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# Rescreening of Persons With a Negative Colonoscopy Result: Results From a Microsimulation Model

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**Background:** Persons with a negative result on screening colonoscopy are recommended to repeat the procedure in 10 years.

**Objective:** To assess the effectiveness and costs of colonoscopy versus other rescreening strategies after an initial negative colonoscopy result.

**Design:** Microsimulation model.

**Data Sources:** Literature and data from the Surveillance, Epidemiology, and End Results program.

**Target Population:** Persons aged 50 years who had no adenomas or cancer detected on screening colonoscopy.

**Time Horizon:** Lifetime.

**Perspective:** Societal.

**Intervention:** No further screening or rescreening starting at age 60 years with colonoscopy every 10 years, annual highly sensitive guaiac fecal occult blood testing (HSFOBT), annual fecal immunochemical testing (FIT), or computed tomographic colonography (CTC) every 5 years.

**Outcome Measures:** Lifetime cases of colorectal cancer, life expectancy, and lifetime costs per 1000 persons, assuming either perfect or imperfect adherence.

**Results of Base-Case Analysis:** Rescreening with any method substantially reduced the risk for colorectal cancer compared with no further screening (range, 7.7 to 12.6 lifetime cases per 1000 persons [perfect adherence] and 17.7 to 20.9 lifetime cases per 1000 persons [imperfect adherence] vs. 31.3 lifetime cases per 1000 persons with no further screening). In both adherence scenarios, the differences in life-years across rescreening strategies were small (range, 30 893 to 30 902 life-years per 1000 persons [perfect adherence] vs. 30 865 to 30 869 life-years per 1000 persons [imperfect adherence]). Rescreening with HSFOBT, FIT, or CTC had fewer complications and was less costly than continuing colonoscopy.

**Results of Sensitivity Analysis:** Results were sensitive to test-specific adherence rates.

**Limitation:** Data on adherence to rescreening were limited.

**Conclusion:** Compared with the currently recommended strategy of continuing colonoscopy every 10 years after an initial negative examination, rescreening at age 60 years with annual HSFOBT, annual FIT, or CTC every 5 years provides approximately the same benefit in life-years with fewer complications at a lower cost. Therefore, it is reasonable to use other methods to rescreen persons with negative colonoscopy results.

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Screening has been shown to reduce the incidence (1–3) and mortality (1–6) of colorectal cancer. Screening rates have increased substantially over the past decade (7, 8). Although alternative screening approaches are sanctioned by guidelines (9, 10), much of the rise in screening has been driven by increased use of colonoscopy (7).

Colonoscopy is a recommended method for routine screening for colorectal cancer (9, 10) and is used for follow-up of persons with positive results on other screening tests (9), such as fecal occult blood testing (FOBT), and for surveillance of those with a family or personal history of adenomas or colorectal cancer (11–13). Although colonoscopy is safe, it can cause complications (14–16) that may be fatal in rare cases (14, 15, 17). Moreover, it requires considerable resources. Thus, strategic use of colonoscopy should be a priority for health care delivery.

Studies of a population-based registry (18) and claims database (19) have shown that the risk for colorectal cancer in persons with a negative colonoscopy result is substantially lower than that for unscreened persons. This has prompted consideration of whether colonoscopy should be repeated 10 years after a negative result, as guidelines recommend (9, 10). These guidelines (and the mathematical models that have evaluated them) assume that persons use only 1 screening test throughout their lives. We assessed whether alternative rescreening strategies for persons who receive a negative result on screening colonoscopy could maximize benefits and minimize costs and harms.

## Methods

### Simulation Model of Colorectal Cancer

We used the Simulation Model of Colorectal Cancer (SimCRC), a model from the National Cancer Institute–sponsored Cancer Intervention and Surveillance Modeling Network (CISNET), to evaluate management strategies for persons aged 50 years with no adenomas or colorectal cancer detected at their first screening colonoscopy. The SimCRC has been used to inform the U.S. Preventive Services Task Force guidelines on colorectal cancer screening (20)

*See also:*

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***Context***

When screening colonoscopy yields a negative result, guidelines recommend repeating the procedure in 10 years.

***Contribution***

This simulation study found that rescreening every 5 years with computed tomographic colonography or rescreening every year with fecal occult blood testing or fecal immunochemical testing led to approximately the same life expectancy as rescreening every 10 years with colonoscopy but had fewer complications and lower cost.

***Caution***

The results of simulation studies depend on the assumptions that go into them.

***Implication***

It is reasonable to use techniques other than colonoscopy to rescreen persons who have a negative result on screening colonoscopy.

*—The Editors*

and coverage determinations by the Centers for Medicare & Medicaid Services for stool DNA testing (21) and computed tomographic colonography (CTC) screening (22).

The SimCRC is programmed in Microsoft Visual C++ 2010 Express (Microsoft, Seattle, Washington). Its specifications have been described elsewhere (23, 24). Briefly, the model's natural history component tracks the development of adenomas and their possible progression to invasive colorectal cancer in the absence of screening. A person enters the model at birth and may develop 1 or more adenomas over time (**Figure 1**). Adenomas may grow from small (1 to 5 mm) to medium (6 to 9 mm) to large (≥10 mm); some may progress to preclinical colorectal cancer. Preclinical cancer may progress in stages (I to IV) and may be detected by symptoms. Relative survival after cancer diagnosis depends on age, tumor site, and stage (25). Persons may die of causes other than colorectal cancer at any age (26).

The screening component of the SimCRC allows detection of adenomas and preclinical colorectal cancer based on the sensitivity of the screening test for lesions of that type and size and, for endoscopic tests, the depth of endoscope insertion. Nonadenomatous polyps are not explicitly modeled but are reflected in false-positive test rates, which allow persons to be referred for follow-up and undergo polypectomy for nonadenomatous polyps. We assume that each detected adenoma is removed, thereby preventing its potential progression to colorectal cancer. Persons with screen-detected colorectal cancer may have a lower risk for cancer death if cancer is detected at an earlier stage.

### Model Calibration

Because the natural history of colorectal cancer is largely unobserved, data to directly inform some model parameters are limited. We inferred their values by calibrating the model to data from autopsy studies on the prevalence, size, location, and multiplicity of adenomas (27–36) and the incidence of colorectal cancer from the Surveillance, Epidemiology, and End Results (SEER) program (25). We used SEER data from 1975 to 1979 because screening for colorectal cancer was rarely done during this period. The calibration approach and fit of the model to these data are provided elsewhere (22–24).

### Rescreening Strategies

We evaluated 5 rescreening strategies for persons with a negative colonoscopy result at age 50 years: no further screening; continuing colonoscopy every 10 years; or rescreening with annual highly sensitive guaiac FOBT (HSFOBT), annual fecal immunochemical testing (FIT), or CTC every 5 years. These strategies are guideline-sanctioned options for routine screening for persons aged 50 years (9, 10) and are therefore reasonable alternatives for rescreening persons with a negative colonoscopy result. Rescreening was assumed to begin at age 60 years (that is, 10 years after the negative colonoscopy result) for all strategies.

