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Evaluating Test Strategies for Colorectal Cancer Screening—Age to Begin, Age to Stop, and Timing of Screening Intervals: A Decision Analysis of Colorectal Cancer Screening for the U.S. Preventive Services Task Force from the Cancer Intervention and Surveillance Modeling Network (CISNET)

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ABSTRACT

Background: The U.S. Preventive Services Task Force requested a decision analysis to inform their update of the recommendations for colorectal cancer (CRC) screening.

Objective: To assess life-years gained and colonoscopy requirements for CRC screening strategies and identify a set of recommendable screening strategies.

Design: Decision analysis using two CRC microsimulation models from the Cancer Intervention and Surveillance Modeling Network.

Data Sources: Derived from recent published literature on test characteristics of single use applications of various screening strategies.

Target Population: U.S. average-risk 40-year-old population.

Perspective: Societal.

Time Horizon: Lifetime.

Interventions: Fecal occult blood tests (FOBTs), flexible sigmoidoscopy, or colonoscopy screening beginning at age 40, 50, or 60 and stopping at age 75 or 85 with screening intervals of 1, 2, or 3 years for FOBT and 5, 10, or 20 years for sigmoidoscopy and colonoscopy.

Outcome Measures: Number of life-years gained compared with no screening and number of colonoscopies and non-colonoscopy tests required.

Results of Base-Case Analysis: Beginning screening at age 50 was consistently better than age 60. Lowering the stop age from 85 to 75 decreased life-years gained by 1% to 4%, while colonoscopy use fell by 4% to 15%. Assuming equally high adherence, four strategies provided comparable life-years gained, namely 10-yearly colonoscopy, annual Hemoccult SENSA or fecal immunochemical test, and 5-yearly flexible sigmoidoscopy in conjunction with Hemoccult SENSA every 2 to 3 years. Annual Hemoccult II alone and 5-yearly flexible sigmoidoscopy alone were less effective.

Results of Sensitivity Analysis: The results were most sensitive to beginning screening at age 40.

Limitations: Stopping age for screening was based only on chronological age.

Conclusions: Our findings support CRC screening from ages 50 to 75 with annual screening with a high sensitivity FOBT, 10-yearly colonoscopy, or high sensitivity FOBT every 2 to 3 years with a 5-yearly flexible sigmoidoscopy.

INTRODUCTION

Despite recent declines in both incidence and mortality (1), colorectal cancer (CRC) remains the second most common cause of cancer death in the United States (2). Screening for CRC reduces mortality through the detection of malignancies at earlier, more treatable stages, as well as through the identification and removal of adenomatous polyps (asymptomatic benign precursor lesions that may lead to CRC). There are a number of tests currently available for screening, such as fecal occult blood testing (FOBT), flexible sigmoidoscopy, and colonoscopy. Screening with FOBT (Hemoccult II) has been shown to reduce CRC mortality by 15% to 33% in randomized controlled trials (3-5) and screening with more sensitive FOBTs, flexible sigmoidoscopy, colonoscopy or combinations of these tests may reduce the burden of CRC even more (6, 7). In the absence of adequate clinical trial data on several recommended screening strategies, microsimulation modeling can provide guidance on the risks, benefits, and testing resources required for different screening strategies to reduce the burden of CRC.

In July 2002, the US Preventive Services Task Force (USPSTF) concluded that there was sufficient evidence to recommend strongly that all average-risk adults 50 years of age and older should be offered CRC screening (8). However, the logistics of screening such as the type of screening test, screening interval, and age to stop screening were not evaluated in terms of the balance of benefits and potential harms. The USPSTF has again addressed CRC screening recommendations with a systematic review of the evidence (9, 10) on screening tests. For this assessment, the Task Force requested a decision analysis to project expected outcomes of various CRC screening strategies. Two independent microsimulation modeling groups from the Cancer Intervention and Surveillance Modeling Network (CISNET), funded by the National Cancer Institute, used a comparative modeling approach to compare life-years gained relative to resource use of different CRC screening strategies. The report to the United States Preventive Services Task Force was published in November 2008 (11). This is a fuller version of that report and includes additional tables and methodological descriptions not included in the publication in *Annals of Internal Medicine*.

METHODS

We used two microsimulation models, MISCAN (MI-crosimulation Screening ANalysis) (12-14) and SimCRC (Simulation Model of Colorectal Cancer) (15), to estimate the life-years gained relative to no screening and the colonoscopies required (i.e., an indicator for resource use and risk of complications) for different CRC screening strategies defined by test, age to begin screening, age to stop screening, and screening interval. We aimed to identify a set of recommendable strategies with comparable clinical benefit and an efficient use of colonoscopy resources. Using two models (i.e., a comparative modeling approach) adds credibility to the results and serves as a sensitivity analysis on the underlying structural assumptions of the models, particularly pertaining to the unobservable natural history of CRC.

Microsimulation Models

A detailed description of the MISCAN and SimCRC models can be found in **Appendix 1**. Standardized model profiles are available online (http://cisnet.cancer.gov/profiles/), which

provide a detailed description of the underlying parameters of the natural history for each model to provide transparency of the models. In brief, both models simulate the life histories of a large population of individuals from birth to death. As each individual ages, there is a chance that an adenoma develops. One or more adenomas can occur in an individual and each can independently develop into preclinical (i.e., undiagnosed) CRC **(Figure 1)**. The risk of developing an adenoma depends on age, sex, and baseline individual risk. The models track the location and size of each adenoma, these characteristics influence disease progression and the chance the adenoma is found by screening. Adenomas can progress from small ($\leq$ 5 mm) to medium (6-9 mm) to large ($\geq$ 10 mm) size. Some adenomas eventually become malignant, transforming to stage I preclinical cancer. A preclinical cancer has a chance of progressing through stages I to IV, and may be diagnosed by symptoms at any stage. Survivorship after diagnosis depends on the stage of disease.

The natural history component of each model was calibrated to 1975-1979 United States clinical incidence data (16) and adenoma prevalence from autopsy studies in the same period (17-26). We used this period because incidence rates and adenoma prevalence had not yet been affected by screening. We adjusted the adenoma prevalence from studies of non-US populations to that of the United States using standardized CRC incidence ratios. The models use all-cause mortality estimates from the US life tables and stage-specific CRC survival data from 1996-1999 SEER) (16). A comparison of outcomes from the natural history components of the models is shown in **Table 1.**

The effectiveness of a screening strategy is modeled through a test's ability to detect lesions (i.e., adenomas, preclinical cancer) which can be removed. Once screening is introduced, a simulated person who has an underlying lesion has a chance of having it detected during a screening round depending on the sensitivity of the test for that lesion and whether the lesion is within the reach of the test. Screened persons without an underlying lesion can have a false-positive test result and undergo an unnecessary follow-up colonoscopy. Hyperplastic polyps are not modeled explicitly but their detection is reflected in the specificity of the screening tests. The models incorporate the risk of fatal complications associated with perforation during colonoscopy. Both models have been validated against the long-term reductions in CRC mortality and CRC incidence with annual FOBT reported in the Minnesota Colon Cancer Control Study (3, 27, 28) and show good concordance with the trial results.

CRC Screening Strategies

In consultation with the USPSTF, we included the following basic strategies: (1) no screening, (2) colonoscopy, (3) FOBT (Hemoccult II, Hemoccult SENSA, or fecal immunochemical test (FIT)), (4) flexible sigmoidoscopy (with biopsy), and (5) flexible sigmoidoscopy combined with Hemoccult SENSA. Payments by the Centers for Medicare and Medicaid Services for the tests are $4.54 for a guaiac based test (either Hemoccult II or Hemoccult SENSA); $22.22 for a fecal immunochemcial test; $161 and $348 for flexible sigmoidoscopy without and with biopsy with pathology evaluation; and $498 and $649 for colonoscopy without and with polypectomy and pathology evaluation (29). The intent of this analysis was to use the number of colonoscopies required per strategy as an indicator of resources and risks required. These payment estimates (reflecting approximately 80% of the allowable charges) serve as a relative indication of resource

allocation but are not intended to be used as a direct comparison of the tests and the effect of the screening strategy.

For each basic strategy we evaluated start ages of 40, 50, and 60 years, and stop ages of 75 and 85 years. For the FOBT strategies we considered screening intervals of 1, 2, and 3 years, and for the sigmoidoscopy and colonoscopy strategies we considered intervals of 5, 10, and 20 years. These variations resulted in 145 strategies: 90 single-test strategies, 54 combination-test strategies, and one no-screening strategy. The stop age reflects the oldest possible age to screen but the actual stopping age is dictated by the start age and screening interval.

In the base case, we assumed 100% adherence for screening tests, follow-up of positive findings, and surveillance of individuals found to have adenomas. Individuals with a positive FOBT or with an adenoma detected by sigmoidoscopy were referred for a follow-up colonoscopy. For years in which both tests were due for the combined strategy, the FOBT was performed first and if positive, the patient was referred for a follow-up colonoscopy. In those years, flexible sigmoidoscopy was done only for those with a negative FOBT. If the follow-up colonoscopy was negative, then the individual was assumed to undergo subsequent screening with colonoscopy with a 10-year interval (as long as the repeat colonoscopy was negative) and did not return to the initial screening schedule, as is the recommendation of the US Multi-Society Task Force and American Cancer Society (7, 30). All individuals with an adenoma detected were followed with colonoscopy surveillance per the Multi-Society guidelines (30, 31). The surveillance interval depended upon the number and size of the adenomas detected on the last colonoscopy, ranging from 3 to 5 years and was assumed to continue for the remainder of the person's lifetime.

We estimated the CRC screening test characteristics from a review of the available literature **(Table 2)** (29). The test characteristics for FIT were based on an update of the literature review in the AHRQ-CMS report on FIT (32). The FIT estimates in this report were updated based on a large study (33) on sensitivity and specificity of FIT published after the FIT AHRQ-CMS report(32). The results of the Morikawa study were similar to the estimates of sensitivity and specificity for CRC used in the previous report on FIT to AHRQ-CMS (32). Consequently the same estimates for the FIT's specificity and sensitivity for CRC were retained from the previous report. However we slightly increased the sensitivity estimates for adenomas for FIT compared to the estimates of the 2003 FIT Report (32). Test characteristics of Hemoccult SENSA were assumed to be similar to that of FIT. Lack of specificity was assumed to be higher for Hemoccult SENSA, resulting in slightly higher sensitivity for adenomas for SENSA compared to FIT. The estimated CRC sensitivity of Hemoccult II was not changed from the 40% estimated in the 2003 FIT report. Sensitivities for adenomas were estimated by assuming the same ratio between adenoma sensitivity and CRC sensitivity as for FIT.

Sensitivity estimates for colonoscopy were based on a recent meta-analysis (34). We assumed the same sensitivity for sigmoidoscopy within the reach of the scope.

Our review was conducted independently of the systematic evidence review conducted for the USPSTF (9, 10) and parallel in time.

Evaluation of Outcomes

1) Determination of efficient strategies

The most effective strategy was defined as the one with the greatest life-years gained relative to no screening. However, it is important to consider the relative intensity of test use required to achieve those gains. The more effective strategies tended to be associated with more colonoscopies on average in a person's lifetime, which translated into an increased risk of colonoscopy-related complications. We used an approach that mirrors that of cost-effectiveness analysis (35) to identify the set of efficient, or dominant, strategies *within each test category*. A strategy was considered dominant when there was no other strategy or combination of strategies that provided more life-years with the same number of colonoscopies. We conducted this analysis separately for each of the five basic screening strategies because the number of non-colonoscopy tests differed by strategy. We then ranked the efficient screening strategies by increasing effectiveness and calculated the incremental number of colonoscopies (ΔCOL) per 1000, the incremental life-years gained (ΔLYG) per 1000 and the incremental number of colonoscopies necessary to achieve a year of life (ΔCOL/ΔLYG) relative to the next less effective strategy, which we refer to as the "efficiency ratio." The line connecting the set of efficient strategies is called the (efficient) frontier. We also identified "near efficient" strategies—strategies that yielded life-years gained within 98% of the efficient frontier.

2) Determination of recommendable strategies at certain level of effectiveness

We further only considered efficient or near-efficient strategies. We assumed that the set of recommendable strategies would all have the same start and stop age, because recommending different start/stop ages by test may be confusing for patients and practitioners. We looked at the incremental number of colonoscopies relative to the life-years gained to determine what would be reasonable start and stop ages. For a given start/stop age we selected a colonoscopy strategy, with the default being the generally recommended 10-year screening interval. From the other test categories we selected strategies with the most comparable screening effectiveness to colonoscopy, and with a *lower* efficiency ratio than that for colonoscopy. This was because strategies that have more intensive use of tests other than colonoscopy should have a lower efficiency ratio than strategies with less intensive (or no) use of non-colonoscopy tests (i.e., this ratio would be higher if other tests were included in the numerator). Alternative sets of recommendable CRC screening strategies were obtained with different colonoscopy strategies selected as the initial comparator.

Sensitivity Analyses

The primary sensitivity analysis was the comparison of findings across two independently-developed microsimulation models. We also performed sensitivity analyses on test characteristics, where we used all of the least-favorable values in a worst-case analysis and all of the most favorable values in a best-case analysis (Table 2). For colonoscopy and sigmoidoscopy, we used the confidence intervals reported in the meta-analysis by van Rijn (34) as the range tested. For FOBT, we used the ranges reported in the literature (9, 10, 29).

To assess the relative impact of decreased adherence, we explored the impact of overall adherence rates of 50% and 80%. We incorporated correlation of screening behavior within an individual by assuming that the population is comprised of four groups: those who are never screened and those with low, moderate, and high adherence, with 10% of the population in the never screened group and 30% in each of the other groups. For the overall 80% adherence

assumption, each time a person is scheduled for a screen there is a 0%, 78%, 89%, and 100% chance that s/he has the test done if in the non-adherent, low, moderate, and high adherence group respectively. For an overall 50% adherence assumption, each time a person is schedule for a screen there is a 0%, 39%, 56%, and 72% chance that s/he has the test done if in the non-adherent, low, moderate, and high adherence group respectively. For both overall screening adherence assumptions (i.e., 50% and 80%) we assumed that adherence with follow-up and surveillance was 75%, 85%, and 95% for those with low, moderate, and high adherence, respectively. We assumed that individuals remain in their screening behavior group.

Role of the Funding Source

NCI supported the infrastructure for the CISNET models. The Agency for Healthcare Research and Quality funded this work and provided project oversight and review. The authors worked with four USPSTF members to specify the overall questions, select the strategies, and resolve methodological issues during the conduct of the review. The draft decision analysis was reviewed by three external peer reviewers (listed in the acknowledgements) and revised for the final version. The authors have sole responsibility for the models and model results.

Institutional Review Board

This research did not include patient-specific information and was exempt from IRB review (exemption 4).

RESULTS

Table 3 presents the life-years gained, the number of colonoscopies, and the efficiency ratio for each efficient and near-efficient strategy for both models for each test for age to begin screening of 50 or 60. All strategies for each test can be found in **Appendix 2** which includes incidence and mortality reductions as well as the number of screening and surveillance tests required for each strategy. The figures of life-years gained relative to the number of colonoscopies and the efficient frontier for each test are given in **Figure 2**.

Age to Begin Screening

The results from the MISCAN and SimCRC models were consistent when evaluating strategies with age to begin screening of 50 or 60 years, with the start age of 50 predominating among the efficient or near efficient strategies (**Table 3**). However, the SimCRC model showed favorable results for the strategies in which screening begins at age 40, but these results were not corroborated by the MISCAN model **(Appendix 3).** To illustrate this difference, **Figure 2** shows the efficient frontier with age 40 included for colonoscopy ("Frontier 40, 50, 60y") and without age 40 ("Frontier 50, 60y"). Because the evidence for both adenoma prevalence at age 40 and the duration of the adenoma-carcinoma sequence is weak, we restricted further analysis to start ages 50 and 60.

Age to Stop Screening

For both models and all tests, lowering the stopping age from 85 to 75 yielded small reductions in life-years gained relative to large reductions in the number of colonoscopies required **(Table 3**). For example, stopping screening at age 75 instead of 85 for 10-yearly colonoscopy would decrease the number of life-years gained with colonoscopy screening by 5 and 2 per 1,000 individuals for MISCAN and SimCRC, respectively, but would substantially decrease the

number of colonoscopies by 398 and 358 per 1,000 individuals for MISCAN and SimCRC, respectively (**Table 3**). This is illustrated by the substantial reduction in the efficiency ratio for these two strategies, from 73 to 30 for MISCAN and 179 to 35 for SimCRC.

Screening Interval

In general, strategies with longer intervals provided fewer life-years gained than strategies with shorter intervals. For all single test strategies, the currently recommended intervals of annual FOBT, 5-yearly flexible sigmoidoscopy, and 10-yearly colonoscopy provided a reasonable ratio of incremental colonoscopies per life-year gained (10 – 35) for ages 50-75 (**Table 3).** The results from both models showed that the current recommendation for the combination of flexible sigmoidoscopy every 5 years with a high sensitivity FOBT annually had a high efficiency ratio and that moving to a strategy of 5-yearly sigmoidoscopy with 3-yearly FOBT would minimally decrease the number of life-years gained with combination screening (by 9 and 17 per 1,000 individuals for MISCAN and SimCRC, respectively) and would substantially decrease the number of colonoscopies (by 765 and 1,011 per 1,000 individuals for MISCAN and SimCRC, respectively for ages 50-75) (**Table 3**). This would substantially reduce the incremental colonoscopies required for an additional life-year gained from 140 to 16 for MISCAN and from 76 to 7 for SimCRC.

Identifying a Set of Recommendable CRC Screening Strategies

In the above analysis we found that a start age of 50 and stop age of 75 was most reasonable when considering both benefit and resource use. For that start/stop age, we first selected the colonoscopy strategy with 10-year intervals, as this has been the recommended interval; shortening the interval resulted in a marked increase in efficiency ratio (from 75 to 30 for MISCAN and 179 to 35 for SimCRC). The efficient and near-efficient strategies for start age of 50 and stop age of 75 are given in **Table 4**. The non-colonoscopy strategies were then chosen to have the same start/stop ages and a lower efficiency ratio, while saving similar life-years as that for colonoscopy (**Table 5a**). The sensitive annual FOBT strategies (Hemoccult SENSA and FIT) were comparable to 10-yearly colonoscopy in terms of life-years gained. The less-sensitive FOBT (Hemoccult II) performed annually did not have comparable effectiveness to the other FOBTs or to colonoscopy. Flexible sigmoidoscopy every 5 years, although showing a reasonable efficiency ratio, did not show comparable effectiveness to the other strategies. The combination of flexible sigmoidoscopy every 5 years with Hemoccult SENSA every 3 years had a reasonable efficiency ratio (lower than that of colonoscopy and the sensitive FOBTs) and had relatively comparable life-years gained. Had we selected the 20-year interval for colonoscopy as the comparator strategy instead of the 10-year interval, the set of strategies would include biennial screening for sensitive FOBT, annual screening for Hemoccult II, and 10-yearly screening with sigmoidoscopy in combination with 3-yearly FOBT. The life-years gained for this set of screening strategies (**Table 5b**) is approximately 8% to 12% lower than that shown in **Table 5a**.

Sensitivity Analysis

Our overall conclusions did not change with variations in test characteristics. As expected, results for the worst-case analysis showed lower life-years gained than the base case, and the best-case analysis had greater life-years gained. For strategies that remained on the efficient frontier, the incremental number of colonoscopies per life-year gained was typically greater than the base-case value with the best-case assumption, and lower with the worst-case assumption.

Figure 3 shows the expected number of colonoscopies and life-years gained for over adherence of 50%, 80% and 100% for the recommended strategies shown in **Table 6**. When adherence was relatively high at 80%, the colonoscopy strategy (i.e., 10-yearly screening from aged 50 to 75) was the most effective in term of life-years gained and Hemoccult SENSA, FIT and the combination strategies all provided life-years gained within 8% of that of the colonoscopy strategy. When overall adherence was only 50%, the colonoscopy strategy was no longer the most effective and Hemoccult SENSA, FIT, and the combination strategies had life-years gained higher or equivalent to that of the colonoscopy strategy. Annual Hemoccult II and flexible sigmoidoscopy every five years remained the two least attractive alternatives in terms of life-years gained across different adherence levels.

DISCUSSION

We used two independent microsimulation models to evaluate different CRC screening strategies defined by screening test, age to begin, interval to repeat, and age to stop screening. Our goal was to provide the USPSTF with information that synthesizes and translates multiple sources of data, such as screening test characteristics, into projections of clinical benefit and resource utilization for multiple screening options. We found several screening strategies (high sensitivity FOBT performed annually, flexible sigmoidoscopy every 5 years with Hemoccult SENSA every 2 to 3 years, and colonoscopy every 10 years) that provide similar gains in life-years – *provided* equally high adherence for all aspects of the screening process. Our analysis also found that annual FOBT with a lower-sensitivity test (e.g., Hemoccult II) and flexible sigmoidoscopy alone resulted in fewer life-years gained relative to other strategies. Our analysis confirmed the current recommendation to begin screening at age 50 in an asymptomatic general population and showed that stopping at age 75 after consecutive negative screenings since age 50 provides almost the same benefit as stopping at age 85 but with substantially fewer colonoscopy resources and risk of complications.

Our decision analysis represents the first time that the USPSTF has included simulation modeling to help inform their decision on recommendations. The USPSTF had previously recommended screening for all asymptomatic persons beginning at age 50 but did not recommend one test over another or an age to stop screening (8). Although randomized controlled trials are the preferred method for establishing effectiveness of (screening) interventions, they are expensive and require long follow-up and can only address a limited number of comparison groups. However, well-validated microsimulation models may be used to highlight the tradeoff between clinical benefit and resource utilization from different screening policies and inform decision making with standardized comparisons of net benefits and risks. The process with which our analysis was conducted represents an important advancement from evidence-based to evidence-informed medicine, and the use of more than one model, as advocated by CISNET, adds credibility when model results agree.

We found that CRC screening with high sensitivity FOBT (Hemoccult SENSA or FIT) provided comparable life-years gained as colonoscopy, even though the individual test characteristics were substantially better for colonoscopy (**Table 2**). This finding was partially due to the fact the FOBT needs to be performed every year compared with every ten years for colonoscopy, and the test characteristics are assumed to remain unchanged with each subsequent screen. For example,

if an adenoma was missed by a screening test in one cycle then the chance that it would be missed again on the next exam is still based on the false-negative rate (1 – sensitivity for adenomas). There is little evidence on whether test sensitivity varies with increasing rounds of testing. Also, a substantial percentage of individuals initially 'assigned' to annual FOBT screening switch to a strategy of colonoscopy screening every ten years because of false-positive FOBT results. For example, with a specificity of 92.5% for Hemoccult SENSA, the percentage of people in a colonoscopy screening program after 10 FOBTs is about 54%, and after 20 FOBTs is about 79%**.**

Previously there has been no recommended stopping age for CRC screening (7, 30). However, our results indicate that continued screening in 75-year-old persons after consecutive negative screens since age 50 will add little benefit. Individuals with continuous negative findings by age 75 are unlikely to either have a missed adenoma at their last screen or to develop an adenoma that progresses to cancer and subsequent cancer death after their last screen. Surveillance colonoscopies for those with adenomas detected are continued without a stopping age. We note that our analysis used chronological age rather than comorbidity-adjusted life expectancy and that the decision to stop screening in practice should consider the age and health of the patient. As a guide, life expectancy at age 75 is 10.5 and 12.5 years for men and women, respectively (36).

There were a few findings that can be explained by model differences. Both models incorporate assumptions about the adenoma-carcinoma sequence (i.e., the development of CRC from adenomas), for which limited data are available to estimate the time that it takes (on average) for an adenoma to develop into preclinical cancer. For example, in the MISCAN model the average time from adenoma development to CRC diagnosis is 10 years among those individuals with CRC diagnosed (i.e., dwell time), whereas in the SimCRC model this value is about 22 years. The implications of these differences were higher life-years gained with screening in general, and more favorable results for beginning screening at age 40, with the SimCRC model. The former implication had minimal impact on our conclusions because the relative findings were consistent across models. The latter implication resulted in eliminating the start age of 40 from consideration. Another difference between the models is the distribution of adenomas in the colorectal tract (see **Appendix 1** and **Table 1**). 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. As a result, the MISCAN model found strategies involving sigmoidoscopy to be more effective than the SimCRC model because a larger proportion of adenomas are within the reach of the sigmoidoscope. Despite this difference, both model results found that the 5-yearly sigmoidoscopy strategy was not as effective as annual screening with a sensitive FOBT or 10-yearly colonoscopy.

There are several limitations and caveats to consider. First, we only evaluated CRC strategies requested by the USPSTF based on their review of the evidence in 2002 (8) and did not include newer screening tests such as CT colonography or the DNA stool test (9, 10, 30). Second, because we were not asked to provide a cost-effectiveness analysis we used the number of colonoscopies as a proxy for resource utilization, as well as non-fatal adverse effects from screening. However, this does not capture all resources required per scenario, although we report the numbers of FOBT and flexible sigmoidoscopy tests required for each strategy. Third, we

assumed 100% adherence with screening, follow-up (i.e., chance of getting a diagnostic colonoscopy if a screening test is positive), and surveillance for all scenarios in order to provide outcomes associated with the strategies as they were specified. In practice, adherence is much lower than 100% and varies across type of screening test. We conducted a sensitivity analysis varying overall adherence but not differentially across strategies. We chose to evaluate strategies assuming equivalent adherence because it is uncertain whether adherence will be higher with non-invasive but more frequent testing, or invasive but less frequent testing. Because we considered three different adherence scenarios in Figure 3, readers are able to compare different adherence levels themselves. We emphasize that in practice adherence is critical and ultimately the best option for a patient is the one that he or she will attend (7, 30). In addition, issues pertaining to the implementation of a screening program, including endoscopy capacity (37-39), professional qualification (40, 41), insurance coverage, shared decision making, and how to increase adherence with CRC screening (42) are important considerations for implementing recommendations in practice.

In conclusion, our results support CRC screening from ages 50 to 75 with a high sensitivity FOBT annually, 10-yearly colonoscopy, or high sensitivity FOBT every 2 to 3 years with a 5-yearly flexible sigmoidoscopy. Our findings were in general support of the 2002 USPSTF CRC screening recommendations with a few exceptions. First, while there is currently no recommended stopping age for CRC screening, we found that continuing screening after age 75 in those individuals who have had regular, consistently negative, screenings since age 50 provides minimal benefit for the resources required. Second, we found that screening with Hemoccult II annually and flexible sigmoidoscopy alone every five years does not provide comparable effectiveness to screening annually with a sensitive FOBT or every ten years with colonoscopy. Lastly, if a sensitive FOBT is used the FOBT screening interval can be extended to three years when used in combination with flexible sigmoidoscopy every five years. These conclusions were corroborated by two independent microsimulation models.

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Reproducible Research Statement
Models are available to approved individuals with written agreement.

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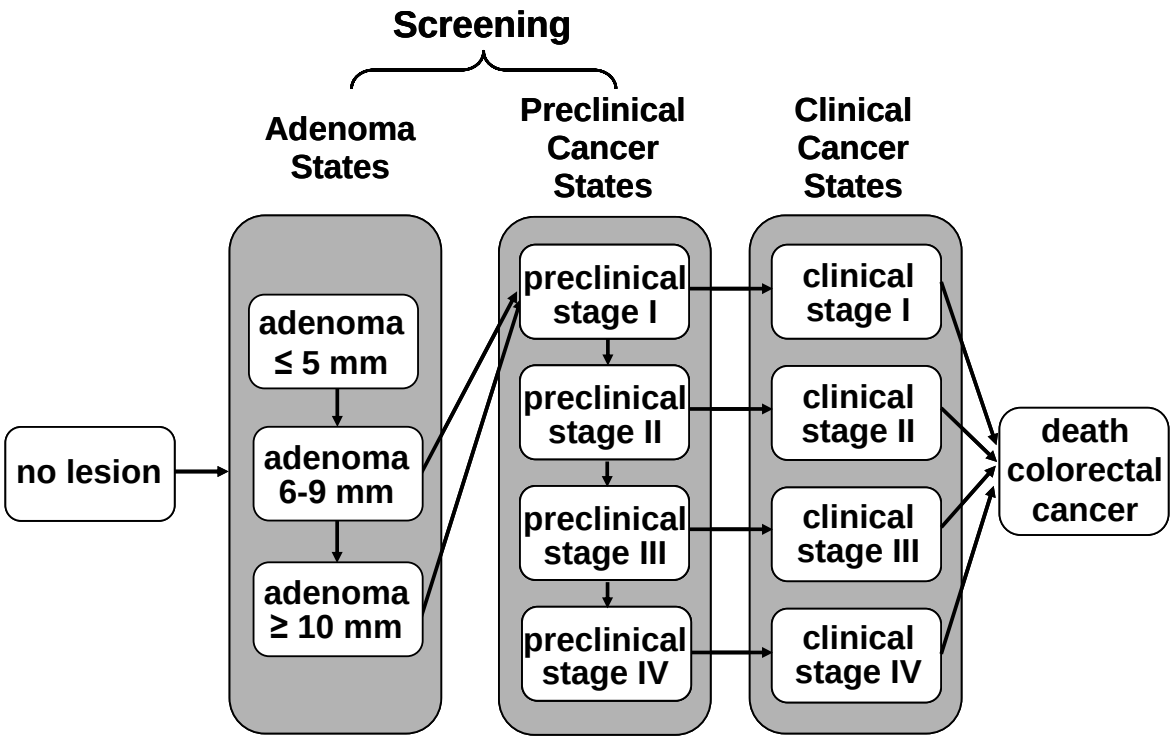


Figure 1. Graphical representation of natural history of disease as modeled by MISCAN and SimCRC models. The opportunity to intervene in the natural history through screening is noted. Screening can either remove a precancerous lesion (i.e., adenoma), thus moving a person to the "No lesion" state, or through early detection, which makes an undiagnosed cancer clinically detected at a potentially earlier stage of disease where it is more amenable to treatment.

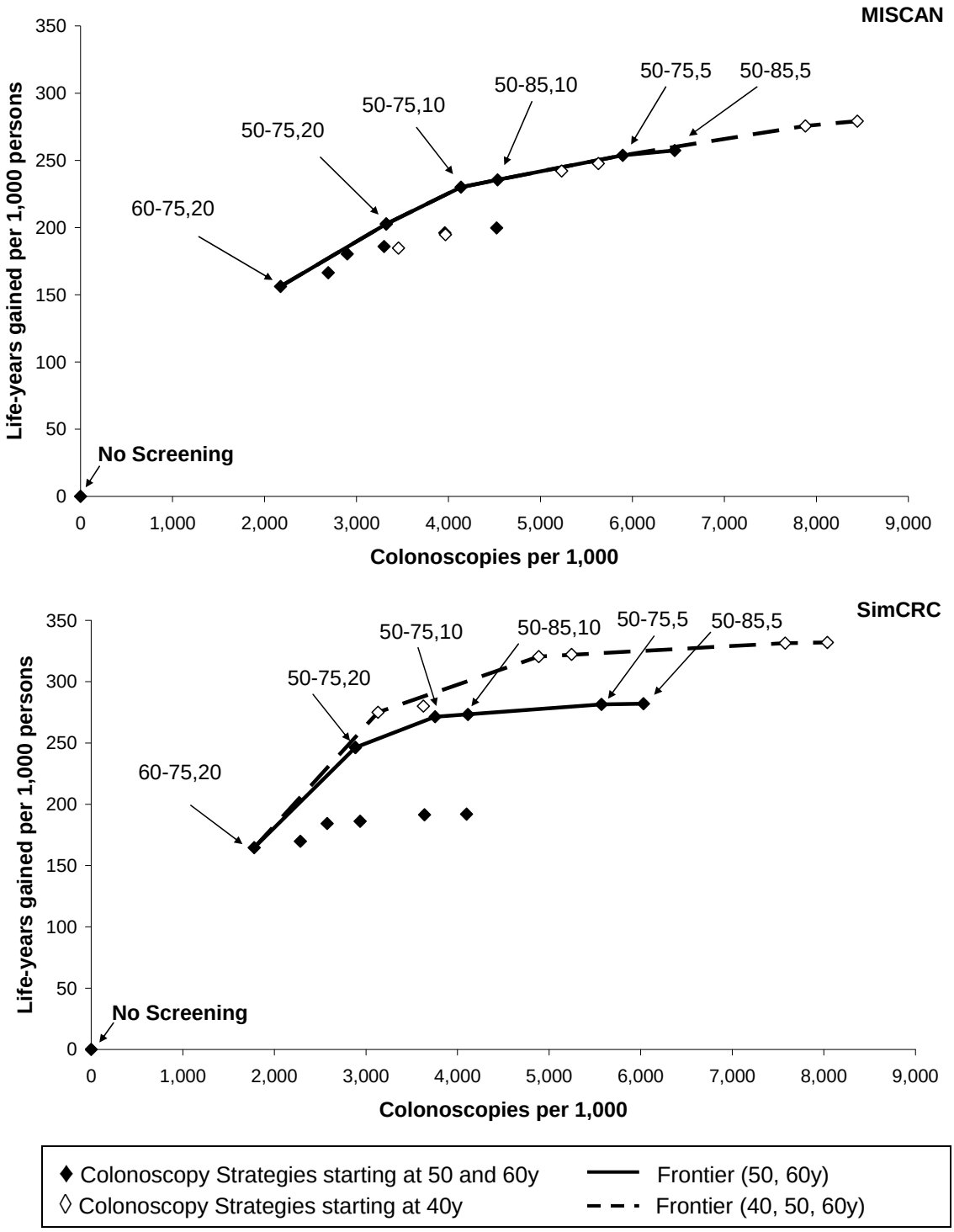


Figure 2a. Colonoscopy strategies. Colonoscopies and life-years gained (compared with no screening) for a cohort of 1,000 40-year-olds for 18 colonoscopy screening strategies that vary by start age, stop age and screening interval. The solid line represents the frontier of efficient strategies.

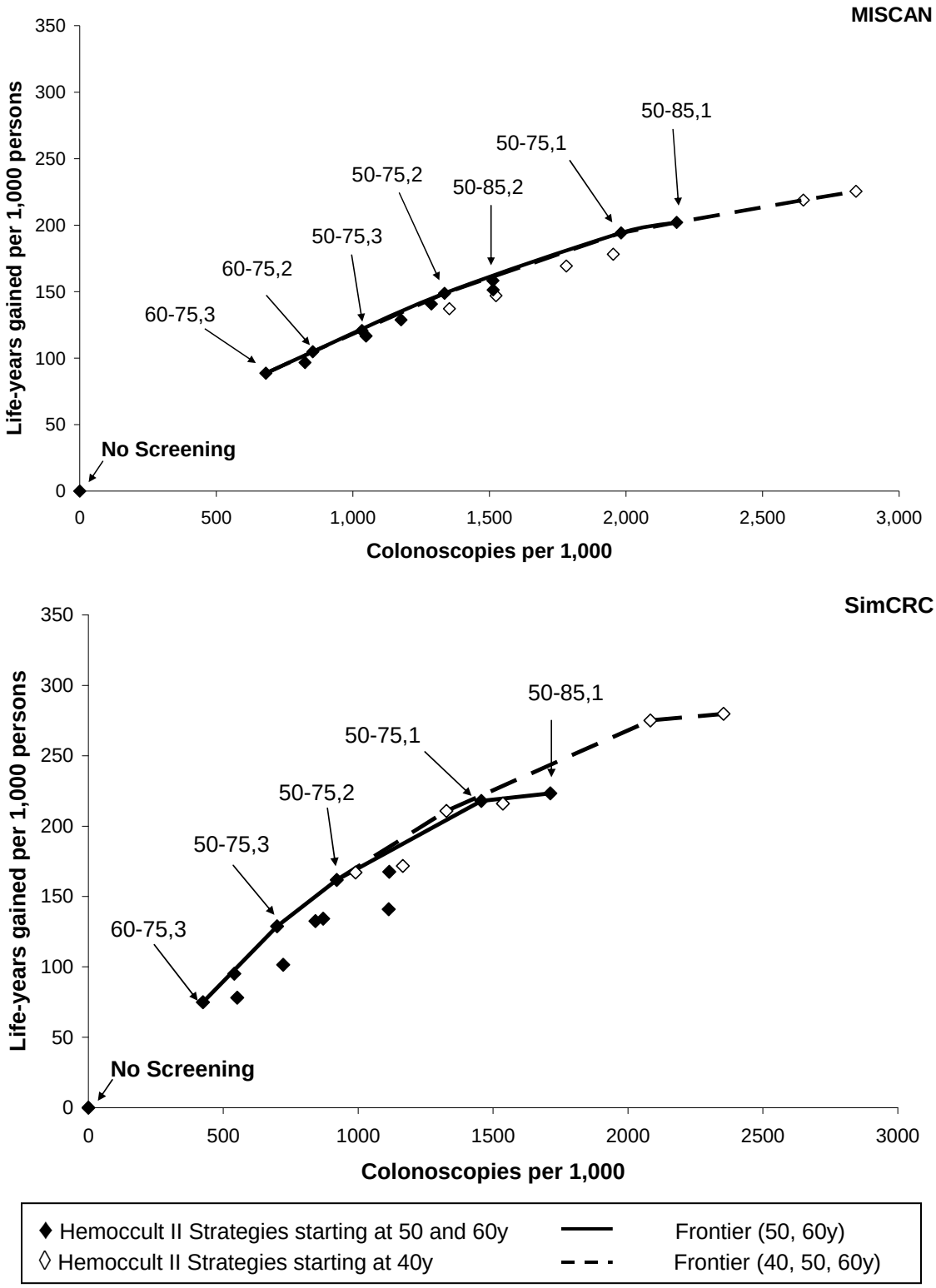


Figure 2b. **Hemoccult II strategies**. Colonoscopies and life-years gained (compared with no screening) for a cohort of 1,000 40-year-olds for 18 Hemoccult II screening strategies that vary by start age, stop age and screening interval. The solid line represents the frontier of efficient strategies.

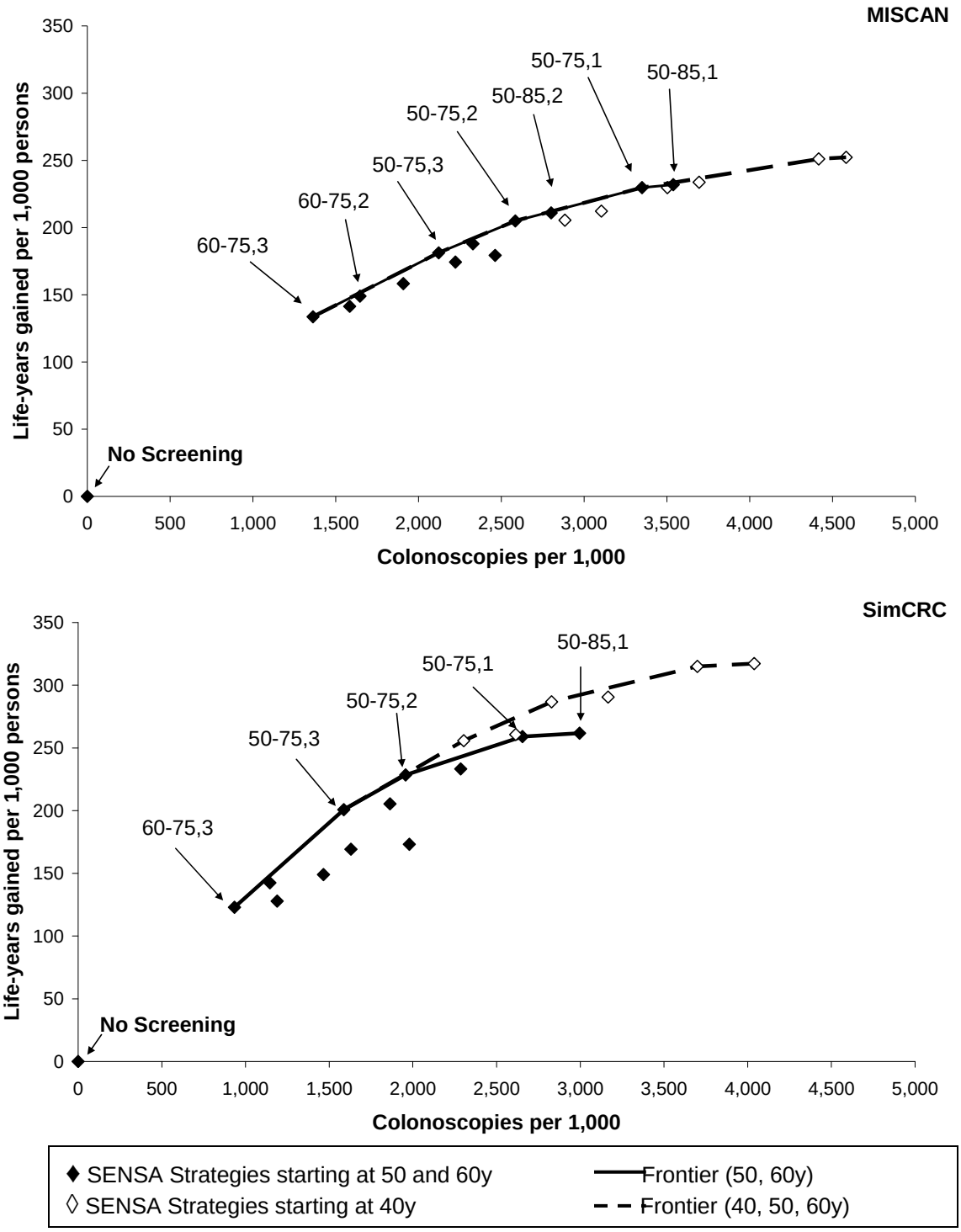


Figure 2c. Hemoccult SENSA strategies. Colonoscopies and life-years gained (compared with no screening) for a cohort of 1,000 40-year-olds for 18 Hemoccult SENSA screening strategies that vary by start age, stop age and screening interval. The solid line represents the frontier of efficient strategies.

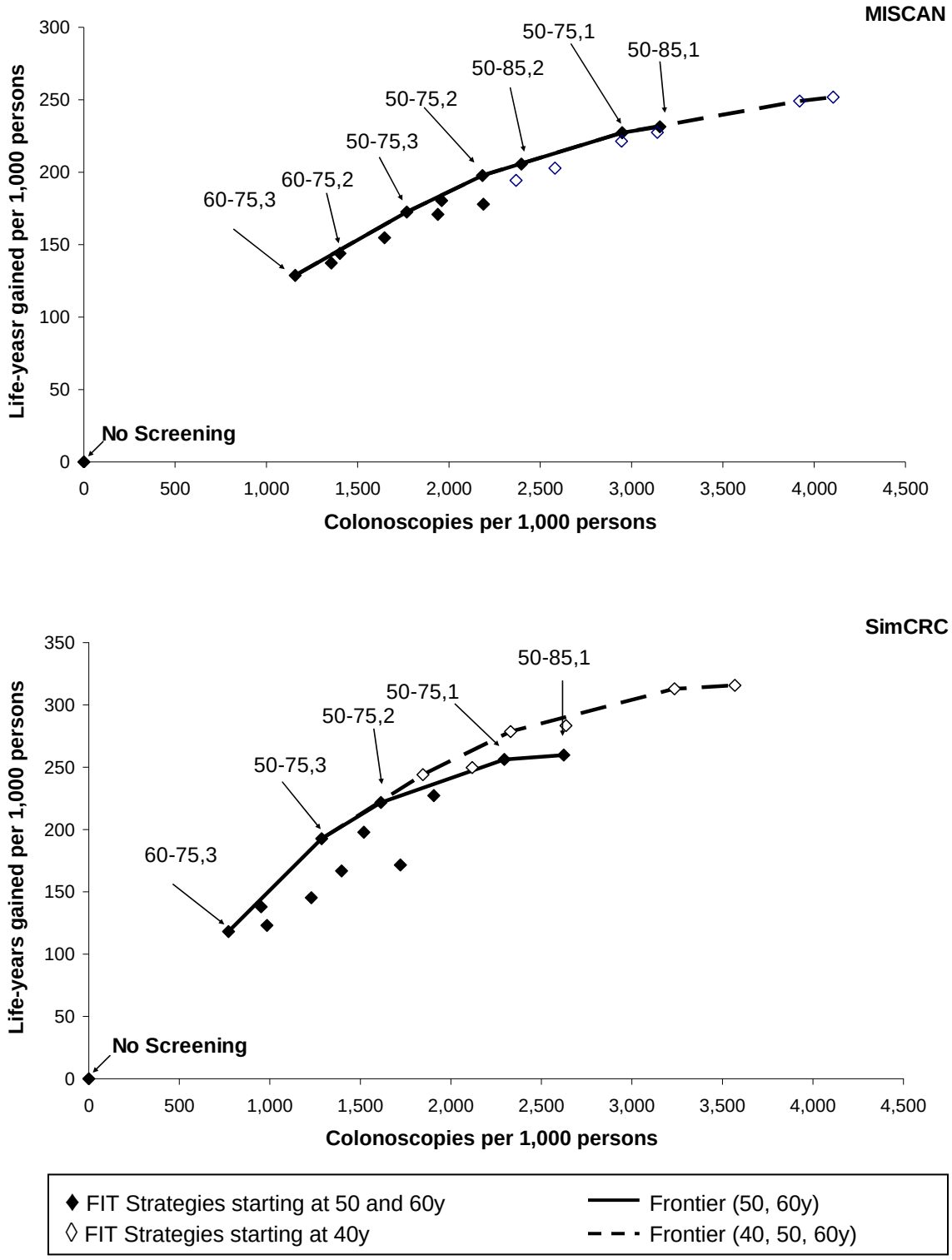


Figure 2d. FIT strategies. Colonoscopies and life-years gained (compared with no screening) for a cohort of 1,000 40-year-olds for 18 FIT screening strategies that vary by start age, stop age and screening interval. The solid line represents the frontier of efficient strategies.

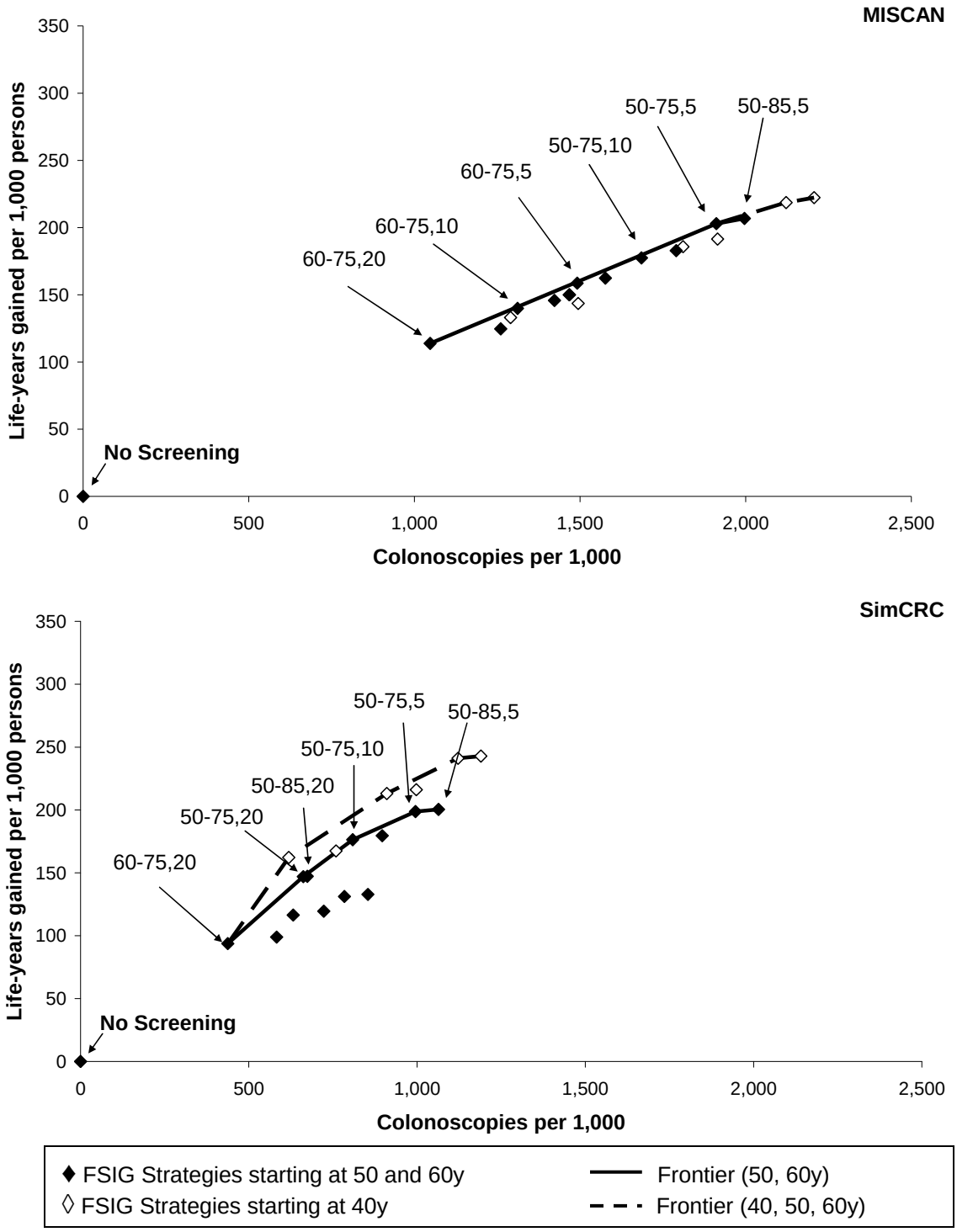


Figure 2e. Flexible sigmoidoscopy strategies. Colonoscopies and life-years gained (compared with no screening) for a cohort of 1,000 40-year-olds for 18 flexible sigmoidoscopy screening strategies that vary by start age, stop age and screening interval. The solid line represents the frontier of efficient strategies.

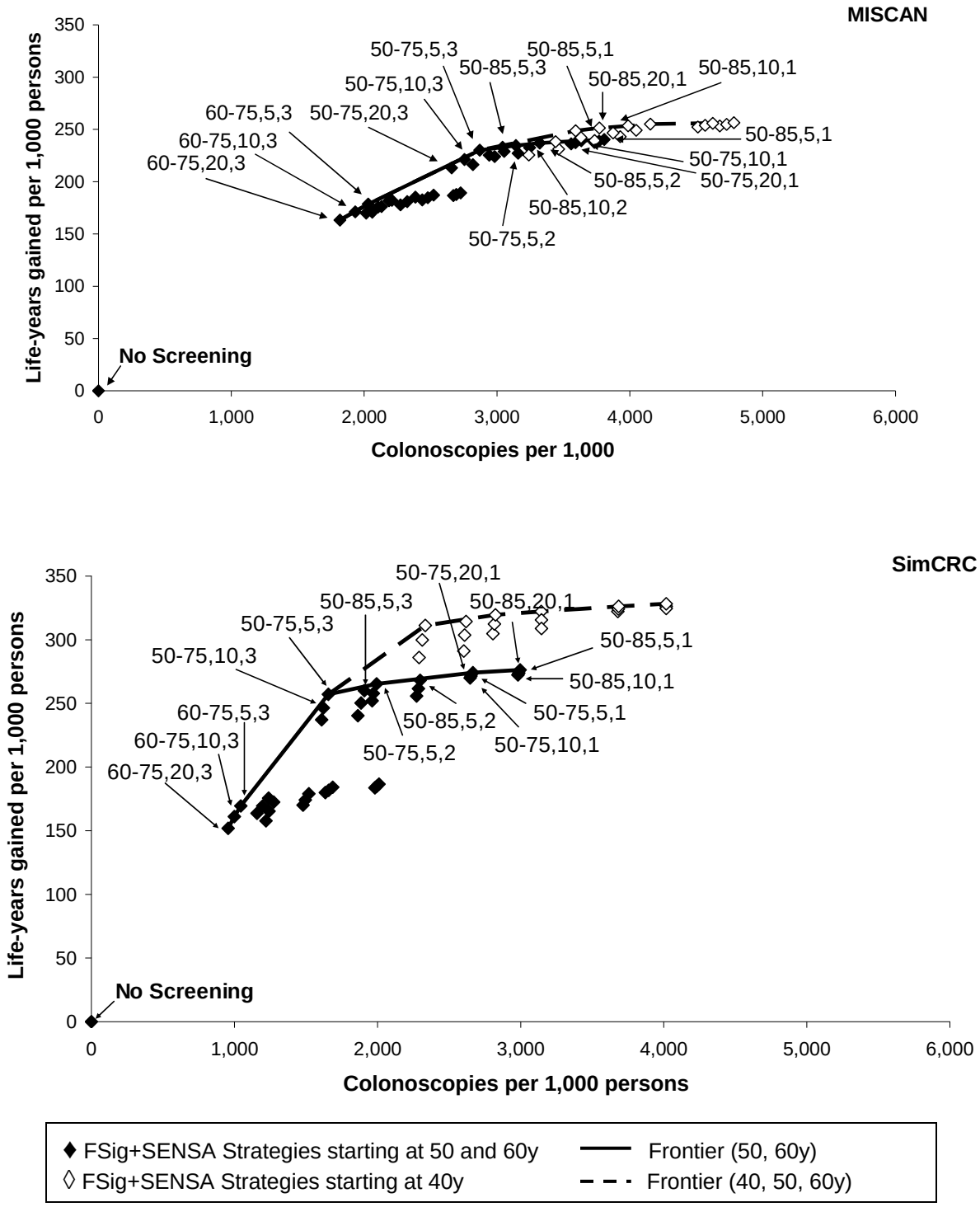


Figure 2f. Flexible sigmoidoscopy with Hemoccult SENSA strategies. Colonoscopies and life-years gained (compared with no screening) for a cohort of 1,000 40-year-olds for 18 colonoscopy screening strategies that vary by start age, stop age and screening interval. The solid line represents the frontier of efficient strategies.

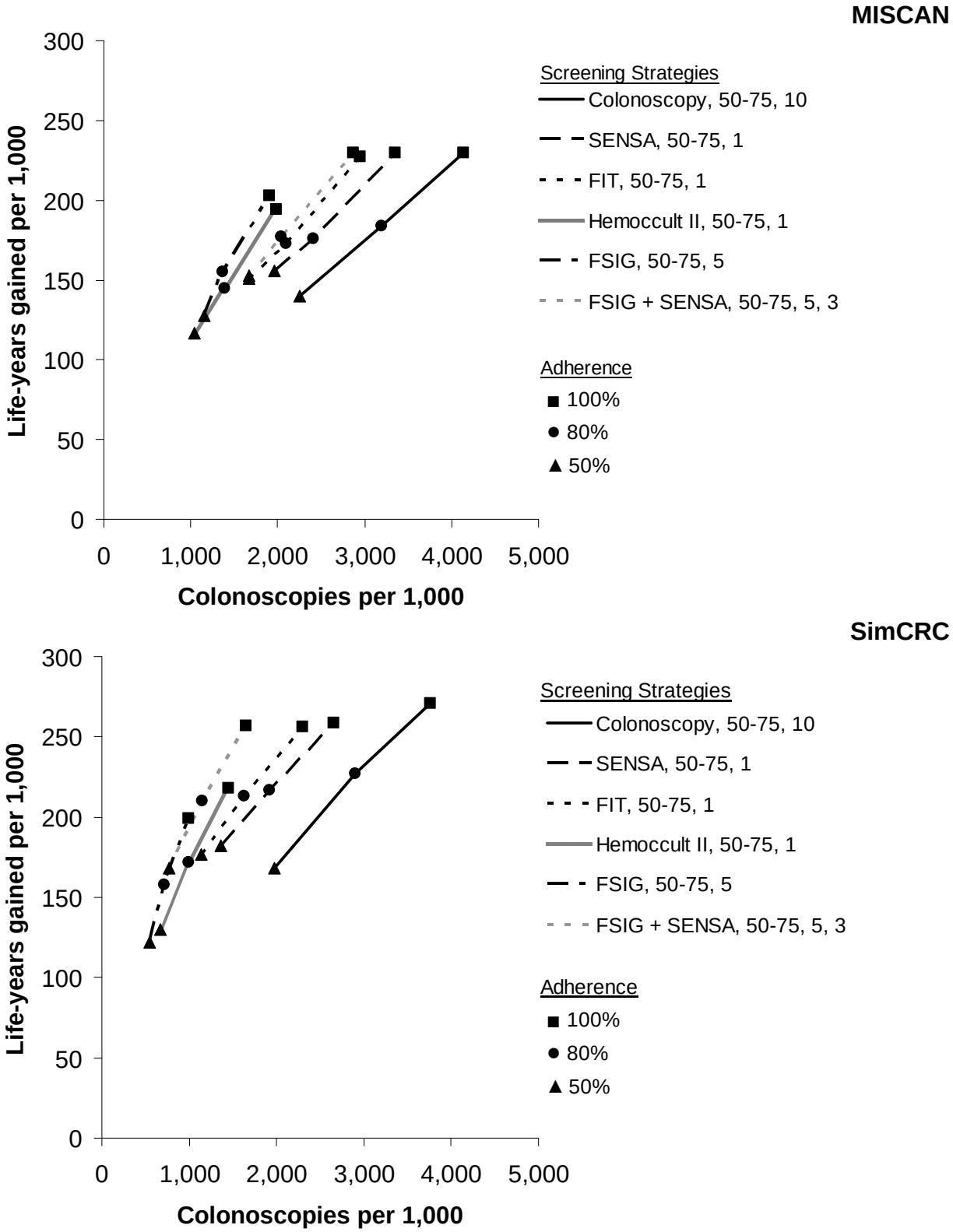


Figure 3. Sensitivity analysis of adherence. Colonoscopies and life-years gained by adherence level for the recommendable set of screening strategies. SENSA = Hemoccult SENSA; FIT = fecal immunochemical test; FSIG = flexible sigmoidoscopy

Table 1. Comparison of the Natural History Outcomes from the MISCAN and SimCRC Models

	MISCAN, by Age			SimCRC, by Age		
Outcome	40y	50y	60y	40y	50y	60y
Adenoma prevalence	10.9%	28.7%	36.7%	10.2%	18.3%	29.5%
Size distribution of adenomas						
≤ 5 mm	60.9%	64.8%	52.6%	59.3%	53.9%	51.1%
6-9 mm	20.9%	19.0%	25.3%	31.6%	34.4%	35.8%
≥ 10 mm	18.2%	16.2%	22.1%	9.1%	11.7%	13.0%
Location of adenomas						
Proximal	34.3%	34.3%	34.3%	62.0%	62.4%	62.8%
Distal	34.5%	34.5%	34.5%	30.5%	30.4%	30.3%
Rectum	31.2%	31.2%	31.2%	7.5%	7.2%	6.8%
Cumulative CRC incidence						
10-year	0.2%	0.7%	1.6%	0.2%	0.7%	1.4%
20-year	0.9%	2.3%	4.0%	0.9%	2.1%	3.4%
Lifetime	7.3%	7.1%	6.4%	6.2%	5.9%	5.3%
Stage distribution of CRC cases						
Stage I	16.6%	21.1%	19.3%	24.0%	21.9%	19.4%
Stage II	23.0%	28.3%	31.4%	39.6%	35.1%	34.8%
Stage III	33.7%	26.3%	26.1%	20.0%	22.2%	22.6%
Stage IV	26.7%	24.4%	23.2%	16.4%	20.7%	23.2%

CRC = colorectal cancer

*Because of rounding, not all percentages age to 100%.

Table 2. Test Characteristics used in the MISCAN and SimCRC Models

Test Characteristic	Base-Case Value	Sensitivity Analysis	
		Best-Case Value	Worst-Case Value
Hemoccult II			
Specificity	98.0%	99.0%	95.0%
Sensitivity adenomas ≤ 5 mm*	2.0%	1.0%	5.0%
Sensitivity adenomas 6-9 mm	5.0%	13.7%	5.0%
Sensitivity adenomas ≥ 10 mm	12.0%	27.5%	8.9%
Sensitivity cancers	40.0%	50.0%	25.0%
Reach	Whole colorectum	Not varied	Not varied
Mortality rate	0	Not varied	Not varied
Hemoccult SENSA			
Specificity	92.5%	95.0%	90.0%
Sensitivity adenomas ≤ 5 mm*	7.5%	5.0%	10.0%
Sensitivity adenomas 6-9 mm	12.4%	26.2%	10.0%
Sensitivity adenomas ≥ 10 mm	23.9%	49.4%	17.7%
Sensitivity cancers	70.0%	87.0%	50.0%
Reach	Whole colorectum	Not varied	Not varied
Mortality rate	0	Not varied	Not varied
Fecal immunochemical test			
Specificity	95.0%	98.0%	92.5%
Sensitivity adenomas ≤ 5 mm*	5.0%	2.0%	7.5%
Sensitivity adenomas 6-9 mm	10.1%	24.0%	7.5%
Sensitivity adenomas ≥ 10 mm	22.0%	48.0%	16.0%
Sensitivity cancers	70.0%	87.0%	50.0%
Reach	Whole colorectum	Not varied	Not varied
Mortality rate	0	Not varied	Not varied
Sigmoidoscopy (within reach)			
Specificity	92.0%	Not varied	Not varied
Sensitivity adenomas ≤ 5 mm	75.0%	79.0%	70.0%
Sensitivity adenomas 6-9 mm	85.0%	92.0%	80.0%
Sensitivity adenomas ≥ 10 mm	95.0%	99.0%	92.0%
Sensitivity cancers†	95.0%	99.0%	92.0%
Reach	80% to sigmoid-descending junction, 40% to splenic flexure	100% to sigmoid-descending junction, 80% to splenic flexure	60% to sigmoid-descending junction, 30% to splenic flexure
Mortality rate	0	Not varied	Not varied
Colonoscopy (within reach)			
Specificity	90.0%	Not varied	Not varied
Sensitivity adenomas ≤ 5 mm	75.0%	79.0%	70.0%
Sensitivity adenomas 6-9 mm	85.0%	92.0%	80.0%
Sensitivity adenomas ≥ 10 mm	95.0%	99.0%	92.0%
Sensitivity cancers	95.0%	99.0%	92.0%
Reach	95% to end of cecum; remaining 5% between rectum and cecum	Not varied	Not varied
Mortality rate	1 per 10,000	Not varied	Not varied

* We assume small adenomas do not bleed and cannot be detected by fecal occult blood tests (FOBTs). The sensitivity of FOBTs for adenomas ≤ 5 mm is based on the false positive rate (i.e., 1 – specificity).
† The sensitivity of sigmoidoscopy for colorectal cancer over the whole colorectum is 72% with MISCAN and 61% with SimCRC.

Table 3. Efficient and Near-Efficient Strategies for Age to Begin Screening of 50 and 60*

Strategy Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons					
	COL	Non-COL Tests	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
Colonoscopy strategies						
MISCAN						
1 COL, 60–75, 20	2175	0	156	–	–	–
2 COL, 50–75, 20	3325	0	203	1150	47	24.7
3 COL, 50–75, 10	**4136**	**0**	**230**	**811**	**27**	**29.6**
4 COL, 50–85, 10	4534	0	236	398	5	72.9
5 COL, 50–75, 5	5895	0	254	1362	18	74.8
6 COL, 50–85, 5	6460	0	257	565	4	156.1
SimCRC						
1 COL, 60–75, 20	1780	0	165	–	–	–
2 COL, 50–75, 20	2885	0	246	1106	82	13.5
3 COL, 50–75, 10	**3756**	**0**	**271**	**871**	**25**	**34.7**
4 COL, 50–85, 10	4114	0	273			Near-efficient
5 COL, 50–75, 5	5572	0	281.6	1816	10	178.8
6 COL, 50–85, 5	6031	0	282.1	459	0.5	975.7
Hemoccult II strategies						
MISCAN						
1 Hemoccult II, 60–75, 3	681	4435	89	–	–	–
2 Hemoccult II, 60–75, 2	854	5784	105	172	16	10.6
3 Hemoccult II, 50–75, 3	1033	6941	121			Near-efficient
4 Hemoccult II, 50–75, 2	1335	9510	149	482	44	11.0
5 Hemoccult II, 50–85, 2	1513	11,162	158			Near-efficient
6 Hemoccult II, 50–75, 1	**1982**	**16,232**	**194**	**647**	**45**	**14.3**
7 Hemoccult II, 50–85, 1	2186	18,409	202	203	8	25.5
SimCRC						
1 Hemoccult II, 60–75, 3	425	4291	75	–	–	–
2 Hemoccult II, 50–75, 3	699	6834	129	275	54	5.1
3 Hemoccult II, 50–75, 2	921	9422	162	221	33	6.7
4 Hemoccult II, 50–75, 1	**1456**	**16,239**	**218**	**536**	**56**	**9.6**
5 Hemoccult II, 50–85, 1	1712	18,262	223	256	5	47.9

Strategy Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons					
	COL	Non-COL Tests	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
	COL	Non-COL Tests	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
Hemoccult SENSA strategies						
MISCAN						
1 Hemoccult SENSA, 60–75, 3	1363	3824	134	–	–	–
2 Hemoccult SENSA, 60–75, 2	1647	4732	149			Near-efficient
3 Hemoccult SENSA, 50–75, 3	2121	5596	181	758	47	16.0
4 Hemoccult SENSA, 50–75, 2	2584	7014	205	463	24	19.5
5 Hemoccult SENSA, 50–85, 2	2801	7679	211			Near-efficient
6 Hemoccult SENSA, 50–75, 1	**3350**	**9541**	**230**	**766**	**25**	**30.9**
7 Hemoccult SENSA, 50–85, 1	3538	9904	232	188	2	80.6
SimCRC						
1 Hemoccult SENSA, 60–75, 3	934	3735	123	–	–	–
2 Hemoccult SENSA, 50–75, 3	1587	5554	201	653	78	8.4
3 Hemoccult SENSA, 50–75, 2	1957	7006	228	370	28	13.3
4 Hemoccult SENSA, 50–75, 1	**2654**	**9573**	**259**	**698**	**31**	**22.9**
5 Hemoccult SENSA, 50–85, 1	2996	9918	262	341	3	128.2
Fecal immunochemical test strategies						
MISCAN						
1 FIT, 60–75, 3	1158	4037	129	–	–	–
2 FIT, 60–75, 2	1403	5098	144			Near-efficient
3 FIT, 50–75, 3	1769	6089	173	611	44	14.0
4 FIT, 50–75, 2	2184	7916	198	415	25	16.5
5 FIT, 50–85, 2	2396	8895	206			Near-efficient
6 FIT, 50–75, 1	**2949**	**11,773**	**227**	**765**	**30**	**25.9**
7 FIT, 50–85, 1	3155	12,582	231	206	4	49.1
SimCRC						
1 FIT, 60–75, 3	772	3943	118	–	–	–
2 FIT, 50–75, 3	1286	6047	193	514	75	6.9
3 FIT, 50–75, 2	1614	7908	222	327	29	11.3
4 FIT, 50–75, 1	**2295**	**11,830**	**256**	**681**	**35**	**19.7**
5 FIT, 50–85, 1	2623	12,587	260	328	3	95.7

Strategy Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons					
	COL	Non-COL Tests	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
Flexible sigmoidoscopy strategies						
MISCAN						
1 FSIG, 60–75, 20	1047	917	114	–	–	–
2 FSIG, 60–75, 10	1311	1531	140			Near-efficient
3 FSIG, 60–75, 5	1491	2617	159			Near-efficient
4 FSIG, 50–75, 10	1685	2339	177			Near-efficient
5 FSIG, 50–75, 5	**1911**	**4139**	**203**	**864**	**89**	**9.7**
6 FSIG, 50–85, 5	1996	4745	207	85	4	22.3
SimCRC						
1 FSIG, 60–75, 20	438	889	94	–	–	–
2 FSIG, 50–75, 20	662	1662	147	224	53	4.2
3 FSIG, 50–85, 20	674	1661	147			Near-efficient
4 FSIG, 50–75, 10	808	2455	176	146	29	5.0
5 FSIG, 50–75, 5	**995**	**4483**	**199**	**187**	**22**	**8.4**
6 FSIG, 50–85, 5	1064	5088	201	68	2	38.5
Flexible sigmoidoscopy plus Hemoccult SENSA strategies						
MISCAN						
1 FSIG + SENSA, 60–75, 20, 3	1817	4142	163	---	---	---
2 FSIG + SENSA, 60–75, 10, 3	1933	4497	171			Near-efficient
3 FSIG + SENSA, 60–75, 5, 3	2031	5220	179	213	15	14.0
4 FSIG + SENSA, 50–75, 20, 3	2658	6192	213			Near-efficient
5 FSIG + SENSA, 50–75, 10, 3	2756	6573	221			Near-efficient
6 FSIG + SENSA, 50–75, 5, 3	**2870**	**7685**	**230**	**839**	**52**	**16.3**
7 FSIG + SENSA, 50–85, 5, 3	3042	8380	233	172	3	60.7
8 FSIG + SENSA, 50–75, 5, 2	3142	8588	235	100	2	62.3
9 FSIG + SENSA, 50–85, 10, 2	3245	8350	232			Near-efficient
10 FSIG + SENSA, 50–85, 5, 2	3321	9267	237	179	2	74.3
11 FSIG + SENSA, 50–75, 20, 1	3558	9590	236			Near-efficient
12 FSIG + SENSA, 50–75, 10, 1	3591	9738	237			Near-efficient
13 FSIG + SENSA, 50–75, 5, 1	3635	10,279	239	314	2	139.8
14 FSIG + SENSA, 50–85, 20, 1	3734	9915	238			Near-efficient
15 FSIG + SENSA, 50–85, 10, 1	3768	10,081	239			Near-efficient
16 FSIG + SENSA, 50–85, 5, 1	3808	10,611	240	172	1	154.5

Strategy Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons					
	COL	Non-COL Tests	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
SimCRC						
1 FSIG + SENSA, 60–75, 20, 3	956	7763	152	–	–	---
2 FSIG + SENSA, 60–75, 10, 3	999	11,104	161	44	9	4.7
3 FSIG + SENSA, 60–75, 5, 3	1045	10,064	169	45	8	5.5
4 FSIG + SENSA, 50-75, 10, 3	1621	12,485	246			Near-efficient
5 FSIG + SENSA, 50–75, 5, 3	**1655**	**11,623**	**257**	**611**	**88**	**7.0**
6 FSIG + SENSA, 50–85, 5, 3	1908	9484	260			Near-efficient
7 FSIG + SENSA, 50–75, 5, 2	1994	12,265	265	338	8	41.7
8 FSIG + SENSA, 50–85, 5, 2	2298	9895	268			Near-efficient
9 FSIG + SENSA, 50–75, 20, 1	2647	10,214	270			Near-efficient
10 FSIG + SENSA, 50–75, 10, 1	2653	14,403	271			Near-efficient
11 FSIG + SENSA, 50–75, 5, 1	2666	13,593	274	673	9	75.7
12 FSIG + SENSA, 50–85, 20, 1	2981	7133	272			Near-efficient
13 FSIG + SENSA, 50–85, 10, 1	2987	5794	274			Near-efficient
14 FSIG + SENSA, 50–85, 5, 1	2996	10,875	276	330	2	154.4

*COL = colonoscopy; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA; ΔCOL = incremental number of colonoscopies compared with the next-best non-efficient strategy; ΔLYG = incremental number of life-years gained compared with the next-best nonefficient strategy. Bold indicates recommendable strategy.

†Age and intervals expressed as years.

‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.

Table 4: Efficient (or near efficient) strategies for start age of 50 and stop age of 75. The number of colonoscopies per life-year gained is calculated *within* screening test category.

Strategy Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons				
	COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
MISCAN					
COL, 50-75, 20	3325	203	1,150	47	24.7
COL, 50-75, 10	**4136**	**230**	**811**	**27**	**29.6**
COL, 50-75, 5	5895	254	1,362	18	74.8
SENSA®, 50-75, 3	2121	181	758	47	16.0
SENSA®, 50-75, 2	2584	205	463	24	19.5
SENSA®, 50-75, 1	**3350**	**230**	**766**	**25**	**30.9**
FIT, 50-75, 3	1769	173	611	44	14.0
FIT, 50-75, 2	2184	198	415	25	16.5
FIT, 50-75, 1	**2949**	**227**	**765**	**30**	**25.9**
Hem II®, 50-75, 3	1033	121			Near efficient
Hem II®, 50-75, 2	1335	149	482	44	11.0
Hem II®, 50-75, 1	**1982**	**194**	**647**	**45**	**14.3**
Fsig, 50-75, 10	1685	177			Near efficient
Fsig, 50-75, 5	**1911**	**203**	**864**	**89**	**9.7**
FsigSENSA®, 50-75, 20,3	2658	213			Near efficient
FsigSENSA®, 50-75, 10,3	2756	221			Near efficient
FsigSENSA®, 50-75, 5,3	**2870**	**230**	**839**	**52**	**16.3**
FsigSENSA®, 50-75, 5,2	3142	235	100	2	62.3
FsigSENSA®, 50-75, 20,1	3558	236			Near efficient
FsigSENSA®, 50-75, 10,1	3591	237			Near efficient
FsigSENSA®, 50-75, 5,1	3635	239	314	2	139.8
SimCRC					
COL, 50-75, 20	2885	246	1,106	82	13.5
COL, 50-75, 10	**3756**	**271**	**871**	**25**	**34.7**
COL, 50-75, 5	5572	282	1,816	10	178.8
SENSA®, 50-75,3	1587	201	653	78	8.4
SENSA®, 50-75,2	1957	228	370	28	13.3
SENSA®, 50-75,1	**2654**	**259**	**698**	**31**	**22.9**
FIT, 50-75,3	1286	193	514	75	6.9
FIT, 50-75,2	1614	222	327	29	11.3
FIT, 50-75,1	**2295**	**256**	**681**	**35**	**19.7**
Hem II®, 50-75,3	699	129	275	54	5.1
Hem II®, 50-75, 2	921	162	221	33	6.7
Hem II®, 50-75, 1	**1456**	**218**	**536**	**56**	**9.6**
Fsig, 50-75, 20	662	147	224	53	4.2
Fsig, 50-75, 10	808	176	146	29	5.0
Fsig, 50-75, 5	**995**	**199**	**187**	**22**	**8.4**
FsigSENSA®, 50-75, 10,3	1621	246			Near efficient

Strategy Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons				
	COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
FsigSENSA®, 50-75, 5,3	**1655**	**257**	**611**	**88**	**7.0**
FsigSENSA®, 50-75, 5,2	1994	265	338	8	41.7
FsigSENSA®, 50-75, 20,1	2647	270			Near efficient
FsigSENSA®, 50-75, 10,1	2653	271			Near efficient
FsigSENSA®, 50-75, 5,1	2666	274	673	9	75.7

*COL = colonoscopy; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA; ΔCOL = incremental number of colonoscopies compared with the next-best non-efficient strategy; ΔLYG = incremental number of life-years gained compared with the next-best nonefficient strategy. Bold indicates recommendable strategy

†Age and intervals expressed as years.

‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.

See text for example shown in bold text.

Table 5a. Outcomes for the Recommendable Set of Efficient Screening Strategies Using Colonoscopy beginning at age 50, Stopping at age 75, and 10 year Interval as Starting Strategy

Strategy Test, Age Begin–Age Stop, Interval*	Outcomes per 1000 Persons			Efficiency ratio†	Incidence Reduction (%)	Mortality Reduction (%)
	COL	Non-COL Tests	LYG			
MISCAN						
COL, 50-75, 10	4136	0	230	29.6	51.9	64.6
Hemoccult SENSA, 50-75, 1	3350	9541	230	30.9	49.7	66.0
FIT, 50-75, 1	2949	11,773	227	25.9	47.2	64.6
Hemoccult II, 50-75, 1	1982	16,232	194	14.3	37.1	55.3
FSIG, 50-75, 5	1911	4139	203	9.7	46.8	58.5
FSIG + SENSA, 50-75, 5, 3	2870	7685	230	16.3	51.2	65.7
SimCRC						
COL, 50-75, 10	3756	0	271	34.7	80.6	84.4
Hemoccult SENSA, 50-75, 1	2654	9573	259	22.9	73.2	81.2
FIT, 50-75, 1	2295	11,830	256	19.7	70.8	80.0
Hemoccult II, 50-75, 1	1456	16,239	218	9.6	56.6	69.0
FSIG, 50-75, 5	995	4483	199	8.4	59.0	62.2
FSIG + SENSA, 50-75, 5, 3	1655	11,623	257	7.0	72.2	79.3

COL = colonoscopy; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA

*Age and intervals expressed as years.

† Efficiency ratio corresponds with ΔCOL/ΔLYG in the Appendix 2 Tables and represents the relative burden per unit of benefit achieved.

Table 5b. Secondary Outcomes for the Recommendable Set of Efficient Screening Strategies Using Colonoscopy beginning at age 50, Stopping at age 75, and 20 Year Interval as Starting Strategy

Strategy Test, Age Begin–Age Stop, Interval*	Outcomes per 1000 Persons			Efficiency ratio†	Incidence Reduction (%)	Mortality Reduction (%)
	COL	Non-COL Tests	LYG			
MISCAN						
COL, 50–75, 20	3325	0	203	24.7	46.6	58.8
Hemoccult SENSA, 50–75, 3	2121	5596	181	16.0	35.9	52.8
FIT, 50–75, 2	2184	7916	198	16.5	38.2	56.2
Hemoccult II, 50-75, 1	1982	16,232	194	14.3	37.1	55.3
FSIG, 50-75, 5	1911	4139	203	9.7	46.8	58.5
FSIG + SENSA, 50–75, 10, 3	2756	6573	221	17.2‡	48.3	63.1
SimCRC						
COL, 50–75, 20	2885	0	246	13.5	72.6	77.3
Hemoccult SENSA, 50–75, 2	1957	7006	228	13.3	61.4	72.5
FIT, 50–75, 2	1614	7908	222	11.3	57.4	69.9
Hemoccult II, 50-75, 1	1456	16,239	218	9.6	56.6	69.0
FSIG, 50-75, 5	995	4483	199	8.4	59.0	62.2
FSIG + SENSA, 50-75, 10, 3	1621	12,485	246	7.4‡	80.6	88.3

COL = colonoscopy; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA

*Age and intervals expressed as years.

† Efficiency ratio corresponds with ΔCOL/ΔLYG in the Appendix 2 Tables and represents the relative burden per unit of benefit achieved.

‡ Near efficient strategy; efficiency ratio represents ratio relative to next least effective non-dominated strategy.

Table 6. Subset of strategies for start age of 50 and stop age of 75 varied by overall adherence to screening (see **Figure 3**).

Strategy Test, Age Begin–Age Stop, Interval*	Outcomes per 1000 Persons					
	50% adherence		**80% adherence**		**100% adherence**	
	COL	**LYG**	**COL**	**LYG**	**COL**	**LYG**
MISCAN						
COL, 50-75, 10	2250	140	3193	184	4136	230
SENSA®, 50-75, 1	1960	156	2405	176	3350	230
FIT, 50-75, 1	1670	151	2099	173	2949	227
Hem II®, 50-75, 1	1041	117	1386	145	1982	194
Fsig, 50-75, 5	1150	128	1369	155	1911	203
FsigSENSA®, 50-75, 5,3	1674	153	2050	177	2870	230
SimCRC						
COL, 50-75, 10	1977	168	2904	227	3756	271
SENSA®, 50-75, 1	1361	182	1920	217	2654	259
FIT, 50-75, 1	1140	177	1629	213	2295	256
Hem II®, 50-75, 1	666	130	993	172	1456	218
Fsig, 50-75, 5	544	122	711	158	995	199
FsigSENSA®, 50-75, 5,3	770	168	1153	210	1655	257

COL = colonoscopy; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA

*Age and intervals expressed as years.

Appendices

Appendix 1. Model descriptions

Appendix 2. Summary results per 1000 40-year old individuals for all strategies and both models

Appendix 3. Results including starting at age 40 in efficient and near-efficient frontiers.

Appendix 1: Model descriptions

We used the MISCAN and SimCRC models from the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) to compare colorectal cancer (CRC) screening strategies that vary by the age to begin screening, the age to stop screening, and screening interval. The use of two models (i.e., a comparative modeling approach) provides a sensitivity analysis on the model structure. While the models were developed independently, they were calibrated to the same data on adenoma prevalence and CRC incidence and they use the same assumptions regarding the sensitivity, specificity, and reach of the various screening tests. Accordingly, differences in findings across models may be attributed to differences in model structure and the assumptions about the natural history of CRC. Brief descriptions of the MISCAN and SimCRC model are provided below.

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

MISCAN Model overview
MISCAN-COLON is a semi-Markov microsimulation program to simulate the effect of screening and other interventions on colorectal cancer (CRC) incidence and mortality. With microsimulation we mean that each individual in the population is simulated separately. The model is semi-Markov in the sense that:

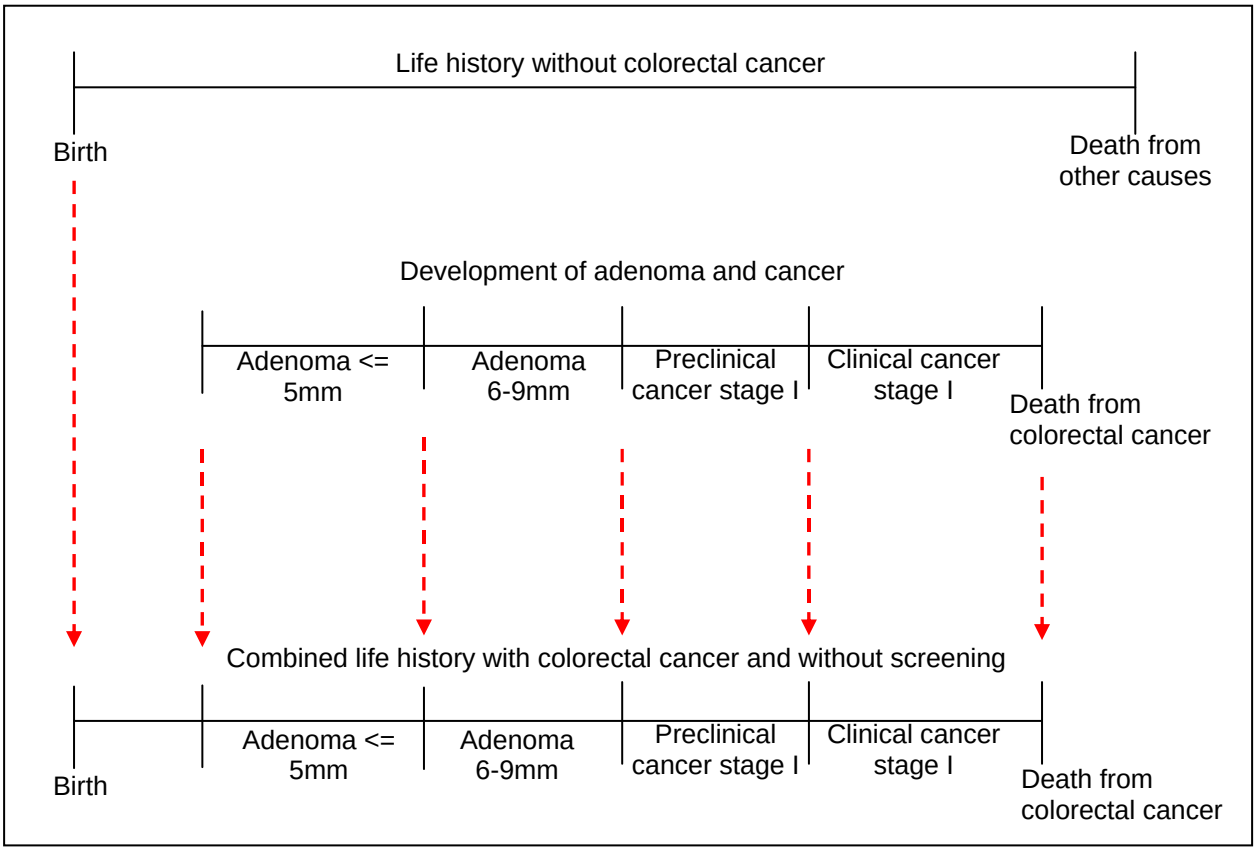
- distributions other than exponential are possible in each disease state
- transitions in one state can depend on transitions in earlier states,
- transitions can be age and calendar time dependent

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

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

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

MISCAN Simulation of an individual
Figure 1a shows how the model generates an individual life history. First MISCAN-COLON generates a time of birth and a time of death of other causes than CRC for an individual. This is shown in the top line of figure 1a. This line constitutes the life history in the absence of CRC. Subsequently, MISCAN-COLON generates adenomas for an individual. For most individuals no adenomas are simulated, for some multiple. In this example MISCAN-Colon has generated two adenomas for the individual. The first adenoma occurs at a certain age and grows in size from small to medium and large adenoma. However this is a non-progressive adenoma, so this adenoma will never transform into cancer. The second adenoma is a progressive adenoma. After having grown to 6-9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and eventually resulting in an earlier death from CRC.

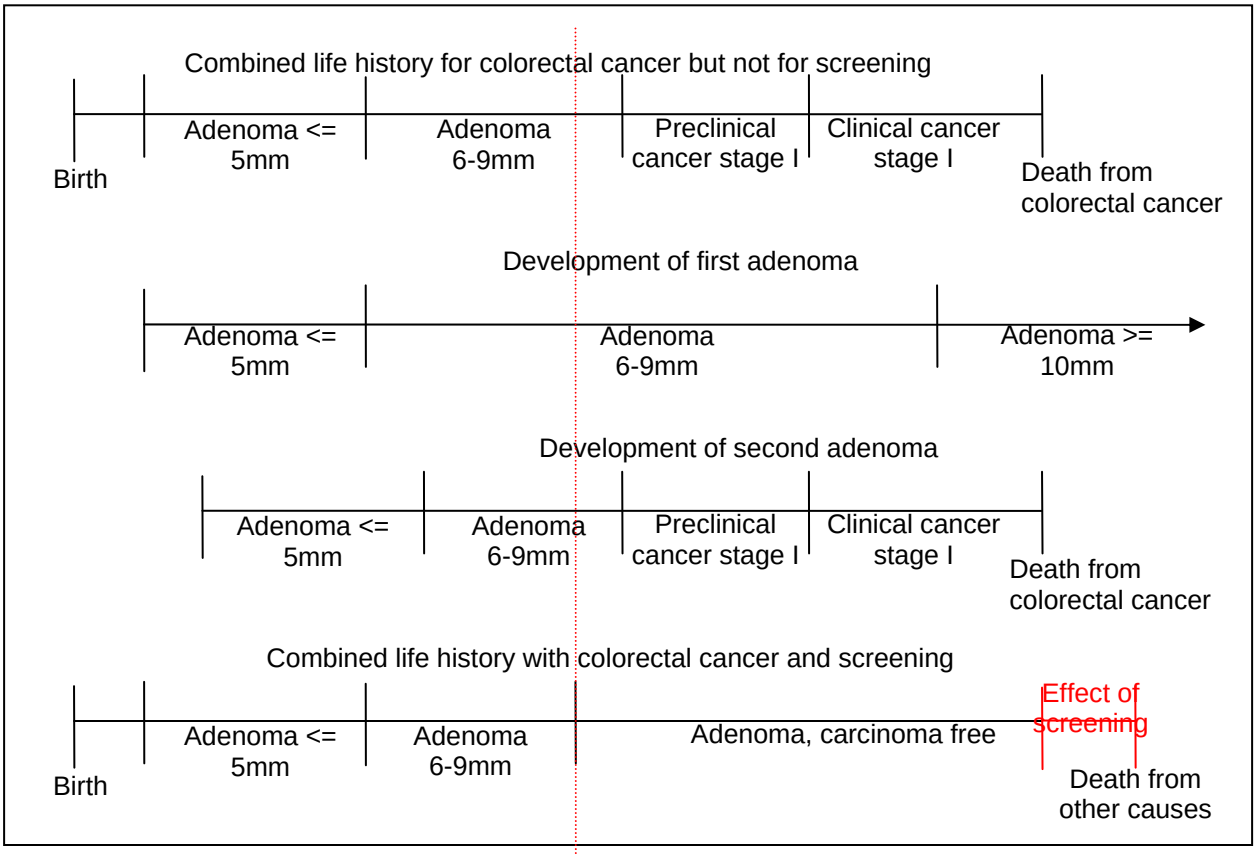


Appendix Figure 1a: Modeling natural history into life

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

MISCAN Simulation of screening
The complete simulation of an individual life history in figure **Appendix 1a** is in a situation without screening taking place. After the model has generated a life history with CRC but without screening, screening is overlaid. This is shown in figure **Appendix 1b**. The first three

lines show the combined life history with CRC and the development of the two adenomas from figure **Appendix 1a**. 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.



Appendix Figure 1b: Modeling screening into life history

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

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

the test for the present lesions. Sensitivity in the model is lesion-specific, where each adenoma or cancer contributes to the probability of a positive test result.

See the model profiler http://cisnet.cancer.gov/profiles/ for a more detailed discussion of the dwell time distributions for the adenomas and colorectal cancer.

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

SimCRC Model

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

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

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

SimCRC simulation of screening. The screening component of the SimCRC model is superimposed on the natural history model. It allows for the detection and removal of adenomas and the diagnosis of preclinical CRC. In a screening year, a person with an underlying (i.e., undiagnosed) adenoma or preclinical cancer faces the chance that the lesion is detected based on the sensitivity of the test for adenomas by size or for cancer and the reach of the test. Individuals who do not have an underlying adenoma or preclinical cancer also face the risk of having a positive screening test (and undergoing unnecessary follow-up procedures) due to the imperfect specificity of the test. While the model does not explicitly simulate non-adenomatous polyps, they are accounted for through the specificity of the test. Additionally, individuals with false-negative screening tests (i.e., individuals with an adenoma or preclinical cancer that was missed by the screening test) may be referred for follow-up due to the detection of non-adenomatous polyps. The model incorporates the risk of fatal and non-fatal complications associated with various screening procedures. It also accounts for the fact that not all individuals are adherent with CRC screening guidelines and that adherence patterns are correlated within an individual.

See the model profiler http://cisnet.cancer.gov/profiles/ for a more detailed discussion of the transition probabilities for the adenomas and colorectal cancer.

Appendix 2. Summary results per 1000 40-year old individuals for all strategies and both models

A2 Table 1: Summary results for all colonoscopy strategies per 1000 40-year old individuals, MISCAN

	Outcomes per 1000 Persons											
Strategy Test, Age Begin-Age Stop, Interval*	Total Tests	Non-COL Tests	COL Tests	Screening Tests	Follow-Up Tests	Surveillance Tests	COMPLIC	Total CRC Cases	CRC Deaths†	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	68	30	0	--	--
COL, 40-75, 5	7,881	0	7,881	5,451	0	2,430	7.9	27	8	276	59.7	73.5
COL, 40-75, 10	5,231	0	5,231	3,093	0	2,138	5.2	32	10	242	52.9	65.9
COL, 40-75, 20	3,456	0	3,456	1,836	0	1,620	3.5	40	15	185	41.5	52.0
COL, 40-85, 5	8,445	0	8,445	5,970	0	2,476	8.4	26	7	279	61.7	75.8
COL, 40-85, 10	5,629	0	5,629	3,426	0	2,203	5.6	30	9	248	55.6	69.2
COL, 40-85, 20	3,967	0	3,967	2,216	0	1,751	4.0	36	13	195	46.5	58.2
COL, 50-75, 5	5,895	0	5,895	3,770	0	2,125	5.9	29	9	254	57.7	71.2
COL, 50-75, 10	4,136	0	4,136	2,188	0	1,948	4.1	33	11	230	51.9	64.6
COL, 50-75, 20	3,325	0	3,325	1,571	0	1,754	3.3	36	12	203	46.6	58.8
COL, 50-85, 5	6,460	0	6,460	4,289	0	2,171	6.5	27	8	257	59.7	73.4
COL, 50-85, 10	4,534	0	4,534	2,521	0	2,013	4.5	31	10	236	54.6	67.9
COL, 50-85, 20	3,325	0	3,325	1,571	0	1,754	3.3	36	12	203	46.6	58.8
COL, 60-75, 5	3,960	0	3,960	2,390	0	1,570	4.0	34	11	196	50.5	63.0
COL, 60-75, 10	2,899	0	2,899	1,451	0	1,448	2.9	37	13	180	45.7	57.6
COL, 60-75, 20	2,175	0	2,175	917	0	1,258	2.2	42	16	156	38.4	48.2
COL, 60-85, 5	4,525	0	4,525	2,909	0	1,616	4.5	32	11	200	52.5	65.3
COL, 60-85, 10	3,300	0	3,300	1,785	0	1,515	3.3	35	12	186	48.5	60.9
COL, 60-85, 20	2,693	0	2,693	1,300	0	1,393	2.7	38	14	166	43.5	54.6

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; LYG = life-years gained compared with no screening
*Age and intervals expressed as years.
† Includes screening related deaths

A2, Table 2: Summary results for all colonoscopy strategies per 1000 40-year old individuals, SimCRC

	Outcomes per 1000 Persons											
Strategy Test, Age Begin-Age Stop, Interval*	Total Tests	Non-COL Tests	COL Tests	Screening Tests	Follow-Up Tests	Surveillance Tests	COMPLIC	Total CRC Cases	CRC Deaths†	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	64	30	0	--	--
COL, 40-75, 5	7,578	0	7,578	5,555	0	2,021	7.6	4	1	331	93.2	95.5
COL, 40-75, 10	4,887	0	4,887	3,130	0	1,757	4.9	8	3	320	87.6	91.0
COL, 40-75, 20	3,131	0	3,131	1,807	0	1,324	3.1	17	7	275	72.8	76.4
COL, 40-85, 5	8,036	0	8,036	5,975	0	2,062	8.0	4	1	332	93.9	96.2
COL, 40-85, 10	5,245	0	5,245	3,423	0	1,821	5.2	6	2	322	89.3	92.6
COL, 40-85, 20	3,627	0	3,627	2,166	0	1,460	3.6	15	6	280	77.1	81.0
COL, 50-75, 5	5,572	0	5,572	3,836	0	1,735	5.6	10	3	282	85.6	88.6
COL, 50-75, 10	3,756	0	3,756	2,236	0	1,520	3.8	12	5	271	80.6	84.4
COL, 50-75, 20	2,885	0	2,885	1,585	0	1,300	2.9	18	7	246	72.6	77.3
COL, 50-85, 5	6,031	0	6,031	4,256	0	1,776	6.0	9	3	282	86.4	89.3
COL, 50-85, 10	4,114	0	4,114	2,530	0	1,584	4.1	12	4	273	82.3	86.0
COL, 50-85, 20	2,885	0	2,885	1,585	0	1,300	2.9	18	7	246	72.6	77.3
COL, 60-75, 5	3,640	0	3,640	2,346	0	1,294	3.6	20	8	191	68.6	72.5
COL, 60-75, 10	2,576	0	2,576	1,437	0	1,139	2.6	23	9	184	64.5	69.0
COL, 60-75, 20	1,780	0	1,780	888	0	891	1.8	29	12	165	54.9	58.8
COL, 60-85, 5	4,099	0	4,099	2,765	0	1,334	4.1	20	8	192	69.4	73.2
COL, 60-85, 10	2,937	0	2,937	1,732	0	1,205	2.9	21	9	186	66.2	70.6
COL, 60-85, 20	2,284	0	2,284	1,252	0	1,031	2.3	26	11	170	59.4	63.6

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; LYG = life-years gained compared with no screening
*Age and intervals expressed as years.
† Includes screening related deaths

A2, Table 3: Summary results for all Hemoccult II strategies per 1000 40-year old individuals, MISCAN

	Outcomes per 1000 Persons											
Strategy Test, Age Begin-Age Stop, Interval*	Total Tests	Non-COL Tests	COL Tests	Screening Tests	Follow-Up Tests	Surveillance Tests†	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	68	30	0	--	--
HII, 40-75, 1	24,581	21,932	2,649	21,932	590	2,059	2.6	40	12	219	41.5	59.6
HII, 40-75, 2	14,982	13,201	1,781	13,201	396	1,385	1.8	47	16	169	30.5	46.7
HII, 40-75, 3	10,833	9,480	1,353	9,480	301	1,053	1.4	52	19	137	24.2	38.0
HII, 40-85, 1	26,544	23,702	2,842	23,702	646	2,197	2.8	38	11	225	43.4	63.3
HII, 40-85, 2	16,642	14,689	1,953	14,689	455	1,499	2.0	46	15	178	32.7	51.6
HII, 40-85, 3	12,386	10,862	1,524	10,862	363	1,162	1.5	50	17	147	26.5	43.5
HII, 50-75, 1	18,214	16,231	1,982	16,231	495	1,487	2.0	43	14	194	37.1	55.3
HII, 50-75, 2	10,845	9,509	1,335	9,509	328	1,008	1.3	50	17	149	26.8	42.7
HII, 50-75, 3	7,974	6,941	1,033	6,941	254	779	1.0	53	20	121	21.5	35.3
HII, 50-85, 1	20,594	18,409	2,186	18,409	564	1,622	2.2	41	12	202	39.4	59.8
HII, 50-85, 2	12,675	11,162	1,513	11,162	393	1,120	1.5	48	16	158	29.3	48.1
HII, 50-85, 3	9,265	8,089	1,176	8,089	306	870	1.2	52	18	129	23.5	39.9
HII, 60-75, 1	11,468	10,181	1,288	10,181	369	918	1.3	48	17	141	28.9	45.4
HII, 60-75, 2	6,637	5,784	854	5,784	238	616	0.9	54	20	105	20.1	33.8
HII, 60-75, 3	5,117	4,436	681	4,436	193	488	0.7	57	22	89	16.5	28.9
HII, 60-85, 1	14,400	12,886	1,514	12,886	458	1,056	1.5	46	15	151	32.0	51.3
HII, 60-85, 2	8,693	7,645	1,048	7,645	315	733	1.0	52	18	117	23.2	40.4
HII, 60-85, 3	6,428	5,603	825	5,603	249	576	0.8	55	20	97	18.5	33.8

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer;Hii = Hemoccult II; LYG = life-years gained compared with no screening
*Age and intervals expressed as years.
† Including colonoscopies for re-screening of individuals with a false-positive Hemoccult II.
‡ Includes screening-related deaths

A2, Table 4: Summary results for all Hemoccult II strategies per 1000 40-year old individuals, SimCRC

Strategy Test, Age Begin-Age Stop, Interval*	Outcomes per 1000 Persons											
	Total Tests	Non-COL Tests	COL Tests	Screening Tests†	Follow-Up Tests	Surveillance Tests	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	64	30	0	--	--
HII, 40-75, 1	24,050	21,967	2,083	22,476	556	1,018	2.1	21	6	275	67.3	78.4
HII, 40-75, 2	14,469	13,142	1,327	13,425	361	683	1.4	33	12	211	49.0	61.3
HII, 40-75, 3	10,389	9,399	990	9,603	269	517	1.0	39	15	167	38.2	49.0
HII, 40-85, 1	25,969	23,615	2,354	24,269	609	1,091	2.3	20	5	280	69.8	81.9
HII, 40-85, 2	16,061	14,525	1,536	14,897	414	750	1.6	31	10	216	51.2	65.4
HII, 40-85, 3	11,825	10,660	1,165	10,926	322	577	1.2	39	14	172	39.9	53.2
HII, 50-75, 1	17,695	16,239	1,456	16,465	452	778	1.5	28	9	218	56.6	69.0
HII, 50-75, 2	10,343	9,422	921	9,545	287	511	0.9	39	14	162	39.6	52.3
HII, 50-75, 3	7,533	6,834	699	6,924	218	391	0.7	45	17	129	30.9	42.3
HII, 50-85, 1	19,974	18,262	1,712	18,603	518	853	1.7	26	8	223	59.2	73.0
HII, 50-85, 2	12,071	10,956	1,115	11,148	346	577	1.1	37	13	168	41.9	56.8
HII, 50-85, 3	8,727	7,886	841	8,024	263	440	0.8	43	16	133	32.4	45.9
HII, 60-75, 1	10,913	10,043	870	10,101	322	490	0.9	39	15	134	38.5	51.3
HII, 60-75, 2	6,180	5,640	540	5,670	199	311	0.5	48	19	95	25.5	37.0
HII, 60-75, 3	4,716	4,291	425	4,314	158	244	0.4	51	21	75	19.9	29.9
HII, 60-85, 1	13,663	12,550	1,113	12,687	405	571	1.1	38	13	141	41.6	56.2
HII, 60-85, 2	8,079	7,357	722	7,431	267	381	0.7	47	17	102	28.0	42.2
HII, 60-85, 3	5,895	5,343	552	5,399	205	291	0.5	51	20	78	21.1	33.2

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; HII = Hemoccult II; LYG = life-years gained compared with no screening
*Age and intervals expressed as years.
† Including colonoscopies for re-screening of individuals with a false-positive Hemoccult II.
‡ Includes screening-related deaths

A2, Table 5: Summary results for all Hemoccult SENSA strategies per 1000 40-year old individuals, MISCAN

Strategy Test, Age Begin-Age Stop, Interval*	Outcomes per 1000 Persons Total Tests	Non-COL Tests	COL Tests	Screening Tests	Follow-Up Tests	Surveillance Tests†	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	68	30	0	--	--
SENSA, 40-75, 1	15,701	11,284	4,416	11,284	925	3,492	4.4	32	9	251	53.4	68.9
SENSA, 40-75, 2	12,379	8,877	3,503	8,877	766	2,736	3.5	36	11	230	46.8	63.4
SENSA, 40-75, 3	10,065	7,181	2,884	7,181	641	2,243	2.9	40	13	206	40.7	57.0
SENSA, 40-85, 1	16,023	11,440	4,583	11,440	939	3,644	4.6	31	9	252	54.1	69.8
SENSA, 40-85, 2	13,020	9,326	3,695	9,326	809	2,885	3.7	35	10	234	48.1	65.8
SENSA, 40-85, 3	10,899	7,794	3,104	7,794	705	2,400	3.1	39	12	212	42.7	60.8
SENSA, 50-75, 1	12,891	9,542	3,350	9,542	839	2,511	3.3	34	10	230	49.7	66.0
SENSA, 50-75, 2	9,599	7,014	2,584	7,014	655	1,929	2.6	40	12	205	41.7	59.0
SENSA, 50-75, 3	7,717	5,596	2,121	5,596	543	1,579	2.1	44	14	181	35.9	52.8
SENSA, 50-85, 1	13,442	9,904	3,538	9,904	871	2,667	3.5	34	10	232	50.7	67.4
SENSA, 50-85, 2	10,480	7,679	2,801	7,679	719	2,082	2.8	38	11	211	43.7	62.4
SENSA, 50-85, 3	8,534	6,205	2,329	6,205	606	1,723	2.3	42	13	188	37.9	56.6
SENSA, 60-75, 1	9,258	7,034	2,223	7,034	679	1,544	2.2	40	13	174	40.6	56.6
SENSA, 60-75, 2	6,379	4,732	1,647	4,732	491	1,156	1.6	46	16	149	32.2	48.3
SENSA, 60-75, 3	5,187	3,824	1,363	3,824	413	950	1.4	49	17	134	27.7	43.7
SENSA, 60-85, 1	10,314	7,852	2,462	7,852	751	1,711	2.5	39	12	179	42.5	59.5
SENSA, 60-85, 2	7,637	5,729	1,908	5,729	589	1,318	1.9	44	14	158	35.2	53.5
SENSA, 60-85, 3	6,145	4,561	1,584	4,561	492	1,092	1.6	48	16	141	30.1	48.3

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA
*Age and intervals expressed as years.
† Including colonoscopies for re-screening of individuals with a false-positive Hemoccult SENSA.
‡ Includes screening-related deaths

A2, Table 6: Summary results for all Hemoccult SENSA strategies per 1000 40-year old individuals, SimCRC

	Outcomes per 1000 Persons											
Strategy Test, Age Begin-Age Stop, Interval*	Total Tests	Non-COL Tests	COL Tests	Screening Tests†	Follow-Up Tests	Surveillance Tests	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	64	30	0	--	--
SENSA, 40-75, 1	14,994	11,294	3,700	12,566	909	1,519	3.7	11	3	315	83.4	89.3
SENSA, 40-75, 2	11,713	8,884	2,829	9,734	743	1,236	2.9	17	5	287	73.3	82.3
SENSA, 40-75, 3	9,465	7,161	2,304	7,819	614	1,032	2.3	23	8	256	63.8	74.1
SENSA, 40-85, 1	15,493	11,454	4,039	12,985	923	1,585	4.0	10	3	317	85.2	91.2
SENSA, 40-85, 2	12,471	9,304	3,167	10,374	784	1,313	3.2	16	4	291	75.7	85.3
SENSA, 40-85, 3	10,338	7,723	2,615	8,554	672	1,112	2.6	22	7	261	66.3	77.9
SENSA, 50-75, 1	12,227	9,573	2,654	10,203	810	1,214	2.7	17	6	259	73.2	81.2
SENSA, 50-75, 2	8,963	7,006	1,957	7,400	620	943	1.9	24	8	228	61.4	72.5
SENSA, 50-75, 3	7,141	5,554	1,587	5,857	505	779	1.6	31	11	201	52.4	64.6
SENSA, 50-85, 1	12,914	9,918	2,996	10,790	840	1,284	3.0	16	5	262	75.3	83.3
SENSA, 50-85, 2	9,916	7,630	2,286	8,209	680	1,027	2.3	23	7	233	64.1	76.1
SENSA, 50-85, 3	7,987	6,124	1,863	6,569	565	853	1.9	29	9	205	54.8	68.3
SENSA, 60-75, 1	8,607	6,977	1,630	7,165	635	807	1.6	30	11	169	53.6	63.8
SENSA, 60-75, 2	5,803	4,657	1,146	4,764	448	591	1.1	38	14	142	42.0	54.2
SENSA, 60-75, 3	4,669	3,735	934	3,811	370	488	0.9	42	16	123	35.3	47.6
SENSA, 60-85, 1	9,720	7,741	1,979	8,126	703	891	2.0	28	10	173	56.3	66.7
SENSA, 60-85, 2	7,055	5,589	1,466	5,830	539	686	1.5	35	12	149	45.4	59.0
SENSA, 60-85, 3	5,600	4,410	1,190	4,595	442	563	1.2	40	14	128	37.6	51.6

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA
*Age and intervals expressed as years.
† Including colonoscopies for re-screening of individuals with a false-positive Hemoccult SENSA.
‡ Includes screening-related deaths

A2, Table 7: Summary results for all FIT strategies per 1000 40-year old individuals, MISCAN

Strategy Test, Age Begin-Age Stop, Interval*	Outcomes per 1000 Persons											
	Total Tests	Non-COL Tests	COL Tests	Screening Tests	Follow-Up Tests	Surveillance Tests†	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	68	30	0	--	--
FIT, 40-75, 1	18,587	14,667	3,921	14,667	846	3,075	3.9	33	10	249	51.4	67.9
FIT, 40-75, 2	13,388	10,443	2,945	10,443	651	2,294	2.9	39	12	221	42.8	60.5
FIT, 40-75, 3	10,417	8,050	2,368	8,050	527	1,841	2.4	43	14	194	36.4	53.3
FIT, 40-85, 1	19,248	15,144	4,104	15,144	876	3,229	4.1	32	9	252	52.4	69.5
FIT, 40-85, 2	14,341	11,200	3,141	11,200	705	2,436	3.1	38	11	228	44.6	63.9
FIT, 40-85, 3	11,495	8,915	2,580	8,915	595	1,985	2.6	42	13	203	38.7	58.1
FIT, 50-75, 1	14,721	11,772	2,949	11,772	743	2,205	2.9	36	11	227	47.2	64.6
FIT, 50-75, 2	10,099	7,915	2,184	7,915	547	1,637	2.2	42	13	198	38.2	56.2
FIT, 50-75, 3	7,858	6,090	1,769	6,090	444	1,324	1.8	46	15	173	32.4	49.7
FIT, 50-85, 1	15,737	12,582	3,155	12,582	794	2,361	3.2	35	10	231	48.8	67.0
FIT, 50-85, 2	11,292	8,896	2,396	8,896	618	1,779	2.4	40	12	206	40.5	60.6
FIT, 50-85, 3	8,841	6,882	1,960	6,882	508	1,451	2.0	44	14	180	34.6	54.2
FIT, 60-75, 1	10,052	8,113	1,939	8,113	580	1,359	1.9	42	14	171	38.2	54.9
FIT, 60-75, 2	6,502	5,099	1,403	5,099	406	997	1.4	48	16	144	29.6	46.1
FIT, 60-75, 3	5,194	4,036	1,158	4,036	340	818	1.2	51	18	129	25.3	41.6
FIT, 60-85, 1	11,677	9,489	2,188	9,489	667	1,521	2.2	40	12	178	40.7	58.9
FIT, 60-85, 2	8,032	6,386	1,647	6,386	501	1,145	1.6	46	15	155	32.8	52.0
FIT, 60-85, 3	6,274	4,919	1,355	4,919	413	942	1.4	49	16	137	27.7	46.7

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; LYG = life-years gained compared with no screening
*Age and intervals expressed as years.
† Including colonoscopies for re-screening of individuals with a false-positive FIT.
‡ Includes screening-related deaths

A2, Table 8: Summary results for all FIT strategies per 1000 40-year old individuals, SimCRC

Strategy Test, Age Begin-Age Stop, Interval*	Outcomes per 1000 Persons											
	Total Tests	Non-COL Tests	COL Tests	Screening Tests†	Follow-Up Tests	Surveillance Tests	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	64	30	0	--	--
FIT, 40-75, 1	17,941	14,705	3,236	15,711	825	1,405	3.2	12	4	313	81.2	88.3
FIT, 40-75, 2	12,782	10,452	2,330	11,076	621	1,085	2.4	20	6	279	68.7	79.4
FIT, 40-75, 3	9,875	8,029	1,846	8,498	495	882	1.9	26	9	244	58.4	70.1
FIT, 40-85, 1	18,725	15,157	3,568	16,398	853	1,474	3.6	11	3	316	83.2	90.5
FIT, 40-85, 2	13,796	11,160	2,636	11,960	673	1,163	2.7	18	5	283	71.2	82.9
FIT, 40-85, 3	10,942	8,824	2,118	9,425	558	959	2.1	25	8	250	60.9	74.4
FIT, 50-75, 1	14,125	11,830	2,295	12,308	709	1,108	2.3	19	6	256	70.8	80.0
FIT, 50-75, 2	9,522	7,908	1,614	8,190	507	825	1.6	27	9	222	57.4	69.9
FIT, 50-75, 3	7,333	6,047	1,286	6,259	405	669	1.3	33	11	193	48.2	61.6
FIT, 50-85, 1	15,210	12,587	2,623	13,270	757	1,183	2.6	17	5	260	73.1	82.6
FIT, 50-85, 2	10,733	8,828	1,905	9,250	575	908	1.9	25	8	227	60.2	74.0
FIT, 50-85, 3	8,305	6,786	1,519	7,102	464	739	1.5	32	10	198	50.5	65.6
FIT, 60-75, 1	9,458	8,061	1,397	8,196	534	728	1.4	31	11	167	51.4	62.5
FIT, 60-75, 2	5,972	5,020	952	5,095	360	517	1.0	39	14	138	39.2	52.2
FIT, 60-75, 3	4,715	3,943	772	3,995	296	424	0.8	43	16	118	32.5	45.5
FIT, 60-85, 1	11,059	9,338	1,721	9,628	617	814	1.7	30	10	172	54.3	66.0
FIT, 60-85, 2	7,451	6,222	1,229	6,394	450	607	1.2	37	13	145	42.5	57.4
FIT, 60-85, 3	5,736	4,752	984	4,881	363	492	1.0	42	15	123	34.6	49.6

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; LYG = life-years gained compared with no screening
*Age and intervals expressed as years.
† Including colonoscopies for re-screening of individuals with a false-positive FIT.
‡ Includes screening-related deaths

A2, Table 9: Summary results for all flexible sigmoidoscopy strategies per 1000 40-year old individuals, MISCAN

Strategy Test, Age Begin-Age Stop, Interval*	Outcomes per 1000 Persons											
	Total Tests	Non-COL Tests	COL Tests	Screening Tests	Follow-Up Tests	Surveillance Tests†	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	68	30	0	--	--
FSIG, 40-75, 5	8,033	5,911	2,122	5,911	347	1,775	2.1	35	12	219	48.2	60.2
FSIG, 40-75, 10	5,086	3,275	1,811	3,275	301	1,510	1.8	40	14	186	41.6	52.2
FSIG, 40-75, 20	3,159	1,869	1,290	1,869	217	1,073	1.3	47	19	133	30.4	38.1
FSIG, 40-85, 5	8,722	6,516	2,206	6,516	383	1,823	2.2	34	11	222	50.2	62.6
FSIG, 40-85, 10	5,575	3,660	1,915	3,660	343	1,572	1.9	38	13	192	44.3	55.7
FSIG, 40-85, 20	3,796	2,302	1,494	2,302	299	1,196	1.5	44	17	144	35.5	44.7
FSIG, 50-75, 5	6,051	4,139	1,911	4,139	342	1,569	1.9	36	13	203	46.8	58.5
FSIG, 50-75, 10	4,023	2,338	1,685	2,338	298	1,388	1.7	40	15	177	40.8	51.3
FSIG, 50-75, 20	3,103	1,636	1,467	1,636	268	1,199	1.5	44	17	150	35.4	45.1
FSIG, 50-85, 5	6,741	4,745	1,996	4,745	379	1,617	2.0	35	12	207	48.8	61.0
FSIG, 50-85, 10	4,513	2,723	1,790	2,723	341	1,450	1.8	38	14	183	43.5	54.7
FSIG, 50-85, 20	3,103	1,636	1,468	1,636	268	1,199	1.5	44	17	150	35.4	45.1
FSIG, 60-75, 5	4,108	2,617	1,491	2,617	323	1,168	1.5	40	15	159	41.0	51.9
FSIG, 60-75, 10	2,842	1,530	1,311	1,530	277	1,034	1.3	44	17	140	35.8	45.5
FSIG, 60-75, 20	1,964	917	1,047	917	204	843	1.0	49	20	114	27.9	35.2
FSIG, 60-85, 5	4,800	3,223	1,577	3,223	360	1,217	1.6	39	14	162	43.1	54.4
FSIG, 60-85, 10	3,342	1,919	1,423	1,919	323	1,100	1.4	42	15	146	38.7	49.1
FSIG, 60-85, 20	2,615	1,354	1,261	1,354	289	972	1.3	45	18	125	33.2	41.9

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening
*Age and intervals expressed as years.
† Including colonoscopies for re-screening of individuals with a false-positive sigmoidoscopy.
‡ Includes screening-related deaths

A2, Table 10: Summary results for all flexible sigmoidoscopy strategies per 1000 40-year old individuals, SimCRC

Strategy Test, Age Begin-Age Stop, Interval*	**Outcomes per 1000 Persons**											
	Total Tests	Non-COL Tests	COL Tests	Screening Tests†	Follow-Up Tests	Surveillance Tests	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	64	30	0	--	--
FSIG, 40-75, 5	7,480	6,358	1,122	6,384	222	874	1.1	22	10	241	64.8	67.7
FSIG, 40-75, 10	4,322	3,412	910	3,430	178	714	0.9	29	12	213	56.2	59.6
FSIG, 40-75, 20	2,482	1,863	619	1,876	110	496	0.6	38	17	162	40.9	43.6
FSIG, 40-85, 5	8,155	6,965	1,190	6,995	252	908	1.2	22	9	243	66.3	69.3
FSIG, 40-85, 10	4,807	3,809	998	3,831	214	762	1.0	27	11	216	58.6	62.3
FSIG, 40-85, 20	3,053	2,294	759	2,308	174	571	0.8	35	15	167	45.2	48.4
FSIG, 50-75, 5	5,478	4,483	995	4,503	217	758	1.0	26	11	199	59.0	62.2
FSIG, 50-75, 10	3,263	2,455	808	2,468	174	621	0.8	31	14	176	51.1	54.7
FSIG, 50-75, 20	2,324	1,662	662	1,670	151	503	0.7	37	16	147	42.4	46.3
FSIG, 50-85, 5	6,152	5,088	1,064	5,114	246	792	1.1	25	11	201	60.6	63.7
FSIG, 50-85, 10	3,746	2,849	897	2,868	210	668	0.9	30	13	180	53.6	57.3
FSIG, 50-85, 20	2,335	1,661	674	1,675	151	509	0.7	37	16	147	42.7	46.5
FSIG, 60-75, 5	3,543	2,759	784	2,771	203	569	0.8	34	15	131	46.5	49.9
FSIG, 60-75, 10	2,185	1,553	632	1,562	159	464	0.6	38	17	116	40.0	43.5
FSIG, 60-75, 20	1,327	889	438	897	96	334	0.4	45	20	94	30.1	32.5
FSIG, 60-85, 5	4,220	3,366	854	3,384	232	604	0.9	34	15	133	48.1	51.5
FSIG, 60-85, 10	2,675	1,952	723	1,965	197	513	0.7	37	16	120	42.6	46.2
FSIG, 60-85, 20	1,906	1,323	583	1,333	162	411	0.6	42	19	99	34.4	37.4

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening
*Age and intervals expressed as years.
† Including colonoscopies for re-screening of individuals with a false-positive sigmoidoscopy.
‡ Includes screening-related deaths

A2, Table 11: Summary results for all combinations of Hemoccult SENSA with flexible sigmoidoscopy strategies per 1000 40-year old individuals, MISCAN

Strategy Test, Age Begin-Age Stop, Interval*	Outcomes per 1000 Persons											
	Total Tests	Non-COL Tests	COL Tests	Screening Tests	Follow-Up Tests	Surveillance Tests†	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	68	30	0	--	--
FSIG+SENSA, 40-75, 5,1	17,268	12,643	4,625	12,643	937	3,688	4.6	30	9	256	55.6	69.9
FSIG+SENSA, 40-75, 5,2	15,169	11,181	3,987	11,181	813	3,174	4.0	31	9	253	54.4	69.1
FSIG+SENSA, 40-75, 5,3	13,754	10,162	3,592	10,162	724	2,868	3.6	32	10	249	53.2	67.9
FSIG+SENSA, 40-75, 10,1	16,599	12,031	4,568	12,031	934	3,634	4.6	31	9	254	55.0	69.5
FSIG+SENSA, 40-75, 10,2	13,941	10,068	3,873	10,068	803	3,070	3.9	32	10	247	52.6	67.7
FSIG+SENSA, 40-75, 10,3	12,143	8,702	3,441	8,702	707	2,734	3.4	34	10	238	50.5	65.4
FSIG+SENSA, 40-75, 20,1	16,393	11,882	4,512	11,882	930	3,582	4.5	31	9	252	54.3	69.2
FSIG+SENSA, 40-75, 20,2	13,389	9,653	3,735	9,653	789	2,946	3.7	34	10	239	50.3	65.9
FSIG+SENSA, 40-75, 20,3	11,330	8,090	3,240	8,090	683	2,557	3.2	36	11	225	46.8	62.2
FSIG+SENSA, 40-85, 5,1	17,562	12,778	4,784	12,778	948	3,836	4.8	30	9	256	56.0	70.5
FSIG+SENSA, 40-85, 5,2	15,795	11,641	4,154	11,641	848	3,307	4.2	30	9	255	55.2	70.2
FSIG+SENSA, 40-85, 5,3	14,575	10,804	3,771	10,804	772	2,998	3.8	31	9	251	54.4	69.6
FSIG+SENSA, 40-85, 10,1	16,908	12,179	4,729	12,179	946	3,784	4.7	30	9	255	55.5	70.2
FSIG+SENSA, 40-85, 10,2	14,558	10,509	4,048	10,509	840	3,208	4.0	32	9	249	53.6	69.2
FSIG+SENSA, 40-85, 10,3	12,948	9,315	3,633	9,315	761	2,873	3.6	33	10	242	52.0	67.7
FSIG+SENSA, 40-85, 20,1	16,715	12,037	4,677	12,037	943	3,734	4.7	31	9	253	54.9	70.0
FSIG+SENSA, 40-85, 20,2	14,051	10,123	3,928	10,123	833	3,095	3.9	33	10	243	51.8	68.0
FSIG+SENSA, 40-85, 20,3	12,208	8,744	3,464	8,744	749	2,715	3.5	35	10	231	49.1	65.6
FSIG+SENSA, 50-75, 5,1	13,914	10,279	3,635	10,279	863	2,772	3.6	31	10	239	53.8	68.2
FSIG+SENSA, 50-75, 5,2	11,730	8,588	3,142	8,588	723	2,419	3.1	33	10	235	52.2	66.9
FSIG+SENSA, 50-75, 5,3	10,555	7,685	2,870	7,685	645	2,225	2.9	33	10	230	51.2	65.7
FSIG+SENSA, 50-75, 10,1	13,329	9,738	3,591	9,738	858	2,733	3.6	32	10	237	52.9	67.7
FSIG+SENSA, 50-75, 10,2	10,751	7,697	3,054	7,697	709	2,345	3.1	34	11	229	50.2	65.3

FSIG+SENSA, 50-75, 10,3	9,329	6,573	2,756	6,573	625	2,130	2.8	35	11	221	48.3	63.1
FSIG+SENSA, 50-75, 20,1	13,149	9,590	3,558	9,590	855	2,703	3.6	32	10	236	52.3	67.4
FSIG+SENSA, 50-75, 20,2	10,390	7,407	2,983	7,407	702	2,281	3.0	35	11	224	48.5	64.2
FSIG+SENSA, 50-75, 20,3	8,851	6,192	2,658	6,192	615	2,044	2.7	37	12	213	45.9	61.4
FSIG+SENSA, 50-85, 5,1	14,419	10,611	3,808	10,611	889	2,919	3.8	31	9	240	54.4	69.1
FSIG+SENSA, 50-85, 5,2	12,589	9,267	3,321	9,267	773	2,548	3.3	32	10	237	53.2	68.4
FSIG+SENSA, 50-85, 5,3	11,422	8,380	3,042	8,380	696	2,346	3.0	32	10	233	52.4	67.5
FSIG+SENSA, 50-85, 10,1	13,850	10,081	3,768	10,081	885	2,883	3.8	32	9	239	53.7	68.8
FSIG+SENSA, 50-85, 10,2	11,596	8,350	3,245	8,350	764	2,481	3.2	33	10	232	51.5	67.4
FSIG+SENSA, 50-85, 10,3	10,160	7,217	2,942	7,217	682	2,260	2.9	34	10	225	49.9	65.6
FSIG+SENSA, 50-85, 20,1	13,649	9,915	3,734	9,915	881	2,852	3.7	32	10	238	52.9	68.4
FSIG+SENSA, 50-85, 20,2	11,140	7,980	3,159	7,980	751	2,409	3.2	34	10	227	49.5	66.0
FSIG+SENSA, 50-85, 20,3	9,522	6,703	2,818	6,703	660	2,159	2.8	36	11	216	46.8	63.3
FSIG+SENSA, 60-75, 5,1	10,067	7,544	2,523	7,544	724	1,799	2.5	36	12	187	46.9	60.6
FSIG+SENSA, 60-75, 5,2	8,037	5,850	2,187	5,850	588	1,599	2.2	37	12	182	45.2	58.8
FSIG+SENSA, 60-75, 5,3	7,251	5,220	2,031	5,220	536	1,494	2.0	38	13	179	44.3	57.9
FSIG+SENSA, 60-75, 10,1	9,607	7,128	2,479	7,128	714	1,765	2.5	37	12	185	45.7	59.7
FSIG+SENSA, 60-75, 10,2	7,330	5,225	2,106	5,225	568	1,537	2.1	39	13	176	42.8	56.6
FSIG+SENSA, 60-75, 10,3	6,431	4,497	1,933	4,497	513	1,421	1.9	40	14	171	41.5	55.3
FSIG+SENSA, 60-75, 20,1	9,401	6,963	2,438	6,963	703	1,735	2.4	38	13	183	44.5	58.8
FSIG+SENSA, 60-75, 20,2	6,939	4,924	2,015	4,924	544	1,471	2.0	41	14	170	40.1	54.2
FSIG+SENSA, 60-75, 20,3	5,960	4,142	1,817	4,142	482	1,336	1.8	42	15	163	38.0	52.0
FSIG+SENSA, 60-85, 5,1	11,035	8,309	2,726	8,309	782	1,944	2.7	35	12	189	47.8	62.0
FSIG+SENSA, 60-85, 5,2	9,242	6,856	2,386	6,856	664	1,722	2.4	36	12	185	46.7	61.0
FSIG+SENSA, 60-85, 5,3	8,305	6,097	2,209	6,097	600	1,609	2.2	37	12	182	45.9	60.1
FSIG+SENSA, 60-85, 10,1	10,594	7,901	2,694	7,901	776	1,917	2.7	36	12	188	47.0	61.6
FSIG+SENSA, 60-85, 10,2	8,520	6,196	2,324	6,196	651	1,673	2.3	38	12	181	44.8	59.7
FSIG+SENSA, 60-85, 10,3	7,414	5,283	2,130	5,283	583	1,547	2.1	38	13	176	43.6	58.3
FSIG+SENSA, 60-85, 20,1	10,446	7,775	2,671	7,775	773	1,898	2.7	36	12	187	46.3	61.2

FSIG+SENSA, 60-85, 20,2	8,231	5,957	2,274	5,957	643	1,631	2.3	39	13	178	43.2	58.7
FSIG+SENSA, 60-85, 20,3	7,036	4,974	2,061	4,974	571	1,491	2.1	40	13	171	41.2	56.5

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA

*Age and intervals expressed as years.

† Including colonoscopies for re-screening of individuals with a false-positive sigmoidoscopy or Hemoccult SENSA.

‡ Includes screening-related deaths

A2, Table 12: Summary results for all combinations of flexible sigmoidoscopy and Hemoccult SENSA strategies per 1000 40-year old individuals, SimCRC

Strategy Test, Age Begin-Age Stop, Interval*	Outcomes per 1000 Persons											
	Total Tests	Non-COL Tests	COL Tests	Screening Tests†	Follow-Up Tests	Surveillance Tests	COMPLIC	Total CRC Cases	CRC Deaths‡	LYG	% Incidence Reduction	% Mortality Reduction
No Screening	0	0	0	0	0	0	0.0	64	30	0	--	--
FSIG+SENSA, 40-75, 5,1	18,606	14,922	3,684	16,189	930	1,487	3.7	9	3	326	86.9	91.2
FSIG+SENSA, 40-75, 5,2	17,269	14,445	2,824	14,854	924	1,491	3.7	9	3	320	86.0	90.8
FSIG+SENSA, 40-75, 5,3	16,603	14,269	2,334	14,193	918	1,492	3.7	9	3	311	85.2	90.4
FSIG+SENSA, 40-75, 10,1	19,102	15,420	3,682	16,611	942	1,549	4.0	7	2	324	88.5	92.9
FSIG+SENSA, 40-75, 10,2	17,769	14,952	2,817	15,278	937	1,554	4.0	8	2	312	87.7	92.5
FSIG+SENSA, 40-75, 10,3	17,116	14,803	2,313	14,626	933	1,557	4.0	8	2	300	87.0	92.2
FSIG+SENSA, 40-75, 20,1	15,656	11,976	3,680	13,616	841	1,199	2.7	14	5	322	79.0	84.5
FSIG+SENSA, 40-75, 20,2	14,450	11,643	2,807	12,425	831	1,194	2.7	14	5	305	77.7	83.7
FSIG+SENSA, 40-75, 20,3	13,907	11,617	2,290	11,888	827	1,192	2.7	15	5	286	76.8	83.3
FSIG+SENSA, 40-85, 5,1	16,340	12,322	4,018	14,210	867	1,263	3.0	12	4	328	80.7	86.2
FSIG+SENSA, 40-85, 5,2	15,144	12,000	3,144	13,023	861	1,260	3.0	13	4	322	79.5	85.6
FSIG+SENSA, 40-85, 5,3	14,568	11,949	2,619	12,454	855	1,259	3.0	14	4	314	78.6	85.2
FSIG+SENSA, 40-85, 10,1	11,495	7,477	4,018	9,994	680	821	1.7	25	9	326	61.8	68.5
FSIG+SENSA, 40-85, 10,2	10,533	7,388	3,145	9,061	666	806	1.6	26	10	316	60.2	67.4
FSIG+SENSA, 40-85, 10,3	10,054	7,446	2,608	8,606	654	794	1.6	26	10	304	58.9	66.6
FSIG+SENSA, 40-85, 20,1	12,602	8,584	4,018	10,972	741	889	2.0	23	9	324	63.7	70.4
FSIG+SENSA, 40-85, 20,2	11,662	8,516	3,146	10,050	731	881	2.0	24	9	309	62.4	69.8
FSIG+SENSA, 40-85, 20,3	11,235	8,633	2,602	9,636	724	875	2.0	24	9	291	61.5	69.3
FSIG+SENSA, 50-75, 5,1	16,259	13,593	2,666	14,281	794	1,184	2.8	11	3	274	83.6	89.2
FSIG+SENSA, 50-75, 5,2	14,259	12,265	1,994	12,289	778	1,192	2.8	13	4	265	80.9	87.4
FSIG+SENSA, 50-75, 5,3	13,278	11,623	1,655	11,319	762	1,197	2.8	15	4	257	78.0	85.4
FSIG+SENSA, 50-75, 10,1	17,056	14,403	2,653	14,976	830	1,250	3.2	10	3	271	85.5	91.3

FSIG+SENSA, 50-75, 10,2	15,048	13,077	1,971	12,969	817	1,262	3.1	11	3	258	83.1	89.8
FSIG+SENSA, 50-75, 10,3	14,106	12,485	1,621	12,028	806	1,272	3.1	13	3	246	80.6	88.3
FSIG+SENSA, 50-75, 20,1	12,861	10,214	2,647	11,258	686	917	2.0	16	5	270	75.0	81.7
FSIG+SENSA, 50-75, 20,2	11,192	9,229	1,963	9,613	665	914	2.0	18	6	252	71.7	79.5
FSIG+SENSA, 50-75, 20,3	10,508	8,899	1,609	8,937	656	915	2.0	20	7	237	69.3	78.0
FSIG+SENSA, 50-85, 5,1	13,871	10,875	2,996	12,148	739	984	2.3	15	5	276	77.0	84.0
FSIG+SENSA, 50-85, 5,2	12,193	9,895	2,298	10,483	724	986	2.3	16	5	268	74.2	82.3
FSIG+SENSA, 50-85, 5,3	11,392	9,484	1,908	9,696	709	987	2.3	18	6	260	71.4	80.7
FSIG+SENSA, 50-85, 10,1	8,781	5,794	2,987	7,650	529	602	1.3	28	10	274	57.8	65.3
FSIG+SENSA, 50-85, 10,2	7,554	5,268	2,286	6,462	504	588	1.2	29	11	262	54.3	62.7
FSIG+SENSA, 50-85, 10,3	6,926	5,041	1,885	5,875	479	572	1.1	32	12	250	50.8	60.0
FSIG+SENSA, 50-85, 20,1	10,114	7,133	2,981	8,834	609	671	1.5	26	10	272	59.9	67.9
FSIG+SENSA, 50-85, 20,2	8,875	6,602	2,273	7,619	592	664	1.5	28	10	256	57.1	66.2
FSIG+SENSA, 50-85, 20,3	8,335	6,472	1,863	7,096	579	660	1.5	29	11	240	54.5	64.6
FSIG+SENSA, 60-75, 5,1	14,599	12,912	1,687	12,919	691	989	2.3	13	4	184	80.6	86.8
FSIG+SENSA, 60-75, 5,2	12,290	11,052	1,238	10,632	668	990	2.3	15	5	176	76.5	83.8
FSIG+SENSA, 60-75, 5,3	11,109	10,064	1,045	9,475	643	991	2.3	18	6	169	71.6	80.0
FSIG+SENSA, 60-75, 10,1	15,553	13,894	1,659	13,761	742	1,050	2.6	12	3	182	82.5	89.1
FSIG+SENSA, 60-75, 10,2	13,225	12,028	1,197	11,444	724	1,057	2.6	13	4	169	78.8	86.7
FSIG+SENSA, 60-75, 10,3	12,103	11,104	999	10,329	709	1,065	2.6	16	5	161	74.7	83.8
FSIG+SENSA, 60-75, 20,1	11,334	9,698	1,636	9,979	595	760	1.7	18	6	180	72.2	79.3
FSIG+SENSA, 60-75, 20,2	9,489	8,331	1,158	8,168	569	752	1.6	21	7	164	67.6	76.1
FSIG+SENSA, 60-75, 20,3	8,719	7,763	956	7,410	557	752	1.6	23	8	152	63.9	73.6
FSIG+SENSA, 60-85, 5,1	12,321	10,311	2,010	10,855	650	816	1.9	17	5	187	74.1	81.6
FSIG+SENSA, 60-85, 5,2	10,436	8,916	1,520	8,994	629	813	1.9	19	6	179	70.0	78.9
FSIG+SENSA, 60-85, 5,3	9,489	8,215	1,274	8,070	606	813	1.9	22	7	172	65.7	76.1
FSIG+SENSA, 60-85, 10,1	7,682	5,689	1,993	6,713	469	500	1.0	29	11	185	55.6	63.2
FSIG+SENSA, 60-85, 10,2	6,381	4,885	1,496	5,457	440	484	1.0	32	12	174	51.2	59.8
FSIG+SENSA, 60-85, 10,3	5,692	4,450	1,242	4,812	408	472	0.9	35	13	165	46.4	55.7

FSIG+SENSA, 60-85, 20,1	8,828	6,846	1,982	7,738	536	554	1.3	27	10	184	57.5	65.6
FSIG+SENSA, 60-85, 20,2	7,475	5,996	1,479	6,416	514	545	1.2	30	11	170	53.7	63.1
FSIG+SENSA, 60-85, 20,3	6,863	5,643	1,220	5,827	496	540	1.2	32	12	158	49.8	60.2

COL = colonoscopy; COMPLIC = complications; CRC = colorectal cancer; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA

* Age and intervals expressed as years.

† Including colonoscopies for re-screening of individuals with a false-positive sigmoidoscopy or Hemoccult SENSA.

‡ Includes screening-related deaths

Appendix 3: Results including starting at age 40 in efficient and near-efficient frontiers

A3, Table 1: Colonoscopy strategies

Strategy Test, Age Begin–Age Stop, Interval†		Outcomes per 1000 Persons				
		COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
MISCAN						
1	COL, 60-75, 20	2,175	156			---
2	COL, 50-75, 20	3,325	203	1,150	47	24.7
3	COL, 50-75, 10	4,136	230	811	27	29.6
4	COL, 50-85, 10	4,534	236	398	5	72.9
5	COL, 40-75, 10	5,231	242			Near efficient
6	COL, 40-85, 10	5,629	248			Near efficient
7	COL, 50-75, 5	5,895	254	1,362	18	74.8
8	COL, 50-85, 5	6,460	257			Near efficient
9	COL, 40-75, 5	7,881	276	1,986	22	90.6
10	COL, 40-85, 5	8,445	279	564	4	158.6
SimCRC						
1	COL, 60-75, 20	1,780	165			---
2	COL, 40-75, 20	3,131	275	1,352	110	12.2
3	COL, 40-75, 10	4,887	320	1,755	45	38.6
4	COL, 40-85, 10	5,245	322			Near efficient
5	COL, 40-75, 5	7,578	331	2,691	11	245.1
6	COL, 40-85, 5	8,036	332	459	1	875.4

COL = colonoscopy; LYG = life-years gained compared with no screening; ΔCOL = incremental number of colonoscopies compared with the next-best non-efficient strategy; ΔLYG = incremental number of life-years gained compared with the next-best non-efficient strategy.
†Age and intervals expressed as years.
‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.

A3, Table 2: Hemoccult II strategies

Strategy Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons				
	COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
MISCAN					
1 Hemoccult II, 60-75, 3	681	89			---
2 Hemoccult II, 60-75, 2	854	105	172	16	10.6
3 Hemoccult II, 50-75, 3	1,033	121			Near-efficient
4 Hemoccult II, 50-75, 2	1,335	149	482	44	11.0
5 Hemoccult II, 50-85, 2	1,513	158			Near-efficient
6 Hemoccult II, 50-75, 1	1,982	194	647	45	14.3
7 Hemoccult II, 50-85, 1	2,186	202	203	8	25.5
8 Hemoccult II, 40-75, 1	2,649	219	464	17	27.7
9 Hemoccult II, 40-85, 1	2,842	225	193	7	29.0
SimCRC					
1 Hemoccult II, 60-75,3	425	75			---
2 Hemoccult II, 50-75,3	699	129	275	54	5.1
3 Hemoccult II, 40-75,2	1,327	211	407	49	8.3
4 Hemoccult II, 40-75,1	2,083	275	756	64	11.8
5 Hemoccult II, 40-85,1	2,354	280	271	5	58.2

COL = colonoscopy; LYG = life-years gained compared with no screening; ΔCOL = incremental number of colonoscopies compared with the next-best non-efficient strategy; ΔLYG = incremental number of life-years gained compared with the next-best non-efficient strategy.
†Age and intervals expressed as years.
‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.

A3, Table 3: Hemoccult SENSA strategies

Strategy Test, Age Begin–Age Stop, Interval†		Outcomes per 1000 Persons				
		COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
MISCAN						
1	Hemoccult SENSA, 60-75, 3	1,363	134			---
2	Hemoccult SENSA, 60-75, 2	1,647	149			Near-efficient
3	Hemoccult SENSA, 50-75, 3	2,121	181	758	47	16.0
4	Hemoccult SENSA, 50-75, 2	2,584	205	463	24	19.5
5	Hemoccult SENSA, 50-85, 2	2,801	211			Near-efficient
6	Hemoccult SENSA, 50-75, 1	3,350	230	766	25	30.9
7	Hemoccult SENSA, 40-75, 2	3,503	230			Near-efficient
8	Hemoccult SENSA, 50-85, 1	3,538	232			Near-efficient
9	Hemoccult SENSA, 40-85, 2	3,695	234			Near-efficient
10	Hemoccult SENSA, 40-75, 1	4,416	251	1066	21	49.9
11	Hemoccult SENSA, 40-85, 1	4,583	252	166	1	132.6
SimCRC						
1	Hemoccult SENSA, 60-75,3	934	123			---
2	Hemoccult SENSA, 50-75,3	1,587	201	653	78	8.4
3	Hemoccult SENSA, 40-75,3	2,304	256	717	55	13.0
4	Hemoccult SENSA, 40-75,2	2,829	287	525	31	16.9
5	Hemoccult SENSA, 40-85,2	3,167	291			Near-efficient
6	Hemoccult SENSA, 40-75,1	3,700	315	871	28	30.9
7	Hemoccult SENSA, 40-85,1	4,039	317	339	2	149.8

COL = colonoscopy; LYG = life-years gained compared with no screening; ΔCOL = incremental number of colonoscopies compared with the next-best non-efficient strategy; ΔLYG = incremental number of life-years gained compared with the next-best non-efficient strategy.
†Age and intervals expressed as years.
‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.

A3, Table 4: FIT strategies

Strategy Test, Age Begin–Age Stop, Interval†		Outcomes per 1000 Persons				
		COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
MISCAN						
1	FIT, 60-75, 3	1,158	129			---
2	FIT, 60-75, 2	1,403	144			Near-efficient
3	FIT, 50-75, 3	1,769	173	611	44	14.0
4	FIT, 50-75, 2	2,184	198	415	25	16.5
5	FIT, 50-85, 2	2,396	206			Near-efficient
6	FIT, 50-75, 1	2,949	227	765	30	25.9
7	FIT, 40-85, 2	3,141	228			Near-efficient
8	FIT, 50-85, 1	3,155	231			Near-efficient
9	FIT, 40-75, 1	3,921	249	972	22	44.3
10	FIT, 40-85, 1	4,104	252	184	3	70.2
SimCRC						
1	FIT, 60-75,3	772	118			---
2	FIT, 50-75,3	1,286	193	514	75	6.9
3	FIT, 40-75,3	1,846	244	560	51	10.9
4	FIT, 40-75,2	2,330	279	484	35	14.0
5	FIT, 40-85,2	2,636	283			Near-efficient
6	FIT, 40-75,1	3,236	313	906	34	26.4
7	FIT, 40-85,1	3,568	316	333	3	118.7

COL = colonoscopy; LYG = life-years gained compared with no screening; ΔCOL = incremental number of colonoscopies compared with the next-best non-efficient strategy; ΔLYG = incremental number of life-years gained compared with the next-best non-efficient strategy.
†Age and intervals expressed as years.
‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.

A3, Table 5: Flexible sigmoidoscopy strategies

Strategy Test, Age Begin–Age Stop, Interval†		Outcomes per 1000 Persons				
		COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
MISCAN						
1	FSIG, 60-75, 20	1,047	114			---
2	FSIG, 60-75, 10	1,311	140			Near-efficient
3	FSIG, 60-75, 5	1,491	159			Near-efficient
4	FSIG, 50-75, 10	1,685	177			Near-efficient
5	FSIG, 50-75, 5	1,911	203	864	89	9.7
6	FSIG, 50-85, 5	1,996	207			Near-efficient
7	FSIG, 40-75, 5	2,122	219	211	16	13.4
8	FSIG, 40-85, 5	2,206	222	84	4	23.0
SimCRC						
1	FSIG, 60-75, 20	438	94			---
2	FSIG, 40-75, 20	619	162	181	68	2.6
3	FSIG, 40-75, 10	910	213	291	51	5.7
4	FSIG, 40-75, 5	1,122	241	212	28	7.5
5	FSIG, 40-85, 5	1,190	243	68	2	38.5

*COL = colonoscopy; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; ΔCOL = incremental number of colonoscopies compared with the next-best non-efficient strategy; ΔLYG = incremental number of life-years gained compared with the next-best non-efficient strategy.

†Age and intervals expressed as years.

‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.

A3, Table 6: Flexible sigmoidoscopy + Hemoccult SENSA strategies

Strategy Test, Age Begin–Age Stop, Interval†		Outcomes per 1000 Persons				
		COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
MISCAN						
1	FSIG+SENSA, 60-75, 20,3	1,817	163			---
2	FSIG+SENSA, 60-75, 10,3	1,933	171			Near-efficient
3	FSIG+SENSA, 60-75, 5,3	2,031	179	213	15	14.0
4	FSIG+SENSA, 50-75, 20,3	2,658	213			Near-efficient
5	FSIG+SENSA, 50-75, 10,3	2,756	221			Near-efficient
6	FSIG+SENSA, 50-75, 5,3	2,870	230	839	52	16.3
7	FSIG+SENSA, 50-85, 5,3	3,042	233			Near-efficient
8	FSIG+SENSA, 50-75, 5,2	3,142	235			Near-efficient
9	FSIG+SENSA, 50–85, 10, 2	3,245	232			Near-efficient
10	FSIG+SENSA, 50-85, 5,2	3,321	237			Near-efficient
11	FSIG+SENSA, 40-75, 5,3	3,592	249	722	19	38.8
12	FSIG+SENSA, 40-85, 5,3	3,771	251	178	3	67.1
13	FSIG+SENSA, 40-75, 5,2	3,987	253			Near-efficient
14	FSIG+SENSA, 40-85, 5,2	4,154	255	384	4	104.3
15	FSIG+SENSA, 40-75, 10,1	4,568	254			Near-efficient
16	FSIG+SENSA, 40-75, 5,1	4,625	256			Near-efficient
17	FSIG+SENSA, 40-85, 5,1	4,784	256	630	1	454.8
SimCRC						
1	FSIG+SENSA, 60-75, 20,3	956	152			---
2	FSIG+SENSA, 60-75, 10,3	999	161	44	9	4.7
3	FSIG+SENSA, 60-75, 5,3	1,045	169	45	8	5.5
4	FSIG+SENSA, 50-75, 10,3	1,621	246			Near-efficient
5	FSIG+SENSA, 50-75, 5,3	1,655	257	611	88	7.0
6	FSIG+SENSA, 40-75, 5,3	2,334	311	678	54	12.5
7	FSIG+SENSA, 40-85, 5,3	2,619	314			Near-efficient
8	FSIG+SENSA, 40-75, 10,2	2,817	312			Near-efficient
9	FSIG+SENSA, 40-75, 5,2	2,824	320	490	8	59.2
10	FSIG+SENSA, 40-85, 5,2	3,144	322	321	3	120.0
11	FSIG+SENSA, 40-85, 10,2	3,145	316			
12	FSIG+SENSA, 40-75, 20,1	3,680	322			Near-efficient
13	FSIG+SENSA, 40-75, 10,1	3,682	324			Near-efficient
14	FSIG+SENSA, 40-75, 5,1	3,684	326	540	4	134.5
15	FSIG+SENSA, 40-85, 20,1	4,018	324			Near-efficient
16	FSIG+SENSA, 40-85, 10,1	4,018	326			Near-efficient
17	FSIG+SENSA, 40-85, 5,1	4,018	328	334	2	168.7

*COL = colonoscopy; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA; ΔCOL = incremental number of colonoscopies compared with the next-best non-efficient strategy; ΔLYG = incremental number of life-years gained compared with the next-best nonefficient strategy. Bold indicates recommendable strategy
†Age and intervals expressed as years.
‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.