Evaluating Test Strategies for Colorectal Cancer Screening: A Decision Analysis for the U.S. Preventive Services Task Force

Ann G. Zauber, PhD; Iris Lansdorp-Vogelaar, MS; Amy B. Knudsen, PhD; Janneke Wilschut, MS; Marjolein van Ballegooijen, MD, PhD; and Karen M. Kuntz, ScD

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

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

Design: Decision analysis using 2 colorectal cancer microsimulation models from the Cancer Intervention and Surveillance Modeling Network.

Data Sources: Derived from the literature.

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

Perspective: Societal.

Time Horizon: Lifetime.

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

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

Results of Base-Case Analysis: Beginning screening at age 50 years was consistently better than at age 60. Decreasing the stop age from 85 to 75 years decreased life-years gained by 1% to 4%, whereas colonoscopy use decreased by 4% to 15%. Assuming equally high adherence, 4 strategies provided similar life-years gained: colonoscopy every 10 years, annual Hemoccult SENSA (Beckman Coulter, Fullerton, California) testing or fecal immuno-chemical testing, and sigmoidoscopy every 5 years with midinterval Hemoccult SENSA testing. Annual Hemoccult II and flexible sigmoidoscopy every 5 years alone were less effective.

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

Limitation: The stop age for screening was based only on chronologic age.

Conclusion: The findings support colorectal cancer screening with the following: colonoscopy every 10 years, annual screening with a sensitive FOBT, or flexible sigmoidoscopy every 5 years with a midinterval sensitive FOBT from age 50 to 75 years.

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

In July 2002, the U.S. Preventive Services Task Force (USPSTF) concluded that there was sufficient evidence to recommend strongly that all average-risk adults 50 years of age or older should be offered colorectal cancer screening (8). However, the logistics of screening, such as the type of screening test, screening interval, and age at which to stop screening, were not evaluated in terms of the balance of benefits and potential harms. The USPSTF has again addressed recommendations for colorectal cancer screening
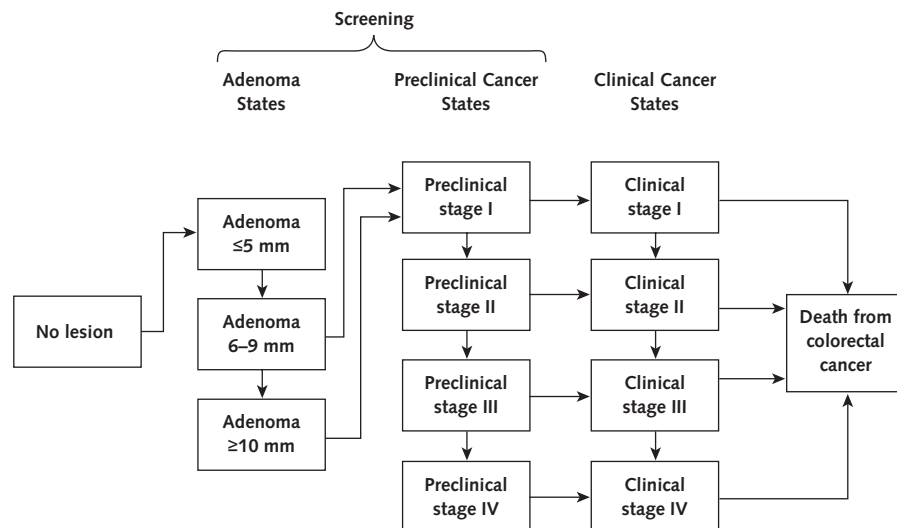
Figure 1. Natural history of disease as modeled by the Microsimulation Screening Analysis and Simulation Model of Colorectal Cancer models.

The opportunity to intervene in the natural history through screening is noted.

with a systematic review of the evidence (9) on screening tests. For this assessment, the USPSTF requested a decision analysis to project expected outcomes of various strategies for colorectal cancer screening. Two independent micro-simulation modeling groups from the Cancer Intervention and Surveillance Modeling Network (CISNET), funded by the National Cancer Institute, used a comparative modeling approach to compare life-years gained relative to resource use of different strategies for colorectal cancer screening.

METHODS

We used 2 microsimulation models, MISCAN (MIcrosimulation Screening Analysis) (10–12) and SimCRC (Simulation Model of Colorectal Cancer) (13), to estimate the life-years gained relative to no screening and the colonoscopies required (that is, an indicator for resource use and risk for complications) for different colorectal cancer screening strategies defined by test, age at which to begin screening, age at which to stop screening, and screening interval. We aimed to identify a set of recommendable strategies with similar clinical benefit and an efficient use of colonoscopy resources. Using 2 models (that is, a comparative modeling approach) adds credibility to the results and serves as a sensitivity analysis on the underlying structural assumptions of the models, particularly pertaining to the unobservable natural history of colorectal cancer.

Microsimulation Models

The **Appendix** (available at www.annals.org) describes the MISCAN and SimCRC models, and standardized model profiles are available at http://cisnet.cancer.gov/pro-

files/. In brief, both models simulate the life histories of a large population of individuals from birth to death. As each individual ages, there is a chance that an adenoma will develop. One or more adenomas can occur in an individual, and each adenoma can independently develop into preclinical (that is, undiagnosed) colorectal cancer (**Figure 1**). The risk for developing an adenoma depends on age, sex, and baseline individual risk. The models track the location and size of each adenoma; these characteristics influence disease progression and the chance that the adenoma will be found by screening. The size of adenomas can progress from small (≤5 mm) to medium (6 to 9 mm) to large (≥10 mm). Some adenomas eventually become malignant, transforming to stage I preclinical cancer. Preclinical cancer has a chance of progressing through stages I to IV and may be diagnosed by symptoms at any stage. Survivorship after diagnosis depends on the stage of disease.

The natural history component of each model was calibrated to 1975–1979 clinical incidence data (14) and adenoma prevalence from autopsy studies in the same period (15–24). We used this period because incidence rates and adenoma prevalence had not yet been affected by screening. We corrected the adenoma prevalence for studies of non-U.S. populations by using standardized colorectal cancer incidence ratios. The models use all-cause mortality estimates from the U.S. life tables and stage-specific data on colorectal cancer survival from the 1996–1999 Surveillance, Epidemiology, and End Results program (14). **Table 1** compares outcomes from the natural history components of the models.

The effectiveness of a screening strategy is modeled through a test's ability to detect lesions (that is, adenomas or preclinical cancer). Once screening is introduced, a simulated person who has an underlying lesion has a chance of having it detected during a screening round depending on the sensitivity of the test for that lesion and whether the lesion is within the reach of the test. Screened persons without an underlying lesion can have a false-positive test result and undergo unnecessary follow-up colonoscopy. Hyperplastic polyps are not modeled explicitly, but their detection is reflected in the specificity of the screening tests. The models incorporate the risk for fatal complications associated with perforation during colonoscopy. Both models have been validated against the long-term reductions in incidence and mortality of colorectal cancer with annual FOBT reported in the Minnesota Colon Cancer Control Study (3, 25, 26) and show good concordance with the trial results.

Strategies for Colorectal Cancer Screening

In consultation with the USPSTF, we included the following basic strategies: 1) no screening, 2) colonoscopy, 3) FOBT (Hemoccult II, Hemoccult SENSA [Beckman Coulter], or fecal immunochemical testing), 4) flexible sigmoidoscopy (with biopsy), and 5) flexible sigmoidoscopy combined with Hemoccult SENSA. For each basic strategy, we evaluated start ages of 40, 50, and 60 years and stop ages of 75 and 85 years. For the FOBT strategies, we considered screening intervals of 1, 2, and 3 years, and for the sigmoidoscopy and colonoscopy strategies, we considered intervals of 5, 10, and 20 years. These variations resulted in 145 strategies: 90 single-test strategies, 54 combination-test strategies, and 1 no-screening strategy. The stop age reflects the oldest possible age at which to screen, but the actual stopping age is dictated by the start age and screening interval.