### Follow-up, Surveillance, and Adherence

We assumed that persons with positive HSFOBT or FIT results or a CTC scan indicating a lesion of 6 mm or larger were referred for follow-up colonoscopy. Because of the possibility of systematic positive results on HSFOBT or FIT due to, for example, persistent gastrointestinal bleeding unrelated to adenomas or colorectal cancer, persons with no adenomas or colorectal cancer detected at follow-up were assumed to discontinue HSFOBT or FIT and resume screening with colonoscopy every 10 years; those with positive CTC findings who had no adenomas or colorectal cancer detected at follow-up were assumed to continue CTC screening. If an adenoma was detected and removed at colonoscopy, the person began colonoscopy surveillance consistent with guidelines (13). We assumed that screening ended after age 75 years for persons with no history of adenomas or colorectal cancer (10), but surveillance continued for life for persons with a history of adenomas.

Reliable estimates for adherence are limited, yet adherence rates may have a major effect on results. Therefore, we considered 2 adherence scenarios: perfect and imperfect. Perfect adherence meant all persons complete each test. In the imperfect scenario, adherence after the initial negative colonoscopy result varied by test and incorporated within-subject correlation for adherence with rescreening (**Appendix Table 1**, available at www.annals.org). Adherence to HSFOBT was based on Department of Veterans Affairs data (37). Among men who exclusively received guaiac FOBT over a 5-year period, 42% received 1 test, 26% received 2, 18% received 3, and 14% received 4 or more. For FIT, we assumed per-test adherence to be 24% higher than with HSFOBT on the basis of the relative increase in uptake with FIT versus guaiac FOBT in a Dutch screening program (38). For the first rescreening colonoscopy, we assumed 52% average adherence on the basis of adherence to a 5-year repeated colonoscopy

among persons with a negative initial result (39). We further assumed that persons had, on average, only 1 of the 2 recommended rescreening colonoscopies (at age 60 or 70 years). For each follow-up and surveillance colonoscopy, we assumed 94% average adherence (2, 38). In the absence of data for CTC, we assumed that the average chance of adhering to the first CTC was the same as that for the repeated colonoscopy (52%) and that persons had an average of 2 CTC scans by age 75 years.

### Test Characteristics, Complications, and Costs

**Table 1** shows the sensitivity and specificity for each screening method. We assumed that 5% of persons would require 2 colonoscopies to achieve a complete examination and that the cecum was eventually examined in 95% of persons. The model incorporated the risks for complications, including perforation, bleeding, and other gastrointestinal events (**Table 2**). We assumed 51.9 deaths per 1000 perforations (17).

The costs of screening tests (**Table 1**) and complications (**Table 2**) were based on 2007 national average Medicare payments and beneficiary copayments (assuming these payments applied to persons aged 50 to 64 years) and patient time costs (**Appendix Table 2**, available at www.annals.org). Because Medicare does not currently reimburse for a screening CTC, we used the payment for a diagnostic study. The cost of bowel preparation was estimated at $23 (46) and an hour of time was valued at $18, the 2010 median hourly wage rate for civilians (45).

The stage- and phase-specific costs of care for colorectal cancer (**Table 2**) were based on analyses of SEER–Medicare linked data. The analyses used the method reported by Yabroff and colleagues (49), with stages reclassified according to the American Joint Committee on Cancer staging algorithm and costs in the last year of life stratified by cause of death. The estimates incorporate patient time costs and copayments (50).

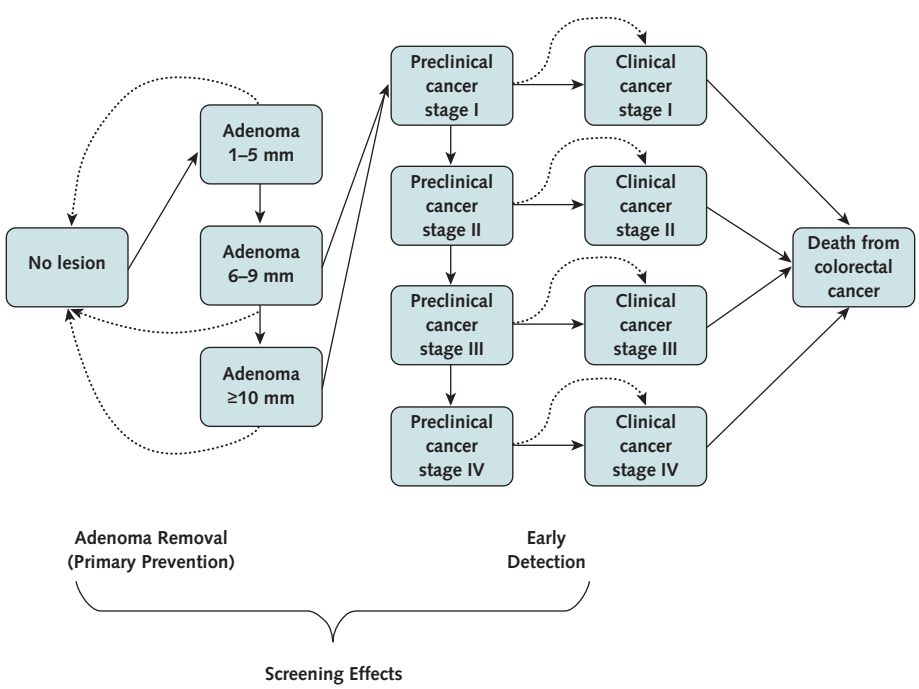
All costs are expressed in 2010 dollars and were inflation-adjusted as needed by using the U.S. Consumer Price Index (51).

### Analysis

We used the SimCRC to estimate the number of colorectal cancer cases and deaths, life-years, perforations and other complications, procedures requiring bowel preparation, and lifetime costs for colorectal screening and cancer care for a hypothetical cohort of persons aged 50 years with a negative screening colonoscopy result under 2 adherence scenarios and 5 rescreening strategies. Outcomes were tallied from the time of the negative result at age 50 years until death. Costs were tallied from the societal perspective.

We performed sensitivity analyses on colonoscopy test characteristics and cecal intubation rate, CTC test characteristics, colonoscopy complication rates, colonoscopy cost, costs of cancer care, and adherence rates (**Tables 1** and **2** and **Appendix Table 1** list the values used in the sensitivity analyses).

*Figure 1.* **The Simulation Model of Colorectal Cancer natural history model (*solid lines*) with the effect of screening noted (*dotted lines*).**




For a brief description of the model, see the Methods section.

