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COST-EFFECTIVENESS OF CT COLONOGRAPHY TO SCREEN FOR COLORECTAL CANCER

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Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN, SimCRC, and CRS-SPIN Models

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Cost-Effectiveness of CT Colonography to Screen for Colorectal Cancer

Report to AHRQ
from the Cancer Intervention and Surveillance Modeling Network (CISNET)
for MISCAN, SimCRC, and CRC-SPIN Models

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Abbreviations that appear in the report

Abbreviation	Definition
ACER	Average cost-effectiveness ratio
AHRQ	Agency for Healthcare Research and Quality
CISNET	Cancer Intervention and Surveillance Modeling Network
CMS	Centers for Medicare and Medicaid Services
COL	Colonoscopy
CPT	Current procedural terminology
CRC	Colorectal cancer
CRC-SPIN	Microsimulation model of Group Health Cooperative
CTC	Computed tomographic colonography
DoD	Department of Defense
DRG	Diagnosis-related group
FIT	Fecal immunochemical test or immunochemical FOBT (iFOBT)
FOBT	Fecal occult blood test
HII	Hemoccult II®, a guaiac-based FOBT
HS	Hemoccult SENSA®, a guaiac-based FOBT
ICER	Incremental cost-effectiveness ratio
MISCAN	Microsimulation model of Memorial Sloan-Kettering Cancer Center and ErasmusMC
NCD	National coverage determination
NCI	National Cancer Institute
NCTC	National CT Colonography Trial
PFS	Physician fee schedule
SEER	Surveillance, Epidemiology, and End Results
SIG	Flexible sigmoidoscopy without biopsy
SIGB	Flexible sigmoidoscopy with biopsy
SimCRC	Microsimulation model of University of Minnesota and Massachusetts General Hospital
USPSTF	United States Preventive Services Task Force
WC	Hypothetical worst-case scenario for CT colonography

ABSTRACT

Background

Despite recent declines in both incidence and mortality, colorectal cancer (CRC) is the second most common cause of cancer death in the United States. CRC screening has been shown to reduce CRC mortality by 15-33% in randomized controlled trials with Hemoccult II fecal occult blood testing (FOBT). Novel CRC screening technologies, such as computed tomography (CT) colonography have been developed but need to be evaluated in terms of their comparability of performance (sensitivity and specificity) in detecting adenomatous polyps and CRC, acceptability to patients, and test-related complications and costs. Accordingly, we conducted a cost-effectiveness analysis of CT colonography and other currently recommended CRC screening strategies.

Methods

We used three microsimulation models from the National Cancer Institute-funded Cancer Intervention and Surveillance Modeling Network (CISNET) consortium to assess the cost-effectiveness of screening for CRC with CT colonography in comparison to the currently-recommended CRC screening strategies. We conducted incremental cost-effectiveness analyses by comparing the incremental costs and benefits with the next best strategy after eliminating dominated strategies (i.e., strategies that are more costly and less effective than another strategy or a combination of other strategies). We conducted a literature review of the evidence for CT colonography to obtain estimates of its sensitivity and specificity for adenomas by size and for CRC. We used previously developed estimates of the direct medical costs of screening, screening-related complications, and treatment, as well as direct beneficiary costs and time costs associated with screening and treatment to be used in analyses from the modified societal perspective. We assumed a per-test cost of $488 for CT colonography (the national average CMS payment for an abdominal CT, a pelvic CT, and image processing) and assumed that the test would be performed every 5 years with individuals with a lesion 6mm or larger referred for colonoscopy. We performed sensitivity and threshold analyses on the cost, screening interval, size of lesion triggering colonoscopy referral, diagnostic performance, and relative adherence of CT colonography.

Results

Assuming equal adherence across all tests, the screening benefit for 5-yeraly CT colonography, measured in terms of discounted life-years gained compared with no screening, was 2-7 life – years lower than colonoscopy screening every 10 years but comparable to that of 5-yearly flexible sigmoidoscopy plus annual FOBT. At a per test cost of $488 the overall costs for the CT colonography strategy were higher than all of the other screening strategies. CT colonography screening could be cost-effective (i.e., be a non-dominated strategy) at per-test cost of $108 to $205 per scan depending on the simulation model used and the test characteristics of CTC. If the cost per scan were $179 to $237, CT colonography screening would have the same cost per life-year gained as colonoscopy. If screening adherence were higher with CT colonography compared with other screening tests, CT colonography screening could be included among the efficient strategies at the base-case cost estimate.

Conclusions

Based on the analyses from three microsimulation models, screening for CRC with CT colonography every 5 years with referral of individuals with a 6 mm or larger lesion to colonoscopy provides a benefit in terms of life-years gained that is comparable to that of five-year flexible sigmoidoscopy with annual FOBT and slightly lower than colonoscopy screening every 10 years. The cost of CT colonography relative to the benefit derived and to the availability and costs of other CRC screening tests, would need to be in the range of $108 to $205 to be a cost-effective alternative to all other available screening modalities, and in the range of $179 to $237 to be cost-effective compared to colonoscopy screening.

BACKGROUND

Colorectal cancer (CRC) is the second most common cause of cancer-related death in the United States (American Cancer Society 2008). It is estimated that 148,810 CRC cases will be diagnosed in 2008 with 49,960 deaths. The lifetime risk of being diagnosed with CRC is 5.7% for men and 5.2% for women; the lifetime risk of dying from CRC is 2.3% and 2.1% in men and women, respectively (Ries 2007). Approximately 70% of CRCs are diagnosed in persons over the age of 65; more than 90% are diagnosed over the age of 50. Only one-third of cases are detected at an early, more curable stage.

The adenoma-carcinoma sequence is considered to be the primary pathway to CRC. In the 1970s the pathologist Basil Morson conceptualized that the adenoma was the precursor lesion for CRC (Morson 1978). Screening for CRC, and its precursor lesion the adenomatous polyp, can effectively reduce CRC mortality. Randomized trials of CRC screening with a fecal occult blood test (FOBT) show a 15% to 33% reduction in CRC mortality with screening (Mandel 1993, 1999; Kronborg 1996, Hardcastle 1996) and an 18% reduction in CRC incidence (Mandel 2000). Observational studies also show that endoscopic polypectomy can markedly reduce CRC incidence and mortality (Winawer 1993, Selby 1992), and randomized controlled trials of screening with flexible sigmoidoscopy are currently in the field (Atkin 2001, Segnan 2002, Prorok 2000). Despite this demonstrated benefit of CRC screening, participation in CRC screening is only 50% in the US population aged 50 or older (Shapiro 2008).

The US Preventive Services Task Force (USPSTF) (USPSTF 2002, Pignone 2002a, USPSTF 2008), the Gastroenterology Multi-Society Task Force (Winawer 1997, 2003, 2006; Levin 2008), and the American Cancer Society (Smith 2006, Winawer 2006; Levin 2008) advocate screening for CRC for asymptomatic average-risk individuals, starting at age 50. In 2002 the USPSTF had concluded that there was insufficient information to recommend one screening strategy over another and recommended a range of screening options including FOBT, flexible sigmoidoscopy (with or without FOBT), or colonoscopy. However in November 2008 the USPSTF updated their recommendations to include stopping CRC screening at age 75 for those who had had consistent negative screenings (USPSTF 2008). They also recommended screening with a sensitive FOBT (i.e., Hemoccult SENSA or a fecal immunochemical test (FIT)), flexible sigmoidoscopy with a sensitive FOBT, or colonoscopy. Hemoccult II and flexible sigmoidoscopy alone were not recommended. The USPSTF decision was informed by microsimulation modeling from two of the Cancer Intervention and Surveillance Modeling Network (CISNET) models used for this report (Zauber 2008a).

New CRC screening tests, such as FIT, the DNA stool test, and computed tomography (CT) colonography have been introduced. In 2003 the MISCAN-Colon investigators provided a cost-effectiveness analysis of FIT to the Agency for Healthcare Research and Quality (AHRQ) for the Centers for Medicare and Medicaid Services (CMS) to inform the decision regarding whether to cover FIT and, if so, at what reimbursement fee (van Ballegooijen 2003) (http://www.cms.hhs.gov/mcd/viewtechassess.asp?where=index&id=20). In 2007, two CISNET modeling groups (MISCAN and SimCRC) conducted a similar cost-effectiveness analysis to that of FIT to estimate the threshold cost for a DNA stool test relative to currently established screening guidelines in response to a request for national coverage determination (NCD) on the

use of a DNA stool test-version 1.1 (the PreGen-Plus™ test) for CRC screening among average-risk individuals every 5 years (http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=212). In this report three CISNET modeling groups conducted a cost-effectiveness analysis of CT colonography to estimate a threshold cost for CT colonography relative to currently recommended screening strategies in response to a National Coverage Analysis (NCA) on the use of CT colonography for CRC screening among average-risk individuals (http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=220).

CT colonography (also known as "virtual colonoscopy") was first described in 1994 by Vining (1994*)* as a CT for the colon. The key conceptual basis for CT colonography arose when it was recognized that thin-slice contiguous abdominal CT images could be reconstructed in software to simulate visualization of the lumen of the colon and create a 'fly-through' display presenting polyps as prominent irregularities jutting from the colonic wall. It took a dozen years for this approach to reach the current state of technical maturity. Technological improvements have continued to refine this process. Between 2000 and 2002, commercial multi-row detector CT scanners advanced from 4-row detector devices to 8, 16 and 64-row assemblies, enabling high-speed imaging of the total abdomen within a single breath-hold, thus nearly eliminating motion artifacts that had hampered earlier efforts. Hardware and software innovations also made possible multi-planar displays and 3D dynamic simulations. A last critical contribution was the development of bowel prep procedures that optimized polyp visualization using CT colonography (Zauber 2008b).

The USPSTF recently (2008) reviewed the evidence for CT colonography as a screening test in the general population and found insufficient evidence to support recommending CT colonography for general population screening for CRC. The primary concerns were the unknown benefits and harms associated with extracolonic findings and the potential risks of radiation exposure with CT procedures. In contrast, the American Cancer Society, the Gastroenterology Multi-Society Task Force, and the American College of Radiology did include CT colonography for average-risk CRC screening in their guidelines (Levin 2008, McFarland 2008). Furthermore the ACS guidelines recommended that all individuals with lesions 6 mm or larger be referred to optical colonoscopy. The rescreening interval suggested was 5 years.

In 1998 CMS began coverage for CRC screening in the general Medicare population. According to Section 410.37 of the Federal Register, new CRC screening tests may be included for CMS coverage by consideration of a NCD. In May 2008 CMS requested a NCD for CT colonography (http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=220). The Coverage and Analysis Group at CMS requested a cost-effectiveness analysis of CT colonography from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this analysis and associated report to the CRC CISNET modeling groups. These groups will deliver their report to the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) meeting that will convene in November, 2008 to consider the NCD for CT colonography in the average-risk population.

In this report we first summarize the evidence on the sensitivity and specificity of CT colonography in CRC screening. Using the best evidence for the test parameters, we then conduct simulations to determine what the reimbursement cost from CMS to providers would

have to be for CT colonography in order for it to be considered comparable to other CRC screening tests from a cost-effectiveness standpoint. To accomplish this we use microsimulation modeling to project lifetime costs, life-years gained, and cost-effectiveness ratios for various CRC screening strategies (including CT colonography strategies). To add robustness to the results we use three microsimulation models, each developed independently by modelers affiliated with CISNET – a modeling consortium funded by the National Cancer Institute (NCI) that focuses on the use of modeling to improve our understanding of the impact of cancer control interventions (e.g., prevention, screening treatment) on population trends in incidence and mortality. The three simulation models, MISCAN, SimCRC, and CRC-SPIN, incorporate the best-available evidence on the natural history of colorectal disease and the screening test characteristics to project outcomes such as life-years gained compared with no screening. The results of the three models are compared; comparable results strengthen the credibility of the findings. The base-case analysis considers CT colonography every 5 years with referral of an individual with one or more lesions 6mm or larger to optical colonoscopy, using the test characteristics from the Department of Defense study (Pickhardt 2003) and the National CT Colonography Trial (NCTC) (Johnson 2008). We also assess several other scenarios as sensitivity analyses.

LITERATURE REVIEW FOR CT COLONOGRAPHY TEST CHARACTERISTICS

Test characteristics for CT colonography were assessed from studies in which subjects receive both CT colonography and colonoscopy. As CT colonography is a rapidly evolving technology, many of the older studies are generally outdated in assessing test characteristic for CT colonography in use today. Early studies were conducted in polyp-rich cohorts using 2D technology with generally encouraging results (Fenlon 1999, Yee 2001). However, studies using these technologies in lower prevalence polyp cohorts, such as seen in screening, had less promising results (Johnson 2003, Cotton 2004, Rockey 2005). Mulhall (2005) conducted a systematic review and meta-analysis of 33 CT colonography studies in 6393 patients published from January 1975 to February 2005 and analyzed the findings by mode of imaging, collimation, reconstruction, type of scanner, use of contrast material, the gold standard for comparison, and software used. However, most of those studies were of higher-risk patients and therefore not applicable for an average-risk screening population. Whitlock and colleagues (2008) conducted a structured systematic literature review of CT colonography to inform the USPSTF in their assessment of whether to recommend CT colonography screening for the average-risk population. They found that only 4 of the studies in the Mulhall analysis were among average-risk patients. Of these, 3 studies were quite small and used older, less accurate scanning technologies. The fourth study, the Department of Defense (DoD) study (Pickhardt 2003), was included in the Whitlock assessment along with studies by Johnson (2007), Kim (2007) and the newly published study reporting the results of the National CT Colonography Trial (NCTC) (Johnson 2008). We used the Whitlock evidence review (2008) to identify studies for our consideration.

We used the two large scale multi-site CT colonography studies conducted in the US using current technology and procedures as our main comparators: the DoD study by Pickhardt (2003) and the NCTC (Johnson 2008). These studies represent the current most promising assessments of CT colonography compared to optical colonoscopy in clinical practice. We did not combine

the results of these two studies but rather used each study as a separate base-case scenario. We also used a retrospective analysis by Pickhardt (2007a) on his original DoD study and a single institution study by Johnson (2007) to assess primary 2D versus 3D readings. We did not include the study by Kim (2007) in our comparisons due to its small size (n= 96) and the fact that it reported sensitivity and specificity for all polyps rather than for adenomas.

Department of Defense Study (Pickhardt 2003)

This study was intended to be proof-of-principal that CT colonography could have high test performance in CRC screening. The study accrued 1233 asymptomatic subjects from military facilities from May 2002 and June 2003 for a same-day CT colonography and optical colonoscopy. Subjects completed a rigorous bowel preparation including a standard 24-hour oral administration of sodium phosphate and bisacodyl. Subjects also had a clear-liquid diet plus barium for solid-stool tagging and diatrizoate meglumine and diatrizoate sodium for the opacification of luminal fluid. Three-dimensional endoluminal display was used for the initial detection of polyps on CT colonography, with 2 dimensional views used in assessing suspected abnormalities. Room air was used to insufflate the colon. A 4-channnel or 8-channel CT scanner was used. Polyps were measured with electronic calipers on the 3D view. Extracolonic findings were also reported. The CT scans were read by one of six board-certified radiologists prior to the optical colonoscopy, all of whom had read a minimum of 25 CT scans prior to the study. Optical colonoscopy was performed by 17 experienced endoscopists (14 gastroenterologists and 3 colorectal surgeons). Polyps were photographed and measured using a calibrated linear probe. The study protocol used segmental unblinding for the optical colonoscopy. The endoscopist reported the clinical findings by segment and then was told the CT colonography results for that segment. At this point the endoscopist could go back to review the segment to see if any polyps were missed. The polyps detected were recorded for optical colonoscopy before and after the CT colonography results were revealed. All polyps were sent for histological review. A polyp matching algorithm was used to compare CT colonography and optical colonoscopy with matching criteria of polyps being in the same segment or adjacent segments with polyp dimensions within a 50% margin of error.

The test characteristics were given both per patient and per adenoma, with 92% sensitivity of CT colonography for adenomas 10 mm or larger and 86% sensitivity for adenomas 6 mm or larger. Specificity was 96% for patients with adenomas 10 mm or larger and 80% for patients with adenomas 6 mm or larger. Results were not reported for lesions measuring less than 6 mm. Extracolonic findings deemed to be of high clinical importance were found in 4.5% of subjects. More patients reported greater discomfort with CT colonography (54%) than with optical colonoscopy (38%), while 8% reported equivalent discomfort. General level of satisfaction with CT colonography was rated excellent by 41% of respondents; only 6% and 2% rated their level of satisfaction as fair or poor. Subjects were slightly more likely to state that of the two tests they preferred CT colonography (49% vs. 41%); 9% reported having no preference.

National CT Colonography Trial (Johnson 2008)

This study, sponsored by the American College of Radiology Imaging Network (ACRIN) and the NCI, was intended to assess the performance of high-quality CT colonography in general community practice. The study accrued 2600 asymptomatic subjects from 15 study centers from February 2005 to December 2006. Ninety-seven percent (2531) of those accrued completed

same-day CT colonography and optical colonoscopy. Bowel preparation included stool tagging, laxative purgation, and fluid tagging. Glucagon was administered prior to CT acquisition and carbon dioxide was used for colon insufflation. Each participating radiologist had interpreted at least 500 CT scans or had participated in a 1.5 day course. All radiologists chosen to participate had to complete a qualifying examination in which they achieved a detection rate of 90% or more for polyps measuring 10 mm or larger. All CT scans were performed with multi-detector scanners with a minimum of 16 rows. The study data were randomly assigned to be read independently with the use of a primary two-dimensional search method (2D image display with 3D endoluminal problem solving) of a primary 3D search method with the addition of 2D display of multiplanar images. Only lesions of size 5 mm or larger were recorded. Same day colonoscopy was performed or supervised by experienced endoscopists without knowledge of the CT colonography findings. Segmental unblinding was not employed. For cases in which CT colonography had detected a polyp 10 mm or larger that was not detected on optical colonoscopy, the patient was advised to have an additional colonoscopy. All lesions 5 mm or larger were centrally reviewed by one experienced gastrointestinal pathologist. Lesion size was determined from the pathology report, unless piecemeal removal was performed, in which case colonoscopy-derived size estimates were used. An algorithm similar to that used in the DoD study was used to match polyps.

Sensitivity was reported both by patient and by adenoma. The per-adenoma sensitivity of CT colonography for adenomas or CRC 10 mm or larger was 84%, which was slightly less than the estimate from the DoD study (92%). Sensitivity for adenomas 6 mm or larger was 70%. Specificity was 86% for patients with adenomas 10 mm or larger and 88% for patients with adenomas 6 mm or larger. Extracolonic findings were observed in 66% of subjects, but only 16% were considered of clinical importance requiring either additional evaluation or urgent care.

Department of Defense Study Primary 2D versus Primary 3D CT Colonography

The DoD study was performed using primary 3D reading. Earlier studies using 2D reading had not obtained as good test performance as that of the DoD study with 3D readings. Ten radiologists, blinded to polyp findings, conducted a retrospective interpretation of 730 CT scans from the original DoD study using a primary 2D approach (Pickhardt 2007a). The primary 2D results were compared with the primary 3D results from the original trial of 1233. Sensitivity for adenomas 6 mm or larger was 44% with the primary 2D approach, compared with 86% for the primary 3D approach. Sensitivity for adenomas 10mm or larger was 75% versus 92% for primary 2D and primary 3D reads, respectively. With a primary 2D approach, per-patient specificity for 2D at the 10 mm threshold for referral was 98% compared to 97% for the 3D evaluation (NB: these specificity estimates are for all polyps, not for adenomas only).

