years with no referral threshold; both CTC strategies were less costly and more effective than colonoscopy screening every ten years. The C/LYS compared with no screening was $4,360 with the 6 mm threshold for referral and $7,140 with an any-lesion referral threshold.

Recommendations for Future Research

The American College of Radiology Imaging Network (ACRIN) has recently concluded a large multicenter study to compare the effectiveness of CTC to conventional colonoscopy. The ACRIN trial was projected to enroll more than 2,300 patients at 15 sites nationwide during a 1-year accrual period. Preliminary results were announced on September 28, 2007. This trial has been viewed as potentially definitive by some investigators and commentators in the field. A website report of the preliminary findings is enclosed as an attachment to this report.

Based on the key areas of uncertainty revealed in this appraisal, and an assessment of which future research findings would have the greatest impact on judgments of CTC's comparative clinical effectiveness and value, ICER recommends that studies be pursued to address the following questions:

1) What is the impact on population screening rates of making CT colonography available?
A key uncertainty is whether CTC availability would increase population screening rates or would largely shift screening from colonoscopy or other methods to CTC. Several different study designs could be envisioned to address this question, including cluster randomized trials and before-after analyses of defined populations such as a health plan cohort. Both studies would be better performed in a national health system where all patient screening can be evaluated over a several-year period, but a large and relatively cohesive health plan cohort, such as that within the Kaiser health plan, would provide very useful information.

2) What is the impact on cancer rates of CTC management of medium-sized polyps vs. traditional management with colonoscopy?
Although this is an area of uncertainty, a randomized trial of CTC screening vs. colonoscopy seems impractical. It is unclear whether patients in a large trial would accept randomization, and during the necessary 10-15 year follow-up it is extremely likely that both CTC and colonoscopy will change significantly enough that data will be uninterpretable.

3) What is the impact of extracolonic findings?
It should be feasible to launch studies of patients receiving CTC that will document more precisely the prevalence of extracolonic findings and ascertain their clinical impact and the costs associated with their follow-up. Such studies could potentially be done through passive retrospective claims database evaluation but would be better performed as prospective cohort studies or patient registries.

4) What is natural history of diminutive and medium-sized polyps?
Much of the current clinical consensus regarding the management of polyps 1-9mm is based on limited data of the natural history of these polyps. Some CTC advocates point to 3 fairly old and small colonoscopy studies that left polyps in place as providing evidence that many, if not most diminutive polyps undergo regression. In these studies, some of the polyps were smaller at follow-up, some were unchanged, and some had grown. In one study, some were not seen at follow-up. A large prospective study of patients undergoing either CTC or colonoscopy would help address the important uncertainty in this area. If there is substantial regression of polyps, then polypectomy with colonoscopy may be overzealous and the benefits of CTC might appear more substantial.

COMPARATIVE VALUE REFERENCES

1. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. JAMA 2000;284(15):1954-61.
2. Chapman I. Adenomatous polypi of large intestine: incidence and distribution. Ann Surg 1963;157:223-6.
3. Arminski TC, McLean DW. Incidence and Distribution of Adenomatous Polyps of the Colon and Rectum Based on 1,000 Autopsy Examinations. Dis Colon Rectum 1964;7:249-61.
4. Blatt LJ. Polyps of the colon and rectum: incidence and distribution. Dis Colon Rectum 1961;4:277-82.
5. Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM. Adenomatous lesions of the large bowel: an autopsy survey. Cancer 1979;43(5):1847-57.
6. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut 1982;23(10):835-42.
7. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. Cancer 1982;49(4):819-25.
8. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. Gut 1992;33(11):1508-14.
9. Johannsen LG, Momsen O, Jacobsen NO. Polyps of the large intestine in Aarhus, Denmark. An autopsy study. Scand J Gastroenterol 1989;24(7):799-806.
10. Clark JC, Collan Y, Eide TJ, et al. Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. Int J Cancer 1985;36(2):179-86.
11. Eide TJ, Stalsberg H. Polyps of the large intestine in Northern Norway. Cancer 1978;42(6):2839-48.
12. SEER*Stat Database: Mortality - All COD, Public-Use With State, Total U.S. (1969-2003), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006. Underlying mortality data provided by NCHS (www.cdc.gov/nchs). 2006. (Accessed at www.seer.cancer.gov.)
13. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Empirically calibrated model of hepatitis C virus infection in the United States. Am J Epidemiol 2002;156(8):761-73.
14. Kirkpatrick S, Gelatt CD, Jr., Vecchi MP. Optimization by Simulated Annealing. Science 1983;220(4598):671-80.
15. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2006. CA Cancer J Clin 2006;56(1):11-25.
16. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin 2006;56(3):143-59; quiz 84-5.
17. Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001--testing for early lung cancer detection. CA Cancer J Clin 2001;51(1):38-75; quiz 7-80.