In the base case, we assumed 100% adherence for screening tests, follow-up of positive findings, and surveillance of persons found to have adenomas. Individuals with a positive FOBT result or with an adenoma detected by sigmoidoscopy were referred for follow-up colonoscopy. For years in which both tests were due for the combined strategy, the FOBT was performed first; if the result was positive, the patient was referred for follow-up colonoscopy. In those years, flexible sigmoidoscopy was done only for patients with a negative FOBT result. If findings on follow-up colonoscopy were negative, the individual was assumed to undergo subsequent screening with colonoscopy with a 10-year interval (as long as results of the repeated colonoscopy were negative) and did not return to the initial screening schedule, as is the recommendation of the U.S. Multi-Society Task Force and American Cancer Society (7, 27). All individuals with an adenoma detected were followed with colonoscopy surveillance per the Multi-Society guidelines (27, 28). The surveillance interval depended on the number and size of the adenomas detected on the last colonoscopy; it ranged from 3 to 5 years and was assumed to continue for the remainder of the person's lifetime.

Table 1. **Comparison of the Natural History Outcomes from the Microsimulation Screening Analysis (*MISCAN*) and Simulation Model of Colorectal Cancer (*SimCRC*) Models**

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

CRC = colorectal cancer.
* Because of rounding, not all percentages add to 100%.

We estimated the test characteristics of colorectal cancer screening from a review of the available literature (**Table 2**) (29). We conducted this review independently of and parallel in time with the systematic evidence review performed for the USPSTF (9).

Evaluation of Outcomes

Determination of Efficient Strategies

The most effective strategy was defined as the one with the greatest life-years gained relative to no screening. However, it is important to consider the relative intensity of test use required to achieve those gains. The more effective strategies tended to be associated with more colonoscopies on average in a person's lifetime, which translated into an increased risk for colonoscopy-related complications. We used an approach that mirrors that of cost-effectiveness analysis (30) to identify the set of efficient, or dominant, strategies within each test category. A strategy was considered dominant when no other strategy or combination of

Table 2. Test Characteristics Used in the Microsimulation Screening Analysis and Simulation Model of Colorectal Cancer Models*

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

* Data obtained from reference 29.
† We assume that small adenomas do not bleed and cannot be detected by fecal occult blood tests (FOBTs). The sensitivity of FOBTs for adenomas ≤5 mm is based on the false-positive rate (that is, 1 – specificity).
‡ The sensitivity of sigmoidoscopy for colorectal cancer over the whole colorectum is 72% with the Microsimulation Screening Analysis model and 61% with the Simulation Model of Colorectal Cancer.

strategies provided more life-years with the same number of colonoscopies. We conducted this analysis separately for each of the 5 basic screening strategies because the number of noncolonoscopy tests differed by strategy. We then ranked the efficient screening strategies by increasing effectiveness and calculated the incremental number of colonoscopies (ΔCOL) per 1000, the incremental life-years gained (ΔLYG) per 1000, and the incremental number of colonoscopies necessary to achieve 1 year of life (ΔCOL/ΔLYG) relative to the next less effective strategy, which we call the "efficiency ratio." The line connecting the set of efficient strategies is called the "efficient frontier." We also identified "near-efficient" strategies—strategies that yielded life-years gained within 98% of the efficient frontier.

Determination of Recommendable Strategies at a Certain Level of Effectiveness

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

Sensitivity Analyses

The primary sensitivity analysis was the comparison of findings across the 2 independently developed microsimulation models. We also performed sensitivity analyses on test characteristics in which we used all of the least favorable values in a worst-case analysis and all of the most favorable values in a best-case analysis (**Table 2**). For colonoscopy and sigmoidoscopy, we used the confidence intervals reported in the meta-analysis by van Rijn and colleagues (31) as the range tested. For FOBT, we used the ranges reported in the literature (9, 29).

To assess the relative effect of decreased adherence, we explored the impact of overall adherence rates of 50% and 80%. We incorporated correlation of screening behavior within an individual by assuming that the population comprises 4 groups: those who are never screened and those with low, moderate, and high adherence; 10% of the population was in the never-screened group and 30% were in each of the other groups. For both overall screening adherence assumptions (that is, 50% and 80%), we assumed that adherence with follow-up and surveillance was 75%, 85%, and 95% for those with low, moderate, and high adherence, respectively. We assumed that individuals remain in their screening behavior group.

Role of the Funding Source

The National Cancer Institute supported the infrastructure for the CISNET models. The Agency for Healthcare Research and Quality funded this work and provided project oversight and review. The authors worked with 4 USPSTF members to specify the overall questions, select the strategies, and resolve methodological issues during the conduct of the review. The draft decision analysis was reviewed by 3 external peer reviewers (listed in the acknowledgments) and was revised for the final version. The authors have sole responsibility for the models and model results.

This research did not include patient-specific information and was exempt from institutional review board review.

RESULTS

Table 3 presents life-years gained, the number of colonoscopies, and the efficiency ratio for each efficient and near-efficient colonoscopy strategy for both models. Similar results for the other tests can be found in the **Appendix Table** (available at www.annals.org). For illustration, **Figure 2** presents the life-years gained relative to the number of colonoscopies and the efficient frontier for all colonoscopy strategies.

Age at Which to Begin Screening

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

Age at Which to Stop Screening

For both models and all tests, decreasing the stop age from 85 to 75 yielded small reductions in life-years gained relative to large reductions in the number of colonoscopies required (**Appendix Table**, available at www.annals.org).

For example, stopping screening at age 75 years instead of 85 years for colonoscopy every 10 years would decrease the number of life-years gained with colonoscopy screening by 5 per 1000 individuals for MISCAN and by 2 per 1000 individuals for SimCRC, but would substantially decrease the number of colonoscopies by 398 and 358 per 1000 individuals for MISCAN and SimCRC, respectively (Table 3). This is illustrated by the substantial reduction in the efficiency ratio for these 2 strategies, from 73 to 30 for MISCAN and 179 to 35 for SimCRC.

Screening Interval

In general, strategies with longer intervals provided fewer life-years gained than did strategies with shorter intervals. For all single test strategies, the currently recommended intervals of annual FOBT, flexible sigmoidoscopy every 5 years, and colonoscopy every 10 years provided a reasonable ratio of incremental colonoscopies per life-year gained (8–35) for ages 50 to 75 years (Appendix Table, available at www.annals.org). The results from both models showed that the current recommendation for the combination of flexible sigmoidoscopy every 5 years with a high-sensitivity FOBT annually had a high efficiency ratio, and that moving to a strategy of sigmoidoscopy every 5 years with FOBT every 3 years would minimally decrease the number of life-years gained with combination screening (by 9 per 1000 individuals for MISCAN and by 17 per 1000 individuals for SimCRC) and would substantially decrease the number of colonoscopies (by 765 per 1000 individuals for MISCAN and by 1011 per 1000 individuals for SimCRC for ages 50 to 75 years) (Appendix Table, available at www.annals.org). This would substantially reduce the incremental colonoscopies required for an additional life-year gained from 140 to 16 for MISCAN and from 76 to 7 for SimCRC.

Identifying a Set of Recommendable Strategies for Colorectal Cancer Screening

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

Table 3. Efficient and Near-Efficient Strategies for Colonoscopy Screening

Test, Age Begin–Age Stop, Interval*	Outcomes per 1000 Persons				
	COL	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG
MISCAN					
COL, 60–75, 20	2175	156	–	–	–
COL, 50–75, 20	3325	203	1150	47	24.7
COL, 50–75, 10	**4136**	**230**	**811**	**27**	**29.6**
COL, 50–85, 10	4534	236	398	5	72.9
COL, 50–75, 5	5895	254	1362	18	74.8
COL, 50–85, 5	6460	257	565	4	156.1
SimCRC					
COL, 60–75, 20	1780	165	–	–	–
COL, 50–75, 20	2885	246	1106	82	13.5
COL, 50–75, 10	**3756**	**271**	**871**	**25**	**34.7**
COL, 50–85, 10	4114	273	358	2	Near-efficient†
COL, 50–75, 5	5572	281.6	1816	10	178.8
COL, 50–85, 5	6031	282.1	459	0.5	975.7

COL = colonoscopy; ΔCOL = incremental number of colonoscopies compared with the next-best nondominated strategy; LYG = life-years gained compared with no screening; ΔLYG = incremental number of life-years gained compared with the next-best nondominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.
* Bold indicates recommendable strategy. Age and intervals expressed as years.
† Strategy yields life-years gained within 98% of the efficient frontier.

Sensitivity Analysis

Our overall conclusions did not change with variations in test characteristics. As expected, results for the worst-case analysis showed fewer life-years gained than results for the base case, and the best-case analysis had more life-years gained. For strategies that remained on the efficient frontier, the incremental number of colonoscopies per life-year gained was typically greater than the base-case value with the best-case assumption and lower with the worst-case assumption.
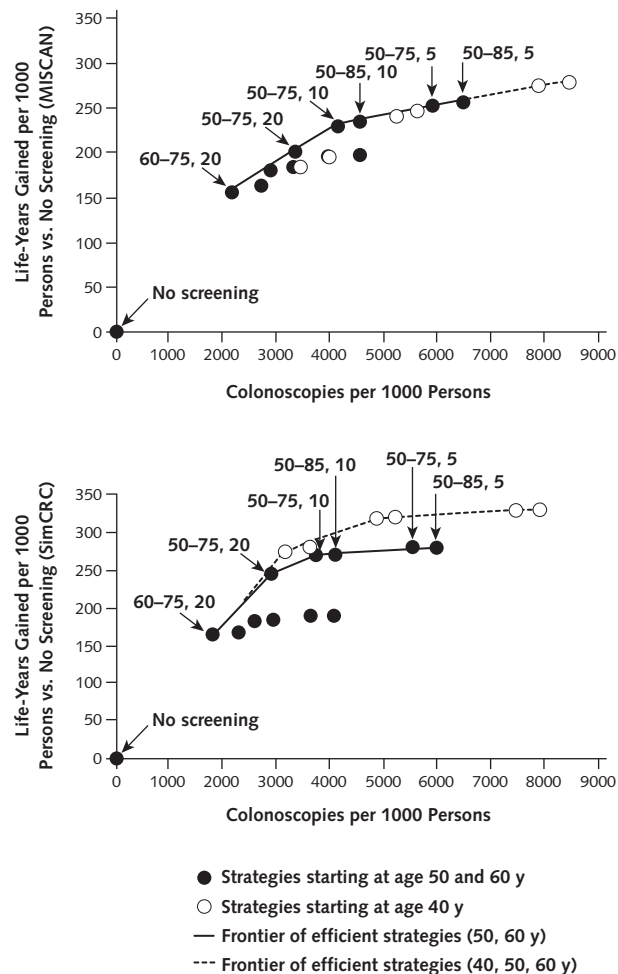
Figure 3 shows the expected number of colonoscopies and life-years gained for adherence of 50%, 80%, and 100% for the recommended strategies shown in **Table 4**. When adherence was relatively high at 80%, the colonoscopy strategy (that is, screening every 10 years from ages 50 to 75) was the most effective in term of life-years gained; Hemoccult SENSA, fecal immunochemical testing, and the combination strategies all provided life-years gained within 8% of those of the colonoscopy strategy. When overall adherence was only 50%, the colonoscopy strategy was no longer the most effective, and Hemoccult SENSA, fecal immunochemical testing, and the combination strategies had life-years gained greater than or equivalent to those of the colonoscopy strategy. Annual Hemoccult II and flexible sigmoidoscopy every 5 years remained the least attractive alternatives in terms of life-years gained across different adherence levels.

DISCUSSION

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

Our decision analysis represents the first time that the USPSTF has included simulation modeling to help inform

Figure 2. **Colonoscopies and life-years gained (compared with no screening) for a cohort of 1000 forty-year-olds for 18 colonoscopy screening strategies that vary by start age, stop age, and screening interval.**

The numbers represent the following: age to begin–age to stop screening, interval. MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.

their decision on recommendations. The USPSTF had previously recommended screening for all asymptomatic persons beginning at age 50 years but did not recommend one test over another or an age at which to stop screening (6). Although randomized, controlled trials are the preferred method for establishing effectiveness of (screening) interventions, they are expensive, require long follow-up, and can address only a limited number of comparison groups. However, well-validated microsimulation models may be used to highlight the tradeoff between clinical benefit and resource utilization from different screening policies and inform decision making with standardized comparisons of net benefits and risks. The process with which our analysis was conducted represents an important advancement from evidence-based to evidence-informed medicine, and the

Table 4. Outcomes for the Recommendable Set of Efficient Screening Strategies

Test, Age Begin–Age Stop, Interval*	Outcomes per 1000 Persons			Efficiency Ratio†	Incidence Reduction, %	Mortality Reduction, %
	COL	Non-COL Tests	LYG			
MISCAN						
COL, 50–75, 10	4136	0	230	29.6	51.9	64.6
Hemoccult SENSA, 50–75, 1	3350	9541	230	30.9	49.7	66.0
FIT, 50–75, 1	2949	11 773	227	25.9	47.2	64.6
Hemoccult II, 50–75, 1	1982	16 232	194	14.3	37.1	55.3
FSIG, 50–75, 5	1911	4139	203	9.7	46.8	58.5
FSIG + SENSA, 50–75, 5, 3	2870	5822	230	16.3	51.2	65.7
SimCRC						
COL, 50–75, 10	3756	0	271	34.7	80.6	84.4
Hemoccult SENSA, 50–75, 1	2654	9573	259	22.9	73.2	81.2
FIT, 50–75, 1	2295	11 830	256	19.7	70.8	80.0
Hemoccult II, 50–75, 1	1456	16 239	218	9.6	56.6	69.0
FSIG, 50–75, 5	995	4483	199	8.4	59.0	62.2
FSIG + SENSA, 50–75, 5, 3	1655	11 623	257	7.0	72.2	79.3

COL = colonoscopy; FIT = fecal immunochemical test; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.
* Age and intervals expressed as years.
† Efficiency ratio corresponds with ΔCOL/ΔLYG in the **Appendix Table** and represents the relative burden per unit of benefit achieved.

use of more than 1 model, as advocated by CISNET, adds credibility when model results agree.

We found that colorectal cancer screening with high-sensitivity FOBT (Hemoccult SENSA or fecal immunochemical test) provided similar life-years gained as colonoscopy, even though the individual test characteristics were substantially better for colonoscopy (**Table 2**). This finding was partially due to the fact the FOBT must be performed every year compared with every 10 years for colonoscopy, and the test characteristics are assumed to remain unchanged with each subsequent screening. For example, if an adenoma was missed by a screening test in one cycle, then the chance that it would be missed again on the next examination is still based on the false-negative rate (1 − sensitivity for adenomas). There is little evidence on whether test sensitivity varies with increasing rounds of testing. In addition, a substantial percentage of individuals receiving annual FOBT screening will eventually have a false-positive screening result with referral for colonoscopy. Once confirmed to be negative by colonoscopy, they then have colonoscopy screening every 10 years, as per guidelines. For example, with a specificity of 92.5% for Hemoccult SENSA, the percentage of people in a colonoscopy screening program is about 54% after 10 FOBTs and about 79% after 20 FOBTs.

There has been no recommended stop age for colorectal cancer screening (7, 27). However, our results indicate that continued screening in 75-year-old persons after consecutive negative screenings since age 50 years will add little benefit. Individuals with continuous negative findings by age 75 years are unlikely to have a missed adenoma at their last screening or to develop an adenoma that progresses to cancer and subsequent death from cancer after their last screening. Surveillance colonoscopies for pa-

tients with adenomas detected are continued without a stopping age. Our analysis used chronologic age rather than comorbidity-adjusted life expectancy, and the decision to stop screening in practice should consider the age and health of the patient. As a guide, life expectancy at age 75 years is 10.5 years for men and 12.5 years for women (32).
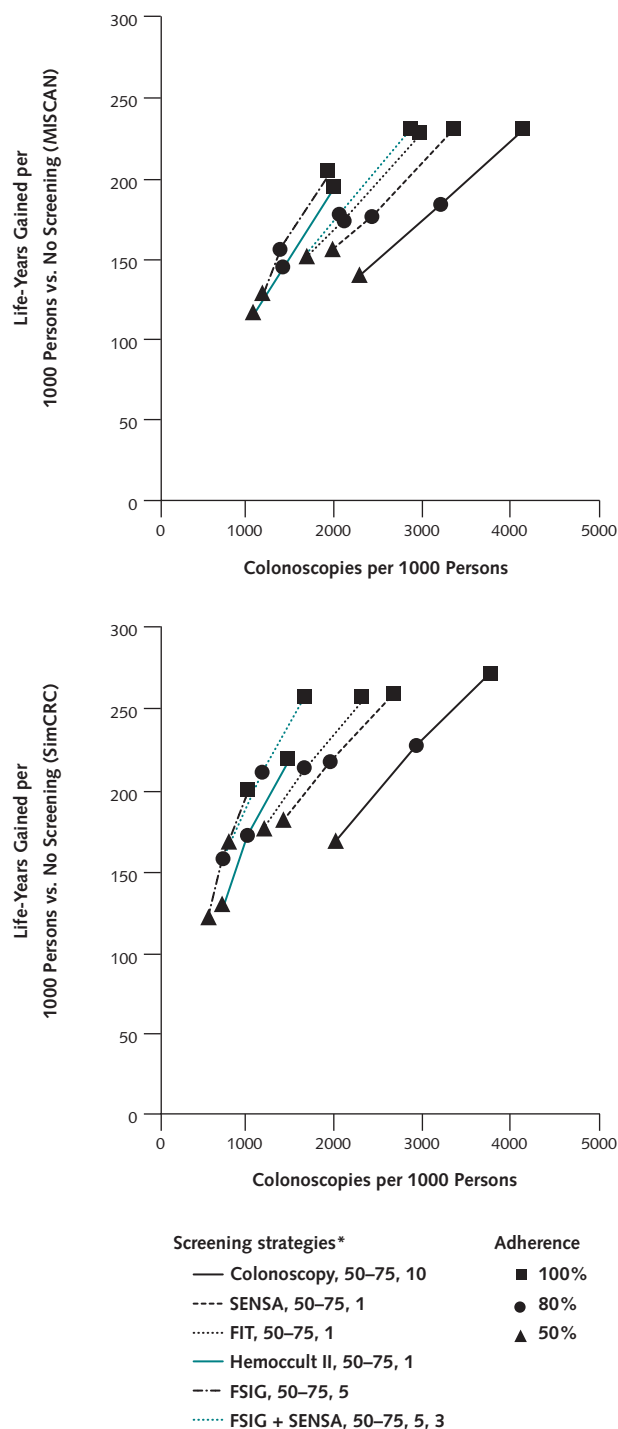
A few findings can be explained by model differences. Both models incorporate assumptions about the adenoma–carcinoma sequence (that is, the development of colorectal cancer from adenomas), for which limited data are available to estimate the time that it takes (on average) for an adenoma to develop into preclinical cancer. For example, in the MISCAN model, the average time from adenoma development to colorectal cancer diagnosis is 10 years among individuals with diagnosed colorectal cancer (that is, dwell time), whereas in the SimCRC model, this value is about 22 years. The implications of these differences were more life-years gained with screening in general, and more favorable results for beginning screening at age 40 years, with the SimCRC model. The former implication had minimal effect on our conclusions because the relative findings were consistent across models. The latter implication resulted in eliminating the start age of 40 years from consideration. Another difference between the models is the distribution of adenomas in the colorectal tract (**Appendix** [available at www.annals.org] and **Table 1**). In the MISCAN model, adenomas are assumed to have the same distribution as colorectal cancers, while the SimCRC model is calibrated to the distribution of adenomas from autopsy studies. As a result, the MISCAN model found strategies involving sigmoidoscopy to be more effective than did the SimCRC model because a larger proportion of adenomas are within the reach of the sigmoidoscope.

Despite this difference, both model results found that the strategy of sigmoidoscopy every 5 years was not as effective as annual screening with a sensitive FOBT or with colonoscopy every 10 years.

There are several limitations and caveats to consider. First, we evaluated only colorectal cancer strategies requested by the USPSTF on the basis of their review of the evidence in 2002 (8), and we did not include newer screening tests, such as computed tomographic colonography or the DNA stool test (9, 27). Second, because we were not asked to provide a cost-effectiveness analysis, we used the number of colonoscopies as a proxy for resource utilization, as well as nonfatal adverse effects from screening. However, this does not capture all resources required per scenario, although we report the numbers of noncolonoscopy tests (that is, FOBT or flexible sigmoidoscopy) required for each strategy. Third, we assumed 100% adherence with screening, follow-up (chance of undergoing diagnostic colonoscopy if a screening test result is positive), and surveillance for all scenarios to provide outcomes associated with the strategies as they were specified. In practice, adherence is much lower than 100% and varies across type of screening test. We conducted a sensitivity analysis that varied overall adherence but not differentially across strategies. We chose to evaluate strategies assuming equivalent adherence because it is uncertain whether adherence will be higher with noninvasive but more frequent testing, or invasive but less frequent testing. Because we considered 3 different adherence scenarios in **Figure 3**, readers can compare different adherence levels themselves. We emphasize that in practice adherence is critical and that ultimately the best option for a patient is the one that he or she will attend (7, 27). In addition, issues pertaining to the implementation of a screening program, including endoscopy capacity (33–35), professional qualification (36, 37), insurance coverage, shared decision making, and how to increase adherence with colorectal cancer screening (38), are important considerations for implementing recommendations in practice.

In conclusion, our results support colorectal cancer screening with colonoscopy every 10 years, a sensitive FOBT annually, or flexible sigmoidoscopy every 5 years with a midinterval sensitive FOBT from age 50 to 75 years. Our findings in general support the 2002 USPSTF recommendations for colorectal cancer screening, with a few exceptions. First, although there is currently no recommended stopping age for colorectal cancer screening, we found that continuing screening after age 75 in individuals who have had regular, consistently negative screenings since age 50 provides minimal benefit for the resources required. Second, we found that screening with Hemoccult II annually and flexible sigmoidoscopy alone every 5 years does not provide effectiveness similar to that of screening annually with a sensitive FOBT or every 10 years with colonoscopy. Finally, if a sensitive FOBT is used, the FOBT screening interval can be extended to 3 years when

Figure 3. Colonoscopies and life-years gained, by adherence level for the recommendable set of screening strategies.

Screening strategies*
— Colonoscopy, 50–75, 10
---- SENSA, 50–75, 1
······ FIT, 50–75, 1
— Hemoccult II, 50–75, 1
–·– FSIG, 50–75, 5
······ FSIG + SENSA, 50–75, 5, 3

Adherence
■ 100%
● 80%
▲ 50%

SENSA = Hemoccult SENSA; FIT = fecal immunochemical testing; FSIG = flexible sigmoidoscopy; MISCAN = Microsimulation Analysis Model; SimCRC = Simulation Model of Colorectal Cancer.
* The numbers represent the following: age to begin–age to stop screening, interval.

used in combination with flexible sigmoidoscopy every 5 years. These conclusions were corroborated by 2 independent microsimulation models.

From Memorial Sloan-Kettering Cancer Center, New York, New York; Erasmus Medical Center, Rotterdam, the Netherlands; Massachusetts General Hospital, Boston, Massachusetts; and University of Minnesota, Minneapolis, Minnesota

Corresponding Author: Ann G. Zauber, PhD, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 East 63rd Street, New York, NY 10065; e-mail, zaubera@mskcc.org.

Current author addresses are available at www.annals.org.

References

1. **Espey DK, Wu XC, Swan J, Wiggins C, Jim MA, Ward E, et al.** Annual report to the nation on the status of cancer, 1975-2004, featuring cancer in American Indians and Alaska Natives. Cancer. 2007;110:2119-52. [PMID: 17939129]

2. **American Cancer Society.** Cancer Facts and Figure 2008. Accessed at www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf on 15 September 2008.

3. **Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al.** Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328:1365-71. [PMID: 8474513]

4. **Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al.** Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348:1472-7. [PMID: 8942775]

5. **Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O.** Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348:1467-71. [PMID: 8942774]

6. **Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, et al.** Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112:594-642. [PMID: 9024315]

7. **Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Gastrointestinal Consortium Panel.** Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology. 2003; 124:544-60. [PMID: 12557158]

8. **U.S. Preventive Services Task Force.** Screening for colorectal cancer: recommendation and rationale. Ann Intern Med. 2002;137:129-31. [PMID: 12118971]

9. **Whitlock EP, Lin JS, Liles E, Beil TL, Fu R.** Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149:638-58.

10. **Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD.** The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res. 1999;32:13-33. [PMID: 10066353]

11. **Loeve F, Brown ML, Boer R, van Ballegooijen M, van Oortmarssen GJ, Habbema JD.** Endoscopic colorectal cancer screening: a cost-saving analysis. J Natl Cancer Inst. 2000;92:557-63. [PMID: 10749911]

12. **Vogelaar I, van Ballegooijen M, Schrag D, Boer R, Winawer SJ, Habbema JD, et al.** How much can current interventions reduce colorectal cancer mortality in the U.S.? Mortality projections for scenarios of risk-factor modification, screening, and treatment. Cancer. 2006;107:1624-33. [PMID: 16933324]

13. **Frazier AL, Colditz GA, Fuchs CS, Kuntz KM.** Cost-effectiveness of screening for colorectal cancer in the general population. JAMA. 2000;284:1954-61. [PMID: 11035892]

14. **Surveillance Epidemiology, and End Results (SEER) Program.** SEER* Stat Database: Incidence—SEER 9 Regs Public Use. Nov 2003 Sub (1973–2001), DCCPS, Surveillance Research Program, Cancer Statistics Branch. Based on the November 2003 submission. Bethesda, MD: National Cancer Institute; April 2004.

15. **Clark JC, Collan Y, Eide TJ, Estève J, Ewen S, Gibbs NM, et al.** Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. Int J Cancer. 1985;36:179-86. [PMID: 4018911]

16. **Blatt LJ.** Polyps of the colon and rectum: incidence and distribution. Dis Colon Rectum. 1961;4:277-82.

17. **Vatn MH, Stalsberg H.** The prevalence of polyps of the large intestine in Oslo: an autopsy study. Cancer. 1982;49:819-25. [PMID: 7055790]

18. **Jass JR, Young PJ, Robinson EM.** Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. Gut. 1992;33:1508-14. [PMID: 1452076]

19. **Johannsen LG, Momsen O, Jacobsen NO.** Polyps of the large intestine in Aarhus, Denmark. An autopsy study. Scand J Gastroenterol. 1989;24:799-806. [PMID: 2799283]

20. **Bombi JA.** Polyps of the colon in Barcelona, Spain. An autopsy study. Cancer. 1988;61:1472-6. [PMID: 3345499]

21. **Williams AR, Balasooriya BA, Day DW.** Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut. 1982;23:835-42. [PMID: 7117903]

22. **Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM.** Adenomatous lesions of the large bowel: an autopsy survey. Cancer. 1979;43:1847-57. [PMID: 445371]

23. **Chapman I.** Adenomatous polypi of large intestine: incidence and distribution. Ann Surg. 1963;157:223-6. [PMID: 14020146]

24. **Arminski TC, McLean DW.** Incidence and distribution of adenomatous polyps of the colon and rectum based on 1,000 autopsy examinations. Dis Colon Rectum. 1964;7:249-61. [PMID: 14176135]

25. **Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al.** The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med. 2000;343:1603-7. [PMID: 11096167]

26. **Mandel JS, Church TR, Ederer F, Bond JH.** Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst. 1999;91:434-7. [PMID: 10070942]

27. **American Cancer Society Colorectal Cancer Advisory Group.** Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008;134:1570-95. [PMID: 18384785]

28. **Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B, et al.** Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin. 2006;56:143-59; quiz 184-5. [PMID: 16737947]

29. **Zauber AG, Lansdorp-Vogelaar I, Wilschut J, Knudsen AB, van Ballegooijen M, Kuntz KM.** Cost-effectiveness of DNA stool testing to screen for colorectal cancer: report to AHRQ and CMS from the Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN and SimCRC Models. Accessed at https://www.cms.hhs.gov/mcd/viewtechassess.asp?from2=viewtech assess.asp&id=212&www.cms.hhs.gov/mcd/viewtechassess.asp?from2=viewtech assess.asp&id=212& on 15 September 2008.

30. **Mark DH.** Visualizing cost-effectiveness analysis [Editorial]. JAMA. 2002; 287:2428-9. [PMID: 11988064]

31. **van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E.** Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol. 2006;101:343-50. [PMID: 16454841]

32. **Arias E.** United States life tables, 2003. Natl Vital Stat Rep. 2006;54:1-40. [PMID: 16681183]

33. **Brown ML, Klabunde CN, Mysliwiec P.** Current capacity for endoscopic colorectal cancer screening in the United States: data from the National Cancer Institute Survey of Colorectal Cancer Screening Practices. Am J Med. 2003;115: 129-33. [PMID: 12893399]

34. **Mysliwiec PA, Brown ML, Klabunde CN, Ransohoff DF.** Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. Ann Intern Med. 2004;141:264-71. [PMID: 15313742]

35. **Seeff LC, Manninen DL, Dong FB, Chattopadhyay SK, Nadel MR, Tangka FK, et al.** Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? Gastroenterology. 2004;127:1661-9. [PMID: 15578502]

36. **Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, et al. ASGE/ ACG Taskforce on Quality in Endoscopy.** Quality indicators for colonoscopy. Am J Gastroenterol. 2006;101:873-85. [PMID: 16635231]

37. **Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL.** Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med. 2006;355:2533-41. [PMID: 17167136]

38. **Baron R, Rimer BK, Berkowitz J, Harris K, eds.** Increasing screening for breast, cervical, and colorectal cancers—recommendations from the Task Force on Community Preventive Services, Methods, Systematic Reviews of Evidence and Expert Commentary. Am J Prev Med. 2008;35: A1-4, S1-76.

Annals of Internal Medicine

Current Author Addresses: Dr. Zauber: Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 East 63rd Street, New York, NY 10065.

Ms. Lansdorp-Vogelaar, Ms. Wilschut, and Dr. van Ballegooijen: Erasmus Medical Center, Dr. Molewaterplein 50, Rotterdam 3000CA, the Netherlands.

Dr. Knudsen: Institute for Technology Assessment, Massachusetts General Hospital, 101 Merrimac Street, Boston, MA 02114.

Dr. Kuntz: University of Minnesota, Division of Health Policy and Management, MMC 729 Mayo, 15-232 PWB, 516 Delaware Street Southeast, Minneapolis, MN 55455.

APPENDIX: MODEL DESCRIPTIONS

We used the MISCAN and SimCRC models from the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) to compare strategies for colorectal cancer screening that vary by the age at which to begin screening, the age at which to end screening, and screening interval. The use of 2 models (that is, a comparative modeling approach) provides a sensitivity analysis on the model structure. Although the models were developed independently, they were calibrated to the same data on adenoma prevalence and colorectal cancer incidence, and they use the same assumptions regarding the sensitivity, specificity, and reach of the various screening tests. Accordingly, differences in findings across models may be attributed to differences in model structure and the assumptions about the natural history of colorectal cancer. Both models are described below.

MISCAN Model
Overview

MISCAN-COLON is a semi-Markov microsimulation model that simulates the effect of screening and other interventions on the incidence and mortality of colorectal cancer. With microsimulation, we mean that each individual in the population is simulated separately. The model is semi-Markov in the following regards: 1) distributions other than exponential are possible in each disease state; 2) transitions in one state can depend on transitions in earlier states; 3) transitions can be dependent on age and calendar time; and 4) all events in the model are discrete, but the durations in each state are continuous—thus, there are no annual transitions in the model.

Simulation of the Natural History of Colorectal Cancer

In the model, colorectal cancer is assumed to develop according to the adenoma–carcinoma sequence. This means that adenomas arise in the population, and some eventually develop into colorectal cancer. We assume that there are 2 types of adenomas: nonprogressive and progressive. Nonprogressive adenomas can grow in size but will never develop into cancer. Progressive adenomas have the potential to develop into cancer if the person in whom the adenoma develops lives long enough.

All adenomas start small (≤5 mm). They can grow in size to medium (6 to 9 mm) and large (≥10 mm) adenomas. Progressive medium-size and large adenomas can transform into malignant cancer stage I (not yet giving symptoms; preclinical cancer). The cancer then eventually progresses from stage I (localized) to stage IV (distant metastasis). In each stage, there is a probability of symptoms developing and clinical detection of the cancer. An adenoma is assumed to take, on average, 20 years to develop into colorectal cancer and become detected by symptoms. However, because many adenomas do not progress to colorectal cancer before the person dies of other causes, the average time a lesion has been present before it is diagnosed as colorectal cancer is approximately 10 years. After clinical detection, a person can die of colorectal cancer or of other causes based on the survival rate. Survival from colorectal cancer is highly dependent on the stage in which the cancer was detected.

Simulation of an Individual

Appendix Figure 1 shows how the model generates an individual life history. MISCAN-COLON first generates a time of birth and a time of death from causes other than colorectal cancer for an individual. This is shown in the top line of **Appendix Figure 1**. This line constitutes the life history in the absence of colorectal cancer. Subsequently, the model generates adenomas for an individual. For most individuals, no adenomas are simulated, for some multiple. In this example, MISCAN-COLON has generated 2 adenomas for the individual. The first adenoma occurs at a certain age and grows from a small to a medium to a large adenoma. However, this is a nonprogressive adenoma and will never transform into cancer. The second adenoma is a progressive adenoma. After having grown to 6 to 9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and eventually resulting in an earlier death from colorectal cancer.

The life history without colorectal cancer and the development of the 2 adenomas are combined into a life history in the presence of colorectal cancer. This means that a person's state is the same as the state of the most advanced adenoma or carcinoma present. If the individual dies of colorectal cancer before dying of other causes, the death age is adjusted accordingly. The combined life history with colorectal cancer is shown in the bottom line of **Appendix Figure 1**.

Simulation of Screening

The complete simulation of an individual life history in **Appendix Figure 1** depicts a situation in which screening does not take place. After the model has generated a life history with colorectal cancer but without screening, screening is overlaid. This is shown in **Appendix Figure 2**. The first 3 lines show the combined life history with colorectal cancer and the development of the 2 adenomas from **Appendix Figure 1**. At the moment of screening, both adenomas are present, then detected and removed. This results in a combined life history for colorectal cancer and screening (bottom line), where the person is free of adenomas and carcinomas after the screening intervention. Because the precursor lesion has been removed, this individual does not develop colorectal cancer and will therefore not die of colorectal cancer. The moment of death is delayed until the moment of death from other causes. The benefit of screening is equal to the

difference between life-years lived in a situation without screening and the situation with screening.

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

The effectiveness of screening depends on the performance characteristics of the test: sensitivity, specificity, and reach. In the model, $1 -$ specificity is defined as the probability of a positive test result in an individual regardless of any adenomas or cancers present. For a person without any adenomas or cancers, the probability of a positive test result is therefore equal to $1 -$ specificity. In individuals with adenomas or cancer, the probability of a positive test result depends on the lack of specificity and the sensitivity of the test for the present lesions. Sensitivity in the model is lesion-specific, where each adenoma or cancer contributes to the probability of a positive test result. The model provides the opportunity to consider the possibility of systematic test results.

SimCRC Model
Overview

The SimCRC model of colorectal cancer was developed to evaluate the effect of past and future interventions on the incidence and mortality of colorectal cancer in the United States. The model is population based, meaning that it simulates the life histories of multiple cohorts of individuals of a given year of birth. These cohorts can be aggregated to yield a full cross-section of the population in a given calendar year. For this analysis, we simulated the life histories of only 1 cohort—those age 40 years in 2005. SimCRC is a hybrid model, a cross between a Markov model and a discrete-event simulation. Although annual (often age-specific) probabilities define the likelihood of transitioning through a series of health states, the model does not have annual cycles. Instead, the age at which a given transition takes place for each simulated individual is drawn from a cumulative probability function.

Simulation of the Natural History of Colorectal Cancer

The SimCRC natural history model describes the progression of underlying colorectal disease (the adenoma–carcinoma sequence) in an unscreened population. Each simulated individual is assumed to be free of adenomas and colorectal cancer at birth. Over time, each person is at risk for forming 1 or more adenomas. Each adenoma may grow in size from small ($\leq$5 mm) to medium (6 to 9 mm) to large ($\geq$10 mm). Medium-size and large adenomas may progress to preclinical colorectal cancer, although most will not in an individual's lifetime. Preclinical cancers may progress in stage (I to IV) and may be detected by the presence of symptoms, becoming a clinical case. Individuals with colorectal cancer may die of their cancer or of other causes.
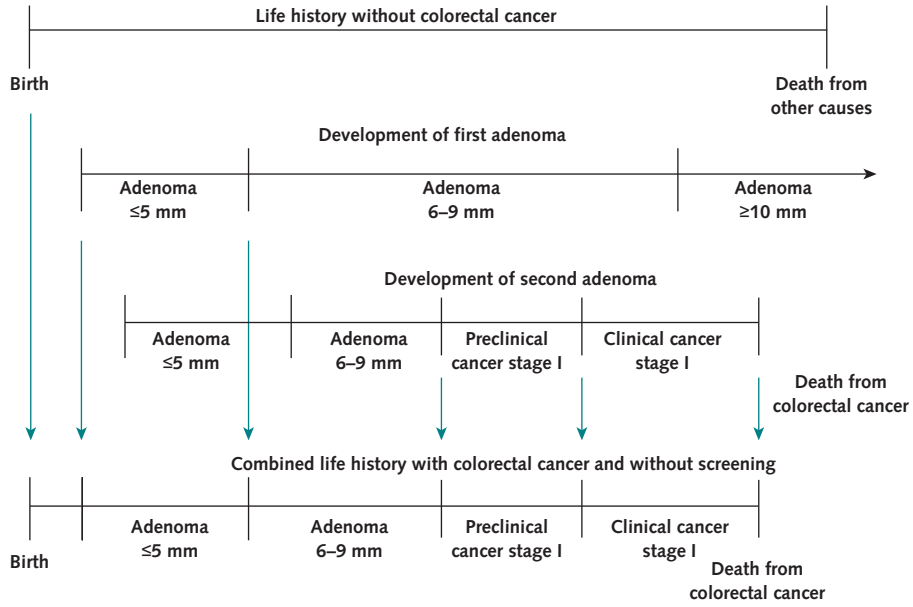
The SimCRC model allows for heterogeneity in growth and progression rates across multiple adenomas within an individual. Although all adenomas have the potential to develop into colorectal cancer, most will not. The likelihood of adenoma growth and progression to colorectal cancer is allowed to vary by location in the colorectal tract (that is, proximal colon vs. distal colon vs. rectum). **Appendix Figure 1** shows how the SimCRC model constructs an individual's life history in the absence of screening for colorectal cancer.
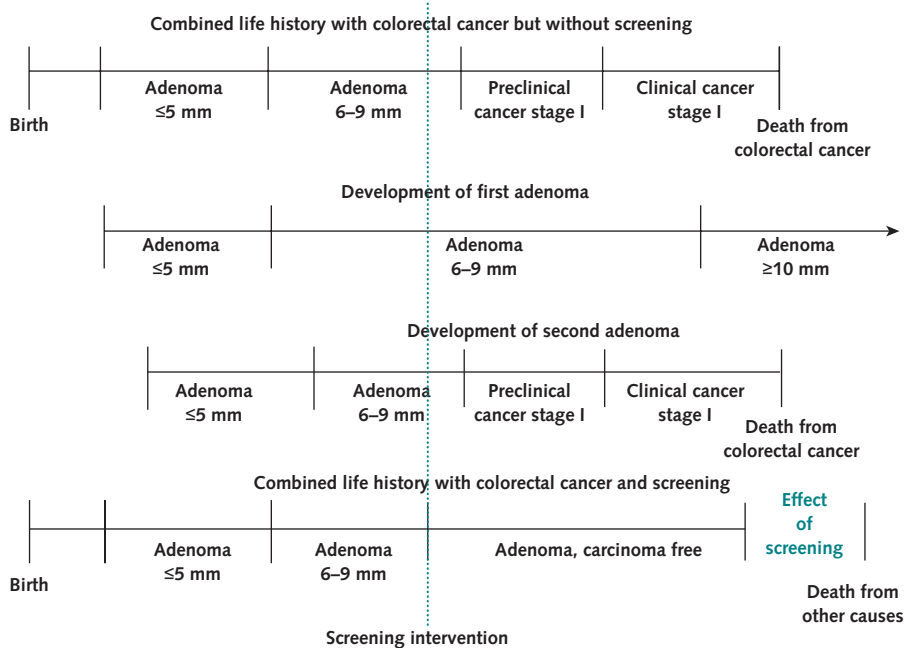
Simulation of Screening

The screening component of the SimCRC model is superimposed on the natural history model. It allows for the detection and removal of adenomas and the diagnosis of preclinical colorectal cancer (**Appendix Figure 2**). In a screening year, a person with an underlying (that is, undiagnosed) adenoma or preclinical cancer faces the chance that the lesion is detected on the basis of the sensitivity of the test for adenomas by size or for cancer and the reach of the test. Individuals who do not have an underlying adenoma or preclinical cancer also face the risk for having a positive screening test result (and for undergoing unnecessary follow-up procedures) because of the imperfect specificity of the test. Although the model does not explicitly simulate nonadenomatous polyps, they are accounted for through the specificity of the test. In addition, individuals with false-negative screening test results (that is, individuals with an adenoma or preclinical cancer that was missed by the screening test) may be referred for follow-up because of the detection of nonadenomatous polyps. The model incorporates the risk for fatal and nonfatal complications associated with various screening procedures. It also accounts for the fact that not all individuals adhere to colorectal cancer screening guidelines and that adherence patterns are correlated within an individual.

The SimCRC model incorporates treatment for invasive cancer, such as adjuvant chemotherapy with 5-fluorouracil, and other improvements in cancer-specific mortality after diagnosis of colorectal cancer. Patients given a diagnosis of colorectal cancer, either by symptom detection or by a positive colonoscopy result, face a monthly cancer-specific mortality rate that is a function of the stage at diagnosis, age at diagnosis (<75 years or ≥75 years), time since diagnosis, and whether the patient received chemotherapy.

Appendix Figure 1. Microsimulation Screening Analysis and Simulation Model of Colorectal Cancer modeling of natural history into life history.

Appendix Figure 2. Microsimulation Screening Analysis and Simulation Model of Colorectal Cancer modeling of screening into life history.

Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons					
	COL	Non-COL Tests	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
Colonoscopy screening						
MISCAN						
COL, 60–75, 20	2175	0	156	–	–	–
COL, 50–75, 20	3325	0	203	1150	47	24.7
COL, 50–75, 10	**4136**	**0**	**230**	**811**	**27**	**29.6**
COL, 50–85, 10	4534	0	236	398	5	72.9
COL, 50–75, 5	5895	0	254	1362	18	74.8
COL, 50–85, 5	6460	0	257	565	4	156.1
SimCRC						
COL, 60–75, 20	1780	0	165	–	–	–
COL, 50–75, 20	2885	0	246	1106	82	13.5
COL, 50–75, 10	**3756**	**0**	**271**	**871**	**25**	**34.7**
COL, 50–85, 10	4114	0	273	–	–	Near-efficient
COL, 50–75, 5	5572	0	281.6	1816	10	178.8
COL, 50–85, 5	6031	0	282.1	459	0.5	975.7
Hemoccult II						
MISCAN						
Hemoccult II, 60–75, 3	681	4435	89	–	–	–
Hemoccult II, 60–75, 2	854	5784	105	172	16	10.6
Hemoccult II, 50–75, 3	1033	6834	121	–	–	Near-efficient
Hemoccult II, 50–75, 2	1335	9510	149	482	44	11.0
Hemoccult II, 50–85, 2	1513	11 162	158	–	–	Near-efficient
Hemoccult II, 50–75, 1	**1982**	**16 232**	**194**	**647**	**45**	**14.3**
Hemoccult II, 50–85, 1	2186	18 262	202	203	8	25.5
SimCRC						
Hemoccult II, 60–75, 3	425	4291	75	–	–	–
Hemoccult II, 50–75, 3	699	6941	129	275	54	5.1
Hemoccult II, 50–75, 2	921	9422	162	221	33	6.7
Hemoccult II, 50–75, 1	**1456**	**16 239**	**218**	**536**	**56**	**9.6**
Hemoccult II, 50–85, 1	1712	18 409	223	256	5	47.9
Hemoccult SENSA						
MISCAN						
Hemoccult SENSA, 60–75, 3	1363	3824	134	–	–	–
Hemoccult SENSA, 60–75, 2	1647	4732	149	–	–	Near-efficient
Hemoccult SENSA, 50–75, 3	2121	5596	181	758	47	16.0
Hemoccult SENSA, 50–75, 2	2584	7014	205	463	24	19.5
Hemoccult SENSA, 50–85, 2	2801	7679	211	–	–	Near-efficient
Hemoccult SENSA, 50–75, 1	**3350**	**9541**	**230**	**766**	**25**	**30.9**
Hemoccult SENSA, 50–85, 1	3538	9904	232	188	2	80.6
SimCRC						
Hemoccult SENSA, 60–75, 3	934	3735	123	–	–	–
Hemoccult SENSA, 50–75, 3	1587	5554	201	653	78	8.4
Hemoccult SENSA, 50–75, 2	1957	7006	228	370	28	13.3
Hemoccult SENSA, 50–75, 1	**2654**	**9573**	**259**	**698**	**31**	**22.9**
Hemoccult SENSA, 50–85, 1	2996	9918	262	341	3	128.2
Fecal immunochemical test						
MISCAN						
FIT, 60–75, 3	1158	4037	129	–	–	–
FIT, 60–75, 2	1403	5098	144	–	–	Near-efficient
FIT, 50–75, 3	1769	6089	173	611	44	14.0
FIT, 50–75, 2	2184	7916	198	415	25	16.5
FIT, 50–85, 2	2396	8895	206	–	–	Near-efficient
FIT, 50–75, 1	**2949**	**11 773**	**227**	**765**	**30**	**25.9**
FIT, 50–85, 1	3155	12 582	231	206	4	49.1
SimCRC						
FIT, 60–75, 3	772	3943	118	–	–	–
FIT, 50–75, 3	1286	6047	193	514	75	6.9
FIT, 50–75, 2	1614	7908	222	327	29	11.3
FIT, 50–75, 1	**2295**	**11 830**	**256**	**681**	**35**	**19.7**
FIT, 50–85, 1	2623	12 587	260	328	3	95.7

Test, Age Begin–Age Stop, Interval†	Outcomes per 1000 Persons					
	COL	Non-COL Tests	LYG	ΔCOL	ΔLYG	ΔCOL/ΔLYG‡
Flexible sigmoidoscopy						
MISCAN						
FSIG, 60–75, 20	1047	917	114	–	–	–
FSIG, 60–75, 10	1311	1531	140	–	–	Near-efficient
FSIG, 60–75, 5	1491	2617	159	–	–	Near-efficient
FSIG, 50–75, 10	1685	2339	177	–	–	Near-efficient
FSIG, 50–75, 5	**1911**	**4139**	**203**	**864**	**89**	**9.7**
FSIG, 50–85, 5	1996	4745	207	85	4	22.3
SimCRC						
FSIG, 60–75, 20	438	889	94	–	–	–
FSIG, 50–75, 20	662	1662	147	224	53	4.2
FSIG, 50–85, 20	674	1661	147	–	–	Near-efficient
FSIG, 50–75, 10	808	2455	176	146	29	5.0
FSIG, 50–75, 5	**995**	**4483**	**199**	**187**	**22**	**8.4**
FSIG, 50–85, 5	1064	5088	201	68	2	38.5
Flexible sigmoidoscopy plus Hemoccult SENSA						
MISCAN						
FSIG + SENSA, 60–75, 20, 3	1817	3211	163	–	–	–
FSIG + SENSA, 60–75, 10, 3	1933	3584	171	–	–	Near-efficient
FSIG + SENSA, 60–75, 5, 3	2031	3338	179	213	15	14.0
FSIG + SENSA, 50–75, 20, 3	2658	5210	213	–	–	Near-efficient
FSIG + SENSA, 50–75, 10, 3	2756	5575	221	–	–	Near-efficient
FSIG + SENSA, 50–75, 5, 3	**2870**	**5822**	**230**	**839**	**52**	**16.3**
FSIG + SENSA, 50–85, 5, 3	3042	7348	233	172	3	60.7
FSIG + SENSA, 50–75, 5, 2	3142	6263	235	100	2	62.3
FSIG + SENSA, 50–85, 10, 2	3245	6594	232	–	–	Near-efficient
FSIG + SENSA, 50–85, 5, 2	3321	7969	237	179	2	74.3
FSIG + SENSA, 50–75, 20, 1	3558	8563	236	–	–	Near-efficient
FSIG + SENSA, 50–75, 10, 1	3591	8399	237	–	–	Near-efficient
FSIG + SENSA, 50–75, 5, 1	3635	7224	239	314	2	139.8
FSIG + SENSA, 50–85, 20, 1	3734	8884	238	–	–	Near-efficient
FSIG + SENSA, 50–85, 10, 1	3768	8716	239	–	–	Near-efficient
FSIG + SENSA, 50–85, 5, 1	3808	8816	240	172	1	154.5
SimCRC						
FSIG + SENSA, 60–75, 20, 3	956	7763	152	–	–	–
FSIG + SENSA, 60–75, 10, 3	999	11 104	161	44	9	4.7
FSIG + SENSA, 60–75, 5, 3	1045	10 064	169	45	8	5.5
FSIG + SENSA, 50-75, 10, 3	1621	12 485	246	–	–	Near-efficient
FSIG + SENSA, 50–75, 5, 3	**1655**	**11 623**	**257**	**611**	**88**	**7.0**
FSIG + SENSA, 50–85, 5, 3	1908	9484	260	–	–	Near-efficient
FSIG + SENSA, 50–75, 5, 2	1994	12 265	265	338	8	41.7
FSIG + SENSA, 50–85, 5, 2	2298	9895	268	–	–	Near-efficient
FSIG + SENSA, 50–75, 20, 1	2647	10 214	270	–	–	Near-efficient
FSIG + SENSA, 50–75, 10, 1	2653	14 403	271	–	–	Near-efficient
FSIG + SENSA, 50–75, 5, 1	2666	13 593	274	673	9	75.7
FSIG + SENSA, 50–85, 20, 1	2981	7133	272	–	–	Near-efficient
FSIG + SENSA, 50–85, 10, 1	2987	5794	274	–	–	Near-efficient
FSIG + SENSA, 50–85, 5, 1	2996	10 875	276	330	2	154.4

COL = colonoscopy; FIT = fecal immunochemical test; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared with no screening; SENSA = Hemoccult SENSA; ΔCOL = incremental number of colonoscopies compared with the next-best nondominated strategy; ΔLYG = incremental number of life-years gained compared with the next-best nondominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.
* Bold indicates recommendable strategy. Additional appendix tables and figures are available at www.ahrq.gov.
† Age and intervals expressed as years.
‡ Near-efficient strategies yield life-years gained within 98% of the efficient frontier.