Johnson 2D versus 3D CT Colonography Study

Johnson (2007) conducted a study of 452 asymptomatic subjects with CT scans interpreted using both a primary 2D and a primary 3D approach. The sensitivity of CT colonography for neoplasms 10 mm or larger using a 1.25mm slice thickness were comparable for primary 2D and primary 3D reads (72% versus 73% respectively). However, the range across three readers was wider for the primary 3D reads (67%-78% for primary 2D reads versus 50-83% for primary 3D reads). Specificity for patients with adenomas 10mm or larger was 97-99% for both reading approaches.

All studies of CT colonography characteristics were for a one-time test. No studies to date evaluate repeat screening with a CT colonography. Therefore, we do not have information on the degree to which false-negative test results are random or systematic.

COST-EFFECTIVENESS ANALYSIS

Overview

We used three existing microsimulation models validated against the best available data (Loeve 1999, 2000, Frazier 2000, Knudsen 2005) to inform CMS and AHRQ in assessing the effectiveness and cost-effectiveness of CT colonography, in comparison with the currently-recommended CRC screening strategies. Although randomized controlled trials are the preferred method for establishing effectiveness of (screening) interventions, they are expensive and require long follow-up. Accordingly, well-validated microsimulation models may be used to estimate the required resources and expected benefits from different screening policies and inform decision making. The validity of the models is based on clinical incidence data before the introduction of screening (1975-1979 SEER data) and the size distribution of adenomas in colonoscopy and autopsy studies (Clark 1985, Blatt 1961, Arminski 1964, Vatn 1982, Jass 1992, Johannsen 1989, Bombi 1988, Williams 1982, Rickert 1979, Chapman 1963, Rutter 2007). The external validity has further been tested on the results of large (randomized) screening and surveillance studies, such as the Minnesota Colon Cancer Control Study (Mandel 1993), the CoCap sigmoidoscopy study (Doria-Rose 2004), and the National Polyp Study (Loeve 2000). The models also use common all-cause mortality estimates from the US life tables and colorectal cancer survival data from SEER (2004). Finally, the models were able to explain observed incidence and mortality trends in the US when accounting for risk factor trends, screening practice and chemotherapy treatment (Vogelaar 2006, Knudsen 2004, 2005). Using three models (i.e., a comparative modeling approach) adds credibility to the modeling results and serves as a sensitivity analysis on the underlying structural assumptions of the models, particularly pertaining to the natural history of colorectal disease. Through the NCI CISNET consortium, standardized profiles of the each model's structure and underlying assumptions are available at http://cisnet.cancer.gov/profiles/.

We used the MISCAN, SimCRC, and CRC-SPIN simulation models to calculate the lifetime costs (discounted and undiscounted) and life expectancy (discounted and undiscounted) for a cohort of 65-year-old individuals residing in the US (i.e., eligible for Medicare benefits) under 14 strategies plus no screening. The 14 CRC screening strategies vary by screening test or combination of tests and screening interval. We conducted an incremental cost-effectiveness analysis from the perspective of CMS and discounted future costs and life years 3% annually (Gold 1996). Strategies that were more costly and less effective were ruled out by simple dominance. Strategies that were more costly and less effective than a combination of other strategies were ruled out by weak dominance. In this report, dominance refers to either simple or weak dominance. The relative performance of the remaining strategies was measured using the incremental cost-effectiveness ratio, defined as the additional cost of a specific strategy, divided by its additional clinical benefit, compared with the next least expensive strategy. All non-dominated (efficient) strategies define the efficient frontier and may be cost-effective depending on the willingness to pay for a life-year gained.

Microsimulation Modeling

The MISCAN, SimCRC, and CRC-SPIN models simulate the life histories of a large population of individuals from birth to death. Each model has a natural history component that tracks the progression of underlying disease in the absence of screening. The models share many characteristics; they use similar model inputs and are calibrated to the same data regarding adenoma prevalence, cancer incidence, and stage distribution. These data were collected and processed as part of CISNET and can be considered the best-available data for informing the simulation models. As each simulated individual ages, there is a chance that an adenomatous polyp – a benign precursor lesion that may lead to CRC – develops. One or more adenomas can occur in any individual and each can develop into preclinical CRC (**Figure 1**). The risk of developing an adenoma depends on age, sex, genetic and other propensity factors. The models track the location in the colon and the size of each adenoma, which influence disease progression and the chance of being found by screening.

Adenomas can grow in size over time. Some adenomas eventually become malignant, transforming to stage I preclinical cancer. A preclinical cancer (i.e., not detected) has a chance of progressing through the stages (from stages I to IV) and may be detected by symptoms at any stage. We assume that adenomas are asymptomatic and can only be detected by a screening test.

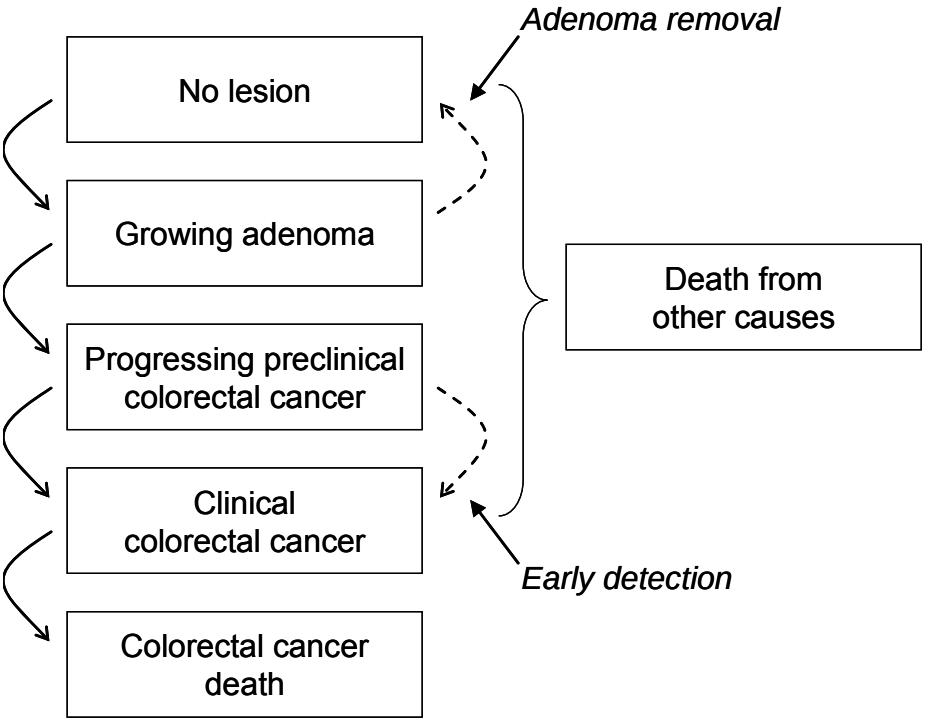


Figure 1. Graphical representation of natural history of colorectal cancer as modeled by MISCAN, SimCRC, and CRC-SPIN models. The opportunity to intervene in the natural history through screening (adenoma detection and removal, and early detection) is noted by the dotted lines.

To project the effectiveness of a screening strategy, the models incorporate a screening component together with the natural history model. The effectiveness of each screening test is modeled through each test's ability to detect lesions (i.e., adenomas, preclinical cancer). Once screening is introduced, a simulated person who has an underlying adenoma or preclinical cancer has a chance of having it detected during a screening year depending on the sensitivity of the test for that lesion. For screened persons without an underlying lesion we apply the false-positive rate (1 – specificity) to determine whether or not that person will undergo an unnecessary follow-up examination. Hyperplastic polyps are not modeled explicitly but are reflected in the specificity of the test. In addition, a percentage of individuals with false-negative test results (i.e., adenoma or preclinical cancer present but not detected) will be referred to colonoscopy because of the detection of a hyperplastic polyp. Flexible sigmoidoscopy can only detect lesions located in the distal colon or rectum, while other tests have the ability to detect lesions in any part of the colorectal tract. Colonoscopy and to a lesser extent, CT colonography, are associated with a small mortality risk due to the risk of perforation during the procedure.

The models include the possibility of multiple adenomas or preclinical cancers. An individual with multiple adenomas, especially multiple adenomas of a larger size, would be more likely on average to be detected by screening than an individual with a single small adenoma. Consequently multiplicity and size of the adenomas, or whether there is a preclinical cancer, are included in estimates of sensitivity and specificity.

Key differences in model structures

Although the models are calibrated to the same data on adenoma prevalence and cancer incidence, the underlying distributions of dwell times (i.e., the total time spent with adenoma and preclinical cancer prior to symptom detection) differ among the three models. A key assumption in the MISCAN model is that there are two types of adenomas: progressive adenomas (adenomas that eventually can become cancer) and non-progressive adenomas (adenomas that cannot become cancer). In the SimCRC and CRC-SPIN models all adenomas have the ability to progress to cancer (although most will not during the lifespan of the individual). An additional difference is that CRC-SPIN models continuous size rather than discrete stages of adenoma size. Although all three models predict similar estimates of adenoma prevalence and CRC incidence, the difference in the adenoma growth assumptions results in different dwell time estimates among the models. In the MISCAN model adenomas and preclinical cancer have been present for 10 years on average before clinical diagnosis, while the estimate is approximately 22 years for SimCRC and 25 years for CRC-SPIN. Little is known about how fast this progression truly occurs. It is estimated that 30% to 50% of the population have one or more adenomas, but it is difficult to measure dwell time in a real population because, by definition, it is the period during which the condition is undiagnosed. As a result of the difference in dwell time, more life-years are gained from screening in the SimCRC and CRC-SPIN models than in the MISCAN model. In the MISCAN model the additional benefit of increasing screening frequency will be greater than that in SimCRC and CRC-SPIN. A summary of each model is in **Appendix 1**.

Another key difference among the models is the distribution of adenomas in the colorectal tract (see **Appendix 2**). In the MISCAN model, adenomas are assumed to have the same distribution as CRCs, while the SimCRC and CRC-SPIN models are calibrated to the distribution of adenomas from autopsy studies. Approximately 30% of CRCs are located in the rectum, while

data from autopsy studies suggest that 8-10% of adenomas are located in the rectum. As a result of this difference, the MISCAN model finds strategies involving sigmoidoscopy to be more effective than the SimCRC and CRC-SPIN models, because a larger proportion of adenomas are within the reach of the sigmoidoscope.

Study Population

We used the natural history models to estimate the distribution of underlying disease for the 65-year-old US population in 2005 in terms of the presence, location, size, and type (adenoma vs. preclinical cancer) of lesions (see **Appendix 2** for comparison of natural history models). We conducted an analysis of the effect of different screening strategies among a 65-year-old cohort of individuals who have never been screened as our base case. However this cohort with no prior screening represents a higher-risk group than a cohort of previously-screened 65-year-old individuals. As a comparison, we conduct a sensitivity analysis for a 50-year-old cohort.

Comparison Screening Strategies (**Table 1**)

In consultation with AHRQ and CMS, we compared CT colonography screening to the basic strategies of screening with FOBT every year, flexible sigmoidoscopy (SIG) every five years, combinations of FOBT and SIG, and colonoscopy every 10 years, which are recommended by the USPSTF (US Preventive Services Task Force 2008); the American Cancer Society (Smith 2006, Levin 2008), and the Multi-Society Task Force (Winawer 1997, 2003, 2006, Levin 2008). No screening was also considered. Although barium enema was included in the older screening recommendations for the USPSTF, it was not included in the newer recommendations and is not considered in this analysis. We evaluated three FOBTs: Hemoccult II (HII), Hemoccult SENSA (HS) and immunochemical FOBT (FIT) and two strategies for SIG (with and without biopsy).

Table 1. Non-CT colonography strategies evaluated in the cost-effectiveness analysis

Strategy	Abbreviation	Interval, test 1 (y)	Interval, test 2 (y)	Biopsy @ SIG?
No screening	--	--	--	--
Hemoccult II	HII	1	--	--
Hemoccult SENSA	HS	1	--	--
Fecal immunochemical test	FIT	1	--	--
Flexible sigmoidoscopy	SIGB	5	--	yes
Flexible sigmoidoscopy	SIG	5	--	no
Hemoccult II, SIG	HII + SIGB	1	5	yes
Hemoccult II, SIG	HII + SIG	1	5	no
Hemoccult SENSA, SIG	HS + SIGB	1	5	yes
Hemoccult SENSA, SIG	HS + SIG	1	5	no
Fecal immunochemical test, SIG	FIT + SIGB	1	5	yes
Fecal immunochemical test, SIG	FIT + SIG	1	5	no
Colonoscopy	COL	10	--	--

-- indicates not applicable

CT Colonography Strategies (**Table 2**)

We compared these screening strategies to CT colonography screening based on the test parameters of the DoD study (Pickhardt 2003) using 3-dimensional imaging as the primary read and the NCTC trial (Johnson 2008) using both 2D and 3D reads. Subjects with lesions 6 mm or larger detected by CT colonography were referred to colonoscopy. Those with no 6 mm or larger polyps detected had a repeat CT colonography in 5 years. The request for the NCD did not specify a repeat screening interval; we used a 5-year to rescreen (Levin 2008). In addition to these two base-case scenarios for CT colonography, we conducted a sensitivity analysis in which we explored CT colonography scenarios using primary 2D reads, referral of individuals with 10 mm or larger lesions for colonoscopy, and a 10-year interval for repeat screening (**Table 2**). We also considered a hypothetical worst-case scenario for CT colonography.

Table 2. CT colonography strategies evaluated in the cost-effectiveness analysis

CT colonography strategy abbreviation	Study	Primary read	Colonoscopy referral threshold (mm)	Screening interval (y)
Strategies evaluated in the base-case analysis				
CTC DoD 3D 6mm 5y	DoD	3D	6	5
CTC NCTC 2D/3D 6mm 5y	NCTC	2D/3D	6	5
Strategies evaluated in sensitivity analyses				
CTC DoD 3D 6mm 10y	DoD	3D	6	10
CTC DoD 3D 10mm 5y	DoD	3D	10	5
CTC DoD 3D 10mm 10y	DoD	3D	10	10
CTC DoD 2D 6mm 5y	DoD	2D	6	5
CTC DoD 2D 6mm 10y	DoD	2D	6	10
CTC DoD 2D 10mm 5y	DoD	2D	10	5
CTC DoD 2D 10mm 10y	DoD	2D	10	10
CTC NCTC 2D/3D 6mm 10y	NCTC	2D/3D	6	10
CTC NCTC 2D/3D 10mm 5y	NCTC	2D/3D	10	5
CTC NCTC 2D/3D 10mm 10y	NCTC	2D/3D	10	10
CTC J 3D 10mm 5y	J	3D	10	5
CTC J 3D 10mm 10y	J	3D	10	10
CTC J 2D 10mm 5y	J	2D	10	5
CTC J 2D 10mm 10y	J	2D	10	10
CTC WC 2D/3D 6mm 5y	WC	2D/3D	6	5
CTC WC 2D/3D 6mm 10y	WC	2D/3D	6	10
CTC WC 2D/3D 10mm 5y	WC	2D/3D	10	5
CTC WC 2D/3D 10mm 10y	WC	2D/3D	10	10

CTC = computed tomography colonography; DoD = Department of Defense study (Pickhardt 2003, 2007a); NCTC = National CT Colonography Trial (Johnson 2008); J = Johnson study (Johnson 2007); WC = hypothetical worst case scenario

For the purposes of this report, we assumed that all individuals begin CRC screening at age 65 (i.e., the age at which Medicare eligibility begins) and end at age 80. Those with adenomas or colorectal cancer detected are assumed to have colonoscopic surveillance according to the Multi-Society guidelines (Winawer 2006, Levin 2008) and continue surveillance with no stopping age.The cohort was followed for their lifetimes to a maximum of age 100. The USPSTF has now recommended a stop age for CRC screening of age 75 (USPSTF 2008; Zauber 2008a) .We used the stopping age of 80 in this report to be consistent with the DNA stool report and because we assume that screening doesn't begin until age 65. We would expect similar ranking of strategies for stop age of 75 as well as 80 given comparable adherence.

Follow-up, surveillance, and adherence
We assumed that any individual with a positive FOBT or a positive CT colonography (defined as the visualization of a lesion of size ≥6 mm) is referred for a follow-up colonoscopy. We evaluated two scenarios for flexible sigmoidoscopy: (1) all detected polyps are biopsied and any person with an adenomatous polyp is referred for a follow-up colonoscopy, and (2) all persons with detected polyps are directly referred for colonoscopy (i.e., no biopsy is performed). For the year in which both FOBT and flexible sigmoidoscopy are due, the FOBT is performed first and if positive, the subject is referred for colonoscopy. Flexible sigmoidoscopy is done only for those with a negative FOBT. If a follow-up colonoscopy is negative, then the subject is assumed to undergo subsequent screening with colonoscopy with a 10-year interval (as long as the repeat colonoscopy is negative) and does not return to the initial screening schedule, as is the recommendation of the US Multi-Society Task Force (Winawer 2006) and ACS (Levin 2008). In other words, once a person has a colonoscopy, the individual remains on a colonoscopy schedule.

If adenomas are detected on colonoscopy then the individual begins surveillance with colonoscopy per the 2006 guidelines from the joint publication of the US Multi-Society Task Force and the American Cancer Society (Winawer 2006; Rex 2006; Levin 2008). Individuals found with one or two adenomas that are both less than 10 mm in size will undergo colonoscopy surveillance every 5-10 years (5 years was used). Individuals with at least one adenoma greater than or equal to 10 mm in size or with 3 or more adenomas will undergo colonoscopy surveillance every 3 years unless the surveillance colonoscopy is normal or only detects one or two adenomas of size <1.0 cm, then the next surveillance colonoscopy would be at 5 years.

For the base-case analysis we assumed that all individuals are 100% adherent with screening, follow-up, and surveillance procedures. In sensitivity analysis we examined less than optimal adherence to determine if differences in adherence affect our results *(see section on sensitivity analyses).*

We specified a stop age of 80 for screening but allowed all individuals with an adenoma detected to continue to have surveillance colonoscopies until a diagnosis of CRC or death from other causes. All simulated individuals were followed until death (or age 100). The life-years gained per scenario were derived relative to no screening.

CRC Screening Test Characteristics

Table 3 contains an overview of test characteristics used in our analyses. For all strategies other than CT colonography, test characteristics were taken from those derived for our previous report on stool DNA screening (Zauber 2007). Test parameters are given by person for the FOBTs and by lesion for CT colonography, colonoscopy, and flexible sigmoidoscopy. We assume that the test performance characteristics for FOBTs and CT colonography are based on assessment of the whole colorectum. For sigmoidoscopy and colonoscopy, the test characteristics apply to the portion of the colorectum reached by the scope. We assumed that 80% of sigmoidoscopy examinations reach the junction of the sigmoid and descending colon and 40% reach the beginning of the splenic flexure. None reach beyond. For colonoscopy, we assumed that an average of 1.05 colonoscopies is performed per subject to obtain a "complete" assessment of the colorectum and that the cecum is reached in 98% of subjects.

