

Colorectal Cancer Screening

An Updated Modeling Study for the US Preventive Services Task Force

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IMPORTANCE The US Preventive Services Task Force (USPSTF) is updating its 2016 colorectal cancer screening recommendations.

OBJECTIVE To provide updated model-based estimates of the benefits, burden, and harms of colorectal cancer screening strategies and to identify strategies that may provide an efficient balance of life-years gained (LYG) from screening and colonoscopy burden to inform the USPSTF.

DESIGN, SETTING, AND PARTICIPANTS Comparative modeling study using 3 microsimulation models of colorectal cancer screening in a hypothetical cohort of 40-year-old US individuals at average risk of colorectal cancer.

EXPOSURES Screening from ages 45, 50, or 55 years to ages 70, 75, 80, or 85 years with fecal immunochemical testing (FIT), multitarget stool DNA testing, flexible sigmoidoscopy alone or with FIT, computed tomography colonography, or colonoscopy. All persons with an abnormal noncolonoscopy screening test result were assumed to undergo follow-up colonoscopy. Screening intervals varied by test. Full adherence with all procedures was assumed.

MAIN OUTCOME AND MEASURES Estimated LYG relative to no screening (benefit), lifetime number of colonoscopies (burden), number of complications from screening (harms), and balance of incremental burden and benefit (efficiency ratios). Efficient strategies were those estimated to require fewer additional colonoscopies per additional LYG relative to other strategies.

RESULTS Estimated LYG from screening strategies ranged from 171 to 381 per 1000 40-year-olds. Lifetime colonoscopy burden ranged from 624 to 6817 per 1000 individuals, and screening complications ranged from 5 to 22 per 1000 individuals. Among the 49 strategies that were efficient options with all 3 models, 41 specified screening beginning at age 45. No single age to end screening was predominant among the efficient strategies, although the additional LYG from continuing screening after age 75 were generally small. With the exception of a 5-year interval for computed tomography colonography, no screening interval predominated among the efficient strategies for each modality. Among the strategies highlighted in the 2016 USPSTF recommendation, lowering the age to begin screening from 50 to 45 years was estimated to result in 22 to 27 additional LYG, 161 to 784 additional colonoscopies, and 0.1 to 2 additional complications per 1000 persons (ranges are across screening strategies, based on mean estimates across models). Assuming full adherence, screening outcomes and efficient strategies were similar by sex and race and across 3 scenarios for population risk of colorectal cancer.

CONCLUSIONS AND RELEVANCE This microsimulation modeling analysis suggests that screening for colorectal cancer with stool tests, endoscopic tests, or computed tomography colonography starting at age 45 years provides an efficient balance of colonoscopy burden and life-years gained.

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Colorectal cancer remains the second leading cause of US cancer deaths.¹ While randomized trials have shown that screening reduces colorectal cancer incidence and colorectal cancer mortality,² there are many ways to screen, and trial-based evaluation of the long-term outcomes of the full spectrum of screening strategies is not feasible. In 2016, the US Preventive Services Task Force (USPSTF) recommended colorectal cancer screening starting at age 50 years and continuing until age 75 years (A recommendation), offering a number of screening modalities.³ To help inform an update of the colorectal cancer screening recommendations,^{3,4} the USPSTF requested an updated modeling study to estimate long-term outcomes of screening strategies, along with an updated evidence review.²

Methods

This analysis updated a 2016 modeling analysis estimating how the benefits, burden, and harms of screening average-risk, asymptomatic adults for colorectal cancer vary by modality, interval for repeated testing, and ages to begin and end screening.⁴ It incorporated recent evidence reporting increasing colorectal cancer incidence rates among recent birth cohorts⁵ and evaluated whether modeled benefits, burden, and harms of screening vary by race and sex. More information about the models and findings from additional analyses are included in the full modeling report.⁶

Model Descriptions

This study used 3 independently developed microsimulation models: Simulation Model of CRC (SimCRC), CRC Simulated Population Model for Incidence and Natural History (CRC-SPIN), and Microsimulation Screening Analysis (MISCAN) for colorectal cancer. All were used in the 2016 analysis,⁴ although they were updated to incorporate observed trends in the population risk of colorectal cancer.⁵ CRC-SPIN was also updated⁷ following a validation study.⁸ Each model has a natural history and a screening component, summarized below. SimCRC was programmed in C++, CRC-SPIN in R, and MISCAN in Delphi.

Natural History Component

All models describe the natural history of colorectal cancer in an average-risk unscreened population, assuming that all colorectal cancer arises from an adenomatous polyp.⁹ Alternative ways in which colorectal cancer can arise, such as from serrated polyps,¹⁰ were not modeled. Simulated persons were assumed to be free of adenomas and colorectal cancer at birth (Figure 1). As they age, they are at risk of developing 1 or more adenomas, each of which may grow in size. Adenomas may progress to preclinical colorectal cancer, after which they may become symptomatic, leading to colorectal cancer diagnosis. Persons may die of other causes at any time¹¹; persons with clinically detected colorectal cancer are also at risk of dying of colorectal cancer.¹²

Each model's natural history component was initially calibrated to adenoma prevalence data and colorectal cancer incidence prior to the dissemination of screening in the US.¹³ The models do not simulate family history of colorectal cancer, although people with a family history are included in the data used to calibrate the models. For this analysis, the natural history components

were adjusted to reflect increasing colorectal cancer incidence among birth cohorts since the 1950s.⁵ The magnitude of the increase was estimated by the ratio of colorectal cancer incidence (excluding tumors that are not the target of colorectal cancer screening) among 20- to 44-year-olds in 2012-2016 (the 5 most recent years of Surveillance, Epidemiology, and End Results [SEER] data available) relative to 1975-1979 (the years of SEER data used for initial model calibration).¹⁴ Base-case analyses assumed this incidence rate ratio (IRR) to be 1.19. Scenario analyses were also simulated assuming IRRs of 1.00 (no change in incidence from the prescreening era) and 1.52 (the approximate upper bound of the 95% CI for the IRR estimated from age-period-cohort modeling of SEER incidence rates; see the Supplement for details on estimation of IRRs). In all scenarios, the increase in incidence was assumed to arise from an increase in adenoma risk that is carried forward with age.

Screening Component

The models' screening components allow for interruption of the adenoma-carcinoma sequence through detection and removal of adenomas and for the detection of preclinical cancer, potentially at an earlier stage (Figure 1). The ability of a test to detect lesions is a function of its sensitivity and, for endoscopic tests, whether the lesion is within reach of the scope (Table 1). All persons with an abnormal noncolonoscopy screening test result were assumed to undergo follow-up colonoscopy. Patients with a history of adenoma(s) were assumed to undergo surveillance with colonoscopy, with surveillance intervals based on published guidelines.¹⁹ The models incorporate the risk of fatal²⁰ and nonfatal²¹ complications from colonoscopy and have been externally validated.²²

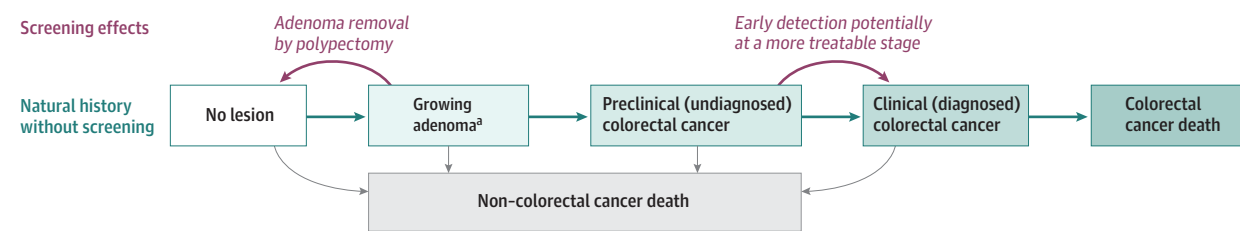
Screening Strategies

The following screening modalities were evaluated: a fecal immunochemical test (FIT) representative of the OC-Sensor family of tests (Polymedco) with a cutoff of 20 µg of hemoglobin per gram of feces; a stool DNA test with a FIT assay (sDNA-FIT), marketed as Cologuard (Exact Sciences); flexible sigmoidoscopy, alone or with FIT; colonoscopy; and computed tomography colonography. Multiple ages to begin screening (45, 50, 55 years) and end screening (70, 75, 80, 85 years) and screening intervals were evaluated for each modality, resulting in 163 unique strategies (Table 2). No screening was performed after the stopping age, but surveillance continued through at least age 85. Perfect adherence with all screening, follow-up, and surveillance procedures was assumed, reflecting outcomes among persons with full willingness to participate.

