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Individualizing Colonoscopy Screening by Gender and Race

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Abstract

BACKGROUND—There is increasing discussion whether colorectal cancer (CRC) screening guidelines should be individualized by gender and race.

OBJECTIVES—To determine individualized colonoscopic screening guidelines by gender and race for the average-risk population and to compare the cost-effectiveness of this approach to that of uniform guidelines for all.

DESIGN—We used the MISCAN-Colon microsimulation model to estimate life-expectancy and lifetime CRC screening and treatment costs in a US cohort of black and white men and women at average risk for CRC. We compared the base case strategy of no screening and 3 competing colonoscopy strategies: (1) the currently recommended “uniform 10-yearly colonoscopy from age 50”, (2) with a shorter interval “uniform 8-yearly colonoscopy from age 51”, and (3) “individualized screening according to gender and race”.

RESULTS—The base case strategy of no screening was the least expensive, yet least effective. The uniform 10-yearly colonoscopy strategy was dominated. The uniform 8-yearly colonoscopy and individualized strategies both increased life-expectancy by 0.0433–0.0435 years per individual at a cost of \$15,565 per life-year gained. In the individualized strategy, African Americans began screening 6 years earlier with a 1 year shorter interval compared to whites. The individualized policies were essentially the same for men and women, because the higher CRC risk in men is offset by their shorter life-expectancy. The results were robust for changes in model assumptions.

CONCLUSIONS—The improvements in costs and effects of individualizing on a population level were only marginal. Individualized guidelines, however, could contribute to decreasing disparities between African Americans and whites. The acceptability and feasibility of individualized guidelines should therefore be explored.

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INTRODUCTION

For the average risk population, the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society recommend starting colorectal cancer (CRC) screening at the age of 50 years with an identical menu of screening options for men and women of all races.^{1, 2} There are separate guidelines for individuals at increased risk due to a family history of CRC, a genetic predisposition (e.g., FAP, HNPCC), or a personal history of colorectal cancer, adenomas, or inflammatory bowel disease. The US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society recommend that these individuals have colonoscopy screening at earlier ages and with higher frequency than the general population.^{1, 2} Race or gender are not used as a basis for modifying recommendations.

Given the differences in CRC risk by gender, race, and ethnicity, debate has arisen whether screening guidelines should be individualized accordingly.³ The American College of Gastroenterology advocates that screening should start earlier in African Americans because of the higher incidence and younger age at presentation of CRC in this population subgroup.⁴ During the period 1997-2001,⁵ African American men had the highest age-specific CRC mortality, while white women had the lowest rate in the US (Figure 1). The four curves of Figure 1 become nearly indistinguishable if the rates for African Americans are shifted five years later compared to the whites (including Hispanics) and five years earlier for women compared to men.⁵ The disparity seems to support individualizing age of screening initiation by gender and race.

Next to mortality, other determinants should be considered for individualizing screening guidelines. Important determinants would be life-expectancy, incidence, stage distribution, survival and costs. A simulation approach can take all these aspects into account and estimate costs and life-years gained, which is a commonly used summary measure for the benefit of cancer screening,⁶ for different screening strategies. In this study, we used the MISCAN-Colon microsimulation model to determine individualized colonoscopy screening guidelines by gender and race for the average-risk population and compare their cost-effectiveness to uniform guidelines with the same screening ages and interval for all.

METHODS

We used the MISCAN-Colon microsimulation model to determine the most cost-effective approach for colonoscopy screening in the average-risk population. The base case strategy was no screening. This strategy was compared to two uniform and one individualized colonoscopy strategies.

MISCAN-Colon Microsimulation Model

The MISCAN microsimulation model was developed at the Department of Public Health, at Erasmus MC, the Netherlands, and has been used to evaluate breast, cervical, colon, and prostate cancer screening. MISCAN-Colon, the CRC version of the MISCAN-model, was developed in collaboration with the US National Cancer Institute and experts in the field of CRC to assess the effect of different interventions on CRC. A graphical representation of the natural history in the model is given in Figure 2, and the main natural history assumptions in the model are listed in Table 1. A detailed description of the model and the data sources that informed the quantification of the model can be found in Appendix 1, in previous publications^{24, 25} and also in a standardized model profiler.²⁶ In brief, the MISCAN-Colon model simulates the relevant biographies of a large population of individuals from birth to death, first without screening and subsequently with the changes that would occur under the implementation of screening. CRC arises in this population according to the adenoma-carcinoma sequence.^{27, 28} More than one adenoma can occur in an individual and each

adenoma can independently develop into CRC. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (10+ mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) will eventually become a clinical cancer. Diagnosis of cancer occurs on average 10 years after the manifestation of the adenoma from which it developed. This development competes with death from other causes. A preclinical cancer may progress from stage I to stage IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. The cure rate and survival after diagnosis without cure depend on the stage of the cancer. The model also simulates how screening can interrupt the development of CRC and how it improves prognosis. With screening, adenomas may be detected and removed and preclinical cancers may be found, depending on sensitivity. In this way, screening may prevent CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life-expectancy of the population with and without screening. We assumed the sensitivity of colonoscopy is 75% (CI: 70-79%) for small adenomas (1-5 mm), 85% (CI: 80-92%) for medium adenomas (6-9 mm), and 95% (CI: 92-99%) for large adenomas (10+ mm) and cancers, based on back-to-back colonoscopy studies.¹⁵ We assumed a specificity of 90% of colonoscopy. This percentage was equal to 1 minus the 10% of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after colonoscopy. Specificity was assumed to be independent of the screening round. We assumed a cecal intubation rate of 95%.¹⁶⁻¹⁸ Harms associated with colonoscopy were assumed to be perforations (0.7 per 1,000 colonoscopies), serosal burns (0.3 per 1,000), bleeds requiring transfusion (0.4 per 1,000) and bleeds not requiring transfusion (1.1 per 1,000), all of which can occur with or without polypectomy.¹⁹⁻²² We assumed that fatal events occur at a rate of 1 per 10,000 colonoscopies.²³

The validity of the model is based on observational data before the introduction of screening, such as clinical incidence and mortality from CRC¹² and the size distribution of adenomas in colonoscopy and autopsy studies.⁷⁻¹¹ The external validity has further been tested on the results of large (randomized) screening and surveillance studies, such as the Minnesota Colon Cancer Control Study,²⁹ the CoCap sigmoidoscopy study²⁹ and the National Polyp Study.³⁰ Finally, the model was able to explain observed incidence and mortality trends in the US when accounting for risk factor trends, screening practice and chemotherapy treatment.³¹

In this study, the model was used to simulate a US cohort born in 1967, subdivided by gender and race (African Americans and whites including Hispanics).³² For all gender and race combinations, age-specific adenoma onset, distribution of cancer localization over the colorectum, distribution of CRC stages, stage-specific CRC survival and all-cause mortality rates were adjusted to reflect observed CRC incidence and mortality and other-cause mortality in the period 1997-2001.¹² Adenoma and cancer progression were assumed to be the same for all genders and races. Subsequently, the model was used to predict costs and life-expectancy for different screening strategies.

According to our model the current recommendation of colonoscopy screening every 10 years from age 50 was not optimally cost-effective, although it was close. To enable a fair and interpretable comparison between uniform and individualized guidelines, we also determined a cost-effective uniform colonoscopy strategy. To obtain this cost-effective uniform strategy, we simulated more than 1,000 colonoscopy screening policies that differed with respect to age to begin screening, screen interval and total number of screenings. Policies that were more costly and less effective than other policies were ruled out as non-efficient by simple dominance. Policies that were more costly and less effective than a combination of other strategies were ruled out as non-efficient by extended dominance. Of the remaining policies, we selected the policy that was closest to the current recommendation with respect to number

of screens and the age to begin screening as the alternative uniform strategy (result: strategy 2).

To obtain individualized guidelines, we first determined the cost-effective colonoscopy policies by population subgroup as described above. For each cost-effective policy, we calculated the incremental cost-effectiveness ratio, defined as the additional cost of a specific policy divided by its additional clinical benefit compared to the closest less expensive cost-effective policy. Next, we combined cost-effective policies, one for each population subgroup, with the same threshold for the incremental cost-effectiveness ratio.^{33, 34} For each of the resulting individualized strategies, the costs and life-years of the four population subgroups were summed. The strategy with total costs closest to that of alternative uniform strategy was used as the individualized strategy (result: strategy 3).

Base Case

The base case for the analysis was absence of screening for CRC. All diagnoses of CRC occurred because of symptoms after which patients received treatment according to current practice.

Competing screening strategies

1. uniform 10-yearly colonoscopy at age 50—In this strategy, all individuals were offered colonoscopy screening at age 50 and every 10 years thereafter up to age 80 according to guidelines.¹

2. uniform 8-yearly colonoscopy at age 51—In this strategy (resulting from the modeling analysis described before), all individuals were offered colonoscopy screening at age 51 and every 8 years thereafter up to age 75

3. Individualized screening according to gender and race—In this strategy, each population subgroup (black and white men and women) was allowed to have a different colonoscopy policy. The policies, that resulted from the modeling analysis described before, were:

- white men: 4 screenings from age 53 to 74 every 7 years
- black men: 5 screenings from age 47 to 75 every 7 years
- white women: 4 screenings from age 53 to 77 every 8 years
- black women: 5 screenings from age 47 to 75 every 7 years.

