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Stool DNA Testing to Screen for Colorectal Cancer in the Medicare Population

A Cost-Effectiveness Analysis

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Background: The Centers for Medicare & Medicaid Services considered whether to reimburse stool DNA testing for colorectal cancer screening among Medicare enrollees.

Objective: To evaluate the conditions under which stool DNA testing could be cost-effective compared with the colorectal cancer screening tests currently reimbursed by the Centers for Medicare & Medicaid Services.

Design: Comparative microsimulation modeling study using 2 independently developed models.

Data Sources: Derived from literature.

Target Population: A cohort of persons aged 65 years. A sensitivity analysis was also conducted, in which a cohort of persons aged 50 years was studied.

Time Horizon: Lifetime.

Perspective: Third-party payer.

Intervention: Stool DNA test every 3 or 5 years in comparison with currently recommended colorectal cancer screening strategies.

Outcome Measures: Life expectancy, lifetime costs, incremental cost-effectiveness ratios, and threshold costs.

Results of Base-Case Analysis: Assuming a cost of $350 per test, strategies of stool DNA testing every 3 or 5 years yielded fewer life-years and higher costs than the currently recommended colorectal cancer screening strategies. Screening with the stool DNA test would be cost-effective at a per-test cost of $40 to $60 for stool DNA testing every 3 years, depending on the simulation model used. There were no levels of sensitivity and specificity for which stool DNA testing would be cost-effective at its current cost of $350 per test. Stool DNA testing every 3 years would be cost-effective at a cost of $350 per test if the relative adherence to stool DNA testing were at least 50% better than that with other screening tests.

Results of Sensitivity Analysis: None of the results changed substantially when a cohort of persons aged 50 years was considered.

Limitation: No pathways other than the traditional adenoma–carcinoma sequence were modeled.

Conclusion: Stool DNA testing could be a cost-effective alternative for colorectal cancer screening if the cost of the test substantially decreased or if its availability would entice a large fraction of otherwise unscreened persons to receive screening.

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Recently, new studies have described the performance characteristics of stool DNA testing for colorectal cancer screening (1, 2). Although 1 study reported low sensitivity of 2 different stool DNA tests for screening-relevant neoplasms (1), Itzkowitz and coworkers (2) validated a new DNA marker and found a sensitivity of 83% for cancer. Further technological advances are expected, so reasons for optimism remain (3). Even if accuracy improves, however, stool DNA testing should be offered only if it is both effective and cost-effective compared with currently recommended screening tests.

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In August 2007, the Centers for Medicare & Medicaid Services (CMS) initiated a National Coverage Determination process to determine whether a stool DNA test, PreGen-Plus, version 1.1 (Exact Sciences Corporation, Madison, Wisconsin), should be covered as an option for colorectal cancer screening among average-risk Medicare enrollees on a national basis (www.cms.gov/mcd/viewdecisionmemo.asp?id=212). PreGen-Plus consists of a panel of 23 molecular markers associated with colorectal cancer. The test analyzes the DNA for 21 specific point alterations in the *APC*, *K-ras*, and *p53* genes; a marker for microsatellite instability known as BAT-26; and a novel marker known as DNA Integrity Assay—all of which have been associated with the presence of cancer. In response to this National Coverage Determination, 2 colorectal cancer modeling groups from the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network were asked to do a cost-effectiveness analysis of screening with the stool DNA test among the average-risk Medicare population. The objective was to identify the reimbursement rate at which this stool DNA test could be cost-effective com-

pared with the colorectal cancer screening tests currently reimbursed by CMS.

Context

Stool DNA testing is less accurate and more expensive than other colorectal cancer screening tests. However, as second-generation tests develop, accuracy is expected to improve and costs may decrease.

Contribution

The investigators identified conditions under which stool DNA testing might be cost-effective. Those included reductions in cost from about $350 to about $50 per test and use of the test by a large proportion of the population who might not otherwise undergo screening by colonoscopy.

Caution

The analysis assumes a traditional adenoma–carcinoma sequence of cancer development.

Implication

Stool DNA testing will not be a cost-effective screening test for the foreseeable future.

—The Editors

METHODS

We evaluated the cost-effectiveness of stool DNA testing by using 2 existing independently developed microsimulation models of the Cancer Intervention and Surveillance Modeling Network consortium: MISCAN (Microsimulation Screening Analysis, Erasmus University Medical Center, Rotterdam, the Netherlands, and Memorial Sloan-Kettering Cancer Center, New York, New York) and SimCRC (Simulation Model of Colorectal Cancer, University of Minnesota, Minneapolis, Minnesota, and Massachusetts General Hospital, Boston, Massachusetts) (4–7).

The Models

The **Appendix** (available at www.annals.org) describes the MISCAN and SimCRC models, and standardized profiles of each model's structure, underlying assumptions, and calibration methods are available at http://cisnet.cancer.gov/profiles/. In brief, each model simulates the life histories of a large population of persons from birth to death and has a natural history component that tracks the progression of underlying colorectal disease in the absence of screening. As each simulated person ages, there is a chance that 1 or more adenomas may develop, depending on age, sex, race, and individual risk. Adenomas can progress from small (≤5 mm) to medium (6 to 9 mm) to large (≥10 mm), and some may eventually become malignant. Preclinical cancer (that is, not detected) has a chance of progressing through stages I to IV and may be detected by symptoms at any stage. With screening, adenomas and preclinical cancer may be detected depending on the sensitivity of the test for that lesion and, for endoscopic tests, whether the lesion is within reach of the endoscope.

The natural history model outcomes were calibrated to prescreening data from autopsy studies (8–18) and clinical incidence data from the Surveillance, Epidemiology, and End-Results (SEER) Program before the introduction of screening (1975 to 1979) (19). The models use all-cause mortality estimates from the U.S. life tables and colorectal cancer survival data from SEER (1996 to 1999). Both models have been validated against the long-term reductions in incidence and mortality of colorectal cancer with annual fecal occult blood testing (FOBT) reported in the Minnesota Colon Cancer Control Study (20–22) and show good concordance with the trial results. **Appendix Table 1** (available at www.annals.org) compares the outcomes predicted by the natural history models for persons aged 65 years.

