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COST-EFFECTIVENESS OF DNA STOOL TESTING TO SCREEN FOR COLORECTAL CANCER

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Cost-Effectiveness of DNA Stool Testing to Screen for Colorectal Cancer

Report to AHRQ and CMS
from the Cancer Intervention and Surveillance Modeling Network (CISNET)
for MISCAN and SimCRC 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
ASC	Ambulatory surgery center
CISNET	Cancer Intervention and Surveillance Modeling Network
CMS	Centers for Medicare and Medicaid Services
COL	Colonoscopy
CPT	Current procedural terminology
CRC	Colorectal cancer
DIA®	DNA Integrity Assay
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
IPPS	Inpatient prospective payment system
MISCAN	Microsimulation model of Memorial Sloan-Kettering Cancer Center and ErasmusMC
NCD	National coverage determination
NCI	National Cancer Institute
OPPS	Outpatient prospective payment system
PFS	Physician fee schedule
sDNA	DNA stool test
SEER	Surveillance, Epidemiology, and End Results
SIG	Flexible sigmoidoscopy
SimCRC	Microsimulation model of University of Minnesota and Massachusetts General Hospital
TEC	Technology Evaluation Center
USPSTF	United States Preventive Services Task Force

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 reduced CRC mortality by 15-33% in randomized controlled trials with Hemoccult II fecal occult blood tests (FOBTs). Novel CRC screening technologies, such as the DNA stool test have been developed but need to be evaluated in terms of their comparability of diagnostic 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 the DNA stool test and other currently recommended CRC screening strategies.

Methods.
We used two microsimulation models from the National Cancer Institute (NCI)-funded Cancer Intervention and Surveillance Modeling Network (CISNET) consortium to assess the cost-effectiveness of screening for CRC with the DNA stool test 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 the DNA stool test to obtain estimates of its sensitivity and specificity for adenomas by size and for CRC. We derived direct medical cost estimates using the Centers for Medicare and Medicaid Services (CMS) reimbursement for screening and treatment, as well as for complications of screening. We also derived 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 $350 for the DNA stool test. We performed sensitivity and threshold analyses on the cost, diagnostic performance, and relative adherence of the DNA stool test. We considered the currently recommended CRC tests of annual Hemoccult II, Hemoccult SENSA®, and a fecal immunochemical test (FIT) with composite test characteristics of Magstream, HemeSelect, Flexsure, Monohaem, OC-Hemodia, and Insure; 5-year flexible sigmoidoscopy with and without biopsy and with and without FOBT annually; and 10-year colonoscopy.

Results.
The screening benefit for the DNA stool test, measured in terms of life-years gained compared with no screening, was lower than that of annual Hemoccult II testing except for 3-year testing with version 1.1 (i.e., PreGen-Plus™) and with a per-test cost of $350, the overall costs were higher than all of the other screening strategies. All DNA stool test strategies considered were dominated by other recommended CRC screening tests. Screening with the DNA stool test version 1.1 would be cost-effective (i.e., be a non-dominated strategy) at per-test cost of $34 to $51 for 5-yearly DNA stool test screening and $40 to $60 for 3-yearly DNA stool testing, depending on the simulation model used. The threshold costs of the DNA stool test version 1.1 increased to $163-$187 for 5-yearly DNA stool testing if the test performance was at a level that was 50% between base-case values and a perfect test (i.e., sensitivity and specificity equal to 1.0) and $329-$364 if a perfect test. The threshold costs of the DNA stool test version 1.1 at 3-yearly intervals were $140 to $167 if the test performance parameters were 50% of the level between base case and a perfect test and $237-$302 if the DNA stool test had perfect test parameters. If the DNA stool test version 1.1 was able to increase screening adherence to 75%, while adherence

for all other strategies remained at 50%, the threshold costs could increase to $83-$141 at 5-yearly intervals of testing and to $314-$391 at 3-yearly interval intervals of testing. With perfect adherence per-test costs could be $472-$740 at 5-yearly intervals and $730-$822 at 3-yearly intervals, assuming an adherence of 50% for all other tests. Analyses conducted from a modified societal perspective yielded threshold per-test costs that were approximately 2 to 3 times greater than the analyses from the CMS perspective.

Conclusions.
These results suggest that screening for CRC with the DNA stool test version 1.1 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 screening tests, would need to be in the range of $34-$60 to be a non-dominated option. Only if significant improvements for the DNA stool test characteristics or relative adherence with DNA stool testing compared with other available options can be demonstrated, will stool DNA testing at the current costs of $350 be cost-effective. These estimates are based on a third-party payer analysis on an unscreened 65-year old cohort. Threshold costs are similar for a 50-year old cohort, but can be somewhat higher from a modified societal perspective ($88 to $134 for 5-yearly testing and $73 to $116 for 3-yearly testing).

BACKGROUND

Colorectal cancer (CRC) is the second most common cause of cancer-related death in the United States (American Cancer Society 2007). It is estimated that 153,760 CRC cases will be diagnosed in 2007 with 52,180 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 less than 50% in the US population of those aged 50 or older (Seeff 2004).

Currently the U.S. Preventive Services Task Force (USPSTF) (US Preventive Services Task Force 2002, Pignone 2002a), the Gastroenterology Multi-Society Task Force (Winawer 1997, 2003, 2006), and the American Cancer Society (Smith 2006, Winawer 2006) advocate screening for CRC for asymptomatic average-risk individuals, starting at age 50. The USPSTF 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. Before July 1, 2001, Medicare law allowed coverage of screening colonoscopies once every 2 years for individuals at high risk for CRC. Individuals not a high risk for CRC qualified for coverage of CRC screening with FOBT, flexible sigmoidoscopy, and barium enema. The Medicare, Medicaid, and SCHIP Benefits Improvement and Protection Act of 2000, however, added coverage of screening colonoscopies once every 10 years for average-risk individuals.

New CRC screening tests, such as the fecal immunochemical test (FIT) and the DNA stool test 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 whether to cover FIT and, if so, at what reimbursement fee (van Ballegooijen 2003). For this report on DNA stool testing, two 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. This report was initiated 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. Details can be found at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=212.

Vogelstein and colleagues (Vogelstein 1988, Fearon & Vogelstein 1990) described the adenoma-carcinoma sequence as a series of genetic mutations in the *APC, K-ras*, and *p53* genes. They also showed that human DNA from cells shed from the colonic epithelium could be detected in stool. These observations are the basis of the DNA stool test, which is designed to detect these mutations in stool samples as a marker for CRC. Whether such markers from genetic mutations in the stool provide a good screening test is under investigation. The first DNA stool screening test, based on the work of Vogelstein and colleagues work and technologies developed by EXACT Sciences Corp., was developed into a testing service by Laboratory Corporation of America Holdings (LabCorp) and became commercially available in August 2003. Marketed as PreGen-Plus, the assay was composed of 23 molecular markers associated with CRC and pre-malignant neoplasms. These markers include 21 point mutations among the *APC, K-ras*, and *p53* genes, one microsatellite instability marker, BAT-26, for epigenetic factors, and a DNA Integrity Assay (DIA®) for long non-apototic DNA.

The DNA stool test had had several improvements in the development of version 1.0 (Ahlquist 2000, Tagore 2003, Calistri 2003, Brand 2004, Syngal 2006) and for the currently available version 1.1 (Whitney 2004). Further developments include a vimentin marker (Chen 2005, Itzkowitz 2007) for a version 2.0 to be commercially available in the future. Additional improvements are to be expected in the future. This report uses the DNA stool test version 1.1 (i.e., PreGen-Plus) as the base case for analysis in accordance with the NCD but we also consider the DNA stool test version 1.0 as an alternative base case.

In this report we first summarize the evidence on the sensitivity and specificity of the DNA stool test. 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 the DNA stool test 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 DNA stool test strategies). To add robustness to the results we use two microsimulation models, each developed independently by modelers affiliated with the Cancer Intervention and Surveillance Modeling Network (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 two simulation models, MISCAN and SimCRC, 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 and the expected number of colonoscopies performed. Both models were among the first to assess the cost-effectiveness of different screening modalities for CRC. The results of the two models will be compared; comparable results strengthen the credibility of the findings.

LITERATURE REVIEW FOR DNA STOOL TEST CHARACTERISTICS

The literature review for the DNA stool test was based on a PubMed search through January 2007 using the following search terms: "(neoplasm* OR cancer) AND (fecal DNA OR stool DNA OR (stool AND DNA))". The same search terms were used in the 2006 Technology Evaluation Center (TEC) report. We assumed that the TEC systematic review of the literature (Technology Evaluation Center, 2006) represented the best evidence at the time and we were primarily interested in identifying the more recent studies. The main additions include an abstract by Ahlqhist (2007) and the publication of the study by Itzkowitz and colleagues (2007) that provides more detailed information than previously available in abstract form. In order to incorporate the most recent information on this emerging technology, we included abstracts when applicable. All studies of DNA stool test characteristics were for a one-time test. No studies to date evaluate repeat screening with a DNA stool test. Therefore, we do not have information on the degree to which false-negative test results are random (i.e., the adenoma or cancer expresses one of the mutations that the test identifies but the test is negative due to random reasons) or systematic (i.e., the adenoma or cancer does not express any of the mutations that the test identifies so the test will continue to be falsely negative on repeat screenings). A summary of the papers is given in **Appendix 1**.

Version 1.0.

EXACT Science developed a test that detects tumor markers in stool. Initial studies of the DNA stool test were performed using a pre-commercial prototype version of this test, which we refer to in this report as version 1.0. Imperiale (2004) conducted a multi-center (81 sites) colonoscopy study in an average-risk asymptomatic population age 50 or older (75% of subjects age 65 or older). Subjects were also given the Hemoccult II guaiac stool test (three cards) and the pre-commercial version of the PreGen-Plus test (i.e., version 1.0) prior to the colonoscopy. The Hemoccult II test was developed in accordance with the daily clinical practice of each site, and the stool DNA stool test was processed centrally by EXACT. The primary clinical findings were minor polyps (17% of subjects had tubular adenomas and 14% had hyperplastic polyps). Of 4404 subjects undergoing colonoscopy, 426 (10%) had one or more advanced adenomas (adenoma $\geq$1 cm or adenoma < 1 cm with villous histology or high-grade dysplasia) and 31 had CRC (0.7%). Of the 426 patients with advanced adenomas, 139 (33%) contained villous histology and 41 (10%) showed high-grade dysplasia. The sensitivity of the DNA stool test version 1.0 for CRC was 52%; 23 (72%) of the cases detected by the DNA stool test were early stage (TNM stage I or II). This sensitivity estimate was lower than that reported in clinical non-screening studies among subjects with advanced symptomatic cases, but was four times higher than the sensitivity of the Hemoccult II for CRC (13%) (p=0.003). The sensitivity of Hemoccult II for detecting CRC was much lower in the Imperiale study than the 40% that has been in an overview of studies (Pignone 2002b). The specificity of the DNA stool test version 1.0 was comparable with that of Hemoccult II. Of particular value in the Imperiale study was the reporting of sensitivity of the DNA stool test version 1.0 and of Hemoccult II by size of adenoma, stage of CRC, and histology. The DNA stool test version 1.0 had higher sensitivity for the adenomas with high-grade dysplasia than for large adenomas without high grade dysplasia or smaller adenomas.

A study with similar design to Imperiale's study is underway by Ahlquist (U01 CA 89389). This study also used the pre-commercial version of the DNA stool test (i.e., version 1.0) and had

planned to accrue 4000 patients by 2006. Interim results among 2507 patients published in abstract form reported that the sensitivity for screening for advanced neoplasia (CRC, high-grade dysplasia, villous component, or adenoma of size ≥1.0 cm) was 20% for the DNA stool test compared with 12% for Hemoccult II (p=0.03), but there was no difference between the detection of CRC or high-grade dysplasia between the tests (sensitivity of 35% for DNA stool test and 39% for Hemoccult II, p=0.76) (Ahlquist 2005). In this report we use the sensitivity and specificity estimates reported by Imperiale (2004) in our analysis of the DNA stool test version 1.0.

Version 1.1 (PreGen-Plus)

The original version of the DNA stool test (version 1.0) used bead-based technology to extract DNA from stool. The currently-available version 1.1 (PreGen-Plus) includes improvements by LabCorp as described by Whitney (2004) and Olson (2005), including the use of a new gel-based DNA capture approach to enhance yield of human sequence specific DNA from stool. This new procedure was assessed by Whitney (2004) on 86 subjects with CRC and 100 subjects found to have no cancers at colonoscopy. Archival stool samples from these patients had been frozen within 24 to 72 hours after collection. Sensitivity for CRC (70%) and specificity (96%) were higher in the Whitney study than in the Imperiale study. We used the sensitivity for CRC and specificity reported by Whitney for our analysis of the DNA stool test version 1.1.

Although Whitney (2004) included a control group of subjects with no cancer detected on colonoscopy, no information was given on the prevalence of adenomas among these subjects. Accordingly, no estimates were provided for the sensitivity of the DNA stool test for adenomas by size. We used data from studies by Tagore (2003) and Syngal (2006) on the sensitivity of the DNA stool test version 1.0 for large adenomas (≥ 1.0 cm). In the absence of any other data on the sensitivity of the DNA stool test version 1.1 for adenomas 0.6-0.9 cm, we assumed that the sensitivity for medium (0.6-0.9 cm) adenomas was unchanged from those reported by Imperiale (2004). We further assumed that adenomas of size <0.5 cm were not detectable by the DNA stool test but could be detected as false positive results (1-specificity) of DNA stool testing.

Ahlquist (2007) presented results on a DNA stool test incorporating an improved marker panel and DNA capture method and compared the test characteristics with those of Hemoccult II and Hemoccult SENSA®. The version of the test was not explicitly stated, but given the inclusion of an improved marker panel and a new marker, vimentin, it is likely a combination of version 1.1. (improved markers and stool management) and version 2.0 (inclusion of vimentin marker). The blinded multi-center study (NCI-CA 89389) had 4010 asymptomatic average-risk adults with colonoscopy. DNA stool testing was conducted on 218 patients from subsets of those with 'screen-relevant neoplasia' (143) and the colonoscopic normal patients (75). Sensitivity for CRC was 58% and specificity 84%. Sensitivity for adenomas ≥1.0 cm was 45%.

Version 2.0

The 52% sensitivity of the DNA stool test for CRC reported by Imperiale (2004) in the study of colonoscopy in an asymptomatic average-risk population was lower than that obtained from studies using clinically detected cancers (Ahlquist (91%) (2000); Tagore (63%) (2003), Calistri (62%) (2003), Brand (69%) (2004), or Syngal (54%) (2006)). Further assessment of the prototype DNA stool test version 1.0 used in the Imperiale study found that the lower-than-

expected sensitivity was due in part to an unexpectedly low rate of positivity for the DIA® component. This issue was also seen in the contemporaneous Ahlquist study (NCI-CA 89389) where specimens were handled similarly. DNA degradation had occurred during transit of specimens to the laboratory even though the protocol was for samples to be immediately chilled and sent by express courier for rapid delivery. A DNA-stabilizing buffer was developed to be applied to the stool immediately on defecation (Itzkowitz 2007) to prevent DNA degradation for several days and enhance the performance. Also a methylation-specific PCR assay was developed to detect aberrant vimentin methylation, which has been associated with CRCs. Itzkowitz and colleagues conducted a clinical trial in 7 centers of the improved gel-based capture (used in version 1.1), the DNA stabilizing buffer, and vimentin markers. Subjects aged 50-80 who were having colonoscopy in general practice were eligible for the study. Those found to have CRC or no polyps were asked to give a stool sample for testing 6-14 days after the colonoscopy was performed and in the case of those with CRC, prior to surgery for CRC. There were 40 patients with CRC (average age 66 and 50% with early-stage CRC) and 122 no-polyp patients (average age 59) enrolled in this study. With respect to the effect of using post-colonoscopy stools versus pre-colonoscopy stools, a study of post-colonoscopy stool samples from patients with CRC conducted during the same time period as the Imperiale study found that the sensitivity estimated using the post-colonoscopy stool samples (43%) was lower than for that from pre-colonoscopy stool samples (52%) for Imperiale's study suggesting that use of post-colonoscopy stools may underestimate the DNA stool test performance.