The test characteristics for CT colonography (**Table 3**) are based on the literature review described above. As CT technology has changed rapidly, we used the sensitivity and specificity estimates from the two recent large-scale CT colonography screening trials (Pickhardt 2003, 2007a; Johnson 2008) for our base-case estimates. We did not combine the estimates from these two studies because of significant heterogeneity in the estimates for sensitivity for adenomas size 6-9 mm and for specificity. Other estimates were evaluated in sensitivity analyses (see section on sensitivity analyses below).

Table 3. Test characteristics used in base-case analysis

	Sensitivity* by adenoma size or CRC (%)				
Test	≤5 mm	6-9 mm	≥10 mm	CRC	Specificity (%)
Hemoccult II	2.0	5.0	12.0	40.0	98.0
Hemoccult SENSA	7.5	12.4	23.9	70.0	92.5
Fecal immunochemical test	5.0	10.1	22.0	70.0	95.0
Sigmoidoscopy†	75.0	85.0	95.0	95.0	92.0‡
Colonoscopy	75.0	85.0	95.0	95.0	90.0‡
CTC DoD 3D 6mm	--	83.6	92.2	92.2	79.6§
CTC NCTC 2D/3D 6mm	--	57.0	84.0	84.0	88.0§

-- indicates sensitivity is not provided because size is smaller than the colonoscopy referral threshold of 6mm

* Sensitivity is provided per individual for stool-based tests and per lesion for endoscopy and CT tests.

† Test characteristics for sigmoidoscopy apply only to lesions in the distal colon and rectum.

‡ The lack of specificity with sigmoidoscopy and colonoscopy reflects the detection of non-adenomatous lesions. With sigmoidoscopy, the presence of non-adenomatous lesions induces biopsy costs (in the case of sigmoidoscopy with biopsy) or results in referral for diagnostic colonoscopy (in the case of sigmoidoscopy without biopsy). With colonoscopy, non-adenomatous lesions are removed and therefore induce polypectomy and biopsy costs.

§ The lack of specificity with CT colonography reflects the detection of non-adenomatous polyps, artifacts, and adenomas smaller than the colonoscopy referral threshold of 6mm.

We assumed conditional independence for all screening tests. In other words, the sensitivity for detecting an adenoma or cancer depended only on the disease status at the time of the screen and did not depend on the test results from previous screening tests.

Costs

The base-case cost-effectiveness analysis was conducted from the payer (CMS) perspective. We also conducted an analysis from a modified societal perspective by including direct costs borne by beneficiaries as well as estimated patient time costs, but excluding costs due to lost productivity caused by early death or disability. Screening costs were based on information provided by CMS on Medicare payments in 2007 for procedures and tests associated with CRC screening and complications of screening. Net costs of CRC-related care were obtained from an analysis of SEER-Medicare linked data.

The screening test costs are provided in **Table 4**. The costs for FOBT, flexible sigmoidoscopy, colonoscopy, complications of screening, pathology, and of colorectal cancer treatment are those used for the cost-effectiveness analysis of the DNA stool test for CMS (Zauber 2007) https://www.cms.hhs.gov/mcd/viewtechassess.asp?from2=viewtechassess.asp&id=212&. Briefly, screening-related costs were based on the set of current procedural terminology (CPT) codes relevant to CRC screening (see Zauber 2007 for CPT codes used) in conjunction with the points of service for the procedures. For procedures with polypectomy or biopsy, we included the associated pathology costs. We assumed that in 5% of exams, a repeat colonoscopy is necessary in order to adequately visualize the colorectum. Instead of modeling incomplete colonoscopies, we increased the costs of a colonoscopy without polypectomy by 5%. For colonoscopy with polypectomy we added the same absolute difference in cost ($25) based on the assumption that polyps were only removed at one of the two colonoscopies. The cost of sedation was included in the cost of colonoscopy, assuming that it is not administered by an anesthesiologist.

Table 4. Screening tests costs based on CMS reimbursement (2007 US dollars)*

Screening test	CMS cost, $	Modified societal cost,** $
Guaiac Hemoccult (II or SENSA)	4.54	21.54
Fecal immunochemical test	22.22	39.22
Flexible sigmoidoscopy	160.78	270.30
Flexible sigmoidoscopy with biopsy	348.19	497.37
Colonoscopy without polypectomy	497.59	794.94
Colonoscopy with polypectomy or biopsy	648.52	979.28
CT colonography*	488.29	643.64

* Based on CMS reimbursement for CT of the abdomen (CPT 74150), CT of the pelvis (CPT 72192), and image processing on an independent workstation (CPT 76377).

** Modified societal costs include beneficiary costs (co-payments) and time costs in addition to the payer costs.

Given that this report was written in conjunction with the NCD for CT colonography for CRC screening in the Medicare population, there is no national CMS reimbursement rate for a screening CT colonography at this time. Accordingly, we use as a proxy the national average

CMS reimbursement (excluding patient co-pays) for an abdominal CT without contrast (CPT code 74150), a pelvic CT without contrast (CPT code 72192) and image processing on an independent workstation (CPT 76377). We obtained estimates of the 2008 rates for these procedures and converted them to 2007 dollars using a decrease of 3.5% in medical care costs to be compatible with the 2007 cost estimates obtained for other screening tests, complications, and colorectal cancer care. This process yielded a base-case cost for CT colonography of $488.29. Note that this is similar to the average reimbursement (excluding beneficiary co-payments) for a diagnostic CT colonography among carriers in the NY area ($486) (personal communication, Bill Larson, Paul Deutch).

Complications of screening

There are essentially no complications from the stool-based screening tests (Hemoccult II, SENSA, or FIT) from the tests themselves. However patients undergoing colonoscopy and, to a lesser extent, flexible sigmoidoscopy and CT colonography are at risk of experiencing complications from the procedures. Because individuals with a positive sigmoidoscopy, CT colonography or stool-based tests are referred for a follow-up colonoscopy, the complications and the associated costs are relevant and accounted for in all of the screening strategies. We used the risks and associated costs of complications with sigmoidoscopy and colonoscopy that we derived for the stool DNA report (**Table 5**) (Zauber 2007). The costs of complications were based on the relevant DRG codes. For CT colonography we assumed a risk of perforation of 4.56 per 100,000 (Pickhardt 2006a). Although perforations from CT colonography may be less severe than those from colonoscopy we conservatively assumed that 5.19% of those who have a perforation die as a result (Gatto 2003), regardless of which test caused the perforation.

Table 5. Summary of risks of endoscopy and CT colonography complications and costs (2007 US dollars)

Complication	Rate per 1000	CMS cost, $	Modified societal cost, $
With colonoscopy			
Perforation	0.7	12,446	12,712
Serosal burn	0.3	5,208	5,474
Bleed with transfusion	0.4	5,208	5,474
Bleed without transfusion	1.1	320	586
With flexible sigmoidoscopy			
Perforation	0.02	12,446	12,712
With CT colonography			
Perforation	0.0456	12,446	12,712

Costs for colorectal cancer treatment

The costs of CRC treatment were also the same as those used in the DNA stool test report (Zauber 2007). Briefly, these costs were derived from comparison of costs for CRC cases relative to those of matched controls in the SEER-Medicare files for the years 1998-2003 (personal communication, Robin Yabroff, Ph.D. and Martin Brown, Ph.D; Yabroff 2008) and vary by phase of care (**Table 6**).

Table 6. Net payments for CRC care during 1998-2003 (in 2007 US dollars)*

AJCC Stage	Initial Phase	Continuing Phase	Last Year of Life: Died from CRC	Last Year of Life: Died from Other Causes
Direct medical costs				
I	25,487	2,028	45,689	11,257
II	35,173	1,890	45,560	9,846
III	42,885	2,702	48,006	13,026
IV	56,000	8,375	64,428	34,975
Modified societal costs				
I	32,720	2,719	56,640	17,408
II	43,752	2,561	56,417	15,740
III	53,003	3,573	59,481	19,413
IV	68,853	10,743	78,227	44,384

* The initial phase of care is the first 12 months following diagnosis, the last-year–of-life phase is the final 12 months of life, and the continuing phase is all the months between the initial and last-year-of-life phases. Cancer-related costs in the continuing phase of care are an annual estimate.

Follow-up costs of extracolonic findings

We did not include the additional medical costs nor potential benefits to follow up of extracolonic findings detected by CT colonography. Although the prevalence of extracolonic findings has been reported (Levin 2008) as well as costs (Pickhardt 2008a), the long-term benefit of working up the various extracolonic findings is not well documented. The implicit assumption that we are making by not formally incorporating these costs and benefits is that, conditional on a CT colonography examination being done, cost-effective approaches to follow-up care of extracolonic finding are being adopted.

Out-of-pocket and time costs

In a sensitivity analysis we added beneficiary costs (co-payments) and time costs to the payer costs for a modified societal perspective. We label this perspective a "modified societal perspective" because while we include the above costs, we do not incorporate productivity costs.

Beneficiary costs associated with screening tests were based on the CMS co-payment per point of service and type of CPT code. To incorporate patient time costs associated with CRC screening we assumed that the value of patient time was equal to the median US wage rate in 2007 from the Bureau of Labor Statistics, $16.64 per hour. We assumed that endoscopy screening requires preparation and recovery. We assumed that the time associated with a colonoscopy procedure was 8 hours, 4 hours with flexible sigmoidoscopy, and 2 hours with CT colonography. Patient time requirements for stool-based screen tests (e.g., Hemoccult II, Hemoccult SENSA, and FIT) were assumed to be 1 hour. For treatment of complications with colonoscopy, sigmoidoscopy, and CT colonography, we assumed that patient time requirements would be on average 16 hours. Modified societal costs for screening are given in the right-hand side of **Table 4**.

The beneficiary costs for treatment were also derived based on the copayment and time costs. Estimated patient deductibles and coinsurance expenses were added by adjusting Part A and Part B payments with Medicare reimbursement ratios provided by the CMS Office of the Actuary. Estimates of time costs for cancer care were from a recently published analysis of the SEER-Medicare linked data (Yabroff 2007) and updated to 2007 dollars using the Consumer Price Index. The treatment costs that were used as model inputs for the modified societal perspective are shown in the bottom half of **Table 6**.

Analysis

Outcomes

Using the base-case inputs, we used each model to project a number of outcomes for each screening strategy. These outcomes include the number of cancers detected, number of cancer deaths averted, life expectancy (discounted and undiscounted) and the lifetime CMS costs (discounted and undiscounted). Differences in results across models reflect the different underlying natural history models.

Incremental cost-effectiveness analysis

For each model, we ranked the 14 screening strategies (no screening, 12 non-CTC screening strategies, 1 candidate CT colonography strategy) by increasing effectiveness (i.e., discounted number of life-years gained compared with no screening). Strategies that were more costly and less effective than another strategy were ruled out by simple dominance. Strategies that were more costly and less effective than a combination of other strategies were ruled out by extended dominance. Remaining strategies were then rank ordered by increasing costs and effectiveness, and incremental cost-effectiveness ratios (ICERs) were calculated by dividing the incremental discounted cost by the incremental discounted life-years gained, relative to the next least expensive option. These strategies represent the set of efficient options. On a plot of costs vs. life-years gained, a line that connects the efficient strategies is called the efficient frontier, and all dominated strategies (simple or extended) lie below this line. If the CT colonography strategy did not lie on the efficient frontier, we then determined the degree to which each of the following parameters would have to change in order for the CT colonography strategy to reach the frontier: unit cost of the CT scan, or relative adherence with CT colonography compared with other screening tests. Because the two base-case CT colonography scenarios do not represent competing options for CT colonography screening but rather two different estimates for test performance, we repeated this process separately for each CT colonography strategy.

Threshold analyses

For each CT colonography strategy, we calculated the maximum cost of a single CT scan for the strategy to be part of the efficient frontier. There were three possible situations to consider when including a CT colonography strategy as an efficient strategy: (1) the CT colonography strategy was less effective than the least effective strategy on the efficient frontier, (2) the CT colonography strategy was more effective than the most effective strategy on the efficient frontier, and (3) the effectiveness of CT colonography strategy was intermediate to the least effective and most effective strategies on the efficient frontier.

In the first case the threshold cost of a CT scan was calculated such that the total cost for the CT colonography strategy was the same as the next least effective efficient strategy (yielding an ICER of 0 for that non-CTC strategy). In the second case the threshold test cost was calculated such that the ICER for the CT colonography strategy compared with the most effective efficient strategy was equal to $50,000 per life-year gained. In the third case we identified the efficient strategy with lowest life-years gained that would still have more life-years gained than the CT colonography strategy. Subsequently the threshold cost was calculated such that the ICER of the CT colonography strategy was equal to the ICER of that selected strategy.

We also considered three sensitivity analyses for the threshold costs. First, we calculated the cost of a single CT scan that would result in the same discounted lifetime cost as no screening. Second, we determined threshold costs for a CT colonography scan such that the test strategy has the same average cost-effectiveness ratio (ACER) as the non-CT colonography strategy with the highest ACER value. ACERs represent the incremental cost per life-year saved of each strategy relative to no screening. Third, we calculated the per-test cost that would allow a CT colonography strategy to have the same ACER as the colonoscopy ACER.

Sensitivity analyses

We first conducted sensitivity analyses where we evaluated alternative scenarios of CT colonography in terms of test performance according to the primary reading approach (2D, 3D, or both 2D and 3D) and the minimum size polyp detected on CT colonography that will trigger a referral for optical colonoscopy. The test parameters for these sensitivity analyses are given in **Table 7** and are based on data reported in the DoD, NCTC, and Johnson 2007 studies. We also considered a hypothetical worst-case scenario that had slightly lower test characteristics than all other scenarios evaluated.

Table 7. CT colonography test characteristics used in sensitivity analysis

CT colonography scenario	Sensitivity by adenoma size or CRC, %				Specificity* (%)
	≤5 mm	6-9 mm	≥10 mm	CRC	
CTC DoD 3D 10mm	--	--	92.2	92.2	96.0
CTC DoD 2D 6mm	--	31.9	75.0	75.0	93.4
CTC DoD 2D 10mm	--	--	75.0	75.0	98.0
CTC NCTC 2D/3D 10mm	--	--	84.0	84.0	86.0
CTC J 3D 10mm	--	--	73.1	73.1	97.6
CTC J 2D 10mm	--	--	72.0	72.0	98.1
CTC WC 2D/3D 6mm	--	30.0	64.0	64.0	78.0
CTC WC 2D/3D 10mm	--	--	64.0	64.0	84.0

-- indicates sensitivity is not provided because size is smaller than the colonoscopy referral threshold of either 6mm or 10mm; DoD = Department of Defense study (Pickhardt 2003, 2007a); NCTC = National CT Colonography Trial (Johnson 2008); J = Johnson study (Johnson 2007); WC = hypothetical worst-case scenario

* The lack of specificity with CT colonography reflects the detection of non-adenomatous polyps, artifacts, and adenomas smaller than the colonoscopy referral threshold.

We also conducted sensitivity analyses where we varied relative adherence of CT colonography relative to the other CRC screening strategies. Some have suggested that CT colonography might entice a previously unscreened individual to undergo screening because it is non-invasive (Levin 2008). Our base-case analysis assumes that 100% of participants adhere to recommendations for the screening tests. To test the impact of differential adherence rates on the threshold CT colonography test cost, we conducted a sensitivity analysis on adherence. We first started with a more realistic 50% adherence rate for all tests (Shapiro 2008). We assumed that 50% of the population would be 100% adherent with a screening strategy and the other 50% would be non-adherent. The impact of modeling adherence in this fashion is that it does not alter the ICERs and it allows us to evaluate the impact of enhancing screening with CT colonography in a previously unscreened segment of the population. We then allowed the overall adherence with the CT colonography strategy to increase from 50% to 55% and 62.5% (a 10% and 25% increase respectively), and identified the corresponding CT colonography threshold costs per scan.

RESULTS

Projected Undiscounted Outcomes with Screening

Undiscounted outcomes associated with the screening strategies are presented in **Table 8A** for the MISCAN model, **Table 8B** for the SimCRC model, and **Table 8C** for the CRC-SPIN model. Without screening we project that 53 to 60 out of every 1000 65-year old individuals will be diagnosed with CRC in their lifetimes. This induces approximately $3.0 to $4.0 million in lifetime direct medical costs ($57 to $71 thousand per CRC case). With screening and removal of adenomas that may have become cancer over time, many of these CRC cases can be prevented assuming 100% adherence to screening regiments; the reduction in the lifetime risk of CRC ranged from 32-49% with annual FOBT (Hemoccult II) screening to 53-85% with 10-year colonoscopy screening (reported ranges reflect differences in projections by model). Some of the benefit associated with the fecal-related tests is a result of the false-positive rate, which leads to individuals being placed on a colonoscopy schedule. In other words, some of the benefit of these tests can be attributed to the fact that a substantial number of individuals with false-positive test results subsequently undergo screening with 10-year colonoscopy. In the MISCAN model the combination of 5-yearly flexible sigmoidoscopy with an annual highly sensitive FOBT (Hemoccult SENSA or FIT) are the two most effective strategies in terms of life-years gained compared with no screening, saving 154 life-years per 1000 persons screened. In the SimCRC and CRC-SPIN models, 10-yearly colonoscopy is most effective, saving 171 and 185 life-years per 1000 persons screened, respectively. Five-yearly CT colonography with a 6mm referral threshold and the most optimistic test characteristics (i.e., DoD study) resulted in 2-7 fewer life-years gained per 1000 individuals compared with 10-yearly colonoscopy, with an increase in lifetime (undiscounted) costs of approximately $600,000-$700,000 per 1000.

Cost-Effectiveness Analysis from Payer Perspective

Table 9 shows the total discounted costs, discounted life-years gained, and the incremental cost-effectiveness ratios for a cohort of 65-year-olds by screening strategy, including no screening, for each model (results for a cohort of 50-year-olds are presented in **Appendix 4**). Note that the incremental cost-effectiveness ratios were calculated using each CT colonography strategy in turn as they are not competing options. The models varied somewhat as to which tests were on the efficient frontier (i.e., were not ruled out by simple or extended dominance). Strategies on the efficient frontier are those strategies with an associated incremental cost-effectiveness ratio and are potentially cost-effective depending on the societal willingness to pay for a life-year gained. All three models showed the CT colonography strategies to be the most costly options. **Figure 2** shows the plots of the discounted life-years gained (compared with no screening), the discounted lifetime direct medical costs (from the Medicare perspective), and the cost-efficient frontier, where each non-dominated strategy is compared with the next least expensive strategy. Hemoccult II was cost-saving compared with no screening for all models. This was the only cost-saving strategy in the MISCAN model. For SimCRC and CRC-SPIN, however, all non-CT colonography strategies were cost-saving compared with no screening. That CT colonography strategies were the most costly can be easily seen from Figure 2 since for all three modes the CT colonography strategies lie to the far right of all screening strategies.

Threshold Analyses

At a cost per test of $488, none of the CT colonography strategies were on the efficient frontier (Figure 2). **Table 10** shows the threshold CT colonography costs under the two base-case scenarios. Threshold analyses indicated that in order for the base-case 5-yearly CT colonography strategies with a 6mm referral threshold to be on the efficient frontier, a CT scan would need to cost between $108 and $205 (depending on the test characteristics and the simulation model used). The range of threshold costs required for CT colonography screening to be on the efficient frontier was wider when considering 10-yearly CTC strategies with a 6mm threshold, ranging from $103 to $371. **Table 10** also presents threshold costs for CT colonography to reach the efficient frontier under different scenarios of the test characteristics for CT colonography (worst-case assumption and 2D reading from the DoD study). The threshold costs were much lower than the base-case values, while the 2D DoD analysis was more consistent with the base-case analysis, although the range was wider.