*Table 1.* **Screening Test Characteristics and Costs Used in the Analyses**

| Analysis and Screening Test | Sensitivity, %* | | | | Specificity, % | Reference | Test Cost, $ | Cost Description |
|---|---|---|---|---|---|---|---|---|
| | Small Adenomas (1–5 mm) | Medium Adenomas (6–9 mm) | Large Adenomas (≥10 mm) | CRC | | | | |
| **Base-case analysis** | | | | | | | | |
| HSFOBT | 7 | 12 | 24 | 70 | 93 | 40 | 23 | 2007 national average Medicare reimbursement for fecal occult blood assay (HCPCS code G0394), adjusted to 2010 dollars, plus the cost of 1 hour of patient time† |
| FIT | 5 | 10 | 22 | 70 | 95 | 40 | 46 | 2007 national average Medicare reimbursement and beneficiary copayment for immunoassay-based fecal occult blood test (HCPCS code G0328), adjusted to 2010 dollars, plus the cost of 1 hour of patient time† |
| Colonoscopy | 75 | 85 | 95 | 95 | 84‡ | 39, 41 | 1153 without polypectomy | Weighted average of 2007 national average Medicare payments and beneficiary copayments for diagnostic colonoscopy (CPT code 45378), colon cancer screening for high-risk person (CPT code G0105), and colon cancer screening for non–high-risk person (CPT code G0121) (40), adjusted to 2010 dollars, plus the costs of colonic preparation§ and 24 hours of patient/escort time† |
| | | | | | | | 1347 with polypectomy | Weighted average of 2007 national average Medicare payments and beneficiary copayments for colonoscopy and biopsy (CPT code 45380), colonoscopy with submucosal injection (CPT code 45381), colonoscopy/control bleeding (CPT code 45382), lesion removal colonoscopy—fulguration (CPT code 45383), lesion removal colonoscopy—hot biopsy (CPT code 45384), and lesion removal colonoscopy—snare polypectomy (CPT code 45385) (40), adjusted to 2010 dollars, plus the costs of colonic preparation§ and 24 hours of patient/escort time† |
| CTC with ≥6-mm threshold for colonoscopy referral | Not provided‖ | 57¶ | 84 | 84** | 88†† | 42 | 530 | 2010 national average Medicare reimbursement‡‡ and beneficiary copayment for a diagnostic CTC (CPT code 74261), plus the costs of colonic preparation§ and 11 hours of patient time† |
| **Sensitivity analysis§§** | | | | | | | | |
| Colonoscopy‖‖ | 60 | 68 | 76 | 76 | 84‡ | Assumption | 577–5765 without polypectomy; 770–5959 with polypectomy | 0.5–5 times the base-case estimate of colonoscopy without polypectomy, plus the incremental cost of polypectomy |
| CTC with ≥6-mm threshold for colonoscopy referral | Not provided‖ | 84¶ | 92 | 95 | 80†† | 43–44 | 530 | Cost estimate was not varied from the base-case value |

CPT = Current Procedural Terminology; CRC = colorectal cancer; CTC = computed tomographic colonography; FIT = fecal immunochemical test; HCPCS = Healthcare Common Procedure Coding System; HSFOBT = highly sensitive guaiac fecal occult blood test.

* Provided per person for HSFOBT and FIT and per lesion for colonoscopy and CTC.

† The value of an hour of patient or caregiver time was assumed to be $18, the 2010 U.S. median hourly wage rate for civilians (45). **Appendix Table 2** (available at www.annals.org) details the amounts of patient and escort time assumed for each test.

‡ The lack of specificity reflects the detection of nonadenomatous lesions, which induce polypectomy and biopsy costs.

§ The cost of colonic preparation is estimated at $23 (the 2010 average wholesale price of GoLYTELY [Braintree Laboratories, Braintree, Massachusetts]) (46).

‖ Adenoma size is smaller than the referral threshold for a colonoscopy.

¶ Sensitivity for CTC for medium adenomas was calculated from published tables (42).

** Sensitivity for CRC was assumed to be the same as for large adenomas.

†† The lack of specificity with CTC reflects the detection of nonadenomatous lesions, artifacts, and adenomas smaller than the 6-mm threshold for referral to colonoscopy.

‡‡ Reimbursement includes implementation of the Outpatient Prospective Payment cap on the technical component of imaging procedures (47).

§§ The sensitivity analysis of colonoscopy test characteristics was performed separately from that of colonoscopy cost.

‖‖ Assuming a 20% reduction in sensitivity from the base-case values. For the sensitivity analysis, we also assumed that only 80% of colonoscopies are complete to the cecum (vs. 95% in the base-case analysis).

*Table 2.* **Complication Rates, Complication Costs, and Stage- and Phase-Specific Costs of CRC Care**

| Analysis and Variable | Risk per 100 000 Persons, by Age Group | | | | | | | Cost† | |
|---|---|---|---|---|---|---|---|---|---|
| | 50–65 y* | 66–69 y | 70–74 y | 75–79 y | 80–84 y | ≥85 y | Reference | Value, $ | Reference |
| **Complication rates and costs** | | | | | | | | | |
| Base-case analysis | | | | | | | | | |
| Colonoscopy | | | | | | | | | |
| Perforation | 36 | 36 | 42 | 52 | 64 | 87 | 16 | 15 985 | 40 |
| Bleeding with transfusion | 89 | 89 | 103 | 127 | 156 | 214 | 16 | 7784 | 40 |
| Bleeding without transfusion | 245 | 245 | 284 | 351 | 430 | 589 | 16 | 1775 | 40 |
| Other gastrointestinal events | 320 | 320 | 400 | 540 | 730 | 880 | 16 | 1195 | 40 |
| CTC | | | | | | | | | |
| Perforation | 5 | 5 | 5 | 5 | 5 | 5 | 48 | 15 985 | 40 |
| Sensitivity analysis | | | | | | | | | |
| Colonoscopy | | | | | | | | | |
| Perforation | 28 | 28 | 32 | 40 | 49 | 67 | 16 | – | – |
| Bleeding with transfusion | 16 | 16 | 18 | 22 | 27 | 37 | 16 | – | – |
| Bleeding without transfusion | 43 | 43 | 50 | 61 | 75 | 103 | 16 | – | – |
| Other gastrointestinal events | 34 | 34 | 42 | 57 | 77 | 93 | 16 | – | – |

| | Annual Costs of Cancer Care, by Phase, $‡ | | | | Source |
|---|---|---|---|---|---|
| | Initial | Continuing | Terminal, CRC Death | Terminal, Non-CRC Death | |
| **Costs of cancer care, by stage** | | | | | |
| Base-case analysis | | | | | Yabroff R, Brown M. Personal communication |
| Stage I | 34 547 | 2907 | 59 719 | 18 473 | |
| Stage II | 46 145 | 2734 | 59 484 | 16 720 | – |
| Stage III | 55 870 | 3793 | 62 705 | 20 581 | – |
| Stage IV | 72 533 | 11 352 | 82 413 | 46 834 | – |
| Sensitivity analysis | | | | | |
| Stage I | 43 184 | 3634 | 74 648 | 23 091 | Assumption§ |
| Stage II | 57 681 | 3417 | 74 355 | 20 901 | – |
| Stage III | 69 838 | 4741 | 78 382 | 25 726 | – |
| Stage IV | 90 667 | 14 189 | 103 017 | 58 542 | – |