As part of all simulated screening strategies, adenoma patients (in whom adenomas had been detected and consequently removed) were kept under colonoscopy surveillance according to the guidelines of the US Multi-Society Task Force on Colorectal Cancer.³⁵

Costs

Screening costs were based on Medicare payments of 2007 for procedures and tests associated with CRC screening and complications of screening.³⁶ The costs of complications were based on the relevant Diagnostic Related Group (DRG) codes.³⁶ The phase-specific costs of CRC (Table 2, footnote) were derived from comparing medical costs of CRC cases relative to matched controls in the SEER-Medicare files.³⁷ The results were reported in 2004 dollars and subsequently updated to 2007 dollars using the medical care component of the Consumer Price Index. Appendix 2 contains a detailed overview of the derivation of the costs. The final cost inputs used in the model are summarized in Table 2.

Outcomes

We projected lifetime costs and life-expectancy for a cohort of 40-year old black and white men and women in the US. Costs and future life-years were discounted at an annual rate of 3%.³⁸

Sensitivity and uncertainty analysis

We performed a one-way sensitivity and a multivariate uncertainty analysis on influential model assumptions:

- The assumption of higher incidence of adenomas versus faster progression of adenomas explaining the risk differences between population subgroups;
- Duration of adenoma-carcinoma sequence;
- CRC risk in African Americans;
- Sensitivity, specificity and complication rate of colonoscopy;
- Costs of colonoscopy, polypectomy, complications and CRC treatment.

Because the focus of the analysis was to assess the cost-effectiveness of individualized guidelines compared to uniform guidelines, we restricted the sensitivity analysis to comparing strategies 2 and 3.

In the one-way sensitivity analysis, each parameter was varied from its original value to a low and high value. For colonoscopy sensitivity and treatment costs, these values were set at the boundaries of the 95% confidence interval. Ranges reported in the literature were used for colonoscopy reach^{16, 20, 39-45}, specificity^{20, 44, 46-48}, perforation rates⁴⁸⁻⁵⁷, and costs of colonoscopy, polypectomy and complications⁴⁶⁻⁵⁸. The average duration between the manifestation of an adenoma and the diagnosis of CRC (base assumption 10 years) was decreased and increased by 50%, while the CRC risk in African Americans was decreased and increased by 10%.

In the multivariate uncertainty analysis, we simulated the uniform 8-yearly colonoscopy and individualized strategies 1,000 times with different sets of parameters. The test characteristic parameters (sensitivity, specificity, reach and complication rate) were drawn from a beta distribution with the mean equal to the base value. For the cost parameters and the CRC risk in African Americans, we assumed log-normal distributions with the median equal to the base value. For all parameters varied, the standard deviation was chosen such that the 95% probability mass overlapped with the low and high values used in the one-way sensitivity analysis. In 50% of runs we assumed a duration of the development of CRC of 20 years, while 10 and 30 years were used in 25% of runs each. In 75% of runs we assumed that the difference in CRC risk between population subgroups was due to different adenoma incidence, while in 25% we assumed the difference was caused by different adenoma progression rates. For each of the 1,000 simulations the difference in costs and life-expectancy between the uniform 8-yearly colonoscopy strategy and the individualized strategy were plotted in a scatterplot.⁵⁹

RESULTS

The life-expectancy and lifetime costs of the no screening, uniform 8-yearly colonoscopy, uniform 10-yearly colonoscopy and individualized strategies are displayed in Table 3. The no screening strategy was the least expensive yet least effective strategy. The uniform 8-yearly colonoscopy and individualized strategies both increased life-expectancy by 0.0433-0.0435 years per individual at a cost of \$15,565 per life-year gained compared with no screening. The

uniform 10-yearly colonoscopy strategy was weakly dominated by both the uniform 8-yearly and the individualized strategy.

Table 4 shows life-expectancy and costs for the uniform 8-yearly and individualized colonoscopy strategies by population subgroup. The increase in screening intensity in African Americans with individualization resulted in 0.0080 years longer life-expectancy in black men, while in black women the life-expectancy increased by 0.0076 years. The redistribution of resources from lower-risk whites to higher-risk African Americans, resulted in a higher starting age (2 years later) with individualization for whites and a slightly decreased life-expectancy in this group by 0.0006 years for men and 0.0016 years for women.

Sensitivity and uncertainty analysis

In the one-way sensitivity analysis we assessed the influence of model assumptions on the differences between uniform 8-yearly colonoscopy and individualized screening. Table 5 shows that in all analyses both strategies were equivalent in costs and effects. The difference in costs never exceeded \$12, and the maximum difference in life-years gained was 0.0005 years. With a longer duration of the adenoma-carcinoma sequence of 30 years, the uniform 8-yearly strategy became most effective, nullifying the already very small advantage of individualized screening. Other influential model assumptions on effectiveness were the disparity in CRC risk, colonoscopy sensitivity and reach and whether disparities in incidence are caused by difference in adenoma onset versus faster progression. Costs were mostly influenced by colonoscopy costs and the duration of the adenoma-carcinoma sequence.

For the multivariate uncertainty analysis, the results from 1,000 simulations comparing the uniform 8-yearly colonoscopy and individualized strategies are shown in Figure 3. In all simulations, the uniform 8-yearly colonoscopy and individualized strategies remained equivalent in costs and effects. The median difference in life-years gained was 0.0002 life-years. The 25% and 75% percentiles of the increase in life-years gained from the individualized strategy compared to the uniform strategy was 0.0001 and 0.0002 life-years respectively, while the 25% and 75% percentiles for the decrease in cost were \$7.20 to \$11.50. For African Americans the 25% and 75% percentiles of additional life-years gained were 0.0063 and 0.0079 years and of additional costs \$260 to \$465. In 83% of the simulations, the individualized strategy was more effective and less costly than the uniform strategy. In 3% of simulations was uniform screening more effective at an incremental cost per life-year gained of \$50,000 or less, and in 7% at costs of \$100,000 or less.

DISCUSSION

The present analysis suggests that 8-yearly uniform and individualized colonoscopy recommendations by gender and race on a total population level are comparable in costs and effects: the overall (total population) benefit of individualization is limited (0.0002 additional life-years gained, \$9.09 lower costs per person). This is explained by the fact that the African American population constitutes no more than approximately 20% of the population. For African Americans, the increase in life-years gained was more substantial (0.0078 life-years, approximately 14% of total life-years saved with screening), decreasing the disparity in incidence and mortality compared to whites. Our results were robust for changes in model assumptions. In 1,000 simulations with different model parameter values, the 8-yearly uniform and individualized strategies remained equivalent in costs and effects. We found that with individualizing screening, African Americans are screened with a one-year shorter interval than whites and start screening 6 years earlier, whereas the recommended screening ages and frequency for men and women remain similar.

Our findings support the recommendation of the American College of Gastroenterology to begin screening 5 years earlier in African Americans than whites. Starting screening at an earlier age without increasing the number of screenings, results in saving 0.0052 additional life-years in African Americans (data not shown). Also increasing the number of screens as recommended from our study, significantly further increases the additional life-years gained to 0.0078. Individualization can therefore play a significant role in reducing disparities between African Americans and whites. Our results are in line with other studies that have shown that the average cost-effectiveness of CRC screening is better in African American men than in other population subgroups.^{60, 61} Based on these results, the authors advocate earlier screening in African Americans. However, basing individualized guidelines on average cost-effectiveness does not necessarily lead to efficient use of resources. In the present analysis, we determined individualized guidelines based on incremental cost-effectiveness and hence ensuring efficient use of resources.^{33, 34}

Besides the current recommendation of four screenings every 10 years from age 50 to age 80, we also used another uniform colonoscopy strategy as a comparator to enable a fair comparison between uniform and individualized screening. We could not use the exact recommendation for that purpose, because it was not optimally cost-effective, although it was close. The current guidelines were not based on a formal decision analysis, but on studies on colonoscopic efficiency¹ and on simplicity and clarity. Individualized guidelines are more complex than uniform ones, and one could therefore argue that recommendations should not be individualized unless benefits are substantial. Individualized screening guidelines may confuse providers and consumers to the point of decreasing adherence. A decrease in adherence will easily offset the gains from individualization. Currently, 40% of African American men and 32% of African American women aged 50 years and older reported having had either a Fecal Occult Blood Test (FOBT) within the past year or a colorectal endoscopy within the past 5 years.⁶² Based on these figures much can be gained from increased adherence to screening guidelines. On the other hand, individualization of screening guidelines must be considered in the context of a general trend towards personalized medical care.^{63, 64} As a result, screening adherence might improve because individuals appreciate that the recommendation is based on their personal risk profile. In any case, in a situation where individualization of medical care and especially of screening, becomes the standard, it would be only natural to account also for race and gender differences, given the expected benefit and regardless of its size. To avoid too much complexity, one could recommend not changing the guidelines for whites but changing screening for African Americans to every 9 years from age 45 years onward (a similar change as the results of this study). Compared with the current screening guidelines, this recommendation would result in 0.0076 more life-years gained for blacks, comparable with the 0.0078 found in this study.

In this analysis, we assumed that all disparities in cancer incidence are caused by differences in adenoma incidence. This assumption is supported by results from the Clinical Outcomes Research Initiative (CORI), showing a higher percentage of adenoma patients with polyps of size > 9mm in African Americans than in whites.⁶⁵ Furthermore, observational studies show that CRC risk factors have a similar effect on adenoma prevalence as on CRC incidence.⁶⁶⁻⁷¹ Theoretically, higher CRC incidence could also be caused by more rapid adenoma and cancer progression. In this case, development of adenomas into CRC would have a shorter duration in blacks than in whites. When we assumed faster progression for blacks, with a strongly reduced average preclinical disease duration, the benefit of individualization slightly reduced.

We assumed that differences in observed CRC incidence and stage distribution between African Americans and whites reflect true differences in risk and are not due to differences in screening utilization. However, considering that screening rates are lower for African

Americans than for whites,⁶² the risk difference between African Americans and whites may be smaller. The sensitivity analysis shows that with a lower CRC risk in African Americans (i.e. smaller difference with whites), the benefit of individualization was reduced. Furthermore, we only considered life-years gained and not quality adjusted life-years. The reason for this is that the effect of CRC screening on quality of life has hardly been studied. There has been one study estimating quality of life 30 days before and after colonoscopy, which found that mental health and vitality domains of quality of life significantly improved after colonoscopy.⁷² However, quality of life at the moment of colonoscopy was not assessed. In population screening large numbers of individuals undergo colonoscopy and even a minor effect of colonoscopy on quality of life will have a large impact on quality adjusted life-years gained. Our results are only influenced by adjusting for quality of life when this differs between population subgroups. Crimmins has shown that African Americans and whites not only differ in life-expectancy (for which we accounted in the present analysis) but also in the proportion of healthy life-years,⁷³ due to the fact that African Americans have more comorbidities at older ages. Therefore, intensive colonoscopy screening at older ages may be less feasible in African Americans and also less beneficial in terms of quality adjusted life years gained, reducing the potential benefit of individualization.

Age-specific CRC incidence and mortality in men reaches levels of risk comparable to women four to eight years later in life.⁷⁴ Also, more women than men need to be screened for the detection of one advanced neoplasia.^{22, 65, 75} Therefore, one may have expected that men need earlier and more intensive screening than women. However, our results show that the cost-effective individualized policies for men and women are comparable. This is due to longer life-expectancy of women. Although women have fewer advanced adenomas than men, more of those adenomas can evolve into CRC during the longer lifetime. This means that the number needed to screen to detect one advanced adenoma in women may be higher than in men, but that the number of detected adenomas needed to prevent one case of CRC is lower. This makes the number needed to screen to prevent one CRC case similar for men and women. Our finding of similar screening strategies is supported by the fact that the absolute number of CRC cases in men and women is comparable.⁷⁶

This study aimed to explore the cost-effectiveness of individualization of screening guidelines. We restricted ourselves to colonoscopy, the preferred method of screening according to the American College of Gastroenterology.⁷⁷ Fortunately, the results can be generalized to other screening modalities. The costs per life-year gained will be different for other screening modalities, but the conclusion that individualization is cost-effective will remain, as well as the result that it is more cost-effective for African Americans to be screened over a wider age range and with greater frequency than whites. We focused the analysis on African American and white (including Hispanics) population subgroups. In a more extensive study Hispanics and non-Hispanics could be considered separately and Asians, Pacific Islanders, American Indians and Alaskan Natives could be included to explore further benefit of individualization. However for these groups, incidence and mortality data will be based on small numbers. CRC incidence and mortality tend to be lower in Hispanics, Asians, Pacific Islanders, American Indians and Alaskan Natives than in whites.⁷⁸ When these data are confirmed, a less intensive screening schedule for these groups could be considered.

In conclusion, our study suggests that 8-yearly uniform and individualized colonoscopy screening are comparable in costs and effects in the total population. However, individualized guidelines could contribute to decreasing disparities between African Americans and whites. The acceptability and feasibility of individualized guidelines should therefore be explored.

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Appendix 1: The MISCAN-Colon microsimulation model

MODEL OVERVIEW

The MISCAN-Colon model is a semi-Markov microsimulation model. The population is simulated individual by individual, and each person can evolve through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the MISCAN-Colon model generates durations in states. This improves model performance. With the assumption of exponential distribution of the duration in each state, this way of simulating leads to the same results as a Markov model with yearly transition probabilities. The advantage of the MISCAN approach is that durations in a certain state need not necessarily be a discrete value but can be continuous. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, adenoma incidence and transitions from one state of disease to another.

The basic structure of MISCAN-Colon is illustrated in figure A1-1. Figure A1-1 clearly demonstrates that MISCAN-Colon consists of three parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is useful to consider them separately.

Figure A1-1.
Structure of MISCAN-Colon

DEMOGRAPHY PART

The demography part of the model simulates individual life histories without colorectal cancer to form a population. For each person, a date of birth and a date of death of other causes than colorectal cancer are simulated. The distribution of births and deaths can be adjusted to represent the population simulated. For example, a population of Caucasian females will have higher death ages than a population of African American males.

NATURAL HISTORY PART

The Natural History part of MISCAN-Colon simulates the development of colorectal cancer in the population. We assume all colorectal cancers develop according to the adenoma-carcinoma sequence of Morson¹ and Vogelstein² (Figure A1-2). For each individual in the simulated population a personal risk index is generated. Subsequently, adenomas are generated in the population according to this personal risk index and an age specific incidence rate of adenomas. This results in no adenomas for most persons and one or more adenomas for others. The distribution of adenomas over the colorectum is simulated according to the observed distribution of colorectal cancer incidence. Each of the adenomas can independently develop into colorectal cancer. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (10+ mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. The survival after clinical diagnosis depends on the stage of the cancer.

Figure A1-2.

Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for colorectal cancer. Adenomas are categorized by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age.

SCREENING PART

Screening interrupts the development of CRC. With screening, adenomas may be detected and removed and cancers may be found, usually in an earlier stage than with clinical diagnosis. In this way screening prevents CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening. The effects of different screening policies can be compared by applying them to identical natural histories.

INTEGRATION OF THE THREE MODEL COMPONENTS

For each individual, the demography part of the model simulates a time of birth and a time of death of other causes than colorectal cancer, creating a life history without colorectal cancer (top line in figure A1-3a). Subsequently adenomas are simulated for that individual. For most individuals no adenomas are generated, for other multiple. In the example in figure A1-3, the person gets two adenomas (2nd and 3rd line in figure A1-3a). The first adenoma arises at a certain age, grows into 6-9 mm and eventually becomes larger than 10 mm. However, this adenoma does not become cancer before the death of the person. The second adenoma is a progressive adenoma. After having grown to 6-9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and diagnosis and eventually resulting in an earlier death from CRC. The life history without CRC and the development of the two adenomas in figure A1-3 together lead to the combined life history with CRC depicted in the bottom line. Because this person dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly.

Figure A1-3a.**Modeling natural history into life history**

After the life history of a person is adjusted for colorectal cancer, the history will now be adjusted for the effects of screening. The effect of screening on life history is explained in figure A1-3b. The top line in this figure is the combined life history for colorectal cancer from figure A1-3a. The development of the separate adenomas is repeated in the second and third line. In this picture there is one screening intervention. During the screening both prevalent adenomas are detected and removed. This results in a combined life history for colorectal cancer and screening (bottom line). From the moment of screening the adenomas are removed and this individual becomes adenoma and carcinoma free. He does not develop cancer because the precursor lesion has been removed. Therefore the person dies at the moment of death from other causes and the effect of screening is the difference in life-years in the situation without screening and the situation with screening. Of course many other possibilities could have occurred: a person could have developed new adenomas after the screening moment, or an adenoma could have been missed by the screening test, but in this case this individual really benefited from the screening intervention.

Figure A1-3b.
Modeling screening into life history

MODEL QUANTIFICATION

For this analysis we developed four different models, for white men, white women, African American men and African American women. For each group we simulated a cohort born in 1967.

DEMOGRAPHY PARAMETERS

There are two types of demography parameters: birth tables and life tables. In this case all individuals were born in 1967. The life tables were derived from the 2000 US Life Table published by the National Center for Health Statistics (<http://www.cdc.gov/nchs/products/pubs/pubd/lftbls/life/1966.htm>). These life tables include colorectal cancer mortality and the demography part simulates mortality from other causes than colorectal cancer. However, we decided not to adjust the life tables because the percentage of colorectal cancer mortality in overall mortality is small and the data on colorectal cancers deaths by age, gender and race are sparse.

NATURAL HISTORY PARAMETERS

The parameters for natural history model that could not be directly estimated from data or fit to reference data, were established based on expert opinion. At two expert meetings at the NCI on June 5-7, 1996, and May 12-13, 1997, a model structure was devised in agreement with the currently accepted model of the adenoma-carcinoma sequence. It was assumed that all cancers are preceded by adenomas.

The expert panel agreed on an estimate of the average sojourn time (i.e., the duration between onset of a progressive adenoma and the clinical diagnosis of subsequent cancer) of 20 years. However, some adenomas do not make it to cancer in that time period, because people die of other causes before the cancer could actually manifest. These are mainly the slower-developing adenomas with a longer duration than the average. The result is that the average duration of the adenomas that actually make it to diagnosed cancer is shorter, on average 10 years. The average duration of cancer in preclinical stages I-IV was 2 years, 1 year, 1.5 years, and 0.8

year, respectively, which resulted in a total average duration of 3.6 years because not every cancer reaches stage IV before clinical diagnosis. These sojourn times were based on the ratio between the stage-specific detection rate at first screening in fecal occult blood test trials and the background incidence, accounting for a 60% sensitivity of fecal occult blood test for all cancer stages.^{3, 4} All durations were governed by an exponential probability distribution. Durations in each of the invasive cancer stages as well as durations in the stages of the noninvasive adenomas were assumed to be 100% associated with each other, but the durations in invasive stages as a whole were independent of durations in noninvasive adenoma stages that precede cancer. These assumptions resulted in an exponential distribution of the total duration of progressive noninvasive adenomas and of the total duration of preclinical cancer, which has also been used in other cancer screening models.^{3, 5}

It was assumed that 30% of the cancers arise from adenomas of 6-9 mm and that 70% arise from larger adenomas. Initially, the preclinical incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localization in the United States in 1978.⁶ During this period, almost no screening was performed. The size distribution of adenomas over all ages was assumed to be 56% for stages less than or equal to 5 mm, 24% for stages 6-9 mm, and 20% for stages greater than or equal to 10 mm.⁷⁻¹¹ The preclinical incidence of non-progressive adenomas that will never grow into cancer was varied until the simulated prevalence of all adenomas was about 15% in age group 50-59 years, 27% in age group 60-69 years, and 33% in age group 70 or more years, in agreement with data from the Kaiser study in Northern California¹² and with data from autopsy and colonoscopy studies.⁷⁻¹¹

For this analysis, the 1978 total population model was adjusted to obtain 1997-2001 models for white and black men and women. We assumed that all difference in CRC incidence between the 1978 general population model and the 1997-2001 race- and gender specific models was caused by differences in adenoma incidence. We therefore adjusted the age-specific incidence of both progressive and non-progressive adenomas so that the colorectal cancer incidence by gender, race, age, stage and location from 1997-2001 was reproduced. The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of colorectal cancers in the United States in 1997-2001.⁶ The stage-specific survival after the clinical diagnosis of colorectal cancer is taken from the Surveillance, Epidemiology, and End Results registry data from 1987 through 2001.⁶

Table A1-2

Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source																																																																			
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2	Fit to multiplicity distribution of adenomas in autopsy studies; ⁹																																																																			
Adenoma incidence per year	Age 60:	1 or more 20%																																																																			
		2 or more 6%																																																																			
		3 or more 2%																																																																			
	Age 90:	1 or more 37%																																																																			
		2 or more 17%																																																																			
		3 or more 9%																																																																			
	Fit to adenoma prevalence in autopsy and colonoscopy studies of 15% in age group 50-59 to 33% in age group 70+, ⁷⁻¹¹ and to cancer incidence per 100,000 in 1997-2001 in SEER registry; ⁶																																																																				
	Age, gender and race dependent																																																																				
	<table><thead><tr><th colspan="2">White</th><th colspan="2">Black</th></tr><tr><th>Men</th><th>Women</th><th>Men</th><th>Women</th></tr></thead><tbody><tr><td>0.0%</td><td>0.0%</td><td>0.0%</td><td>0.0%</td></tr><tr><td>0.2%</td><td>0.1%</td><td>0.2%</td><td>0.2%</td></tr><tr><td>0.4%</td><td>0.4%</td><td>1.0%</td><td>0.6%</td></tr><tr><td>0.9%</td><td>0.6%</td><td>1.3%</td><td>1.2%</td></tr><tr><td>1.6%</td><td>1.0%</td><td>2.0%</td><td>1.5%</td></tr><tr><td>2.9%</td><td>1.8%</td><td>3.0%</td><td>2.3%</td></tr><tr><td>3.2%</td><td>2.2%</td><td>3.3%</td><td>2.4%</td></tr><tr><td>3.2%</td><td>2.2%</td><td>3.7%</td><td>2.5%</td></tr><tr><td>3.2%</td><td>2.3%</td><td>4.3%</td><td>2.5%</td></tr><tr><td>1.8%</td><td>1.2%</td><td>1.3%</td><td>1.0%</td></tr><tr><td>1.4%</td><td>1.1%</td><td>1.1%</td><td>0.5%</td></tr></tbody></table>		White		Black		Men	Women	Men	Women	0.0%	0.0%	0.0%	0.0%	0.2%	0.1%	0.2%	0.2%	0.4%	0.4%	1.0%	0.6%	0.9%	0.6%	1.3%	1.2%	1.6%	1.0%	2.0%	1.5%	2.9%	1.8%	3.0%	2.3%	3.2%	2.2%	3.3%	2.4%	3.2%	2.2%	3.7%	2.5%	3.2%	2.3%	4.3%	2.5%	1.8%	1.2%	1.3%	1.0%	1.4%	1.1%	1.1%	0.5%															
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Fit to adenoma prevalence in autopsy studies, ⁷⁻¹¹ cancer incidence in SEER registry in 1978; ⁶																																																																					
Probability that a new adenoma is progressive	Dependent on age at onset:																																																																				

Model parameter	Value	Source																											
Regression of adenomas	No significant regression of adenomas																												
Mean duration of development of progressive adenomas to clinical cancer	20 years	Expert opinion																											
Mean duration of preclinical cancer	3.6 years	Expert opinion*																											
Mean duration of adenoma	16.4 years	Estimated from cancer detection rate at first screening and background cancer incidence in FOBT trials. ^{3,4}																											
Percent of non-progressive adenomas that stay 6-9mm	50%	20 years - 3.6 years																											
Percent of non-progressive adenoma that become 10mm or larger	50%	Fit to size distribution of adenomas in autopsy studies: ⁷⁻¹¹ 1-5mm: 56% 6-9 mm: 24% 10+ mm: 20%																											
Percent of cancers that develops from 6-9mm adenoma and from 10+mm adenoma	30% of cancer develops from 6-9 mm, 70% from 10+mm	Fit to size distribution of adenomas in autopsy studies: ⁷⁻¹¹ 1-5mm: 56% 6-9 mm: 24% 10+ mm: 20%																											
Localization distribution of adenomas and cancer	Dependent on gender and race:	Expert opinion																											
	<table> <tr> <th></th><th>White</th><th>Black</th></tr> <tr> <td></td><td>Men</td><td>Women</td></tr> <tr> <td>Rectum:</td><td>22%</td><td>15%</td></tr> <tr> <td>Rectosigmoid junction:</td><td>9%</td><td>8%</td></tr> <tr> <td>Sigmoid colon:</td><td>23%</td><td>20%</td></tr> <tr> <td>Descending colon:</td><td>5%</td><td>6%</td></tr> <tr> <td>Transverse colon (incl flexures):</td><td>14%</td><td>16%</td></tr> <tr> <td>Ascending colon:</td><td>12%</td><td>15%</td></tr> <tr> <td>Cecum:</td><td>16%</td><td>21%</td></tr> </table>		White	Black		Men	Women	Rectum:	22%	15%	Rectosigmoid junction:	9%	8%	Sigmoid colon:	23%	20%	Descending colon:	5%	6%	Transverse colon (incl flexures):	14%	16%	Ascending colon:	12%	15%	Cecum:	16%	21%	Directly estimated from SEER 1997-2001. ⁶
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Ascending colon:	12%	15%																											
Cecum:	16%	21%																											
10-year survival after clinical diagnosis of CRC	Dependent on stage, gender and race:	Directly estimated from SEER 1997-2001. ⁶																											

Model parameter	Value		Source	
	White		Black	
	Men	Women	Men	Women
Stage I:	95%	96%	71%	89%
Stage II:	76%	80%	73%	68%
Stage III:	58%	52%	40%	43%
Stage IV:	7%	4%	5%	3%

* To be estimated from randomized controlled endoscopy trials, data not yet available.

SCREEN PARAMETERS

We assumed a cecal intubation rate of 95%.¹³⁻¹⁵ The sensitivity of colonoscopy for each lesion within realized reach was based on back-to-back colonoscopy studies: 75% in adenomas less than or equal to 5 mm, 85% in adenomas 6-9 mm, and 95% in adenomas greater than or equal to 10 mm and cancers.¹⁶ At detection, lesions are removed immediately. The percentage of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after colonoscopy has been estimated from Kaiser data:¹⁷ 10%. This percentage was assumed to be independent of the screening round.

The stage-specific survival of patients with screen-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage.¹⁸ Removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma. Risks of complications reported in organized screening programs¹⁹⁻²¹ are lower than those reported for general practice colonoscopies.^{22, 23} The major complications of colonoscopy are perforations (which can occur with or without polypectomy), serosal burns, bleeds requiring transfusion and bleeds not requiring transfusion.¹⁹⁻²³ We estimated a rate of death among persons of 0.1 per 1,000 colonoscopies.²⁴

Table A1-3

Parameter	Value	Source
Sensitivity colonoscopy	Dependent on stage of disease Adenoma 1-5mm: 75% Adenoma 6-9mm: 85% Adenoma 10+ mm: 95% Preclinical cancer: 95%	Back-to-back colonoscopy studies ¹⁶
Cecal intubation rate	95%	General practice ^{13, 14} and guidelines ¹⁵
Complication rate with colonoscopy	2.4 per 1,000 colonoscopies	Organized screening programs ¹⁹⁻²¹ and general practice ^{22, 23}
Perforation	0.7 per 1,000	
Serosal burn	0.3 per 1,000	
Bleed with transfusion	0.4 per 1,000	
Bleed without transfusion	1.1 per 1,000	
Fatal complication rate with colonoscopy	0.1 per 1,000 colonoscopies	Prospective endoscopy study ²⁴
Probability to develop cancer from removed adenoma	0%	Expert opinion
Survival after screen detection of cancer	As after clinical diagnosis in the same stage	FOBT trial ¹⁸

MODEL OUTPUTS

The model generates the following output, both undiscounted and discounted:

Demography

1. Life-years lived in the population by calendar year and age
2. Deaths from other causes than colorectal cancer by calendar year and age

Natural history

1. Colorectal cancer cases by calendar year, stage and age
2. Colorectal cancer deaths by calendar year and age
3. Life-years lived with colorectal cancer by calendar year, stage and age
4. Total number of life years with surveillance for adenoma patients
5. Total number of life years with initial therapy after screen-detected or clinical invasive cancer by stage
6. Total number of life years with continuing therapy after screen-detected or clinical invasive cancer by stage
7. Total number of life years with terminal care before death from other causes by stage
8. Total number of life years with terminal care before death from colorectal cancer by stage

Screening

1. Number of invitations for screen-tests, screen-tests, diagnostic tests, surveillance and opportunistic screen tests by calendar year
2. Number of positive and negative test results per preclinical state and per year
3. Total number of life years lived, life years lost due to cancer, number of specific deaths and non specific deaths
4. Number of screenings that prevented cancer by year of screening
5. Number of screenings that detected cancer early by year of screening
6. Number of surveillance tests that prevented cancer by year of surveillance
7. Number of surveillance tests that detected cancer early by year of surveillance
8. Number of life years gained due to screening by year of screening

Appendix 2: Derivation of costs

GENERAL

Screening costs were based on information provided by CMS on Medicare payments of 2007 for procedures and tests associated with CRC screening and complications of screening.²⁵ Net costs of the management of invasive CRC treatment were obtained from an analysis of SEER-Medicare data.²⁶ Only direct medical costs were considered, including the co-pays from the beneficiaries.

SCREENING COSTS

Costs for colonoscopy were based on the set of CPT (costs for procedure and treatment) codes relevant to CRC screening in conjunction with the points of service for the procedure. The CPT codes for screening are those stated by the National Coverage Decision (<http://www.medicare.gov/health/coloncancer.asp>) for the CRC screening benefit as well as those for associated colonic biopsy or polypectomy (personal communication, John Allen, M.D., and Joel Brill, M.D.). We used the national unadjusted payment amounts under the physician fee schedule for these analyses. Using the national unadjusted payment means that the costs do not adjust for payment for the geographic location.

Points of service considered for screening were the outpatient prospective payment system (OPPS) and the ambulatory surgery center payment system (ASC) with the associated facility charge, and the physician fee schedule (PFS) office system. We did not include any CPT codes of screening associated with in-patient procedures as registered in the inpatient prospective payment system (IPPS). Complication costs were based primarily on in-patient DRG level reimbursement costs.

Screening procedure costs were based on a weighted average of procedures per setting. The cost values per setting and CPT code are given in tables A2-1 to A2-3. The costs for the ASC setting include the ASC payment rates and the PFS facility charge (Table A2-1). The costs for the OPPS setting included the OPPS payment rates and the PFS facility charge (Table A2-2). For the PFS office setting we used the office payment rates (Table A2-3). The costs for colonoscopy without polypectomy were based on CPT codes 45378 (diagnostic colonoscopy), G0105 (colon screen in high risk individuals) and G0121 (colon cancer screening for non high risk individual). Costs for colonoscopy with polypectomy or biopsy were composed of codes 45380 (colonoscopy and biopsy), 45381 (colonoscopy, submucous injection), 45382

(colonoscopy/control bleeding), 45383 (lesion removal colonoscopy - fulguration), 45384 (lesion removal colonoscopy-hot biopsy) and 45385 (lesion removal colonoscopy-snare polypectomy).

Table A2-1

Ambulatory surgery center (ASC) payment rates

CPT Code	ASC Payment, \$			PFS* - Facility, \$			Total ASC (ASC payment + PFS), \$		
	Medicare (M)	Beneficiary (B)	Total (M+B)	Medicare (M)	Beneficiary (B)	Total (M+B)	Beneficiary (B)	Medicare (M)	Total (M+B)
Colonoscopy without polypectomy									
45378	357	89	446	158	39	197	129	514	643
G0105	335	111	446	158	39	197	151	492	643
G0121	335	111	446	158	39	197	151	492	643
Colonoscopy with polypectomy									
45380	357	89	446	188	47	235	136	545	681
45381	357	89	446	178	44	222	134	534	668
45382	357	89	446	239	60	299	149	596	745
45383	357	89	446	246	61	307	151	602	753
45384	357	89	446	198	49	247	139	554	693
45385	357	89	446	223	56	279	145	580	725
Pathology									
88305	NA	NA	NA	NA	NA	NA	NA	NA	NA

* Physician fee schedule

Table A2-2

Outpatient prospective payment system (OPPS) payment rates

CPT Code	OPPS Payment, \$			PFS- Facility, \$			Total OPPS (OPPS payment + PFS), \$		
	Medicare (M)	Beneficiary (B)	Total (M+B)	Medicare (M)	Beneficiary (B)	Total (M+B)	Beneficiary (B)	Medicare (M)	Total Cost (M+B)
Colonoscopy without polypectomy									
45378	353	186	539	158	39	197	225	511	736
G0105	335	111	446	158	39	197	151	492	643
G0121	335	111	446	158	39	197	151	492	643
Colonoscopy with polypectomy									
45380	353	186	539	188	47	235	233	541	774
45381	353	186	539	178	44	222	230	531	761
45382	353	186	539	239	60	299	246	592	838
45383	353	186	539	246	61	307	247	599	846
45384	353	186	539	198	49	247	235	551	786
45385	353	186	539	223	56	279	242	576	818
Pathology									
88305	21	11	32	30	8	38	18	52	70

Table A2-3

Office payment rates

CPT Code	PFS- Office Medicare (M), \$	PFS- Office Beneficiary (B), \$	PFS- Office Total (M+B), \$
Colonoscopy without polypectomy			
45378	298	74	372
G0105	298	74	372
G0121	298	74	372
Colonoscopy with polypectomy			
45380	354	88	442
45381	343	86	429
45382	472	118	590
45383	419	105	524
45384	349	87	436
45385	398	100	498
Pathology			
88305	82	21	103

Polyp removal and pathology review

For the procedures with polypectomy or biopsy we included a pathology charge (CPT code 88305). The Medicare payment rates per jar were \$82.40 for the PFS office and ASC setting, and \$51.59 for the OPPS setting. All biopsies or polyps are reviewed by pathology. We assumed a separate jar is submitted to pathology for each of 4 colon segments. The intention of a separate jar for separate segments is that the resection area could be identified should the patient require surgery. We used the simplified assumption of four segments; right colon (cecum and ascending), transverse (hepatic flexure and transverse colon), left colon (splenic flexure, descending colon, and sigmoid), and rectum. Data from the National Colonoscopy Study with screening colonoscopy for individuals aged 40-69 were used to provide the estimate of 1.38 as the average number of jars per patient with polyps (hyperplastic, other polyps, and adenomas) where there is one jar for polyps in each of the 4 sections (personal communication, Ann Zauber, Ph.D.).

Consequently, we used the pathology fee times 1.38 as the pathology cost associated with colonoscopy with polypectomy. Total costs per setting and CPT code are given with and without pathology charge (Table A2-4)

Table A2-4
ASC, OPFS, and office payment rates with the addition of pathology costs (when applicable)

CPT Code	Total ASC			Total OPFS			Total PFS		
	Beneficiary	Medicare	Beneficiary with pathology review [†]	Medicare with pathology review [†]	Beneficiary	Medicare	Beneficiary with pathology review	Medicare with pathology review	Beneficiary with pathology review
Colonoscopy without polypectomy									
45378	129	514	129	514	226	511	74	298	298
G0105	151	492	151	492	151	492	74	298	298
G0121	151	492	151	492	151	492	74	298	298
Colonoscopy with polypectomy									
45380	136	545	165	659	233	541	88	354	467
45381	134	534	162	648	231	531	86	343	457
45382	149	596	177	710	246	592	118	472	586
45383	151	602	179	716	248	599	105	419	533
45384	139	554	167	668	236	551	87	349	463
45385	145	580	173	694	242	576	100	398	512

* All values shown in 2007 dollars.

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

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

The total costs per CPT code were calculated based on the frequencies for points of service as weights for the costs (Table A2-5). The total costs per screening procedure are based on the total costs per CPT code that are part of the procedure. The costs were weighted by the frequencies of the CPT codes (Table A2-6).

Table A2-5

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

CPT Code	% of procedures ASC (a)	% of procedures OPPS (b)	% of procedures Office (c)	Total % (d=a+b+c)	ASC * Weight (a/d)	OPPS * Weight (b/d)	Office * Weight (c/d)	Beneficiary Weighted Cost by PoS* (B)	Medicare Weighted Cost by PoS** (M)	Total Weighted Cost by PoS (B+M)
Colonoscopy without polypectomy										
45378	42.8	40.3	4.2	87.2	0.49	0.46	0.05	171	502	673
G0105	53.1	43.3	2.8	99.3	0.54	0.44	0.03	149	487	635
G0121	51.0	44.5	3.2	98.7	0.52	0.45	0.03	148	486	634
Colonoscopy with polypectomy										
45380	47.3	38.1	3.3	88.7	0.53	0.43	0.04	192	631	824
45381	46.0	40.8	2.3	89.1	0.52	0.46	0.03	192	622	814
45382	20.4	29.8	1.8	52.0	0.39	0.57	0.03	216	679	894
45383	42.3	46.9	4.5	93.6	0.45	0.50	0.05	211	684	895
45384	47.8	44.6	3.0	95.4	0.50	0.47	0.03	197	640	837
45385	48.5	41.5	3.8	93.7	0.52	0.44	0.04	202	666	868

* Out of ASC, OPPS, and office.

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

Table A2-6

Costs of colonoscopy with and without polyps*

CPT Code	Beneficiary Weighted Cost by PoS (B)	Medicare Weighted Cost by PoS (M)	Total Weighted Cost by PoS (B+M)	Total number of procedures per CPT code	Weights by CPT code (w)	Weighted Beneficiary Costs by PoS and CPT code (w*B)	Weighted Medicare Costs by PoS and CPT code (w*M)	Total Weighted Costs by PoS and CPT code (w*(B+M))
Colonoscopy without polypectomy								
45378	171	502	673	1,270,881	0.71	122	358	480
G0105	149	487	635	208,073	0.12	17	57	74
G0121	148	486	634	302,860	0.17	25	83	108
Total						164	498	662
Colonoscopy with polypectomy								
45380	192	631	824	879,279	0.38	74	242	316
45381	192	622	814	33,907	0.01	3	9	12
45382	216	679	894	12,530	0.01	1	4	5
45383	211	684	895	89,884	0.04	8	27	35
45384	197	640	837	381,305	0.17	33	106	139
45385	202	666	868	896,966	0.39	79	260	339
Total						198	649	846

COSTS OF TREATING COMPLICATIONS OF COLONOSCOPY

The costs of complications with colonoscopy were based on DRG codes of similar procedures. We assumed that all perforations and bleeds with transfusion would entail a hospitalization. We assumed that bleeds without transfusion would be handled by an emergency room visit (\$320). The cost of perforation was based on DRG 442 for other OR procedures for injuries with complications (\$12,446); bleeding with transfusion (all of whom are considered to require hospitalization) was based on DRG 452 for complications of treatment with complications or comorbidities (\$5,208); and serosal burn generally requires a two-day hospitalization, which was assumed to be the same cost as that as for the bleed with transfusion.

COSTS FOR COLORECTAL CANCER TREATMENT

The cost of CRC treatment was derived from comparison of costs for CRC cases relative to those of matched controls in the SEER-Medicare files.²⁶ Cost data were reported in 2004 dollars and subsequently updated to 2007 dollars using the medical care component of the Consumer Price Index.

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

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

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

Because control subjects did not have a date of cancer diagnosis, they were randomly assigned a “pseudo-diagnosis date” that corresponded to the date of diagnosis of one of the pool of cancer cases. Months of observation and costs of care were assigned to phases of care in the same manner used with cases. In addition to frequency matching by gender, 5-year age group and SEER area strata, controls were also matched to cases by phase of care in up to a 1:5 case: control ratio based on the number of controls available for each stratum. To reflect costs

associated with cancer care in the last year of life, cancer patients who died of cancer were matched to continuing controls, and cancer patients who died of other causes were matched to last year of life controls. As with cancer patients, average monthly estimates of cost of care were calculated for each phase of care for each of group of controls.

For months in which patients received coverage through managed care or were without both Medicare part A and part B, costs and months of observation time were excluded because these data would not completely capture the care received during this period.

Cost estimates—Cancer-related medical costs were estimated as differences in costs for cases and controls by phase of care. The analysis used Medicare payments to reflect costs of care, rather than billed charges. Payments for Medicare Part A (inpatient services) and Part B (outpatient services) were calculated separately. The Hospital Wage Index and the Medicare Economic Index were used to adjust for inflation in Medicare Parts A and B estimates, respectively, during 1998-2003. We also adjusted for geographic variability in costs of care across SEER sites. New treatments including biologicals, such as Avastin and Erbitux,²⁷ have come into use in the past 3 years; these new drugs are markedly more expensive than the previous drugs. However the cost of these new drugs would not be captured by the 2004 reimbursement base available for this case-control study. Estimated patient deductibles and coinsurance expenses were added by adjusting Part A and Part B payments with Medicare reimbursement ratios provided by CMS's Office of the Actuary. Over the time period studied, these averaged about 8% for Part A and about 30% for Part B (Table A2-7).

Table A2-7

Net payments for CRC care during 1998-2003 (in \$2007)*

			Last Year of Life	
AJCC Stage	Initial Phase	Continuing Phase	Died of Cancer	Died of Other Causes
Direct Medical Costs				
I	28,668	2,395	51,935	12,703
II	39,700	2,237	51,712	11,035
III	48,951	3,249	54,776	14,708
IV	64,801	10,419	73,522	39,679

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

Appendix 3: Detailed overview of efficient screening policies for the total population and each population subgroup

APPENDIX 3A total population (uniform)

Efficient screening policies characterized by age range, screening interval and number of scheduled examinations and expressed as the 3% discounted life-time costs and life-expectancy of the policy.

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs (\$) ^{*,†}	Life-expectancy at age 40 [*]
1	n.a.	70-70	1,701	22.4063
1	n.a.	65-65	1,720	22.4120
1	n.a.	64-64	1,725	22.4131
1	n.a.	63-63	1,731	22.4142
1	n.a.	62-62	1,737	22.4151
1	n.a.	61-61	1,747	22.4158
2	14	60-74	1,827	22.4213
2	14	59-73	1,845	22.4223
2	14	58-72	1,866	22.4233
3	9	57-75	2,010	22.4282
3	10	53-73	2,125	22.4315
3	9	53-71	2,151	22.4322
4	8	52-76	2,301	22.4353
4	8	51-75	2,349	22.4362
5	6	51-75	2,563	22.4390
5	7	47-75	2,733	22.4407
6	6	47-77	2,923	22.4426
7	5	48-78	3,077	22.4436
7	5	47-77	3,170	22.4441
8	5	47-82	3,223	22.4443
8	5	46-81	3,329	22.4448
8	5	43-78	3,659	22.4462
9	5	43-83	3,707	22.4464
10	5	43-88	3,732	22.4465
10	5	42-87	3,860	22.4466

^{*} Average of results for population subgroups, weighted by size of population subgroup

[†] Lifetime per person cost for CRC screening and treatment after age 40

APPENDIX 3B

White Men

Efficient screening policies characterized by age range, screening interval and number of scheduled examinations and expressed as the 3% discounted life-time costs and life-expectancy of the policy.

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs (\$)†	Life-expectancy at age 40
1	n.a.	70-70	1,824	21.9125
1	n.a.	65-65	1,831	21.9186
1	n.a.	63-63	1,836	21.9211
1	n.a.	62-62	1,840	21.9221
1	n.a.	61-61	1,848	21.9229
2	14	60-74	1,916	21.9276
2	14	59-73	1,933	21.9288
2	14	58-72	1,953	21.9297
3	9	57-75	2,082	21.9343
3	8	57-73	2,104	21.9350
3	8	56-72	2,141	21.9360
3	9	53-71	2,220	21.9383
4	7	53-74	2,361	21.9412
4	7	52-73	2,413	21.9421
5	6	51-75	2,609	21.9445
6	6	47-77	2,962	21.9478
7	5	48-78	3,103	21.9488
8	5	47-82	3,241	21.9493
8	5	43-78	3,684	21.9511
9	5	43-83	3,723	21.9512
10	5	43-88	3,742	21.9513
10	5	42-87	3,871	21.9513

† Lifetime per person cost for CRC screening and treatment after age 40

APPENDIX 3C

Black Men

Efficient screening policies characterized by age range, screening interval and number of scheduled examinations and expressed as the 3% discounted life-time costs and life-expectancy of the policy.

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs (\$)†	Life-expectancy at age 40
1	n.a.	64-64	1,746	19.8487
1	n.a.	63-63	1,750	19.8503
1	n.a.	62-62	1,754	19.8519
1	n.a.	61-61	1,760	19.8533
1	n.a.	60-60	1,767	19.8546
1	n.a.	59-59	1,777	19.8558
2	15	58-73	1,840	19.8612
2	14	58-72	1,846	19.8616
2	14	57-71	1,866	19.8629
3	11	53-75	2,035	19.8721
3	10	53-73	2,056	19.8731
3	10	52-72	2,090	19.8745
3	9	52-70	2,116	19.8754
4	9	48-75	2,342	19.8822
4	8	48-72	2,401	19.8834
5	7	47-75	2,582	19.8871
5	7	46-74	2,652	19.8882
6	6	47-77	2,735	19.8894
6	6	46-76	2,817	19.8904
6	6	45-75	2,906	19.8913
7	5	44-74	3,249	19.8945
8	5	43-78	3,402	19.8956
8	5	42-77	3,527	19.8961
9	5	42-82	3,556	19.8962
10	5	42-87	3,570	19.8962

† Lifetime per person cost for CRC screening and treatment after age 40

APPENDIX 3D

White Women

Efficient screening policies characterized by age range, screening interval and number of scheduled examinations and expressed as the 3% discounted life-time costs and life-expectancy of the policy.

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs (\$)†	Life-expectancy at age 40
1	n.a.	72-72	1,563	23.4026
1	n.a.	71-71	1,567	23.4035
1	n.a.	70-70	1,573	23.4045
1	n.a.	65-65	1,606	23.4091
1	n.a.	64-64	1,614	23.4099
1	n.a.	63-63	1,624	23.4106
2	14	61-75	1,721	23.4167
2	14	60-74	1,742	23.4177
2	14	59-73	1,762	23.4185
2	14	58-72	1,785	23.4192
3	9	57-75	1,950	23.4242
3	10	53-73	2,069	23.4265
4	8	53-77	2,221	23.4293
4	8	52-76	2,267	23.4301
4	8	51-75	2,314	23.4309
5	7	51-79	2,458	23.4326
5	6	51-75	2,551	23.4336
6	6	47-77	2,925	23.4365
7	6	46-82	3,074	23.4374
8	5	46-81	3,363	23.4387
9	5	44-84	3,634	23.4396
9	5	43-83	3,750	23.4399
10	5	43-88	3,785	23.4399
10	5	42-87	3,911	23.4400

† Lifetime per person cost for CRC screening and treatment after age 40

APPENDIX 3E Black Women

Efficient screening policies characterized by age range, screening interval and number of scheduled examinations and expressed as the 3% discounted life-time costs and life-expectancy of the policy.

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs (\$)†	Life-expectancy at age 40
1	n.a.	63-63	1,716	21.9029
1	n.a.	62-62	1,721	21.9045
1	n.a.	61-61	1,729	21.9059
1	n.a.	60-60	1,736	21.9071
1	n.a.	59-59	1,748	21.9081
2	15	59-74	1,819	21.9139
2	14	58-72	1,842	21.9157
2	15	57-72	1,857	21.9167
2	14	57-71	1,865	21.9171
3	11	53-75	2,060	21.9277
3	10	52-72	2,117	21.9307
4	8	51-75	2,299	21.9359
4	8	49-73	2,403	21.9385
5	7	47-75	2,671	21.9435
6	6	47-77	2,851	21.9464
6	6	46-76	2,934	21.9475
8	5	43-78	3,567	21.9525
9	5	43-83	3,613	21.9527
9	5	42-82	3,737	21.9530
10	5	42-87	3,765	21.9530

† Lifetime per person cost for CRC screening and treatment after age 40

List of Acronyms

CRC	Colorectal Cancer
FOBT	Fecal Occult Blood Test
FAP	Familial Adenomatous Polyposis
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
WTP	Willingness to pay

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Figure 1.

US age-specific colorectal cancer mortality rates per 100,000 white men, African American men, white women, and African American women, 1997-2001 ⁵.

Figure 2.

Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for colorectal cancer. Adenomas are categorized by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age. It is assumed that the proportion of progressive adenomas increases from 16% at age 65 years to 37% at age 75 years, and 96% at age 100 years. It is assumed that 50% of non-progressive adenomas will remain 6-9 mm stage until death and that 50% will progress to the ≥ 10 mm stage. For progressive adenomas, it is assumed that 30% will develop through the sequence ≤ 5 mm adenoma $\rightarrow$ 6-9 mm adenoma $\rightarrow$ preclinical cancer stage I and that 70% will develop through the sequence ≤ 5 mm adenoma $\rightarrow$ 6-9 mm adenoma $\rightarrow$ ≥ 10 mm adenoma $\rightarrow$ preclinical cancer stage I. The mean duration time for progressive adenoma is assumed to be 16.4 years (with an exponential distribution). The mean duration time for preclinical cancer is assumed to be 2 years (stage I), 1 year (stage II), 1.5 years (stage III), and 0.8 years (stage IV). The model is calibrated to reproduce observed CRC incidence, stage distribution and survival by gender and race (see Methods and Materials).

Figure 3.

Multivariate uncertainty analysis using 1,000 simulations. This analysis simultaneously varies all parameters over the full range of possible values. Each point represents the incremental costs and life-years gained of uniform 8-yearly colonoscopy screening over individualized screening generated in one simulation. 83% of points fall in the upper left corner of the graph, meaning that uniform screening is both less effective and more costly than individualized screening. The solid lines represent the willingness to pay (WTP) thresholds of \$50,000 and \$100,000. Points to the right and under this line represent simulations in which uniform screening was more effective than individualized screening at incremental costs of \$50,000 or less/\$100,000 or less respectively.

Table 1

Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2	Fit to multiplicity distribution of adenomas in autopsy studies; ⁷
Adenoma incidence per year	Age 60:	
	1 or more	20%
	2 or more	6%
	3 or more	2%
	Age 90:	
	1 or more	37%
	2 or more	17%
	3 or more	9%
	Fit to adenoma prevalence in autopsy and colonoscopy studies of 15% in age group 50-59 to 33% in age group 70+, ⁷⁻¹¹ and to cancer incidence per 100,000 in 1997-2001 in SEER registry; ¹²	
	Age	
Age, gender and race dependent	White	
	Men	Women
	0-20:	0.1
	20-24:	0.7
	25-29:	1.5
	30-34:	3.6
	35-39:	7.1
	40-44:	12.9
	45-49:	26.3
	50-54:	51.5
Age, gender and race dependent	Black	
	Men	Women
	0-20:	0.1
	20-24:	0.6
	25-29:	1.8
	30-34:	3.5
	35-39:	5.8
	40-44:	11.1
	45-49:	22.2
	50-54:	37.8
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	20-24:	0.7
	25-29:	1.5
	30-34:	3.6
	35-39:	7.1
	40-44:	12.9
	45-49:	26.3
	50-54:	51.5
Age, gender and race dependent	Black	
	Men	Women
	0-20:	0.1
	20-24:	0.6
	25-29:	1.8
	30-34:	3.5
	35-39:	5.8
	40-44:	11.1
	45-49:	22.2
	50-54:	37.8
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	20-24:	0.7
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Age, gender and race dependent	White	
	Men	Women

Model parameter	Value	Source
Regression of adenomas	0-65 years: 14% 65-100 years: linearly increasing from 14% to 96%	
Mean duration of development of progressive adenomas to clinical cancer	No significant regression of adenomas 20 years	Expert opinion *
Mean duration of preclinical cancer	3.6 years	Estimated from cancer detection rate at first screening and background cancer incidence in FOBT trials. 13,14
Mean duration of adenoma	16.4 years	20 years - 3.6 years
Percent of non-progressive adenomas that stay 6-9mm	50%	Fit to size distribution of adenomas in autopsy studies; 7-11 1-5mm: 56% 6-9 mm: 24% 10+ mm: 20%
Percent of non-progressive adenoma that become 10mm or larger	50%	Fit to size distribution of adenomas in autopsy studies; 7-11 1-5mm: 56% 6-9 mm: 24% 10+ mm: 20%
Percent of cancers that develops from 6-9mm adenoma and from 10+mm adenoma	30% of cancer develops from 6-9 mm, 70% from 10+mm	Expert opinion
Localization distribution of adenomas and cancer	Dependent on gender and race:	Directly estimated from SEER 1997-2001. ⁶
	White	Black
	Men	Women
Rectum:	22%	19%
Rectosigmoid junction:	9%	8%
Sigmoid colon:	23%	20%
Descending colon:	5%	6%
Transverse colon (incl flexures):	14%	16%
Ascending colon:	12%	15%
Cecum:	16%	21%
10-year survival after clinical diagnosis of CRC	Dependent on stage, gender and race:	Directly estimated from SEER 1997-2001. ⁶

Model parameter	Value		Source	
	White	Black		
	Men	Men	Women	
Stage I:	95%	71%	89%	
Stage II:	76%	73%	68%	
Stage III:	58%	40%	43%	
Stage IV:	7%	5%	3%	
Sensitivity colonoscopy				Van Rijn 2007, ¹⁵
Adenoma < 5 mm:	75%			
Adenoma 6-9 mm:	85%			
Adenoma 10+ mm:	95%			
Cancer:	95%			
Cecal intubation rate with colonoscopy	95%			Aslinia 2006, ¹⁶ Cotterill 2005, ¹⁷ Rex 2002, ¹⁸
Complications with colonoscopy	Per 1,000 colonoscopies:			Levin 2006, ¹⁹ Lieberman 2000, ²⁰ Pox 2007, ²¹
Perforations	0.7			Regula 2006, ²² Jentschura 1994, ²³
Fatal perforations	0.1			
Serosal burn	0.3			
Bleeds with transfusion	0.4			
Bleeds without transfusion	1.1			

* To be estimated from randomized controlled endoscopy trials, data not yet available.

Table 2

Unit costs in 2007\$ (confidence interval) for screening and CRC treatment, used as inputs for the MISCAN-Colon model

Procedure	Screening costs ³⁶		CRC treatment costs ³⁷			Terminal care, death other cause [*]
	Cost [*]	Stage	Initial [*]	Continuous [*]	Terminal care, death CRC [*]	
Colonoscopy	\$662	I	\$ 28,668 (\$27,905-\$29,432)	\$ 2,395 (\$2,179-\$2,612)	\$ 51,935 (\$49,690-\$54,181)	\$ 12,703 (\$10,533-\$14,870)
Colonoscopy with polypectomy	\$846	II	\$ 39,700 (\$38,876-\$40,525)	\$ 2,237 (\$2,036-\$2,440)	\$ 51,712 (\$49,989-\$53,434)	\$ 11,035 (\$9,214-\$12,856)
Treatment of perforation	\$12,446	III	\$ 48,951 (\$47,924-\$49,976)	\$ 3,249 (\$2,966-\$3,531)	\$ 54,776 (\$53,204-\$56,348)	\$ 14,708 (\$11,993-\$17,422)
Treatment of serosal burn	\$5,208	IV	\$ 64,801 (\$62,420-\$67,181)	\$ 10,419 (\$9,249-\$11,590)	\$ 73,522 (\$71,800-\$75,243)	\$ 39,679 (\$31,826-\$47,532)
Treatment of bleed with transfusion	\$5,208					
Treatment of bleed without transfusion	\$320					

* Costs for cancer care were divided into three clinically relevant phases of care - initial, continuing and terminal care. The initial phase was defined as the first 12 months following diagnosis, the terminal phase was defined as the final 12 months of life, and the continuing phase was defined as all months between the initial and last year of life phases of care. For patients surviving less than 24 months after diagnosis, the final 12 months of observation and costs of care were then allocated first to the last year of life phase, because the content of care for patients with short survival is more similar to the last year of life phase than the initial phase. The remainder of months of observation and costs were allocated to the initial phase, with no contribution to the continuing phase.

Table 3

Results from cost-effectiveness analysis

Strategy	CRC cases/100,000 from age 40 to age 100	CRC deaths/100,000 from age 40 to age 100 *	Life-expectancy at age 40 †	Lifetime per person cost for CRC screening and treatment after age 40 †	ICER †
No screening	5712	2027	22.3929	\$ 1,663	Base Case
Uniform 10-yearly cspy	3026	794	22.4340	\$ 2,310	Dominated
Uniform 8-yearly cspy	2901	751	22.4362	\$ 2,349	\$ 15,565
Individualized	2882	739	22.4363	\$ 2,340	\$ 15,565

ICER: Incremental Cost-Effectiveness Ratio

* Including procedural deaths from colonoscopy complications

† 3% discounted

Table 4

Comparison of 3% discounted costs and life-expectancy between the uniform 8-yearly colonoscopy and individualized strategies, by gender and race and for the total population.

Population subgroup	Uniform 8-yearly colonoscopy strategy		Individualized strategy		Difference in life-expectancy	
	Uniform strategy	Costs (\$) *	Individualized strategy	Costs (\$) *	LE-40	
White Men	4 screens, every 8 years, age: 51-75	2,408	4 screens, every 7 years, age: 53-74	2,361	21,9412	-0.0006
Black Men	4 screens, every 8 years, age: 51-75	2,240	5 screens, every 7 years, age: 47-75	2,582	19,8871	+0.0080
White Women	4 screens, every 8 years, age: 51-75	2,314	4 screens, every 8 years, age: 53-77	2,221	23,4293	-0.0016
Black Women	4 screens, every 8 years, age: 51-75	2,299	5 screens, every 7 years, age: 47-75	2,671	21,9435	+0.0076
Total Population [†]		2,349		2,340	22,4363	+0.0002

LE-40: Life-expectancy at age 40

* Lifetime per person cost for CRC screening and treatment after age 40

[†] Average of results for population subgroups, weighted by size of population subgroup

Table 5

Results one-way sensitivity analysis: Comparison between 3% discounted costs and life-expectancy in the total population between the uniform 8-yearly colonoscopy and individualized strategies, for different model assumptions

Model parameter	Differences of the individualized strategy compared to the uniform 8-yearly colonoscopy strategy			
	Low value		High value	
	Gain in LE	ICER Costs (\$) *	Gain in LE	ICER Costs (\$) *
Base assumptions	+0.0002	-9.09	+0.0002	-9.09
Fast progression of adenomas [†]	+0.0001	-7.89	Dominant	Dominant
Duration adenoma carcinoma sequence ^{**}	+0.0005	-10.11	Dominant	\$ 546,213
Risk African Americans ^{**}	+0.0001	-6.67	Dominant	-9.40
Reach colonoscopy ^{**}	+0.0003	-8.01	Dominant	-8.09
Sensitivity colonoscopy ^{**}	+0.0002	-8.58	Dominant	-7.82
Specificity colonoscopy ^{**}	+0.0002	-8.05	Dominant	-7.97
Cost colonoscopy ^{**}	+0.0002	-4.18	Dominant	-11.56
Cost polypectomy ^{**}	+0.0002	-8.03	Dominant	-7.65
Complication rate of colonoscopy ^{**}	+0.0002	-7.93	Dominant	-8.09
Costs treatment complications ^{**}	+0.0002	-7.99	Dominant	-8.51
Cost treatment ^{**}	+0.0002	-8.05	Dominant	-7.96

LE: Life-expectancy

ICER: Incremental Cost-effectiveness ratio. Italic numbers represent the incremental cost per life-year gained of the uniform 8-yearly colonoscopy strategy compared to the individualized strategy. "Dominant" means that the individualized strategy was both more effective and less costly than the uniform strategy.

Risk African Americans: low value = 10% lower risk, high value = 10% higher risk than values in Table 1

Reach colonoscopy: low value = 80% reach cecum, high value = 99% reach cecum

Sensitivity colonoscopy: low and high values set at confidence intervals (see MISCAN-Colon microsimulation model in Methods)

Specificity colonoscopy: low value = 0.78, high value = 1

Cost colonoscopy: low value = \$285, high value = \$1012

Cost polypectomy: low value = \$159, high value = \$507

Complication rate colonoscopy: low value = 1 per 1,000, high value = 4 per 1,000

Cost complications: low value = \$4,360, high value = \$26,000

Cost treatment: low and high values set at confidence intervals (see Table 2)

* Lifetime per person cost for CRC screening and treatment after age 40

[†] For this assumption there is no high or low value. It was just varied from the base assumption where differences in CRC risk were caused by differences in adenoma incidence. In this sensitivity analysis it was assumed that differences were caused by differences in progression rates of adenomas

** Duration: low value = 10 years, high value = 30 years