Colorectal Cancer Screening Strategies

The National Coverage Determination requested that we evaluate the health effects and costs associated with stool DNA testing every 5 years. In light of the similarities between FOBT and stool DNA screening, we also evaluated a shorter interval of 3 years. We compared the health effects and costs of both strategies with those from the screening strategies currently covered by Medicare (23) and included in most colorectal cancer screening guidelines (24–27): annual FOBT; flexible sigmoidoscopy every 5 years; flexible sigmoidoscopy every 5 years in conjunction with annual FOBT or FOBT every 3 years; and colonoscopy every 10 years. We considered 3 FOBTs (Hemoccult II, Hemoccult SENSA [both manufactured by Beckman Coulter, Fullerton, California], and an immunochemical FOBT) and 2 strategies for sigmoidoscopy (with and without biopsy). In the strategy of sigmoidoscopy with biopsy, a biopsy is done on all detected polyps, and only persons with an adenomatous polyp are referred for a follow-up colonoscopy. In the strategy of sigmoidoscopy without biopsy, all patients with detected polyps are directly referred for colonoscopy. In our primary or base-case analysis, we assumed all persons begin colorectal cancer screening at age 65 years and stop at age 80 years.

Follow-up, Surveillance, and Adherence Assumptions

We assumed that a person with a positive FOBT, sigmoidoscopy, or stool DNA test result would be referred for follow-up colonoscopy and, if that result was negative, would undergo subsequent screening with colonoscopy every 10 years. Persons with adenomas that were detected and removed by colonoscopy (screening or diagnostic) were assumed to undergo colonoscopy surveillance per guidelines (that is, every 3 years among persons with an adenoma of 10 mm or larger or with 3 or more adenomas of any size detected at the last colonoscopy, and every 5 years otherwise) (28). We assumed that surveil-

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

Test	Test Characteristics						Test Costs, by Perspective, $		
	Sensitivity* for Adenomas, by Size, and for CRC, %				Specificity, %	Source (Reference)			
	≤5 mm	6–9 mm	≥10 mm	CRC			CMS†	Modified Societal‡	Source (Reference)
Stool DNA (version 1.1)	4	12	43	70	96	(29–32)	350	367	(33)
Hemoccult II§	2	5	12	40	98	(34)	5	22	Medicare
Hemoccult SENSA§	7	12	24	70	93	(34)	5	22	Medicare
iFOBT	5	10	22	70	95	(34–37)	22	39	Medicare
Sigmoidoscopy without biopsy‖	75	85	95	95	92¶	By assumption	161	270	Medicare
Sigmoidoscopy with biopsy‖	75	85	95	95	92¶	By assumption	348	497	Medicare
Colonoscopy without polypectomy	75	85	95	95	90¶	(38)	522	835	Medicare
Colonoscopy with polypectomy	75	85	95	95	90¶	(38)	673	1019	Medicare
Sensitivity analysis									
Stool DNA (version 1.0)	5	12	15	52	95	(1, 29)	350	367	(33)
Stool DNA (version 2.0)	15	22	55	90	85	(39)	350	367	(33)

CMS = Centers for Medicare & Medicaid Services; CRC = colorectal cancer; iFOBT = immunochemical fecal occult blood test.
* Per individual for fecal occult blood tests and per lesion for endoscopy.
† Costs reflect 2007 CMS payment rates and do not include beneficiary copayments or patient time costs.
‡ Costs reflect 2007 CMS payment rates, beneficiary copayments, and patient time costs.
§ Beckman Coulter, Fullerton, California.
‖ Test characteristics for sigmoidoscopy apply only to lesions in the distal colon and rectum.
¶ The lack of specificity with endoscopic tests reflects the detection of nonadenomatous lesions. With sigmoidoscopy, the presence of nonadenomatous lesions leads to biopsy costs (in the case of sigmoidoscopy with biopsy) or referral for colonoscopy (in the case of sigmoidoscopy without biopsy). With colonoscopy, nonadenomatous lesions are removed and therefore lead to polypectomy and biopsy costs.

lance continued until the diagnosis of colorectal cancer or death. For the base-case analysis, we assumed persons were 100% adherent to the screening test of interest and with the recommended follow-up and surveillance; alternative adherence assumptions were explored in a sensitivity analysis.

Test Characteristics

Test characteristics were based on literature review (**Table 1**). For the stool DNA test, we used the sensitivity for cancer and specificity based on PreGen-Plus, version 1.1 (32). We used studies of the older version of the stool DNA test, version 1.0, to estimate the sensitivity of the test for detecting adenomas (29–31) because the estimates were not available for version 1.1. We further assumed that adenomas smaller than 5 mm were not detectable by the stool DNA test but could be detected as a false-positive result based on the lack of specificity of the test. Patients undergoing colonoscopy and sigmoidoscopy were assumed to be at risk for serious complications (**Table 2**). No complications occurred from FOBT or stool DNA tests.

Costs

The base-case cost-effectiveness analysis was conducted from the CMS perspective. Screening test costs were based on Medicare payments in 2007 (**Table 1**) (46). For the stool DNA test, we used a private insurer reimbursement of $350 as a base case (33). The costs of complications were based on the relevant diagnosis-related group codes (**Table 2**) (46). Net costs of colorectal cancer–related care were obtained from an analysis of 1998 to 2003 SEER-Medicare linked data (47) (Yabroff R, Brown M. Personal communication.) and were updated to 2007 dollars by using the overall Consumer Price Index. Costs from that period do not reflect the use of the expensive monoclonal antibodies bevacizumab and cetuximab. The costs vary by stage at diagnosis and phase of care (**Table 2**).

Cost-Effectiveness Analysis

We used the simulation models to calculate the lifetime costs and life expectancy for a previously unscreened cohort of Medicare beneficiaries aged 65 years under 19 competing strategies, including no screening. We conducted an incremental cost-effectiveness analysis from the perspective of CMS and discounted future costs and life-years by 3% annually to account for time preferences for present over future outcomes (48). Strategies that were more costly and less effective than another strategy were ruled out by strong dominance. Strategies that were more costly and less effective than a combination of other strategies were ruled out by weak dominance. The relative performance of the remaining strategies was measured by using the incremental cost-effectiveness ratio, defined as the additional cost of a specific strategy divided by its additional clinical benefit compared with the next least-expensive strategy. All nondominated strategies represent the set of potentially cost-effective options (depending on the willingness to pay for a life-year gained) and lie on the efficient frontier.

Threshold Analysis

If the stool DNA strategies were found to be dominated by the currently reimbursed screening options, for each stool DNA strategy we calculated the maximum cost per stool DNA test (that is, the threshold cost) for that strategy to lie on the efficient frontier (that is, be cost-effective). Second, because the stool DNA test is still evolving (3), we identified the threshold stool DNA costs for scenarios in which the diagnostic performance of the stool DNA test was improved. The base-case estimates of the sensitivities for small, medium, and large adenomas and for cancer, as well as the estimate for specificity, were increased by 10%, 25%, 50%, 75%, and 100% of the difference between the base-case values and perfect sensitivity and specificity. Finally, because some have suggested that the availability of a stool DNA test as an option for colorectal cancer screening might entice a previously unscreened person to undergo screening, we also identified threshold stool DNA costs for scenarios in which we allowed the adherence of stool DNA strategies to be greater than that of all other screening strategies. For this analysis we assumed an overall adherence rate of 57% for each test (that is, the percentage of Medicare-eligible persons who were adherent to colorectal cancer screening recommendations in the 2005 National Health Interview Survey) (49), with this 57% of the population completely adherent to screening and the remainder completely nonadherent. Modeling adherence in this manner allowed us to evaluate the effect of enhancing screening participation among a previously unscreened segment of the population. We varied the adherence for a stool DNA strategy from 57% to 100%. Subsequently, threshold costs for stool DNA were calculated comparing overall costs and life-years saved by using stool DNA at these higher adherence rates to competing strategies at an adherence rate of 57%.

Sensitivity Analysis

To evaluate how the estimated stool DNA threshold costs were influenced by our assumptions, we also identified threshold costs in sensitivity analyses with alternative assumptions. First, we explored the effect of a screening interval of 1 year for stool DNA testing. Second, we considered alternative stool DNA test versions. We evaluated version 1.0 (the only stool DNA test that has been evaluated in a general population setting) (1, 29) and a newer version of the stool DNA test (version 2.0) (39). **Table 1** shows the test characteristics.

Next, we repeated our base-case threshold analysis for a cohort of persons aged 50 years with screening beginning at age 50 years, as recommended in colorectal cancer screening guidelines (24–27). Finally, we conducted an analysis from a modified societal perspective by including direct costs borne by beneficiaries, as well as patient-time costs. We did not incorporate productivity costs. **Tables 1** and **2** show cost inputs for the modified societal perspective.

Role of the Funding Source

The Agency for Healthcare Research and Quality and the National Cancer Institute supported the research for

Table 2. **Model Inputs for Complication Rates and Costs and CRC Treatment Costs**

Test Complication	Complication Rate per 1000 Procedures	Complication Cost, by Perspective, $*		Annual Cost of Cancer Treatment, by Stage at Diagnosis, Phase of Care, and Perspective, $*†				
				Stage	Initial	Continuing	Terminal, by Cause of Death	
		CMS	Modified Societal				CRC	Other Cause
					CMS Perspective			
Sigmoidoscopy (40)								
Perforation	0.02	12 446	12 712	I	25 487	2028	45 689	11 257
Colonoscopy (41–45)				II	35 173	1890	45 560	9846
Perforation	0.7	12 446	12 712	III	42 885	2702	48 006	13 026
Serosal burn	0.3	5208	5474	IV	56 000	8375	64 428	34 975
					Modified Societal Perspective‡			
Bleeding event with transfusion	0.4	5208	5474					
Bleeding event without transfusion	1.1	320	586	I	32 720	2719	56 640	17 408
				II	43 752	2561	56 417	15 740
FOBT	0	NA	NA	III	53 003	3573	59 481	19 413
Stool DNA test	0	NA	NA	IV	68 853	10 743	78 227	44 384

CMS = Centers for Medicare & Medicaid Services; CRC = colorectal cancer; FOBT = fecal occult blood test; NA = not applicable.
* Costs from the CMS perspective do not include beneficiary copayments, patient time costs, or lost productivity due to early death or disability. Costs from the modified societal perspective include beneficiary copayments and patient time costs but do not include lost productivity due to early death or disability.
† The initial phase of care is the first 12 mo after diagnosis, the last year of life phase is the final 12 mo of life, and the continuing phase is all the months between the initial and last year of life phases.
‡ To incorporate patient time costs associated with CRC screening, we assumed that the value of patient time was equal to the median U.S. wage rate in 2007 from the Bureau of Labor Statistics ($16.64 per h). We assumed that the time associated with a colonoscopy was 8 h, with flexible sigmoidoscopy lasting 4 h, and FOBTs lasting 1 h. For treatment of complications with colonoscopy and sigmoidoscopy, we assumed that patient time requirements would be 16 h on average. Estimated patient deductibles and coinsurance expenses for CRC treatment were added by adjusting Part A and Part B payments with Medicare reimbursement ratios provided by the CMS Office of the Actuary.

this report. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or decision to submit this manuscript for publication.

RESULTS

In the absence of screening, the 2 models project that 57 of every 1000 persons aged 65 years will receive a diagnosis of colorectal cancer in their lifetime (**Table 3**). With screening, many of these cases can be prevented. Assuming 100% adherence, the reduction in the lifetime risk for colorectal cancer ranged from 32% to 40% with annual Hemoccult II screening to 53% to 72% with colonoscopy screening every 10 years (the reported ranges reflect differences in projections by model). Colorectal cancer risk reduction with stool DNA testing was similar to that of Hemoccult II and varied from 30% to 49% depending on the simulation model and the interval used.

Figure 1 shows a plot of total life-years gained (compared with no screening) and total lifetime direct medical costs from the Medicare perspective for each of the 18 screening strategies, and the efficient frontier: the economically rational subset of choices. Stool DNA testing every 5 years was the least effective of all evaluated screening strategies, whereas the 3-year strategy was only slightly more effective than annual Hemoccult II. Assuming reimbursement at $350 per test, both stool DNA testing strategies were the most expensive, lying to the far right of the cost-efficient frontier. Although dominated by the currently recommended screening options, the costs per life-year gained compared with no screening were less than $15 000 for both screening intervals and models (**Appendix Table 2**, available at www.annals.org).

Table 3. **Undiscounted Number of Cases of and Deaths From CRC Per 1000 Persons Aged 65 Years, by Screening Scenario***

Scenario	MISCAN		SimCRC	
	CRC Cases	CRC Deaths	CRC Cases	CRC Deaths
No screening	57	27	57	27
HII	39	13	34	12
HS	32	10	25	8
iFOBT	33	11	26	8
SIGB	30	11	28	12
SIG	30	11	26	11
HII + SIGB	29	10	22	8
HII + SIG	28	10	21	7
HS + SIGB	27	9	18	6
HS + SIG	27	9	18	6
HS (3 y) + SIGB	29	10	22	8
HS (3 y) + SIG	28	10	22	8
iFOBT + SIGB	28	9	19	6
iFOBT + SIG	27	9	18	6
iFOBT (3 y) + SIGB	29	10	23	8
iFOBT (3 y) + SIG	28	10	22	8
COL	27	10	16	6
Stool DNA (3 y)	37	13	29	10
Stool DNA (5 y)	40	15	34	13

COL = colonoscopy every 10 y; CRC = colorectal cancer; HII = annual Hemoccult II; HS = annual Hemoccult SENSA; HS (3 y) = Hemoccult SENSA every 3 y; iFOBT = annual immunochemical fecal occult blood test; iFOBT (3 y) = immunochemical fecal occult blood test every 3 y; SIG = sigmoidoscopy without biopsy every 5 y; SIGB = sigmoidoscopy with biopsy every 5 y.
* Hemoccult II and Hemoccult SENSA are manufactured by Beckman Coulter, Fullerton, California.

Threshold Analyses

Threshold analyses indicated that to be cost-effective, the stool DNA test would need to cost $34 to $51 when done every 5 years or $40 to $60 when done every 3 years, depending on the simulation model used. Analysis of 3- and 5-year stool DNA testing with the SimCRC model identified no sensitivity or specificity estimates for which the threshold value of the cost of the stool DNA test could be greater than its base-case value of $350 and still lie on the efficient frontier (**Figure 2**). With the MISCAN model, the cost of the stool DNA test may increase to $364 if the test is perfect with respect to sensitivity and specificity and if offered every 5 years.

Analyses with the MISCAN model showed that adherence to stool DNA testing has to be almost 50% better than with other tests for stool DNA testing every 3 years to be on the frontier at the base-case cost of $350 (**Figure 2**). With the SimCRC model, the relative adherence to stool DNA testing had to be 50% to 75% better than adherence to other methods for stool DNA testing every 3 years to be on the frontier at the base-case cost of $350.

Sensitivity Analyses

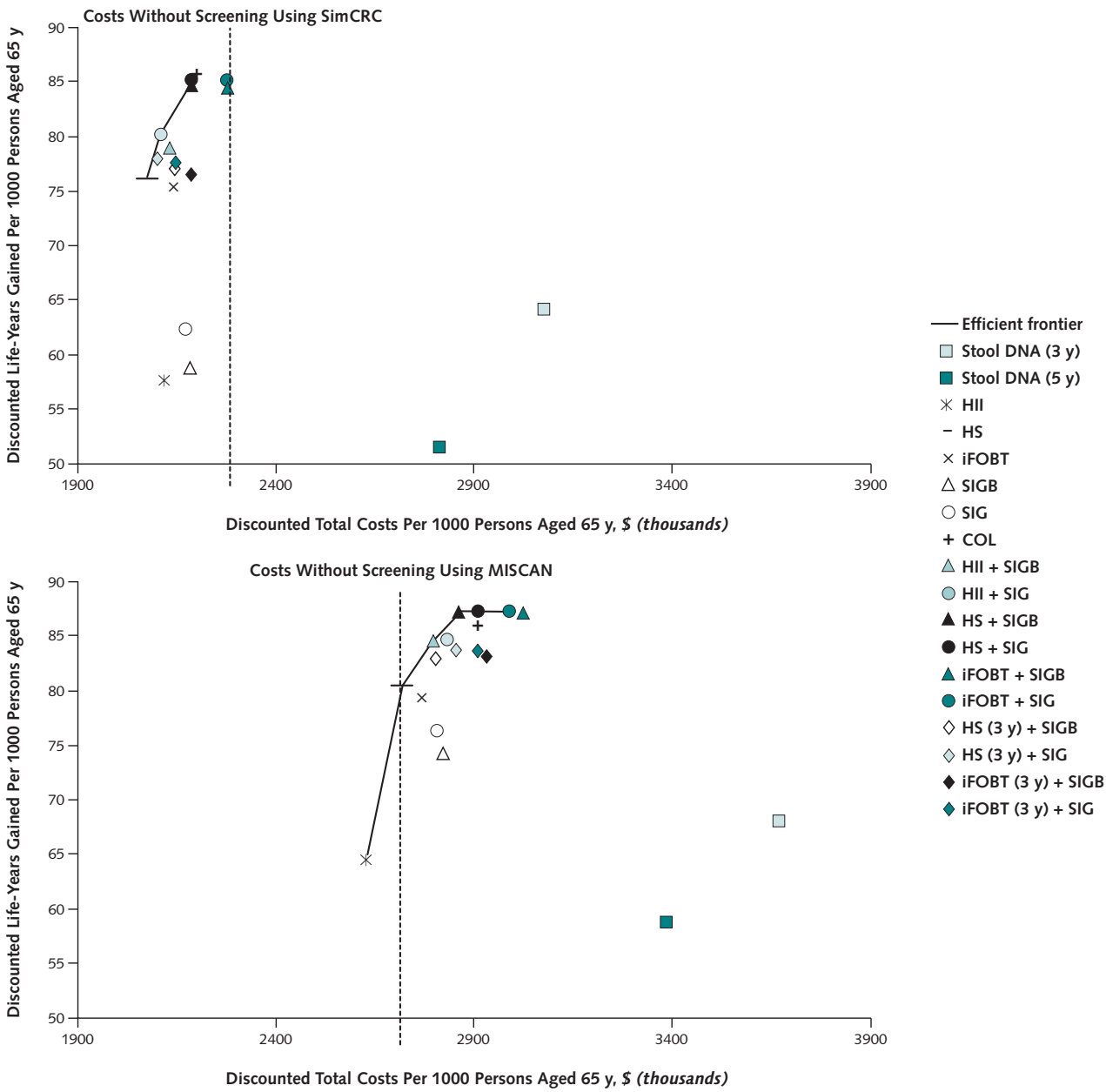
Offering DNA testing annually did not change the threshold costs ($40 to $48). No threshold cost exists at which the stool DNA testing with version 1.0 could be a cost-effective alternative for colorectal cancer screening. For version 2.0, threshold costs were $2 to $31, which are less than the base-case threshold costs. Only from a modified societal perspective did the threshold costs of the stool DNA testing (excluding copayments and patient-time costs) increase somewhat compared with the base-case estimate: $88 to $134 for the 5-year interval and $73 to $116 for the 3-year interval. The higher frequency of FOBT scenarios results in considerably higher additional time costs than with stool DNA screening, allowing for higher per-test costs for the stool DNA test.

None of these results changed substantially when considering a cohort of persons aged 50 years instead of persons aged 65 years in the Medicare-eligible cohort. The threshold costs would have to decrease to $27 to $52 for stool DNA testing to be on the efficient frontier.

DISCUSSION

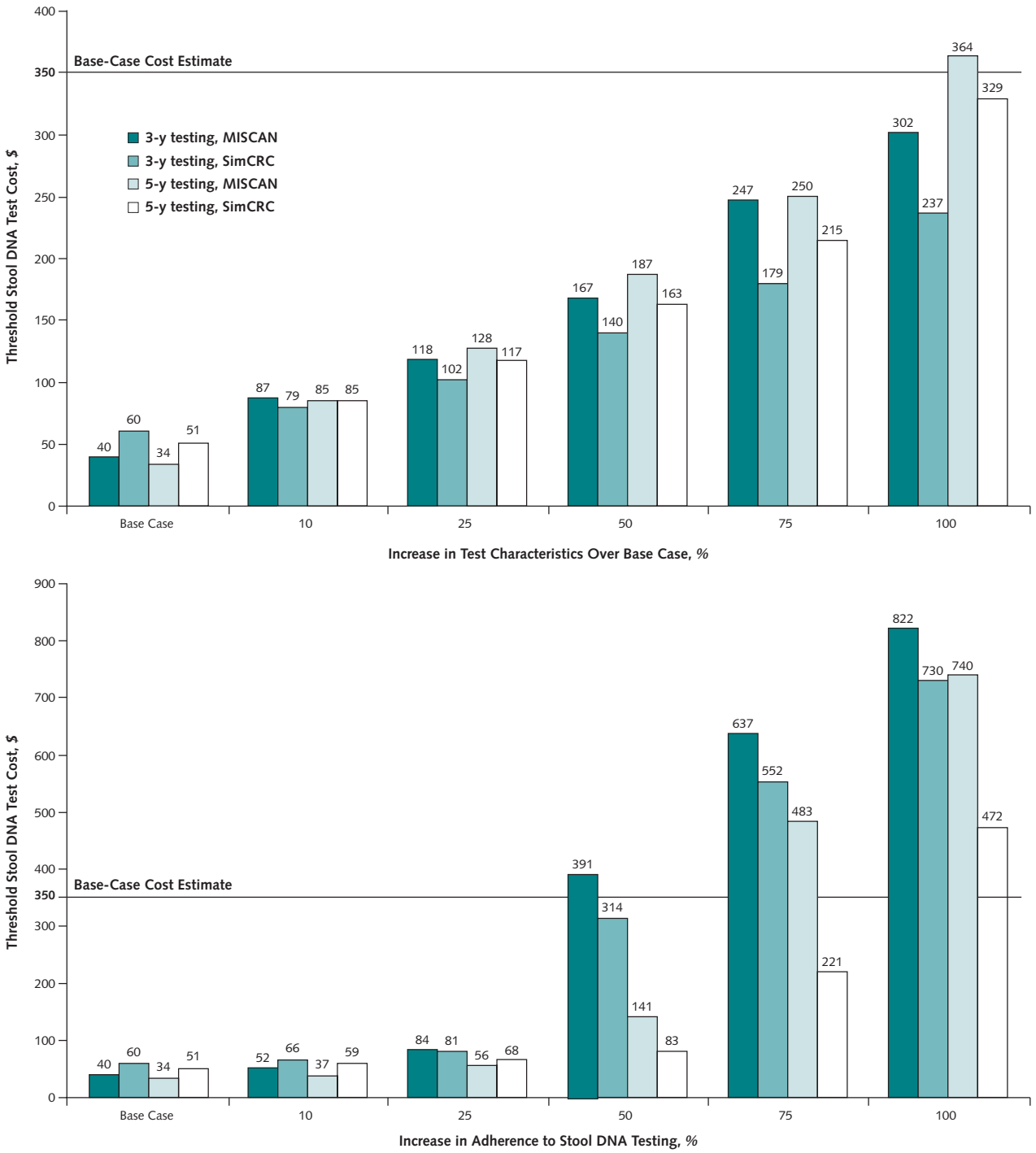
Our analysis showed that stool DNA testing every 3 and 5 years were both more costly and less effective than annual screening with a sensitive FOBT. Screening with a stool DNA test would be an efficient strategy at a per-test

Figure 1. **Discounted costs and discounted life-years gained per 1000 persons aged 65 years for 18 colorectal cancer screening strategies and the efficient frontier connecting the efficient strategies.**



Discounted costs and life-years reflect total costs and life-years gained of a screening program (SimCRC [*top*] or MISCAN [*bottom*]), accounting for time preference for present over future outcomes. Life-years gained are plotted on the *y*-axis, and total costs are plotted on the *x*-axis. Each possible screening strategy is represented by a point (50). Strategies that form the solid line connecting the points lying left and upward are the economically rational subset of choices. This line is called the *efficient frontier*. The inverse slope of the line represents the incremental cost-effectiveness ratio of the connected strategies (values presented in **Appendix Table 2** [available at www.annals.org]). Points lying to the right and beneath the line represent the dominated strategies. Stool DNA testing has higher costs and fewer life-years gained than Hemoccult SENSA, and the stool DNA strategies are therefore strongly dominated. Hemoccult II and Hemoccult SENSA are manufactured by Beckman Coulter, Fullerton, California. COL = colonoscopy every 10 y; HII = annual Hemoccult II; HS = annual Hemoccult SENSA; HS (3 y) = Hemoccult SENSA every 3 y; iFOBT = annual immunochemical fecal occult blood test; iFOBT (3 y) = immunochemical fecal occult blood test every 3 y; SIG = sigmoidoscopy without biopsy every 5 y; SIGB = sigmoidoscopy with biopsy every 5 y.

Figure 2. **Cost thresholds of stool DNA tests at which the stool DNA strategies are more efficient than other reimbursed colorectal cancer screening strategies for different levels of test characteristics (*top*) and adherence (*bottom*).**



All sensitivities and the specificity for stool DNA were improved from their baseline value up to 100%; the percentage on the *x*-axis represents the relative improvement over that interval, and the absolute improvement varies depending on the baseline value for sensitivity and specificity. Adherence for stool DNA was improved from its baseline value of 57% up to 100%; the percentage on the *x*-axis represents the relative improvement over that interval.

cost of $34 to $60, depending on the screening interval (3 or 5 years) and model used. Only if the relative adherence to stool DNA testing were 50% better than other screening tests would the test be cost-effective at current test costs. These results hold both for the Medicare-eligible population as well as the general screening population. The fact that 2 independently developed models come to similar conclusions with respect to cost-effectiveness and threshold costs of stool DNA screening shows the robustness of the results for model uncertainties, particularly pertaining to the natural history of colorectal disease.

We had anticipated that stool DNA testing would be dominated by screening with a sensitive FOBT given that the stool DNA test has similar sensitivity and specificity as those of Hemoccult SENSA, with a cost that is almost 80 times greater. Consequently, the aim of our analysis was to explore the conditions under which stool DNA testing could compete with the existing screening tests. We have explored only the potential of stool DNA testing for colorectal cancer screening. The test might also have prognostic or even treatment implications (for example, through risk stratification based on genetic markers or by guiding the use of genomic-targeted therapies). However, in this case, the test becomes a diagnostic tool that can be administered at the time of diagnosis of colorectal cancer rather than a presymptomatic screening test. The evaluation of the cost-effectiveness of a stool DNA test as a diagnostic test is beyond the scope of our analysis.

Because stool DNA testing is still evolving (3), we evaluated threshold costs for improved test characteristics. Such improvements can be expected, given technological advances in the form of more sensitive polymerase chain reaction strategies (3). However, the threshold costs for the latest published version of the stool DNA test (version 2.0) (39) are less than those for the base-case stool DNA test (version 1.1) because of the many unnecessary colonoscopies brought about by the considerably lower specificity. Even under the extreme assumption of perfect sensitivity and specificity, the threshold cost for the stool DNA test remained less than $350 at intervals of 3 or 5 years.

Substantially higher adherence to stool DNA testing would make stool DNA screening cost-effective at $350. However, although the stool DNA test has been shown to be acceptable for patients who have already agreed to participate in a screening program (51, 52), no evidence supports that screening adherence to stool DNA testing would be substantially better than with other tests. Adherence needs to be 50% better than even FOBT, and because both types of tests are noninvasive, this is unlikely. In the absence of this adherence benefit, stool DNA remains dominated.

Stool DNA testing is currently included in the American Cancer Society guidelines for colorectal cancer screening (24). Twelve U.S. states and the District of Columbia have legislative mandates requiring that certain insurers should offer all screening options of the current American Cancer Society guidelines. As a consequence, coverage of stool DNA screening is now mandated in these states (53). For every person aged 65 years who switches from Hemoccult SENSA or colonoscopy screening to stool DNA screening, colorectal cancer screening costs would increase on average by $750 to $1250 (results not shown), whereas the life-years saved would on average decrease. Currently, 2.6 million persons aged 65 years live in the United States (54), so on a national level, stool DNA screening could potentially lead to an unnecessary expenditure of $3 billion per year and an unnecessary 10 400 to 23 400 cases of colorectal cancer and 5200 to 13 000 colorectal cancer deaths when compared with Hemoccult SENSA, an alternative noninvasive screening test. These figures would be even higher if the complete target population for screening from age 50 years were considered.

Our findings are similar to those of 2 published cost-effectiveness analyses of stool DNA screening (55, 56). Like ours, both analyses concluded that the stool DNA test was dominated by currently recommended colorectal cancer screening tests. Wu and colleagues (56) found threshold costs that were slightly higher ($57 to $70) than the threshold costs in our analysis. However, those threshold costs were based on a willingness to pay $13 000 per life-year gained compared with no screening. Song and coworkers (55) found threshold costs of $195 when comparing stool DNA testing every 2 years with colonoscopy every 10 years and assuming considerably higher colonoscopy costs. A similar comparison in the MISCAN and SimCRC models yielded threshold costs of $205 to $213.

The models have several limitations. First, they simulate the progression from adenoma to colorectal cancer by increasing the size of the adenomas over time. Because adenoma size and the presence of villous components or high-grade dysplasia are highly correlated (57), size indirectly represents histology and grade. However, neither model separately simulates the step from adenoma with low-grade dysplasia to an adenoma with high-grade dysplasia. If the advantage of a stool DNA test is detection of a smaller adenoma at the stage of high-grade dysplasia, we may underestimate its effectiveness. Second, we assumed that all types of colorectal cancer arise through the traditional adenoma–carcinoma sequence, with a linear sequence of mutations in the *APC*, *K-ras*, and *p53* genes. Recent data indicate the probable existence of at least 1 alternative pathway to colorectal cancer through a mutation of the *BRAF* gene (58). Existence of different pathways will probably not influence the performance of FOBT because bleeding of a lesion is unlikely to be related to the pathway. It may influence sensitivity of endoscopy because lesions from this pathway are more likely to be proximal and sessile or flat and therefore more difficult to find. However, for the stool DNA test, the lesion in question may have acquired a gene mutation not assessed by the test. In this case, a person with a false-negative result on such a test will have a higher-than-average probability of

having a negative test result with subsequent screenings. Consequently, we may have overestimated the benefit and the threshold cost of this test.

In conclusion, our analysis shows that future developments of the stool DNA test should not only focus on improving test characteristics but also on reducing test cost. The first stool DNA assay that reached the market was expensive ($795); a more recent stool assay for vimentin methylation alone was introduced this year at a cost of $220 (3). These numbers offer hope that further technological refinements will permit substantial cost reductions. We currently lack good information on the performance characteristics of these new tests. When the performance levels of newer versions of the stool DNA test become available, the results of our sensitivity analysis can be used to determine their cost-effectiveness. If the cost of the test is higher than the threshold costs associated with the level of performance of the new test, it will not be cost-effective. Our analysis shows that improving tests characteristics alone is insufficient to make stool DNA testing cost-effective. Without further cost reductions, stool DNA screening will not be a cost-effective alternative for average-risk colorectal cancer screening in the Medicare population or the general screening population.

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Appendix: Model Descriptions

Microsimulation Models

The MISCAN and SimCRC models from the National Cancer Institute Cancer Intervention and Surveillance Modeling Network consortium were used to address the question of the cost-effectiveness of screening with stool DNA testing. The models used common inputs and assumptions concerning the screening tests but use their independently developed natural history models in addressing these questions.

Description of the MISCAN Model for Natural History and Intervention

MISCAN Model Overview

MISCAN is a semi-Markov microsimulation model to simulate the effect of screening and other interventions on colorectal cancer incidence and mortality. The model has been programmed in Borland Delphi 7 Enterprise (Borland, Austin, Texas). With microsimulation, we mean that each individual in the population is simulated separately. The model is semi-Markov in the sense that distributions other than exponential are possible in each disease state, transitions in 1 state can depend on transitions in earlier states, and transitions can be age- and (calendar) time-dependent. All events in the model are discrete, but the durations in each state are continuous. Hence, no annual transitions occur in the model.

The development of colorectal cancer in the model is assumed to occur according to the adenoma–carcinoma sequence. This means that adenomas arise in the population, some of which eventually develop into colorectal cancer. We assume that 2 types of adenomas exist: progressive and nonprogressive adenomas. 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 are initially small (≤5 mm). They can grow in size to medium (6 to 9 mm) and large (≥10 mm). Progressive medium and large adenomas can transform into malignant cancer stage I, not yet giving symptoms (preclinical cancer). The cancer then progresses from stage I (localized) eventually to stage IV (distant metastasis). In each stage, there is a probability of the cancer giving symptoms and being clinically detected. The time between the onset of a progressive adenoma and the clinical detection of colorectal cancer is assumed to be on average 20 years. After clinical detection, a person can die of colorectal cancer or of other causes based on the survival rate. The survival from colorectal cancer is highly dependent on the stage in which the cancer was detected.

MISCAN Simulation of an Individual

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

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 the state a person is in is the same as the state of the most advanced adenoma or cancer present. If he dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly. The combined life history with colorectal cancer is shown in the bottom line of **Appendix Figure 1**.

MISCAN Simulation of Screening

The complete simulation of an individual life history in **Appendix Figure 1** is in a situation without screening taking 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, detected, and removed. This results in a combined life history for colorectal cancer and screening (bottom line), in which the person has no adenoma or carcinoma

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 with screening and the situation without screening (**Appendix Figure 2**).

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 would have been that one of the adenomas was missed, but in the present example, the individual really benefited from the screening intervention.

The effectiveness of screening depends on the performance characteristics of the test done: sensitivity, specificity, and reach. In the model, 1 minus the specificity is defined as the probability of a positive test result in a person, regardless of any adenomas or types of cancer present. For a person without any adenomas or cancer, the probability of a positive test result is therefore equal to 1 minus the specificity. In persons 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, in which each adenoma or cancer contributes to the probability of a positive test result.

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

Description of the SimCRC Model for Natural History and Intervention

SimCRC Model Overview

The SimCRC model of colorectal cancer was developed to evaluate the effect of past and future interventions on colorectal cancer incidence and mortality in the United States. The programming language Visual C++ 2008 Express Edition (Microsoft, Seattle, Washington) was used to program the model. The model is population based, meaning that it simulates the life histories of several cohorts of persons of a given birth year. 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—persons aged 65 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.

SimCRC Simulation of the Natural History of Colorectal Cancer

The SimCRC natural history model describes the progression of underlying colorectal disease (that is, the adenoma–carcinoma sequence) among 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 (≤5 mm) to medium (6 to 9 mm) to large (≥10 mm). Medium and large adenomas may progress to preclinical colorectal cancer, although most will not in an individual's lifetime. Preclinical cancer 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 cancer or of other causes.

The SimCRC model allows for heterogeneity in growth and progression rates across several adenomas within a person. 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.

SimCRC Simulation of Screening

The screening component of the SimCRC model is superimposed on the natural history model. It allows for the detection and removal of adenomas and the diagnosis of preclinical 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 based on the sensitivity of the test for adenomas by size or for cancer and, for endoscopic tests, the reach of the endoscope. Persons who do not have an underlying adenoma or preclinical cancer also face the risk for having a positive screening test (and undergoing unnecessary follow-up procedures) due to 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, persons with false-negative screening test results (that is, persons 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 persons adhere to colorectal cancer screening guidelines and that adherence patterns are correlated within a person.

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

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

Variable	MISCAN					SimCRC				
Adenoma prevalence at age 65 y, %	39.8					37.1				
Number of adenomas per 1000 persons, by site and size at age 65 y	**≤5 mm**	**6–9 mm**	**≥10 mm**	**Total**		**≤5 mm**	**6–9 mm**	**≥10 mm**	**Total**	
Proximal colon	121.2	69.9	61.8	–		171.8	185.8	23.9	–	
Distal colon	134.4	77.4	68.4	–		123.9	18.3	41.4	–	
Rectum	133.5	76.8	68.1	–		8.7	16.0	15.6	–	
Distribution of adenomas, by site and size at age 65 y, %										
Proximal colon	15	9	8	31		28	31	4	63	
Distal colon	17	10	8	35		20	3	7	30	
Rectum	16	9	8	34		1	3	3	7	
CRC incidence among cancer-free population (age 65 y), %	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**Total**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**Total**
10-y	0.4	0.7	0.5	0.5	2.1	0.4	0.7	0.5	0.5	2.1
20-y	0.8	1.6	1.0	1.0	4.4	0.8	1.5	1.0	1.2	4.4
Lifetime	1.0	2.1	1.3	1.3	5.7	0.9	1.9	1.3	1.5	5.7

CRC = colorectal cancer.

Appendix Table 2. Discounted Costs and Discounted Life-Years Gained per 1000 Persons Aged 65 Years Without Colorectal Cancer Screening and With 18 Colorectal Cancer Screening Strategies and Associated Incremental and Average Cost-Effectiveness Ratios*

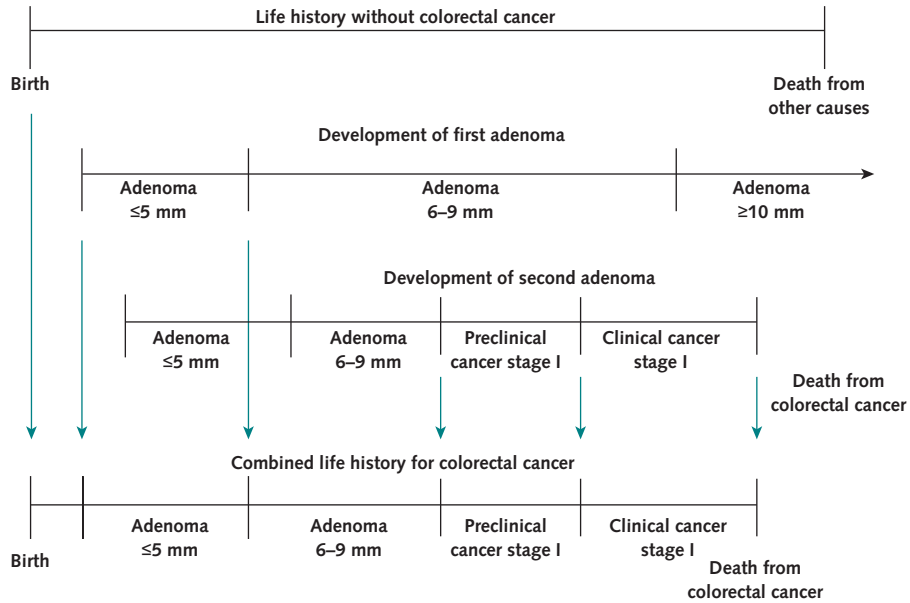
Strategy	MISCAN				SimCRC			
	Discounted Costs, $	**Discounted LYG**	**CER, $**	**ICER, $**	**Discounted Costs, $**	**Discounted LYG**	**CER, $**	**ICER, $**
No screening	2 714 600	0	NA	d	2 295 600	0	NA	d
HII	2 630 600	65.1	CS	–	2 122 000	57.9	CS	d
HS	2 715 300	80.4	10	5600	2 078 600	76.1	CS	–
IFOBT	2 776 800	79.4	800	d	2 155 700	75.0	CS	d
SIGB	2 823 200	74.3	1500	d	2 189 100	58.7	CS	d
SIG	2 810 500	76.2	1300	d	2 176 800	62.4	CS	d
HS (3 y) + SIGB	2 798 200	83.1	1000	d	2 143 200	77.0	CS	d
HS (3 y) + SIG	2 857 200	83.7	1700	d	2 106 600	77.9	CS	d
iFOBT (3 y) + SIGB	2 932 700	82.9	2600	d	2 187 300	76.6	CS	d
iFOBT (3 y) + SIG	2 912 300	83.6	2400	d	2 148 700	77.5	CS	d
HII + SIGB	2 793 800	84.1	900	20 800	2 127 300	79.0	CS	d
HII + SIG	2 840 500	84.6	1500	d	2 113 600	80.2	CS	8500
HS + SIGB	2 863 800	87.1	1700	23 900	2 187 800	84.7	CS	d
HS + SIG	2 909 400	87.1	2200	d	2 187 000	85.2	CS	14 700
iFOBT + SIGB	3 025 600	87.1	3600	d	2 282 400	84.6	CS	d
iFOBT + SIG	2 992 800	87.2	3200	924 800	2 283 000	85.1	CS	d
COL	2 906 100	86.2	2200	d	2 199 800	85.5	CS	42 600
Stool DNA (3 y)†	3 673 500	68.0	14 100	d	3 081 300	64.2	12 200	d
Stool DNA (5 y)†	3 382 900	58.8	11 400	d	2 814 300	51.4	10 000	d

– = indicates default strategy (i.e., the least costly and least effective nondominated strategy); CER = cost-effectiveness ratio vs. no screening; COL = colonoscopy every 10 y; d = dominated; HII = annual Hemoccult II; HS = annual Hemoccult SENSA; HS (3 y) = Hemoccult SENSA every 3 y; ICER = incremental cost-effectiveness ratio; iFOBT (3 y) = immunochemical fecal occult blood test every 3 y; iFOBT = annual immunochemical fecal occult blood test; LYG = life-years gained vs. no screening; NA = not applicable; SIG = sigmoidoscopy without biopsy every 5 y; SIGB = sigmoidoscopy with biopsy every 5 y.

* Hemoccult II and Hemoccult SENSA are manufactured by Beckman Coulter, Fullerton, California.

† The 2 stool DNA strategies are not competing options. They are shown here together for comparison purposes only. The ICERs are assessed separately using each stool DNA strategy in turn.

Appendix Figure 1. **MISCAN and SimCRC modeling of natural history into life history.**



Appendix Figure 2. **MISCAN and SimCRC modeling of screening into life history.**