CRC = colorectal cancer; CTC = computed tomographic colonography.
* The risks for colonoscopy complications were based on a study of Medicare beneficiaries (16). We assumed that the risks for persons aged ≤65 y were the same as for those aged 66–69 y, the proportion of serious gastrointestinal events that were perforations (vs. bleeding) did not vary by age, and bleeding alone was never fatal.
† Costs of complications were not varied in the sensitivity analysis.
‡ Estimates include beneficiary copayments and patient time costs. The initial phase is the first 12 mo after diagnosis, the terminal phase is the final 12 mo of life, and the continuing phase is all months between the initial and terminal phases, annualized. Simulated persons who survived ≤12 mo were assigned only terminal costs (or a fraction thereof); those who survived >12 mo but ≤24 mo were assigned terminal and initial costs (or a fraction thereof); and those who survived >24 mo were assigned terminal, initial, and continuing costs.
§ We assumed a 25% increase compared with the base-case estimates.


## Role of the Funding Source

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## RESULTS

### Base-Case Analysis

#### *Perfect Adherence*

The SimCRC predicts that 15% of persons with a negative colonoscopy result at age 50 years would have colonoscopy-detected adenomas or colorectal cancer at age 60 years. The corresponding estimate for persons with a positive result at age 50 years is 31%, assuming no surveillance colonoscopies are performed between ages 50 and 60 years.

With no further screening, 31.3 per 1000 persons aged 50 years with negative screening colonoscopy results would be diagnosed with colorectal cancer in their lifetimes and 11.9 per 1000 persons would die of the disease. Compared with no further screening, all rescreening strategies substantially reduced colorectal cancer risk. With perfect adherence, continuing colonoscopy screening every 10 years yielded the fewest cancer cases (7.7 per 1000 persons) and deaths (2.4 per 1000 persons) but the most perforations and other complications (1.1 and 20.9 per 1000 persons, respectively) (**Table 3**). Rescreening with CTC yielded slightly more cases (9.3 per 1000 persons) and deaths (2.7 per 1000 persons) than continuing colonoscopy and nearly halved the rates of perforation and other complications (0.7 and 10.1 per 1000 persons, respectively) but had the most procedures requiring bowel preparation (3982 per 1000 persons with CTC vs. 2592 per 1000 persons with colonoscopy). Rescreening with HSFOBT or FIT yielded 11.4 and 12.6 cases per 1000

*Table 3.* **CRC Cases, CRC Deaths, Life-Years, Perforations, Other Complications, Procedures Requiring Bowel Preparation, and Lifetime Costs per 1000 Persons Aged 50 Years With a Negative Screening Colonoscopy Result, by Adherence Scenario and Rescreening Strategy***

| Adherence Scenario and Rescreening Strategy | Outcomes per 1000 Persons | | | | | | |
|---|---|---|---|---|---|---|---|
| | CRC Cases | CRC Deaths† | Life-Years | Perforations | Other Complications‡ | Procedures Requiring Bowel Preparation§ | Lifetime Costs, $ *(thousands)*‖ |
| **Perfect adherence** | | | | | | | |
| Continue with colonoscopy every 10 y | 7.7 | 2.4 | 30 902 | 1.1 | 20.9 | 2592 | 3840 |
| Switch to CTC every 5 y | 9.3 | 2.7 | 30 899 | 0.7 | 10.1 | 3982 | 3673 |
| Switch to yearly HSFOBT | 11.4 | 3.2 | 30 895 | 0.7 | 13.0 | 1557 | 3069 |
| Switch to yearly FIT | 12.6 | 3.5 | 30 893 | 0.6 | 10.9 | 1282 | 3059 |
| No further screening | 31.3 | 11.9 | 30 821 | 0.0 | 0.0 | 31 | 2446 |
| **Imperfect adherence** | | | | | | | |
| Continue with colonoscopy every 10 y | 17.7 | 6.4 | 30 867 | 0.6 | 11.0 | 1361 | 3084 |
| Switch to CTC every 5 y | 17.8 | 6.1 | 30 869 | 0.4 | 5.6 | 2135 | 2993 |
| Switch to yearly HSFOBT | 20.9 | 6.7 | 30 865 | 0.3 | 5.6 | 672 | 2588 |
| Switch to yearly FIT | 20.5 | 6.4 | 30 868 | 0.3 | 5.2 | 626 | 2634 |
| No further screening | 31.3 | 11.9 | 30 821 | 0.0 | 0.0 | 31 | 2446 |

CRC = colorectal cancer; CTC = computed tomographic colonography; FIT = fecal immunochemical test; HSFOBT = highly sensitive guaiac fecal occult blood test.
* Assumes that screening resumes at age 60 y and ends after age 75 y and that surveillance of persons with a history of adenomas continues for life.
† Includes deaths from screening complications.
‡ Bleeding and other gastrointestinal events.
§ Includes CTCs and screening, diagnostic, and surveillance colonoscopies. Does not include procedures performed after cancer diagnosis.
‖ Includes costs of screening, follow-up, surveillance, complications, diagnosis of symptomatic cases, and cancer care.

persons and 3.2 and 3.5 deaths per 1000 persons, respectively, with complication rates similar to those of CTC. The number of procedures requiring bowel preparation was 1557 per 1000 persons for HSFOBT and 1282 per 1000 persons for FIT. All rescreening strategies yielded similar life-years, ranging from 30 893 per 1000 persons for FIT to 30 902 per 1000 persons for colonoscopy (**Table 3**), a difference of 3 days per person.

With lifetime screening- and cancer-related costs of $3840 per person, continuing colonoscopy screening was the most costly strategy (**Table 3**). Compared with continuing colonoscopy, cost savings were $166 per person with CTC, $771 per person with HSFOBT, and $781 per person with FIT. **Appendix Table 3** (available at www.annals.org) lists discounted life-years and costs.

### *Imperfect Adherence*

With imperfect adherence, continuing colonoscopy yielded the fewest colorectal cancer cases (17.7 per 1000 persons), followed closely by switching to CTC (17.8 per 1000 persons) (**Table 3**). Switching to CTC yielded the fewest cancer deaths (6.1 per 1000 persons), compared with 6.4 deaths per 1000 persons with colonoscopy, 6.4 deaths per 1000 persons with FIT, and 6.7 deaths per 1000 persons with HSFOBT. Continuing colonoscopy yielded the highest rate of perforation and other complications (0.6 and 11.0 per 1000 persons, respectively). For CTC, these rates were 0.4 and 5.6 per 1000 persons, respectively, but CTC required more procedures with bowel preparation (2135 per 1000 persons vs. 1361 per 1000 persons with colonoscopy). The FOBT strategies had perforation and complication risks similar to those of CTC (0.3 and 5.2 to 5.6 per 1000 persons, respectively) but required fewer procedures with bowel preparation (626 to 672 per 1000 persons). The differences in life-years across rescreening strategies were small, ranging from 30 865 per 1000 persons for HSFOBT to 30 869 per 1000 persons for CTC, a difference of 1 day per person.

All other strategies yielded lower screening- and cancer-related costs than continuing colonoscopy ($3084 per person with a negative colonoscopy result at age 50 years [**Table 3**]), with cost savings from switching from colonoscopy of $91 per person for CTC, $450 per person for FIT, and $495 per person for HSFOBT.

## Sensitivity Analysis

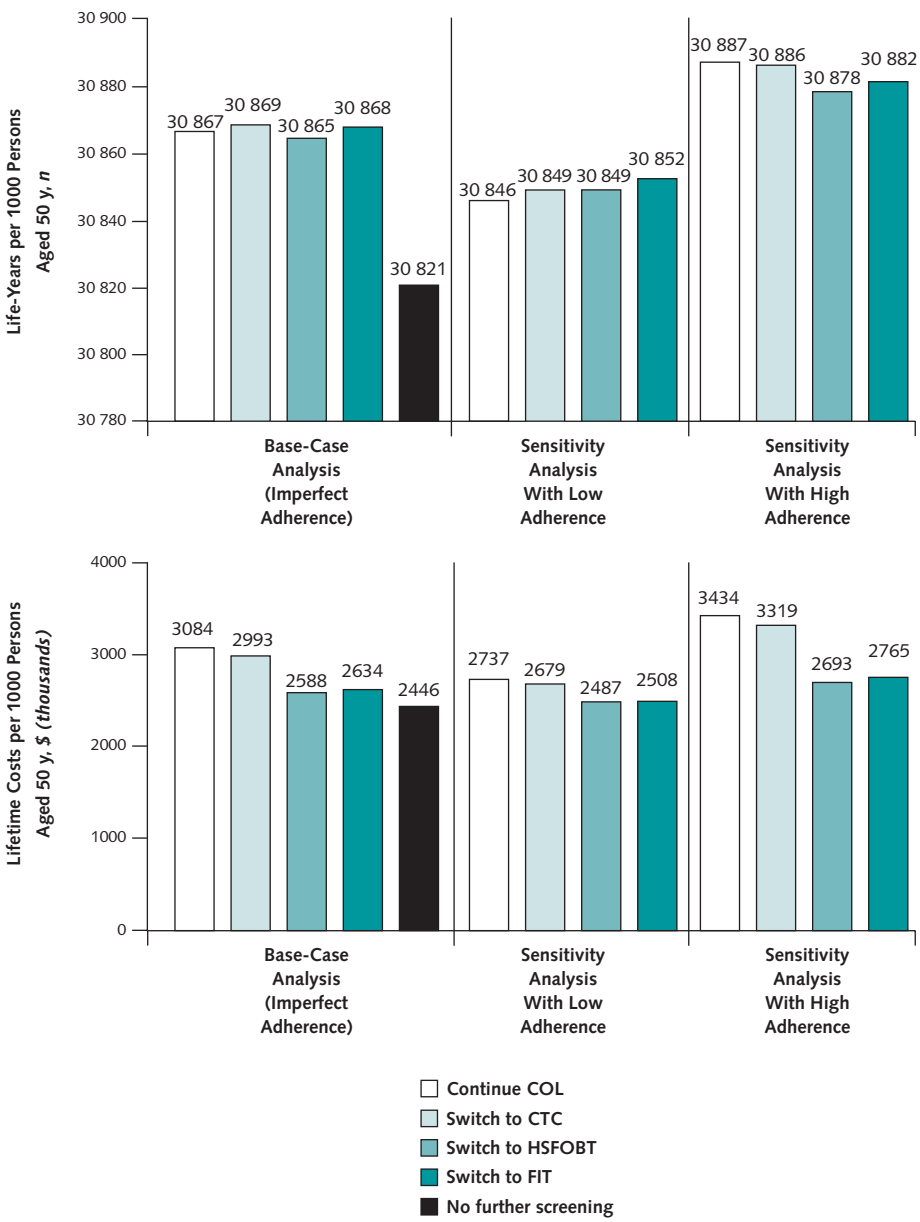
Although the absolute number of life-years changed with assumptions about colonoscopy test characteristics and cecal intubation rate (**Appendix Table 4**, available at www.annals.org), CTC test characteristics (**Appendix Table 5**, available at www.annals.org), and colonoscopy risks (data not shown), the differences in life-years across rescreening strategies remained small (≤4 days per person). The cost savings from rescreening with a strategy other than colonoscopy decreased.

Because colonoscopies are performed in all rescreening strategies, the lifetime costs of all strategies changed with the cost of colonoscopy. If colonoscopy cost was one half of the base-case estimate, all rescreening strategies (including continuing colonoscopy) yielded similar lifetime costs. As colonoscopy cost increased above the base-case estimate,

the cost savings from rescreening with other methods increased (**Appendix Figure 1**, available at www.annals.org). Because there were few cancer cases, the findings were relatively insensitive to higher costs of cancer care (**Appendix Figure 2**, available at www.annals.org).

The results were sensitive to test-specific imperfect adherence rates. If adherence to each rescreening strategy was simultaneously lower or simultaneously higher than in the base-case, the life-years remained similar across tests (**Figure 2**, *top*). However, if adherence was higher than in the base case for some strategies and lower for others, the differences in life-years across tests increased to a maximum of 40 years per 1000 persons (30 846 life-years per 1000 persons with low adherence to continued colonoscopy vs. 30 886 life-years per 1000 persons with high adherence to rescreening with CTC), or 15 days per person. In such a case, switching to CTC was no longer cost-saving (lifetime costs, $2737 per person with low adherence to continued

***Figure 2.*** **Life-years (*top*) and lifetime costs (*bottom*) per 1000 persons aged 50 years with a negative screening colonoscopy result and imperfect adherence.**




**Appendix Table 1** (available at www.annals.org) provides the assumptions for the sensitivity analysis on adherence rates. COL = colonoscopy; CTC = computed tomographic colonography with ≥6-mm threshold for colonoscopy referral; FIT = fecal immunochemical test; HSFOBT = highly sensitive guaiac fecal occult blood test.

colonoscopy vs. $3319 per person with high adherence to rescreening with CTC) (**Figure 2**, *bottom*).