Table 10 also reports the secondary analyses where different criteria were used to calculate the CT scan cost thresholds. Note, that the primary analysis represents the theoretically correct analysis. The threshold costs tended to be slightly higher when compared with no screening and when compared with the strategy with the highest ACER. In order for the base-case CT colonography strategies (i.e., 5-yearly screening with a 6mm referral threshold) to have the same ACER compared with no screening as the colonoscopy strategy, a CT scan would have to cost between $179 and $237 (depending upon the CT colonography test characteristics and the model used). In only one case the threshold cost was greater than the base-case unit cost estimate of $488; this was the threshold cost that made 10-yearly CT colonography screening with a 6mm referral threshold cost-neutral compared with no screening and was true for only one model (**Table 10**). **Figures 3-6** illustrate threshold cost values graphically.

Sensitivity Analyses

The threshold costs associated with varying the test characteristics for CT colonography strategies with a 10 mm colonoscopy referral threshold are shown in **Table 11**. Threshold analyses indicated that in order for 5-yearly CT colonography with a 10mm referral threshold to be on the efficient frontier, a CT scan would need to cost in the range of $98 to $192 for primary 3D reads, $49 to $135 for mixed 2D and 3D reads, and $73 to $160 for primary 2D reads (depending on the test characteristics and the simulation model used). The ranges of threshold costs were wider when considering 10-yearly CT colonography strategies with a 10mm threshold, ranging from $71 to $238 for primary 3D reads, $3 to $167 for mixed 2D and 3D reads, and $72 to $175 for primary 2D reads. Using the secondary criteria to determine thresholds, the threshold costs tended to be slightly higher than the primary analysis (i.e., on the efficient frontier). In no case was the threshold cost greater than the base-case unit cost estimate of $488.

If individuals who would not be screened otherwise would get screened with CT colonography, its cost-effectiveness would improve. The threshold costs for the test to lie on the efficient frontier under varying adherence assumptions are shown in **Table 12**. With a 10% improvement in CT colonography screening adherence compared with other tests (i.e., 55% overall adherence), the CT colonography cost threshold for being on the efficient frontier increased to $293-$408. With a 25% improvement in CT colonography screening adherence compared with

other tests (i.e., 62.5% overall adherence), the CT colonography cost threshold for being on the efficient frontier increased to $547-$694.

Table 13 contains the results of the threshold analysis from a modified societal perspective. From this perspective the threshold costs that result in a CT colonography strategy reaching the efficient frontier are $154-$336 for the 5-yearly testing with a 6 mm referral threshold and $166-$480 for 10-yearly testing with a 6 mm referral threshold. These thresholds costs are a bit higher than those from the payer perspective. The higher frequency of Hemoccult II and Hemoccult SENSA scenarios results in considerably higher additional time costs than with CT screening, allowing for higher per-test costs for the CT scan. The total threshold costs include co-payments and patient time costs. To obtain CMS reimbursement rates co-payments and patient time costs should be subtracted from the total threshold costs. Assuming no co-payments and patient time costs of $17 per hour yields CMS reimbursement rates of $26-$181 for 5-yearly CT colonography screening with a 6mm referral threshold and $11-$325 for 10-yearly CTC screening.

All analyses were conducted for the Medicare population aged 65 years and older assuming no prior CRC screening among this group. To assess the effect of this assumption, we evaluated the cost-effectiveness of the 15 screening strategies for a cohort of 50-year-olds, with screening starting at age 50. Results are presented in **Appendix 4.** The CT colonography strategies remained the most costly of the screening strategies considered. Threshold analyses indicated that in order for 5-yearly CT colonography with a 6mm referral threshold to be on the efficient frontier, a CT scan would need to cost between $72 and $179 (depending on the test characteristics and the simulation model used), which was lower than we found in the analysis of 65-year-old individuals. The range of threshold costs was wider when considering 10-yearly CT colonography strategies with a 6mm threshold, ranging from $15 to $220, which is also lower than the Medicare payer analysis.

Table 8A. Undiscounted costs by type, number of life-years gained, and number of cases of CRC per 1000 65-year-olds, by screening scenario – MISCAN

	Costs ($)							Outcomes		
Scenario	Screening	Follow-Up	Polyp Resection	Surveillance	Complications	CRC Treatment	Total Costs	LYG	SymDx CRC	ScnDx CRC
No screening	0	0	0	0	0	4,030,647	4,030,647	0	57	0
HII	45,577	207,470	86,984	418,620	15,647	2,927,696	3,701,995	116.5	18	21
HS	31,762	370,237	125,488	693,037	26,573	2,501,443	3,748,541	142.8	12	20
FIT	178,116	318,912	116,129	614,068	23,317	2,573,214	3,823,757	141.0	12	21
SIGB	516,641	193,530	115,568	545,450	19,110	2,415,702	3,806,002	132.2	16	14
SIG	378,703	268,592	124,815	633,967	23,143	2,371,694	3,800,914	135.4	15	15
HII + SIGB	471,033	279,361	130,886	665,461	24,154	2,098,139	3,669,035	149.1	11	17
HII + SIG	355,281	333,025	136,711	730,181	26,790	2,275,248	3,857,236	149.9	11	17
HS + SIGB	344,285	398,694	145,073	819,404	30,834	2,016,539	3,754,829	154.1	10	17
HS + SIG	262,997	422,676	147,776	854,913	32,091	2,208,379	3,928,832	154.1	10	17
FIT + SIGB	507,549	356,996	140,678	765,688	28,504	2,229,174	4,028,589	154.3	10	18
FIT + SIG	402,045	391,252	144,355	811,232	30,469	2,219,036	3,998,390	154.3	10	18
COL	776,369	0	152,502	677,187	36,327	2,198,866	3,841,252	151.6	12	15
CTC DoD 3D 6mm 5y	1,007,280	354,666	135,665	748,110	27,561	2,264,920	4,538,212	149.5	11	17
CTC NCTC 2D/3D 6mm 5y	1,129,911	290,386	123,520	644,144	23,369	2,375,757	4,587,088	142.7	13	17

LYG = life-years gained compared with no screening; SymDx CRC = symptom-detected colorectal cancer; ScnDx CRC = screen-detected colorectal cancer

Table 8B. Undiscounted costs by type, number of life-years gained, and number of cases of CRC per 1000 65-year-olds, by screening scenario – SimCRC

	Costs ($)							Outcomes		
Scenario	Screening	Follow-Up	Polyp Resection	Surveillance	Complications	CRC Treatment	Total Costs	LYG	SymDx CRC	ScnDx CRC
No screening	0	0	0	0	0	3,540,411	3,540,411	0	60	0
HII	74,558	189,224	63,882	251,236	11,119	2,213,526	2,803,544	113.9	14	21
HS	121,839	359,983	100,870	409,826	20,408	1,636,905	2,649,832	150.7	8	18
FIT	248,015	305,726	91,444	371,278	17,606	1,711,732	2,745,801	148.3	8	19
SIGB	458,414	129,774	153,495	302,136	11,130	1,795,444	2,850,392	120.6	19	10
SIG	452,330	218,999	82,962	355,829	15,267	1,684,643	2,810,029	128.0	16	10
HII + SIGB	522,284	251,218	168,972	239,952	13,014	1,446,187	2,641,626	157.7	7	15
HII + SIG	529,760	331,172	89,836	255,648	15,279	1,395,290	2,616,985	160.1	7	15
HS + SIGB	437,692	388,531	171,293	417,676	21,751	1,255,331	2,692,275	169.3	6	14
HS + SIG	444,054	442,437	114,584	431,707	23,361	1,231,886	2,688,030	170.2	5	13
FIT + SIGB	628,080	342,482	171,280	366,098	18,916	1,278,827	2,805,683	168.9	6	14
FIT + SIG	638,476	405,523	107,594	379,303	20,723	1,251,488	2,803,107	169.9	5	14
COL	783,430	0	137,876	598,884	32,857	1,124,529	2,677,576	171.3	6	11
CTC DoD 3D 6mm 5y	1,115,618	348,524	114,329	500,485	23,565	1,172,674	3,275,196	168.2	6	12
CTC NCTC 2D/3D 6mm 5y	1,213,047	280,882	101,516	441,470	19,842	1,288,954	3,345,711	160.2	7	12

LYG = life-years gained compared with no screening; SymDx CRC = symptom-detected colorectal cancer; ScnDx CRC = screen-detected colorectal cancer

Table 8C. Undiscounted costs by type, number of life-years gained, and number of cases of CRC per 1000 65-year-olds, by screening scenario – CRC-SPIN

	Costs ($)							Outcomes		
Scenario	Screening	Follow-Up	Polyp Resection	Surveillance	Complications	CRC Treatment	Total Costs	LYG	SymDx CRC	ScnDx CRC
No screening	0	0	0	0	0	2,999,824	2,999,824	0	53	0
HII	80,263	169,980	50,324	200,706	10,036	1,663,309	2,174,619	114.5	17	12
HS	135,166	353,732	83,847	337,414	19,782	1,057,232	1,987,173	155.1	7	11
FIT	267,328	293,055	74,803	302,324	16,660	1,160,290	2,114,460	150.4	8	11
SIGB	478,290	110,463	209,824	269,120	10,365	1,211,533	2,289,595	133.7	17	4
SIG	474,358	206,889	72,375	311,882	14,770	1,079,869	2,160,144	142.2	14	5
HII + SIGB	479,837	221,064	204,285	347,052	15,715	877,095	2,145,048	163.7	7	7
HII + SIG	476,977	289,511	86,877	373,491	18,922	813,753	2,059,531	166.7	7	7
HS + SIGB	420,636	374,095	189,459	415,934	22,787	692,561	2,115,471	175.9	5	7
HS + SIG	425,961	404,518	100,708	426,792	24,437	666,213	2,048,629	176.8	4	7
FIT + SIGB	581,132	320,807	194,795	394,441	20,268	729,944	2,241,386	174.4	5	7
FIT + SIG	567,998	364,345	96,403	411,602	22,497	694,657	2,157,501	175.8	5	7
COL	822,584	0	118,456	506,142	33,208	496,246	1,976,636	184.9	3	5
CTC DoD 3D 6mm 5y	1,202,218	329,204	92,468	398,610	21,994	610,307	2,654,802	177.7	5	5
CTC NCTC 2D/3D 6mm 5y	1,287,352	258,000	83,325	363,894	18,549	686,995	2,698,114	172.2	6	5

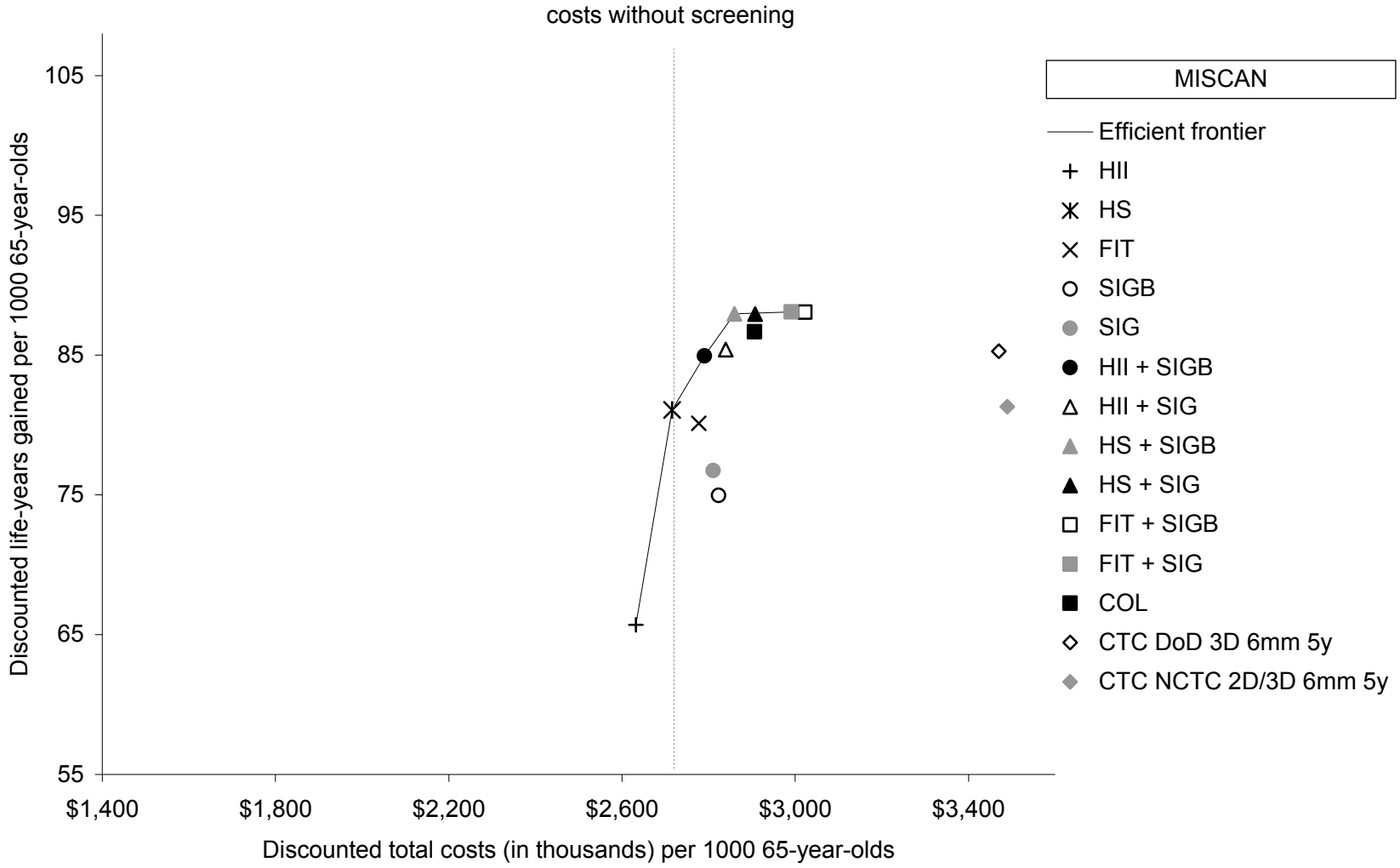
LYG = life-years gained compared with no screening; SymDx CRC = symptom-detected colorectal cancer; ScnDx CRC = screen-detected colorectal cancer

Table 9. Discounted costs and life-years gained per 1000 65-year-olds without CRC screening and with 14 CRC screening strategies and associated incremental cost-effectiveness ratios

Strategy	MISCAN			SimCRC			CRC-SPIN		
	Discounted Costs ($)	Discounted LYG	ICER ($)	Discounted Costs ($)	Discounted LYG	ICER ($)	Discounted Costs ($)	Discounted LYG	ICER ($)
No Screening	2,714,556	0	d	2,367,514	0	d	1,976,803	0	d
HII	2,631,879	65.7	---	2,082,788	59.9	d	1,536,474	64.0	d
HS	2,715,683	81.1	5,455	2,042,708	81.1	---	1,482,449	87.3	---
FIT	2,777,228	80.1	d	2,116,618	79.8	d	1,574,679	84.7	d
SIGB	2,823,217	75.0	d	2,168,782	65.2	d	1,716,321	75.8	d
SIG	2,810,249	76.7	d	2,151,925	69.1	d	1,626,360	80.4	d
HII + SIGB	2,790,651	84.9	19,381	2,085,889	85.7	d	1,656,317	92.9	d
HII + SIG	2,839,118	85.4	d	2,072,929	87.0	5,147	1,590,434	94.5	d
HS + SIGB	2,859,815	88.0	22,940	2,151,806	92.5	d	1,666,766	99.9	d
HS + SIG	2,907,440	87.9	d	2,150,786	93.0	12,938	1,611,331	100.5	d
FIT + SIGB	3,022,139	88.1	d	2,244,313	92.3	d	1,768,508	99.2	d
FIT + SIG	2,990,860	88.1	988,660	2,244,650	92.8	d	1,699,373	99.9	d
COL	2,906,228	86.7	d	2,173,712	93.8	27,737	1,600,155	105.5	6,465
CTC DoD 3D 6mm 5y*	3,469,661	85.3	d	2,674,721	92.0	d	2,156,740	101.2	d
CTC NCTC 2D/3D 6mm 5y*	3,489,238	81.3	d	2,706,113	87.2	d	2,172,677	98.0	d

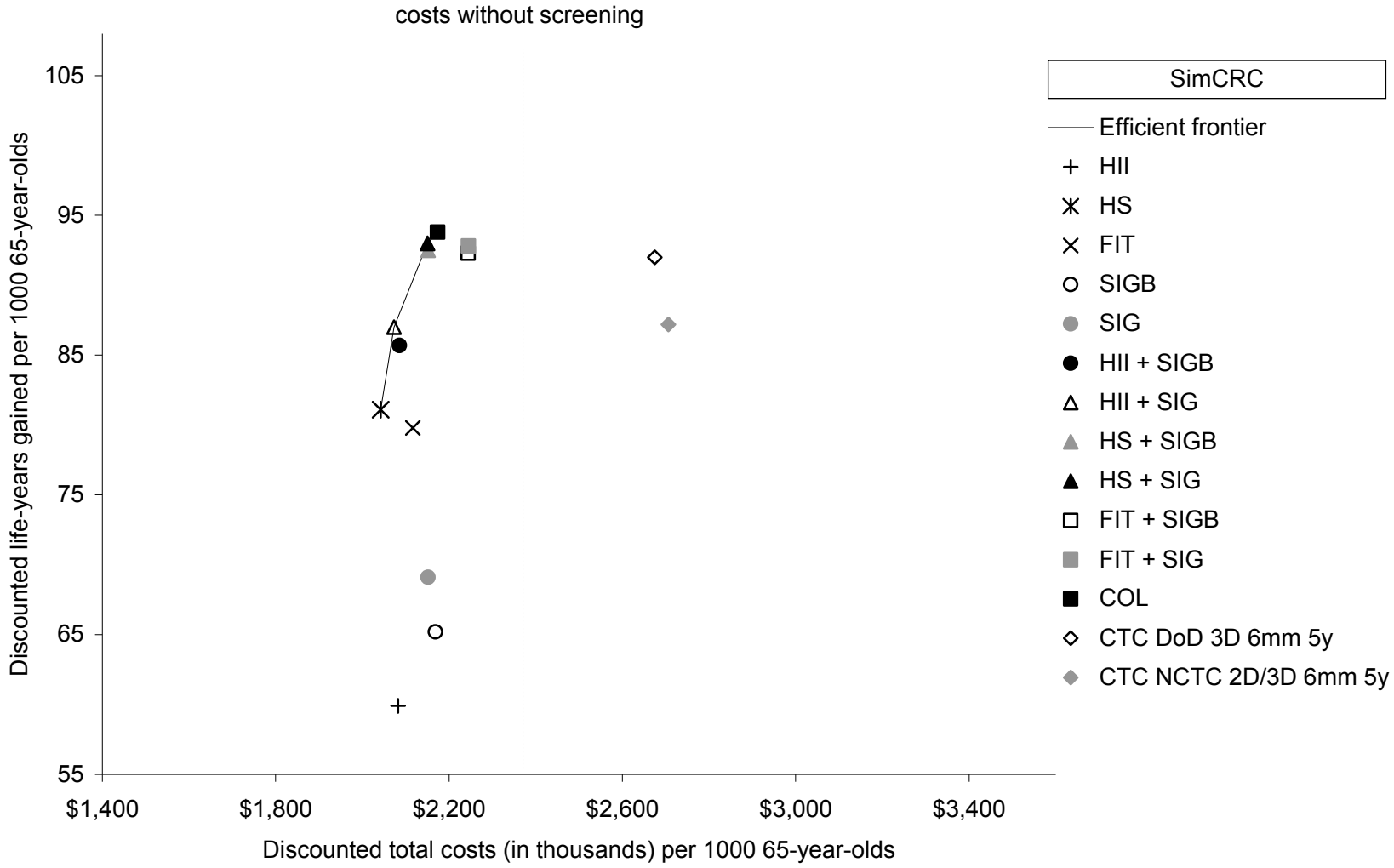
--- indicates default strategy (i.e., the least costly and least effective non-dominated strategy)
LYG = life-years gained vs. no screening; ICER = incremental cost-effectiveness ratio; d = dominated
* The two CTC strategies are not competing options; they represent a range of estimates of CTC test characteristics. They are shown here together for comparison purposes only. The ICERs are assessed separately using each CTC strategy in turn.