Outcomes

Outcomes were simulated for a hypothetical cohort of average-risk US adults who were unscreened and free of diagnosed colorectal cancer at age 40 years and were tallied through death. The primary benefit of screening was expressed as life-years gained (LYG) from the prevention or delay of colorectal cancer death, accounting for the loss of years from fatal complications. The burden of screening was measured by the lifetime number of required colonoscopies. Numbers of noncolonoscopy tests were also reported. Harms were expressed by the number of colonoscopy complications (serious gastrointestinal events [perforations, bleeding, transfusion], other gastrointestinal events [paralytic ileus, nausea and vomiting, dehydration, abdominal pain], and cardiovascular events

Figure 1. Natural History of Colorectal Cancer and the Effects of Screening as Simulated by SimCRC, CRC-SPIN, and MISCAN



The opportunity to intervene in the natural history through screening (adenoma detection and removal and early detection) is noted in red. Screening can either remove a precancerous lesion (ie, adenoma), thus moving a person to the “no lesion” state, or diagnose a preclinical cancer, which, if detected at an earlier stage, may be more amenable to treatment. Each person’s life history is simulated in the absence of screening and in the presence of screening, such that the effect of a given screening strategy on each simulated person’s outcomes are known.

^a Simulation Model of CRC (SimCRC) and Microsimulation Screening Analysis

(MISCAN) simulate categorical adenoma size (1 to <6 mm; 6 to <10 mm; ≥10 mm), whereas CRC Simulated Population Model for Incidence and Natural History (CRC-SPIN) simulates continuous adenoma size. SimCRC and CRC-SPIN assume that all adenomas have the potential to progress to colorectal cancer, whereas MISCAN assumes that some adenomas are nonprogressive (ie, they do not grow or progress to cancer after reaching a certain size category) and that the likelihood that an adenoma is progressive increases with age. None of the models simulate adenoma histology.

[myocardial infarction, angina, arrhythmia, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, shock]).²¹ Other outcomes included the number of colorectal cancer cases and colorectal cancer deaths.

Analysis

Model output was analyzed in R version 3.6.1 (R Foundation for Statistical Computing). The relative efficiency of colorectal cancer screening across strategies was assessed by evaluating the trade-off in burden (colonoscopies) vs benefits (LYG). Because of large differences in the number of noncolonoscopy tests across modalities, efficiency analyses were performed by class of screening modality. FIT and sDNA-FIT were grouped together as exclusively stool-based modalities with comparable burden. The remaining modalities each comprised a unique class because of differences in bowel preparation, invasiveness, need for sedation, and number and type of noncolonoscopy tests.

Within each class, the subset of strategies that provide an efficient balance of colonoscopies and LYG were identified. A strategy is efficient if no other strategy, or combination of strategies, within the class is estimated to provide more LYG and require fewer colonoscopies. Strategies were compared by plotting their estimated LYG (relative to no screening) on the horizontal axis and their estimated number of lifetime colonoscopies on the vertical axis. The “efficient frontier” is the line connecting the efficient strategies.²³ Strategies on the efficient frontier were compared using an efficiency ratio, which represents the estimated number of additional colonoscopies required for each additional LYG. Because an inefficient strategy providing outcomes similar to an efficient strategy may be a reasonable option on other grounds²³ (eg, for consistency of screening ages across modalities), efficiency ratios were also calculated for “near-efficient” strategies, defined a priori as being within 3 days of life gained per person of the efficient frontier. For the strategies highlighted by the USPSTF in 2016, this absolute distance of 3 days is generally consistent with the relative measure used in the 2016 decision analysis (ie, LYG within 2% of the efficient frontier).⁴ Hereafter, “efficient” refers to both efficient and near-efficient strategies.

Analyses by Race and Sex

In consultation with the USPSTF, analyses were conducted by race and sex for the 2 most commonly-used screening modalities in the US: colonoscopy and FIT.²⁴ Prior to performing these analyses, we conducted a comprehensive review of the literature on race and colorectal cancer.²⁵ We concluded that the primary driver of differences in colorectal cancer incidence by race is access to screening and subsequent care, rather than biological differences in natural history. This review found that Black-White differences in colorectal cancer incidence began only after the dissemination of screening, that there is strong evidence that Black adults have had lower rates of colorectal cancer screening than White adults, and that there is limited evidence for Black-White differences in findings at screening, including detection of adenomas, advanced adenomas, and colorectal cancer.²⁵ Accordingly, the modeling analyses assumed no differences in the natural history of colorectal cancer by race (ie, development of clinically detected colorectal cancer in the absence of screening), incorporating only Black-White differences in all-cause mortality¹¹ and in stage-specific relative survival after diagnosis.¹²

Results

In the absence of screening, the models simulated identical life expectancy among 40-year-olds with no prior diagnosis of colorectal cancer, 40.2 years, and estimated that 77 to 85 per 1000 40-year-olds would be diagnosed with colorectal cancer in their lifetimes and 32 to 34 would die of colorectal cancer (eTable 1 in the Supplement). Compared with no screening, all colorectal cancer screening strategies were estimated to yield substantial increases in life expectancy (171-381 LYG per 1000) and reductions in the lifetime number of colorectal cancer cases and colorectal cancer deaths (16-74 and 15-32 cases and deaths averted per 1000, respectively). In the models, lifetime colonoscopies ranged from 624 to 6817 per 1000, and the lifetime number of colonoscopy complications ranged from 5 to 22 per 1000 (ranges are across strategies and models; see the full report⁶ for detailed outcomes).

Efficiency Analysis

Figure 2, Figure 3, and eFigures 1 through 3 in the Supplement show the estimated number of lifetime number of colonoscopies and LYG per 1000 for each screening strategy within a class. Although absolute estimation differed by model, general patterns were similar. Within each class, estimated LYG from screening increased when screening was initiated in the models at an earlier age, although the increase was smaller for MISCAN compared with SimCRC and CRC-SPIN.

Forty-nine unique screening strategies were efficient for all 3 models (Table 3). The majority (41/49) were those with screening starting at age 45 years. None of the strategies highlighted in the 2016 USPSTF colorectal cancer screening recommendations,³ which specified screening from ages 50 to 75, were efficient in all 3 models.

Unlike the age to begin screening, no single age to end screening was predominant among efficient strategies. However, for most modalities, the estimated increase in LYG from extending screening beyond age 75 years was small in comparison with the increase in colonoscopies (Table 3). For example, with 10-yearly colonoscopy starting at age 45, extending the age to end screening from 75 to 85 was estimated to increase lifetime colonoscopies by 5% to 6% (from 4212-4300 to 4449-4566 per 1000; ranges are across models), whereas LYG increased by less than 1% (from 301-369 to 302-370 per 1000). With annual FIT from age 45, extending the age to end screening from age 75 to age 80 years was estimated to increase lifetime colonoscopies by 5% to 7% (from 1602-1824 to 1710-1923 per 1000) and LYG by 1% to 3% (from 291-348 to 300-355 per 1000). Extending the age to end FIT screening from age 80 to age 85 was estimated to increase lifetime colonoscopies by 3% to 4% (to 1769-1990 per 1000) and LYG by less than 1% to 1% (to 303-356 per 1000).

With the exception of computed tomography colonography (5-year interval), efficient strategies within each class included multiple screening intervals; no interval was predominant (Table 3). The number of additional colonoscopies required for each additional LYG increased with shorter screening intervals. For colonoscopy from age 45 to 75 years, shortening the interval from 10 to 5 years was estimated to increase the lifetime colonoscopies by 42% to 46% across models (from 4212-4300 to 6016-6235 per 1000), while LYG was estimated to increase by 3% to 7% (from 301-369 to 321-380 per 1000) (Table 3).

Of the 16 efficient stool-based strategies, 11 were those with FIT (Table 3, Figure 3), including triennial, biennial, and annual FIT screening starting at age 45 years. Annual and biennial sDNA-FIT strategies starting at age 45 were also efficient, albeit with a relatively high colonoscopy burden relative to the LYG. For example, compared with annual FIT from ages 45 to 85, screening with biennial sDNA-FIT from ages 45 to 80 was estimated to increase the lifetime number of colonoscopies by 10% to 15% (from 1769-1990 to 2012-2181 per 1000; range is across models), while LYG were estimated to be similar to the FIT strategy (+1% in CRC-SPIN [from 319 to 322 per 1000], unchanged in SimCRC [356 per 1000], and -2% in MISCAN [from 303 to 298 per 1000]). None of the models found the triennial sDNA-FIT strategies to be efficient relative to other stool-based options.

In general, estimated LYG with 5-yearly sigmoidoscopy were comparable to LYG with biennial FIT (Table 3). Sigmoidoscopy with interval FIT was estimated to provide LYG and colorectal cancer deaths averted similar to those estimated for colonoscopy screening over the same age range.

Table 1. Screening Test Characteristics Used in the Analysis

Screening test/test characteristic	Value	Source
FIT (per person)		
Specificity	0.97	
Sensitivity for adenomas 1 to <6 mm	0.07 ^a	Lin et al, ² 2021
Sensitivity for adenomas 6 to <10 mm		
Sensitivity for adenomas ≥10 mm	0.22 ^b	
Sensitivity for colorectal cancer	0.74	
sDNA-FIT (per person)		
Specificity	0.91	
Sensitivity for adenomas 1 to <6 mm	0.15 ^a	Lin et al, ² 2021
Sensitivity for adenomas 6 to <10 mm		
Sensitivity for adenomas ≥10 mm	0.42 ^b	
Sensitivity for colorectal cancer	0.94	
Colonoscopy (within reach, per lesion)^c		
Specificity	0.86 ^d	Schroy et al, ¹⁵ 2013
Sensitivity for adenomas 1 to <6 mm	0.75	van Rijn et al, ¹⁶ 2006
Sensitivity for adenomas 6 to <10 mm	0.85	van Rijn et al, ¹⁶ 2006
Sensitivity for adenomas ≥10 mm	0.95	van Rijn et al, ¹⁶ 2006
Sensitivity for colorectal cancer	0.95	By assumption ^e
SIG (within reach, per lesion)		
Specificity	0.87 ^d	Weissfeld et al, ¹⁷ 2005
Sensitivity for adenomas 1 to <6 mm	0.75	By assumption ^f
Sensitivity for adenomas 6 to <10 mm	0.85	By assumption ^f
Sensitivity for adenomas ≥10 mm	0.95	By assumption ^f
Sensitivity for colorectal cancer	0.95	By assumption ^f
CTC (per lesion)		
Specificity	0.88 ^g	
Sensitivity for adenomas 1 to <6 mm	NR	
Sensitivity for adenomas 6 to <10 mm	0.57	Johnson et al, ¹⁸ 2008
Sensitivity for adenomas ≥10 mm	0.84	
Sensitivity for colorectal cancer	0.84 ^e	

Abbreviations: CTC, computed tomography colonography; FIT, fecal immunochemical test (with positivity cutoff of 20 µg of hemoglobin per gram of feces); NR, not reported (adenoma size < 6 mm [the threshold size for referral to colonoscopy]); sDNA-FIT, multitarget stool DNA test with a fecal immunochemical assay; SIG, flexible sigmoidoscopy.

^a For persons with nonadvanced adenomas. For persons with adenomas 1 mm to <6 mm, sensitivity was assumed to equal the positivity rate in persons without adenomas. Sensitivity for persons with adenomas 6 mm to <10 mm was chosen such that the weighted mean sensitivity for persons with adenomas 1 mm to <6 mm and 6 mm to <10 mm was equal to the sensitivity for nonadvanced adenomas.

^b For persons with advanced adenomas (ie, adenomas ≥10 mm, adenomas with advanced histology, or both); the studies in the meta-analysis in Lin et al² did not provide sensitivity for adenomas ≥10 mm separately from advanced adenomas.

^c The same test characteristics were assumed to apply to all colonoscopies, regardless of indication. No correlation in findings at CTC or SIG and follow-up colonoscopy was assumed.

^d The lack of specificity with endoscopy reflects detection of nonadenomatous polyps, which, in the case of sigmoidoscopy, may lead to unnecessary follow-up colonoscopy, and in the case of colonoscopy, leads to unnecessary polypectomy, which is associated with an increased risk of complications.

^e Sensitivity for cancer was assumed to be the same as sensitivity for adenomas ≥10 mm because of the small number of cancers detected in screening studies.

^f Sensitivity for flexible sigmoidoscopy was assumed to equal that of colonoscopy within reach of the sigmoidoscope and 0 for lesions beyond reach of the scope.

^g The lack of specificity with CTC reflects detection of nonadenomatous lesions ≥6 mm, artifacts, stool, and adenomas smaller than the 6-mm threshold for colonoscopy referral that are measured as ≥6 mm.

Table 2. Screening Strategies Evaluated by the Models^a

Modality	Screening interval, y	Age to begin screening, y	Age to end screening, y ^b	No. of (unique) strategies ^c
No screening				1 (1)
COL	5, 10, 15	45, 50, 55	70, 75, 80, 85	36 (26)
CTC	5, 10	45, 50, 55	70, 75, 80, 85	24 (20)
SIG	5, 10	45, 50, 55	70, 75, 80, 85	24 (20)
FIT	1, 2, 3	45, 50, 55	70, 75, 80, 85	36 (36)
sDNA-FIT	1, 2, 3	45, 50, 55	70, 75, 80, 85	36 (36)
SIG + FIT ^d	10_1, 10_2	45, 50, 55	70, 75, 80, 85	24 (24)
Total				181 (163)

Abbreviations: COL, colonoscopy; CTC, computed tomography colonography; FIT, fecal immunochemical test (with positivity cutoff of 20 µg of hemoglobin per gram of feces); sDNA-FIT, multitarget stool DNA test with a fecal immunochemical assay; SIG, flexible sigmoidoscopy without biopsy.

^a See the full report⁶ for a complete list of screening strategies evaluated by the models.

^b Age to end screening is the last age at which screening happens; screening tests could be performed at but not after this age.

^c The number of unique strategies excludes those with different ages to end

screening that result in screens at the same ages (eg, COL every 10 years from ages 50-70 years and from ages 50-75 years both result in screening at ages 50, 60, and 70 years).

^d The first interval is for SIG and the second interval is for FIT. If SIG and FIT were due the same year, it was assumed that the FIT was performed first. Persons with a positive FIT result did not have a SIG. Instead they had a follow-up colonoscopy. Those with a negative FIT result had a SIG, and those with SIG findings subsequently had a follow-up colonoscopy.

Figure 4 and Figure 5 summarize the model-estimated changes in outcomes if screening were to begin at age 45 years instead of age 50 for strategies highlighted by the USPSTF in 2016.³ Models that lowered the age to begin screening showed 22 to 27 additional LYG (8%-9% increase), 2 to 3 fewer colorectal cancer cases (4%-6% reduction), and 0.9 to 1 fewer colorectal cancer deaths (3%-5% reduction) but also showed 0.1 to 2 additional complications (1%-14% increase) and required 161 to 784 additional colonoscopies (10%-23% increase) and 0 (with colonoscopy) to 3553 additional noncolonoscopy tests (no change to a 24% increase) over the lifetimes of 1000 persons (numbers are mean estimates across models).

Findings by Race and Sex

Compared with the total population, model-estimated life expectancy among unscreened 40-year-olds with no prior colorectal cancer diagnosis was 2 years higher for White women (42.2 vs 40.2 years), similar for Black women (40.1 years), 2 years lower for White men (38.4 years), and 5 years lower for Black men (35.2 years). In the absence of screening, the model-estimated lifetime number of diagnosed colorectal cancer cases was higher for White men compared with the total population (86 vs 81 cases per 1000, respectively; estimates are the mean across models) and lower than the total population for the other groups (77 cases per 1000 White women, 73 cases per 1000 Black men, and 70 cases per 1000 Black women) (eTable 1 in the Supplement).

Among men, the models estimated that the lower lifetime risk of colorectal cancer diagnosis also led to a lower lifetime risk of colorectal cancer death in Black vs White adults in the absence of screening (eTable 1 in the Supplement) despite the worse Black vs White relative survival after colorectal cancer diagnosis.¹² The pattern differed for women by race: Black women were estimated to have lower lifetime colorectal cancer incidence than White women in the absence of screening but higher lifetime risk of colorectal cancer death. This implies that the difference in Black vs White lifetime colorectal cancer incidence was offset by the worse Black vs White relative survival after colorectal cancer diagnosis.¹²

Because of these differences in the estimated lifetime risk of colorectal cancer death among Black vs White adults by sex in the absence of screening, estimated LYG from both colonoscopy and FIT were generally lower for Black vs White men and generally similar for Black vs White women (eFigures 4-5 in the Supplement). However, efficient strategies for each race-sex group were generally the same, and efficiency ratios were similar by race among each sex (eTables 2-3 in the Supplement), suggesting that with equal access to quality care, the relative balance of the colonoscopy burden and the LYG from screening differs slightly by sex but not by race. For example, across models, efficiency ratios for 10-yearly colonoscopy from age 45 to 75 years ranged from 48 to 143 for White men, 46 to 142 for Black men, 57 to 100 for White women, and 51 to 93 for Black women. Among all 4 race-sex groups, efficient screening options for all 3 models were predominantly those beginning at age 45 (eFigures 4-5 and eTables 2-3 in the Supplement).

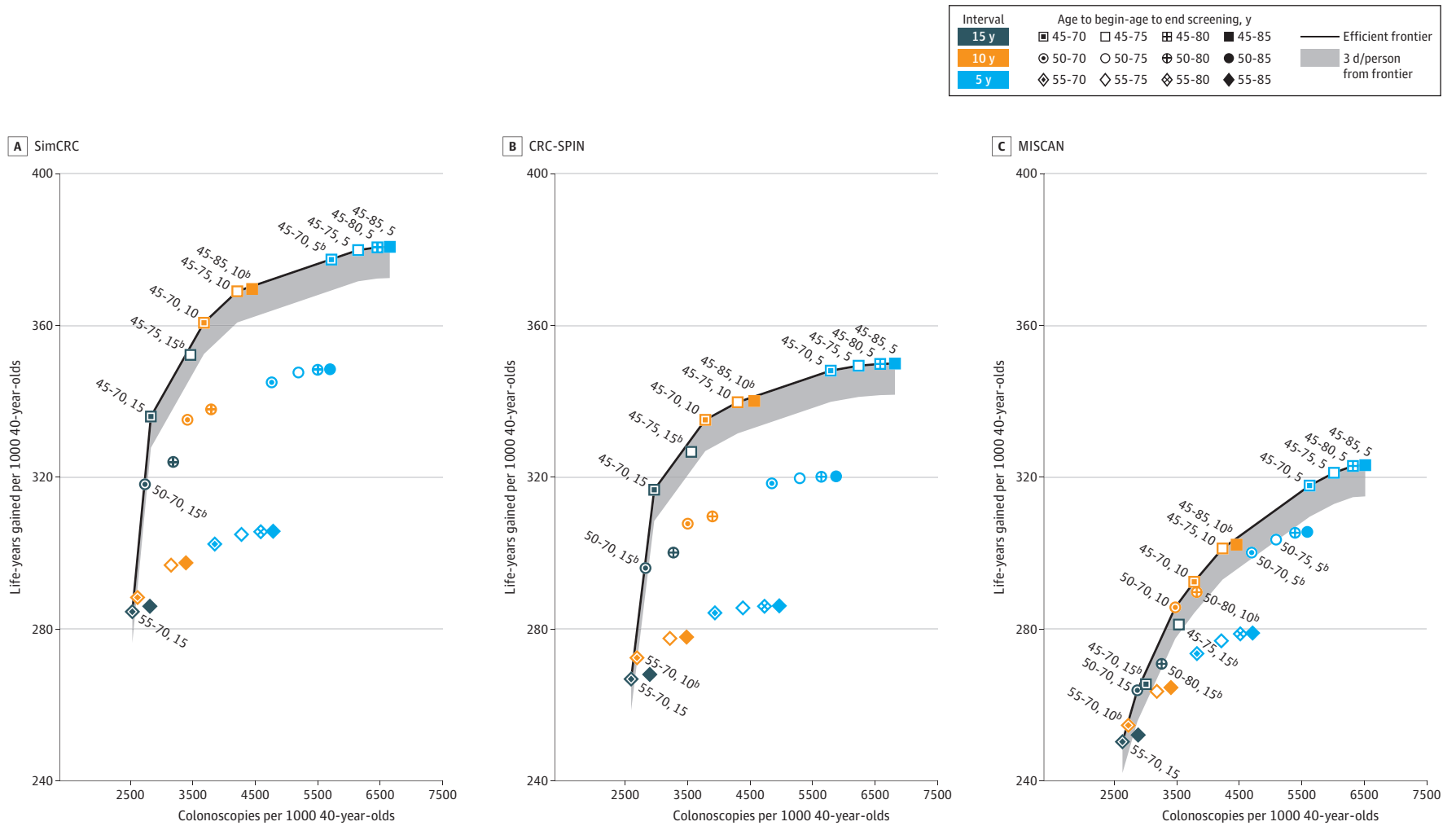
Scenario Analyses

For each modality, efficient strategies were similar for the 3 colorectal cancer population risk scenarios (eTables 4-8, eFigures 6-7 in the Supplement); efficient strategies in all 3 models were primarily those with screening beginning at age 45 years regardless of risk scenario.

Potential Implications of Adherence

Because this analysis was intended to inform population guidelines, perfect adherence to screening strategies was assumed to estimate achievable benefit for people who adhere to recommendations. However, perfect adherence does not occur in daily life.² The potential implications of nonadherence can be inferred by comparing model-estimated outcomes with different start ages and screening intervals. These comparisons are described in the Supplement and are highlighted in eTables 9 through 12 in the Supplement. For example, lack of adherence with annual FIT from ages 45 to 75 years, resulting in a 3-year screening interval, was estimated to reduce LYG by 18% to 23% (eTable 12 in the Supplement). Similarly, lack of adherence with 10-yearly colonoscopy,

Figure 2. Lifetime Number of Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies^a



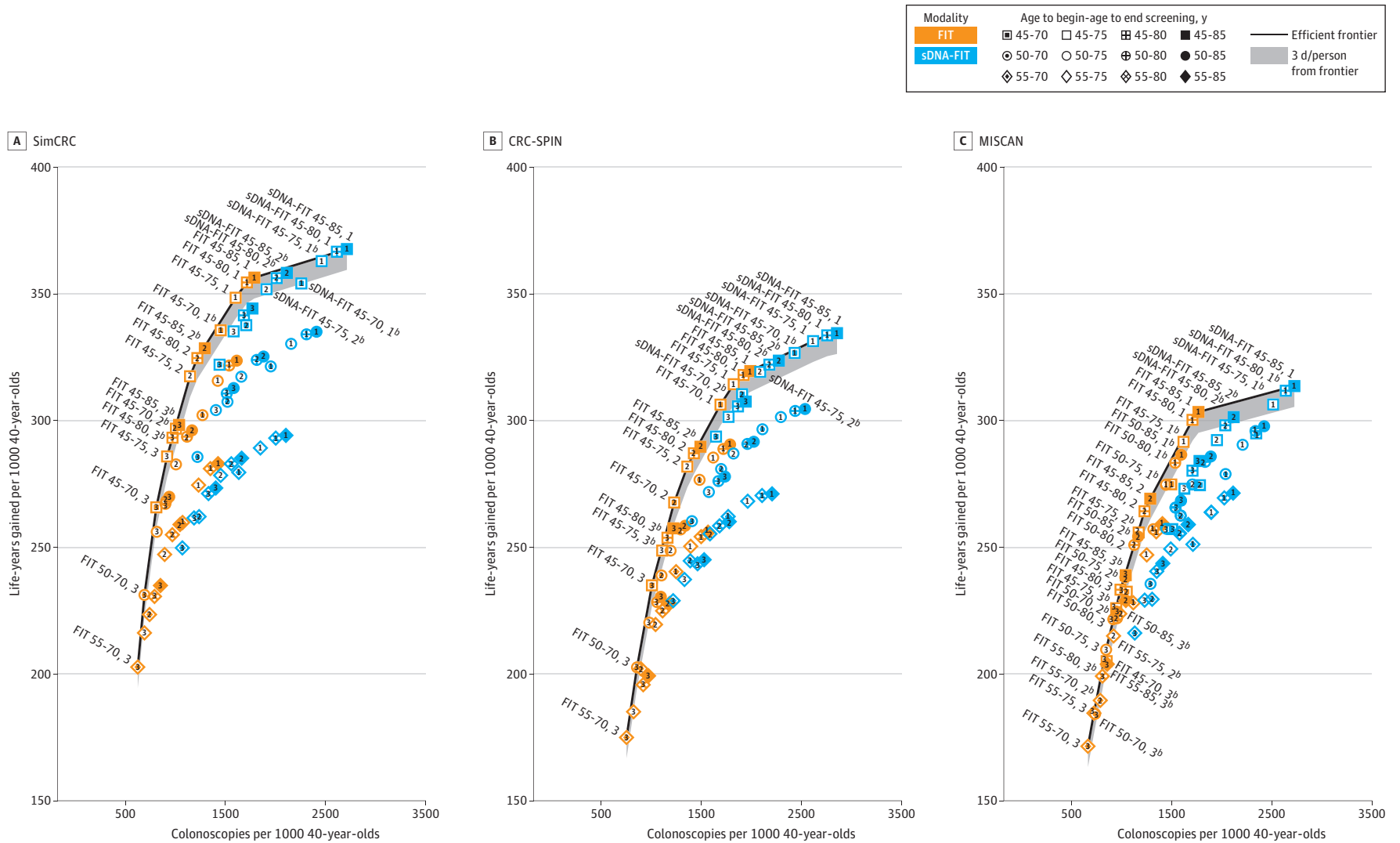
CRC-SPIN indicates CRC Simulated Population Model for Incidence and Natural History; MISCAN, Microsimulation Screening Analysis; SimCRC, Simulation Model of CRC.

^a Analyses assume an increased population incidence of colorectal cancer based on an incidence rate ratio comparing incidence among current 20- to 44-year-olds (ie, in 2012-2016) vs 20- to 44-year-olds in the period

used for initial model calibration (ie, 1975-1979) of 1.19. An interactive version of this figure is available at <https://resources.cisnet.cancer.gov/projects/#crrc/uspstf2021/explorer>

^b Near-efficient strategy.

Figure 3. Lifetime Number of Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Stool-Based Screening Strategies^a



See Figure 2 legend for expanded abbreviations.

^a Analyses assume an increased population incidence of colorectal cancer based on an incidence rate ratio comparing incidence among current 20- to 44-year-olds (ie, in 2012-2016) vs 20- to 44-year-olds in the period

used for initial model calibration (ie, 1975-1979) of 1.19. An interactive version of this figure is available at <https://resources.cisnet.cancer.gov/projects/#ccrc/uspstf2021/explorer>

^b Near-efficient strategy.

Table 3. Outcomes for Efficient and Near-Efficient Strategies With SimCRC, CRC-SPIN, and MISCAN^a

Unique strategies simulated, No.	Efficient or near-efficient strategies with all models ^b		Range of outcomes per 1000 across models						Efficiency ratio (ΔCOL/ΔLYG) ^e
	No.	Strategy ^c	COLs	Non-COL tests ^d	Complications	CRC			
						Cases	Deaths	LYG	
Colonoscopy									
26	11	COL 55-70, 15	2532-2630	0	13-14	21-40	7-11	250-285	Default ^f
		COL 50-70, 15	2734-2868	0	11-13	18-40	6-11	264-318	6 ^g -18
		COL 45-70, 15	2829-3006	0	10-12	18-41	6-12	265-336	6-85 ^g
		COL 45-75, 15	3463-3558	0	15-16	14-37	4-10	281-352	38 ^g -59 ^g
		COL 45-70, 10	3679-3782	0	12-14	13-37	4-10	292-361	34-45
		COL 45-75, 10	4212-4300	0	15-17	12-34	3-8	301-369	52-112
		COL 45-85, 10	4449-4566	0	17-19	11-34	3-8	302-370	227 ^g -828 ^g
		COL 45-70, 5	5626-5789	0	15-17	10-32	3-8	318-377	84-180 ^g
		COL 45-75, 5	6016-6235	0	17-19	10-31	3-7	321-380	116-344
		COL 45-80, 5	6320-6581	0	19-20	9-30	2-7	323-381	169-736
		COL 45-85, 5	6516-6817	0	20-22	9-30	2-7	323-381	926-2190
Strategy highlighted in 2016		COL 50-75, 10	3414-3500	0	13-15	15-36	5-9	286-335	D, D, 28
Stool tests (FIT or sDNA-FIT)									
72	16	FIT 55-70, 3	624-754	4637-4710	5-7	47-65	17-20	171-203	Default ^f
		FIT 50-70, 3	691-858	5663-5757	5-7	43-64	15-20	184-231	2-6 ^g
		FIT 45-70, 3	810-1007	7299-7435	6-8	38-62	13-18	205-266	3-6 ^g
		FIT 45-75, 3	917-1110	8300-8475	7-9	36-60	11-16	226-286	5-7 ^g
		FIT 45-80, 3	971-1163	8866-9043	8-10	35-60	10-14	233-293	6-8 ^g
		FIT 45-75, 2	1147-1361	11420-11731	8-11	29-55	9-13	256-318	7-9
		FIT 45-80, 2	1220-1426	12249-12576	9-12	28-54	7-12	264-325	8-12
		FIT 45-85, 2	1288-1492	13160-13487	10-13	27-54	6-11	269-329	12-25 ^g
		FIT 45-75, 1	1602-1824	18950-19680	10-13	20-46	6-10	291-348	15 ^g -16
		FIT 45-80, 1	1710-1923	20622-21368	11-14	19-45	5-9	300-355	14-27
		FIT 45-85, 1	1769-1990	21850-22567	12-15	19-44	4-8	303-356	19-43
		sDNA-FIT 45-80, 2	2012-2181	9928-10167	11-14	18-43	5-9	298-356	26 ^g -176 ^g
		sDNA-FIT 45-85, 2	2114-2275	10620-10828	13-15	17-42	4-8	301-358	69 ^g -375 ^g
		sDNA-FIT 45-75, 1	2462-2617	13494-13888	12-14	15-38	4-9	306-363	53-251 ^g
		sDNA-FIT 45-80, 1	2614-2758	14608-14966	13-15	14-37	4-8	311-367	62-104 ^g
		sDNA-FIT 45-85, 1	2713-2856	15424-15721	14-16	14-36	3-8	313-368	94-111
Strategies highlighted in 2016		sDNA-FIT 50-75, 3	1405-1576	5939-6074	9-12	26-50	8-12	257-304	D, D, D
		FIT 50-75, 1	1423-1619	15562-16160	9-12	23-47	7-11	274-316	D, D, 29 ^g
		sDNA-FIT 50-75, 1	2156-2295	11132-11463	11-14	18-39	6-9	290-330	D, D, D
Flexible sigmoidoscopy									
20	7	SIG 55-70, 10	907-1340	1623-1708	7-10	35-48	13-16	204-210	Default ^f
		SIG 45-70, 10	1155-1635	2480-2622	7-10	29-45	11-14	234-262	4-73 ^g
		SIG 45-75, 10	1360-1800	2946-3173	9-12	26-43	9-12	245-278	13 ^g -18
		SIG 45-70, 5	1586-2020	4013-4446	9-11	25-40	9-12	263-302	11-20
		SIG 45-75, 5	1680-2119	4389-4935	10-12	24-39	8-11	269-309	19-27
		SIG 45-80, 5	1749-2196	4681-5326	11-13	23-38	7-10	271-311	29-49
		SIG 45-85, 5	1793-2235	4877-5602	12-13	23-38	7-10	272-312	78-98
Strategy highlighted in 2016		SIG 50-75, 5	1510-1927	3646-4134	10-12	26-40	9-11	256-279	D, D, 19 ^g

(continued)

Table 3. Outcomes for Efficient and Near-Efficient Strategies With SimCRC, CRC-SPIN, and MISCAN^a (continued)

Unique strategies simulated, No.	Efficient or near-efficient strategies with all models ^b		Range of outcomes per 1000 across models						
	No.	Strategy ^c	COLs	Non-COL tests ^d	Complications	CRC			Efficiency ratio (ΔCOL/ΔLYG) ^e
						Cases	Deaths	LYG	
Flexible sigmoidoscopy + FIT									
24	10	SIG + FIT 55-70, 10_2	1230-1547	6084-6685	8-11	27-45	9-13	241-266	Default ^f
		SIG + FIT 50-70, 10_2	1512-1835	8519-9277	9-12	22-42	7-11	274-314	6 ^g -9
		SIG + FIT 45-70, 10_2	1617-1947	10174-11005	9-12	20-42	7-11	280-340	5-24 ^g
		SIG + FIT 45-75, 10_2	1835-2130	11710-12693	11-13	18-39	5-9	294-354	15-22
		SIG + FIT 45-80, 10_2	1889-2154	12266-13375	11-14	17-39	4-9	296-357	15-25
		SIG + FIT 45-70, 10_1	1903-2148	15867-17141	10-13	17-40	6-10	292-353	19 ^g -88 ^g
		SIG + FIT 45-85, 10_2	1988-2235	13131-14286	13-15	17-39	4-8	298-358	38 ^g -78 ^g
		SIG + FIT 45-75, 10_1	2102-2331	17858-19217	11-14	15-37	4-9	304-363	22 ^g -34
		SIG + FIT 45-80, 10_1	2203-2379	19076-20649	12-15	15-37	4-8	307-366	21-53
		SIG + FIT 45-85, 10_1	2293-2463	20204-21763	14-16	14-37	3-8	309-367	46-81
Strategy highlighted in 2016		SIG + FIT 50-75, 10_1	1840-2048	14257-15636	11-13	18-39	6-10	287-330	D, D, 18 ^g
Computed tomography colonography									
20	5	CTC 55-70, 10	939-1029	1695-1705	7-9	32-57	12-19	181-245	Default ^f
		CTC 45-70, 5	1569-1677	4372-4436	9-11	20-45	6-12	271-348	11-21 ^g
		CTC 45-75, 5	1672-1791	4804-4893	10-13	18-42	5-11	283-355	11-21
		CTC 45-80, 5	1744-1882	5131-5254	11-14	17-40	4-9	288-358	13-38
		CTC 45-85, 5	1790-1939	5348-5504	12-15	17-40	4-9	290-359	32-104
Strategy highlighted in 2016		CTC 50-75, 5	1519-1626	4006-4088	10-12	20-43	6-11	268-325	D, D, 9

Abbreviations: COL, colonoscopy; CRC, colorectal cancer; CTC, computed tomography colonography; D, dominated; FIT, fecal immunochemical test (with positivity cutoff of 20 µg of hemoglobin per gram of feces); LYG, life-years gained compared with no screening; sDNA-FIT, multitarget stool DNA test with a fecal immunochemical assay; SIG, flexible sigmoidoscopy.

^a Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer risk among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19. See the full report⁶ for details.

^b For comparison purposes, strategies highlighted by the US Preventive Services Task Force in 2016³ are included even though they were not estimated to be efficient or near-efficient in all 3 models in this analysis.

^c Strategies are denoted by the screening modality, age to begin screening-age to end screening, interval. For example, CTC 50-75, 5 indicates CTC every 5 years

from age 50 years to age 75 years and SIG + FIT 50-75, 10_1 indicates sigmoidoscopy every 10 years and annual FIT from age 50 years to age 75 years.

^d For SIG + FIT, the number reported is the total number of tests. Numbers of each test can be found in the full report.⁶

^e None of the strategies highlighted by the US Preventive Services Task Force in 2016³ were estimated to be efficient or near efficient in all 3 models. For these strategies, the efficiency ratio column indicates whether the 2016 highlighted strategy was dominated and not near efficient (D) or, if efficient, the efficiency ratio in SimCRC, CRC-SPIN, and MISCAN, respectively. For all other strategies, this column indicates the range of efficiency ratios across models.

^f Strategy requiring the fewest colonoscopies and providing the fewest LYG.

^g Near efficient (ie, within 3 days of life gained per person of the efficient frontier).

resulting in a 15-year interval, was estimated to reduce LYG by 4% to 7%; if adherent with only the first colonoscopy, LYG would be estimated to decrease by 25% to 44%.

Discussion

This comparative modeling study yielded largely consistent findings across models: assuming perfect adherence, routine screening for colorectal cancer was estimated to reduce the lifetime risk of being diagnosed with and of dying of colorectal cancer, with possibly substantial LYG. Most of the efficient strategies were those with screening beginning at age 45 years. No consistent pattern emerged for the age to end screening, although the estimated LYG from continued screening after age 75 were small. For most modalities, no

screening interval was predominant. Efficient strategies were robust to assumptions about population risk of colorectal cancer.

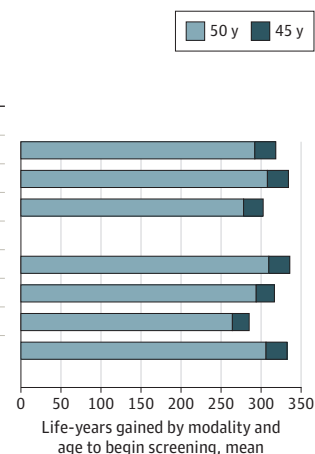
The findings from this analysis are consistent with those of the 2016 decision analysis of colorectal cancer screening for the USPSTF.⁴ However, in 2016, there was limited evidence to support screening before age 50 years. While no trials have reported on the effect of screening among asymptomatic adults aged 45 to 49 and data on the findings at screening at these ages remain sparse,²⁶⁻²⁸ there is clearer evidence that colorectal cancer incidence in the US is increasing before age 50.^{5,29}

The SimCRC and CRC-SPIN models estimated that most (and often, nearly all) efficient strategies begin at age 45 years. The estimated LYG and colonoscopy burden of screening were lowest for MISCAN, and MISCAN found strategies with screening beginning at older ages to be efficient, in addition to strategies beginning at age

Figure 4. Benefits of Colorectal Cancer Screening Strategies Highlighted by the US Preventive Services Task Force in 2016³ and the Change in Outcomes When Screening Is Started at Age 45 Years Instead of Age 50

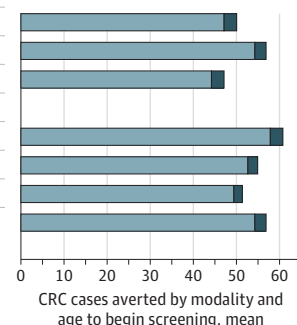
A Benefit: Estimated life-years gained per 1000 individuals screened^a

Screening modality and frequency	Life-years gained if start screening at age 50 y				Additional life-years gained if start screening at age 45 y			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT every year	316	285	274	292	33	29	17	26
sDNA-FIT every year	330	301	290	307	33	30	16	26
sDNA-FIT every 3 y ^b	304	271	257	278	31	30	16	25
Direct visualization tests								
COL every 10 y	335	308	286	310	34	32	16	27
CTC every 5 y	325	287	268	293	31	26	14	24
SIG every 5 y	279	256	256	264	30	24	13	22
SIG every 10 y plus FIT every year	330	301	287	306	33	29	17	26



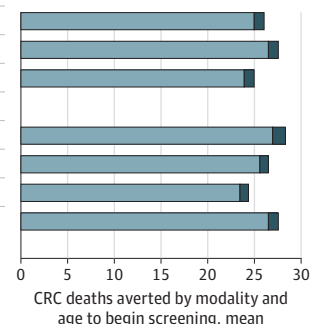
B Benefit: CRC cases averted per 1000 individuals screened^a

Screening modality and frequency	CRC cases averted if start screening at age 50 y				Additional CRC cases averted if start screening at age 45 y			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT every year	55	53	33	47	4	3	1	3
sDNA-FIT every year	63	59	41	54	4	3	1	3
sDNA-FIT every 3 y ^b	51	51	31	44	4	3	1	3
Direct visualization tests								
COL every 10 y	67	62	45	58	4	3	2	3
CTC every 5 y	64	57	38	53	3	2	1	2
SIG every 5 y	56	51	41	49	3	2	1	2
SIG every 10 y plus FIT every year	63	59	41	54	4	3	2	3



C Benefit: CRC deaths averted per 1000 individuals screened^a

Screening modality and frequency	CRC deaths averted if start screening at age 50 y				Additional CRC deaths averted if start screening at age 45 y			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT every year	27	24	23	25	1	1	0.6	1
sDNA-FIT every year	29	26	25	27	1	1	0.6	1
sDNA-FIT every 3 y ^b	26	23	22	24	1	1	0.6	1
Direct visualization tests								
COL every 10 y	29	26	25	27	2	1	1	1
CTC every 5 y	29	25	23	26	1	1	0.5	0.9
SIG every 5 y	25	22	23	23	1	0.9	0.4	0.9
SIG every 10 y plus FIT every year	29	26	25	26	1	1	0.9	1



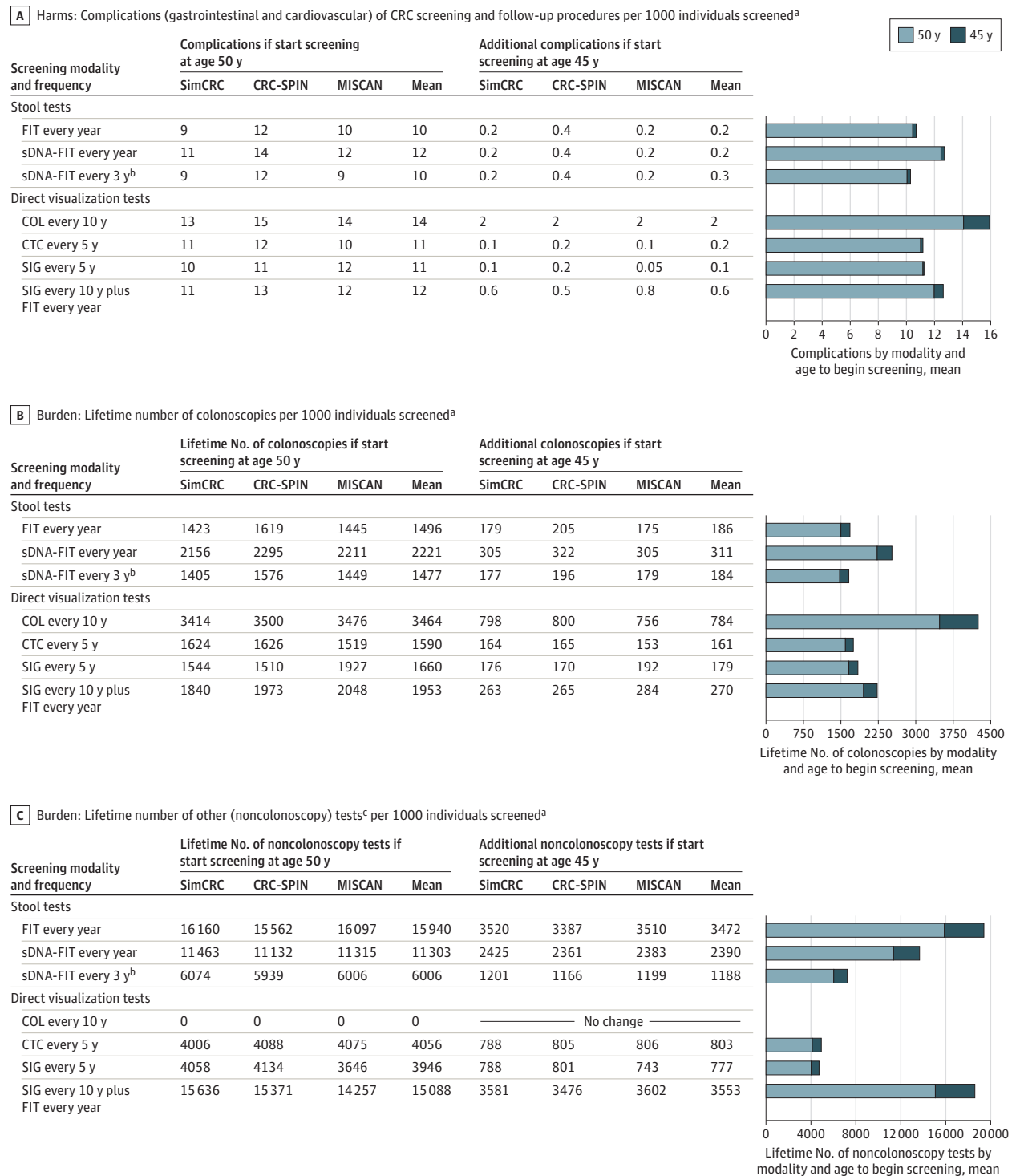
COL indicates colonoscopy; CRC, colorectal cancer; CRC-SPIN, CRC Simulated Population Model for Incidence and Natural History; CTC, computed tomography colonography; FIT, fecal immunochemical test; MISCAN, Microsimulation Screening Analysis; sDNA-FIT, multitarget stool DNA test with a fecal immunochemical assay; SIG, flexible sigmoidoscopy; SimCRC, Simulation Model of CRC.

^a Outcomes expressed over the lifetimes of 1000 40-year-olds who start screening at age 45 or at age 50 and are screened to age 75, assuming an

increased population incidence of CRC based on an incidence rate ratio comparing incidence among current 20- to 44-year-olds (ie, in 2012-2016) vs 20- to 44-year-olds in the period used for initial model calibration (ie, 1975-1979) of 1.19.

^b Compared with other options for stool-based screening, this strategy was not estimated to provide an efficient balance of the burden (ie, lifetime number of colonoscopies) and the benefit (life-years gained) of screening.

Figure 5. Complications, Colonoscopy Burden, and Noncolonoscopy Burden of Colorectal Cancer Screening Strategies Highlighted by the US Preventive Services Task Force in 2016³ and the Change in Outcomes When Screening Is Started at Age 45 Years Instead of Age 50



See Figure 4 legend for expanded abbreviations.

^a Outcomes expressed over the lifetimes of 1000 40-year-olds who start screening at age 45 or at age 50 and are screened to age 75, assuming an increased population incidence of CRC based on an incidence rate ratio comparing incidence among current 20- to 44-year-olds (ie, in 2012-2016) vs 20- to 44-year-olds in the period used for initial model calibration (ie, 1975-1979) of 1.19.

^b Compared with other options for stool-based screening, this strategy was not estimated to provide an efficient balance of the burden (ie, lifetime number of colonoscopies) and the benefit (life-years gained) of screening.

^c Other (noncolonoscopy) tests include FIT, sDNA-FIT, CTC, SIG.

45 identified by SimCRC and CRC-SPIN. Prior work examining differences in model estimation found that these differences are primarily attributable to assumptions about the nature of adenomas.¹³ With SimCRC and CRC-SPIN, all adenomas have the potential to progress to colorectal cancer. With MISCAN, some adenomas are assumed to be nonprogressive, and the probability that an adenoma is nonprogressive decreases with age at onset. Because of this age dependency, which is the result of model structure and calibration, MISCAN estimates a smaller benefit from removing adenomas present at age 45 compared with SimCRC or CRC-SPIN.

A key change from the 2016 analysis is inclusion of analyses examining the benefits, harms, and colonoscopy burden of colorectal cancer screening strategies by race and sex. Based on a recent review of the literature on race and colorectal cancer,²⁵ these analyses assumed that the risk of developing adenomas and the progression of adenomas to colorectal cancer did not differ by Black vs White race. However, the analyses incorporated race- and sex-specific all-cause mortality rates¹¹ and relative survival probabilities after colorectal cancer diagnosis.¹² Because Black adults have a shorter life expectancy than White adults,¹¹ the model-estimated lifetime incidence of colorectal cancer diagnosis in the absence of screening was lower in Black vs White adults by sex (eTable 1 in the Supplement). While this lower lifetime incidence in the absence of screening may appear to conflict with current SEER data demonstrating higher colorectal cancer incidence among Black adults,¹⁴ SEER incidence rates are observed in the presence of screening. Racial disparities in screening have been well documented. Black adults are less likely than White adults to be up to date with screening recommendations, to receive colonoscopy after an abnormal noncolonoscopy test result, and to be screened by endoscopists with higher adenoma detection rates.²⁵

Unlike the current analysis, MISCAN and SimCRC analyses to inform the 2018 American Cancer Society (ACS) colorectal cancer screening guidelines³⁰ assumed differences in natural history by Black vs White race. These analyses were carried out before publication of recent reviews demonstrating limited evidence of Black vs White differences in findings at colorectal cancer screening.^{25,31} Accordingly, differences in outcomes by race were larger in analyses for the ACS than in this analysis. However, both analyses found that starting screening at age 45 years provided an efficient balance of colonoscopies and LYG for the asymptomatic average-risk population as a whole and by race.

Findings from this analysis for the total population are also largely consistent with MISCAN analyses for the ACS for the total population,³² despite use of different estimates of the magnitude of the observed increase in colorectal cancer incidence among recent birth cohorts. Analyses for the ACS were based on (larger) published estimates⁵ of the increase in incidence, which included tumors that are not the target of colorectal cancer screening (eg, carcinoid tumors). These tumors were excluded from analysis of SEER data used to inform risk scenarios for the USPSTF. Because the incidence of adenocarcinoma is increasing more slowly than that of carcinoid tumors of the colon or rectum,²⁹ the estimated increase in population risk of colorectal cancer is lower when these tumors are excluded (see the Supplement for details). However, despite the different assumptions about colorectal cancer incidence rates in the absence of screening, analyses for the USPSTF described here and analyses

for the ACS both suggest that starting colorectal cancer screening at age 45 years provides an efficient balance of the colonoscopy burden and the LYG from screening.

With many recommended options for colorectal cancer screening, deciding which strategy to adopt may be overwhelming for patients and their clinicians. In addition to helping patients decide whether to begin screening at age 45 years or at age 50, the estimated long-term outcomes from the models may help inform the trade-offs of screening with one approach over another. For example, if choosing among the screening strategies recommended by the USPSTF in 2016, a patient who wishes to maximize LYG and minimize the lifetime risk of colorectal cancer diagnosis may opt for 10-yearly colonoscopy screening, while a patient who wishes to minimize the lifetime number of colonoscopies required may opt for screening with either 3-yearly sDNA-FIT or annual FIT. For whichever option is chosen, model findings may also help illustrate to patients the potential implications of failure to adhere with recommended screening ages and intervals.

A strength of this study is that it used 3 distinct simulation models to estimate the LYG and colonoscopy burden of screening. Each model is based on different assumptions about the natural history of colorectal cancer, although all are calibrated to similar end points.¹³ Their differences—in dwell times, location of adenomas, progressive vs nonprogressive adenomas, among others—provide a range of outcomes that reflect a sensitivity analysis on underlying model assumptions. The similar relative estimations across classes of screening modalities and similar rankings of strategies within classes of modalities across the 3 models demonstrate the robustness of the findings.

Limitations

This study has several limitations. First, although the modeling results provide a lifetime framework for evaluating benefits and burdens from a screening program, empirical data on test sensitivity and specificity are based on a single screen. Outcomes at repeated rounds of stool testing have been reported in 2 small studies^{33,34}; findings suggest that test results are correlated. While all 3 models assumed independence of repeated tests, an analysis using MISCAN showed that incorporation of correlated results across repeated screening tests would have only a modest effect on model-estimated outcomes.³³

Second, the models did not simulate the serrated polyp pathway to colorectal cancer¹⁰ because of insufficient evidence on the prevalence of serrated polyps by age, their malignant potential, and the ability of screening tests to detect them. A modeling study by Greuter et al³⁵ estimated the effect of incorporating the serrated pathway on screening effectiveness and found little difference in model results when assuming that 0% vs 30% of cancers arise from this pathway. Exploratory analyses with MISCAN also showed that inclusion of the serrated pathway had limited effect on optimal screening strategies.³⁶

Third, the models assumed that the increased population risk of colorectal cancer arises from an increase in adenoma risk. Whether the observed increase in colorectal cancer incidence among younger adults is caused (instead or in addition) by faster progression to malignancy is unknown. In prior analyses with MISCAN³² the effects of each of these assumptions were evaluated; findings with respect to screening initiation at age 45 years were robust.

Fourth, models can only approximate reality. While the models described here have been extensively calibrated and validated, they are limited by uncertainty in the data used to inform inputs and assumptions. Nevertheless, model-based estimates are important because they provide patients and their clinicians with information they can use to make decisions about when and how to screen for colorectal cancer. Such decisions would otherwise be left to individual judgement, as that information cannot feasibly be obtained from clinical studies. Modeling studies are not a substitute for empirical evidence. Instead they synthesize, build from, and

extend empirical evidence to provide insights into questions about screening practices.

Conclusions

This microsimulation modeling analysis suggests that screening for colorectal cancer with stool tests, endoscopic tests, or computed tomography colonography starting at age 45 years provides an efficient balance of colonoscopy burden and life-years gained.

ARTICLE INFORMATION

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Health Care System and University of Washington]). Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final report.

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