With the DNA stabilization buffer and a gel-based DNA purification method, the sensitivity for CRC was 72% for the DNA stool test version 2.0. The sensitivity of the DIA component with the gel-based purification increased from 3% to 65%. Specificity was 89%, lower than the 95% specificity of version 1.0. Vimentin alone had a sensitivity of 73% and specificity of 87%. The least complex assay consisting of two markers—aberrant hypermethylation of vimentin and a two-site DIA (DIA-DY)—had a maximum sensitivity of 88% with a specificity of 82%. These estimates of sensitivity and specificity were from training set analyses designed to determine optimal markers and cutoff values and represent a reduced set of markers from those tested in the Imperiale study. A validation set analysis in an unselected screening population is needed for confirmation of these results. However these initial observations suggest that a test with the two markers (vimentin+DY) could provide sensitivity of 88% and might be the basis for an assay kit that could be managed by many clinical laboratories. Given the post-colonoscopy collection of stool, the adenoma was not studied with the newer markers. The authors noted the need to assess this version for detection of adenomas. Version 2.0 is not yet commercially available. We do consider an optimistic version 2.0 result for a sensitivity analysis on test performance. We use the slightly improved estimates of 90% sensitivity and 85% for specificity as a hypothetical best case for version 2.0. As Itzkowitz notes, it is not known how the new version 2.0 assay will perform in a screening study where most cancers are at an earlier stage where sensitivity tends to be lower and how it will perform in adenoma detection. Also of interest is further confirmation of the specificity of the version 2.0, which was lower than for earlier versions and could mean that this version of the DNA stool test is not necessarily specific for CRC neoplasia. The DNA stool test is continuing to evolve. Version 2.0 is included in the analysis as a sensitivity analysis.

COST-EFFECTIVENESS ANALYSIS

Overview

We used two existing microsimulation models validated against the best available data (Loeve 1999, 2000, Vogelaar 2006, Frazier 2000) to inform the CMS and AHRQ in assessing the effectiveness and cost-effectiveness of the DNA stool test, 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), more recent data on CRC survival (1996-1999 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). 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 (using data from 1996-1999). 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 two 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-COLON and SimCRC 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 17 competing strategies, including no screening. The 16 CRC screening strategies vary by diagnostic 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.

Microsimulation Modeling

The MISCAN and SimCRC 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. As each 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, race, 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 progress from small (1-5 mm) to medium (6-9 mm) to large (10+ mm) size. 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.

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 is 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. A subject with multiple adenomas, especially multiple adenomas of a larger size, would be more likely on average to be detected by screening than a subject 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.

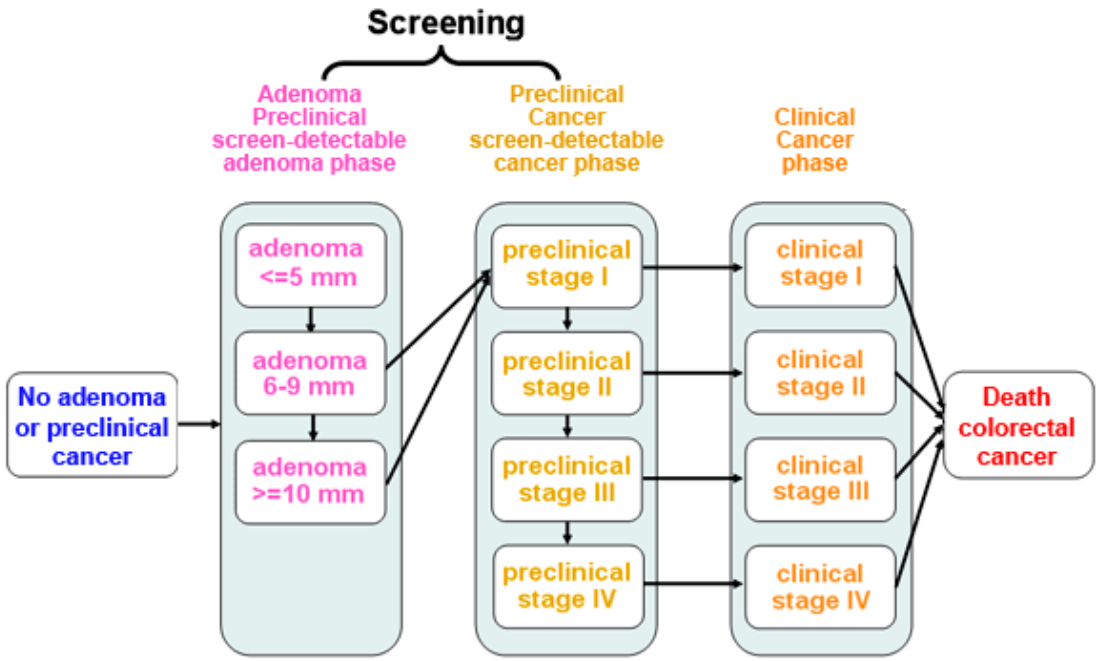

Figure 1: Graphical representation of natural history of disease as modeled by MISCAN and SimCRC models. The opportunity to intervene in the natural history through screening is noted.

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., time from adenoma initiation to development of CRC) differ between the two 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 model all adenomas have the ability to progress to cancer (although most will not during the lifespan of the individual). Although both models predict the same adenoma prevalence and CRC incidence, the difference in the adenoma growth assumptions results in different dwell time estimates between the MISCAN and SimCRC models. The dwell time is defined as the average time between adenoma formation and clinical cancer detection among all cases of cancer. 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. 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 model than in the MISCAN model. In the MISCAN model the additional benefit of increasing screening frequency will be greater than that in SimCRC. A summary of each model is in **Appendix 2**.

Another key difference between the models is the distribution of adenomas in the colorectal tract (see Appendix 3). In the MISCAN model, adenomas are assumed to have the same distribution as CRCs, while the SimCRC model is 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 model, since a larger proportion of adenomas are within the reach of the sigmoidoscope.

As part of the CISNET consortium, we have thoroughly compared the models and found that differences in the average duration of the adenoma-carcinoma sequence explain most of the differences in model predictions.

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 3** for comparison of natural history models). We conducted the 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. The cohort was followed for life (ending at age 100). All inputs were standardized between the two models, including diagnostic performance criteria, costs, and screening and follow-up assumptions.

Screening Strategies

In consultation with AHRQ and CMS, we compared the basic strategies of no screening, screening with FOBT every year, flexible sigmoidoscopy (SIG) every five years, combinations of FOBT and SIG, and colonoscopy every 10 years as recommended by the American Cancer Society (Smith 2006), the USPSTF (US Preventive Services Task Force 2002; Pignone 2002a) and the Multi-Society Task Force (Winawer 1997, 2003, 2006), along with screening with the DNA stool test **(Table 1).** Although barium enema is included in the screening recommendations, it was not considered in this analysis. We evaluated three FOBTs: Hemoccult II (HII), Hemoccult SENSA (HS) and immunochemical FOBT (FIT); two strategies for SIG (with and without biopsy); and two versions of the DNA stool test: the pre-commercial version 1.0 and the commercial version 1.1 (currently available and marketed as PreGen-Plus). The request for NCD asks for consideration of the DNA stool test every 5 years. We also evaluated a 3-year interval in these analyses. 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.

Table 1. Strategies considered in the cost-effectiveness analysis

	Test(s)	Abbreviation	Interval (test 1)	Interval (test 2)	Biopsy @SIG?
1	None		na	na	na
2	DNA stool test (version 1.0)	sDNA-3 (v1.0)	3 years	na	na
3	DNA stool test (version 1.1)	sDNA-3 (v1.1)	3 years	na	na
4	DNA stool test (version 1.0)	sDNA-5 (v1.0)	5 years	na	na
5	DNA stool test (version 1.1)	sDNA-5 (v1.1)	5 years	na	na
6	Hemoccult II	HII	1 year	na	na
7	Hemoccult SENSA	HS	1 year	na	na
8	Fecal immunochemical test	FIT	1 year	na	na
9	Flexible sigmoidoscopy	SIGB	5 years	na	yes
10	Flexible sigmoidoscopy	SIG	5 years	na	no
11	Hemoccult II, SIG	HII+SIGB	1 year	5 years	yes
12	Hemoccult II, SIG	HII+SIG	1 year	5 years	no
13	Hemoccult SENSA, SIG	HS+SIGB	1 year	5 years	yes
14	Hemoccult SENSA, SIG	HS+SIG	1 year	5 years	no
15	FIT, SIG	FIT+SIGB	1 year	5 years	yes
16	FIT, SIG	FIT+SIG	1 year	5 years	no
17	Colonoscopy	COL	10 years	na	na

Follow-up, surveillance, and adherence

We assumed that any individual with a positive FOBT or a positive DNA stool test 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 patients 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 Multi-Society Task Force (Winawer 2006). 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). All 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. The life-years gained per scenario were derived relative to no screening.

CRC Screening Test Characteristics

For the 2003 cost-effectiveness report to AHRQ and CMS on FIT we conducted a literature review for FIT, flexible sigmoidoscopy and colonoscopy (van Ballegooijen 2003). We updated that literature review for those tests and included the recent articles by Morikawa (2005 and 2007), Levi (2007), Vilkin (2005), Guitttet (2007), Fraser (2006), Smith (2006), and Allison (2007). The literature on the DNA stool test was summarized above. 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.

As noted in the 2003 FIT report (van Ballegooijen, 2003), the screening studies for Hemoccult SENSA and FIT are primarily based on higher-risk populations, who were already undergoing colonoscopy and were willing to do a pre-colonoscopy FOBT, or were studies where only the patients with positive tests were evaluated with colonoscopy. Consequently the test parameters for sensitivity from these studies could be higher than that found in a general population screening study.

Fecal immunochemical test (FIT)

There are multiple FITs with varying cut points for positivity, number of slides, number of days tested, and preparations reported in the literature. In the 2003 report by van Ballegooijen we reviewed the literature for FIT, including HemeSelect, Monhaem, Flexsure, Magstream 1000 Hem SP, and Insure. The 2003 report was primarily based on the performance of the Insure test. We updated the estimates for FIT based on a large study on sensitivity and specificity of the Magstream 1000/ Hem SP FIT (Morikawa 2005). The results of the Morikawa study for CRC were 66% sensitivity for CRC and 95% specificity for CRC which were similar to the estimates of sensitivity of 70% and specificity of 95% used in the previous report on FIT to AHRQ and CMS (van Ballegooijen 2003). Consequently we retained the estimates of FIT's specificity and sensitivity for cancer from the previous report. However detection rates for adenomas were slightly higher than in the 2003 FIT report. Because the sensitivity estimates for adenomas in the 2003 report were based on limited data, we used the adenoma sensitivity estimates reported in the Morikawa papers (2005, 2007) for the current report. A new study by Allison (2007) for a FlexSure OBT (currently marketed as Hemoccult ICT by Beckman Coulter) had sensitivity for CRC of 82% and for advanced adenomas was 29.5%. Specificity for the FIT was 98%. The test characteristics used in this analysis are within the confidence intervals of this study.

Hemoccult SENSA
We assumed that the sensitivities of Hemoccult SENSA for adenomas and CRC were similar to those of FIT. However specificity was assumed to be lower for Hemoccult SENSA (van Ballegooijen 2003). In addition to yielding more false-positive results, the lower specificity of Hemoccult SENSA results in a greater number of chance findings of adenomas; consequently adenoma detection with SENSA was considered to be slightly higher than with FIT. In the October 2007 paper by Allison, the sensitivity of Hemoccult SENSA for CRC was 64% (lower than for the FIT comparator) and for advanced adenomas was 41% (higher than for the FIT comparison). Specificity was 98% similar as that for the FIT comparator. Our sensitivity estimates for Hemoccult SENSA are within the confidence intervals of this study. The specificity is significantly higher than assumed in our analysis, but this high specificity is not corroborated by other studies.

Hemoccult II
The estimated CRC sensitivity of Hemoccult II was not changed from the 40% estimated in the 2003 report which was based on a synthesis of the randomized controlled trials (Mandel 1993, Kronborg 1996 and Hardcastle (1996). This sensitivity is considerably higher than the 13% found by Imperiale (2004), but in line with the 47% that Ahlquist (2007) found. One of the reasons for this may be that in the Imperiale study Hemoccult II was not centrally processed. The 40% sensitivity figure is consistent with the randomized trial results according to earlier modeling studies (Gyrd-Hansen 1997, Hardcastle 1996) and other Hemoccult II studies (See **Appendix A** tables from the FIT cost-effectiveness report to CMS for an overview of studies). We assessed the effect of a lower sensitivity of Hemoccult II on the threshold costs of DNA stool screening in a sensitivity analysis. Sensitivities of Hemoccult II for adenomas were estimated by assuming the same ratio between adenoma sensitivity and CRC sensitivity as for FIT.

Flexible sigmoidoscopy
We assumed the same sensitivity for flexible sigmoidoscopy as for colonoscopy within the reach of the scope. The reach of the flexible sigmoidoscopy is generally measured and reported in terms of centimeters of reach rather than location in the colon. However, the models represent adenomas and CRCs by location. We used the correspondence of location and centimeters from the anus from autopsy studies (Eide 1978) as well as the clinical study of Adam (2000) that used an electromagnetic imaging device to record the 3-dimensional position of the scope to estimate the reach for flexible sigmoidoscopy. In a Kaiser Permanente study, 60 cm or more of the colorectum was visualized in 63% of sigmoidoscopies, and at least 40 cm of the colorectum was reached in 83% of sigmoidoscopies (Doria-Rose 2004). 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.

Colonoscopy
Sensitivity estimates for colonoscopy were based on a recent meta-analysis (van Rijn 2006). In screening studies the reach of the colonoscopy has been high with over 90% reaching the cecum. An incomplete colonoscopy should be followed by another colonoscopy or some other procedure to ensure that the entire colon is visualized. We therefore assume that 5% of subjects will have more than one colonoscopy to visualize the entire colon. In the models we assume that an

average of 1.05 colonoscopies is performed per subject to obtain colonoscopic examination and that the cecum is reached in 98% of subjects.

Table 2 contains an overview of test characteristics used in our analyses.

Table 2. Estimates of test characteristics used in analysis

Test	Sensitivity* by adenoma size or CRC (%)				Specificity (%)
	≤5 mm	6-9 mm	≥10 mm	CRC	
FOBT Hemoccult II	2.0	5.0	12.0	40.0	98.0
FOBT Hemoccult SENSA	7.5	12.4	23.9	70.0	92.5
FIT	5.0	10.1	22.0	70.0	95.0
DNA stool test (v1.0)	5.0	12.0	15.0	52.0	95.0
DNA stool test (v1.1)	4.0	12.0	43.0	70.0	96.0
DNA stool test (hypothetical version 2.0)	15.0	22.1	55.0	90.0	85.0
Colonoscopy	75.0	85.0	95.0	95.0	90.0†
Sigmoidoscopy††	75.0	85.0	95.0	95.0	92.0†

* Sensitivity is provided per individual for stool-based tests and per lesion for endoscopy tests.
† The lack of specificity with colonoscopy and sigmoidoscopy screening reflects the detection of non-adenomatous lesions. With colonoscopy these non-adenomatous lesions are removed and therefore induce polypectomy costs. With sigmoidoscopy the presence of non-adenomatous lesions induces biopsy costs (in case of sigmoidoscopy with biopsy) or results in referral for diagnostic colonoscopy (in case of sigmoidoscopy without biopsy).
†† Test characteristics for sigmoidoscopy only apply to the distal colon and rectum.

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.

Screening and complication costs

Costs for screening tests were based on the set of current procedural terminology (CPT) codes relevant to CRC screening in conjunction with the points of service for the procedures. The CPT codes for screening are those stated by the NCD (http://www.medicare.gov/health/coloncancer.asp) for the CRC screening benefit as well as those for associated colonic biopsy or polypectomy (personal communication, John Allen, M.D., and Joel Brill, M.D.). We used the national (i.e., unadjusted for geographic location) payment amounts under the Physician Fee Schedule (PFS) for these analyses. The unadjusted costs rather than the RVUs were used because they more directly reflected the costs for Medicare.

Payer cost for Hemoccult II, Hemoccult SENSA, FIT, and DNA stool test do not include additional charges for points of service because these costs are related only to the clinical laboratory fee schedule (http://www.cms.hhs.gov/ClinicalLabFeeSched/).

The PreGen-Plus was assumed to cost $350 per test based on private insurer reimbursement (Perrone 2007).

Points of service considered for screening were the Outpatient Prospective Payment System (OPPS) and the Ambulatory Surgery Center (ASC) Payment System with the associated facility charge, and the PFS office system. We did not include CPT codes for screening associated with inpatient procedures as registered in the Inpatient Prospective Payment System (IPPS) because screening endoscopies are not typically performed as inpatient procedures. The percentages of procedures by point of service were obtained from CMS. Given that in-patient procedures were excluded, the total percent does not sum to 100%. The percent per point of service out of the total percent for the OPPS, ASC, and PFS procedures were used as weights in obtaining an overall average cost for each procedure. Complication costs were based primarily on inpatient DRG-level reimbursement costs.

Screening procedure costs were based on a weighted average of procedures per setting. The cost values per setting and CPT code are given in **Appendix 4**. The costs for the ASC setting include the ASC payment rates and the PFS facility charge (**Appendix 4, Table 2**). The costs for the OPPS setting included the OPPS payment rates and the PFS facility charge (**Appendix 4**, **Table 3**). For the PFS office setting we used the office payment rates (**Appendix 4, Table 4**). The costs for colonoscopy without polypectomy were based on CPT codes 45378 (diagnostic colonoscopy), G0105 (colon screen in high risk individuals) and G0121 (colon cancer screening for non high risk individual). Costs for colonoscopy with polypectomy or biopsy were composed of codes 45380 (colonoscopy and biopsy), 45381 (colonoscopy, submucous injection), 45382 (colonoscopy/control bleeding), 45383 (lesion removal colonoscopy – fulguration), 45384 (lesion removal colonoscopy-hot biopsy) and 45385 (lesion removal colonoscopy-snare polypectomy).