18. 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(2):132-41.
19. Arias E. United States life tables, 2003. Hyattsville, MD: National Center for Health Statistics; 2006.
20. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003;349(23):2191-200.
21. Pickhardt PJ. Incidence of colonic perforation at CT colonography: review of existing data and implications for screening of asymptomatic adults. Radiology 2006;239(2):313-6.
22. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101(2):343-50.
23. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129(2):422-8.
24. Zauber AG, Lansdorp-Vogelaar I, Wilschut J, Knudsen AB, van Ballegooijen M, Kuntz KM. Cost-effectiveness of DNA stool testing to screen for colorectal cancer: Report to AHRQ and CMS from the Cancer Intervention and Suveillance Modeling Network (CISNET) for MISCAN and SimCRC models; 2007.
25. Jentschura D, Raute M, Winter J, Henkel T, Kraus M, Manegold BC. Complications in endoscopy of the lower gastrointestinal tract. Therapy and prognosis. Surg Endosc 1994;8(6):672-6.
26. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004;351(26):2704-14.
27. Greenberg PD, Bertario L, Gnauck R, et al. A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. Am J Gastroenterol 2000;95(5):1331-8.
28. Levi Z, Hazazi R, Rozen P, Vilkin A, Waked A, Niv Y. A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test. Aliment Pharmacol Ther 2006;23(9):1359-64.
29. Rozen P, Knaani J, Samuel Z. Performance characteristics and comparison of two immunochemical and two guaiac fecal occult blood screening tests for colorectal neoplasia. Dig Dis Sci 1997;42(10):2064-71.
30. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007;99(19):1462-70.
31. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996;334(3):155-9.
32. Nakama H, Kamijo N. Accuracy of immunological fecal occult blood testing for colorectal cancer screening. Prev Med 1994;23(3):309-13.
33. Fraser CG, Matthew CM, Mowat NA, Wilson JA, Carey FA, Steele RJ. Immunochemical testing of individuals positive for guaiac faecal occult blood test in a screening programme for colorectal cancer: an observational study. Lancet Oncol 2006;7(2):127-31.
34. Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med 2007;146(4):244-55.

35. Adam IJ, Ali Z, Shorthouse AJ. How accurate is the endoscopist's assessment of visualization of the left colon seen at flexible sigmoidoscopy? Colorectal Disease 2000;2(1):41-4.
36. Doria-Rose VP, Levin TR, Selby JV, Newcomb PA, Richert-Boe KE, Weiss NS. The incidence of colorectal cancer following a negative screening sigmoidoscopy: implications for screening interval. Gastroenterology 2004;127(3):714-22.
37. Brown ML, Riley GF, Potosky AL, Etzioni RD. Obtaining long-term disease specific costs of care: application to Medicare enrollees diagnosed with colorectal cancer. Med Care 1999;37(12):1249-59.
38. Schrag D. The price tag on progress--chemotherapy for colorectal cancer. N Engl J Med 2004;351(4):317-9.
39. Pickhardt PJ, Taylor AJ, Kim DH, Reichelderfer M, Gopal DV, Pfau PR. Screening for colorectal neoplasia with CT colonography: initial experience from the 1st year of coverage by third-party payers. Radiology 2006;241(2):417-25.
40. National Center for Health Statistics (2006). Data File Documentation, National Health Interview Survey, 2005 (machine readable data file and documentation). National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland.
41. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: a consensus proposal. Radiology 2005;236(1):3-9.
42. Schoenfeld P. Small and diminutive polyps: implications for colorectal cancer screening with computed tomography colonography. Clin Gastroenterol Hepatol 2006;4(3):293-5.
43. Butterly LF, Chase MP, Pohl H, Fiarman GS. Prevalence of clinically important histology in small adenomas. Clin Gastroenterol Hepatol 2006;4(3):343-8.
44. Pickhardt PJ. CT colonography (virtual colonoscopy) for primary colorectal screening: challenges facing clinical implementation. Abdom Imaging 2005;30(1):1-4.
45. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med 2007;357(14):1403-12.
46. Gold MR SJ, Russell LB, Weinstein MC, eds. Cost-effectiveness in health and medicine. New York, NY: Oxford University Press; 1996.
47. Vijan S, Hwang I, Inadomi J, et al. The cost-effectiveness of CT colonography in screening for colorectal neoplasia. Am J Gastroenterol 2007;102(2):380-90.
48. Hassan C, Zullo A, Laghi A, et al. Colon cancer prevention in Italy: cost-effectiveness analysis with CT colonography and endoscopy. Dig Liver Dis 2007;39(3):242-50.
49. Pickhardt PJ, Hassan C, Laghi A, Zullo A, Kim DH, Morini S. Cost-effectiveness of colorectal cancer screening with computed tomography colonography: the impact of not reporting diminutive lesions. Cancer 2007;109(11):2213-21.