Figure 2, Panel A. Discounted costs and discounted life-years gained per 1000 65-year-olds for 14 CRC screening strategies* and the efficient frontier connecting the efficient strategies – MISCAN



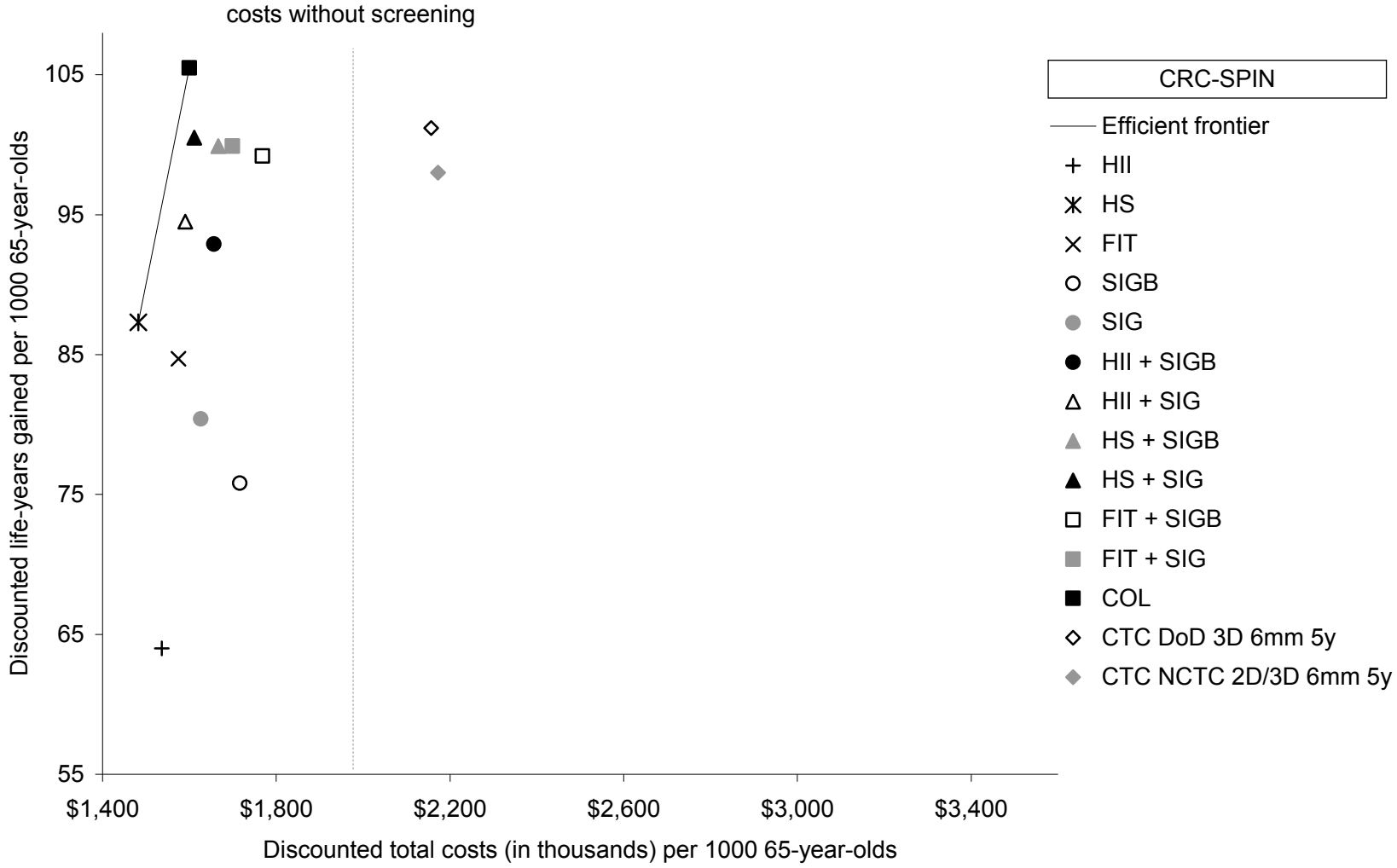
* The two CTC strategies are not competing options; they represent a range of estimates of CTC test characteristics. They are shown here together for comparison purposes only. The ICERs are assessed separately using each CTC strategy in turn.

Figure 2, Panel B. Discounted costs and discounted life-years gained per 1000 65-year-olds for 14 CRC screening strategies* and the efficient frontier connecting the efficient strategies – SimCRC



* The two CTC strategies are not competing options; they represent a range of estimates of CTC test characteristics. They are shown here together for comparison purposes only. The ICERs are assessed separately using each CTC strategy in turn.

Figure 2, Panel C. Discounted costs and discounted life-years gained per 1000 65-year-olds for 14 CRC screening strategies* and the efficient frontier connecting the efficient strategies – CRC-SPIN



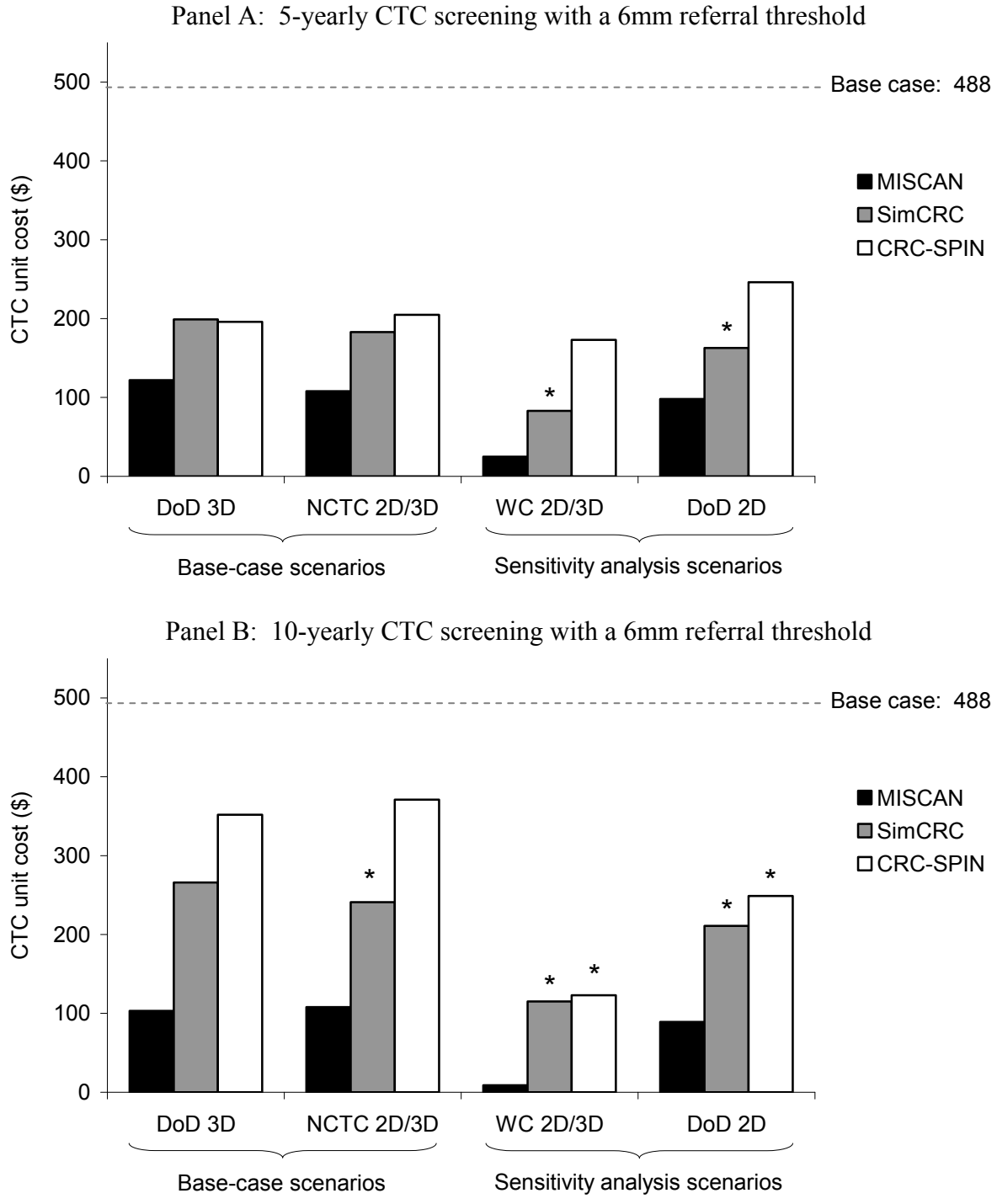
* The two CTC strategies are not competing options; they represent a range of estimates of CTC test characteristics. They are shown here together for comparison purposes only. The ICERs are assessed separately using each CTC strategy in turn.

Table 10. Threshold analysis on CT colonography test characteristics for scenarios with a 6mm colonoscopy referral threshold: unit cost of CT colonography screening test resulting in equal outcomes compared to other recommended CRC screening strategies for different estimates of CT colonography test characteristics*

CTC outcome	Base cases		Sensitivity analysis †	
	CTC DoD 3D 6mm	CTC NCTC 2D/3D 6mm	CTC WC 2D/3D 6mm	CTC DoD 2D 6mm
	5-yearly CTC screening			
On efficient frontier	122, **196**, *199*	108, *183*, **205**	25, *83*‡, **173**	98, *163*‡, **246**
Cost-neutral vs. no screening	76, *323*, **398**	105, *324*, **398**	38, *251*, **336**	112, *308*, **393**
Equal to highest ACER	238, *258*, **294**	245, *268*, **304**	179, *197*, **233**	232, *261*, **303**
Equal to colonoscopy ACER	179, **210**, *221*	194, **227**, *237*	127, **150**, *167*	188, **231**, *235*
	10-yearly CTC screening			
On efficient frontier	103, *266*, **352**	108, *241*‡, **371**	9, *115*‡, **123**‡	89, *211*‡, **249**‡
Cost-neutral vs. no screening	114, *482*, **599**	143, *473*, **599**	68, *351*, **472**	147, *435*, **582**
Equal to highest ACER	320, *396*, **450**	325, *398*, **455**	237, *285*, **325**	303, *372*, **442**
Equal to colonoscopy ACER	244, **330**, *348*	258, **339**, *356*	175, **206**, *248*	246, **328**, *337*

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)
* MISCAN values in plain text; SimCRC values in italics; CRC-SPIN values in bold
† See Table 7 for the test characteristics used in these scenarios
‡ CTC strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount

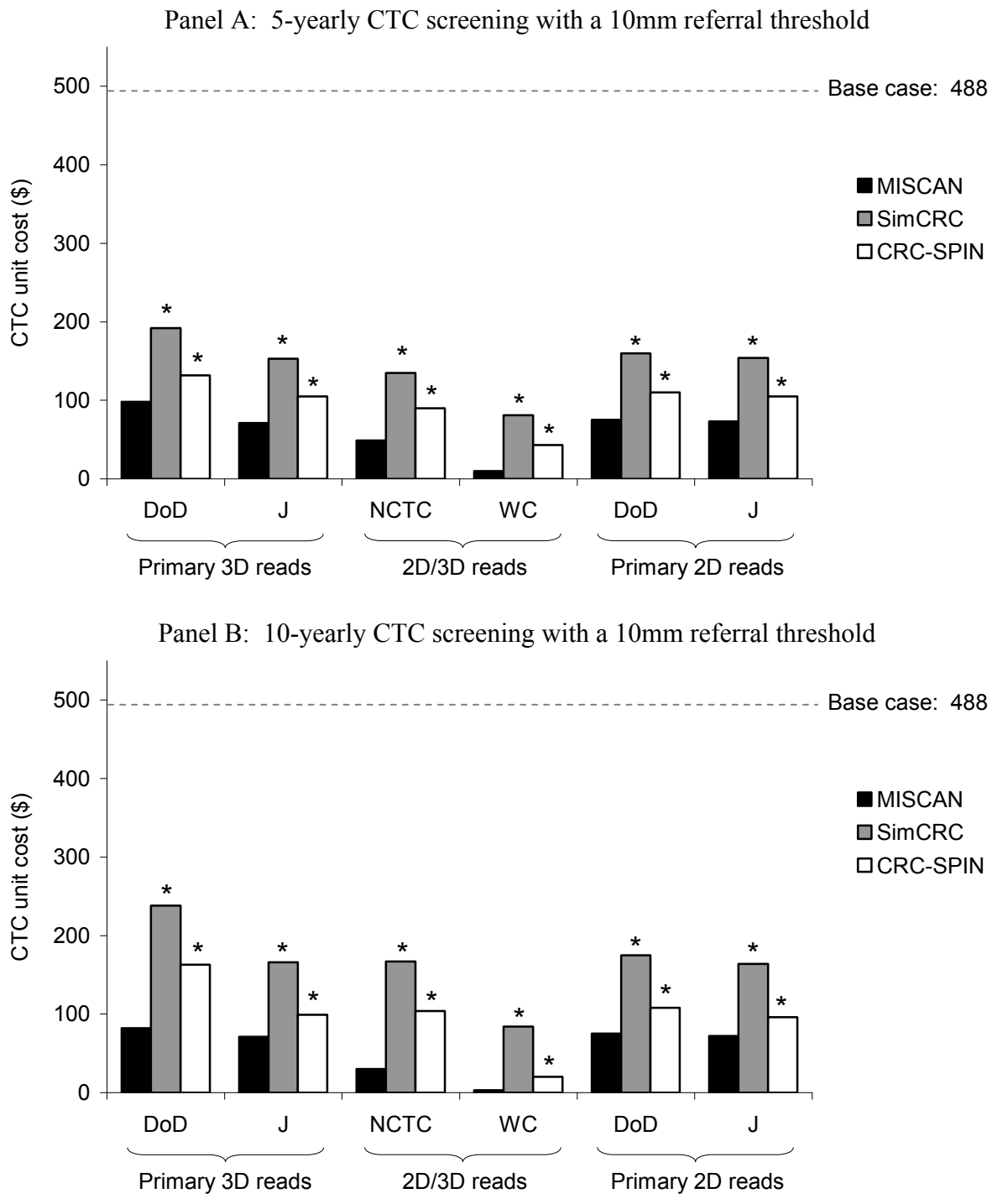
Figure 3. CT colonography unit cost thresholds (in 2007 US dollars) at which CT colonography strategies with a 6mm colonoscopy referral threshold are efficient screening options compared to other recommended CRC screening strategies



DoD = Department of Defense Study (Pickhardt 2003, 2007a); NCTC = National CT Colonography study (Johnson 2008); WC = hypothetical worst-case scenario

* CTC strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount

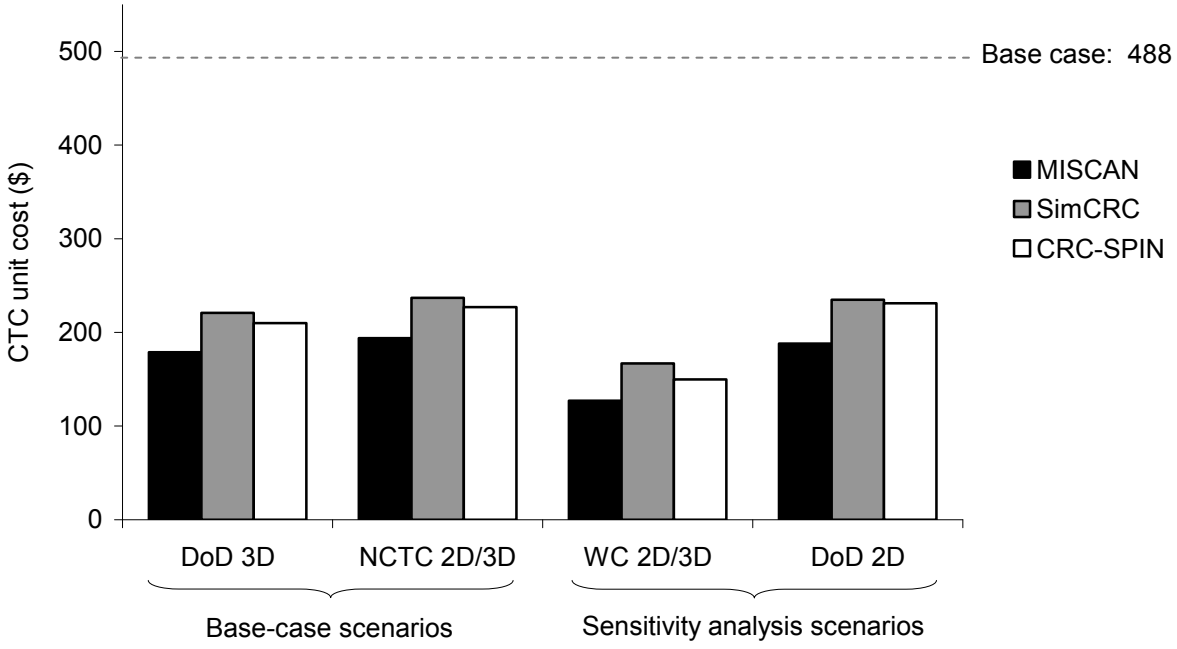
Figure 4. CT colonography unit cost thresholds (in 2007 US dollars) at which CT colonography strategies with a 10mm colonoscopy referral threshold are efficient screening options compared to other recommended CRC screening strategies



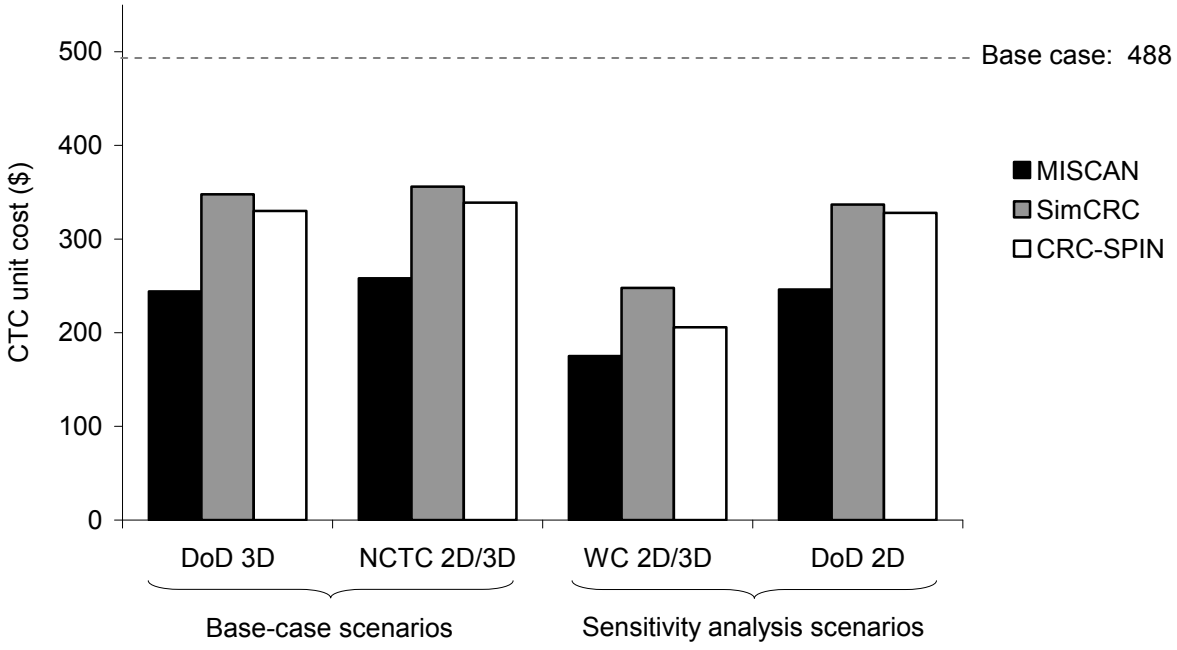
DoD = Department of Defense Study (Pickhardt 2003, 2007a); J = Johnson study (Johnson 2007); NCTC = National CT Colonography study (Johnson 2008); WC = hypothetical worst-case scenario
* CTC strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount

Figure 5. CT colonography unit cost thresholds (in 2007 US dollars) at which CT colonography strategies with a 6mm colonoscopy referral threshold have an average cost effectiveness ratio (ACER) equal to that of colonoscopy screening

Panel A: 5-yearly CTC screening with a 6mm referral threshold



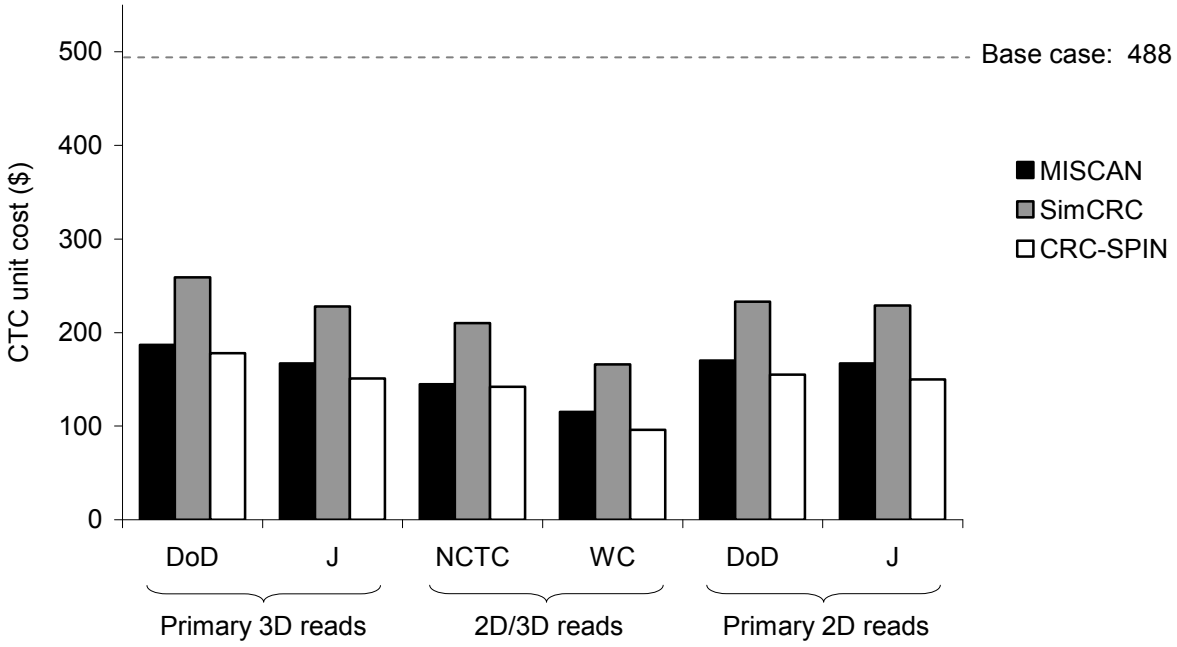
Panel B: 10-yearly CTC screening with a 6mm referral threshold



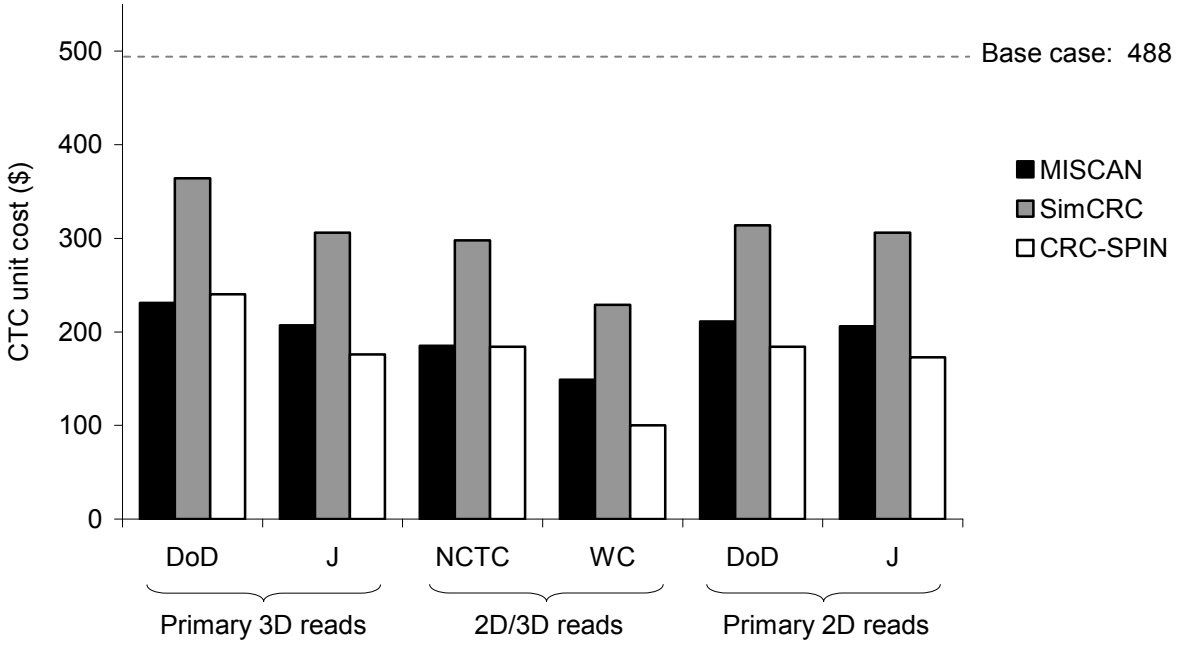
DoD = Department of Defense Study (Pickhardt 2003, 2007a); NCTC = National CT Colonography study (Johnson 2008); WC = hypothetical worst-case scenario

Figure 6. CT colonography unit cost thresholds (in 2007 US dollars) at which CT colonography strategies with a 10mm colonoscopy referral threshold have an average cost effectiveness ratio (ACER) equal to that of colonoscopy screening

Panel A: 5-yearly CTC screening with a 10mm referral threshold



Panel B: 10-yearly CTC screening with a 10mm referral threshold



DoD = Department of Defense Study (Pickhardt 2003, 2007a); J = Johnson study (Johnson 2007); NCTC = National CT Colonography study (Johnson 2008); WC = hypothetical worst-case scenario

Table 11. Threshold analysis on CT colonography test characteristics for scenarios with a 10mm colonoscopy referral threshold: unit cost of CT colonography screening test resulting in equal outcomes compared to other recommended CRC screening strategies for different estimates of CT colonography test characteristics*

CTC outcome	Sensitivity analysis scenarios with 10mm colonoscopy referral thresholds					
	Primary 3D reads		2D/3D reads		Primary 2D reads	
	CTC DoD 3D 10mm	CTC J 3D 10mm	CTC NCTC 2D/3D 10mm	CTC WC 2D/3D 10mm	CTC DoD 2D 10mm	CTC J 2D 10mm
			5-yearly CTC screening			
On efficient frontier	98, **132**‡, *192*‡	71, **105**‡, *153*‡	49, **90**‡, *135*‡	10, **43**‡, *81*‡	75, **110**‡, *160*‡	73, **105**‡, *154*‡
Cost-neutral vs. no screening	118, *327*, **329**	106, *284*, **297**	68, *284*, **309**	43, *232*, **265**	110, *290*, **301**	107, *284*, **296**
Equal to highest ACER	227, **246**, *284*	202, **216**, *248*	190, **216**, *237*	157, **172**, *189*	206, **221**, *254*	201, **215**, *248*
Equal to colonoscopy ACER	**178,** 187, *259*	**151**, 167, *228*	**142,** 145, *210*	**96**, 115, *166*	**155**, 170, *233*	**150**, 167, *229*
			10-yearly CTC screening			
On efficient frontier	82, **163**‡, *238*‡	71, **99**‡, *166*‡	30, **104**‡, *167*‡	3, **20**‡, *84*‡	75, **108**‡, *175*‡	72, **96**‡, *164*‡
Cost-neutral vs. no screening	139, *457*, **487**	127, *382*, **420**	88, *393*, **440**	61, *311*, **356**	131, *391*, **428**	128, *380*, **417**
Equal to highest ACER	285, **350**, *397*	253, **285**, *333*	242, **299,** *332*	200, **215**, *259*	258, **293**, *342*	252, **282**, *332*
Equal to colonoscopy ACER	231, **240**, *364*	**176**, 207, *306*	**184**, 185, *298*	**100**, 149, *229*	**184,** 211, *314*	**173**, 206, *306*

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)
* MISCAN values in plain text; SimCRC values in italics; CRC-SPIN values in bold
† See Table 7 for the test characteristics used in these scenarios
‡ CTC strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount

Table 12. Threshold analysis on CT colonography adherence: unit cost of CT colonography screening test resulting in equal outcomes compared to other recommended CRC screening strategies for different levels of adherence with CT colonography screening*

	Base case (CTC DoD 3D 6mm 5y)	Sensitivity Analysis on CTC Adherence†	
CTC outcome	Adherence 50% for all strategies	CTC adherence 55%	CTC adherence 62.5%
On efficient frontier	122, **196**, *199*	*293*‡, **360**‡, *408*‡	*547*‡, **668**‡, *694*‡
Cost-neutral vs. no screening	76, *323*, **398**	76, *323*, **398**	76, *323*, **398**
Equal to highest ACER	238, *258*, **294**	238, *258*, **294**	238, *258*, **294**
Equal to colonoscopy ACER	179, **210**, *221*	179, **210**, *221*	179, **210**, *221*

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)
* MISCAN values in plain text; SimCRC values in italics; CRC-SPIN values in bold
† Strategies other than CTC remain at 50% adherence
‡ CTC strategy is on the frontier with an incremental cost-effectiveness ratio (ICER) of $50,000 if the cost is at least this amount

Table 13. Threshold analysis from modified societal perspective: unit costs for CT colonography screening test resulting in equal outcomes compared to other recommended CRC screening strategies for modified societal perspective

CTC outcome	Total threshold costs (includes co-payments and patient time costs)		CMS reimbursement rates (excludes co-payments and patient time costs)	
	CTC DoD 3D 6mm	CTC NCTC 2D/3D 6mm	CTC DoD 3D 6mm	CTC NCTC 2D/3D 6mm
	5-yearly CTC screening			
On efficient frontier	181, **318**, *332*	154, *324*, **336**	26, **163**, *177*	NT, *169*, **181**
Cost-neutral vs. no screening	NT, *288*, **406**	12, *321*, **432**	NT, *133*, **250**	NT, *166*, **277**
Equal to highest ACER	294, *433*, **476**	303, *445*, **496**	139, *278*, **321**	148, *290*, **341**
Equal to colonoscopy ACER	215, **340**, *347*	234, *371*, **372**	60, **185**, *191*	79, *216*, **217**
	10-yearly CTC screening			
On efficient frontier	166, *476*, **480**	176, *428*, **474**	11, *321*, **325**	21, *272*, **318**
Cost-neutral vs. no screening	NT, *471*, **646**	28, *494*, **671**	NT, *315*, **491**	NT, *339*, **515**
Equal to highest ACER	398, *662*, **747**	405, *661*, **768**	243, *507*, **591**	250, *506*, **613**
Equal to colonoscopy ACER	298, *548*, **552**	316, *562*, **580**	143, *393*, **397**	161, *406*, **425**

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained); NT = no threshold found (i.e., negative CTC test cost)

* MISCAN values in plain text; SimCRC values in italics; CRC-SPIN values in bold

† CTC strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount

DISCUSSION

Summary of Results

We conducted a cost-effectiveness analysis of CT colonography in comparison with the currently recommended CRC screening tests of colonoscopy, flexible sigmoidoscopy, and FOBT (guaiac Hemoccult II and SENSA, and FIT) in response to a request by AHRQ and CMS for a National Coverage Determination. The analysis is based on a cohort of previously unscreened 65-year-old individuals followed over their lifetimes and is conducted from both the CMS payer perspective and a modified societal perspective. We evaluated two recent large-scale CT colonography studies as our base case with referral to optical colonoscopy for a CT colonoscopy-detected lesion of 6 mm or larger diameter and with repeat screening with CT colonography every 5 years. Sensitivity analyses were conducted for referral of individuals with only larger lesions (10 mm or larger) and for longer repeat screening intervals (10 years) as well as for worse case test parameters. Even though the life-years gained by 5-yearly CT colonography with a 6 mm referral for optical colonoscopy were roughly comparable to those from colonoscopy screening every 10 years, the overall costs of both base case CT colonography strategies were higher than all of the other screening strategies considered and were dominated. However if CT colonography reimbursement costs were relatively lower than that of colonoscopy, or CT colonography adherence was differentially higher than for other CRC screening tests, including colonoscopy, then screening with CT colonography would be a cost-effective alternative.

At first it may seem surprising that CT colonography, based on the best evidence available to date, was not cost-effective when compared with the other CRC screening tests since the CT colonography sensitivity for the larger adenomas and CRC is comparable to that of optical colonoscopy and the cost for CT colonography was less that of optical colonoscopy. However, the strategy of CT colonography screening is not a single test but a two-step procedure with those with 6 mm or larger polyps referred to optical colonoscopy. In addition, repeat screening is every 5 years rather than every 10 years as for colonoscopy. Consequently the aim of this analysis was also to explore the conditions under which CT colonography (or for that matter any other new test) could be considered cost-effective compared with the existing screening tests. We therefore conducted threshold analyses to determine what a CT colonography would have to cost in order for one of the CT colonography strategies to lie on the efficient frontier (i.e., be a non-dominated strategy). CT colonography screening could be cost-effective (i.e., be a non-dominated strategy) at a cost of $108 to $205 per scan depending on the simulation model used and the test characteristics of CT colonography. If the cost per test were $179 to $237, CTC would provide additional years of life at the same cost per year as colonoscopy (with CMS reimbursement of approximately $500 for colonoscopy without polypectomy and $650 for colonoscopy with polypectomy).

We conducted sensitivity analyses to address the question of whether with increased adherence CT colonography would be on the efficient frontier. For this analysis we assumed that adherence was 50% for the currently-recommend tests and that there was increased adherence with the CT colonography test strategies among unscreened individuals. If screening adherence were higher with CT colonography compared with other screening tests, CT colonography screening could be included among the efficient strategies at the base-case cost estimate of $488

We assumed that all in the cohort of 65-year-old individuals were previously unscreened. In reality, many subjects entering the Medicare program will have had CRC screening before age 65. Of those with prior screening, only those without adenomas detected are still eligible for average-risk screening. Adenoma patients should undergo more frequent surveillance with colonoscopy (Winawer 2006) than those with no neoplasia. This means that on average the eligible population for average-risk screening entering Medicare will be at lower risk than an unscreened population. Accordingly we may have overestimated the life-years gained from screening. However, this holds for all tests and strategies and is therefore not expected to significantly influence our results, because the relative performance of one test over the other remains the same. We assessed the potential effect of the assumption of an unscreened 65-year-old population by determining threshold costs for CTC screening when screening a 50-year-old cohort from age 50 onwards; the results did not change substantially.

Cost-effectiveness of Currently Recommended Test Strategies

As reported in the DNA stool test report to CMS, (Zauber 2007) an important finding from our analysis is that the currently recommended CRC screening tests provide good value for the resources spent. Hemoccult II, the test proven in randomized controlled trials to reduce CRC mortality by 15-33%, with a $4.54 CMS reimbursement, is cost-saving relative to no screening. Other FOBTs as well as flexible sigmoidoscopy and colonoscopy provided additional life-years gained over Hemoccult II, often with reasonable costs. Our favorable cost-effectiveness result for the CRC screening strategies is likely due to the increasing costs of CRC-related care and the costs of the screening tests not increasing at the same rate or even lower than previously reported. In this analysis all the costs come from the same source: Medicare reimbursement. The costs for treating CRC stage III and IV and incurable CRC have been increasing since the introduction of newer therapies. The reason that the SimCRC and CRC-SPIN models found more cost-saving strategies than the MISCAN model is likely due to the fact that they find a great reduction in cancer incidence with CRC screening because of their longer dwell times.

Evaluation of New Screening Tests in Relationship to Current Recommendations

CRC screening guidelines from the Multi-Society Task Force were published in 1997 for currently available tests but the authors also considered how to evaluate new screening tests as well. The guidelines state that a newer test could be substituted for a currently recommended test (or added to the recommendations) if evidence were available to demonstrate that the new test had: (1) a comparable performance for sensitivity and specificity in detecting cancer or adenomatous polyps at comparable stages, (2) was equally acceptable to patients, and (3) had comparable or lower complication rates and costs (Winawer 1997). We address each of these issues below.

Strength of the evidence for CT colonography as a screening test

The two well-designed studies used as our base cases demonstrate that CT colonography has comparable sensitivity to detect adenomas 10 mm or larger and CRCs as optical colonoscopy but slightly lower sensitivity to detect adenomas of size 6-9 mm. Furthermore adenomas of size <6 mm are not reported at all for CT colonography (Zalis 2005). The natural history of adenomas <6 mm is not well known (2008a, Butterly 2006, O'Brien 1990). The risk of high-grade dysplasia or invasive CRC is lower in these smaller adenomas than those ≥6 mm but the smaller lesions are also the most common. Repeat CT colonography screening at 5-year intervals with referral to

optical colonoscopy for those lesions of larger size is one way to offset the optical colonoscopy screening strategy of removing all polyps.

The specificity of CT colonography varied for the two base cases, with the DoD study having higher sensitivity but lower specificity than the NCTC. Lack of specificity is also a factor in optical colonoscopy which detects and removes hyperplastic and other polyps as well as the adenomas less than 6 mm in size. In the analyses we assumed 90% specificity for optical colonoscopy to take into account the detection and removal of non-adenomas in optical colonoscopy screening.