We assumed that polypectomy was not performed with flexible sigmoidoscopy screening. However, we distinguished flexible sigmoidoscopy with and without biopsy. For flexible sigmoidoscopy without biopsy we used CPT codes 45330 (diagnostic sigmoidoscopy) and G0104 (CA screen; flexi sigmoidoscope). Flexible sigmoidoscopy with biopsy was based on CPT code 45331 (sigmoidoscopy and biopsy).

Polyp removal and pathology review

For the procedures with polypectomy or biopsy we included a pathology charge (CPT code 88305). The Medicare payment rates per jar were $82.40 for the PFS office and ASC settings, and $51.59 for the OPPS setting. We assumed that all biopsies and removed polyps are reviewed by pathology and that a separate jar is submitted to pathology for each of 4 colon segments so that the resection area could be identified should the patient require surgery. Data from the National Colonoscopy Study were used to provide the estimate of 1.38 as the average number of jars per patient with polyps (hyperplastic, other polyps, and adenomas) (personal communication, Ann Zauber, Ph.D.). Consequently, we multiplied the pathology fee by 1.38 to obtain the average pathology cost associated with colonoscopy with polypectomy. Total costs per setting and CPT code are given with and without pathology charge (**Appendix 4, Table 5**).

Multiple polyps requiring the same type of polypectomy removal within a single colonoscopy do not add an incremental charge to the procedure. However if different types of polypectomy are required in removing multiple polyps then CMS reimburses 100% for the most expensive procedure and 50% of the facility cost for the second procedure. As a simplifying assumption we use the weights of procedures by CPT type and do not consider different fees for different combinations of endoscopy CPT codes for polyp removal.

The total costs per CPT code were weighted by the frequencies for points of service (**Appendix 4, Table 6**). The total costs per screening procedure were based on the total costs per CPT code that are part of the procedure and weighted by the frequencies of the CPT codes (**Appendix 4, Table 7**). If the colon is not adequately visualized, a repeat colonoscopy is typically performed. CMS reimburses the second colonoscopy at the same rate as for the initial colonoscopy. We assumed 5% of the colonoscopies are incomplete and need to be repeated. Instead of modeling incomplete colonoscopies, we increased the costs of a colonoscopy without polypectomy ($497.59) by 5%, resulting in $522.47. For colonoscopy with polypectomy we added the same absolute difference of $25, resulting in $673.4 (648.52 + 25). The additional $25 reflects repeat colonoscopies assuming that polyps were only removed at one of the two colonoscopies. The cost of sedation is included in the cost of colonoscopy, assuming that it is not administered by an anesthesiologist. The resulting costs per screening test are provided in **Table 3**.

Table 3. Screening tests costs based on the CMS cost reimbursement ($2007)

Screening test	CMS cost, $	Modified societal cost, $
Guaiac Hemoccult (II or SENSA)	4.54	21.54
Immunochemical fecal occult blood test (FIT)	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
DNA stool test version 1.0 and version 1.1 (assumption)	350.00	367.00

Complications of screening

The harms as well as the benefits of screening must be taken into account. There are essentially no complications from the stool-based screening tests (Hemoccult II, SENSA, FIT, or DNA stool test) from the tests themselves. However patients undergoing colonoscopy and, to a lesser extent, flexible sigmoidoscopy are at risk of experiencing complications from the procedures. Since individuals with a positive sigmoidoscopy or stool-based test are referred for a follow-up colonoscopy, the complications and the associated costs are relevant and accounted for in all of the screening strategies.

Risks of complications reported in organized screening programs (Lieberman 2000, Regula 2006, Pox 2007) are lower than those reported for general practice colonoscopies. (Levin 2002, 2006) and have not focused on the older ages. Also risks of complications of colonoscopy have declined over time. The major complications of colonoscopy are perforations, which can occur with or without polypectomy, serosal burns, bleeds requiring transfusion and bleeds not requiring

transfusion (Levin 2006, Lieberman 2000, Pox, 2005, Klabunde (2007), and personal communication from Drs. John Allen and Joel Brill). Dehydration was also cited as a complication of colonoscopy in an assessment in the Medicare population (personal communication; Joan Warren, Ph.D. and Carrie Klabunde, Ph.D). All available data were used in deriving the complication rate estimates (Table 4).

The costs of complications were based on the relevant DRG codes. We assumed that a patient with a perforation or a bleed with transfusion would require hospitalization and that a patient with a bleed that does not require transfusion would be treated in an emergency room visit. The cost of perforation was based on DRG 442 (other OR procedures for injuries with colon cancer) and bleeding with transfusion was based on DRG 452 (complications with treatment of colon cancer). A patient with a serosal burn generally requires a two-day hospitalization, which we assumed to cost the same as a bleed with transfusion.

We estimated a rate of death among persons with a therapeutic colonoscopy (i.e., a colonoscopy with adenoma removal) of 1 per 10,000 (Jentschura 1994). A summary of the costs and risks of complications is provided in **Table 4.**

Table 4. Summary of costs and risks of endoscopy complications

Complication	Rate per 1000	Cost, $2007
With colonoscopy		
Perforation	0.7	12,446
Serosal burn	0.3	5,208
Bleed with transfusion	0.4	5,208
Bleed without transfusion	1.1	320
With flexible sigmoidoscopy		
Perforation	0.02	12,446

Costs for colorectal cancer treatment

The cost of CRC treatment was derived from comparison of costs for CRC cases relative to those of matched controls in the SEER-Medicare files (personal communication, Robin Yabroff, Ph.D. and Martin Brown, Ph.D.). The methods used to estimate phase-specific costs of CRC were based on a previous analysis of SEER-Medicare data (Brown 1999). Cost data were reported in 2004 dollars and subsequently updated to 2007 dollars using the medical care component of the Consumer Price Index (CPI). While there is some differing of opinion about the use of the medical care component of the CPI vs. the overall index, the difference between the two is not large for this period of time.

Patients with a diagnosis of invasive CRC between 1973 and 2002 and aged 65 or above at some time between 1998 and 2003 were selected from SEER-Medicare (N = 124,793). Cancer patients with a prior cancer diagnosis (N= 20,277), or who were identified as having cancer through a death certificate or autopsy were excluded (N=623). An additional 24,920 patients were excluded because they were enrolled in managed care throughout the observation period or did not have both Medicare part A and part B at any point during the observation period. The remaining 76,722 CRC patients were included.

Potential controls were individuals without any cancer diagnoses recorded by SEER and aged 65 or above during the observation period, 1998-2003. A total of 170,491 controls were selected from a 5% random sample of Medicare enrollees and frequency matched to cases by gender, 5-year age strata (65-69, 70-74, 75-79, 80+) and SEER registry areas.

Phase of care definitions. Phase of care definitions were based on prior studies of direct medical costs. For cancer patients, months of observation and cost of care between 1998 and 2003 were divided into three clinically relevant phases of care – initial, last year of life, and continuing care based on the month of service on the Medicare claim. Date of death (or its absence) in the Medicare enrollment file through 2004 was used to determine vital status. Cause of death (cancer, non-cancer) was identified from SEER. The initial phase was defined as the first 12 months following diagnosis, the last-year-of-life phase was defined as the final 12 months of life, and the continuing phase was defined as all months between the initial and last-year-of-life phases of care. Not all cancer patients contributed to all phases of care, however. For patients surviving less than 24 months after diagnosis, the final 12 months of observation and costs of care were then allocated first to the last-year-of-life phase, because the content of care for patients with short survival is more similar to the last–year-of-life phase than the initial phase. The remainder of months of observation and costs were allocated to the initial phase, with no contribution to the continuing phase. Patients diagnosed prior to 1997 who survived beyond 2003 contributed months and costs of care only to the continuing phase. Within each tumor site and phase of care, average monthly estimates of cost of care were calculated.

Because control subjects did not have a date of cancer diagnosis, they were randomly assigned a "pseudo-diagnosis date" that corresponded to the date of diagnosis of one of the pool of cancer cases. Months of observation and costs of care were assigned to phases of care in the same manner used with cases. In addition to frequency matching by gender, 5-year age group and SEER area strata, controls were also matched to cases by phase of care. To reflect costs associated with cancer care in the last year of life, cancer patients who died of cancer were matched to continuing controls, and cancer patients who died of other causes were matched to last-year-of-life controls. As with cancer patients, average monthly estimates of cost of care were calculated for each phase of care for each of group of controls. For months in which patients received coverage through managed care or were without both Medicare part A and part B, costs and months of observation time were excluded because these data would not completely capture the care received during this period.

Cost estimates. Cancer-related medical costs were estimated as differences in costs for cases and controls by phase of care. The analysis used Medicare payments to reflect costs of care, rather than billed charges. Payments for Medicare Part A (inpatient services) and Part B (outpatient services) were calculated separately. The Hospital Wage Index and the Medicare Economic Index were used to adjust for inflation in Medicare Parts A and B estimates, respectively, during 1998-2003. We also adjusted for geographic variability in costs of care across SEER sites. New treatments including biologicals, such as Avastin and Erbitux (Schrag 2004), have come into use in the past 3 years; these new drugs are markedly more expensive than the previous drugs. However the cost of these new drugs would not be captured by the 2004 reimbursement base available for this case-control study. The costs that were used as model inputs from the payer perspective are shown in the top half of **Table 5**.

Table 5. Net payments for CRC care during 1998-2003 (in $2007)*

AJCC Stage	Initial Phase	Continuing Phase	Last Year of Life: Died of Cancer	Last Year of Life: Died of 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.

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 and with flexible sigmoidoscopy was 4 hours. Patient time requirements for stool-based screen tests (e.g., Hemoccult II, Hemoccult SENSA, FIT and DNA stool test) were assumed to be 1 hour. For treatment of complications with colonoscopy and sigmoidoscopy, we assumed that patient time requirements would be on average16 hours. Modified societal costs for screening are given in the right-hand size of **Table 3**.

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. Over the time period studied, these averaged about 8% for Part A and about 30% for Part B. 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. This study estimates the frequencies of relevant medical services, including physician office visits, emergency room visits, chemotherapy, radiation therapy, hospitalizations, imaging procedures, and ambulatory surgeries. Average service frequencies were then combined with estimates of patient time for each category of service, and the value of patient time was then assigned. Net patient time costs associated with cancer care were calculated by subtracting mean values for control subjects from mean values for patients by service category in the initial, continuing, and last-year-of-life phases of care. Total time costs were estimated to be $4,052 for

the initial phase of care and $4,705 for the last-year-of-life phase of care. These estimates of time costs are a somewhat different than estimates reported previously (Yabroff 2005), primarily due to refined methods and a longer observation period, and inclusion of additional services (i.e., imaging procedures). In that 2005 study the time costs associated with initial, continuing (per month), and terminal phases were $4592, $25, and $2788, respectively. Because the 2007 analysis did not provide time costs for the continuing phase of care, we used a monthly cost of $27. The treatment costs that were used as model inputs from the payer perspective are shown in the bottom half of **Table 5**.

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 17 screening strategies 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 none of the DNA stool test strategies lie on the efficient frontier, we then determined the degree to which each of the following parameters would have to change in order for one of the DNA stool test strategies to reach the frontier: unit cost of the DNA stool test, diagnostic performance of the DNA stool test, or relative adherence with the DNA stool test compared with other screening tests.

Threshold analysis
Next, we identified threshold costs for the DNA stool test using the version 1.0 and version 1.1 assumptions. For each DNA stool test strategy, we calculated the maximum costs of a single DNA stool test for the strategy to be part of the efficient frontier. There were three possible situations to consider when including one of the DNA stool test strategies as an efficient strategy: (1) the DNA stool test strategy was less effective than the least effective strategy on the efficient frontier, (2) the DNA stool test strategy was more effective than the most effective strategy on the efficient frontier, and (3) the effectiveness of the DNA stool test strategy was intermediate to the least effective and most effective strategies on the efficient frontier.

In the first case the threshold costs of the DNA stool test were calculated such that the ICER for the least effective efficient strategy compared with the DNA stool test strategy is equal to the

previous ICER of the next least effective efficient strategy (prior to the addition of the DNA stool test strategy). In the second case the threshold test costs were calculated such that the ICER for the DNA stool test strategy compared with the most effective efficient strategy is equal to $100,000 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 DNA stool test strategy. Subsequently the threshold costs were calculated such that the ICER of the DNA stool test strategy is equal to the ICER of that selected strategy.

While calculating ICERs for competing alternatives is the theoretically correct approach for optimizing the health of a population under constrained resources (Gold 1996), we also determined threshold costs for the DNA stool test such that the test strategy has the same average cost-effectiveness ratio (ACER) as at least one other recommended CRC screening strategy. ACERs represent the incremental cost per life-year saved of each strategy relative to no screening. We calculated the per-test cost that would allow a DNA stool test strategy to have the same ACER as the non-DNA stool test strategy with the lowest and the highest ACER values. When the strategy with the lowest ACER was cost-saving we calculated the per-test cost for the DNA stool test that would make that strategy cost neutral (i.e., the same lifetime discounted costs as no screening). The disadvantage of this latter approach is that with the threshold costs calculated this way, the DNA stool test strategy could be less effective and more costly than other screening strategies.

Sensitivity analysis

In analyses of the impact of alternative assumptions about key model parameters (often called sensitivity analyses), it is customary to vary the uncertain parameters around the best estimates (i.e., the base-case estimates). We anticipated that DNA stool testing, based on evidence available to date, would not be cost-effective when compared with the other CRC screening tests, given that the DNA stool test was not more sensitive or specific than Hemoccult SENSA and yet almost 80 times as expensive. Therefore, we focused our sensitivity analyses on varying the diagnostic performance characteristics in only a more favorable direction. In addition, we varied the test performance of the DNA stool test beyond what is clinically plausible; namely, a perfect test. This represents a solely hypothetical scenario.

The NCD is requested for PreGen-Plus (i.e., DNA stool test version 1.1) based on Whitney (2004). Version 2.0 is in development based on the training set analysis of the Itzkowitz study where sensitivity for cancer was 88% and specificity 82%. Given the potential for further evolution of the DNA stool test, we created a hypothetical best-case version 2.0 with 90% sensitivity and 85% specificity. The sensitivity for adenomas by size was increased proportionally by the same increase (29%) as for the increase in sensitivity for cancer from version 1.1 to version 2.0.

We identified the threshold DNA stool test costs for this scenario and other hypothetical scenarios in which the diagnostic performance of the DNA stool test was varied from the base-case version 1.1 values to the perfect test assumption. The sensitivities for small, medium, large adenomas and cancer, as well as the specificity of the base-case estimate were increased by a percentage of the difference between the base-case values (version 1.1) and perfect sensitivity and specificity. The percentages used were 10%, 25%, 50%, 75% and 100% and were multiplied

by the difference between perfection (sensitivity and specificity of 1.0) and the version 1.1 base-cases values and added to the base-case version 1.1 values (**Table 6**).

Table 6. DNA stool test sensitivity and specificity values used in sensitivity analysis

Test Assumption	Sensitivity by adenoma size or CRC, %				Specificity (%)
	≤5 mm	6-9 mm	≥10 mm	Cancer	
sDNA (v1.1)	4	12	43	70	96
sDNA (v1.1) + 10%	13	20	48	73	96
sDNA (v1.1) + 25%	27	33	57	77	97
sDNA (v1.1) + 50%	51	55	71	85	98
sDNA (v1.1) + 75%	75	77	85	92	99
sDNA (v1.1) + 100%	100	100	100	100	100

We also identified threshold DNA stool test costs of scenarios where we allowed the adherence of DNA stool test strategies to be greater than that of all other screening strategies. We took an approach similar to examining DNA stool test characteristics to assess the impact of differential adherence with a DNA stool test compared with other screening tests. Our base-case analysis assumes that 100% of participants adhere to recommendations for the screening tests. Some have suggested that use of DNA stool testing might entice a previously unscreened individual to undergo screening because it is non-invasive, requires no dietary restrictions or bowel preparation, and can be conducted at home and shipped from any location. Schroy (2005) assessed the patients' test preferences in the Imperiale study and found more people preferred the DNA stool test (45%) than Hemoccult II (32%) or colonoscopy (15%). To test the impact of differential adherence rates on the threshold DNA stool test cost, we conducted a sensitivity analysis on adherence where we first started with a more realistic adherence rate for all tests of 50%. We assumed that an individual would be either 100% adherent to a screening strategy or non-adherent. The impact of modeling adherence in this fashion is the it does not alter the ICERs and it allows us to evaluate the impact of enhancing screening with the DNA stool test in a previously unscreened segment of the population. We then allowed adherence for the DNA stool test strategy to be better than the other primary screening tests, which were set at an adherence rate of 50%. The adherence with the DNA stool test strategy was varied from 50% to 55%, 62.5%, 75%, 87.5% and 100% representing a 10%, 25%, 50%, 75% and 100% increase in adherence.

Since a previous analysis of the cost-effectiveness of the DNA stool test by Song and colleagues (2004) concluded that DNA stool testing every two years with a per-test cost of $195 resulted in life-years gained and costs comparable to those of colonoscopy screening every ten years, we also evaluated the threshold costs DNA stool test costs using a two-year screening interval. We also evaluated the cost-effectiveness of DNA stool testing among a cohort of 50-year-olds, since current recommendations suggest that individuals at average risk begin CRC screening at age 50.

RESULTS

Projected Undiscounted Outcomes with Screening

Undiscounted outcomes associated with the screening strategies are presented in **Table 7A** for the MISCAN model and **Table 7B** for the SimCRC model. Without screening we project that 57 out of every 1,000 65-year old individuals will be diagnosed with CRC in their lifetimes. This induces approximately $3.4 to $4.0 million in lifetime direct medical costs ($60 to $71 thousand per CRC case). With screening, many of these CRC cases can be prevented assuming 100% adherence to screening regiments; the reduction in the lifetime risk of CRC ranged from 32-39% with annual FOBT (Hemoccult II) screening to 53-72% with 10-year colonoscopy screening (reported ranges describe differences between projections by model). Some of the benefit associated with the fecal-related tests is because 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 are placed on 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, saving 153 life-years per 1000 persons screened. In the SimCRC model 10-yearly colonoscopy is most effective, saving 159 life-years per 1000 persons screened. For all screening strategies except the DNA stool test strategies, the costs of screening, follow-up and surveillance (including treatment of colonoscopy complications) are smaller than the savings from foregone treatment of prevented CRC cases. The DNA stool testing strategies under the base-case assumptions (i.e., version 1.0 and version 1.1 with a per-test cost of $350) were the most costly screening strategies. In addition, all but the 3-yearly version 1.1 strategy were less effective than annual Hemoccult II. Life-years saved varied from 58 to 122 per 1000 persons screened depending on the version of the DNA stool test, the screening interval and the simulation model used. The total costs ranged from $3.6 million to $5.2 million per 1000.

Cost-Effectiveness Analysis from Payer Perspective

Table 8 shows the total discounted costs, discounted life-years gained, and the incremental cost-effectiveness ratios for 17 screening strategies, including no screening, for each model (results for a cohort of 50-year-olds are presented in **Appendix 6**). The models varied somewhat as to which tests were on the efficient frontier (i.e., were not ruled out by simple or extended dominance). Both models showed DNA stool test version 1.0 strategies to be the most expensive options when offered every three years at a cost of $350, and still more expensive than the other alternatives when offered at 5 year intervals. Under the DNA stool version 1.1 test assumptions, screening every three years with DNA stool testing resulted in more life-years gained than the cheapest test Hemoccult II. All other scenarios with the DNA stool test result in fewer life-years gained than the other tests (this finding true with both models). **Figure 2** shows a plot 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 and this result was consistent for both models. There were several other strategies found to be cost-saving in the SimCRC analysis and near cost-saving in the MISCAN analysis (**Table 8**).

Threshold Analyses

At the base-case cost for a DNA stool test of $350, none of the DNA stool test strategies were on the efficient frontier. Threshold analyses indicated that with the version 1.0 test assumptions, lowering the cost to $0 would not move the DNA stool test strategy to the frontier (**Table 9**). In order to be on the efficient frontier the DNA stool test version 1.1 can have a maximum unit cost of $34-$51 (based on MISCAN and SimCRC, respectively) when offered every 5 years, or $40-$60 (based on MISCAN and SimCRC, respectively) when offered every 3 years. The threshold costs are slightly higher when compared with no screening, and even higher when compared with the strategy with the highest ACER. In no case was the threshold cost as high as the base-case unit cost estimate of $350. (This finding held when evaluating DNA stool testing among a cohort of 50-year-olds—see **Appendix 6**).

Sensitivity analyses

The threshold costs with varying sensitivity and specificity for the DNA stool test are shown in **Table 9**. Analysis with the SimCRC model identified no scenarios for which the threshold value of the cost of the DNA stool test could be greater than its base-case value of $350 and still be on the efficient frontier. With the MISCAN model, the cost of the DNA stool test may rise to $364 if the test is perfect with respect to sensitivity and specificity and if offered every 5 years. Our analysis showed that there were no other assumptions that yielded a threshold cost as high as $350. This was true whether comparing to other tests on an incremental cost-effectiveness basis or comparing with ACERs. For example, when comparing with ACER values of alternative screening strategies the unit cost of the DNA stool test has to be lower than $288 (SimCRC) or $324 (MISCAN), even if the test was perfect.

If individuals who would not be screened otherwise would get screened with a DNA stool test strategy, the cost-effectiveness of the DNA stool testing strategy test would improve. The threshold costs for the test to lie on the efficient frontier under varying adherence assumptions are shown in **Table 10**. Analyses with the MISCAN model showed that adherence has to increase to almost 75% (with other tests at 50%) for 3-yearly DNA stool testing to be on the frontier with the base-case cost of $350. Analyses with the SimCRC model showed that adherence has to be between 75% and 87.5% for 3-yearly DNA stool testing to be on the frontier with the base-case cost of $350.

Table 11 contains the results of the threshold analysis from a modified societal perspective. From this perspective the threshold costs that result in the DNA stool test reaching the efficient frontier are $105-$151 for the 5-yearly DNA stool test strategy and $90-$133 for 3-year DNA stool testing (version 1.1). These thresholds costs are considerably 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 DNA stool screening, allowing for higher per-test costs for the DNA stool test. 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 yields CMS reimbursement rates of $88-$134 for 5-yearly DNA stool testing and $73-$116 for 3-yearly DNA stool testing.

We also looked at the potential effect of lower Hemoccult II sensitivity on the threshold costs for the DNA stool test. For the SimCRC model, this would not influence the threshold costs, because Hemoccult II is not on the efficient frontier. According to the MISCAN model, Hemoccult II is one of the efficient strategies and on the frontier. With a 13% sensitivity for CRC, the most that could happen is that Hemoccult II would no longer be on the frontier. This would change threshold cost to $17 for version 1.0 irrespective of 3 or 5-year interval. For version 1.1 the threshold costs would become $69 for DNA stool screening every 5 years and $60 for every 3 years. So for both models the threshold costs did not change dramatically.

All analyses were conducted for the Medicare population aged 65 years and older and we assumed no prior screening in this group. To assess the effect of this assumption, we evaluated the cost-effectiveness of the 17 screening strategies for a cohort of 50-year-olds, with screening starting at age 50. Results are presented in **Appendix 6**. The DNA stool tests remained the most expensive of the test considered. In the SimCRC analysis, DNA stool testing every 3 years with version 1.1 continued to be the only DNA stool test that provided more life-years gained than annual screening with Hemoccult II; in the MISCAN analysis, all four DNA stool tests evaluated were less effective than annual Hemoccult II. At a per-test cost of $350, both models found the DNA stool test strategies to be the most expensive of the strategies considered; the per-test cost would have to fall to $27-$52 to be on the efficient frontier.

Finally, the threshold costs of DNA stool testing (version 1.1) every 2 years were estimated to be $44 for MISCAN and $62 for SimCRC.

Table 7A. Undiscounted costs (by type), number of life-years gained, and number of cases of CRC per 1,000 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
sDNA-3 (v1.0)	$1,419,427	$181,848	$72,878	$350,014	$13,292	$3,159,608	$5,197,067	92	25	18
sDNA-3 (v1.1)	$1,362,699	$199,796	$91,934	$443,832	$16,086	$2,784,833	$4,899,180	120	18	19
sDNA-5 (v1.0)	$1,013,408	$136,033	$56,152	$262,042	$9,949	$3,372,775	$4,850,360	73	31	15
sDNA-5 (v1.1)	$977,050	$163,499	$78,796	$368,694	$13,301	$2,988,979	$4,590,318	104	22	18
HII	$45,567	$207,506	$87,025	$418,971	$15,657	$2,925,082	$3,699,806	116	18	21
HS	$31,752	$370,324	$125,518	$693,308	$26,582	$2,500,216	$3,747,699	142	11	20
FIT	$178,070	$318,965	$116,195	$614,451	$23,328	$2,571,850	$3,822,859	140	12	21
SIGB	$516,675	$193,588	$115,573	$545,369	$19,109	$2,415,712	$3,806,025	131	16	14
SIG	$378,688	$268,724	$124,836	$634,022	$23,148	$2,372,366	$3,801,783	135	15	15
HII + SIGB	$471,001	$279,352	$130,885	$665,263	$24,149	$2,102,977	$3,673,628	148	11	17
HII + SIG	$355,287	$332,971	$136,711	$730,017	$26,785	$2,277,709	$3,859,480	149	11	17
HS + SIGB	$344,189	$398,645	$145,063	$819,206	$30,828	$2,022,441	$3,760,373	153	10	17
HS + SIG	$262,943	$422,609	$147,761	$854,744	$32,085	$2,211,166	$3,931,308	153	10	17
FIT + SIGB	$507,503	$356,940	$140,680	$765,510	$28,498	$2,234,254	$4,033,384	153	10	18
FIT + SIG	$402,034	$391,163	$144,354	$811,076	$30,463	$2,221,929	$4,001,019	153	10	17
COL	$776,378	$0	$152,503	$677,095	$36,325	$2,198,557	$3,840,859	151	12	15

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

Table 7B. Undiscounted costs (by type), number of life-years gained, and number of cases of CRC per 1,000 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	$3,406,503	$3,406,503	0	57	0
sDNA-3 (v1.0)	$1,468,511	$172,574	$55,388	$210,571	$10,279	$2,595,692	$4,513,016	83	20	20
sDNA-3 (v1.1)	$1,448,098	$178,178	$65,416	$265,912	$11,634	$1,931,696	$3,900,933	122	12	18
sDNA-5 (v1.0)	$1,046,873	$127,259	$42,469	$157,897	$7,799	$2,813,180	$4,195,476	58	27	18
sDNA-5 (v1.1)	$1,031,352	$139,686	$53,868	$214,483	$9,291	$2,201,285	$3,649,965	99	17	18
HII	$75,126	$190,907	$63,945	$249,401	$11,699	$2,233,227	$2,824,305	111	13	22
HS	$122,603	$363,995	$101,136	$407,203	$21,525	$1,648,494	$2,664,956	143	6	18
FIT	$250,342	$308,947	$91,616	$368,816	$18,539	$1,726,963	$2,765,224	141	7	19
SIGB	$549,359	$130,176	$68,055	$297,321	$10,841	$1,791,959	$2,847,711	111	18	10
SIG	$457,544	$220,570	$82,655	$351,252	$15,398	$1,686,085	$2,813,504	118	15	11
HII + SIGB	$612,219	$253,306	$82,674	$238,708	$13,117	$1,465,526	$2,665,551	148	6	15
HII + SIG	$533,441	$334,296	$89,970	$254,103	$15,600	$1,412,301	$2,639,711	150	6	15
HS + SIGB	$501,725	$392,829	$110,795	$415,367	$22,411	$1,263,911	$2,707,038	158	4	14
HS + SIG	$447,431	$447,502	$114,907	$429,300	$24,196	$1,239,606	$2,702,942	159	4	14
FIT + SIGB	$701,117	$345,956	$102,925	$364,191	$19,389	$1,289,776	$2,823,355	157	5	14
FIT + SIG	$643,031	$409,891	$107,860	$377,288	$21,379	$1,261,588	$2,821,036	158	4	14
COL	$793,467	$0	$138,695	$597,506	$34,731	$1,113,881	$2,678,281	159	4	12

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

Table 8. Discounted costs and life-years gained per 1,000 65-year-olds without CRC screening and with 16 CRC screening strategies and associated incremental cost-effectiveness ratios (ICERs)

	MISCAN			SimCRC		
Strategy	Discounted costs	Discounted life-years gained	ICER	Discounted costs	Discounted life-years gained	ICER
No Screening	$2,714,556	0	d	$2,295,628	0	d
sDNA-3 (v1.0)	$3,860,227	51.4	d	$3,473,214	42.2	d
sDNA-3 (v1.1)	$3,673,499	68.0	d	$3,081,338	64.2	d
sDNA-5 (v1.0)	$3,533,981	40.9	d	$3,147,621	28.6	d
sDNA-5 (v1.1)	$3,382,910	58.8	d	$2,814,315	51.4	d
HII	$2,630,626	65.1	---	$2,121,988	57.9	d
HS	$2,715,327	80.4	$5,600	$2,078,632	76.1	---
FIT	$2,776,790	79.4	d	$2,155,730	75.0	d
SIGB	$2,823,196	74.3	d	$2,189,080	58.7	d
SIG	$2,810,490	76.2	d	$2,176,765	62.4	d
HII + SIGB	$2,793,754	84.1	$20,800	$2,127,263	79.0	d
HII + SIG	$2,840,538	84.6	d	$2,113,618	80.2	$8,600
HS + SIGB	$2,863,769	87.1	$23,900	$2,187,768	84.7	d
HS + SIG	$2,909,359	87.1	d	$2,187,042	85.2	$14,600
FIT + SIGB	$3,025,571	87.1	d	$2,282,357	84.6	d
FIT + SIG	$2,992,773	87.2	$924,800	$2,283,025	85.1	d
COL	$2,906,064	86.2	d	$2,199,809	85.5	$40,200

--- indicates default strategy (i.e., the least costly and least effective non-dominated strategy)
d = dominated

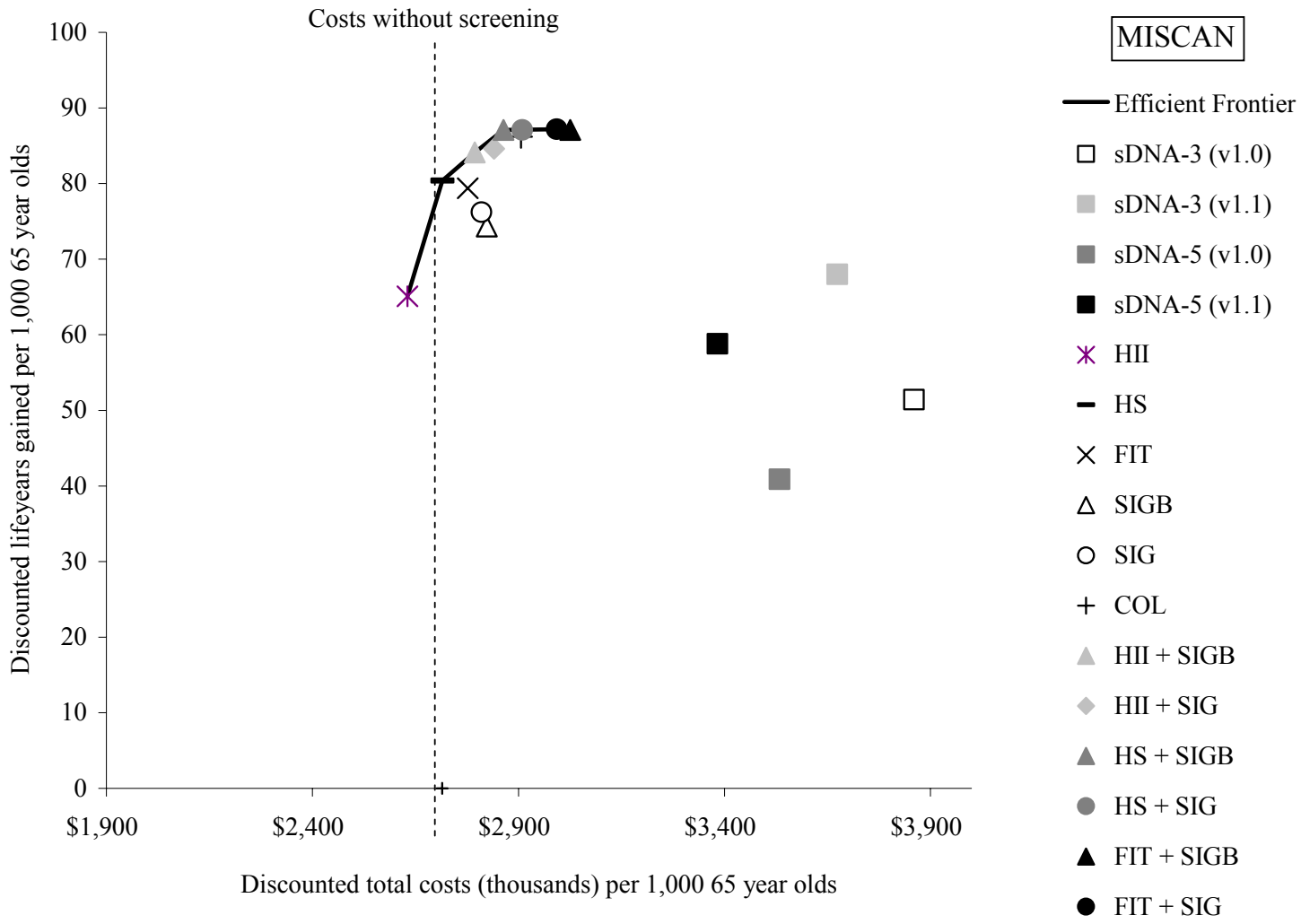

Figure 2 – Panel A Discounted costs and discounted life-years gained per 1,000 65-year-olds for 16 CRC screening strategies and the efficient frontier connecting the efficient strategies - MISCAN

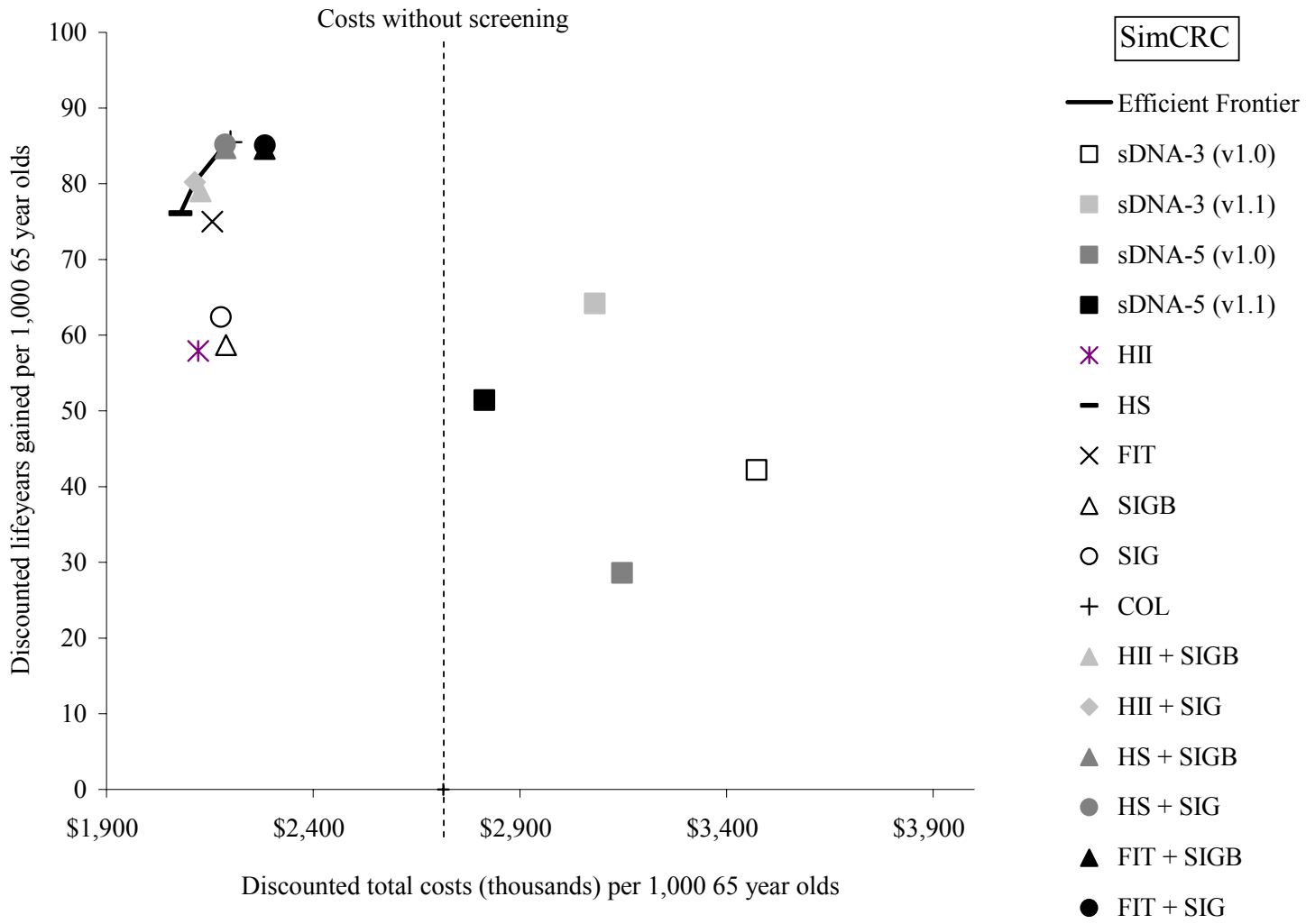

Figure 2 – Panel B Discounted costs and discounted life-years gained per 1,000 65-year-olds for 16 CRC screening strategies and the efficient frontier connecting the efficient strategies – SimCRC

Table 9. Threshold analysis on DNA stool test characteristics: unit costs for DNA stool test resulting in equal cost-effectiveness (ACER and ICER) compared to current recommended CRC screening strategies for different combinations of test sensitivity and specificity*

	Base cases			Sensitivity analysis of hypothetical test characteristics (sensitivity + specificity) †				
	sDNA (v1.0)	sDNA (v1.1)	sDNA (v2.0)	sDNA (v1.1) + 10%	sDNA (v1.1) + 25%	sDNA (v1.1) + 50%	sDNA (v1.1) + 75%	sDNA (v1.1) + 100% (=perfect)
				5-yearly DNA stool testing				
On efficient frontier	*NT*, NT	34‡, *51*‡	2, *31*‡	85, *85*‡	*117*‡, 128	*163*, 187	*215*, 250§	*329*§, 364§
Cost-neutral vs. no screening	*7*, 16	69, *139*	32, *131*	115, *177*	138, *214*	154, *251*	159, *273*	163, *288*
Equal to highest ACER	*5*, 76	*136*, 157	148, *126*	*173*, 217	*209*, 259	*245*, 295	*267*, 312	*281*, 324
				3-yearly DNA stool testing				
On efficient frontier	*NT*, NT	40, *60*‡	17, *41*‡	*79*‡, 87	*102*, 118	*140*, 167	*179*§, 247§	*237*§, 302§
Cost-neutral vs. no screening	*13*, 17	60, *123*	23, *118*	96, *146*	108, *167*	117, *188*	121, *200*	123, *207*
Equal to highest ACER	*11*, 70	*120*, 133	125, *114*	*143*, 176	*163*, 202	*183*, 223	*195*, 234	*202*, 241

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)
ICER = incremental cost-effectiveness ratio (calculated using discounted costs and life-years gained)
NT = no threshold found (i.e., negative DNA stool test cost)
* MISCAN values in plain text; SimCRC values in italics
† See Table 6 for the sensitivity and specificity estimates used in these scenarios
‡ DNA stool test strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount
§ DNA stool test strategy is on the frontier with ICER of $100,000 if the cost is at least this amount

Table 10. Threshold analysis on DNA stool test adherence: unit costs for DNA stool test resulting in equal cost-effectiveness (ACER and ICER) compared to current recommended CRC screening strategies for different levels of adherence with DNA stool screening*

sDNA (v1.1)	Base cases	Sensitivity Analysis on sDNA adherence†				
	Adherence 50% for all strategies	sDNA adherence 55%	sDNA adherence 62.5%	sDNA adherence 75%	sDNA adherence 87.5%	sDNA adherence 100%
			5-yearly DNA stool testing			
On efficient frontier	34‡, *51*‡	37‡, *59*‡	56, *68*‡	*83*, 141§	*221*§, 483§	*472*§, 740§
Cost-neutral vs. no screening	69, *139*	69, *139*	69, *139*	69, *139*	69, *139*	69, *139*
Equal to highest ACER	*136*, 157	*136*, 157	*136*, 157	*136*, 157	*136*, 157	*136*, 157
			3-yearly DNA stool testing			
On efficient frontier	40, *60*‡	52, *66*‡	*81*, 84	*314*§, 391§	*552*§, 637§	*730*§, 822§
Cost-neutral vs. no screening	60, *123*	60, *123*	60, *123*	60, *123*	60, *123*	60, *123*
Equal to highest ACER	*120*, 133	*120*, 133	*120*, 133	*120*, 133	*120*, 133	*120*, 133

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)
ICER = incremental cost-effectiveness ratio (calculated using discounted costs and life-years gained)
* MISCAN values in plain text; SimCRC values in italics
† Strategies other than DNA stool test remain at 50% adherence
‡ DNA stool test strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount
§ DNA stool test strategy is on the frontier with ICER of $100,000 if the cost is at least this amount

Table 11. Threshold analysis from modified societal perspective: unit costs for DNA stool test resulting in equal cost-effectiveness (ACER and ICER) compared to current recommended CRC screening strategies for modified societal perspective

	Total Threshold costs (includes co-payments and patient time costs)			CMS reimbursement rates (excludes co-payments and patient time costs)		
	sDNA (v1.0)	sDNA (v1.1)	sDNA (v2.0)	sDNA (v1.0)	sDNA (v1.1)	sDNA (v2.0)
			5-year DNA stool testing			
On efficient frontier	*NT*, 54‡	105‡, *151*	50, *110*	*NT*, 37	88, *134*	33, *93*
Cost-neutral vs. no screening	*NT*, 25	97, *151*	36, *110*	*NT*, 8	80, *134*	19, *93*
Equal to highest ACER	*31*, 131	*239*, 254	*232*, 243	*14*, 114	*222*, 237	*215*, 226
			3-year DNA stool testing			
On efficient frontier	*NT*, 35‡	90, *133*	56, *97*	*NT*, 18	73, *116*	39, *80*
Cost-neutral vs. no screening	*NT*, 23	83, *133*	21, *97*	*NT*, 6	66, *116*	4, *80*
Equal to highest ACER	*44*, 118	*212*, 213	201, *208*	*27*, 101	*195*, 196	*191*, 184

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)
ICER = incremental cost-effectiveness ratio (calculated using discounted costs and life-years gained)
NT = no threshold found (i.e., negative DNA stool test cost)
* MISCAN values in plain text; SimCRC values in italics
‡ DNA stool test 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 the DNA stool test 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 CMS. 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 versions of the DNA stool test—version 1.0 (a pre-commercial version of PreGen-Plus) and version 1.1 (currently commercially available through LabCorp and marketed as PreGen-Plus)—and screening intervals of 3 and 5 years. For three of the four DNA stool testing strategies evaluated, the screening benefit, measured in terms of life-years gained compared with no screening, was lower than that of annual Hemoccult II testing; the number of life-years gained was higher than that of annual Hemoccult II testing if the DNA stool test is performed every 3 years with version 1.1. However, the overall costs of all four DNA stool testing strategies were higher than all of the other screening strategies considered. The DNA stool test strategies considered were all more costly and less effective that an alternative strategy (i.e., strongly dominated) or a combination of other strategies (i.e., weakly dominated).

The fact that DNA stool testing, based on evidence available to date, was not cost-effective when compared with the other CRC screening tests had been anticipated, given that the DNA stool test was not more sensitive or specific than Hemoccult SENSA and yet almost 80 times as expensive. Consequently the aim of this analysis was also to explore the conditions under which the DNA stool test (or for that matter any other new test) could compete with the existing screening tests. We therefore conducted threshold analyses to determine what a DNA stool test would have to cost in order for one of the DNA stool test strategies to lie on the efficient frontier (i.e., be a non-dominated strategy). Our results indicate that the version 1.0 strategy could never be a cost-effective alternative compared to the current recommended screening strategies (i.e., it remains more costly and less effective than other strategies even if the test is free). Screening with the PreGen-Plus (version 1.1) test would lie on the efficient frontier at a cost of $34-$51 for a 5-yearly DNA stool testing and $40-60 for a 3-yearly DNA stool testing.

We also conducted sensitivity analyses to assess how potential changes in the sensitivity and specificity estimates, especially for adenomas, would affect the threshold analysis on the DNA stool test cost. We included a third sensitivity analysis for a hypothetical version for the DNA stool test (version 2.0) with enhanced sensitivity and specificity over that of the latest reported development for the test. Even for the enhanced test the threshold value for the DNA stool test was $17-$41 with an interval of three years and $2-$31 with a 5-year interval. Version 2.0 actually has lower threshold costs than version 1.1 because it has a lower specificity (even though the sensitivity is higher). With lower specificity, more people are referred to colonoscopy and colonoscopy-related costs become a larger portion of total costs. Hence, there are fewer screening tests with which to lower the total costs; hence lower costs per DNA stool test are required. We further allowed the sensitivity and specificity of the DNA stool test to range upwards from the version 1.1 estimates to a perfect test. The sensitivity and specificity of the DNA stool test were allowed to increase to even that of a perfect test and the threshold cost for the DNA test remained below or close to $350.

We conducted a second sensitivity analyses to address the question of whether with increasing adherence the DNA stool test would be on the efficiency frontier. For this analysis we assumed that adherence was 50% for the currently recommend tests and that there was increased adherence with the DNA stool test strategies among unscreened individuals. If the DNA stool test version 1.1 was able to increase screening adherence by 50% to 75% adherence, the threshold costs could increase to $83-$141 at 5-yearly intervals of testing and to $314-$391 at 3-yearly intervals of testing. With perfect adherence per-test the costs could be $472-$740 at 5-yearly intervals and $730-$822 at 3-yearly intervals, assuming an adherence of 50% for all other tests.

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 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. This means that we 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 DNA stool screening when screening a 50-year old cohort from age 50 onwards. This did not change the results significantly.

Analyses conducted from a modified societal perspective yielded threshold per-test costs that were approximately 2 to 3 times greater than the analyses from the CMS perspective.

Cost-effectiveness of Currently Recommended Test Strategies

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 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 model found more cost-saving strategies is likely due to the fact that it finds a great reduction in cancer incidence with CRC screening because of its longer dwell time. Using the SimCRC model we found that if the total discounted treatment costs decrease by about 10%, then only Hemoccult II, Hemoccult SENSA, and Hemoccult II with sigmoidoscopy with biopsy are cost-saving. If the treatment costs decrease by 12% only Hemoccult II and Hemoccult SENSA are cost-saving, and if they decrease by 22% none of the strategies is cost-saving.

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 the DNA stool test as a screening test

The PreGen-Plus (version 1.1) test, as reported by Whitney, achieves a sensitivity for CRC as high as that reported for FIT and Hemoccult SENSA, with a higher sensitivity for large adenomas than with FIT or Hemoccult SENSA and with a specificity as high as FIT. However these estimates from the Whitney study were based on archived samples rather than a clinical trial of screening. The subsequent clinical study by Itzkowitz (2007) using the version 1.1 assay obtained a sensitivity of 72.5%, comparable to that of Whitney but had considerably lower specificity (89%) compared to Whitney (96%). Consequently the PreGen-Plus test has better sensitivity for CRC compared with Hemoccult II, more comparable sensitivity for CRC as FIT and Hemoccult SENSA, better sensitivity than Hemoccult II, SENSA and FIT for large adenomas ($\geq$1.0 cm) and comparable or lower specificity as FIT and Hemoccult SENSA. There are no direct data on the sensitivity of the DNA stool test version 1.1 for detecting adenomas of any size; there are only data using version 1.0. This lack of evidence is relevant because the ability of a screening test to prevent CRC is through the identification and removal of adenomas. In addition, information on programmatic use of stool DNA (i.e., repeated screening) is not available; all the reported studies have been based on results of a one-time test. Future studies are needed to assess repeat screenings and the impact of a programmatic utilization of DNA stool test.

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 or flexible sigmoidoscopy, restrict their diet for Hemoccult II or colonoscopy, restrict NSAID use with Hemoccult II, have contact with the stool for any of the FOBTs, and go to a medical setting for an invasive procedure for colonoscopy or flexible sigmoidoscopy. Colonoscopy procedures have a small but real risk of perforations and due to sedation, require an escort to and from the procedure. The DNA stool test does not require a bowel prep or dietary restriction, and requires only limited contact with the stool (i.e., one sample, which can be shipped for processing from any location). The patient satisfaction evaluation by Schroy (2005) in the Imperiale study suggests that the DNA stool test is acceptable to patients who have already agreed to participate in a screening program. Schroy's patient survey was also used in routine clinical practice. Eighteen percent of patients who completed a PreGen-Plus completed the survey and reported that the collection process was easy to perform and that they were likely to use the test again. A recent report by Schroy (2007) noted that ambulatory care patients without prior endoscopy CRC or stool DNA screening, stated a preference for CRC screening as colonoscopy screening (51%), followed by stool DNA.

Consequently these studies demonstrate a stated willingness to use stool DNA screening in a percentage of patients interested in CRC screening. Our sensitivity analysis on adherence suggests that adherence would need to increase substantially for the DNA stool test to become cost-effective if the test cost was $350.

Evidence on comparable or lower complication rates and costs
There are no known complications associated with the DNA stool test itself (aside from the potential of false positive or false negative results) and the test is therefore comparable to its stool-based alternatives. The proposed costs of $350 are considerably higher than those of the stool alternatives ($4.54 for Hemoccult II and SENSA, $22.22 for FIT). Our analysis shows that at these costs screening with the DNA stool test is not a cost-effective alternative to the current screening recommendations and therefore does not meet the guidelines for new screening tests.

Consistency of Results from Two Microsimulation Models
All analyses were conducted by two 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 two modeling groups strengthens the credibility of our results and can be viewed as a sensitivity analysis of the underlying natural history assumptions. Both models have been calibrated to CRC incidence rates from a pre-screening era. Both models have been extensively validated against clinical trial data on Hemoccult II screening. The two models do differ in the dwell time from adenoma to clinically detectable CRC. MISCAN assumes a shorter dwell time and SimCRC a longer dwell time. Based on this difference in dwell time, the MISCAN model estimates fewer life-years saved from removing adenomas than SimCRC and MISCAN estimates a greater benefit for shorter rescreening intervals for adenoma-sensitive tests than does SimCRC. The fact that both models come to similar conclusions with respect to cost-effectiveness and threshold costs of DNA stool 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 the DNA stool test. In particular if affects the tests with respect to detection of adenomas.

Other Cost-effectiveness Analyses
There is one published cost-effectiveness analysis for the DNA stool test (Song, Fendrick, and Ladabaum 2004) and one published abstract (Parekh, Fendrick, and Ladabaum 2006). In the Parekh analysis a sensitivity of 52% for CRC and 18% for large polyps and a specificity of 94% were assumed, comparable to our version 1.0 test characteristics. Parekh (2006) found that at a DNA stool test cost of $300, 5-yearly stool DNA screening costs $18,000 per life-year gained. At a cost of $350 per test we found that screening with the DNA stool test version 1.0 from age 50 onwards, costs $25,000 per life-year gained in the MISCAN model and $21,000 in the SimCRC model, which are comparable. In a sensitivity analysis, Parekh also looked at test characteristics comparable to our version 2.0 test. With these test characteristics, he found costs of $13,000 per life-year gained. This number compares well with the MISCAN model at $13,000 per life-year gained and the SimCRC model at $6,000 per life-year gained. In the Song analysis, the authors assumed that the sensitivity of the DNA stool test was 65% for CRC and 40% for

large polyps with a 95% specificity, comparable to our version 1.1 test characteristics. Song (2004) concluded that the DNA stool test was dominated by currently recommended CRC screening tests. If the DNA stool test was given at 2-year intervals at a cost of $195 then it would be comparable with colonoscopy (Song 2004). Their conclusion of dominance is corroborated by our findings. For comparison reasons we also looked at the threshold costs for stool DNA screening (version 1.1) if offered every 2 years. Our threshold costs of $44 for MISCAN and $62 for SimCRC are considerably lower than estimated by Song. There are two main reasons for this difference. In the first place, Song uses a different comparator for determining the threshold costs, namely colonoscopy. In our analysis 2-yearly DNA stool screening is not as effective as colonoscopy screening, although it is close. Secondly, costs for colonoscopy are considerably higher in the Song analysis compared to our colonoscopy cost estimates. If we would compare 2-yearly DNA stool version 1.1 testing with colonoscopy screening and assume double colonoscopy costs (approximately the difference between our and Song's estimates), we would get threshold costs of $213 in both the MISCAN and SimCRC models, which is very comparable to the $195 estimate reported by Song.

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, neither model separately simulates the step from adenoma with low-grade dysplasia to an adenoma with high-grade dysplasia. If the advantage of the DNA stool test is detection of a smaller adenoma at the stage of high-grade dysplasia, then both models may be underestimating its effectiveness. We also did not allow for the de novo cancers (cancers that arise without a prior adenoma state). In the presence of de novo cancers the results of tests focusing on detecting only cancers becomes relatively more favorable. Because with Hemoccult II there is hardly any sensitivity for adenomas this tests becomes relatively more favorable compared to the other tests, including the DNA stool test. When Hemoccult II is the comparator (as with the MISCAN model), the threshold costs for the DNA stool test would become even lower. When Hemoccult SENSA is the comparator (as with the SimCRC model), the threshold costs would not change substantially. 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 this 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 endoscopy, as certain lesions may be more difficult to find (e.g., in a fold). However for the DNA stool test the lesion in question may have acquired a gene mutation not assessed by the DNA stool test, which means that if the DNA stool test was negative the first

time because the gene mutation is not one assessed by the DNA stool test, it will be missed in all subsequent screens unless the neoplasm acquires and begins expressing a gene mutation assessed by the test. Consequently, our assumption of conditional independence does not hold for DNA stool test, and we may have overestimated the true benefit of DNA stool test. This implies that the true threshold costs for may be lower than estimated by these analyses in this report.

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. For example, we compared 3-yearly stool DNA testing with annual Hemoccult screening, although the performance characteristics of both tests are comparable. It is likely that the threshold cost of the DNA stool test version 1.1 would be considerably lower than the estimated $34-$60 if compared with 3-yearly or 5-yearly Hemoccult SENSA testing. 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 the NHIS data 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. In the case of an anticipated decrease in colonoscopy reimbursement we would expect minimal changes to our conclusions about screening with the DNA stool test because the comparator used to calculate threshold test costs was FOBT and not colonoscopy.

Costs for CRC treatment were for the period 1998 to 2003. However there was minimal usage of the biologics in the period assessed so these new costs for biological are not a part of this study. 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 a lower 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. Because we are comparing the DNA stool test strategies with FOBT strategies, and because both types of test strategies have comparable reductions in cancer incidence, we would not expect increases in CRC treatment cost to have a large impact on our estimates of threshold test costs (and we would anticipate that any change would be to decrease the threshold test cost values). There is also a difference in the years that

we used to estimate survival (1996-1999). The impact of having cancer mortality estimates that are too high would be that the screening effectiveness would also be too high. For comparisons of tests that have similar cancer incidence reductions, as in the case of DNA stool test and FOBT, we expect the impact to be small but would favor the DNA stool test.

With the exception of the Warren, Klabunde, and Brown upcoming manuscript, 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 the DNA stool test (version 1.1) 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 $34 to $51 for 5-yearly DNA stool testing and $40-$60 for 3-yearly DNA stool testing to be a non-dominated strategy, provided that the estimates of sensitivity and specificity as stated from the Whitney study (2004) are obtained in a screening setting. These estimates are based on the analysis of an unscreened 65-year-old cohort using a payer perspective. Threshold costs are similar for a 50-year old cohort (range of threshold test costs: $27 to $52), but can be somewhat higher when the analysis is performed using a modified societal perspective ($88 to $134 for 5-yearly testing and $73 to $116 for 3-yearly testing).

There is a potential for the DNA stool test as a CRC screening test in an average-risk population, especially if a two-marker assay were to be developed with lower cost. However, further testing and validation in a population-based screening setting is required to ensure that the test parameters are achieved in an assay with fewer markers and that the specificity can be kept as high if not higher. The well-designed trial by Imperiale evaluated the DNA stool test in a screening population. The Imperiale results suggested that the DNA stool test in a screening setting had higher sensitivity but worse specificity than the Hemoccult II test and carried a considerably higher cost than the Hemoccult II test. The version 1.1 DNA stool test has not been tested in a screening setting. Studies in a symptomatic population suggest that stool DNA testing has sensitivity for CRC comparable to that of the FIT, with higher sensitivity for large adenomas than FIT, and comparable specificity as FIT, but also with a considerably higher cost than FIT.

Certainly, if DNA stool screening were to be adopted by a significant number of individuals who would not have been screened otherwise, its relative value would increase substantially. However, this behavior would have to coincide with high adherence rates with follow-up and surveillance colonoscopy.

Finally, we conclude that the science is promising for the use of DNA stool-based technology in the future. However, the current evidence suggests that this test is not a cost-effective screening tool if the cost were to remain as high as $350.

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APPENDICES

1. Summary of literature review on DNA stool test and FIT, including tables from the 2003 FIT report

2. Model descriptions: (a) MISCAN and (b) SimCRC

3. Comparison of outcomes from the natural history component of the models

4. Derivation of costs per screening test by point of service for frequency weights, CPT codes and resulting cost estimates

5. Additional outcomes of the analyses

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

Appendix 1. Summary of recent literature review on DNA stool test and FIT

Table A.1.1. Test characteristics for DNA stool test (version 1.0) followed by colonoscopy for all

Author, Year Journal	N in study	Country, year	Sensitivity, %				Specificity (no polyps), %
			CRC	CRC or high-grade dysplasia	Aden ≥1.0 cm, villous, HGD)	Aden < 1 cm	
Imperiale, 2004 N Engl J Med*	2,507	US	51.6 (34.8-68.0)	40.8 (30.2-52.5)	15.1 (12.0-19.0)	8.0 (5.9-12.7)	94.4 (93.1-95.5)
Ahlquist, in progress MAYO-MC9944 NCI P930-CA15083†	4,000 to be enrolled	US					
Ahlquist, 2005 abstract NCI U10-CA8938‡	2,502 average for 2005	US		35.0 20			96.0

* Asymptomatic average risk population, with family history of 14%. Test with 22 markers plus DNA integrity (pre commercial version 1.0), compared with Hemoccult II.

† RCT of no red meat, NSAIDS, vitamin C, or multivitamins versus no vitamin C or multivitamin 3 days before DNA stool sample.

‡ Study design similar to Imperiale; to be completed in 2007. RCT of FOBT and multitarget DNA-based assay panel testing followed by colonoscopy in the detection of CRC. Project began June, 2001 and ended August, 2007 (information from CRISP (1/23/2007).

Table A.1.2. Test characteristics for PreGen-Plus (version 1.1)

Author, Year Journal	N in study	Country, year	Sensitivity, %				Specificity (no polyps), %
			CRC	CRC or high-grade dysplasia	Aden ≥1.0 cm)	Aden < 1 cm	
Ahlquist, 2007 abstracts NCI U10-CA8938*	4010 subjects 218 with sDNA	US, 2007	58	49 46	45		84.0
Whitney, 2004§ J Mol Diagn	86 CRC, 100 col neg pts	US, 2004	70.0 (59.0-79.0)				96.0 (91.5-99.4)
Itzkowitz, 2007 Clin Gastroenterol†	40 CRC, 122 col neg pts	US, 2007	72.5 (57.2-83.9)				89.3 (82.6-93.7)

* Study design similar to Imperiale; to be completed in 2007. RCT of FOBT and multitarget DNA-based assay panel testing followed by colonoscopy in the detection of CRC. Project began June, 2001 and ended August, 2007 (information from CRISP (1/23/2007).

† Archived stool samples from CRC and colonoscopy negative patients. Same Itzkowitz study of 40 CRC and 122 colonoscopy negative patients as reported for version 2.0. The updated version 1.1 assay was conducted on the stool samples of these patients.

Table A.1.3. Test characteristics for DNA stool test (version 1.0) preselected colorectal cancer and controls

Author, Year Journal	N in study	Country, year	Sensitivity, %				Specificity (no polyps), %
			CRC	CRC or high-grade dysplasia	Aden ≥1.0 cm, villous, HGD)	Aden < 1 cm	
Ahlquist, 2000 Gastroenterology	22 CRC, 11 aden>1 cm, 28 no polyps	US	91.0		82.0 (48.0-98.0)		93.0
Tagore, 2003 Clin Colorectal Cancer	52 CRC. 28 adv aden, 113 neg col, 99 minor pol	US	63.5 (49.0-76.4) Stg I 75.0 Stg II 67.0		57.1 (37.2-75.5) HGD 86.0 lrg ad 48.0	6.1 (2.3-12.7)	96.8 (92.7-98.4)
Calistri, 2003 Gastroenterology	56 CRC 38 healthy		62.0				97
Brand, 2004 Am J Gastroenterol	16 CRC	US	69				
Syngal, 2006 Cancer	68 CRC, 23 adv aden	US, 09/2001 – 04/2003	63 Stage I 39% Stage II,III, IV 72%	54	26 (10-48) HGD 33		

Table A.1.4. Test characteristics for DNA stool test (potential version 2.0) selected colorectal cancer and controls

Author, Year Journal	N in study	Country, year	Sensitivity, %				Specificity (no polyps), %
			CRC	CRC or high-grade dysplasia	Aden ≥1.0 cm, villous, HGD)	Aden < 1 cm	
Itzkowitz, 2007* Clin Gastroenterol Hepatol	40 CRC, 122 no polyps	US	87.5 (73.9-94.5)				82.0 (74.2-87.8)

* Post-colonoscopy DNA stool samples in all CRC and sample of no polyps. Training set analysis without validation study. First set of sensitivities for modified version 1.0; second set for version 2.0 with 2 markers as noted here.

Table A.1.5. Fecal immunochemical test (FIT) followed by colonoscopy for all – updates beyond 2003 FIT report

Author, Year Journal	N in study	Country, year	Sensitivity, %				Specificity (no polyps), %
			CRC	CRC or high-grade dysplasia	Aden ≥1.0 cm, villous, HGD)	Aden < 1 cm	
Morikawa, 2005* Gastroenterology	21,805	Japan, 1983-2002	65.8 (55.4-76.3)	27.1 (23.9-30.3) (just HGD)	20.0 aden≥1 cm 33.0 HGD	See below	95.5 (95.2-95.8)
Morikawa 2007* Am J Gastroenterology	Same study as above	Japan 1983-2002	As above		As above	7%	As above
Levi, 2007† Ann Intern Med (Updates Vilkin 2005 Am J Gastroenterology)	1,000	Israel	75-ng/mL threshold 94.0 (82.9-100)	67% (57.4-76.7)			87.5 (85.4-89.6 for CC and 91.4 (89.6-93.2) for crc or adv adenoma

* Magstream 1000/Hem SP, average-risk population having comprehensive health exam with FIT and then colonoscopy during 1983-2002. Sensitivity is higher for high-grade dysplasia (HGD) than for larger adenoma. One day test.

† Three-day samples using two thresholds 75 and 100 ng/mL , where 100 ng/mL is the manufacturer-recommended level. High-risk population. Average fecal hemoglobin levels used in comparing groups. .Japanese FIT was used.

Table A.1.6. Fecal immunochemical test (FIT) – updates beyond 2003 FIT report

Author, Year Journal	N in study	Country, year	Sensitivity, %				Specificity (no polyps), %
			CRC	CRC or high-grade dysplasia	Aden ≥1.0 cm, villous, HG)	Aden < 1 cm	
Guittet, 2007* Gut	10,804	France, 2004-2005	76	53	50	17	97
Fraser, 2006† Lancet Oncol	795	Scotland '04-'05	95	90.1			
Smith, 2006‡ Cancer	2351 screening cohort and 161 symptomatic	Australia 2002-2004	87.5 92.3 for Stage I.	55	43	28	97
Allison 2007§ J Natl Cancer Inst	5841 Kaiser Permanente	California 1997-1999	81.8 (47.8-96.8)		29.5 21.4-48.9		98

* Screening program for ages 50-74 with Immudia/RPHA FIT (Magstream 100/Hem SP, with Hemoccult II as comparator. Colonoscopy for positive on either test – 20% of positives did not get colonoscopy. Used Schatzkin's ratios of sensitivities and ratio of false positive rates.

† Guaiac Hemascreen positive results given FIT and then colonoscopy.

‡ Enterix-InSure vs. Hemoccult SENSA. Screening 2000-2004 for high risk. Diagnostic cohort April 2002-Sept 2003.

§ FlexSure OBT

Table A.1.7. FIT compared with guaiac FOBT – updates for guaiac FOBT beyond 2003 FIT report

Author, Year Journal	N in study	Country, year	Sensitivity, %				Specificity (no polyps), %
			CRC	CRC or high-grade dysplasia	Aden ≥1.0 cm, villous, HG)	Aden < 1 cm	
Guittet, 2007* Gut	10,804	France, 2004-2005	67	31	26	24	99.9
Smith, 2006† Cancer	2,351 screening cohort and 161 symptomatic	Australia 2002-2004 screening	54 31 for Stage I	32	23	26	97.5
Allison 2007‡ J Natl Cancer Inst	5841 Kaiser Permanente	California 1997-1999	64.3 35.6-86.0		41.3 32.7-50.4		98

* Screening program for ages 50-74, with Magstream 100/Hem SP as comparator. Colonoscopy for positive on either test – 20% of positives did not get colonoscopy. Used Schatzkin's ratios of sensitivities and ratio of false positive rates.

† Enterix vs Hemoccult SENSA

‡ Hemoccult SENS compared with FlexSure OBT at Kaiser Permanente

Appendix tables from the immunochemical fecal occult blood test cost-effectiveness report to CMS (van Ballegooijen 2003), with updated literature

Table Appendix 1.A Guaiac Hemoccult II (un-rehydrated and rehydrated) – from FIT report, 2003

Author, Year Journal	N in Study	Country	Sensitivity CRC, %	Sensitivity large aden, %	Spec, %
Studies with colonoscopy follow-up and negative tests with surveillance of at least one year					
Hemoccult II un-reydrated					
Allison, 1996 N Engl J Med	8,065	US	37.1	30.1	98.1
Petrelli, 1994 Surg Oncol	8,933	US	37.1	--	98.1
Robinson, 1994 Br J Surg	1,489	UK	11.1	--	98.9
Hemoccult II rehydrated					
Castiglione, 1996 Br J Cancer	8,008	Italy	68.2	52.9	94.1
Randomized controlled trials					
Hemoccult II un-rehydrated					
Mandel, 1993 N Engl J Med	45,000	US	80.8	--	97.7
Hardcastle, 1996 Lancet	150,000	UK	58.6	--	96.8
Kronberg, 1996 Lancet	60,000	Denmark	55.5	--	99.3
Gyrd-Hansen, 1997 Int J Epidemiol	60,000	Denmark	62.1	--	--
Hemoccult II rehydrated					
Mandel, 1993 N Engl J Med	45,000	US	92.2	--	90.4
Church, 1997 JNCI	45,000	US	90	--	--
Studies with FOBT followed by colonoscopy for all					
Hemoccult II un-rehydrated					
Greenberg, 2000 Am J Gastroenterol	554	9 centers in world	85.7	20.5	92.8
Zauber, 2002 Gastroenterology	881	US	--	23	91
Hemoccult II rehydrated					
Lieberman, 2001 N Engl J Med	2,885	US	50	21.6*	93.8

* Sensitivity for small adenoma = 7.0%.

Table Appendix 1.B. Guaiac Hemoccult SENSA – from FIT report, 2003

Author, Year Journal	N in Study	Country	Sensitivity CRC, %	Sensitivity large aden, %	Spec, %
Studies with colonoscopy follow-up and negative tests with or without surveillance of at least one year					
Allison, 1996 N Engl J Med	8,065	US	79.4	68.6	87.5
Cole, 2003 Gastroenterology	460	Australia	38.5	--	--
Studies with FOBT followed by colonoscopy for all					
Greenberg, 2000 Am J Gastroenterol	554	9 centers in world	78.6	35.9	90.5

Table Appendix 1.C. Immunochemical FOBT – from FIT report, 2003

Author, Year Journal	N in Study	Country	Sensitivity CRC, %	Sensitivity large aden, %	Spec, %
Studies with colonoscopy follow-up and negative tests with surveillance of at least one year					
HemeSelect Allison, 1996 N Engl J Med	8,065	US	68.8	66.7	95.2
Robinson, 1994 Br J Surg	1,489	UK	100	--	90.8 (94.9)
Castiglione, 1996 Br J Cancer	8,008	Italy	95.5	78.6	92.0 (92.7)
Monhaem Nakama, 1994 Prev Med	3,365	Japan	91	--	96.0
Nakama, 1994 Prev Med	3,365	Japan	71.4	--	95.6
Nakama, 1999 Hepatol-Gastro	4,611	Japan	88.9	--	93.1
Insure Cole, 2003 Gastroenterol	460	Australia	85	--	--
Randomized control trials					
None					
Studies with FOBT followed by colonoscopy or flexible sigmoidoscopy for all					
Flexsure Young, 2003 J Med Screen		Australia	80	--	97.2
Greenberg, 2000 Am J Gastro	554	World	87.5	--	86.2
HemeSelect Allison, 2002 Gastroenterology	5356	US	81.8*	25.4	97.5
Greenberg, 2000 Am J Gastro	554	World	83.3	--	88.2
Nakama, 1999 HepGastro	4611	Japan	83.3	50.7	96
Magstream 1000/Hem SP Wong, 2003 Cancer	250	China	62	47	93
Insure Young, 2003 J Med Screen		Australia	75	--	97.8

Table Appendix 1.D. Package inserts

Company, Year	Country	Sens CRC, %	Sens large aden %	Sens small aden %	Spec %
Hemoccult II un-rehydrated					
Beckman-Coulter, 2000	US	86	53	32	98
Hemoccult SENSA					
Beckman-Coulter, 2000	US	92	67	43	96.5
Immunochemical Test Insure					
Enterix, 2003	US	87	47.4	--	97.7

Table Appendix 1.E. Estimates from cost-effectiveness assumptions and guidelines

Author, Year Journal	Sensitivity CRC %	Sensitivity large aden %	Sensitivity small aden %	Spec, %
Cost-Effectiveness Models				
Hemoccult II un-rehydrated				
Frazier, 2000 JAMA	33	--	2	97
Loeve, 1999 Comput Biomed Res	60	5	2	98
Sonnenberg, 2000 Ann Intern Med	40	--	--	97.5
Wagner, 1996 Prev	60	--	--	90
Hemoccult II rehydrated				
Frazier, 2000 JAMA	60	--	--	90
Loeve, 1999 Comput Biomed Res	70	20	--	90
Khandker, 2000 Int J Tech Assess	60	10	6	92
Guidelines Recommendations				
Hemoccult II un-rehydrated				
Winawer, 1997 Gastroenterology	60	--	--	90
Australian, 1997 Austral Health Tech	50	10	--	92

Table F. Studies comparing multiple FOBTs

Author, Year	Hemoccult II unrehydrated	Hemoccult II rehydrated	Hemoccult SENSA	Immunochemical	Fecal DNA
Allison, 1996	X		X	HemeSelect	
Allison. 2002			X	HemeSelect or FlexSure	
Castilgone, 1996		X		HemeSelect (1 day + and +/-)	
Robinson, 1994	X			Hemeselect 3 day	
Greenberg, 2000	X		X	HemeSelect and FlexSure	
Young, 2003				InSure and FlexSure	
Cole, 2003			X	InSure	
Guittet, 2007	X			Magstream 1000/Hem SP	
Allison, 2007			X	FlexSureOBT	
Alqhuist, 2007	X		X		X
Imperiale, 2004	X				X

Additional references for Appendix from van Ballegooijen (2003) on immunochemical FOBT cost effectiveness analysis (not included in main reference section).

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Hardcastle JD, Thomas WM, Chamberlain J, et al. Randomised, controlled trial of faecal occult blood screening for colorectal cancer. Results for first 107,349 subjects. *Lancet* 1989;1:1160-4.

Khandker RK, Dulski JD, Kilpatrick JB, Ellis RP, Mitchell JB, Baine WB. A decision model and cost-effectiveness analysis of colorectal cancer screening and surveillance guidelines for average-risk adults. Int J Technology Assessment in Health Care. 2000;16:799-810.

Lieberman DA,Weiss DG for the VA Cooperative Study Group. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med* 2001;345:555-60.

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Wagner JL, Tunis S, Brown M, Ching A, Almeida R. Cost-effectiveness of colorectal cancer: screening in average risk adults. In Young GP, Rozen P, Levin B. eds, *Prevention and Early Detection of Colorectal Cancer.* London: WB Saunders, 1996.

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Appendix 2: Model Descriptions

Microsimulation models. The MISCAN and SimCRC models from the NCI CISNET program are used to address the question of the cost-effectiveness of DNA stool testing. The models used common inputs and assumptions concerning the screening tests but use their independently developed natural history models in addressing these questions.

Appendix 2A. 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 2a. 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.

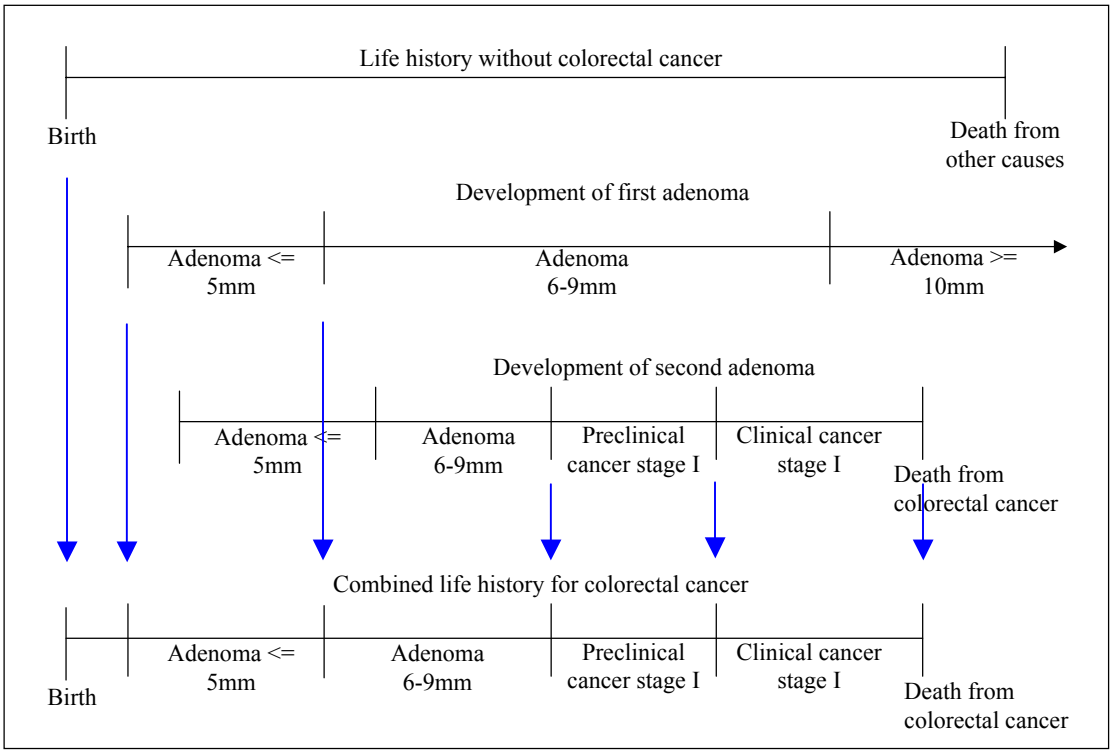

Figure 2a: Modeling natural history into life history

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 2a.

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 overlayed. 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.

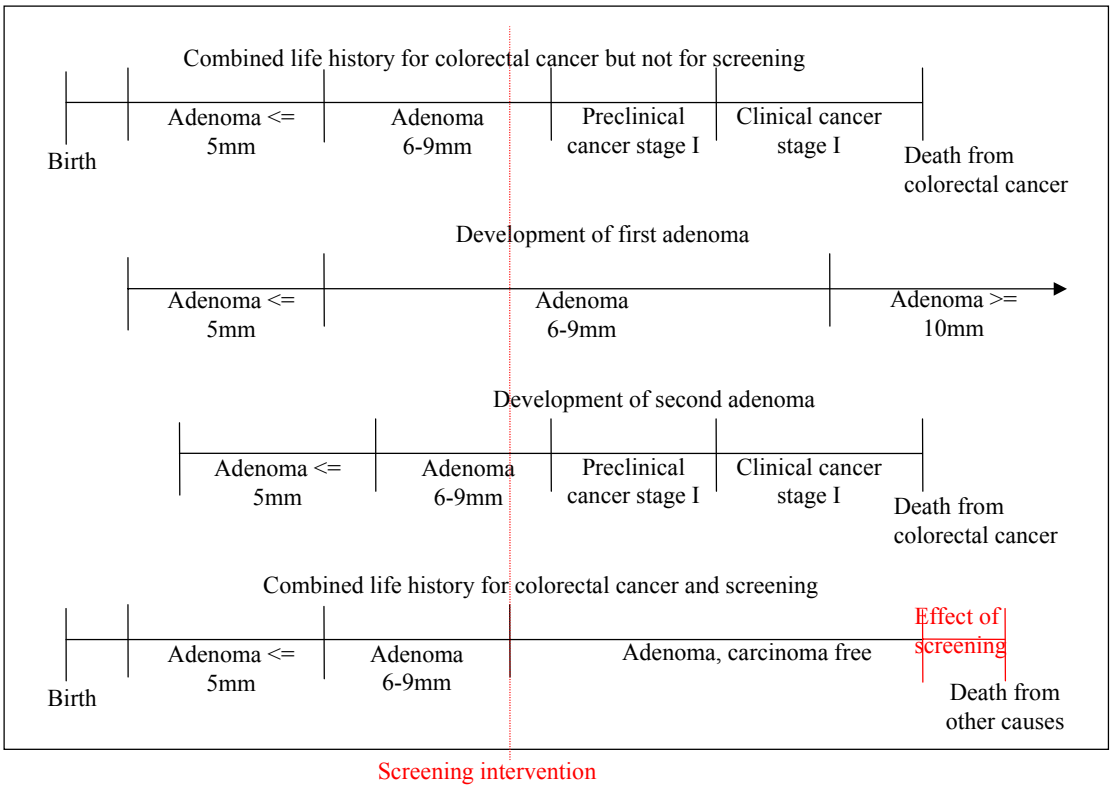

Figure 2b: Modeling screening into life history

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.

The model provides the opportunity to consider the possibility of systematic test results. This can be very important in the case of DNA stool screening where only a limited amount of DNA mutations can be investigated. If an adenoma or cancer occurs from a mutation different from the mutations tested for, this lesion cannot be detected by the DNA stool test and will yield a systematic negative test result. We will explore the effect of negative systematic test results as part of the sensitivity analyses.

Appendix 2B. Description of the SimCRC summary of natural history and intervention model

SimCRC Natural History Model

The SimCRC natural history model describes the progression of underlying disease among an unscreened population. It models the transitions from normal colonic epithelium to small adenomas (defined as 1-5 mm), from small to medium adenomas (defined as 6-9mm), from medium to large adenomas (defined as ≥10 mm) or to preclinical cancer, from large adenomas to preclinical cancer (stages I-IV), and from preclinical to symptom-detected CRC. This disease process is allowed to progress separately for three segments of the CRC tract (i.e., the proximal colon, the distal colon, and the rectum) and we allow for multiple lesions per person.

The model is calibrated by simulating the life histories of cohorts of individuals under a given set of parameter values and comparing the model-predicted outcomes with observed data on the prevalence, location, size, and multiplicity of adenomas and the prevalence of preclinical cancer from autopsy studies by age and sex and the stage- and location-specific incidence of CRC by age, sex, and race from the SEER Program. We used likelihood-based goodness of fit scores to evaluate the simultaneous fit to these data and we searched the parameter space using the simulated annealing algorithm. All predictions are very close to falling within one standard error of the observed data. The best-fitting model also provides an excellent fit to the overall risk of developing CRC by age.

SimCRC Screening Model

The natural history model has a screening component that incorporates the impact of the various FOBT technologies, flexible sigmoidoscopy, and colonoscopy. The effectiveness of each screening test is modeled through each test's ability to detect lesions (i.e., adenomas, preclinical cancer). In the natural history model (i.e., in the absence of screening), all disease states are undetected except for the symptom-detected cancer states. 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 as a function of his or her adherence rate and the sensitivity of the test. Test sensitivity can vary depending upon the size of the adenoma and the presence of a preclinical cancer. The three tests vary in terms of their test characteristics, reach, and risk. FOBT has the ability to detect a lesion in any segment of the colorectal system, but tends to have relatively poorer test characteristics compared with the other screening modalities. We model the test sensitivity for all tests as lesion-based. When a simulated person undergoes a test, each adenoma or preclinical cancer residing in the colon or rectum that is within reach has the chance of being detected, based on the lesion-specific sensitivity. We assume that colonoscopy is recommended for all persons with a positive FOBT or flexible sigmoidoscopy. For screened persons without an underlying lesion we apply the false-positive fraction (1 – specificity) to determine whether or not that person will undergo unnecessary follow-up examination. We also incorporate the chance of sending a person to colonoscopy with only hyperplastic polyps. Hyperplastic polyps are not modeled explicitly but are reflected in the specificity of the test. In addition, a percentage of false-negative patients (i.e., adenoma or preclinical cancer present but not detected by sigmoidoscopy) will be referred to colonoscopy because of the detection of a hyperplastic polyp. Colonoscopy is associated with a small mortality risk due to the risk of perforations during the procedure.

Appendix 3: Comparison of the two models on natural history outcomes

MISCAN

Adenoma prevalence, age 65: 39.8%

Number of adenomas per 1000 by site and size, age 65

	<5mm	6-9mm	10+mm
Prox	121.2	69.9	61.8
Distal	134.4	77.4	68.4
Rectum	133.5	76.8	68.1

Distribution of adenomas by site and size, age 65 (%)

	<5mm	6-9mm	10+mm	total
Prox	15	9	8	31
Distal	17	10	8	35
Rectum	16	9	8	34

CRC incidence among cancer-free 65-year-old population, %

	Stage1	Stage2	Stage3	Stage4	Total
10-year	0.4	0.7	0.5	0.5	2.1
20-year	0.8	1.6	1.0	1.0	4.4
lifetime	1.0	2.1	1.3	1.3	5.7

SimCRC

Adenoma prevalence, age 65: 37.1%

Number of adenomas per 1000 by site and size, age 65

	<5mm	6-9mm	10+mm
Prox	171.8	185.8	23.9
Distal	123.9	18.3	41.4
Rectum	8.7	16.0	15.6

Distribution of adenomas by site and size, age 65 (%)

	<5mm	6-9mm	10+mm	total
Prox	28	31	4	63
Distal	20	3	7	30
Rectum	1	3	3	7

CRC incidence among cancer-free 65-year-old population, %

	Stage1	Stage2	Stage3	Stage4	Total
10-year	0.4	0.7	0.5	0.5	2.1
20-year	0.8	1.5	1.0	1.2	4.4
lifetime	0.9	1.9	1.3	1.5	5.7

Appendix 4. Derivation of costs per screening test by point of service for frequency weights, CPT codes and resulting cost estimates.

Table A.4.1. CPT codes for screening with flexible sigmoidoscopy and colonoscopy.

CPT code	Description
Flexible sigmoidoscopy (no polyp)	
45330	Diagnostic sigmoidoscopy
G0104	CA screen; flexible sigmoidoscope
Flexible sigmoidoscopy (with biopsy)*	
45331	Sigmoidoscopy and biopsy
Colonoscopy (without polypectomy)	
45378	Diagnostic colonoscopy
G0105	Colon screen in high risk individuals
G0121	Colon cancer screening for non high risk individual
Colonoscopy (with polypectomy)	
45380	Colonoscopy and biopsy
45381	Colonoscopy, submucous injection
45382	Colonoscopy/control bleeding
45383	Lesion removal colonoscopy -fulguration
45384	Lesion remove colonoscopy-hot biopsy
45385	Lesion removal colonoscopy-snare polypectomy
Pathology	
88305	Tissue examination by pathologist

* Under the assumption that there is no polypectomy associated with flexible sigmoidoscopy.

Table A.4.2. Ambulatory surgery center (ASC) payment rates

	ASC Payment, $			PFS*- Facility, $			Total ASC (ASC Payment + PFS), $		
CPT Code	Total (B+M)	Beneficiary (B)	Medicare (M)	Total (B+M)	Beneficiary (B)	Medicare (M)	Beneficiary (B)	Medicare (M)	Societal Costs (B+M)
Flexible sigmoidoscopy without biopsy									
45330	NA	NA	NA	56.0	11.2	44.8	NA	44.8	NA
G0104	NA	NA	NA	56.0	11.2	44.8	NA	44.8	NA
Flexible sigmoidoscopy with biopsy									
45331	299.2	59.8	239.4	67.0	13.4	53.6	73.2	293.0	366.2
Colonoscopy without polypectomy									
45378	446	89.2	356.8	197.0	39.4	157.6	128.6	514.4	643
G0105	446	111.5	334.5	197.0	39.4	157.6	150.9	492.1	643
G0121	446	111.5	334.5	197.0	39.4	157.6	150.9	492.1	643
Colonoscopy with polypectomy									
45380	446	89.2	356.8	235.0	47.0	188.0	136.2	544.8	681
45381	446	89.2	356.8	222.0	44.4	177.6	133.6	534.4	668
45382	446	89.2	356.8	299.0	59.8	239.2	149	596	745
45383	446	89.2	356.8	307.0	61.4	245.6	150.6	602.4	753
45384	446	89.2	356.8	247.0	49.4	197.6	138.6	554.4	693
45385	446	89.2	356.8	279.0	55.8	223.2	145	580	725
Pathology									
88305	NA	NA	NA	NA	NA	NA	NA	NA	NA

* Physician fee schedule

Table A.4.3. Outpatient prospective payment system (OPPS) payment rates

	OPPS Payment, $			PFS- Facility, $			Total OPPS (OPPS Payment + PFS), $		
CPT Code	Total (B+M)	Beneficiary (B)	Medicare (M)	Total (B+M)	Beneficiary (B)	Medicare (M)	Beneficiary (B)	Medicare (M)	Societal Cost (B+M)
Flexible sigmoidoscopy without biopsy									
45330	299.24	64.4	234.84	56	11.2	44.8	75.6	279.64	355.24
G0104	224.92	56.23	168.69	56	11.2	44.8	67.43	213.49	280.92
Flexible sigmoidoscopy with biopsy									
45331	299.24	64.4	234.84	67	13.4	53.6	77.8	288.44	366.24
Colonoscopy without polypectomy									
45378	538.99	186.06	352.93	197	39.4	157.6	225.46	510.53	735.99
G0105	446	111.5	334.5	197	39.4	157.6	150.9	492.1	643
G0121	446	111.5	334.5	197	39.4	157.6	150.9	492.1	643
Colonoscopy with polypectomy									
45380	538.99	186.06	352.93	235	47	188	233.06	540.93	773.99
45381	538.99	186.06	352.93	222	44.4	177.6	230.46	530.53	760.99
45382	538.99	186.06	352.93	299	59.8	239.2	245.86	592.13	837.99
45383	538.99	186.06	352.93	307	61.4	245.6	247.46	598.53	845.99
45384	538.99	186.06	352.93	247	49.4	197.6	235.46	550.53	785.99
45385	538.99	186.06	352.93	279	55.8	223.2	241.86	576.13	817.99
Pathology									
88305	32.03	10.84	21.19	38	7.6	30.4	18.44	51.59	70.03

Table A.4.4. Office payment rates

CPT Code	PFS-Office Total (B+M), $	PFS- Office Beneficiary (B), $	PFS- Office Medicare (M), $
Flexible sigmoidoscopy without biopsy			
45330	124	24.8	99.2
G0104	124	24.8	99.2
Flexible sigmoidoscopy with biopsy			
45331	160	32	128
Colonoscopy without polypectomy			
45378	372	74.4	297.6
G0105	372	74.4	297.6
G0121	372	74.4	297.6
Colonoscopy with polypectomy			
45380	442	88.4	353.6
45381	429	85.8	343.2
45382	590	118	472
45383	524	104.8	419.2
45384	436	87.2	348.8
45385	498	99.6	398.4
Pathology			
88305	103	20.6	82.4

Table A.4.5. Select OPPS, ASC, and office payment rates with the addition of pathology costs (when applicable)

	Total ASC				Total OPPS				Total PFS			
CPT Code	Beneficiary	Medicare	Beneficiary with pathology review†	Medicare with pathology review†	Beneficiary	Medicare	Beneficiary with pathology review	Medicare with pathology review	Beneficiary	Medicare	Beneficiary with pathology review	Medicare with pathology review
Flexible sigmoidoscopy without biopsy												
45330	NA	NA			75.6	279.6			24.8	99.2		
G0104	NA	NA			67.4	213.5			24.8	99.2		
Flexible sigmoidoscopy with biopsy												
45331	73.2	293.0	101.7	406.7	77.8	288.4	103.2	359.6	32	128	60.4	241.7
Colonoscopy without polypectomy												
45378	128.6	514.4			225.46	510.5			74.4	297.6		
G0105	150.9	492.1			150.9	492.1			74.4	297.6		
G0121	150.9	492.1			150.9	492.1			74.4	297.6		
Colonoscopy with polypectomy												
45380	136.2	544.8	164.6	658.5	233.1	540.9	258.5	612.1	88.4	353.6	116.8	467.3
45381	133.6	534.4	162.0	648.1	230.5	530.5	255.9	601.7	85.8	343.2	114.2	456.9
45382	149	596	177.4	709.7	245.9	592.1	271.3	663.3	118.0	472	146.4	585.7
45383	150.6	602.4	179.0	716.1	247.5	598.5	272.9	669.7	104.8	419.2	133.2	532.9
45384	138.6	554.4	167.0	668.1	235.5	550.5	260.9	621.7	87.2	348.8	115.6	462.5
45385	145	580	173.4	693.7	241.9	576.1	267.3	647.3	99.6	398.4	128.0	512.1

* All values shown in 2007 dollars.

† In the ASC setting pathology review is farmed out to external labs, for which PFS Office rates apply.

Table A.4.6. Percent of procedures by place of service (PoS), weights per place of service, and cost of individual procedures weighted by place of service

CPT Code	ASC % of proce-dures by PoS (a)	OPPS % of procedures by PoS (b)	Office % of proce-dures by PoS (c)	Total % (d = a+b+c)	ASC Weight* (a/d)	OPPS Weight* (b/d)	Office Weight * (c/d)	Beneficiary weighted cost by PoS ** (B)	Medicare weighted cost by PoS ** (M)	Society weighted cost by PoS (B+M)
Flexible sigmoidoscopy without biopsy										
45330	0	26.22	43.26	69.48	0	0.38	0.62	43.97	167.29	211.26
G0104	0	22.08	72.86	94.94	0	0.23	0.77	34.71	125.78	160.49
Flexible sigmoidoscopy with biopsy										
45331	24	27	16.09	67.09	0.36	0.40	0.24	82.17	348.19	430.37
Colonoscopy without polypectomy										
45378	42.78	40.26	4.18	87.22	0.49	0.46	0.05	170.71	502.22	672.94
G0105	53.11	43.32	2.84	99.27	0.54	0.44	0.03	148.71	486.54	635.25
G0121	50.95	44.53	3.22	98.7	0.52	0.45	0.03	148.40	485.75	634.16
Colonoscopy with polypectomy										
45380	47.26	38.13	3.29	88.68	0.53	0.43	0.04	192.28	631.47	823.75
45381	46	40.79	2.32	89.11	0.52	0.46	0.03	192.11	621.90	814.01
45382	20.35	29.84	1.8	51.99	0.39	0.57	0.03	215.63	678.79	894.43
45383	42.25	46.85	4.49	93.59	0.45	0.50	0.05	211.09	684.10	895.19
45384	47.8	44.6	3.02	95.42	0.50	0.47	0.03	197.39	639.92	837.31
45385	48.49	41.48	3.75	93.72	0.52	0.44	0.04	201.90	665.91	867.81

Out of ASC, OPPS, and office.

** Weighted average of costs from table 5 including pathology (if applicable) by PoS

Table A.4.7. Costs of flexible sigmoidoscopy and colonoscopy with and without polyps*

CPT Code	Beneficiary Weighted Cost by PoS (B)	Medicare Weighted Cost by PoS (M)	Society Weighted Cost by PoS (B+M)	Total number of procedures per HCPCS code	Weights by HCPCS code (w)	Weighted Beneficiary Costs by PoS and HCPCS code (w*B)	Weighted Medicare Costs by PoS and HCPCS code (w*M)	Weighted Society Costs by PoS and HCPCS code (w*(B+M))
Flexible sigmoidoscopy without biopsy								
45330	43.97	167.29	211.26	74,032	0.84	37.07	141.06	178.13
G0104	34.71	125.78	160.49	13,770	0.16	5.44	19.73	25.17
Total						**42.52**	**160.78**	**203.30**
Flexible sigmoidoscopy with biopsy								
45331	82.17	348.19	430.37	29,349	1.00	82.17	348.19	430.37
Total						**82.17**	**348.19**	**430.37**
Colonoscopy without polypectomy								
45378	170.71	502.22	672.94	1,270,881	0.71	121.76	358.21	479.97
G0105	148.71	486.54	635.25	208,073	0.12	17.37	56.82	74.18
G0121	148.40	485.75	634.16	302860	0.17	25.22	82.57	107.79
Total						**164.35**	**497.59**	**661.94**
Colonoscopy with polypectomy								
45380	192.28	631.47	823.75	879279	0.38	73.70	242.05	315.76
45381	192.11	621.90	814.01	33907	0.01	2.84	9.19	12.03
45382	215.63	678.79	894.43	12530	0.01	1.18	3.71	4.89
45383	211.09	684.10	895.19	89884	0.04	8.27	26.81	35.08
45384	197.39	639.92	837.31	381305	0.17	32.81	106.37	139.18
45385	201.90	665.91	867.81	896966	0.39	78.95	260.39	339.34
Total						**197.75**	**648.52**	**846.28**

Appendix 5: Additional outcomes of the analyses

Table A.5.1. Discounted costs and discounted life-years gained per 1,000 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
sDNA-3 (v1.0)	3,860,227	1,145,671	51	22,300
sDNA-5 (v1.0)	3,533,981	819,425	41	20,046
sDNA-3 (v1.1)	3,673,499	958,943	68	14,105
sDNA-5 (v1.1)	3,382,910	668,354	59	11,375
HII	2,630,626	-83,930	65	CS
HS	2,715,327	771	80	10
FIT	2,776,790	62,234	79	784
SIGB	2,823,196	108,640	74	1,463
SIG	2,810,490	95,934	76	1,258
HII + SIGB	2,793,754	79,198	84	941
HII + SIG	2,840,538	125,982	85	1,488
HS + SIGB	2,863,769	149,213	87	1,714
HS + SIG	2,909,359	194,803	87	2,237
FIT + SIGB	3,025,571	311,015	87	3,569
FIT + SIG	2,992,773	278,217	87	3,190
COL	2,906,064	191,508	86	2,222

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.5.2. Discounted costs and discounted life-years gained per 1,000 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	2,295,628	NA	0	NA
sDNA-3 (v1.0)	3,473,214	1,177,586	42	27,927
sDNA-5 (v1.0)	3,147,621	851,993	29	29,757
sDNA-3 (v1.1)	3,081,338	785,710	64	12,233
sDNA-5 (v1.1)	2,814,315	518,688	51	10,089
HII	2,121,988	-173,640	58	CS
HS	2,078,632	-216,995	76	CS
FIT	2,155,730	-139,898	75	CS
SIGB	2,189,080	-106,547	59	CS
SIG	2,176,765	-118,862	62	CS
HII + SIGB	2,127,263	-168,365	79	CS
HII + SIG	2,113,618	-182,010	80	CS
HS + SIGB	2,187,768	-107,860	85	CS
HS + SIG	2,187,042	-108,586	85	CS
FIT + SIGB	2,282,357	-13,271	85	CS
FIT + SIG	2,283,025	-12,602	85	CS
COL	2,199,809	-95,819	85	CS

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

Appendix 6. Results for a cohort of 50-year-olds.

Table A.6.1. Discounted costs and life-years gained per 1,000 50-year-olds without CRC screening and with 16 CRC screening strategies and associated incremental cost-effectiveness ratios (ICERs)

	MISCAN			SIMCRC		
Strategy	Discounted costs, $	Discounted life-years gained	ICER, $/LYG	Discounted costs, $	Discounted life-years gained	ICER, $/LYG
No Screening	2,320,612	0.0	---	2,036,136	0	d
sDNA-5 (v1.1)	3,642,389	53.2	d	2,726,214	78.2	d
sDNA-5 (v1.0)	4,211,263	68.4	d	3,094,526	50.3	d
sDNA-3 (v1.1)	3,516,538	70.7	d	3,179,868	94.4	d
sDNA-3 (v1.0)	4,070,936	84.0	d	3,550,184	69.1	d
HII	2,368,129	85.3	600	1,638,377	90.6	---
HS	2,614,056	100.1	16,600	1,741,434	108.8	5,700
FIT	2,686,825	99.7	d	1,822,228	107.8	d
SIGB	2,725,052	88.4	d	1,927,596	82.5	d
SIG	2,759,328	91.7	d	1,939,260	89.8	d
HII + SIGB	2,832,993	102.5	d	1,849,712	110.8	d
HII + SIG	2,824,003	102.5	d	1,867,650	112.1	d
HS + SIGB	2,954,756	104.4	79,400	1,972,598	115.9	32,500
HS + SIG	2,935,288	104.1	d	1,995,878	116.3	62,200
FIT + SIGB	3,090,981	105.0	105,800	2,098,370	116.1	d
FIT + SIG	3,059,692	104.5	d	2,126,315	116.5	741,500
COL	3,010,788	102.1	d	2,086,929	115.6	d

--- indicates default strategy (i.e., the least costly and least effective non-dominated strategy)
d = dominated

Table A.6.2. Threshold analysis on DNA stool test characteristics: unit costs for DNA stool costs resulting in equal cost-effectiveness (ACER and ICER) compared to current recommended CRC screening strategies for different combinations of test sensitivity and specificity for colorectal cancer screening beginning at age 50*

	Screening and counting from age 50		
	sDNA (v1.0)	sDNA (v1.1)	sDNA (v2.0)
	5-yearly DNA stool testing		
On efficient frontier	*NT*, 8‡	37‡, *41*‡	NT, *10*
Cost-neutral vs. no screening	NT, *49*	24, *154*	NT, *142*
Equal to highest ACER	*60*, 100	165, *171*	*167*, 168
	3-yearly DNA stool testing		
On efficient frontier	*NT*, 3‡	27‡, *52*	4, *27*
Cost-neutral vs. no screening	NT, *49*	18, *126*	NT, *112*
Equal to highest ACER	*60*, 88	135, *140*	134, *134*

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)
ICER = incremental cost-effectiveness ratio (calculated using discounted costs and life-years gained)
NT = no threshold found (i.e., negative DNA stool test cost)
* MISCAN values in plain text; SimCRC values in italics
‡ DNA stool test strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount