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Should Colorectal Cancer Screening Be Considered in Elderly Persons Without Previous Screening?

A Cost-Effectiveness Analysis

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Background: The U.S. Preventive Services Task Force recommends against routine screening for colorectal cancer (CRC) in adequately screened persons older than 75 years but does not address the appropriateness of screening in elderly persons without previous screening.

Objective: To determine at what ages CRC screening should be considered in unscreened elderly persons and to determine which test is indicated at each age.

Design: Microsimulation modeling study.

Data Sources: Observational and experimental studies.

Target Population: Unscreened persons aged 76 to 90 years with no, moderate, and severe comorbid conditions.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: One-time colonoscopy, sigmoidoscopy, or fecal immunochemical test (FIT) screening.

Outcome Measures: Quality-adjusted life-years gained, costs, and costs per quality-adjusted life-year gained.

Results of Base-Case Analysis: In unscreened elderly persons with no comorbid conditions, CRC screening was cost-effective up to age 86 years. Screening with colonoscopy was indicated up to age 83 years, sigmoidoscopy was indicated at age 84 years, and FIT was indicated at ages 85 and 86 years. In unscreened persons with moderate comorbid conditions, screening was cost-effective up to age 83 years (colonoscopy indicated up to age 80 years, sigmoidoscopy at age 81 years, and FIT at ages 82 and 83 years). In unscreened persons with severe comorbid conditions, screening was cost-effective up to age 80 years (colonoscopy indicated up to age 77 years, sigmoidoscopy at age 78 years, and FIT at ages 79 and 80 years).

Results of Sensitivity Analyses: Results were most sensitive to assuming a lower willingness to pay per quality-adjusted life-year gained.

Limitation: Only persons at average risk for CRC were considered.

Conclusion: In unscreened elderly persons CRC screening should be considered well beyond age 75 years. A colonoscopy is indicated at most ages.

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In its most recent recommendation statement on colorectal cancer (CRC) screening, the U.S. Preventive Services Task Force (USPSTF) recommends screening using fecal occult blood testing, sigmoidoscopy, or colonoscopy, starting at age 50 years and continuing up to age 75 years (1). The USPSTF recommends against routine screening in persons older than 75 years with an adequate screening history (1). This latter recommendation is warranted by an analysis showing that the benefits of continuing screening from age 50 to 85 years instead of 75 years do not justify the additional colonoscopies required (2). Although the USPSTF did not address the appropriateness of screening in inadequately screened elderly persons, this recommendation has led many members of the medical community to believe that no one older than 75 years should be screened for CRC (3, 4). However, because unscreened elderly persons are at greater risk for CRC than adequately screened elderly persons, screening them is likely to be effective and cost-effective up to a more advanced age. If so, the lack of more specific recommendations on the age to stop screening may result in an unfounded denial of access to screening in elderly persons who were never screened for CRC—a group representing 23% of all U.S. persons older than 75 years (5).

Many other elderly persons continue to be screened up to their late 80s or early 90s (6). However, at these ages, screening is not likely to be cost-effective, even in those without previous screening. First, the high risk for death of competing disease at advanced age tends to offset the benefits of screening (7, 8). Second, the risks for screening-induced harms (colonoscopy-related complications and overdiagnosis and overtreatment of CRC) increase with increasing age (9).

The objective of this study was to determine up to what age CRC screening should be considered in elderly persons without previous screening and to determine which screening test—colonoscopy, sigmoidoscopy, or fecal immunochemical test (FIT)—is indicated at what age.

See also:

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We performed separate analyses for elderly persons with no, moderate, and severe comorbid conditions because the effectiveness and cost-effectiveness of screening depend heavily on a person's life expectancy.

Context

Some guidelines caution against routine screening for colorectal cancer in persons older than 75 years who have already been screened, but these guidelines ignore persons who have not been screened.

Contribution

This study estimates that screening persons who have not been screened has good value up to age 86 years for persons with no comorbid conditions, up to age 83 years for those with moderate comorbid conditions, and up to age 80 years for those with severe comorbid conditions.

Caution

Only persons at average risk for colorectal cancer were studied.

Implication

Screening should be considered for some persons older than 75 years who have not already been screened.

—The Editors

METHODS

We used the Microsimulation Screening Analysis–Colon (MISCAN-Colon) model (Erasmus University Medical Center, Rotterdam, the Netherlands) to quantify the effectiveness and costs of screening.

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Center. The model's structure, underlying assumptions, and calibration are described in the **Appendix** (available at www.annals.org). In brief, MISCAN-Colon simulates the life histories of a large population from birth to death. As each simulated person ages, 1 or more adenomas may develop. These adenomas can progress from small (≤5 mm) to medium (6 to 9 mm) to large (≥10 mm) size. Some adenomas can develop into preclinical cancer, which may progress through stages I to IV. During each stage, CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the localization of the cancer, and the person's age (10).

Screening will alter some of the simulated life histories: Some cancer cases will be prevented by the detection and removal of adenomas; other cancer cases will be detected in an earlier stage with a more favorable survival. However, screening can also result in serious complications and overdiagnosis and overtreatment of CRC (that is, the detection and treatment of cancer that would not have been diagnosed without screening). By comparing all life histories with screening with the corresponding life histories without screening, MISCAN-Colon quantifies the effectiveness of screening as well as the associated costs.

MISCAN-Colon was calibrated to the age-, stage-, and localization-specific incidence of CRC as seen in the SEER (Surveillance, Epidemiology, and End Results) Program before the introduction of screening (that is, between 1975 and 1979) and the age-specific prevalence and multiplicity distribution of adenomas seen in autopsy studies (11–21). The preclinical duration of CRC and the adenoma dwell time were calibrated to the rates of interval and surveillance-detected cancer seen in randomized, controlled trials evaluating screening using guaiac fecal occult blood tests and a 1-time sigmoidoscopy (22–26).

Model Inputs

Populations Simulated

For each age between 76 and 90 years, we simulated a cohort of 10 million elderly persons without previous screening with no, moderate, and severe comorbid conditions (a total of 45 cohorts). Compared with cohorts of adequately screened elderly persons, the risk for CRC in these cohorts was substantially greater: CRC and adenomas were prevalent in 0.3% and 14.1%, respectively, of simulated patients aged 80 years with negative screening colonoscopies at ages 50, 60, and 70 years and in 2.6% and 44.9%, respectively, of simulated patients aged 80 years without previous screening.

We used comorbid condition level–specific life tables to simulate elderly persons with no, moderate, and severe comorbid conditions (27). Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions are present.

Screening Strategies

We simulated 1-time colonoscopy, 1-time sigmoidoscopy, and 1-time FIT screening within each cohort. Test characteristics and complication rates for each screening test are given in **Appendix Table 1** (available at www.annals.org). Patients with an adenoma or CRC detected during sigmoidoscopy or with a positive FIT result were referred for a diagnostic colonoscopy. Persons with adenomas detected and removed during a screening or diagnostic colonoscopy were assumed to have colonoscopy surveillance according to the current guidelines (28). We assumed that surveillance continued until the diagnosis of CRC or

Table 1. **Utility Losses and Costs Associated With CRC Screening**

Variable	Screening Tests and Complications	Initial Care	Continuing Care	Terminal Care, Ending in CRC Death	Terminal Care, Ending in Other-Cause Death
Utility loss, *QALYs**					
Per FIT	0	–	–	–	–
Per sigmoidoscopy					
Without biopsy	0.0027	–	–	–	–
With biopsy	0.0027	–	–	–	–
Per colonoscopy					
Without polypectomy/biopsy	0.0055	–	–	–	–
With polypectomy/biopsy	0.0055	–	–	–	–
Per complication of colonoscopy	0.0384	–	–	–	–
Per LY with CRC care†‡					
Stage I CRC	–	0.12	0.05	0.70	0.05
Stage II CRC	–	0.18	0.05	0.70	0.05
Stage III CRC	–	0.24	0.24	0.70	0.24
Stage IV CRC	–	0.70	0.70	0.70	0.70
Costs, $§					
Per FIT	42	–	–	–	–
Per sigmoidoscopy					
Without biopsy	299	–	–	–	–
With biopsy	557	–	–	–	–
Per colonoscopy					
Without polypectomy/biopsy	887	–	–	–	–
With polypectomy/biopsy	1096	–	–	–	–
Per complication of colonoscopy	6045	–	–	–	–
Per LY with CRC care†					
Stage I CRC	–	36 683	3050	63 809	19 176
Stage II CRC	–	49 234	2870	63 555	17 279
Stage III CRC	–	59 759	4021	67 041	21 457
Stage IV CRC	–	77 790	12 178	88 368	49 866

CRC = colorectal cancer; FIT = fecal immunochemical test; LY = life-year; QALY = quality-adjusted life-year.
* The loss of quality of life associated with a particular event.
† Care for CRC was divided in 3 clinically relevant phases: initial, continuing, and terminal care. The initial care phase was defined as the first 12 mo after diagnosis; the terminal care phase was defined as the final 12 mo of life; the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between patients with CRC who were dying of CRC and those dying of another cause. For patients surviving less than 24 mo, the final 12 mo were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.
‡ Utility losses for LYs with initial care were derived from a study by Ness et al (29). For LYs with continuing care for stage I and II CRC, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV CRC, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for CRC, we assumed the utility loss for LYs with initial care for stage IV CRC. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.
§ Costs are presented in 2013 U.S. dollars and include copayments and patient time costs (i.e., the opportunity costs of spending time on screening or being treated for a complication or CRC) but do not include travel costs, costs of lost productivity, and unrelated health care and non–health care costs in added years of life. We assumed that the value of patient time was equal to the median wage rate in 2012: $16.71/h (30). We assumed that FITs, sigmoidoscopies, colonoscopies, and complications used up 1, 4, 8, and 16 h of patient time, respectively. Patient time costs were already included in the estimates for the costs of LYs with CRC care obtained from a study by Yabroff et al (31).

death. Adherence to screening and diagnostic and surveillance colonoscopies was assumed to be 100%.

We restricted ourselves to 1-time colonoscopy and 1-time sigmoidoscopy screening because performing more screening colonoscopies or sigmoidoscopies is unlikely to be cost-effective at older age. We explored the effect of FIT screening during 2 consecutive years in a sensitivity analysis.

Utility Losses Associated With CRC Screening

We assumed a utility loss (that is, a loss of quality of life) equal to 2 full days of life per colonoscopy (0.0055 quality-adjusted life-years [QALYs]), 1 day of life per sigmoidoscopy (0.0027 QALYs), and 2 weeks of life per complication (0.0384 QALYs) (**Table 1**). We also assigned a utility loss to each LY with CRC care (29).

The assignment of utility losses to LYs with CRC care works 2 ways: On the one hand, screening prevents cancer by the detection and removal of adenomas, thereby reducing LYs with CRC care and hence resulting in a gain of quality of life. On the other hand, screening results in overdiagnosis and overtreatment of cancer, resulting in LYs with CRC care in persons who would never have been diagnosed with CRC without screening and hence a loss of quality of life. The net effect on quality of life depends on the balance between cancer cases prevented and cancer cases overdiagnosed and can be either positive or negative.

Costs Associated With CRC Screening

The cost-effectiveness analyses were conducted from a societal perspective. The costs of colonoscopy, sigmoidoscopy, and FIT were based on 2007 Medicare payment

rates and copayments (**Table 1**) (32). The costs of complications were obtained from a cost analysis of cases of unexpected hospital use after endoscopy in 2007 (33). We added patient time costs to both (30). The costs of LYs with CRC care were obtained from an analysis of SEER–Medicare linked data and included copayments and patient time costs (31). We adjusted all costs to reflect the 2013 level using the U.S. Consumer Price Index (34).

The assignment of costs to LYs with CRC care also works 2 ways: On the one hand, screening prevents cancer, reducing the costs of CRC care. On the other hand, screening results in overtreatment of cancer, increasing these costs. The net effect can be either a reduction or an increase in costs.

Outcomes

For each cohort, we quantified the effectiveness (that is, the number of CRC cases prevented, CRC deaths prevented, LYs gained, and QALYs gained) and costs of 1-time colonoscopy, sigmoidoscopy, and FIT screening, applying the conventional 3% annual discount rate for both.

Analyses

We first determined the cost-effectiveness of each screening strategy compared with no screening for all cohorts. For each comorbid condition level, we determined the upper age at which each screening strategy was cost-effective compared with no screening, assuming a willingness to pay per QALY gained of $100 000.

We subsequently performed an analysis to determine the optimal screening strategy for each cohort (that is, the most effective, still cost-effective screening strategy). To do so, we first excluded all dominated screening strategies (that is, those that were more costly and less effective than other strategies or combinations of other strategies). We determined the incremental cost-effectiveness ratio for all remaining strategies ("efficient strategies"): the additional costs per additional QALY gained compared with the next less effective and costly efficient strategy. From the efficient strategies, we selected the optimal strategy, again assuming a willingness to pay per QALY gained of $100 000.

Sensitivity Analyses

We repeated our analyses, assuming half and twice the base-case utility losses for colonoscopy, sigmoidoscopy, and complications; a utility loss of 0.12, 0.18, 0.24, and 0.70 QALYs for each LY with continuing care for stage I, II, III, and IV CRC, respectively; 25% higher and 25% lower costs for colonoscopy, sigmoidoscopy, and FIT; 25% higher and 25% lower costs for CRC care; twice the base-case miss rates for adenomas and CRC for both sigmoidoscopy and colonoscopy; no surveillance in patients with adenomas; 25% higher and 25% lower risk for CRC in all cohorts; and a willingness to pay per QALY gained of $50 000. Further, we explored the effect of FIT screening during 2 consecutive years.

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

Role of the Funding Source

The study was supported by the National Cancer Institute. The funding source had no role in the study's design, conduct, and reporting.

RESULTS

Effectiveness

The effectiveness of CRC screening in unscreened elderly persons declined with increasing age (**Table 2**). For example, 1-time colonoscopy screening prevented fewer CRC deaths (4.5 vs. 11.9 per 1000 persons) and resulted in fewer LYs gained (12.3 vs. 68.5 per 1000 persons) in healthy persons aged 90 years than in healthy persons aged 76 years. Moreover, whereas colonoscopy screening prevented 15.4 CRC cases per 1000 healthy persons aged 76 years, it resulted in overdiagnosis and hence overtreatment of 7.7 CRC cases per 1000 healthy persons aged 90 years. As a result, colonoscopy screening resulted in a positive overall effect on length and quality of life (that is, a net health benefit) in healthy persons aged 76 years (67.2 QALYs gained per 1000 persons) but in a net harm in healthy persons aged 90 years (1.7 QALYs lost per 1000 persons).

One-time sigmoidoscopy and, particularly, 1-time FIT screening were generally less effective than 1-time colonoscopy screening (**Table 2**). For example, in healthy persons aged 76 years, colonoscopy screening resulted in 67.2 QALYs gained per 1000 persons, whereas sigmoidoscopy and FIT screening resulted in 53.9 and 24.2 QALYs gained per 1000 persons, respectively. The only exceptions were seen at the most advanced ages, at which FIT screening was most effective—a result primarily explained by the 0 utility loss associated with this test. In persons with moderate and, particularly, severe comorbid conditions, screening was less effective than in persons without comorbid conditions (**Appendix Table 3**, available at www.annals.org).

Costs

Whereas the effectiveness of screening in unscreened elderly persons declined with increasing age, the net costs of screening increased substantially (**Table 3**). While colonoscopy screening was associated with a lifetime cost of $725 000 per 1000 healthy persons aged 76 years, it was associated with a lifetime cost of $2 130 000 per 1000 healthy persons aged 90 years. This increase was again explained by the shift from preventing to overtreating CRC with age.

Besides being the most effective strategy, colonoscopy screening was also the most expensive (**Table 3**). For ex-

Table 2. **Effectiveness of 1-Time Colonoscopy, Sigmoidoscopy, and FIT Screening in Elderly Persons Without Previous Screening With No Comorbid Conditions***

Screening Strategy, by Age	CRC Cases Prevented, *n*†	CRC Deaths Prevented, *n*	LYs Gained, *n*‡	Effect on Quality of Life, *QALYs*§					QALYs Gained, *n*‖
				Screening Tests	Diagnostic Colonoscopies	Surveillance Colonoscopies	Complications	LYs With CRC Care¶	
1-time colonoscopy									
76 y**	15.4	11.9	68.5	−5.5	0	−3.2	−0.6	+8.1	67.2
80 y	10.4	10.7	52.9	−5.5	0	−2.8	−0.7	+3.0	46.9
85 y	0.8	7.4	28.3	−5.5	0	−2.0	−0.9	−2.9	17.1
90 y	−7.7	4.5	12.3	−5.5	0	−1.4	−1.1	−6.1	−1.7
1-time sigmoidoscopy									
76 y	12.0	9.4	54.6	−2.7	−1.6	−2.2	−0.4	+6.2	53.9
80 y	8.2	8.7	43.1	−2.7	−1.7	−2.0	−0.5	+2.3	38.6
85 y	0.6	6.0	23.1	−2.7	−1.7	−1.4	−0.6	−2.3	14.3
90 y	−6.2	3.7	9.9	−2.7	−1.6	−1.0	−0.7	−4.9	−1.0
1-time FIT									
76 y	1.7	4.1	25.9	0	−0.4	−0.5	−0.1	−0.6	24.2
80 y	0.2	4.2	22.5	0	−0.4	−0.4	−0.1	−2.2	19.2
85 y	−2.8	3.4	13.8	0	−0.5	−0.4	−0.1	−3.8	9.0
90 y	−6.2	2.3	6.6	0	−0.5	−0.3	−0.2	−4.7	0.9

CRC = colorectal cancer; FIT = fecal immunochemical test; LY = life-year; QALY = quality-adjusted life-year.

* Results are based on a comparison with no screening, reported per 1000 persons, and discounted by 3% per year. Persons are classified as having no comorbid conditions if none of the following conditions are present: an ulcer, a history of acute myocardial infarction, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

† Negative values occur when the number of CRC cases prevented by screening is exceeded by the number of CRC cases overdiagnosed by screening.

‡ The effect of screening on quantity of life.

§ The effect of the screening test, diagnostic colonoscopies, surveillance colonoscopies, complications, and LYs with CRC care on quality of life. Values are derived by multiplying number(s) of events with the corresponding utility loss(es) per event stated in **Table 1.** For example, when applying the 1-time colonoscopy screening strategy, 1000 persons have a screening colonoscopy in each cohort. Because the utility loss per screening colonoscopy is 0.0055 QALYs, the total utility loss due to screening colonoscopies is 5.5 QALYs in each cohort.

‖ The effect of screening on quantity and quality of life incorporated in 1 measure (i.e., the net health benefit of screening), calculated by adding LYs gained and all effects on quality of life. Discrepancies between the columns may occur due to rounding.

¶ Screening results in a gain of quality of life by preventing LYs with CRC care and a loss of quality of life by adding LYs with CRC care. The net effect can be a gain of quality of life (positive value) or a loss of quality of life (negative value). As a result of the shift from preventing to overdiagnosing CRC with increasing age, the net effect on quality of life becomes less favorable with age. Whereas 1-time colonoscopy screening in unscreened elderly without comorbid conditions reduced the total number of LYs with CRC care for stage III or IV CRC at age 76 y (−14 LYs per 1000 persons), it increased this number of LYs at age 90 y (+16 LYs per 1000 persons).

** More detailed results for this cohort are given in **Appendix Table 2** (available at www.annals.org).

ample, in healthy persons aged 76 years, the costs of colonoscopy screening were $725 000 per 1000 persons compared with $439 000 and $218 000 for sigmoidoscopy and FIT screening, respectively. In persons with moderate and, particularly, severe comorbid conditions, screening was not only less effective but also more costly (**Appendix Table 4**, available at www.annals.org).

Cost-Effectiveness Compared With No Screening

As the effectiveness of screening declined with increasing age and the costs increased substantially, the cost-effectiveness of screening deteriorated rapidly with age (**Figure 1**). In unscreened elderly persons without comorbid conditions, colonoscopy and sigmoidoscopy screening were cost-effective up to age 85 years, whereas FIT screening was cost-effective up to age 86 years. In elderly persons with moderate comorbid conditions, colonoscopy and sigmoidoscopy screening were cost-effective up to age 82 years, whereas FIT screening was cost-effective up to age 83 years. In persons with severe comorbid conditions, colonoscopy and sigmoidoscopy screening were cost-effective up to age 79 years, whereas FIT screening was cost-effective up to age 80 years.

Incremental Cost-Effectiveness

We determined the optimal screening strategy for each cohort on the basis of the incremental cost-effectiveness ratios of the efficient screening strategies. In unscreened elderly persons with no comorbid conditions, colonoscopy screening was most effective and still cost-effective up to age 83 years (**Appendix Table 5** [available at www.annals.org] and **Figure 2**), sigmoidoscopy screening was the optimal strategy at age 84 years, and FIT screening was the optimal strategy at ages 85 and 86 years. In elderly persons with moderate comorbid conditions, colonoscopy screening was the optimal strategy up to age 80 years, sigmoidoscopy screening was the optimal strategy at age 81 years, and FIT screening was the optimal strategy at ages 82 and 83 years. In persons with severe comorbid conditions, colonoscopy screening was the optimal strategy up to age 77 years, followed by sigmoidoscopy screening at age 78 years and FIT screening at ages 79 and 80 years.

Sensitivity Analyses

Besides comorbid condition level, the upper age at which screening was cost-effective was most sensitive to lowering the willingness-to-pay threshold to $50 000 per

QALY gained (**Appendix Table 6**, available at www.annals.org). Based on this threshold, screening unscreened elderly persons with no, moderate, and severe comorbid conditions should be considered up to age 84, 80, and 77 years, respectively. The upper ages at which screening should be considered were robust to all other sensitivity analyses.

The tests that were indicated at specific ages differed substantially between analyses (**Appendix Table 6**). Besides the threshold for the willingness to pay per QALY gained, the level of CRC risk and utility losses associated with colonoscopy, sigmoidoscopy, and complications were the most important factors in this respect.

In persons aged 84 years without comorbid conditions and persons aged 78 years with severe comorbid conditions, sigmoidoscopy screening was not cost-effective compared with FIT screening during 2 consecutive years (**Appendix Table 6**). In persons aged 85 years without comorbid conditions, persons aged 82 years with moderate comorbid conditions, and persons aged 79 and 80 years with severe comorbid conditions, FIT screening during 2 consecutive years was cost-effective compared with 1-time FIT screening.

DISCUSSION

Our study shows that in elderly persons without previous screening for CRC, screening remains cost-effective well beyond age 75 years, which is the recommended age to discontinue screening in adequately screened persons (**Table 4**). In unscreened elderly persons with no comorbid conditions, screening was cost-effective up to age 86 years. Screening with colonoscopy was most effective and still cost-effective up to 83 years, sigmoidoscopy was indicated at age 84 years, and FIT was indicated at ages 85 and 86 years. In unscreened elderly persons with moderate comorbid conditions, screening was cost-effective up to age 83 years (colonoscopy indicated up to age 80 years, sigmoidoscopy at age 81 years, and FIT at ages 82 and 83 years). In persons with severe comorbid conditions, screening was cost-effective up to age 80 years (colonoscopy indicated up to age 77 years, sigmoidoscopy at age 78 years, and FIT at ages 79 and 80 years).

In a situation when an elderly person is willing to have only 1 type of screening test, the cost-effectiveness of that test compared with no screening becomes relevant. In such a person without comorbid conditions, colonoscopy and sigmoidoscopy screening can be considered up to age 85 years and FIT screening can be considered up to age 86 years. The ages for similar persons with moderate comorbid conditions are 82 years for colonoscopy and sigmoidoscopy and 83 years for FIT; for persons with severe comorbid conditions, the ages are 79 years for colonoscopy and sigmoidoscopy and 80 years for FIT.

Table 3. **Costs of 1-Time Colonoscopy, Sigmoidoscopy, and FIT Screening in Elderly Persons Without Previous Screening With No Comorbid Conditions***

Screening Strategy, by Age	Cost (Thousands), $					
	Screening Tests†	Diagnostic Colonoscopies	Surveillance Colonoscopies	Complications	LYs With CRC Care‡	Total§
1-time colonoscopy						
76 y‖	983	0	569	98	−925	725
80 y	987	0	484	114	−483	1102
85 y	987	0	350	137	230	1705
90 y	986	0	239	168	737	2130
1-time sigmoidoscopy						
76 y‖	387	309	397	64	−718	439
80 y	392	331	345	75	−380	764
85 y	392	330	251	89	189	1251
90 y	390	323	169	106	592	1580
1-time FIT						
76 y‖	42	80	88	14	−7	218
80 y	42	87	78	17	130	355
85 y	42	93	62	23	356	577
90 y	42	98	46	29	541	756

CRC = colorectal cancer; FIT = fecal immunochemical test; LY = life-year.

* Results are based on a comparison with no screening, reported per 1000 persons, and discounted by 3% per year. Persons are classified as having no comorbid conditions if none of the following conditions are present: an ulcer, a history of acute myocardial infarction, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

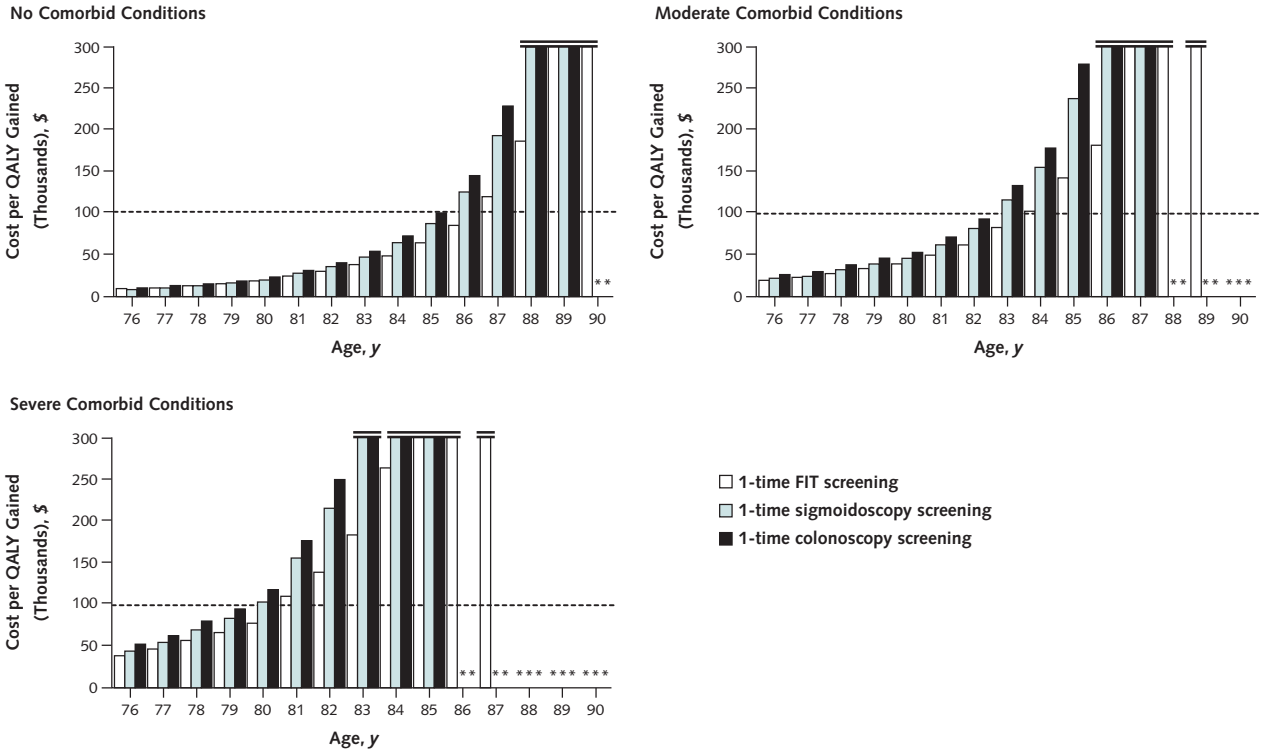
† At very advanced age, the costs of screening colonoscopies and sigmoidoscopies show a slight decline. This is explained by the small observed decrease in the prevalence of adenomas/CRC at very advanced age (11–18, 20, 21).

‡ Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be an increase in costs (positive value) or a decrease in costs (negative value).

§ Discrepancies between the columns may occur due to rounding.

‖ More detailed results for this cohort are given in **Appendix Table 2** (available at www.annals.org).

Figure 1. **Cost-effectiveness of 1-time colonoscopy, sigmoidoscopy, and FIT screening compared with no screening in elderly persons without previous screening with no, moderate, and severe comorbid conditions.**



Results are presented per 1000 persons and discounted by 3% per year. Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions are present. The dashed line indicates a willingness to pay per QALY gained of $100 000. Screening strategies costing less than $100 000 per QALY gained are considered cost-effective. Asterisks for missing screening strategies indicate that they were associated with a net health loss rather than a benefit (**Appendix Table 3** [available at www.annals.org] and **Table 2**). FIT = fecal immunochemical test; QALY = quality-adjusted life-year.

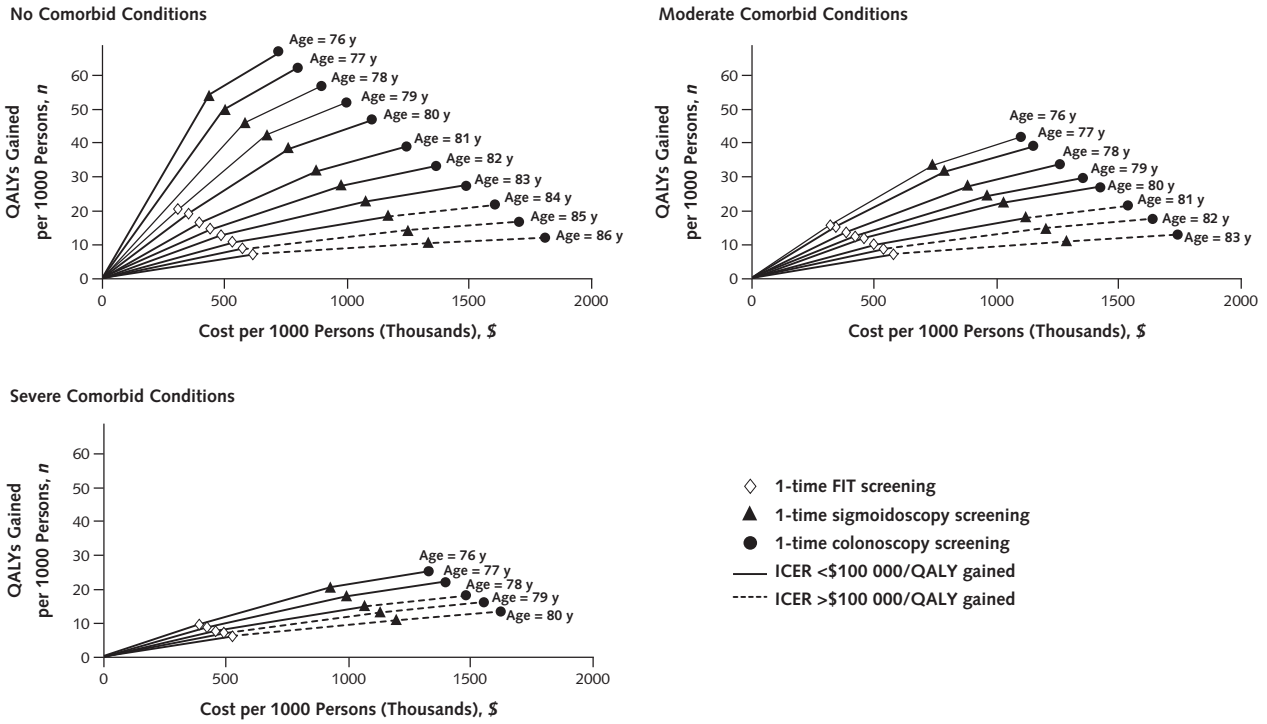
Although the incidence of CRC increases up to very advanced ages (19), the effectiveness of screening declines with increasing age. This decline is primarily explained by the increasing risk for other-cause death with age, which reduces both the probability that screening will prevent CRC death and the number of LYs gained if death is prevented. Moreover, the risks for screening-induced harms (colonoscopy-related complications and, more importantly, overdiagnosis and overtreatment of CRC) increase with age (9). At the same time, the shift from preventing to overtreating CRC causes the net costs of screening to increase with age. Together, these phenomena explain the rapid deterioration of the cost-effectiveness of screening with increasing age.

Although colonoscopy every 10 years, sigmoidoscopy every 5 years, and FIT every year are almost equally effective when applied from age 50 to 75 years (1, 2), colonoscopy is more effective than sigmoidoscopy and FIT when only 1 screening examination is performed because of its greater overall sensitivity for adenomas and CRC. However, because colonoscopy is also more expensive than sigmoidoscopy and FIT and because the effectiveness of all screening tests is marginal at very advanced ages, screening with colonoscopy is not cost-effective compared with sigmoidoscopy and FIT at the most advanced ages at which screening should be considered.

Screening remains cost-effective up to a more advanced age in persons without comorbid conditions than in those with comorbid conditions because their more favorable life expectancy increases the probability that screening will prevent CRC, thus increasing the effectiveness of screening while simultaneously reducing the costs of CRC care.

To our knowledge, our study is the first to investigate the net health benefit and the cost-effectiveness of CRC screening in persons older than 75 years without previous screening. An earlier study by Ko and Sonnenberg (7) demonstrated that the effectiveness of screening for preventing CRC death declines with increasing age, whereas the probability of screening-related complications increases

Figure 2. **The incremental cost-effectiveness of the efficient screening strategies in elderly persons without previous screening with no, moderate, and severe comorbid conditions.**



Results are presented per 1000 persons and discounted by 3% per year. Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions are present. In elderly persons without previous screening with no, moderate, or severe comorbid conditions, none of the screening strategies are cost-effective from age 87, 84, and 81 years onward, respectively (**Figure 1**). For each age, the efficient screening strategies are connected by an efficiency frontier. A solid line indicates that the ICER of a screening strategy is <$100 000 per QALY gained, implying that the strategy is considered cost-effective. A dashed line indicates that the ICER of a screening strategy exceeds $100 000 per QALY gained, implying that the strategy is not considered cost-effective. FIT = fecal immunochemical test; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

with age. Further, a study by Lin and colleagues (8) demonstrated that the number of LYs gained by screening declines with age, resulting in an increase in the number of colonoscopies required per LY gained. However, neither study considered costs or measured the overdiagnosis and overtreatment of cancer, which is the most important adverse effect of screening in elderly persons. As a result, these studies cannot easily be used to determine whether unscreened elderly persons should be screened. Some other, more recent studies have suggested that screening should be continued after age 75 years (3, 4). However, these studies did not distinguish between adequately

Table 4. **Results Summary of CRC Screening Indicated in Elderly Persons Without Previous Screening**

Comorbid Condition Level*	Age up to Which CRC Screening Should Be Considered, y	Screening Strategy Indicated, by Age										
		76 y	77 y	78 y	79 y	80 y	81 y	82 y	83 y	84 y	85 y	86 y
No comorbid conditions	86	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT
Moderate comorbid conditions	83	COL	COL	COL	COL	COL	SIG	FIT	FIT			
Severe comorbid conditions	80	COL	COL	SIG	FIT	FIT						

COL = 1-time colonoscopy; CRC = colorectal cancer; FIT = 1-time fecal immunochemical test; SIG = 1-time sigmoidoscopy.
* Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions are present.

screened elderly persons and elderly persons without previous screening. Further, these studies based their conclusions only on CRC incidence data.

The USPSTF selected its recommended screening strategies on the basis of the number of colonoscopies required per LY gained (undiscounted) (1, 2), but we based our conclusions on the costs per QALY gained (discounted at 3% per year). We did so for 2 reasons. First, policymakers should be able to compare the efficiency of a wide range of health interventions; the USPSTF outcome measure does not allow for this. Second, we believe that effects on both length and quality of life should be considered. However, the 2 approaches led to screening recommendations associated with similar numbers of colonoscopies per LY gained: Screening with colonoscopy as recommended by the USPSTF (that is, at ages 50, 60, and 70 years) required 30 to 35 colonoscopies per LY gained (2). Also, screening with colonoscopy in unscreened persons aged 83 years with no comorbid conditions, for example, required 32 colonoscopies per LY gained.

Our study has 2 main limitations. First, we did not perform separate analyses by sex and race. However, we do not expect that results from such analyses would have differed much from those reported here because a substantial part of the difference in life expectancy between men and women and between black and white persons is explained by differences in the prevalence of moderate and severe comorbid conditions. Also, persons with the most favorable life expectancy (that is, white females) are at lowest risk for CRC and vice versa. Hence, the effect of life expectancy on the cost-effectiveness of screening is counterbalanced by the effect of CRC risk (at least partially) (35). Second, we did not perform separate analyses for identifiable high-risk subgroups, such as elderly persons with a family history of CRC (36). In some of these subgroups, screening may be cost-effective up to a more advanced age.

Our analysis highlights some future research directions. First, future research should determine the optimal number of FIT screenings in elderly persons who are relatively young and not willing to have a screening colonoscopy or sigmoidoscopy. Second, other research should study how the benefits, burden, and harms of screening affect patient decisions about CRC screening. Third, studies evaluating the appropriate age to stop screening by comorbid condition level are also required for adequately screened persons.

In conclusion, our study demonstrates that in the 23% of U.S. elderly persons without previous screening, CRC screening should be considered well beyond age 75 years. In unscreened elderly persons with no comorbid conditions, CRC screening should be considered up to age 86 years (up to age 83 years for those with moderate comorbid conditions and up to age 80 years for those with severe comorbid conditions). Screening with colonoscopy is indicated at most ages.

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Appendix: MISCAN-Colon

General Model Structure

MISCAN-Colon is a stochastic microsimulation model for CRC programmed in Delphi (Borland Software, Scotts Valley, California). It can be used to explain and predict trends in CRC incidence and mortality rates and to quantify the effects and costs of primary prevention of CRC, screening for CRC, and surveillance after polypectomy.

The term "microsimulation" implies that persons are moved through the model one at a time, rather than as proportions of a cohort. This allows future state transitions to depend on past transitions, giving the model a "memory." Further, unlike most traditional Markov models, MISCAN-Colon does not use yearly transition probabilities; instead, it generates durations in states, thereby increasing model flexibility and computational performance. The term "stochastic" implies that the model simulates sequences of events by drawing from distributions of probabilities or durations, rather than using fixed values. Hence, the results of the model are subject to random variation.

MISCAN-Colon consists of 3 modules: a demography module, natural history module, and screening module.

The Demography Module

Using birth and life tables that are representative of the population under consideration, MISCAN-Colon draws a date of birth and date of non-CRC death for each person simulated. In MISCAN-Colon, the maximum age a person can achieve is exactly 100 years.

The Natural History Module

Transitions

As each simulated person ages, 1 or more adenomas may develop (**Appendix Figure 1**). These adenomas can be either progressive or nonprogressive. Both progressive and nonprogressive adenomas can grow in size from small (≤5 mm) to medium (6 to 9 mm) to large (≥10 mm); however, only progressive adenomas can develop into preclinical cancer. Preclinical cancer may progress through stages I to IV; however, during each stage, CRC may be diagnosed because of symptoms. After clinical diagnosis, CRC survival is simulated using age-, stage-, and localization-specific survival estimates for clinically diagnosed CRC obtained from a study by Rutter and colleagues (10). For persons with synchronous CRCs at diagnosis, the survival of the most advanced cancer is used. The date of death for patients with CRC is set to the earliest simulated death (either due to CRC or another cause).

Transition Probabilities and Durations in States

A person's risk for adenomas depends on the person's age and risk index. As a result of the latter, most persons develop no adenomas and some develop many. We assumed that the distribution of adenomas over the colon and rectum equals the distribution of cancer cases as seen in SEER before the introduction of screening (19). The age-specific onset of adenomas and the dispersion of the personal risk index were calibrated to data on the prevalence and multiplicity distribution of adenomas as seen in autopsy studies (**Appendix Figure 2**) (11–18, 20, 21). The age-specific probability of adenoma progressivity and the age- and localization-specific transition probabilities between preclinical cancer stages and between preclinical and clinical cancer stages were simultaneously calibrated to SEER data on the age-, stage-, and localization-specific incidence of CRC as seen before the introduction of screening (**Appendix Figure 3**) (19).

The average durations of the preclinical cancer stages were calibrated to the rates of screen-detected and interval cancer seen in randomized, controlled trials (RCTs) evaluating screening using guaiac fecal occult blood tests (23, 24, 26). This exercise has been described extensively by Lansdorp-Vogelaar and colleagues (25). The average duration from the emergence of an adenoma (state 2) until progression into preclinical cancer (state 7) (that is, the adenoma dwell time) was calibrated to the rates of interval cancer (including surveillance-detected cancer) seen in a RCT evaluating 1-time sigmoidoscopy screening (**Appendix Figure 4**) (22). We assumed an equal overall dwell time for adenomas developing into CRC from a medium size (30% of all CRCs) and from a large size (70% of all CRCs). All durations in the adenoma and preclinical cancer phases were drawn from exponential distributions. Durations within the adenoma and preclinical cancer phases were assumed to be perfectly correlated (that is, if a small adenoma grows into a medium-sized adenoma rapidly, it will also grow into a large adenoma or develop into CRC rap-

idly); however, durations in the adenoma phase were assumed to be uncorrelated with durations in the preclinical cancer phase (that is, a rapidly growing adenoma does not necessarily develop into a rapidly progressing cancer). The proportion of medium-sized, nonprogressive adenomas growing large and the average duration in the medium-size, nonprogressive adenoma state (state 5) were calibrated to size-specific adenoma detection rates seen in a Dutch RCT on colonoscopy screening (data not shown).

The Screening Module

Screening will alter some of the simulated life histories: Some cancer cases will be prevented by the detection and removal of adenomas; other cancer cases will be detected in an earlier stage with a more favorable survival. Because the stage-specific survival of screen-detected CRC as seen in RCTs on guaiac fecal occult blood testing was substantially more favorable than that of clinically detected CRC, even after correcting for lead-time bias (25), we assigned those screen-detected cancer cases that would have been clinically detected in the same stage a survival corresponding to a cancer that is 1 stage less progressive. Hence, a cancer screen-detected in stage II that would also have been clinically diagnosed in stage II is assigned the survival of a clinically diagnosed stage I cancer. The only exceptions were screen-detected stage IV cancer cases. These cases were always assigned the survival of a clinically diagnosed stage IV cancer.

Besides modeling positive health effects of screening, we also modeled colonoscopy-related complications and overdiagnosis and overtreatment of CRC (that is, the detection and treatment of cancer that would not have been diagnosed without screening) (9).

Integrating Modules

The demography module generates a date of birth and date of non-CRC death for each person simulated, creating a life history without adenomas or CRC. In patient A in **Appendix Figure 5**, the natural history module generates an adenoma. This adenoma progresses into preclinical cancer, which is diagnosed because of symptoms in stage II and results in CRC death before non-CRC death would have occurred. In the screening module, a screening examination is simulated, indicated by the blue arrow. During this examination, the adenoma is detected and, as a result, both CRC and CRC death are prevented. Hence, in patient A, screening prolongs life by the amount indicated by the green arrow. Patient B also develops an adenoma, and although this adenoma does progress into preclinical cancer, patient B would never have been diagnosed with CRC in a scenario without screening (see Life History 2). However, during the screening examination simulated in the screening module, again indicated by the blue arrow, CRC is screen-detected in stage I. Hence, in this patient, screening results in overdiagnosis of CRC: It detects a cancer that would never have been diagnosed in a scenario without screening. Hence, screening does not prolong life, but it does result in additional LYs with CRC care (overtreatment) as indicated by the red arrow.

Appendix Table 1. **Test Characteristics of Colonoscopy, Sigmoidoscopy, and FIT**

Test Characteristic	Test		
	Colonoscopy	Sigmoidoscopy	FIT
Specificity, %	90*	92*	98‡
Sensitivity, %			
Small adenomas (≤5 mm)	75†	75†	0‡
Medium adenomas (6–9 mm)	85†	85†	5‡
Large adenomas (≥10 mm)	95†	95†	26‡
CRCs that would not have been clinically detected in their current stage	95†	95†	41‡
CRCs that would have been clinically detected in their current stage	95†	95†	77‡
Reach	95% reaches the cecum; the reach of the remaining 5% is distributed uniformly over colon and rectum	100% reaches the rectosigmoid junction, 88% reaches the sigmoid-descending junction, 6% reaches the splenic flexure§	Whole colon and rectum
Complication rate			
Positive result	Increases exponentially with age (from 20 per 1000 colonoscopies at age 76 y to 48 per 1000 colonoscopies at age 90 y)‖	0	0
Negative result	0	0	0
Mortality rate			
Positive result	0.033 per 1000 colonoscopies¶	0	0
Negative result	0	0	0

CRC = colorectal cancer; FIT = fecal immunochemical test.
* We assumed that in 10% of all negative colonoscopy results and in 8% of all negative sigmoidoscopy results a nonadenomatous lesion was detected, resulting in a polypectomy or a biopsy, respectively.
† The sensitivity of colonoscopy and sigmoidoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates seen in tandem colonoscopy studies (39).
‡ The test characteristics of FIT were fitted to the positivity rates and detection rates seen in the first screening round of the Dutch screening trial. We assumed that the probability that a CRC bleeds and thus the sensitivity of FIT for CRC depends on the time until clinical diagnosis, in concordance with our findings for guaiac fecal occult blood tests (25).
§ The reach of sigmoidoscopy was obtained from a study by Painter et al (38).
‖ Age-specific risks for complications of colonoscopy requiring a hospital admission or emergency department visit were obtained from a study by Warren et al (9).
¶ The mortality rate associated with colonoscopies with a polypectomy was derived by multiplying the risk for a perforation obtained from a study by Warren et al (9) by the risk for death given a perforation obtained from a study by Gatto et al (37).

Appendix Table 2. **Effects of 1-Time Colonoscopy Screening in Persons Aged 76 Years Without Previous Screening With No Comorbid Conditions***

Effect	Screening	No Screening	Screening − No Screening†
Effects on health care use, *n*			
Colonoscopies			
Screening with polypectomy/biopsy	461	0	461
Screening without polypectomy/biopsy	539	0	539
Surveillance with polypectomy/biopsy	219	0	219
Surveillance without polypectomy/biopsy	370	0	370
Complications of colonoscopy	16.2	0	16.2
LYs with initial CRC care‡			
Stage I	11.5	6.4	5.1
Stage II	8.0	12.4	−4.4
Stage III	5.1	7.3	−2.2
Stage IV	0.7	2.9	−2.2
LYs with continuing CRC care			
Stage I	92.8	34.9	57.9
Stage II	60.0	61.6	−1.6
Stage III	33.9	30.7	3.2§
Stage IV	1.5	5.2	−3.7
LYs with terminal care, ending in CRC death			
Stage I	0.5	0.7	−0.2
Stage II	1.0	2.6	−1.6
Stage III	1.5	3.2	−1.8
Stage IV	1.1	5.8	−4.7
LYs with terminal care, ending in other-cause death			
Stage I	8.3	5.1	3.2
Stage II	5.4	9.3	−4.1
Stage III	2.9	4.6	−1.7
Stage IV	0.2	1.0	−0.8
Effects on health			
CRC cases, *n*	27.9	43.4	−15.4
CRC deaths, *n*	4.5	16.4	−11.9
LYs lost due to CRC, *n*	32.5	100.9	−68.5‖
Utility losses, *QALYs*			
Screening colonoscopies	5.5	0	5.5
Surveillance colonoscopies	3.2	0	3.2
Complications of colonoscopy	0.6	0	0.6
LYs with CRC care	25.7	33.8	−8.1
Total	35.1	33.8	1.3
QALYs lost (LYs lost due to CRC + total utility loss), *n*	67.5	134.7	−67.2¶
Effects on costs (thousands), *$*			
Screening colonoscopy	983	0	983
Surveillance colonoscopy	569	0	569
Complications of colonoscopy	98	0	98
LYs with CRC care	2404	3329	−925
Total	4054	3329	725**

CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year.
* Results per 1000 persons, discounted at 3% per year. Persons are classified as having no comorbid conditions if none of the following conditions are present: an ulcer, a history of acute myocardial infarction, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.
† Discrepancies between columns may occur due to rounding.
‡ Because screening results in prevention and earlier detection of CRC, it reduces the total numbers of LYs with initial care for CRC, terminal care for CRC, and terminal care for other causes in patients with CRC; however, because screening improves the average survival of patients with CRC, it increases the total number of LYs with continuing care for CRC.
§ The increase in LYs with continuing care for stage III CRC is explained by the more favorable average survival that we model for screen-detected vs. clinically detected cancer as described in the **Appendix**.
‖ The number of LYs gained by screening (**Table 2**).
¶ The number of QALYs gained by screening (**Table 2**).
** The costs of screening (**Table 3**).

Appendix Table 3. **Effectiveness of 1-Time Colonoscopy, Sigmoidoscopy, and FIT Screening in Elderly Persons Without Previous Screening With Moderate and Severe Comorbid Conditions***

Screening Strategy, by Comorbid Condition Level and Age	CRC Cases Prevented, *n*†	CRC Deaths Prevented, *n*	LYs Gained, *n*‡	Effect on Quality of Life, *QALYs*§					QALYs Gained, *n*‖
				Screening Tests	Diagnostic Colonoscopies	Surveillance Colonoscopies	Complications	LYs With CRC Care¶	
Moderate comorbid conditions									
1-time colonoscopy									
76 y	8.8	9.0	46.3	−5.5	0	−2.6	−0.6	+3.8	41.4
80 y	4.0	8.1	35.2	−5.5	0	−2.2	−0.7	−0.0	26.8
85 y	−4.3	5.6	18.9	−5.5	0	−1.6	−0.8	−4.2	6.8
90 y	−11.0	3.5	8.8	−5.5	0	−1.1	−1.0	−6.1	−4.8
1-time sigmoidoscopy									
76 y	6.8	7.2	36.9	−2.7	−1.6	−1.8	−0.4	+2.9	33.4
80 y	3.1	6.6	28.7	−2.7	−1.7	−1.6	−0.4	−0.1	22.2
85 y	−3.5	4.6	15.4	−2.7	−1.7	−1.1	−0.5	−3.4	5.9
90 y	−8.8	2.9	7.1	−2.7	−1.6	−0.7	−0.6	−4.9	−3.5
1-time FIT									
76 y	−0.1	3.3	17.9	0	−0.4	−0.4	−0.1	−1.5	15.6
80 y	−1.9	3.4	15.4	0	−0.4	−0.4	−0.1	−2.8	11.7
85 y	−4.8	2.7	9.4	0	−0.5	−0.3	−0.1	−4.0	4.6
90 y	−7.7	1.9	4.8	0	−0.5	−0.2	−0.2	−4.4	−0.5
Severe comorbid conditions									
1-time colonoscopy									
76 y	2.6	6.7	32.3	−5.5	0	−2.0	−0.5	+1.4	25.7
80 y	−2.2	5.9	23.3	−5.5	0	−1.6	−0.6	−1.7	13.9
85 y	−9.4	4.0	12.2	−5.5	0	−1.1	−0.8	−4.5	0.4
90 y	−14.6	2.6	5.8	−5.5	0	−0.7	−1.0	−5.7	−7.1
1-time sigmoidoscopy									
76 y	2.0	5.3	25.8	−2.7	−1.6	−1.4	−0.3	+1.1	20.8
80 y	−1.9	4.8	19.0	−2.7	−1.7	−1.2	−0.4	−1.4	11.6
85 y	−7.6	3.3	10.0	−2.7	−1.7	−0.8	−0.5	−3.6	0.6
90 y	−11.7	2.1	4.6	−2.7	−1.6	−0.5	−0.6	−4.5	−5.4
1-time FIT									
76 y	−2.2	2.5	12.7	0	−0.4	−0.3	−0.1	−1.8	10.1
80 y	−4.2	2.5	10.4	0	−0.4	−0.3	−0.1	−2.9	6.7
85 y	−7.1	2.0	6.2	0	−0.5	−0.2	−0.1	−3.7	1.7
90 y	−9.5	1.4	3.2	0	−0.5	−0.1	−0.2	−4.0	−1.7

CRC = colorectal cancer; FIT = fecal immunochemical test; LY = life-year; QALY = quality-adjusted life-year.

* Results are based on a comparison with no screening, reported per 1000 persons, and discounted by 3% per year. Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction and severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

† Negative values occur when the number of CRC cases prevented by screening is exceeded by the number of CRC cases overdiagnosed by screening.

‡ The effect of screening on quantity of life.

§ The effect of the screening test, diagnostic colonoscopies, surveillance colonoscopies, complications, and LYs with CRC care on quality of life. Values are derived by multiplying number(s) of events with the corresponding utility loss(es) per event stated in **Table 1**. For example, when applying the 1-time colonoscopy screening strategy, 1000 persons have a screening colonoscopy in each cohort. Because the utility loss per screening colonoscopy is 0.0055 QALYs, the total utility loss due to screening colonoscopies is 5.5 QALYs in each cohort.

‖ The effect of screening on quantity and quality of life incorporated in 1 measure (i.e., the net health benefit of screening), calculated by adding LYs gained and all effects on quality of life. Discrepancies between the columns may occur due to rounding.

¶ Screening results in a gain of quality of life by preventing LYs with CRC care and a loss of quality of life by adding LYs with CRC care. The net effect can be a gain of quality of life (positive value) or a loss of quality of life (negative value). As a result of the shift from preventing to overdiagnosing CRC with increasing age, the net effect on quality of life becomes less favorable with age.

Appendix Table 4. **Costs of 1-Time Colonoscopy, Sigmoidoscopy, and FIT Screening in Elderly Persons Without Previous Screening With Moderate and Severe Comorbid Conditions***

Screening Strategy, by Comorbid Condition Level and Age	Cost (Thousands), $					
	Screening Tests†	Diagnostic Colonoscopies	Surveillance Colonoscopies	Complications	LYs With CRC Care‡	Total§
Moderate comorbid conditions						
1-time colonoscopy						
76 y	983	0	462	90	−434	1102
80 y	987	0	388	106	−57	1425
85 y	987	0	278	131	502	1898
90 y	986	0	185	161	838	2170
1-time sigmoidoscopy						
76 y	387	309	323	58	−336	742
80 y	392	331	278	69	−41	1029
85 y	392	330	199	84	409	1414
90 y	390	323	132	100	673	1618
1-time FIT						
76 y	42	80	72	13	116	324
80 y	42	87	63	16	252	460
85 y	42	93	50	22	448	655
90 y	42	98	36	28	578	782
Severe comorbid conditions						
1-time colonoscopy						
76 y	983	0	354	83	−91	1329
80 y	987	0	288	99	250	1625
85 y	987	0	199	123	658	1967
90 y	986	0	131	154	868	2139
1-time sigmoidoscopy						
76 y	387	309	248	52	−67	930
80 y	392	331	206	63	207	1200
85 y	392	330	143	77	534	1477
90 y	390	323	94	95	698	1600
1-time FIT						
76 y	42	80	56	12	204	395
80 y	42	87	47	15	337	528
85 y	42	93	36	20	493	685
90 y	42	98	26	27	576	769

CRC = colorectal cancer; FIT = fecal immunochemical test; LY = life-year.

* Results are based on a comparison with no screening, reported per 1000 persons, and discounted by 3% per year. Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction and severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

† At very advanced age, the costs of screening colonoscopies and sigmoidoscopies show a slight decline. This is explained by the small observed decrease in the prevalence of adenomas/CRC at very advanced age (11–18, 20, 21).

‡ Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be an increase in costs (positive value) or a decrease in costs (negative value).

§ Discrepancies between the columns may occur due to rounding.

Appendix Table 5. **ICERs of the Efficient Screening Strategies in Elderly Persons Without Previous Screening, by Comorbid Condition Level***

Screening Strategy, by Comorbid Condition Level and Age†	QALYs Gained, *n*‡	Incremental QALYs Gained, *n*§	Cost (Thousands), $‡	Incremental Cost (Thousands), $§	ICER (Thousands), $/QALY‖	Optimal Screening Strategy¶
No comorbid conditions						
76 y**						
Sigmoidoscopy	53.9	53.9	439	439	8	
Colonoscopy	67.2	13.3	725	285	21	X
77 y**						
Sigmoidoscopy	50.3	50.3	503	503	10	
Colonoscopy	62.3	12.1	799	296	24	X
78 y**						
Sigmoidoscopy	46.2	46.2	588	588	13	
Colonoscopy	57.1	10.9	898	310	28	X
79 y						
FIT	20.5	20.5	313	313	15	
Sigmoidoscopy	42.5	22.0	673	360	16	
Colonoscopy	52.1	9.6	998	325	34	X
80 y						
FIT	19.2	19.2	355	355	18	
Sigmoidoscopy	38.6	19.4	764	409	21	
Colonoscopy	46.9	8.4	1102	338	40	X
81 y						
FIT	16.6	16.6	398	398	24	
Sigmoidoscopy	32.1	15.5	878	480	31	
Colonoscopy	39.0	7.0	1244	366	52	X
82 y						
FIT	14.8	14.8	444	444	30	
Sigmoidoscopy	27.5	12.7	976	532	42	
Colonoscopy	33.3	5.8	1365	390	67	X
83 y						
FIT	12.9	12.9	488	488	38	
Sigmoidoscopy	22.8	9.9	1076	588	59	
Colonoscopy	27.4	4.7	1490	414	88	X
84 y						
FIT	11.0	11.0	535	535	49	
Sigmoidoscopy	18.3	7.3	1171	636	87	X
Colonoscopy	22.0	3.7	1608	437	118	
85 y						
FIT	9.0	9.0	577	577	64	X
Sigmoidoscopy	14.3	5.3	1251	674	127	
Colonoscopy	17.1	2.7	1705	454	168	
86 y						
FIT	7.2	7.2	619	619	86	X
Sigmoidoscopy	10.7	3.4	1332	714	210	
Colonoscopy	12.5	1.8	1810	478	266	
Moderate comorbid conditions						
76 y						
FIT	15.6	15.6	324	324	21	
Sigmoidoscopy	33.4	17.8	742	418	23	
Colonoscopy	41.4	8.0	1102	361	45	X
77 y						
FIT	15.0	15.0	347	347	23	
Sigmoidoscopy	31.6	16.6	789	443	27	
Colonoscopy	38.9	7.4	1153	363	49	X
78 y						
FIT	13.5	13.5	387	387	29	
Sigmoidoscopy	27.3	13.8	885	497	36	
Colonoscopy	33.5	6.2	1262	377	61	X
79 y						
FIT	12.4	12.4	426	426	34	
Sigmoidoscopy	24.3	11.9	966	540	45	
Colonoscopy	29.5	5.2	1356	390	75	X
80 y						
FIT	11.7	11.7	460	460	39	
Sigmoidoscopy	22.2	10.5	1029	569	54	
Colonoscopy	26.8	4.6	1425	396	86	X

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Appendix Table 5—**Continued**

Screening Strategy, by Comorbid Condition Level and Age†	QALYs Gained, *n*‡	Incremental QALYs Gained, *n*§	Cost (Thousands), $‡	Incremental Cost (Thousands), $§	ICER (Thousands), $/QALY‖	Optimal Screening Strategy¶
81 y						
FIT	9.9	9.9	500	500	51	
Sigmoidoscopy	17.8	7.9	1121	621	79	X
Colonoscopy	21.5	3.7	1537	416	112	
82 y						
FIT	8.6	8.6	542	542	63	X
Sigmoidoscopy	14.7	6.1	1204	662	109	
Colonoscopy	17.6	2.8	1638	434	155	
83 y						
FIT	7.0	7.0	583	583	83	X
Sigmoidoscopy	11.0	4.1	1290	707	172	
Colonoscopy	13.0	2.0	1744	453	227	
Severe comorbid conditions						
76 y						
FIT	10.1	10.1	395	395	39	
Sigmoidoscopy	20.8	10.8	930	535	50	
Colonoscopy	25.7	4.8	1329	399	83	X
77 y						
FIT	9.1	9.1	425	425	47	
Sigmoidoscopy	18.2	9.1	995	571	63	
Colonoscopy	22.4	4.1	1400	404	99	X
78 y						
FIT	8.1	8.1	460	460	57	
Sigmoidoscopy	15.3	7.2	1071	611	85	X
Colonoscopy	18.6	3.3	1483	412	125	
79 y						
FIT	7.4	7.4	493	493	67	X
Sigmoidoscopy	13.6	6.1	1134	640	105	
Colonoscopy	16.4	2.8	1554	420	150	
80 y						
FIT	6.7	6.7	528	528	79	X
Sigmoidoscopy	11.6	4.8	1200	672	140	
Colonoscopy	13.9	2.3	1625	424	184	

FIT = fecal immunochemical test; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

* QALYs gained and costs per 1000 persons, discounted at 3% per year. Results are also displayed in **Figure 2**. Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions are present. In elderly persons without previous screening with no, moderate, and severe comorbid conditions, none of the screening strategies are cost-effective from age 87, 84, and 81 y onward, respectively (**Figure 1**).

† All screening strategies consist of a 1-time screening examination followed by diagnostic and surveillance colonoscopies if indicated.

‡ Compared with no screening.

§ Compared with the next less effective and costly efficient strategy, which is no screening for the first screening strategy mentioned at each age.

‖ Incremental cost per incremental QALY gained.

¶ The most effective, still cost-effective screening strategy based on a willingness to pay per QALY gained of $100 000.

** In elderly persons without previous screening with no comorbid conditions aged 76 to 78 y, FIT screening is dominated by a combination of sigmoidoscopy screening and no screening (**Figure 2**).

Appendix Table 6. **Results of Sensitivity Analyses for CRC Screening Indicated in Elderly Persons Without Previous Screening**

Analysis, by Comorbid Condition Level	Age Up to Which CRC Screening Should Be Considered, *y*	Screening Strategy Indicated, by Age														
		76 y	77 y	78 y	79 y	80 y	81 y	82 y	83 y	84 y	85 y	86 y	87 y	88 y	89 y	90 y
No comorbid conditions																
Base case	86	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT				
Utility loss from COL, SIG, and complication × 0.5	86	COL	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT				
Utility loss from COL, SIG, and complication × 2	86	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT	FIT	FIT				
Utility loss LYs with continuing care stage I and II CRC = 0.12 and 0.18, respectively	84	COL	COL	COL	COL	COL	COL	COL	SIG	SIG						
Costs of COL, SIG, and FIT × 1.25	86	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT	FIT				
Costs of COL, SIG, and FIT × 0.75	86	COL	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT				
Costs of CRC care × 1.25	86	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT				
Costs of CRC care × 0.75	87	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT	FIT			
Miss rates for COL and SIG × 2	86	COL	COL	COL	COL	COL	COL	COL	COL	FIT	FIT	FIT				
No surveillance in adenoma patients	86	COL	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT				
CRC risk × 1.25	86	COL	COL	COL	COL	COL	COL	COL	COL	COL	COL	FIT				
CRC risk × 0.75	86	COL	COL	COL	COL	COL	SIG	SIG	SIG	FIT	FIT	FIT				
2 annual FITs as an additional screening strategy	86	COL	COL	COL	COL	COL	COL	COL	COL	2 FITs	2 FITs	FIT				
Willingness to pay per QALY gained = $50 000	84	COL	COL	COL	COL	COL	SIG	SIG	FIT	FIT						
Moderate comorbid conditions																
Base case	83	COL	COL	COL	COL	COL	SIG	FIT	FIT							
Utility loss from COL, SIG, and complication × 0.5	84	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT						
Utility loss from COL, SIG, and complication × 2	83	COL	COL	COL	SIG	FIT	FIT	FIT	FIT							
Utility loss LYs with continuing care stage I and II CRC = 0.12 and 0.18, respectively	81	COL	COL	COL	COL	SIG	SIG									
Costs of COL, SIG, and FIT × 1.25	83	COL	COL	COL	COL	SIG	FIT	FIT	FIT							
Costs of COL, SIG, and FIT × 0.75	84	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT						
Costs of CRC care × 1.25	83	COL	COL	COL	COL	COL	SIG	FIT	FIT							
Costs of CRC care × 0.75	84	COL	COL	COL	COL	COL	SIG	FIT	FIT	FIT						
Miss rates for COL and SIG × 2	83	COL	COL	COL	COL	COL	SIG	FIT	FIT							
No surveillance in adenoma patients	84	COL	COL	COL	COL	COL	COL	COL	FIT	FIT						
CRC risk × 1.25	83	COL	COL	COL	COL	COL	COL	COL	FIT							
CRC risk × 0.75	83	COL	COL	SIG	SIG	SIG	FIT	FIT	FIT							
2 annual FITs as an additional screening strategy	83	COL	COL	COL	COL	COL	SIG	2 FITs	FIT							
Willingness to pay per QALY gained = $50 000	80	COL	COL	SIG	SIG	FIT										
Severe comorbid conditions																
Base case	80	COL	COL	SIG	FIT	FIT										
Utility loss from COL, SIG, and complication × 0.5	80	COL	COL	COL	SIG	SIG										
Utility loss from COL, SIG, and complication × 2	80	SIG	FIT	FIT	FIT	FIT										
Utility loss LYs with continuing care stage I and II CRC = 0.12 and 0.18, respectively	78	COL	SIG	SIG												

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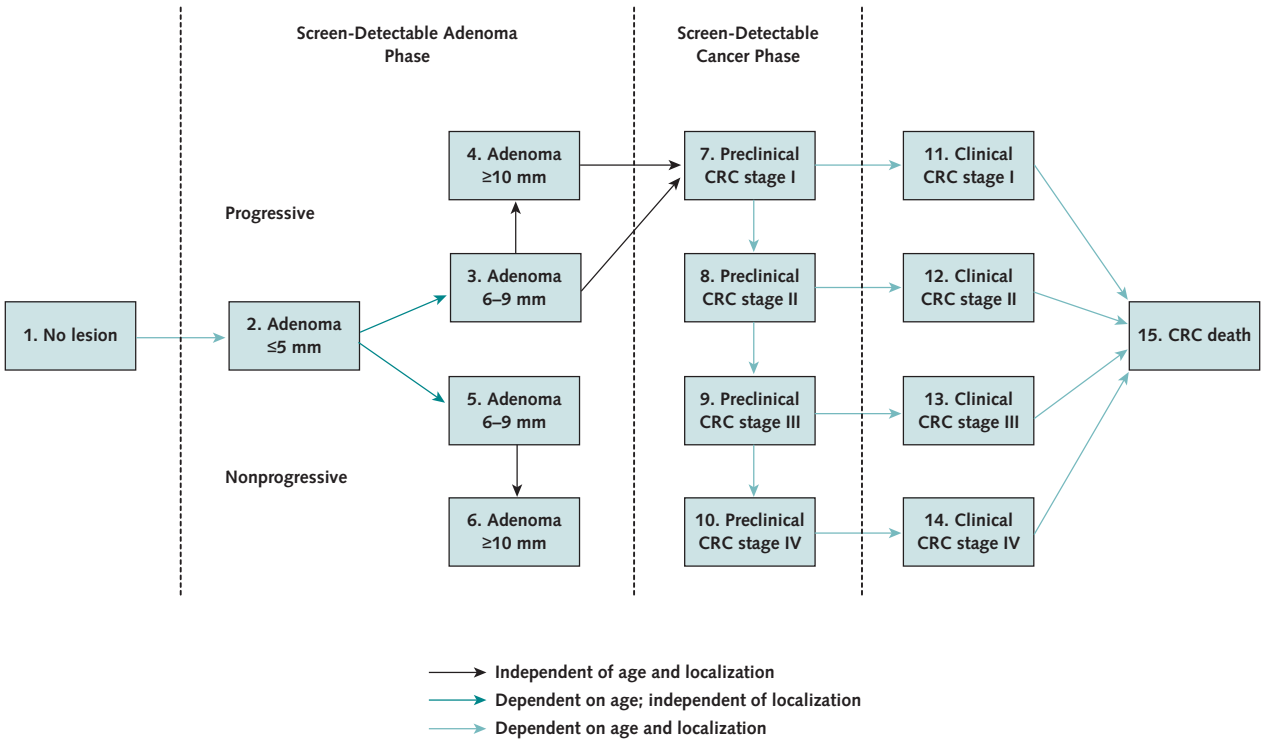
Appendix Table 6—**Continued**

Analysis, by Comorbid Condition Level	Age Up to Which CRC Screening Should Be Considered, *y*	Screening Strategy Indicated, by Age														
		76 y	77 y	78 y	79 y	80 y	81 y	82 y	83 y	84 y	85 y	86 y	87 y	88 y	89 y	90 y
Costs of COL, SIG, and FIT × 1.25	80	SIG	SIG	FIT	FIT	FIT										
Costs of COL, SIG, and FIT × 0.75	80	COL	COL	COL	SIG	SIG										
Costs of CRC care × 1.25	80	COL	COL	SIG	SIG	FIT										
Costs of CRC care × 0.75	81	COL	COL	SIG	FIT	FIT	FIT									
Miss rates for COL and SIG × 2	80	COL	COL	FIT	FIT	FIT										
No surveillance in adenoma patients	81	COL	COL	COL	SIG	FIT	FIT									
CRC risk × 1.25	80	COL	COL	COL	COL	FIT										
CRC risk × 0.75	80	SIG	SIG	FIT	FIT	FIT										
2 annual FITs as an additional screening strategy	80	COL	COL	2 FITs	2 FITs	2 FITs										
Willingness to pay per QALY gained = $50 000	77	SIG	FIT													

COL = 1-time colonoscopy screening; CRC = colorectal cancer; FIT = 1-time fecal immunochemical test screening; LY = life-year; QALY = quality-adjusted life-year; SIG = 1-time sigmoidoscopy screening; 2 FITs = fecal immunochemical test screening during 2 consecutive years.

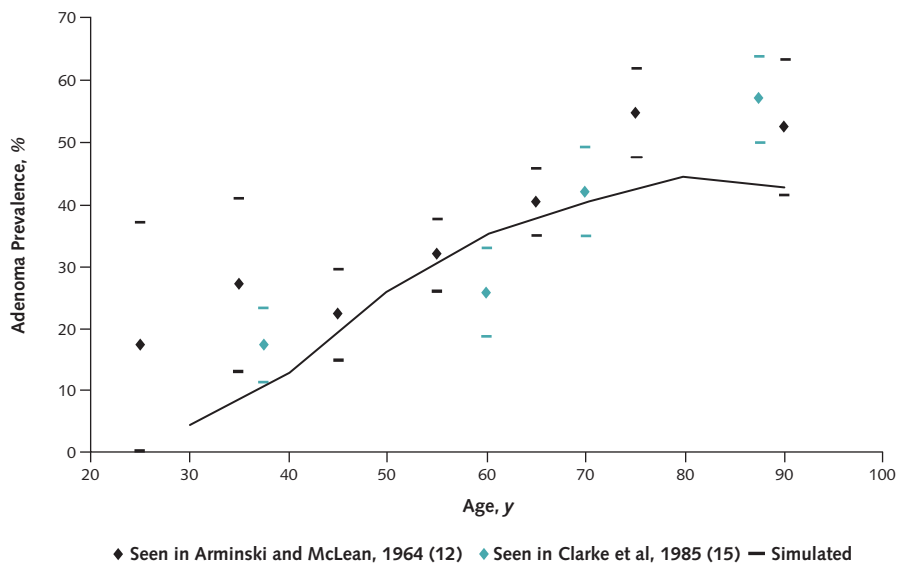
* Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis or AIDS; and no comorbid conditions if none of these conditions are present.

Appendix Figure 1. **Overview of the natural history module of Microsimulation Screening Analysis–Colon.**



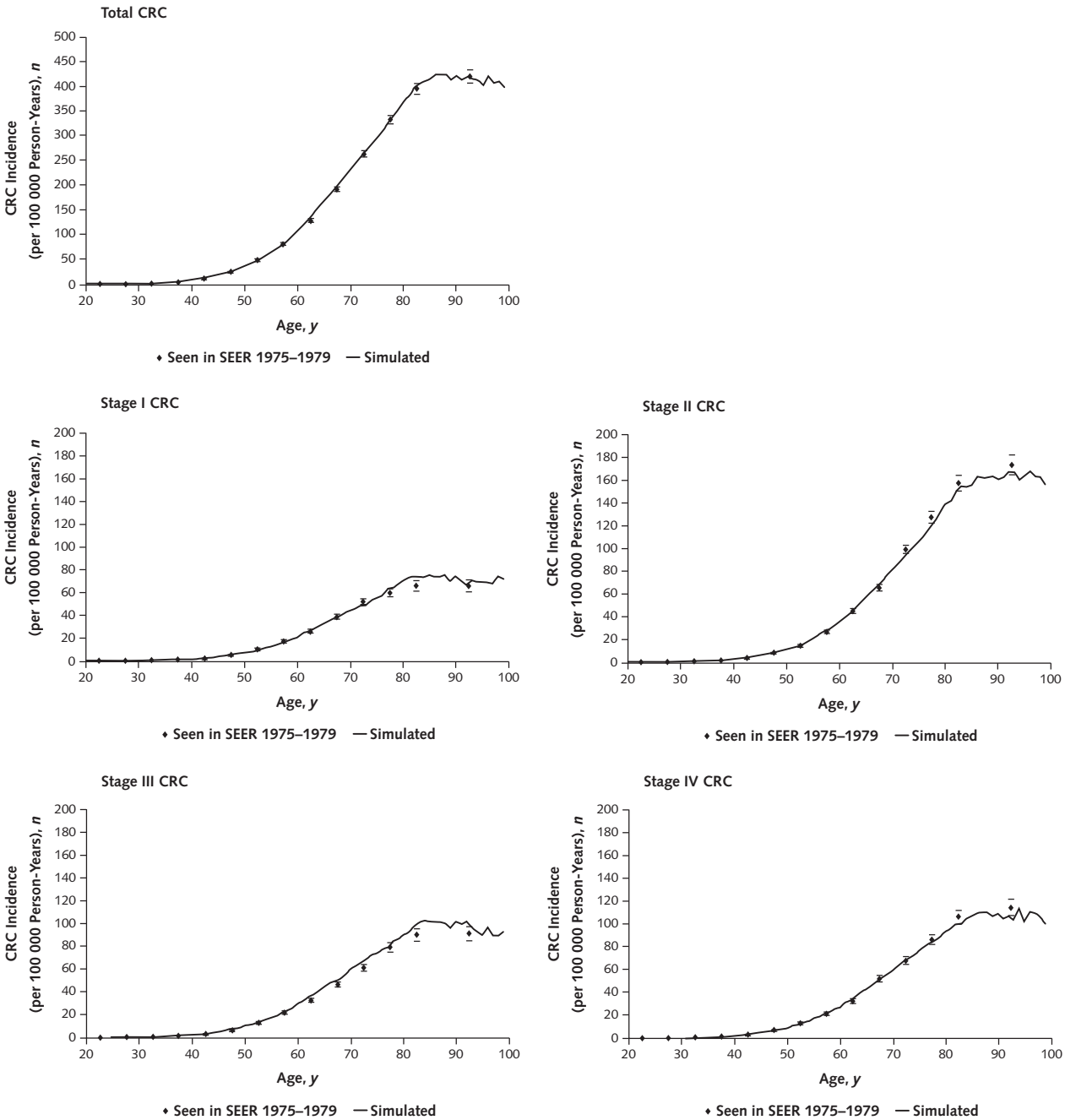
CRC = colorectal cancer.

Appendix Figure 2. **Adenoma prevalence seen in selected autopsy studies versus prevalence simulated by Microsimulation Screening Analysis–Colon.**



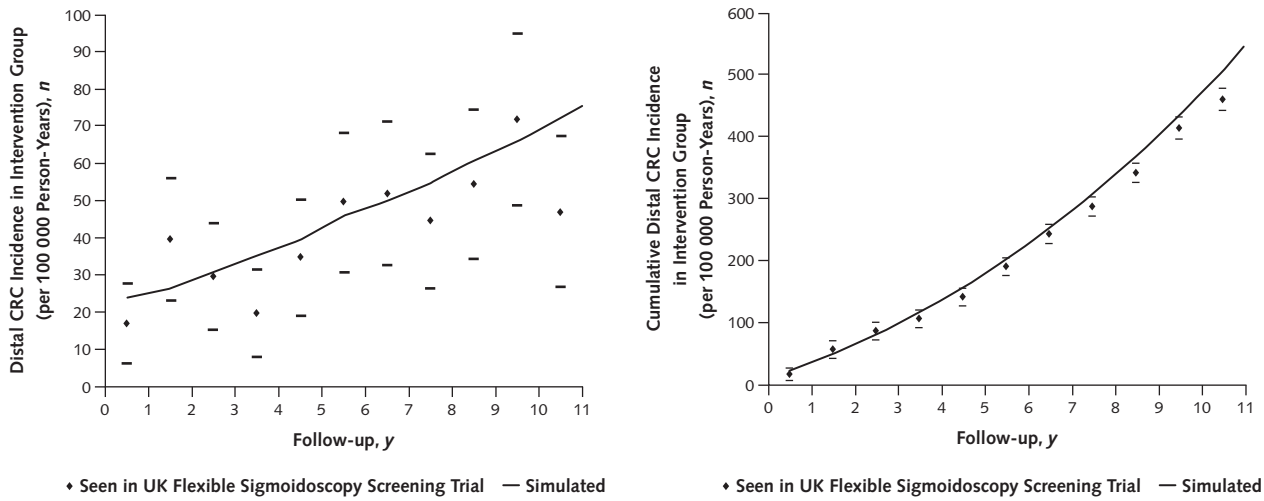
Observed results are shown only for the 2 largest studies on which the model has been calibrated. The model has additionally been calibrated to 8 other autopsy studies. Bars above and below the diamonds indicate 95% CIs.

Appendix Figure 3. **CRC incidence seen before the introduction of screening versus incidence simulated by Microsimulation Screening Analysis–Colon.**



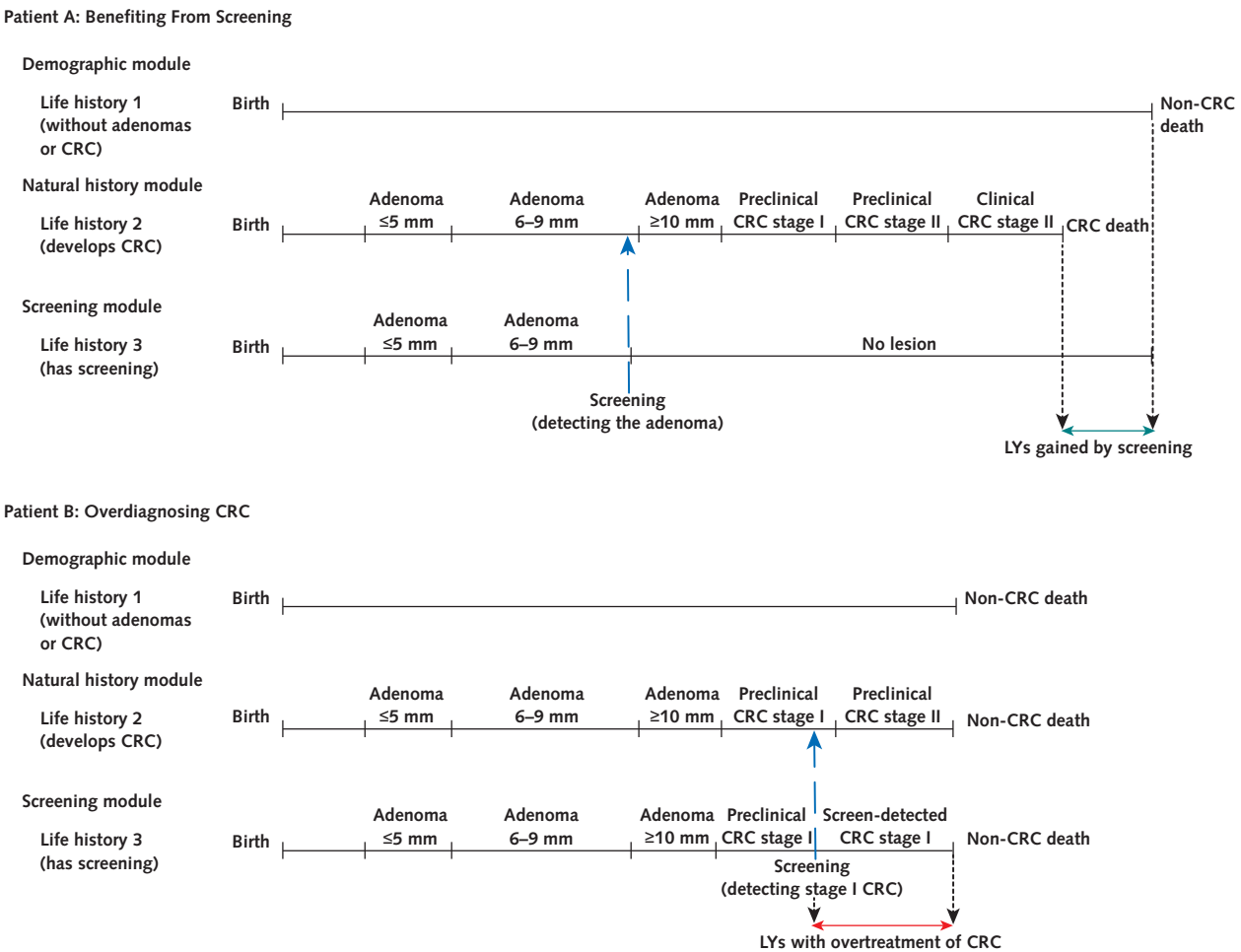
Bars above and below the diamonds indicate 95% CIs. CRC = colorectal cancer; SEER = Surveillance, Epidemiology, and End Results.

Appendix Figure 4. **Distal CRC incidence seen in the intervention group of the UK Flexible Sigmoidoscopy Screening Trial versus incidence simulated by Microsimulation Screening Analysis–Colon.**



Bars above and below the diamonds indicate 95% CIs. CRC = colorectal cancer; UK = United Kingdom.

Appendix Figure 5. **Integrating modules for 2 example patients.**



CRC = colorectal cancer; LY = life-year.