The evidence to date has primarily been for a one-point-in-time assessment of CT colonography. Information on programmatic use of CT colonography (i.e., repeated screening) is not yet available. Future studies are needed to assess repeat screenings and the impact of a programmatic utilization of CT colonography.

The evidence shows that there is a strong learning curve for CT colonography and that readers must have standardized rigorous training and proper technique to obtain the good test parameters observed in the well-designed trials. Quality measures for CT colonography are in development (McFarland 2008). New techniques or modifications of older techniques must be evaluated as to their test performance characteristics.

Additional techniques are demonstrated for optical colonoscopy to detect flat adenomas (Soetikno 2008) and the clinical importance of flat adenomas has been discussed (Lieberman, 2008b). The CT colonography literature has also discussed detection of flat lesions (Fidler 2002, Park 2007). Additional techniques to detect flat adenomas have not been included in the modeling for this report.

Acceptability to patients as a screening test

The currently-recommended CRC screening tests all require considerably more patient involvement than screening tests for other diseases. The individual undergoing screening must complete a cleansing bowel prep for colonoscopy, flexible sigmoidoscopy as well as for CT colonography, restrict their diet for Hemoccult II, colonoscopy, and CT colonography; and restrict NSAID use with Hemoccult II; have contact with the stool for any of the FOBTs; and go to a medical setting for colonoscopy, flexible sigmoidoscopy, or CT colonography. Colonoscopy procedures have a small but real risk of perforations and due to sedation, require an escort to and from the procedure. Although CT colonography is non-invasive it does require a cathartic bowel preparation just as for optical colonoscopy, as well as stool tagging. In addition, a positive CT colonography requires referral for optical colonoscopy as is the case for other two-step procedures. Whether same-day CT colonography and optical colonoscopy for those with a positive CT colonography is possible in the general medical practice is not yet known although there is discussion of this as a practice model (Pickhardt 2006b). If not, then the referred patient must undergo two cathartic preparations. The patient impression is often that CT colonography is 'virtual' and non-invasive. It is not known whether the adherence to optical colonoscopy referral for those with positive CT colonography will be as high or higher as those with positive findings on other CRC screening tests. Although non-cathartic preparations have been developed for CT colonography (Callstrom 2001, Iannaccone 2004) they involve both dietary restriction over a

number of days and ingestion of various oral contrast agent (Pickhardt 2007b). Consequently, the non-cathartic preparations are not 'prepless'. Also same-day optical colonoscopy cannot be performed in those with non-cathartic preparations if the CT colonography is positive for lesions of size 6 mm or larger.

There is a low level of radiation exposure with CT colonography. The long-terms effects of cumulative exposure to radiation that would be associated with interval screening with CT colonography are unknown. In addition, concern for radiation risk on part of patient or physician could affect willingness to adhere to CTC screening.

In addition to findings within the colorectal tract, CT colonography may identify extracolonic findings (Hara 2000, Pickhardt 2008a). The extent to which these finding may lead to early diagnosis of a potentially lethal disease, or just a false-positive finding resulting in extra work-up and additional exposure to radiation is also not well established (USPSTF 2008; Whitlock 2008).

Patient-stated preference for CT colonography relative to other CRC screening tests has been investigated in those who have had CT colonography. Pickhardt conducted a survey of patient preferences for repeat CT colonography versus repeat optical colonoscopy in his DoD study (2003) and demonstrated a slight preference for CT colonography. Gluecker (2003) addressed patient preferences for those having CT colonography and colonoscopy versus those with CT colonography and double contrast barium enema; CT colonography was preferred. Further studies of patient preference for CT colonography versus optical colonoscopy for the initial screen and of the willingness to have optical colonoscopy if CT colonography is positive are needed, especially among subjects who have been unwilling to perform any of the current CRC screening tests (Levin 2008).

Although there are these potential problems in obtaining high adherence for CT colonography, if adherence for CT colonography could be achieved at only slightly higher levels (10% to25% over current CRC screening levels of 50%) our sensitivity analysis on adherence suggests that CT colonography would become cost-effective.

Evidence on comparable or lower complication rates and costs
There are perforation complications associated with CT colonography but at a lower rate and with less substantial level of complications as colonoscopic complications (Whitlock 2008). There is radiation exposure with CT colonography but at a low level. The harm of low-level radiation has been difficult to assess. Furthermore followup of extracolonic findings detected on CT colonography does contribute to a higher cumulative dose of radiation exposure that should be taken into account (Brenner 2007, Levin 2008). Risk may be small, but certainly not negligible.

CT colonography is associated with exposure to radiation, which we did not consider in the current analysis. Brenner (2007) estimated that the excess cancer risk from a pair of CT colonography scans using typical current scanner techniques is about 0.14% for a 50-year old and half that for a 70-year old. This estimate is controversial, because it was based on simulation calibrated to atomic bomb survivors. Multiple CT colonography screens will increase the radiation dose proportionally and most likely also the radiation risks. We found that CT

colonography is only compatible to colonoscopy screening if offered seven times (every 5 years between ages 50 and 80), potentially leading to an excess cancer risk of approximately 0.47%. This will lead to life-years lost due to CT colonography which are not negligible compared to the life-years gained. We did not take these excess cancer cases into account, because there is good evidence that radiation dose with CT colonography can be reduced by at least a factor of 5 (and perhaps as much as 10), while still maintaining sensitivity and specificity for polyps larger than approximately 5 mm (Brenner 2005). With these dose reductions, excess risk of cancer from CTC becomes negligible.

CT colonography generally costs less than optical colonoscopy on a per scan basis but the overall screening strategy for CT colonography screening is more expensive than other screening strategies in general as demonstrated here given comparable adherence.

Consistency of Results from Three Microsimulation Models

All analyses were conducted by three separate microsimulation modeling groups of the NCI-sponsored modeling consortium, CISNET, using independently developed models but with common inputs. The comparability of the findings of the three modeling groups strengthens the credibility of our results and can be viewed as a sensitivity analysis on the underlying natural history assumptions. All three models have been calibrated to CRC incidence rates from a pre-screening era. All the models have been extensively validated against clinical trial data on Hemoccult II screening. The models do differ in the dwell time from adenoma to clinically detectable CRC. The MISCAN model assumes a shorter dwell time compared with the SimCRC and CRC-SPIN models. Based on this difference in dwell time, the MISCAN model estimates fewer life-years saved from removing adenomas as a result of screening than the SimCRC and CRC-SPIN models, and estimates a greater benefit for shorter rescreening intervals for adenoma-sensitive tests than does the other two models. The fact that all three models come to similar conclusions with respect to cost-effectiveness and threshold costs of CT colonography screening shows the robustness of the results for uncertainties in the duration of the adenoma-carcinoma sequence.

The distribution of dwell time from adenoma to carcinoma is not known with certainty. The uncertainty on dwell time affects the assessment of all the screening tests, including CT colonography. In particular it affects the tests with respect to detection of adenomas.

Other Cost-effectiveness Analyses

This report is the first cost-effectiveness analysis using the new estimates of test performance from the DoD and NCTC trials in the 65-year-old-age group. Other cost-effectiveness analyses based on test performance of earlier CT colonography technology or in a 50-year-old cohort include Sonnenberg (1999), Ladabaum (2004), Vijan (2007), Pickhardt (2007c, 2008b) and Scherer (2008).

Limitations of Modeling Assumptions

The models simulate the progression from adenoma to CRC by increasing the size of the adenomas over time. Because adenoma size, villous component, and high-grade dysplasia are highly correlated (O'Brien 1990), the size representation indirectly represents histology and high grade. However, the models do not separately simulate the step from adenoma with low-grade

dysplasia to an adenoma with high-grade dysplasia. We also did not allow for de novo cancers (cancers that arise without a prior adenoma state). Lastly, we assumed that SEER incidence data prior to the time of active CRC screening in the US is a good representation of the cancer incidence expected today in an unscreened population. However, because there has been a small net improvement in CRC lifestyle risk factors for CRC over time (Knudsen 2004, 2005), estimates of CRC incidence may be overestimated. The impact of overestimating CRC incidence is that all CRC screening benefits are also overestimated, though we would not expect significant differences in the relative benefit across strategies.

In the current analysis, we assumed conditional independence of repeat screenings. Consequently we assumed that there were no systematic false-negative results for adenomas and cancers. This is likely a reasonable assumption for FOBT and FIT testing because bleeding of a lesion is assumed to be a random event, so that if a test misses a lesion the first time, then it has approximately the same probability of catching a bleed on the next screen. This assumption may be less reasonable for optical endoscopy, as certain lesions may be more difficult to find (e.g., in a fold) but is a reasonable assumption for CT colonography which can detect lesions on folds (Pickhardt 2004).

In this analysis, we included the current recommendations for average-risk CRC screening as the comparator strategies. We did not consider alternative screening intervals for the currently recommended screening tests. We also made the assumptions that screening would stop at age 80 and that individuals would remain on a surveillance schedule for their lifetime, which may not be realistic assumptions for what occurs in practice.

In our sensitivity analysis of screening adherence we assumed that individuals would be either fully adherent with a screening strategy or never screened. This is an oversimplification of what occurs in practice, but is closer to reality than an assumption that individuals show up randomly to their scheduled screens. A recent study by Coups et al. (2007) of data from the 2000 National Health Interview Survey found that almost 40% of the US population aged 50 and older were adherent with CRC screening guidelines and only 13% were screened but not according to guidelines (the remaining group was never screened).

Limitations of Cost Estimates

The costs of the screening tests, as well as the costs of complications associated with screening (primarily colonoscopy), were based on 2007 Medicare reimbursement rates. To the extent that these rates change differentially in the future (e.g., a decrease in the reimbursement rate for colonoscopy) our results will change.

Costs for CRC treatment were for the period 1998 to 2003. In this period use of the expensive biological therapies cetuximab and bevacizumab was limited (Schrag 2004). We would expect that inclusion of these costs as later data become available would make the cost-effectiveness more favorable overall. CRC screening can have two potentially beneficial effects: 1) primary prevention of CRC through detection and removal of adenomas that might have eventually become cancer, and 2) early detection of CRC, when it is in an earlier stage that is more amenable to treatment. In general, those strategies that are associated with a higher reduction in

cancer incidence (i.e., act largely through primary prevention rather than early detection,) will have a greater net savings.

With the exception of the Warren, Klabunde, and Brown upcoming manuscript (Klabunde 2007), there are few data specifically on colonoscopy complications in the Medicare population. For example, the Warren analysis reports hospitalization for dehydration following colonoscopy. This complication was not cited in the general population studies across ages. Complications rates are generally lower in organized screening programs, which often focus on the age group of 50 to 65 for CRC screening. Consequently a program to track complications in Medicare beneficiaries who receive CRC screening would be of value to assess the magnitude of risk for this age group.

CONCLUSIONS

The results of this cost-effectiveness analysis suggest that CT colonography does provide a benefit in terms of life-years gained compared with no screening but the cost, relative to the benefit derived and to the availability and costs of other CRC tests, would need to be in range of $108 to $205 to be a non-dominated strategy, provided that the estimates of sensitivity and specificity as stated in the DoD study (Pickhardt 2003) and NCTC (Johnson 2008) are obtained in community-based screening settings. Our findings are based on the analysis of an unscreened 65-year-old cohort using a payer perspective under the assumption of a 5-yearly screening interval for CT colonography with referral to colonoscopy for 6 mm lesions or larger. Threshold costs are similar for a 50-year old cohort (range of $72 to $179) but can be somewhat higher when the analysis is performed using a modified societal perspective ($154 to $336).

There is great potential for CT colonography as a CRC screening test in an average-risk population, especially if adherence for CT colonography is differentially higher than that of other CRC screening tests. CT colonography is a rapidly evolving technology; new techniques must be evaluated in average risk population and the radiation risks and benefit of detection of extracolonic findings determined.

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APPENDICES

1. Model descriptions: (a) MISCAN, (b) SimCRC, (c) CRC-SPIN

2 Comparison of outcomes from the natural history component of the models

3. Additional outcomes of the analyses

4. Results for analyses of 50-year-old cohort

Appendix 1: Model descriptions

Microsimulation models. The MISCAN, SimCRC, and CRC-SPIN models from the NCI CISNET consortium were used to address the question of the cost-effectiveness of screening with CT colonography. The models used common inputs and assumptions concerning the screening tests but use their independently developed natural history models in addressing these questions.

Appendix 1a. Description of the MISCAN-COLON model for natural history and intervention

MISCAN Model overview
MISCAN-COLON is a semi-Markov microsimulation program to simulate the effect of screening and other interventions on colorectal cancer (CRC) incidence and mortality. With microsimulation we mean that each individual in the population is simulated separately. The model is semi-Markov in the sense that:
- distributions other than exponential are possible in each disease state
- transitions in one state can depend on transitions in earlier states,
- transitions can be age and calendar time dependent

All events in the model are discrete, but the durations in each state are continuous. Hence, there are no annual transitions in the model.

The development of CRC in the model is assumed to occur according to the adenoma carcinoma sequence. This means that adenomas arise in the population, some of which eventually develop into CRC. We assume that there are two types of adenomas: progressive and non-progressive adenomas. Non-progressive adenomas can grow in size, but will never develop into a cancer. Progressive adenomas have the potential to develop into cancer, if the person in whom the adenoma develops lives long enough.

All adenomas start as a small (1-5 mm) adenoma. They can grow in size to medium (6-9 mm) and large (10+ mm) adenoma. Progressive medium and large adenomas can transform into a malignant cancer stage I, not yet giving symptoms (preclinical cancer). The cancer then progresses from stage I (localized) eventually to stage IV (distant metastasis). In each stage there is a probability of the cancer giving symptoms and being clinically detected. The time between the onset of a progressive adenoma and the clinical detection of CRC is assumed to be on average 20 years. After clinical detection a person can die of CRC, or of other causes based on the survival rate. The survival from CRC is highly dependent on the stage in which the cancer was detected.

MISCAN Simulation of an individual
Figure 2a shows how the model generates an individual life history. First MISCAN-COLON generates a time of birth and a time of death of other causes than CRC for an individual. This is shown in the top line of figure 1a. This line constitutes the life history in the absence of CRC. Subsequently, MISCAN-COLON generates adenomas for an individual. For most individuals no adenomas are simulated, for some multiple. In this example MISCAN-Colon has generated two adenomas for the individual. The first adenoma occurs at a certain age and grows in size from

small to medium and large adenoma. However this is a non-progressive adenoma, so this adenoma will never transform into cancer. The second adenoma is a progressive adenoma. After having grown to 6-9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and eventually resulting in an earlier death from CRC.

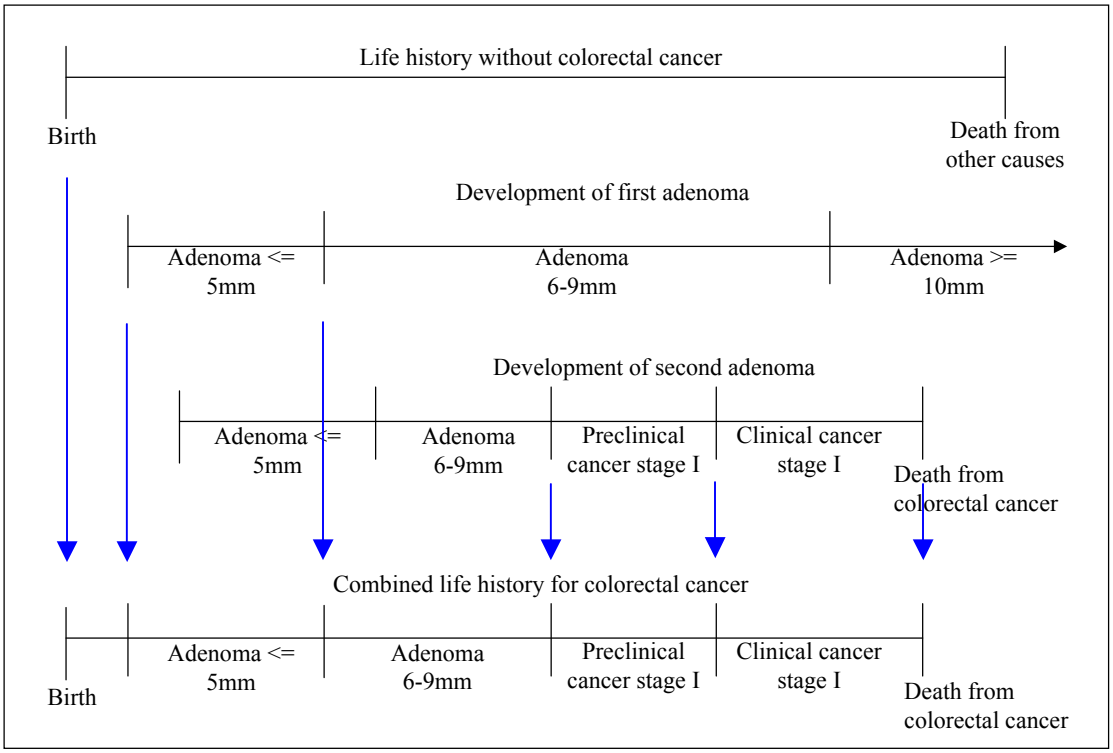

Figure A.1.1a: Modeling natural history into life

The life history without CRC and the development of the two adenomas are combined into a life history in the presence of CRC. This means that the state a person is in is the same as the state of the most advanced adenoma or carcinoma present. If he dies from CRC before he dies from other causes, his death age is adjusted accordingly. The combined life history with CRC is shown in the bottom line of figure 1b.

MISCAN Simulation of screening

The complete simulation of an individual life history in figure 2a is in a situation without screening taking place. After the model has generated a life history with CRC but without screening, screening is overlaid. This is shown in figure 2b. The first three lines show the combined life history with CRC and the development of the two adenomas from figure 2a. At the moment of screening both adenomas are present, detected and removed. This results in a combined life history for CRC and screening (bottom line), where the person is adenoma-carcinoma free after the screening intervention. Because the precursor lesion has been removed this individual does not develop CRC and will therefore not die of CRC. The moment of death is delayed until the moment of death of other causes. The benefit of screening is equal to the difference between life-years lived in a situation with screening and the situation with screening.

