Almost 149,000 persons in the United States are newly diagnosed with colorectal cancer each year (1). Approximately one-third of these patients die of the disease, making colorectal cancer the second leading cause of cancer death (1). Randomized clinical trials published between 2003 and 2004 have shown that improvements in chemotherapy can lengthen the median survival of patients who are diagnosed with advanced stages of colorectal cancer increased over the scenarios. Screening strategies considered were annual guaiac fecal occult blood testing (FOBT), annual immunochemical FOBT, sigmoidoscopy every 5 years, colonoscopy every 10 years, and the combination of sigmoidoscopy every 5 years and annual guaiac FOBT. Analyses were conducted from the perspective of the health-care system for a cohort of 50-year-old individuals who were at average risk of colorectal cancer and were screened with 100% adherence from age 50 years to age 80 years and followed up until death.

Compared with no screening, the treatment savings from preventing advanced colorectal cancer and colorectal cancer deaths by screening more than doubled with the widespread use of new chemotherapies. The lifetime average treatment savings were larger than the lifetime average screening costs for screening with Hemoccult II, immunochemical FOBT, sigmoidoscopy, and the combination of sigmoidoscopy and Hemoccult II (average savings vs costs per individual in the population: Hemoccult II, $1398 vs $859; immunochemical FOBT, $1756 vs $1565; sigmoidoscopy, $1706 vs $1575; sigmoidoscopy and Hemoccult II $1931 vs $1878). Colonoscopy did not become cost saving, but the total net costs of this strategy decreased from $1317 to $296 per individual in the population.

With the increase in chemotherapy costs for advanced colorectal cancer, most colorectal cancer screening strategies have become cost saving. As a consequence, screening is a desirable approach not only to reduce colorectal cancer incidence and mortality but also to control the costs of colorectal cancer treatment.
Screening is another cornerstone for reducing the number of life-years lost because of colorectal cancer. Colorectal cancer is particularly well suited for screening because of its long preclinical phase and the favorable survival of patients whose disease is detected at an early stage. Randomized controlled trials have shown that biennial and annual screening with an unrehydrated guaiac-based fecal occult blood test (FOBT) (Hemoccult II; SmithKline Diagnostics, Palo Alto, CA) can reduce colorectal cancer mortality by 15%–33% (5–9). Although the extent of the efficacy of screening by endoscopy for the prevention of colorectal cancer has yet to be demonstrated in prospective randomized controlled trials (10–14), several case–control studies suggest that endoscopic screening is associated with a 50%–90% reduction in colorectal cancer incidence and mortality (15–17). Colorectal cancer screening not only is an effective tool for reducing colorectal cancer mortality but also has been estimated to reach this goal at acceptable costs (18). For example, in five cost-effectiveness analyses, the estimated average cost per life-year gained of screening with Hemoccult II ranged from $5691 to $17 805 (18). These estimates are well below the frequently used cost-effectiveness threshold for medical interventions of $50 000 per life-year gained. Also below this threshold are the estimated average costs per life-year gained of screening with colonoscopy, with estimates ranging from $9038 to $22 012 per life-year gained, and with sigmoidoscopy, with estimates ranging from $12 477 to $39 359 (18).

Although these cost-effectiveness ratios are quite favorable, colorectal cancer screening still requires a considerable net investment by insurance companies and governments, which has resulted in some hesitancy to implement colorectal cancer screening programs. However, none of these cost-effectiveness studies took into account the marked increase in treatment costs for colorectal cancer. It is interesting that although treatment costs for advanced colorectal cancer (and thus the savings when these cancers are prevented) have increased substantially over the past decade (3,19), the costs of screening have remained stable (20,21). To our knowledge, no studies have explicitly evaluated the effect of increasing treatment costs on the savings from colorectal cancer screening. This topic is of particular importance for the many countries worldwide that are currently deciding whether to introduce population screening programs for colorectal cancer. If screening were to become cost saving, governments and insurance companies might be more inclined to invest in colorectal cancer screening programs because these investments would be recovered in the near-term future. In this analysis, we used the MISCAN-Colon microsimulation model to test the hypothesis that colorectal cancer screening would become cost saving with the widespread use of new chemotherapeutic agents.

**Methods**

**MISCAN-Colon Microsimulation Model**

The MISCAN microsimulation model was developed at the Department of Public Health (Erasmus MC, University Medical Center, Rotterdam, the Netherlands) and has been used to evaluate screening programs for breast, cervical, colorectal, and prostate cancers. The colorectal cancer version of the MISCAN-model, MISCAN-Colon, was developed in collaboration with the US National Cancer Institute and experts in the field of colorectal cancer to evaluate colorectal cancer intervention programs and policies. The MISCAN-Colon model is part of the Cancer Intervention and Surveillance Modeling Network of the National Cancer Institute (22). A detailed description of the model and the data sources that inform the quantification of the model can be found in Supplementary Appendix 1 (available online), in previous studies performed with the model (23–25), and in a standardized model profile (26). Briefly, the MISCAN-Colon model simulates the relevant biographies of a large population of fictitious individuals from birth to death, first in the absence of screening and subsequently with the changes that are predicted to occur under the implementation of a screening program. Colorectal cancer is assumed to arise in this population according to the adenoma–carcinoma sequence, in which every cancer is preceded by an adenoma (27,28). The model assumed that more than one adenoma could occur in an individual and that each adenoma 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).
based on size categories available in reference data (29–38), and never regress. The model also assumed that most adenomas will never develop into cancer (nonprogressive adenomas), but some of the ones that do (progressive adenomas) could eventually become malignant and transform to become a stage I cancer. The cancer may then progress from stage I to stage IV. For cancers of every stage, there is a chance that the cancer would be diagnosed because of symptoms. Patient survival after clinical diagnosis depends on the stage of the cancer at diagnosis. Good longitudinal data from endoscopy trials are not yet available to estimate the progression rate from adenoma to cancer; therefore, this rate was established based on expert opinion.

The model also simulates the point at which screening interrupts the development of colorectal cancer. During screening, adenomas may be detected and removed, preventing colorectal cancer incidence and thereby mortality. Also cancers may be found during screening, usually in an earlier stage than when identified during clinical diagnosis. Because we assumed the same stage-specific survival for screen-detected cancers as for clinically diagnosed cancers, finding a cancer in an earlier stage improves prognosis and may further prevent colorectal cancer death. The life-years gained by screening were calculated by comparing the model-predicted life-years lived in the population with and without screening.

The validity of the model has previously been tested. The validity of the model is based on observational data collected before the introduction of screening, such as clinical colorectal cancer incidence and mortality data (39) and the size distribution of adenomas in autopsy studies (29–38). The model has been further validated using the data from several large randomized screening and surveillance studies, such as the CoCap sigmoidoscopy study (23), the Minnesota Colon Cancer Control Study (23), and the National Polyp Study (40). Finally, the model was able to reproduce the observed colorectal cancer incidence and mortality trends in the United States while accounting for how the secular trends in risk factor prevalence, screening practice, and chemotherapy treatment affected the natural history of the disease (ie, the adenoma–carcinoma sequence). In this latter analysis, all model parameters were fixed based on estimates from external (ie, non–Surveillance, Epidemiology, and End Results [non–SEER]) data sources. With these fixed parameters, the model-predicted colorectal cancer incidence and mortality rates for 1980–2002 were within 5% of the rates observed in SEER (41).

Study Population
We used the MISCAN-Colon model to estimate the distribution of underlying disease for the 50-year-old US population in 2008 in terms of the presence, location, size, and type (adenoma vs preclinical cancer) of lesions. We conducted the microsimulation analysis of the effect of different screening strategies among a cohort of 10 million individuals beginning at age 50 years. The cohort was followed up until death.

Scenarios
We evaluated three treatment scenarios: “past,” “present,” and “near future.” For the past scenario, we assumed that colorectal cancer survival and treatment costs were those observed for 1990–1994. For the present scenario, survival and treatment costs for 1998–2003 were assumed. Finally, for the near-future scenario, we assumed improved survival and increased treatment costs compared with the 1998–2003 levels, based on the most recent clinical trial results (2).

Screening Strategies
The screening strategies included the base case strategy of no screening and the five colorectal cancer screening strategies that are recommended by the American Cancer Society, the US Multi-Society Task Force, and the American College of Radiology (42) and the US Preventive Services Task Force (43), which include an annual FOBT with unrehydrated Hemoccult II, annual immunochromocytic FOBT, sigmoidoscopy every 5 years, colonoscopy every 10 years, or annual Hemoccult II in combination with sigmoidoscopy every 5 years. In all scenarios, screening began at age 50 years and was discontinued after age 80 years.

Follow-up, Surveillance, and Adherence
We assumed that any simulated individual with a positive FOBT was referred for a follow-up colonoscopy. We assumed that all polyps detected during flexible sigmoidoscopy were biopsied, and any simulated person with an adenomatous polyp was referred for a follow-up colonoscopy. For the year in which both FOBT and flexible sigmoidoscopy were due, the FOBT was performed first and if positive, the simulated individual was referred for follow-up colonoscopy; flexible sigmoidoscopy was only performed for those with a negative FOBT. Simulated individuals with a negative follow-up colonoscopy returned to the original screening strategy. If adenomas were detected by colonoscopy, then the individual began surveillance with colonoscopy as recommended by the 2006 guidelines from the US Multi-Society Task Force, the American Cancer Society, and the American College of Radiology (44). All individuals with one or two adenomas that were each less than 10 mm in size underwent colonoscopy surveillance every 5 years. Individuals with at least one adenoma greater than or equal to 10 mm in size or with three or more adenomas of any size underwent colonoscopy surveillance every 3 years. When the surveillance colonoscopy was normal or detected only one or two adenomas less than 1.0 cm in size, the next surveillance colonoscopy was scheduled for 5 years later.

We assumed that all simulated individuals were 100% adherent with screening, follow-up, and surveillance procedures. We specified 80 years as the age to stop screening (ie, final screening at age 80 years); however, all individuals with an adenoma detected continued to have surveillance colonoscopies until a diagnosis of colorectal cancer or death from other causes. All simulated individuals were followed up until death.

Colorectal Cancer Screening Test Characteristics
Our assumptions for sensitivity and specificity of the colorectal cancer screening tests (Supplementary Appendix Table 1, available online) were based on a literature review conducted for the Agency for Health Care Research and Quality (21). Sensitivity and specificity were assumed to be independent of screening round and age. In addition, we assumed that 8% of persons without adenomas at sigmoidoscopy and 10% of persons without adenomas at
colonoscopy incurred additional costs because of biopsy, removal, and pathology of nonadenomatous polyps. The rate of serious nonfatal complications was assumed to be 2.4 per 1000 colonoscopies (45–48). The rate of fatal events was assumed to be 0.1 per 1000 colonoscopies (49).

**Survival Estimates**

Survival estimates by disease stage for the past and present scenarios were obtained from the SEER database for cancers diagnosed in 1990–1994 and 1998–2003, respectively (50). For those diagnosed in 1998–2003, we used the period estimation feature in SEER*Stat software to estimate long-term survival for diagnoses (50). Survival estimates for the near-future scenario were derived by applying the hazard ratios for median survival from clinical trials (2) to the 1998–2003 stage-specific relative survival rates. Thus, we assumed that the hazard ratios found in the trials could be generalized to the total population, despite the selection bias of healthy younger patients in these trials. Table 1 summarizes relative survival rates used in this analysis by disease stage and scenario.

**Costs**

This analysis was conducted from a health-care system perspective and included only direct medical costs (patient time costs and productivity costs were not included). The costs of colorectal cancer treatment for the past and present scenarios were derived from a comparison of costs for colorectal cancer case patients relative to those of control subjects without a cancer diagnosis matched by sex, age, and SEER registry area in merged SEER and Medicare files from 1990–1994 and 1998–2003, respectively (51,52). Costs of care were divided into three clinically relevant phases of care: initial, continuing, and terminal care. The initial phase of care was defined as the first 12 months following diagnosis [the first 6 months following diagnosis for the past scenario, in concordance with cost data (51)]. The terminal phase of care was defined as the final 12 months of life, and the continuing phase was defined as all months between the initial and terminal phases of care. The terminal phase for colorectal cancer patients was further subdivided into terminal care preceding colorectal cancer death and terminal care preceding death from other causes. For patients who survived less than 24 months after diagnosis, the final 12 months of observation and costs of care were allocated to the terminal phase because the care for patients with short survival is more similar to the terminal phase than to the initial phase after diagnosis. The remainder of survival time was allocated to the initial phase (ie, none were allocated to the continuing phase). Treatment cost data were updated to 2007 dollars by using the medical care component of the Bureau of Labor Statistics Consumer Price Index (53).

The treatment costs in the near-future scenario were based on the present scenario costs and the drug prices as presented by Schrag (3). For example, in the near-future scenario, we assumed that stage IV disease was initially treated with 5-FU in combination with oxaliplatin (FOLFOX). In the present scenario, we assumed that stage IV disease was treated with 5-FU in combination with irinotecan (FOLFIRI). The difference in drug costs between FOLFIRI and FOLFOX is approximately $2500 per cycle (3). We assumed that patients with stage IV disease received six drug cycles in the first year of treatment. Thus, initial treatment for stage IV disease in the near-future scenario cost approximately $15 000 more than that in the present scenario. Because FOLFOX has also been proven to be effective for stage III disease (54), we assumed the same initial treatment and, thus, treatment costs for stage III disease as for stage IV disease. For the terminal care phase preceding colorectal cancer death (irrespective of the original stage at diagnosis), we assumed that six cycles of bevacizumab was added as second-line treatment, making terminal treatment $60 000 more expensive in the near-future scenario than in the present scenario. For the other phases of care, the costs in the near-future scenario were the same as in the present scenario. The final cost inputs used in the model are summarized in Table 2.

The unit costs for screening (Table 3) were based on 2007 Medicare payments for procedures and tests associated with colorectal cancer screening and complications of screening, including...

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**Table 1.** Five- and 10-year relative survival, by stage and treatment scenario, used as inputs for the MISCAN-Colon model*

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Stage</th>
<th>Past scenario</th>
<th>Present scenario</th>
<th>Near-future scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5-year survival</td>
<td>10-year survival</td>
<td>5-year survival</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>94.1</td>
<td>89.1</td>
<td>93.9</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>81.0</td>
<td>72.3</td>
<td>82.1</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>56.5</td>
<td>48.7</td>
<td>61.5</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>6.2</td>
<td>4.5</td>
<td>8.0</td>
</tr>
</tbody>
</table>

* Survival estimates are presented as percentages.

**Table 2.** Unit costs per person per year in 2007 US dollars for colorectal cancer treatment, by stage, phase of care, and treatment scenario, used as inputs for the MISCAN-Colon model*

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Stage</th>
<th>Initial</th>
<th>Continuous</th>
<th>Death from CRC</th>
<th>Death from other cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past</td>
<td>I</td>
<td>24 472</td>
<td>2033</td>
<td>36 495</td>
<td>7361</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>31 878</td>
<td>2033</td>
<td>36 534</td>
<td>4849</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>35 742</td>
<td>3727</td>
<td>38 485</td>
<td>7515</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>34 132</td>
<td>8809</td>
<td>37 288</td>
<td>12 906</td>
</tr>
<tr>
<td>Present</td>
<td>I</td>
<td>28 668</td>
<td>2395</td>
<td>51 935</td>
<td>12 703</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>39 700</td>
<td>2237</td>
<td>51 712</td>
<td>11 035</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>48 951</td>
<td>3249</td>
<td>54 776</td>
<td>14 708</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>64 801</td>
<td>10 419</td>
<td>73 522</td>
<td>39 679</td>
</tr>
<tr>
<td>Near future</td>
<td>I</td>
<td>28 668</td>
<td>2395</td>
<td>111 935</td>
<td>12 703</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>39 700</td>
<td>2237</td>
<td>111 712</td>
<td>11 035</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>79 801</td>
<td>3249</td>
<td>114 776</td>
<td>14 708</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>79 801</td>
<td>10 419</td>
<td>133 522</td>
<td>39 679</td>
</tr>
</tbody>
</table>

* Costs for 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 the period between the initial and terminal phases of care. The terminal phase for colorectal cancer patients was further subdivided into terminal care preceding colorectal cancer death and terminal care preceding death from other causes. For patients surviving less than 24 months after diagnosis, the final 12 months of observation and costs of care were allocated to the terminal phase because the care for patients with short survival is more similar to the terminal phase than to the initial phase after diagnosis. The remainder of survival time was allocated to the initial phase, and no time was allocated to the continuing phase.

**Note:** CRC, colorectal cancer

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The main focus of this article was to test the hypothesis that colorectal cancer screening would become cost saving with the widespread introduction of new chemotherapies, we only present results of the sensitivity analysis for the near-future scenario.

### Results

Because the natural history of colorectal cancer and the sensitivity of the screening tests remained unchanged between the treatment scenarios, the number of colorectal cancers (screen-detected and clinically diagnosed cancers) per 1000 individuals by stage for each screening strategy was the same for all treatment scenarios (Table 4). According to the model, without screening, 66 per 1000 simulated 50-year-old individuals were clinically diagnosed with colorectal cancer in their lifetime, corresponding to a lifetime background risk of 6.6%. Almost 50% of the patients in the no-screening situation were diagnosed with late-stage (stage III or IV) disease. With screening (assuming 100% adherence), the number of cancers prevented per 1000 individuals ranged from 24 (37%) with annual Hemoccult II screening to 36 (56%) with colonoscopy screening every 10 years. Screening improved the stage distribution in that it decreased the number of colorectal cancers in stages II, III, and IV and increased the number in stage I. The percent reduction in cancers in stages II–IV for all five screening strategies compared with no screening was similar; there were fewer stage I cancers with the endoscopy strategies than with the FOBT strategies.

For all screening strategies, the savings from cancers and cancer deaths that were prevented by screening increased progressively from the past scenario to the present and near-future scenarios (Table 5, Figure 1). Because the per-person costs of treatment increased, for the most part, for stages III and IV between the scenarios (Table 2) and the incidence reduction of cancers in these stages was similar for all test strategies (Table 4), the increase in total savings from the past to the near-future scenario was also similar for all tests. On average, total savings increased by 43% from the past scenario to the present scenario and by another 56% from the present scenario to the near-future scenario. Because screening costs remained stable over all scenarios (Table 5, Figure 1), the absolute total net costs of screening decreased at the same rate as the absolute treatment savings increased. As a result, for the near-future scenario, the lifetime average treatment savings were larger than the lifetime average screening costs for screening with Hemoccult II, immunochemical FOBT, sigmoidoscopy, and the combination of sigmoidoscopy and Hemoccult II (average savings vs costs per individual in the population: Hemoccult II, $1398 vs $859; immunochemical FOBT, $1756 vs $1565; sigmoidoscopy,
$1706 vs $1575; sigmoidoscopy and Hemoccult II $1931 vs $1878). For colonoscopy, the screening costs remained larger than the treatment savings ($2254 vs $1958), but the total net costs of this strategy decreased from $1317 per individual in the population in the past scenario to $296 in the near-future scenario.

We plotted the net per-person costs of the different screening strategies over time for the near-future scenario (Figure 2). Because most of the screening costs occur immediately after the introduction of a program but the savings do not begin to accumulate substantially until some years later, the screening strategies do not become cost saving until after several decades. Hemoccult II was the screening strategy for which the savings from treatment outweighed the costs in the shortest amount of time after initiation of the screening program. This strategy became cost saving 26 years after the start of the program. Immunochemical FOBT, sigmoidoscopy, and the combination of sigmoidoscopy and Hemoccult II become cost saving after several decades.

### Table 5. Costs and savings of colorectal cancer screening by screening strategy and scenario, 3% discounted to age 50 years*

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Scenario</th>
<th>Screening</th>
<th>Follow-up and surveillance†</th>
<th>Treatment of colorectal cancer</th>
<th>Savings‡</th>
<th>Total net costs§</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>Past</td>
<td>0</td>
<td>0</td>
<td>1927</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>0</td>
<td>0</td>
<td>2542</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Near future</td>
<td>0</td>
<td>0</td>
<td>3519</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hemoccult II</td>
<td>Past</td>
<td>71</td>
<td>788</td>
<td>1367</td>
<td>560</td>
<td>299</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>71</td>
<td>788</td>
<td>1707</td>
<td>835</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Near future</td>
<td>71</td>
<td>788</td>
<td>2121</td>
<td>1398</td>
<td>−539</td>
</tr>
<tr>
<td>Immunochemical FOBT</td>
<td>Past</td>
<td>325</td>
<td>1241</td>
<td>1172</td>
<td>755</td>
<td>810</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>325</td>
<td>1241</td>
<td>1451</td>
<td>1091</td>
<td>474</td>
</tr>
<tr>
<td></td>
<td>Near future</td>
<td>325</td>
<td>1241</td>
<td>1762</td>
<td>1756</td>
<td>−191</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>Past</td>
<td>657</td>
<td>918</td>
<td>1111</td>
<td>816</td>
<td>759</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>657</td>
<td>918</td>
<td>1407</td>
<td>1135</td>
<td>440</td>
</tr>
<tr>
<td></td>
<td>Near future</td>
<td>657</td>
<td>918</td>
<td>1813</td>
<td>1706</td>
<td>−131</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Past</td>
<td>1397</td>
<td>858</td>
<td>990</td>
<td>937</td>
<td>1317</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1397</td>
<td>858</td>
<td>1239</td>
<td>1304</td>
<td>951</td>
</tr>
<tr>
<td></td>
<td>Near future</td>
<td>1397</td>
<td>858</td>
<td>1561</td>
<td>1968</td>
<td>296</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy +</td>
<td>Past</td>
<td>672</td>
<td>1206</td>
<td>1034</td>
<td>893</td>
<td>984</td>
</tr>
<tr>
<td>Hemoccult II</td>
<td>Present</td>
<td>672</td>
<td>1206</td>
<td>1285</td>
<td>1257</td>
<td>621</td>
</tr>
<tr>
<td></td>
<td>Near future</td>
<td>672</td>
<td>1206</td>
<td>1588</td>
<td>1931</td>
<td>−53</td>
</tr>
</tbody>
</table>

* Costs and savings are expressed as the lifetime average per individual in the population. — = not applicable; FOBT = fecal occult blood test.
† Includes costs of diagnostic follow-up, surveillance tests, and treatment of complications.
‡ Treatment costs without screening minus treatment costs for specific strategy.
§ Sum of costs for specific strategy minus sum of costs without screening.

Figure 1. Screening costs (including diagnostic follow-up and surveillance) and treatment savings of colorectal cancer screening (lifetime average per individual in the population) by screening strategy and treatment scenario with costs and savings 3% discounted to age 50 years. HemII = Hemoccult II; iFOBT = immunochemical fecal occult blood test; Flexsig = flexible sigmoidoscopy; Cscopy = colonoscopy.

Figure 2. Cumulative net costs (including costs of screening, diagnostic follow-up, and surveillance and savings of treatment) of screening a cohort for colorectal cancer from age 50 years to age 80 years, by screening strategy and the number of years since start of screening for the near-future scenario (per individual in the population) with net costs 3% discounted to start of screening. The curves for the screening strategies that include endoscopy show a sawtooth pattern because of the long screening interval. In the fecal occult blood test (FOBT) strategies, screening costs are accumulated each year and these curves therefore have a smooth pattern.
became cost saving more than 37, 40, and 44 years, after the respective screening programs were initiated.

Sensitivity Analysis

Only the Hemoccult II screening strategy remained cost saving in the near-future scenario for all six alternative model assumptions (Table 6). Immunochemical FOBT, sigmoidoscopy, and the combination of sigmoidoscopy and Hemoccult II were no longer cost saving when colonoscopy costs were 25% higher than the base case value, when costs were discounted at an annual rate of 5%, or when colorectal cancer risk was half the base case value. All strategies were cost saving when colonoscopy costs were 25% lower than the base case value, when costs were discounted at an annual rate of 0%, or when colorectal cancer risk was double the base case value. Surprisingly, the results for most of the screening strategies were robust for increases and decreases in chemotherapy costs and the proportion of patients receiving chemotherapy. The combination of sigmoidoscopy with Hemoccult II was the only screening modality other than colonoscopy that was no longer cost saving when the chemotherapy costs decreased by 25% or chemotherapeutics were administered to 25% fewer patients compared with the base case values. With a doubling of the adenoma progression rate, only the Hemoccult II and immunochemical FOBT strategies remained cost saving, whereas with half the adenoma progression rate, all strategies except colonoscopy were cost saving.

The results were robust for sampling variability: Hemoccult II, immunochemical FOBT, sigmoidoscopy, and the combination of sigmoidoscopy and Hemoccult II were cost saving in all 100 repeat simulations, whereas colonoscopy was not. The difference in net costs of screening between the simulation run with maximum net costs and the simulation run with minimum net costs was $14–$17, depending on the screening strategy.

Discussion

We found that the treatment savings from screening were more than twice as high in the near-future scenario (with expensive chemotherapies, such as oxaliplatin for stage III and IV disease and bevacizumab and cetuximab for stage IV disease) than in the past scenario for all test strategies. This increase in savings makes screening with Hemoccult II, immunochemical FOBT, sigmoidoscopy, and the combination of sigmoidoscopy and Hemoccult II cost saving. Although colonoscopy did not become cost saving in the near-future scenario, the total net costs of this strategy decreased substantially. Because colonoscopy screening reduces colorectal cancer incidence more than any other screening strategy according to the model (Table 4), we anticipated that the increase in per-person treatment costs from the past to the near-future scenario would have the largest impact on savings from colonoscopy. Although the savings with colonoscopy screening were the greatest, they were not substantially greater than the savings from immunochemical FOBT because the additional incidence reduction from colonoscopy screening is mostly in stage I cancers, for which treatment costs have risen only slightly.

The crucial assumption in this analysis was that treatment costs increase rapidly over time, whereas screening costs remain stable. Observations in the recent past confirm this assumption. For example, from 1990–1994 to 1998–2003, treatment costs per person have increased by up to 200%, depending on the stage of disease at diagnosis (51,52), whereas unit screening costs have not (20,21).

The treatment costs in the near-future scenario were based on increases in price between the current chemotherapies (5-FU and FOLFIRI) and newly available chemotherapies (FOLFOX and bevacizumab). However, the treatment costs for these new drugs may eventually decrease when they are available as the generic forms, which would decrease the treatment savings from screening. The sensitivity analysis showed that even with chemotherapy costs that were 25% lower than the base case value, three of the five screening strategies still remained cost saving. However, treatment costs have a tendency to increase despite wide-scale application of chemotherapies (51,52). Furthermore, we do not expect to have seen the end of developments in chemotherapy for colorectal cancer. The second-line treatment of bevacizumab for recurrent disease is already being investigated as first-line treatment for stage IV disease (55) and as adjuvant therapy for stage III disease and advanced stage II disease (56). These developments are likely to further increase the treatment savings from screening. By using different cost value inputs, additional savings from screening with these newer chemotherapy standards can be calculated (see Appendix Table 1).

Table 6. Sensitivity analysis for different model parameter assumptions: overview of colorectal cancer screening strategies that are cost saving in the near-future scenario*  

<table>
<thead>
<tr>
<th>Model assumption†</th>
<th>High value</th>
<th>Low value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression rate of adenomas</td>
<td>Hemoccult II, immunochemical FOBT</td>
<td>All strategies except colonoscopy</td>
</tr>
<tr>
<td>Colorectal cancer risk</td>
<td>All strategies</td>
<td>Hemoccult II</td>
</tr>
<tr>
<td>Colonoscopy costs</td>
<td>Hemoccult II</td>
<td>All strategies</td>
</tr>
<tr>
<td>Costs of new chemotherapies</td>
<td>All strategies except colonoscopy</td>
<td>Hemoccult II, immunochemical FOBT, flexible sigmoidoscopy</td>
</tr>
<tr>
<td>Discount rate</td>
<td>Hemoccult II</td>
<td>All strategies</td>
</tr>
<tr>
<td>% of patients who get new chemotherapies</td>
<td>NA</td>
<td>Hemoccult II, immunochemical FOBT, flexible sigmoidoscopy</td>
</tr>
</tbody>
</table>

* FOBT = fecal occult blood test; NA = not applicable.
† Adenoma progression rate: low value = half the base case value, high value = double the base case value; Colorectal cancer risk: low value = half the base case risk, high value = double the base case risk; Colonoscopy costs: low value = 25% lower than the base case, high value = 25% higher than the base case; Costs of new chemotherapies: low value = 25% lower than the base case, high value = 25% higher than the base case; Discount rate: low value = 0%, high value = 5%; % of patients who get new chemotherapies: low value = 75%.
This study has several limitations. First, we did not include therapies other than chemotherapy, such as radiotherapy for rectal cancer and extensive surgery for metastatic disease in this analysis, which continue to become more widely available, further increasing treatment costs and survival. We may, therefore, have underestimated the increase in treatment costs from the present scenario to the near-future scenario. Second, we assumed that all patients with stage III or IV disease received the new chemotherapies in the near-future scenario, whereas in actual practice, elderly patients with comorbidities probably will not receive the full dose or will receive no chemotherapy at all. Incorporating a lower dissemination of chemotherapy in elderly patients into the model would limit the increase in treatment costs and thus the savings from screening. Because in the present scenario the treatment savings from FOBT screening were already close to the screening costs, our conclusion that colorectal cancer screening is cost saving was robust to these uncertainties.

The new chemotherapies will not only increase treatment costs but will also decrease colorectal cancer mortality by postponing or sometimes even preventing colorectal cancer death. Because of this improved survival, fewer people will die of colorectal cancer and fewer life-years will be gained by screening. However, the shifting balance between the screening costs and the treatment savings of colorectal cancer screening with the introduction of new chemotherapies reflects the higher costs per life-year saved of these new treatments compared with screening. It is therefore important to realize that with the introduction of expensive chemotherapies that have high costs per life-year gained, screening becomes increasingly more cost-effective. We purposely did not present the effects of the different screening strategies because no results from randomized controlled trials on the efficacy of endoscopy screening are available. Therefore, modeling results indicating that one test is superior to another would be preliminary because the model may have overestimated or underestimated the potential efficacy of endoscopy screening, mainly because of uncertainty about the progression rate of adenomas. The aim of this analysis was therefore not to recommend one screening strategy over another but rather to examine whether colorectal cancer screening in general would become cost saving with the introduction of new and expensive chemotherapies.

We assumed 100% adherence with screening, diagnostic follow-up, and surveillance. This assumption would not influence the results of our analysis. Incomplete adherence to screening would decrease screening costs and treatment savings proportionally, such that the relative difference between screening costs and treatment savings would not be influenced. In the case of occasional adherence to screening (some but not all screening rounds are attended by an individual), the savings from screening would even increase somewhat more than the screening costs.

Most of the previous US cost-effectiveness studies did not find that colorectal cancer screening was cost saving (18). However, those studies were conducted before the widespread introduction of the new expensive chemotherapies and therefore used lower estimates for colorectal cancer treatment costs than we assumed in the near-future scenario. To determine whether our estimates were within an order of magnitude of those used in these previous studies, we tried to estimate what the net costs of screening for these other models would be with higher treatment costs. Only two of the previous cost-effectiveness studies provided sufficient data on the number of colorectal cases and deaths with and without screening to allow a rough estimate of what the additional savings would be with higher treatment costs (20,57). We calculated the additional treatment savings in these studies by multiplying the number of colorectal cancers prevented by the average difference in initial treatment costs between the present scenario and the near-future scenario ($15 000 undiscounted [Table 2], to incorporate discounting we discounted this difference by 3% for a period of 25 years as an average in the multiplication [$7164]) and the number of colorectal cancer deaths prevented by the average difference in terminal phase of care costs ($60 000 undiscounted, or $28 656 with 3% discounted for a period of 25 years) and summing these two multiplications. For the study by Sonnenberg et al. (20), this summation amounted to additional savings per 100 000 individuals of $20 million for FOBT, $44 million for sigmoidoscopy, and $95 million for colonoscopy. FOBT and colonoscopy screening would thus be cost saving with the higher treatment costs. Sigmoidoscopy screening did not become cost saving, but the test costs assumed by Sonnenberg et al. for sigmoidoscopy screening were considerably higher than those in our study. For the study by Ladabaum et al. (57), the additional savings was $855 per individual. With these additional savings, the net costs of colonoscopy screening would decrease from $1150 per individual to $295 per individual, a similar decrease as estimated in our study.

Three earlier studies concluded that sigmoidoscopy and colonoscopy screening were cost saving (25,58,59). In this study, colonoscopy screening was not cost saving mainly because of the higher costs we assumed for colonoscopy. The cost estimates in this study were based on Medicare reimbursement rates, whereas those in the earlier studies reflect (European) costs in organized screening programs. In Europe, the newly available chemotherapies are as expensive as they are in the United States (60), but the screening test costs are lower (58,59,61). Therefore, treatment savings from screening in Europe would be comparable with those in the United States, although the screening costs are lower, making the net savings from screening in Europe even greater than those in the United States. For example, the current reimbursement rate for a screening colonoscopy in Germany is approximately one-third of that in the United States (59). Assuming the German reimbursement rate for colonoscopy, colonoscopy screening would become cost saving, even more so than Hemocult II screening. The immunochemical FOBT that is mostly used in Europe (OC-Hemodia Latex; Eiken Chemical Co, Tokyo, Japan) costs approximately the same as a Hemocult II test (62). Assuming these costs for immunochemical FOBT instead of the costs assumed in this analysis would make immunochemical FOBT even more cost saving than we estimated.

This analysis revealed that it takes 25–40 years after the start of a screening strategy before the treatment savings of that strategy outweigh its costs. This finding has important implications for insurance companies. If insurers anticipate that beneficiaries will not stay in their program for more than 5 years, they may be less inclined to cover a colorectal cancer screening program despite the long-term savings of such a program. In the United States, most...
### Appendix Table 1. Cost estimates and simulated number of life-years for colorectal cancer care per 1000 individuals for the near-future scenario by stage, phase of care, and screening strategy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Initial care</th>
<th>Continuous care</th>
<th>Terminal care, death from colorectal cancer</th>
<th>Terminal colorectal cancer care, death other causes</th>
<th>Treatment of colorectal cancer costs, $†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
<td>Stage II</td>
<td>Stage III</td>
<td>Stage IV</td>
<td>Stage I</td>
</tr>
<tr>
<td></td>
<td>28 668</td>
<td>39 700</td>
<td>79 801</td>
<td>79 801</td>
<td>2395</td>
</tr>
<tr>
<td>Life-years</td>
<td>No</td>
<td>5.6</td>
<td>10.0</td>
<td>6.6</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Hem II</td>
<td>11.4</td>
<td>4.8</td>
<td>2.7</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>iFOBT</td>
<td>11.1</td>
<td>3.6</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Flexsig</td>
<td>7.0</td>
<td>4.5</td>
<td>2.8</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Cscopy</td>
<td>7.3</td>
<td>3.7</td>
<td>2.2</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Flexsig + Hem II</td>
<td>8.7</td>
<td>3.5</td>
<td>2.0</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Costs for 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 the period between the initial and terminal phases of care. The terminal care phase of colorectal cancer patients was further subdivided into terminal care preceding colorectal cancer death and terminal care preceding death of other causes. 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 terminal phase. The remaining time was allocated to the initial phase, with no contribution to the continuing phase. Hem II = Hemoccult II; iFOBT = immunochemical fecal occult blood test; Flexsig = flexible sigmoidoscopy; Cscopy = colonoscopy; Flexsig + Hem II = flexible sigmoidoscopy and Hemoccult II.

† Average costs for colorectal cancer treatment per 1000 individuals in the population, excluding costs of diagnosis of symptom-detected cases. Calculated as sum of yearly cost inputs multiplied by the number of life-years with care by phase and stage of disease. For example, treatment costs in the No-screening strategy are equal to 5.6 × $28 668 + 10.0 × $39 700 + 6.6 × $79 801 + 3.3 × $79 801 + 65.2 × $2395 + 93.9 × $2237 + 59.8 × $3249 + 8.5 × $10 419 + 0.5 × $111 935 + 2.3 × $111 712 + 2.6 × $114 776 + 5.1 × $133 522 + 3.8 × $12 703 + 6.2 × $11 035 + 3.5 × $14 708 + 0.7 × $39 679 = $3 490 000. This number is slightly different from the number reported in Table 3 in the main text ($3 519 000), which also includes the costs for diagnosis of colorectal cancer ($29 000).
people move from having private health insurance before age 65 years to relying on government-subsidized coverage through Medicare at age 65 years. Our findings suggest that private insurance companies will bear most of the colorectal cancer screening costs, whereas Medicare will reap the most benefits in terms of treatment savings. Therefore, insurance companies may still not be inclined to implement screening programs, unless Medicare is willing to share some of the screening costs for those younger than 65 years. There are good incentives for Medicare to consider inclining to implement screening programs, unless Medicare is not cost-effective for colorectal cancer. Medicare at age 65 years. Our findings suggest that private insurers will be inclined to implement colorectal cancer screening programs, unless Medicare is not cost-effective for colorectal cancer. Consequently, FOBT, sigmoidoscopy, and the combination of sigmoidoscopy and FOBT will become cost saving and colonoscopy screening nearly so. The results are based on US data, but will, as reasoned before, probably also be applicable to Europe. Given the potential cost savings from screening, screening not only is desirable from the perspective of governments and insurance companies to reduce colorectal cancer incidence and mortality but also will help to contain the increasing costs for the management of colorectal cancer.

In conclusion, the increasingly costly management of colorectal cancer will approximately double the treatment savings from screening. Consequently, FOBT, sigmoidoscopy, and the combination of sigmoidoscopy and FOBT will become cost saving and colonoscopy screening nearly so. The results are based on US data, but will, as reasoned before, probably also be applicable to Europe. Given the potential cost savings from screening, screening not only is desirable from the perspective of governments and insurance companies to reduce colorectal cancer incidence and mortality but also will help to contain the increasing costs for the management of colorectal cancer.

References
4. Yabroff KR, Mariotto AB, Feuer E, Brown ML. Projections of the costs and long-term treatment savings involve the same organizing party and there will be more inclination to implement a colorectal cancer screening program.


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