## DISCUSSION

Colonoscopy is a well-accepted strategy for preventing colorectal cancer death (52), and efforts to promote its use have increased the proportion of Americans who report having had the procedure (7, 8). However, the value of alternative rescreening strategies for persons with a negative initial result is uncertain. Ideally, a randomized trial would address this question but such a study is unlikely to be done. Results from a validated simulation model can therefore be informative.

It is debatable whether policy decisions and clinical recommendations should be informed by analyses that assume perfect adherence rates or those that incorporate imperfect rates that are more realistic but poorly described. We therefore evaluated both adherence scenarios. Of note, our conclusions were similar across scenarios. Compared with the currently recommended strategy of continuing colonoscopy every 10 years after an initial negative result, all other rescreening options we examined provide approximately the same benefit in life-years with fewer complications at a lower cost. Therefore, it is reasonable to use other methods to rescreen persons with negative colonoscopy results.

Our findings have several implications. Colonoscopy has become the accepted standard for colorectal cancer screening in the United States; however, there are not enough trained colonoscopists to perform all of the necessary screening procedures. Rescreening with methods other than colonoscopy may help solve this shortage because it would free up scarce colonoscopy personnel to perform more primary screening examinations.

From a policy perspective, the potential cost savings (in 2010 dollars) from switching to FIT or HSFOBT after a negative screening colonoscopy result rather than continuing colonoscopy are considerable. For every person who switches, $450 to $495 is saved over his or her lifetime (assuming imperfect adherence). Data from the 2008 National Health Information Survey (53) indicate that approximately 40% of persons aged 50 to 54 years had an endoscopy within the recommended intervals, and 92% reported colonoscopy as their most recent endoscopic procedure. On average, no adenomas or colorectal cancer is detected in 82% of initial screening colonoscopies (39). This suggests that if the estimated 6.5 million persons aged 50 to 54 years who had negative results in 2008 (40% × 92% × 82% × 21.5 million persons aged 50 to 54 years [54]) were rescreened with yearly FIT or HSFOBT, $3 billion could be saved over the course of their lives. The cost savings from switching to CTC every 5 years after a negative result are lower yet still substantial ($0.6 billion), although these savings could be at least partially offset by the costs of working up extracolonic findings.

Our analysis has limitations. We did not consider the risks and costs of radiation exposure from CTC because the radiation-related cancer risk was estimated to be very small compared with the reduction in colorectal cancer risk from CTC screening (55). We also did not include the risks, potential benefits, or costs associated with incidental findings detected by CTC. The prevalence of clinically significant incidental findings in asymptomatic populations ranges from 7% to 11%, and the average cost of their work-up in U.S. settings has been estimated at $28 to $99 per person screened (56). When these costs are confirmed, as well as any potential cost savings (and gains in life expectancy) associated with earlier detection of clinically significant disease, they should be included in the assessment of a CTC strategy.

Data from several studies (19, 57–59) suggest that colonoscopy may offer less protection from right-sided than from left-sided disease. We did not incorporate this finding into our analysis because the reasons for the difference remain unclear but probably involve a combination of technical and biological factors that may affect the location-specific effectiveness of colonoscopy as well as other screening methods. When additional data that confirm the magnitude of the effect and clarify the mechanism become available, they should be incorporated into an assessment of all methods.

Data on test-specific adherence are limited, particularly among persons who already had a colonoscopy and in whom no adenomas or colorectal cancer was detected. Imperiale and colleagues (39) reported 52% adherence to repeated colonoscopy 5 years after a negative result. It is unclear whether adherence 10 years after a negative colonoscopy result would differ. In the absence of data for CTC, we assumed that adherence to the first CTC was equal to that of a repeated colonoscopy (52%) and that persons have an average of 2 CTC scans by age 75 years. Many have suggested that for initial screening, adherence may be higher to CTC than to colonoscopy (60–62), although such claims have been based on small single-institution studies. A Dutch population-based study (63) found that screening uptake was higher for CTC than for colonoscopy. However, CTC was performed without cathartic bowel preparation. It is unclear whether uptake would be higher in persons who had cathartic bowel preparation (as modeled in our analysis). Our estimates of adherence with FOBT were based on data from a veteran population over a 5-year period; adherence may differ among the general screening population and over longer periods. Furthermore, adherence to FOBT may differ among persons who had already opted for colonoscopy.

In conclusion, compared with the currently recommended strategy of continuing colorectal cancer screening with colonoscopy every 10 years after an initial negative result, rescreening at age 60 years with yearly HSFOBT, yearly FIT, or CTC every 5 years yield similar life-years with fewer complications and lower cost. Therefore, it is

reasonable to use other methods to rescreen persons with negative colonoscopy results.

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*Appendix Table 1.* **Average Number of Additional Screening Tests, by Strategy and Adherence Group***

| Analysis and Rescreening Strategy | Recommended Additional Screening Tests, *n*†‡ | Average Additional Screening Tests, by Adherence Group, *n*‡ | | |
|---|---|---|---|---|
| | | Low | Moderate | High |
| **Base-case analysis** | | | | |
| Yearly HSFOBT | 16 | 2.8 | 5.6 | 8.4 |
| Yearly FIT | 16 | 3.5 | 6.9 | 10.4 |
| CTC every 5 y | 4 | 1.0 | 2.0 | 3.0 |
| Colonoscopy every 10 y | 2 | 0.5 | 1.0 | 1.5 |

| | | Average Additional Screening Tests, *n*§ |
|---|---|---|
| **Sensitivity analysis** | | |
| Yearly HSFOBT | 16 | |
| Low adherence | | 2.8 |
| High adherence | | 8.4 |
| Yearly FIT | 16 | |
| Low adherence | | 3.5 |
| High adherence | | 10.4 |
| CTC every 5 y | 4 | |
| Low adherence | | 1.0 |
| High adherence | | 3.0 |
| Colonoscopy every 10 y | 2 | |
| Low adherence | | 0.5 |
| High adherence | | 1.5 |

CTC = computed tomographic colonography; FIT = fecal immunochemical test; HSFOBT = highly sensitive guaiac fecal occult blood test.
* To account for correlation in a person's adherence to repeated procedures, we assumed that the population consisted of 3 equally sized groups: persons with low adherence, those with moderate adherence, and those with high adherence. In the base-case analysis, the chance of adhering to a given scheduled test varied by adherence group, yielding the number of additional screening tests shown here.
† Recommendations from references 9 and 10.
‡ Among persons who resume screening at age 60 y, survive to the last recommended age of screening (75 y), and have no findings.
§ For each method, the average number of tests for the low and high scenarios are the average number of tests for the low and high adherence groups, respectively, in the base-case analysis. For the sensitivity analysis, we assumed that the adherence was the same across the 3 groups.

## *Appendix Table 2.* Assumptions for Time Costs for Screening and Complications

| Variable | Waking Hours of Patient/Escort Time | Source and Description |
|---|---|---|
| **Screening test** | | |
| HSFOBT | 1 | Assumption |
| FIT | 1 | Assumption |
| Colonoscopy | 24 | Based on an estimate of the amount of time from initiation of colonic preparation to return to routine activities after colonoscopy (64). We doubled the estimated travel and procedure time to account for the escort's time and subtracted 16 h of sleep. |
| CTC | 11 | In the absence of data on the patient time requirements for CTC, we used an estimate of the amount of time spent on colonoscopy (64), excluding the time components that are not relevant for CTC (that is, time associated with sedation and onsite recovery, time from recovery to return to routine activities, and escort time) and 8 h of sleep. |
| **Complication** | | |
| Perforation | 160 | Assumption (10 d, minus 8 h/d of sleep) |
| Bleeding requiring transfusion | 112 | Assumption (7 d, minus 8 h/d of sleep) |
| Bleeding not requiring transfusion | 64 | Assumption (4 d, minus 8 h/d of sleep) |
| Other gastrointestinal complications | 32 | Assumption (2 d, minus 8 h/d of sleep) |

CTC = computed tomographic colonography; FIT = fecal immunochemical test; HSFOBT = highly sensitive guaiac fecal occult blood test.

## *Appendix Table 3.* Discounted Life-Years and Discounted Lifetime Costs per 1000 Persons Aged 50 Years With a Negative Screening Colonoscopy Result, by Adherence Scenario and Rescreening Strategy*

| Adherence Scenario and Rescreening Strategy | Outcomes per 1000 Persons Aged 50 Years | |
|---|---|---|
| | Life-Years | Lifetime Costs, *$ (thousands)*† |
| **Perfect adherence** | | |
| Continue with colonoscopy every 10 y | 19 723 | 2212 |
| Switch to CTC every 5 y | 19 722 | 2046 |
| Switch to yearly HSFOBT | 19 720 | 1611 |
| Switch to yearly FIT | 19 720 | 1602 |
| No further screening | 19 693 | 1021 |
| **Imperfect adherence** | | |
| Continue with colonoscopy every 10 y | 19 710 | 1607 |
| Switch to CTC every 5 y | 19 710 | 1527 |
| Switch to yearly HSFOBT | 19 709 | 1229 |
| Switch to yearly FIT | 19 710 | 1267 |
| No further screening | 19 693 | 1021 |

CTC = computed tomographic colonography; FIT = fecal immunochemical test; HSFOBT = highly sensitive guaiac fecal occult blood test.
* Life-years and costs discounted at 3% per year. Assumes that screening resumes at age 60 y and ends after age 75 y and that surveillance of persons with a history of adenomas continues for life.
† Includes costs of screening, follow-up, surveillance, complications, diagnosis of symptomatic cases, and cancer care.

## *Appendix Table 4.* Sensitivity Analysis of Colonoscopy Test Characteristics and Cecal Intubation Rate*

| Adherence Scenario and Rescreening Strategy | Outcomes per 1000 Persons Aged 50 y With a Negative Colonoscopy Result | | | | | | |
|---|---|---|---|---|---|---|---|
| | CRC Cases | CRC Deaths† | Life-Years | Perforations | Other Complications‡ | Procedures Requiring Bowel Preparation§ | Lifetime Costs, $ *(thousands)*‖ |
| **Perfect adherence** | | | | | | | |
| Continue with colonoscopy every 10 y | 15.4 | 5.3 | 30 849 | 1.1 | 20.3 | 2546 | 4489 |
| Switch to CTC every 5 y | 16.2 | 5.3 | 30 849 | 0.7 | 10.4 | 4026 | 4384 |
| Switch to yearly HSFOBT | 19.7 | 6.4 | 30 839 | 0.7 | 12.6 | 1538 | 3793 |
| Switch to yearly FIT | 20.8 | 6.7 | 30 837 | 0.6 | 10.6 | 1277 | 3793 |
| No further screening | 39.7 | 15.6 | 30 758 | 0.0 | 0.0 | 40 | 3222 |
| **Imperfect adherence** | | | | | | | |
| Continue with colonoscopy every 10 y | 26.2 | 9.8 | 30 808 | 0.6 | 10.5 | 1332 | 3806 |
| Switch to CTC every 5 y | 25.7 | 9.3 | 30 812 | 0.4 | 5.7 | 2162 | 3749 |
| Switch to yearly HSFOBT | 29.3 | 10.2 | 30 806 | 0.3 | 5.4 | 674 | 3351 |
| Switch to yearly FIT | 28.8 | 9.8 | 30 810 | 0.3 | 5.2 | 634 | 3397 |
| No further screening | 39.7 | 15.6 | 30 758 | 0.0 | 0.0 | 40 | 3222 |

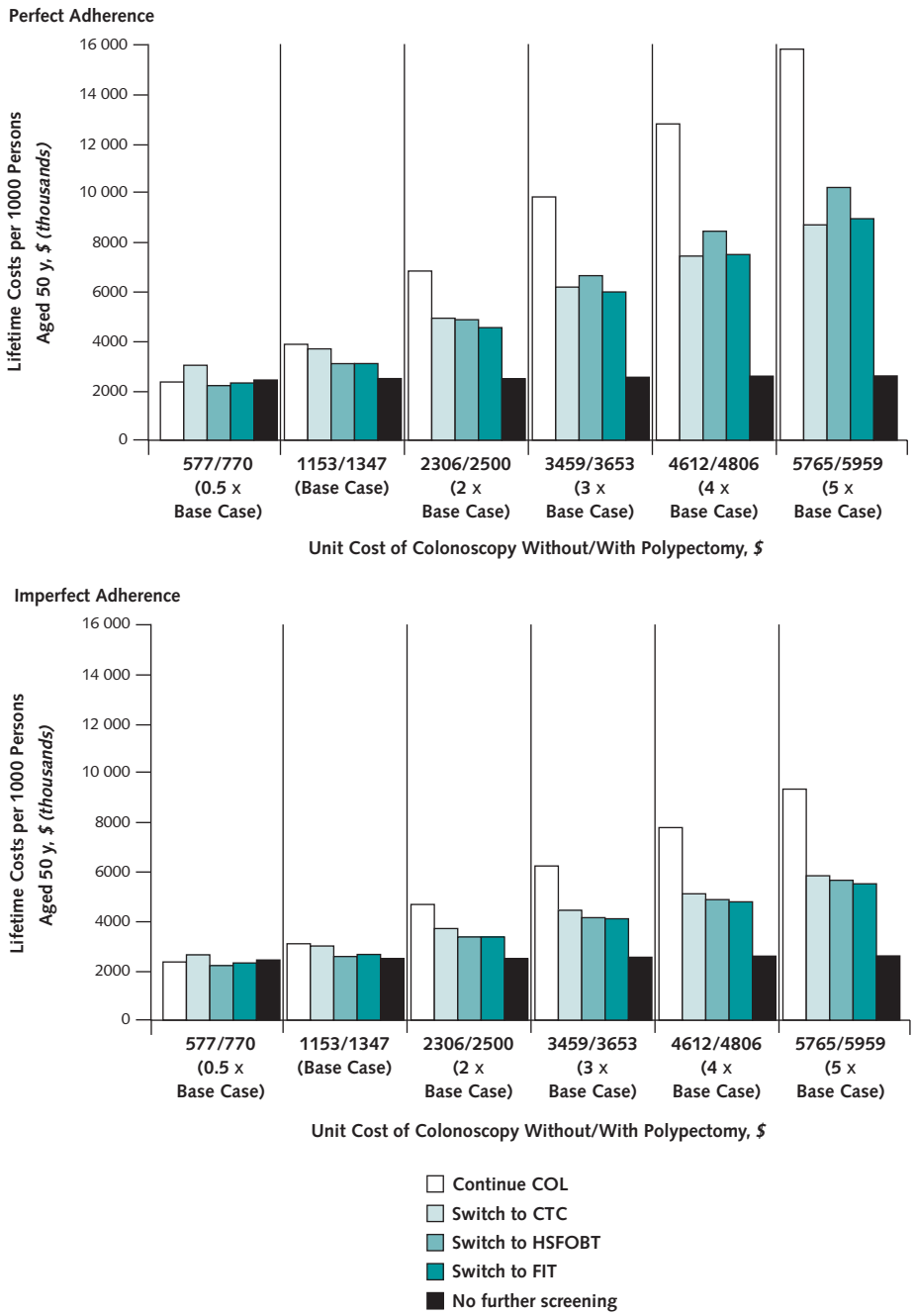
CRC = colorectal cancer; CTC = computed tomographic colonography; HSFOBT = highly sensitive guaiac fecal occult blood test; FIT = fecal immunochemical test.
* Assumes that screening resumes at age 60 y and ends after age 75 y and that surveillance of persons with a history of adenomas continues for life. **Table 1** lists values used in the sensitivity analysis.
† Includes deaths from screening complications.
‡ Bleeding and other gastrointestinal events.
§ Includes CTCs and screening, diagnostic, and surveillance colonoscopies. Does not include procedures performed after cancer diagnosis.
‖ Includes costs of screening, follow-up, surveillance, complications, diagnosis of symptomatic cases, and cancer care.

## *Appendix Table 5.* Sensitivity Analysis of CTC Characteristics*

| Adherence | Outcomes per 1000 Persons Aged 50 y With a Negative Colonoscopy Result | | | | | | |
|---|---|---|---|---|---|---|---|
| | CRC Cases | CRC Deaths† | Life-Years | Perforations | Other Complications‡ | Procedures Requiring Bowel Preparation§ | Lifetime Costs, $ *(thousands)*‖ |
| Perfect | 7.5 | 2.1 | 30 904 | 0.8 | 12.8 | 4113 | 3834 |
| Imperfect | 16.2 | 5.5 | 30 873 | 0.4 | 7.2 | 2262 | 3073 |

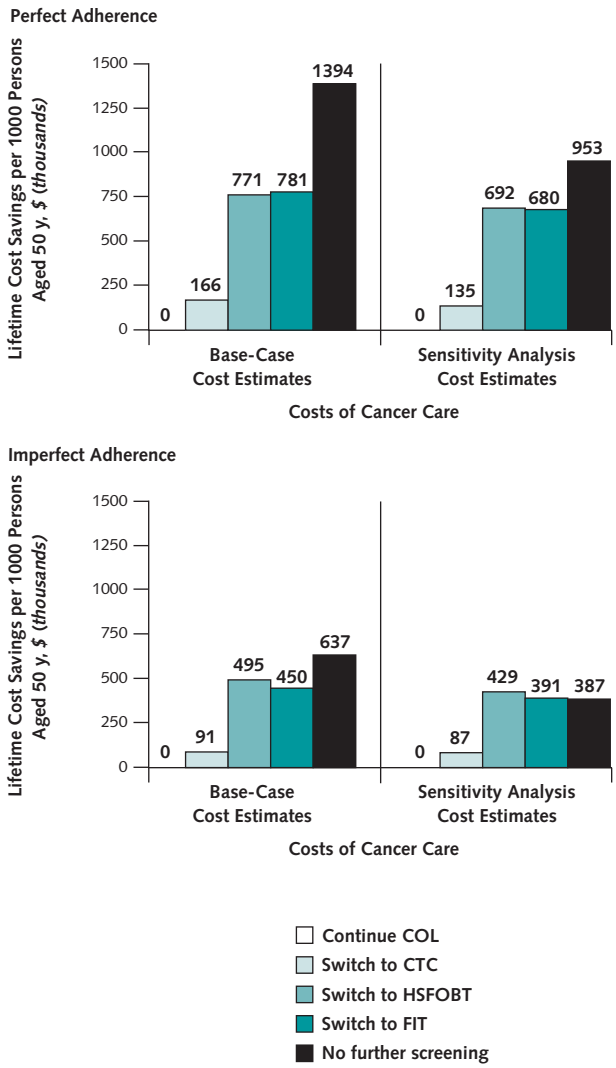
CRC = colorectal cancer; CTC = computed tomographic colonography.
* Assumes that screening resumes at age 60 y and ends after age 75 y and that surveillance of persons with a history of adenomas continues for life. **Table 1** lists values used in the sensitivity analysis.
† Includes deaths from screening complications.
‡ Bleeding and other gastrointestinal events.
§ Includes CTCs and screening, diagnostic, and surveillance colonoscopies. Does not include procedures performed after cancer diagnosis.
‖ Includes costs of screening, follow-up, surveillance, complications, diagnosis of symptomatic cases, and cancer care.

*Appendix Figure 1.* **Sensitivity analysis on the unit cost of a colonoscopy, assuming perfect (*top*) or imperfect (*bottom*) adherence.**




Lifetime costs of rescreening strategies for persons with a negative screening colonoscopy result at age 50 years. COL = colonoscopy; CTC = computed tomographic colonography with ≥6-mm threshold for colonoscopy referral; FIT = fecal immunochemical test; HSFOBT = highly sensitive guaiac fecal occult blood test.

*Appendix Figure 2.* **Sensitivity analysis on the costs of cancer care, assuming perfect (*top*) or imperfect (*bottom*) adherence.**




Lifetime cost savings from using methods other than colonoscopy every 10 y. COL = colonoscopy; CTC = computed tomographic colonography with ≥6-mm threshold for colonoscopy referral; FIT = fecal immunochemical test; HSFOBT = highly sensitive guaiac fecal occult blood test.