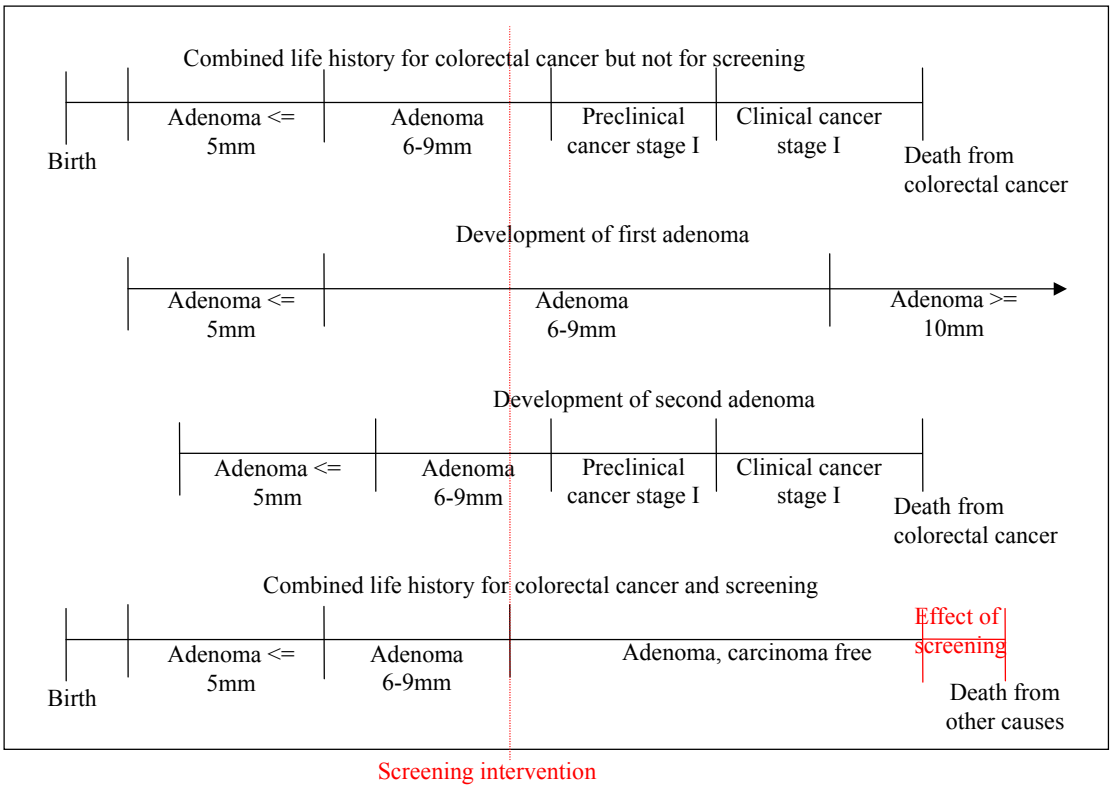

Figure A.1.1b: Modeling screening into life history

Many other scenarios could have occurred. A person could have developed a third adenoma after the screening moment and could still have died of CRC. Another possibility would have been that one of the adenomas was missed, but in the presented example the individual really benefited of the screening intervention.

The effectiveness of screening depends on the performance characteristics of the test performed: sensitivity, specificity and reach. In the model, one minus the specificity is defined as the probability of a positive test result in an individual irrespective of any adenomas or cancers present. For a person without any adenomas or cancers, the probability of a positive test result is therefore equal to one minus the specificity. In individuals with adenomas or cancer the probability of a positive test result is dependent on the lack of specificity and the sensitivity of the test for the present lesions. Sensitivity in the model is lesion-specific, where each adenoma or cancer contributes to the probability of a positive test result.

Appendix 1b. Description of the SimCRC model for natural history and intervention model

SimCRC Model

SimCRC overview. The SimCRC model of CRC was developed to evaluate the impact of past and future interventions on CRC incidence and mortality in the U.S. The model is population-based, meaning that it simulates the life histories of multiple cohorts of individuals of a given year of birth. These cohorts can be aggregated to yield a full cross-section of the population in a given calendar year. For this analysis, we simulated the life histories of only one cohort—those aged 65 years in 2005. SimCRC is a hybrid model, specifically it is a cross between a Markov model and a discrete event simulation. While annual (often age-specific) probabilities define the likelihood of transitioning through a series of health states, the model does not have annual cycles. Instead, the age at which a given transition takes place for each simulated individual is drawn from a cumulative probability function.

SimCRC simulation of the natural history of CRC. The SimCRC natural history model describes the progression of underlying colorectal disease (i.e., the adenoma-carcinoma sequence) among an unscreened population. Each simulated individual is assumed to be free of adenomas and CRC at birth. Over time, he is at risk of forming one or more adenomas. Each adenoma may grow in size from small (≤ 5 mm) to medium (6-9 mm) to large (≥ 10 mm). Medium and large adenomas may progress to preclinical CRC, although most will not in an individual's lifetime. Preclinical cancers may progress in stage (I-IV) and may be detected via symptoms, becoming a clinical case. Individuals with CRC may die from their cancer or from other causes.

The SimCRC model allows for heterogeneity in growth and progression rates across multiple adenomas within an individual. While all adenomas have the potential to develop into CRC, most will not. The likelihood of adenoma growth and progression to CRC is allowed to vary by location in the colorectal tract (i.e., proximal colon vs. distal colon vs. rectum).

SimCRC simulation of screening. The screening component of the SimCRC model is superimposed on the natural history model. It allows for the detection and removal of adenomas and the diagnosis of preclinical CRC. In a screening year, a person with an underlying (i.e., undiagnosed) adenoma or preclinical cancer faces the chance that the lesion is detected based on the sensitivity of the test for adenomas by size or for cancer 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 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 non-adenomatous polyps. The model incorporates the risk of fatal and non-fatal complications associated with various screening procedures. It also accounts for the fact that not all individuals are adherent with CRC screening guidelines and that adherence patterns are correlated within an individual.

Appendix 1c. Description of CRC-CPIN model for natural history and intervention

Model overview

For this analysis we will use the ColoRectal Cancer Simulated Population model for Incidence and Natural history (CRC-SPIN). CRC-SPIN is a semi-Markov microsimulation program to simulate the effect of screening and other interventions on colorectal cancer (CRC) incidence and mortality. With microsimulation we mean that each individual in the population is simulated separately. The model is semi-Markov in the sense that:

- distributions other than exponential are possible in each disease state
- transitions can be age, location, and calendar time dependent

All events in the model are discrete, but the durations in each state are continuous. Hence, there are no annual transitions in the model.

The CRC-SPIN model assumes that all colorectal cancers arise from an adenoma and models shifts from adenoma initiation to preclinical and clinically detectable CRC in continuous time using four components, described below. CRC-SPIN does not model adenomas <1mm, and implicitly assume that these are unobservable.

1. Adenoma Risk: CRC-SPIN models the occurrence of 1mm adenomas with a non-homogeneous Poisson process. Risk is modeled using a log-linear model. Baseline individual-level log-risk varies across individuals and has a Normal distribution. CRC-SPIN models systematic differences in the log-risk of adenomas for men and women, and by age. Age-effects are modeled using a piecewise linear age effect on log-risk with four age-risk intervals: [20,50), [50,60), [60,70), and (70. Under the CRC-SPIN model, individuals younger than 20 are not at risk of developing 1mm adenomas. Once initiated, adenomas are assigned a location using a multinomial distribution across 6 possible sites of the large intestine (from proximal to distal, with probabilities in parenthesis): 1) cecum (0.08); 2) ascending colon (0.23); 3) transverse colon (0.24); 4) descending colon (0.12); 5) sigmoid colon (0.24); and 6) rectum (0.09).

2. Adenoma Growth: CRC-SPIN models adenoma growth as a continuous process. We assume that adenoma growth varies independently across adenomas, both within and between individuals, and we allow different adenoma growth distributions for adenomas in the colon and rectum. The growth model used by CRC-SPIN is asymmetric, with exponential growth early that slows to allow an asymptote at 50mm, the maximum adenoma size. CRC-SPIN simulates adenoma growth by first simulating the time to reach 10mm using a type 2 extreme value distribution, and then solving for growth parameters. The type 2 extreme value distribution has a long right tail but does not heavily weight small values that indicate fast growth.

3. Transition from Adenoma to Invasive Cancer: CRC-SPIN models the cumulative probability of adenoma transition up to size s as a function of location (colon or rectum) and age at adenoma initiation. For an adenoma initiated at age a in the colon of a man, the probability of transition to preclinical cancer at or before size s is given by by (c(s,a) = (([ln((1cms) + (2cm(a-50)]/ (3. where (( ) is the standard Normal cumulative distribution function. Cumulative transition probabilities for adenomas in the male rectum, and adenomas in the female colon and rectum have the same form, but with different parameters. For each adenoma, the size at

transition is independently generated by simulating a Uniform[0,1] pseudodeviate and using an inverse cumulative distribution look-up.

4. Sojourn Time: Under the CRC-SPIN model, sojourn time is defined as the time from transition to preclincal cancer to clinical detection, defined as the onset of symptoms leading to detection in the absence of screening. We assume that the sojourn time of each preclinical cancer is independent and has a lognormal distribution that depends on adenoma location (colon or rectum).

Clinical Outcomes: Stage and Survival: Once a cancer becomes clinically detectable, CRC-SPIN simulates size and stage at clinical detection. We specify an overall (unconditional) distribution for tumor size at clinical detection using observed SEER size at detection from 1975-1979. We base the conditional distribution of stage given size on estimates from multinomial logistic regression models for the same SEER data. These models include linear and quadratic effects of tumor size on stage at detection. Given cancer size, we determine size during the preclinical period using an exponential model, which assumes a minimum cancer size of 0.5mm and replacement of adenoma cells with cancer cells until the cancer overtakes the adenoma.

Colorectal cancer relative survival probabilities are based on Cox proportional hazards models for relative survival applied to SEER survival data for cases diagnosed from 1975 to 1979, estimated using the CANSURV program (http://srab.cancer.gov/cansurv/). Proportional hazards models were stratified by location (colon or rectum) and AJCC stage. Age and sex were included as covariates. Age was treated as continuous, though people 25-34 were grouped with 35 year olds and people 90+ were grouped with 90 year olds due to small cell sizes. Other cause mortality uses survival probabilities based on product-limit estimates for age and birth-year cohorts from the National Center for Health Statistics Databases.

Simulation of screening
Individual life histories are simulated assuming there is no screening for colorectal cancer. After these life histories are simulated, screening is applied, to allow comparison of events with and without screening. The effectiveness of screening depends on the performance characteristics of the test performed: sensitivity, specificity and reach (for endoscopic tests). In the model, one minus the specificity is defined as the probability of a positive test result in an individual irrespective of any adenomas or cancers present. For a person without any adenomas or cancers, the probability of a positive test result is therefore equal to one minus the specificity. In individuals with adenomas or cancer the probability of a positive test result is dependent on the lack of specificity and the sensitivity of the test for the present lesions. Sensitivity in the model is lesion-specific, where each adenoma or cancer contributes to the probability of a positive test result.

Appendix 2: Comparison of the MISCAN, SimCRC and CRC-SPIN models on natural history outcomes

Outcome	MISCAN	SimCRC	CRC-SPIN
Adenoma prevalence, age 65:	39.8%	37.2%	30.7%
Number of adenomas per 1000 by site and size, age 65			
Proximal colon			
≤ 5 mm	121.2	171.7	190.2
6-9 mm	69.9	186.2	67.8
≥ 10 mm	61.8	23.9	40.8
Distal colon			
≤ 5 mm	134.4	124.2	124.5
6-9 mm	77.4	18.2	44.4
≥ 10 mm	68.4	41.6	26.7
Rectum			
≤ 5 mm	133.5	8.7	14.1
6-9 mm	76.8	16.0	9.1
≥ 10 mm	68.1	15.8	20.2
Distribution of adenomas by site and size, age 65 (%)			
Proximal colon			
≤ 5 mm	15	28	35
6-9 mm	9	31	13
≥ 10 mm	8	4	8
Total	31	63	56
Distal colon			
≤ 5 mm	17	20	23
6-9 mm	10	3	8
≥ 10 mm	8	7	5
Total	35	30	36
Rectum			
≤ 5 mm	16	1	3
6-9 mm	9	3	2
≥ 10 mm	8	3	4
Total	34	7	8
CRC incidence among cancer-free 65-year-old population, %			
10-year			
Stage I	0.4	0.4	0.3
Stage II	0.7	0.7	0.7
Stage III	0.5	0.5	0.5
Stage IV	0.5	0.5	0.3
Total	2.1	2.2	1.8

Outcome	MISCAN	SimCRC	CRC-SPIN
CRC incidence among cancer-free 65-year-old population, %			
20-year			
Stage I	0.8	0.8	0.7
Stage II	1.6	1.5	1.4
Stage III	1.0	1.0	1.0
Stage IV	1.0	1.2	0.7
Total	4.4	4.6	3.9
Lifetime			
Stage I	1.0	1.0	0.9
Stage II	2.1	2.0	1.9
Stage III	1.3	1.4	1.4
Stage IV	1.3	1.6	1.0
Total	5.7	6.0	5.3

Appendix 3: Additional outcomes of the analyses

Table A.3.1. Discounted costs and discounted life-years gained per 1000 65-year olds and average cost-effectiveness ratios, by CRC screening scenario – MISCAN

Scenario	Discounted Costs, $	Net Discounted Costs, $	Discounted LYG	ACER, $/LYG
No screening	2,714,556	0	0	NA
HII	2,631,879	-82,677	65.7	CS
HS	2,715,683	1,127	81.1	14
FIT	2,777,228	62,672	80.1	782
SIGB	2,823,217	108,661	75.0	1,450
SIG	2,810,249	95,693	76.7	1,247
HII + SIGB	2,790,651	76,095	84.9	896
HII + SIG	2,839,118	124,562	85.4	1,459
HS + SIGB	2,907,440	145,259	88.0	1,651
HS + SIG	2,859,815	192,884	87.9	2,194
FIT + SIGB	3,022,139	307,583	88.1	3,492
FIT + SIG	2,990,860	276,304	88.1	3,137
COL	2,906,228	191,672	86.7	2,211
CTC DoD 3D 6mm 5y	3,469,651	755,095	85.3	8,854
CTC NCTC 2D/3D 6mm 5y	3,489,227	774,671	81.3	9,526

ACER = average cost-effectiveness ratio compared with no screening; LYG = life-years gained compared with no screening; NA = not applicable; CS = cost-saving

Table A.3.2. Discounted costs and discounted life-years gained per 1000 65-year olds and average cost-effectiveness ratios, by CRC screening scenario – SimCRC

Scenario	Discounted Costs, $	Net Discounted Costs, $	Discounted LYG	ACER, $/LYG
No screening	2,367,514	0	0	NA
HII	2,082,788	-284,726	59.9	CS
HS	2,042,708	-324,806	81.1	CS
FIT	2,116,618	-250,896	79.8	CS
SIGB	2,168,782	-198,733	65.2	CS
SIG	2,151,925	-215,589	69.1	CS
HII + SIGB	2,085,889	-281,625	85.7	CS
HII + SIG	2,072,929	-294,585	87.0	CS
HS + SIGB	2,151,806	-215,708	92.5	CS
HS + SIG	2,150,786	-216,728	93.0	CS
FIT + SIGB	2,244,313	-123,201	92.3	CS
FIT + SIG	2,244,650	-122,864	92.8	CS
COL	2,173,712	-193,802	93.8	CS
CTC DoD 3D 6mm 5y	2,674,721	307,206	92.0	3,340
CTC NCTC 2D/3D 6mm 5y	2,706,113	338,599	87.2	3,881

ACER = average cost-effectiveness ratio compared with no screening; LYG = life-years gained compared with no screening; NA = not applicable; CS = cost-saving

Table A.3.3. Discounted costs and discounted life-years gained per 1000 65-year olds and average cost-effectiveness ratios, by CRC screening scenario – CRC-SPIN

Scenario	Discounted Costs, $	Net Discounted Costs, $	Discounted LYG	ACER, $/LYG
No screening	1,976,803	0	0	NA
HII	1,536,474	-440,329	64.0	CS
HS	1,482,449	-494,354	87.3	CS
FIT	1,574,679	-402,123	84.7	CS
SIGB	1,716,321	-260,482	75.8	CS
SIG	1,626,360	-350,443	80.4	CS
HII + SIGB	1,656,317	-320,486	92.9	CS
HII + SIG	1,590,434	-386,369	94.5	CS
HS + SIGB	1,666,766	-310,037	99.9	CS
HS + SIG	1,611,331	-365,472	100.5	CS
FIT + SIGB	1,768,508	-208,295	99.2	CS
FIT + SIG	1,699,373	-277,430	99.9	CS
COL	1,600,155	-376,648	105.5	CS
CTC DoD 3D 6mm 5y	2,156,740	179,938	101.2	1,777
CTC NCTC 2D/3D 6mm 5y	2,172,677	195,874	98.0	1,999

ACER = average cost-effectiveness ratio compared with no screening; LYG = life-years gained compared with no screening; NA = not applicable; CS = cost-saving

Appendix 4: Results for a cohort of 50-year-olds.

Table A.4.1. Discounted costs and life-years gained per 1000 50-year-olds without CRC screening and with 14 CRC screening strategies and associated incremental cost-effectiveness ratios

Strategy	MISCAN			SimCRC			CRC-SPIN		
	Discounted Costs ($)	Discounted LYG	ICER ($)	Discounted Costs ($)	Discounted LYG	ICER ($)	Discounted Costs ($)	Discounted LYG	ICER ($)
No screening	2,320,612	0.0	---	2,066,811	0.0	d	1,685,545	0	d
HII	2,369,426	85.4	571	1,631,942	102.3	---	1,299,145	84.1	---
HS	2,615,292	100.2	16,605	1,742,331	124.9	4,904	1,445,618	105.9	6,727
FIT	2,688,092	99.7	d	1,821,510	123.6	d	1,537,215	103.5	d
SIGB	2,725,559	89.2	d	1,925,847	96.7	d	1,724,857	85.9	d
SIG	2,760,602	92.2	d	1,935,992	104.5	d	1,656,998	93.2	d
HII + SIGB	2,832,410	103.0	d	1,847,372	127.8	d	1,717,055	107.0	d
HII + SIG	2,823,342	102.9	d	1,865,864	129.3	d	1,674,508	109.0	d
HS + SIGB	2,952,372	104.8	73,336	1,974,606	133.7	26,215	1,731,501	113.2	d
HS + SIG	2,933,686	104.4	d	1,997,694	134.1	54,647	1,702,870	113.6	33,413
FIT + SIGB	3,151,945	105.6	272,160	2,099,318	133.9	d	1,921,951	112.7	d
FIT + SIG	3,058,485	105.0	d	2,127,049	134.4	503,405	1,859,241	113.4	d
COL	3,011,165	101.8	d	2,090,696	132.5	d	1,818,835	116.7	d
CTC DoD 3D 6mm 5y*	3,685,253	100.6	d	2,692,564	131.4	d	2,477,458	112.9	d
CTC NCTC 2D/3D 6mm 5y*	3,751,074	96.1	d	2,752,347	126.6	d	2,521,670	109.9	d

--- indicates default strategy (i.e., the least costly and least effective non-dominated strategy)
LYG = life-years gained vs. no screening; ICER = incremental cost-effectiveness ratio; d = dominated
* The two CTC strategies are not competing options; they represent a range of estimates of CTC test characteristics. They are shown here together for comparison purposes only. The ICERs are assessed separately using each CTC strategy in turn.

Table A.4.2. Threshold analysis on CT colonography test characteristics: unit cost of CT colonography screening test resulting in equal outcomes compared to other recommended CRC screening strategies for CRC screening beginning at age 50*

	Screening and counting from age 50	
CTC outcome	CTC DoD 3D 6mm 5y	CTC NCTC 2D/3D 6mm 5y
	5-yearly CTC screening	
On efficient frontier	72, *167*, **179**	79, *148*, **174**
Cost-neutral vs. no screening	NT, **182**, *230*	2, **210**, *246*
Equal to highest ACER	*254*, 260, **273**	259, *266*, **289**
Equal to colonoscopy ACER	216, **234**, *240*	224, *254*, **255**
	10-yearly CTC screening	
On efficient frontier	15, *171*, **188**	23, *166*, **220**†
Cost-neutral vs. no screening	NT, **308**, *356*	18 **339**, *363*
Equal to highest ACER	338, *388*, **435**	332, *390*, **456**
Equal to colonoscopy ACER	286, **308**, *369*	288, *374*, **404**

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)
* MISCAN values in plain text; SimCRC values in italics; CRC-SPIN values in bold
† CTC strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount