

The Impact of the Rising Colorectal Cancer Incidence in Young Adults on the Optimal Age to Start Screening: Microsimulation Analysis I to Inform the American Cancer Society Colorectal Cancer Screening Guideline

Elisabeth F. P. Peterse, MSc ¹; Reinier G. S. Meester, PhD ^{1,2}; Rebecca L. Siegel, MPH³; Jennifer C. Chen, MPH⁴; Andrea Dwyer, BS^{5,6}; Dennis J. Ahnen, PhD⁷; Robert A. Smith, PhD ⁸; Ann G. Zauber, PhD⁴; and Iris Lansdorp-Vogelaar, PhD¹

BACKGROUND: In 2016, the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model was used to inform the US Preventive Services Task Force colorectal cancer (CRC) screening guidelines. In this study, 1 of 2 microsimulation analyses to inform the update of the American Cancer Society CRC screening guideline, the authors re-evaluated the optimal screening strategies in light of the increase in CRC diagnosed in young adults, who were assumed to carry forward escalated disease risk as they age. Life-years gained (LYG; benefit), the number of colonoscopies (COL; burden) and the ratios of incremental burden to benefit (efficiency ratio [ER] = $\Delta\text{COL}/\Delta\text{LYG}$) were projected for different screening strategies. Strategies differed with respect to test modality, ages to start (40 years, 45 years, and 50 years) and ages to stop (75 years, 80 years, and 85 years) screening, and screening intervals (depending on screening modality). The authors then determined the model-recommended strategies in a similar way as was done for the US Preventive Services Task Force, using ER thresholds in accordance with the previously accepted ER of 39. **METHODS:** The authors adjusted the MISCAN-Colon model to reflect the higher CRC incidence in young adults, who were assumed to carry forward escalated disease risk as they age. Life-years gained (LYG; benefit), the number of colonoscopies (COL; burden) and the ratios of incremental burden to benefit (efficiency ratio [ER] = $\Delta\text{COL}/\Delta\text{LYG}$) were projected for different screening strategies. Strategies differed with respect to test modality, ages to start (40 years, 45 years, and 50 years) and ages to stop (75 years, 80 years, and 85 years) screening, and screening intervals (depending on screening modality). The authors then determined the model-recommended strategies in a similar way as was done for the US Preventive Services Task Force, using ER thresholds in accordance with the previously accepted ER of 39. **RESULTS:** Because of the higher CRC incidence, model-predicted LYG from screening increased compared with the previous analyses. Consequently, the balance of burden to benefit of screening improved and now 10-yearly colonoscopy screening starting at age 45 years resulted in an ER of 32. Other recommended strategies included fecal immunochemical testing annually, flexible sigmoidoscopy screening every 5 years, and computed tomographic colonography every 5 years. **CONCLUSIONS:** This decision-analysis suggests that in light of the increase in CRC incidence among young adults, screening may be offered earlier than has previously been recommended. *Cancer* 2018;124:2964-73. © 2018 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: advisory committees, colorectal neoplasms, early detection of cancer, incidence, models, preventive health services, theoretical.

INTRODUCTION

It is estimated that in 2018, > 50,000 colorectal cancer (CRC) deaths will occur in the United States,¹ making CRC the second most common cause of cancer death in men and women combined.² CRC death often can be prevented by CRC screening,³ which is recommended from ages 50 years to 75 years by the US Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS).^{4,5} For the population as a whole, CRC incidence and mortality have been declining for several decades, much of which is attributed to an increase in CRC screening uptake.² However, in adults aged <50 years among whom screening currently is not routinely recommended for those at average risk, CRC incidence

Corresponding author: Elisabeth F.P. Peterse, MSc, Department of Public Health, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands; e.peterse@erasmusmc.nl

¹Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands; ²Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University, Stanford, California; ³Surveillance Information Services, American Cancer Society, Atlanta, Georgia; ⁴Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York; ⁵University of Colorado Cancer Center, Denver, Colorado; ⁶Fight Colorectal Cancer, Springfield, Missouri; ⁷University of Colorado Cancer Center and Gastroenterology of the Rockies, Denver, Colorado; ⁸Cancer Control Department, American Cancer Society, Atlanta, Georgia

See companion article on pages 2974-85, this issue.

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

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has been increasing since the mid-1990s.⁶⁻¹¹ Based on national data, CRC now is the most commonly diagnosed cancer and the most common cause of cancer death in American men aged <50 years.^{12,13}

In the recently updated USPSTF guidelines,⁴ screening was recommended to begin at age 50 years, despite the fact that 2 of 3 colorectal microsimulation models of the Cancer Intervention and Surveillance Modeling Network (CISNET) suggested that starting screening at age 45 years provided a more favorable balance between the benefits and burden of screening compared with starting at age 50 years.¹⁴ As described in the USPSTF recommendation statement, reasons for not lowering the recommended age to start screening were the lack of agreement between all 3 CISNET models and the limited empirical data related to screening before age 50 years.⁴ However, accumulating evidence has demonstrated a persistent increase in CRC incidence in adults aged <50 years.^{2,6} Although the elevated background risk likely will be carried forward with these generations as they age due to the cohort effect,⁶ it is unlikely that it will be observed in CRC incidence data for those aged ≥55 years because it is counteracted by the increased uptake of screening in those ages.

The CISNET microsimulation models that were used to inform the 2016 USPSTF CRC screening guidelines were calibrated to CRC incidence rates from the Surveillance, Epidemiology, and End Results (SEER) program registries during 1975 through 1979.¹⁴ This time frame was chosen because there was little CRC screening in this period. As a result, these models did not account for the recent increase in CRC incidence in individuals aged <50 years. Therefore, at the request of the ACS, we re-evaluated the optimal age to start screening, age to stop screening, and the screening interval incorporating contemporary trends in young adults to inform the update of the ACS CRC screening guideline.

MATERIALS AND METHODS

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model to evaluate the optimal age to start screening, age to stop screening, and screening interval. First, we adjusted the model to reflect the increased CRC incidence in more recent birth cohorts. Second, the benefits and harms of the different screening strategies were predicted. Third, the balance between the benefits and the burden of screening was used to select model-recommended strategies. The methods used for these steps are described in the section below. Analyses were similar to those performed

to inform USPSTF guideline recommendations (see Supporting Table 1 for a summary of all differences).¹⁴

MISCAN-Colon

The MISCAN-Colon model used in this study was developed by the Department of Public Health within Erasmus University Medical Center in Rotterdam, the Netherlands, and has been described in detail elsewhere.^{15,16} It is part of CISNET, a consortium of cancer decision modelers sponsored by the National Cancer Institute (NCI). In brief, the model generates, with random variation, the individual life histories for a large cohort to simulate the US population in terms of life expectancy and cancer risk. Each simulated person ages over time and may develop ≥1 adenomas that can progress from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm) in size. Some adenomas develop into preclinical cancer, which may progress through stages I to IV. During each disease transition point, CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the location of the cancer, and the person's age. Some simulated life histories are altered by screening through the detection and removal of adenomas or diagnosing CRC in an earlier stage, resulting in a better prognosis. Screening also results in high rates of detection and removal (overtreatment) of polyps, the majority of which would not progress to invasive disease, and may result in fatal complications from colonoscopy with polypectomy,^{15,17,18} all of which are considered in the model.

Model incorporation of increase in CRC incidence

The original MISCAN-Colon model was calibrated to CRC incidence in 1975-1979. To incorporate the increased CRC incidence in recent birth cohorts, we adjusted the model based on the observed increase since that period as estimated by Siegel et al.⁶ Age-period-cohort modeling of SEER data performed by Siegel et al revealed that the increase in CRC incidence currently is confined to ages <55 years and primarily is the result of a strong birth cohort effect that began in those born in the 1950s. Consequently, these and subsequent generations will carry forward escalated disease risk as they age.⁶ Affected cohorts are only now reaching the age to initiate screening, which will likely somewhat counteract the trend. In our analyses, we simulated a cohort of adults aged 40 years in 2015, and assumed that this cohort had a 1.591-fold increased CRC incidence across all ages compared with the original model. This incidence multiplier was based on the incidence rate ratio (IRR) for CRC of the 1935 birth cohort (those aged 40 years in 1975)

TABLE 1. Screening Strategies Evaluated by the Microsimulation Model

Screening Modality	Age to Start Screening, Years	Age to Stop Screening, Years)	Screening Interval, Years	No. of (Unique) Strategies ^a
No screening				1 (1)
Colonoscopy	40, 45, 50	75, 80, 85	5, 10, 15	27 (20)
Stool-based tests				
Fecal immunochemical test	40, 45, 50	75, 80, 85	1, 2, 3	27 (27)
High-sensitivity guaiac-based FOBT	40, 45, 50	75, 80, 85	1, 2, 3	27 (27)
Multitarget stool DNA test	40, 45, 50	75, 80, 85	1, 3, 5	27 (27)
Flexible sigmoidoscopy	40, 45, 50	75, 80, 85	5, 10	18 (15)
Computed tomographic colonography	40, 45, 50	75, 80, 85	5, 10	18 (15)
Total				145 (132)

Abbreviation: FOBT, fecal occult blood test.

^aThe number of unique strategies excluded the strategies that overlap (eg, colonoscopy every 10 years from ages 50 to 80 years and from ages 50 to 85 years both include colonoscopies at ages 50, 60, 70, and 80 years and therefore are not unique strategies).

compared with the 1975 birth cohort (those aged 40 years in 2015).¹⁹ In accordance with the data, we assumed that the increase in CRC incidence was mostly confined to an increase in tumors in the rectum and the distal colon.⁶ In the base case analysis, we assumed that the increase in CRC incidence was caused by a higher prevalence of adenomas. In a sensitivity analysis, we explored how our results differed with the alternative assumption of stable adenoma prevalence, but faster progression to malignancy.

Screening Strategies

Six screening modalities were evaluated: 1) colonoscopy; 2) fecal immunochemical testing (FIT); 3) high-sensitivity guaiac-based fecal occult blood testing (HSgFOBT); 4) multitarget stool DNA testing (FIT-DNA); 5) flexible sigmoidoscopy (SIG); and 6) computed tomographic colonography (CTC). Multiple ages to begin and stop screening and multiple screening intervals were evaluated for each modality (Table 1). Test characteristics are described by Knudsen et al,¹⁴ and are presented in Supporting Table 2. A 40-year-old US cohort free of CRC was simulated, thereby only evaluating the effect of the different screening strategies in a population of individuals to whom the screening guidelines for average-risk individuals apply. These 40-year-olds were assumed to have a 100% adherence to screening, follow-up, and surveillance.²⁰

The benefit of screening was measured by the number of life-years gained (LYG) from the screening strategy, and corrected for life-years lost due to screening complications. The number of required colonoscopies was used as a measure of the aggregate burden of screening, and included colonoscopies for screening, follow-up, surveillance, and the diagnosis of symptomatic cancer. Because

this measure of burden does not capture the burden of other screening modalities, direct comparisons of the benefit and burden across screening strategies were limited to those with similar noncolonoscopy burden. Therefore, only the stool-based tests were grouped, which resulted in 4 classes of screening modalities: 1) colonoscopy; 2) stool-based modalities (FIT, HSgFOBT, and FIT-DNA); 3) SIG; and 4) CTC.

Efficient and Near-Efficient Screening Strategies

The LYG and colonoscopy burden were plotted for each screening strategy by class of screening modalities. Strategies providing the largest incremental increase in LYG per additional colonoscopy were connected, thereby composing the efficient frontier. All strategies on the efficient frontier were considered efficient screening options,²¹ whereas others fell below the frontier and were dominated. Weakly dominated strategies that had LYG within 98% of the efficient frontier were defined as near-efficient; other strategies below the efficient frontier were considered inefficient. For efficient and near-efficient strategies, the incremental number of colonoscopies (ΔCOL), the incremental number of LYG (ΔLYG), and the efficiency ratio (ER) ($\Delta\text{COL}/\Delta\text{LYG}$) relative to the next less effective efficient strategy were calculated.

Model-Recommended Screening Strategies

A predefined algorithm was used to select model-recommended screening strategies (Fig. 1).¹⁴ First, the efficient frontier for the colonoscopy strategies was generated (step 1), after which a benchmark colonoscopy screening strategy was selected that 1) was an efficient or near-efficient colonoscopy screening strategy, 2) had LYG no less than the previously recommended colonoscopy

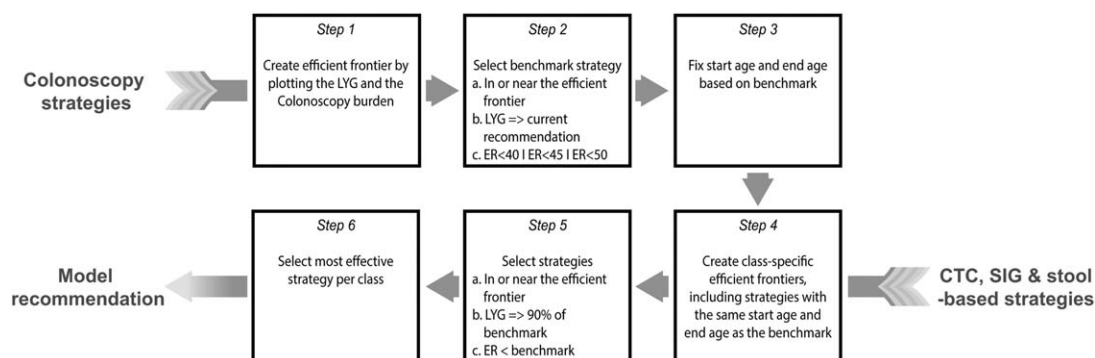


Figure 1. Algorithm used to select model-recommended strategies. LYG indicates life-years gained (current recommendation is colonoscopy screening from ages 50 to 75 years every 10 years); ER, efficiency ratio. The ER is calculated as and is an incremental burden-to-benefits ratio. Threshold ERs of 40, 45, and 50 colonoscopies per LYG were evaluated. The stool-based strategies (fecal immunochemical test, high-sensitivity guaiac-based fecal occult blood test, and multitarget stool DNA test) were combined into 1 class because they have a similar noncolonoscopy burden. CTC, computed tomographic colonography; SIG, flexible sigmoidoscopy.

every 10 years from ages 50 to 75 years, and 3) had an efficiency ratio ($ER = \Delta COL / \Delta LYG$) of ≤ 40 , 45, or 50 incremental colonoscopies per LYG (step 2). We decided to evaluate different ER thresholds in liaison with recommendations for cost-effectiveness analysis, for which it is recommended to evaluate multiple willingness-to-pay thresholds.²² We analyzed ER thresholds of 40, 45, and 50, in accordance with the efficiency ratio for the MISCAN-Colon model in the USPSTF analyses, in which 39 was considered an acceptable number of colonoscopies per LYG and 114 was not, suggesting the threshold of an acceptable number of colonoscopies per LYG was in-between those values.¹⁴

Next, the start age and stop age of screening were fixed at those of the colonoscopy benchmark strategy (step 3), because different start ages and stop ages for different screening modalities are not easy to implement in practice because this may complicate the communication between physicians and patients. Simplifying a regimen has been shown to be an important intervention to increase patient adherence,²³ and therefore recommending different start ages or stop ages for the different screening modalities may result in lower participation. For the noncolonoscopy screening modalities, within-class efficient frontiers were created, with the same start age and stop age as the benchmark colonoscopy strategy (step 4), and selected were 1) efficient or near-efficient strategies that 2) had at least 90% of the LYG compared with the benchmark colonoscopy strategy and 3) had ERs lower than the benchmark colonoscopy strategy (step 5). Among all strategies within a class of screening modality fulfilling all the above criteria, only the most

effective strategies were recommended by the model (step 6).

Assumptions Evaluated in the Sensitivity Analyses

Three major assumptions were made that potentially influenced the results, which therefore were explored in the sensitivity analyses. First, as mentioned above, we assumed that the increase in CRC incidence was caused by an increase in adenoma onset in our primary analyses. Therefore, we explored faster adenoma progression to malignancy in a sensitivity analysis. Second, we assumed that the 1975 birth cohort will carry forward the increased CRC incidence as they age. Therefore, we increased incidence only $<$ age 50 years in a sensitivity analysis. Third, we used an IRR of 1.591 because this is applicable to the 1975 birth cohort. Incidence rate ratios of 1.2, 1.3... 2.3 and 2.4 were explored in a sensitivity analysis, with higher ratios being potentially informative for more recent birth cohorts.

RESULTS

A total of 132 unique screening strategies were evaluated (Table 1). The CRC deaths averted per 1000 40-year-olds ranged from 25 for triennial HSgFOBT from ages 50 to 75 years to 40 for colonoscopy every 5 years from ages 40 to 85 years (Supporting Table 3). The lifetime number of colonoscopies per 1000 40-year-olds, used as a measure of burden, ranged from 1433 for triennial FIT screening from ages 50 to 75 years to 8671 for colonoscopy every 5 years from ages 40 to 85 years, whereas the number of LYG compared with no screening, used to measure benefit, ranged from 284 for triennial HSgFOBT from ages 50

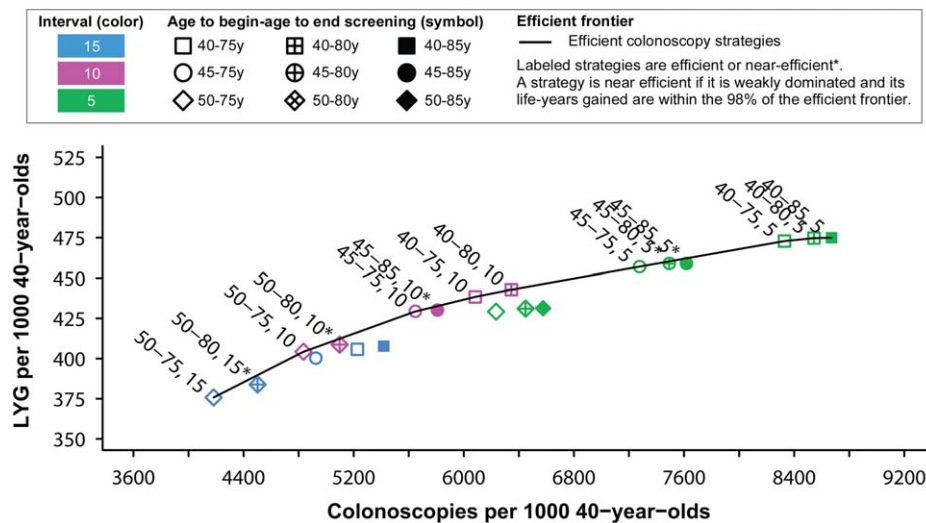


Figure 2. Lifetime number of colonoscopies and life-years gained (LYG) for colonoscopy screening strategies.

to 75 years to 475 for colonoscopy every 5 years from ages 40 to 85 years (see Supporting Table 3).

Efficient and Near-Efficient Screening Strategies

The LYG compared with the number of colonoscopies required and the efficient frontier for the colonoscopy strategies are presented in Figure 2. Nine efficient and 5 near-efficient (LYG within 98% of the efficient frontier) colonoscopy strategies were identified, in which the ERs (incremental burden-to-benefits ratios) for the colonoscopy strategies ranged from 11 colonoscopies per LYG for screening every 15 years from ages 50 to 75 years to 569 for colonoscopy screening every 5 years from ages 40 to 85 years (see Supporting Table 4). The current colonoscopy screening recommendation (screening every 10 years from ages 50-75 years) was 1 of the 9 efficient strategies and had an ER of 23. The plots of the other screening modalities can be found in Supporting Information Figures 1 to 3. Twenty-two of 25 stool-based strategies in or near the efficient frontier were FIT strategies, demonstrating that FIT screening largely dominated the other stool-based strategies (Supporting Fig. 1).

Model-Recommended Strategies

The colonoscopy strategy recommended by the model was screening every 10 years from ages 45 to 75 years with an ER of 32 incremental colonoscopies per LYG (Table 2). This strategy was selected because it was on the efficient frontier and had the highest number of LYG among the strategies with ERs <40 and 45. Compared with the current recommendation (screening every 10 years from

ages 50-75 years), this strategy resulted in 25 (+6.2%) additional LYG accompanied by an increase in 810 (+17%) colonoscopies per 1000 40-year-olds.

Class-specific efficient frontiers for strategies other than colonoscopy were created, including only those strategies with the same start age and stop age as the benchmark colonoscopy strategy (Table 2). Per screening class, 1 screening strategy was in or near the efficient frontier, had an ER smaller than the benchmark colonoscopy strategy, and had at least 90% of the LYG from the benchmark strategy, thereby fulfilling the criteria to be recommended by the model. In addition to colonoscopy screening every 10 years, our model recommended FIT screening annually, SIG every 5 years, and CTC every 5 years from ages 45 to 75 years (Table 2).

With an ER threshold of 50, screening was recommended from ages 40 to 75 years by colonoscopy every 10 years, FIT every year, SIG every 5 years, and CTC every 5 years (Supporting Table 5). Irrespective of the ER threshold, no HSgFOBT and FIT-DNA strategies were recommended. HSgFOBT strategies were not on the efficient frontier and for the few efficient FIT-DNA strategies that were, the ER was higher than the colonoscopy benchmark.

Sensitivity Analyses

As shown in Table 3, alternative assumptions that were explored in the sensitivity analyses influenced the model recommendations. First, when the increased CRC incidence was incorporated as faster adenoma progression to malignancy rather than higher adenoma onset, the model

TABLE 2. Outcomes for Screening Strategies With Similar Age to Start and Age to Stop Screening as the Selected Benchmark Colonoscopy Strategy

Modality and Age to Start/Age to End/Interval, Years	Outcomes per 1000 40-year-olds										
	No. of Stool Tests	No. of SIGs	No. of CTCs	No. of COLs	LYG	Complications	CRC Deaths Averted ^a	ER ^b	ER < Benchmark ^c	LYG ≥ 90% of Benchmark	Model-Recommended Strategy ^d
COL	0	0	0	5646	429	23	37	32	-	-	Yes
Stool tests											
FIT 45/75/3	8038	0	0	1619	310	11	27	5	Yes	No	No
FIT 45/75/2	10,973	0	0	1994	352	13	30	9	Yes	No	No
HSgFOBT 45/75/3	7405	0	0	2024	310	13	27	Dominated	-	No	No
FIT-DNA 45/75/5	4949	0	0	2157	333	14	29	Dominated	-	No	No
HSgFOBT 45/75/2	9776	0	0	2516	354	15	30	Dominated	-	No	No
FIT-DNA 45/75/3	6644	0	0	2640	376	16	32	Dominated	-	No	No
FIT 45/75/1	17,835	0	0	2698	403	16	34	14	Yes	Yes	Yes
HSgFOBT 45/75/1	14,366	0	0	3364	403	18	34	Dominated	-	Yes	Yes
FIT-DNA 45/75/1	12,019	0	0	3851	426	19	36	50	No	Yes	Yes
Flexible sigmoidoscopy											
SIG 45/75/10	0	2691	0	3314	373	19	33	9	Yes	No	No
SIG 45/75/5	0	3865	0	3761	403	20	35	15	Yes	Yes	Yes
CT colonography											
CTC 45/75/10	0	0	3045	2106	322	14	29	6	Yes	No	No
CTC 45/75/5	0	0	4630	2666	390	16	34	8	Yes	Yes	Yes

Abbreviations: COL, colonoscopy; CRC, colorectal cancer; CTC, computed tomographic colonography; ER, efficiency ratio; FIT, fecal immunochemical test; FIT-DNA, multitarget stool DNA test; HSgFOBT, high-sensitivity guaiac-based fecal occult blood test; LYG, life-years gained; SIG, flexible sigmoidoscopy.

^a In the absence of screening, the model predicted 45 deaths from CRC.

^b Calculated as *incremental colonoscopies w.r.t. previous efficient strategy*. It is an incremental burden-to-benefits ratio.

^c A strategy can only be recommended by the model if it has an ER lower than the ER of the benchmark strategy (COL every 10 years from ages 45 to 75 years).

^d A strategy is recommended by the model if it is an efficient or a near-efficient strategy with a lower burden-to-benefits ratio and at least 90% of the LYG compared with the benchmark strategy (COL screening every 10 years from ages 45 to 75 years).

^e This strategy was selected by the model when an ER threshold of 40 or 45 incremental colonoscopies per LYG was applied.

TABLE 3. Model-Recommended Colonoscopy Strategies Under Alternative Model Assumptions Evaluated in the Sensitivity Analyses

Scenario	Recommended Colonoscopy Strategies, Start Age/End Age/Interval, Years		
	ER < 40	ER < 45	ER < 50
Base case ^a	45/75/10	45/75/10	40/75/10
Faster adenoma progression	40/75/10	40/75/10	40/75/10
Higher incidence only < 50 y	50/75/10 ^b	40/75/10	40/75/10
Different IRR			
1.2	50/75/10	50/75/10	40/75/10
1.3	50/75/10	45/75/10	40/75/10
1.4	45/75/10	45/75/10	40/75/10
1.5	45/75/10	45/75/10	40/75/10
1.6	45/75/10	45/75/10	40/75/10
1.7	45/75/10	40/75/10	40/75/10
1.8	45/75/10	40/75/10	40/75/10
1.9	45/75/10	40/75/10	40/80/10
2.0	40/75/10	40/80/10	45/75/5
2.1	40/75/10	45/75/5	40/75/5
2.2	40/80/10	45/75/5	40/75/5
2.3	40/80/10	40/75/5	40/75/5
2.4	45/75/5	40/75/5	40/75/5

Abbreviations: ER, efficiency ratio; IRR, incidence rate ratio.

Colonoscopy strategies are described by age at which to start screening/age to stop screening/screening interval. ER thresholds of 40, 45, and 50 colonoscopies per life-year gained were evaluated.

^aIn our base case analyses, we assumed an IRR of 1.591 and we assumed that the higher incidence was caused by an increase in adenoma onset instead of faster adenoma progression. Furthermore, we assumed that the current generation of 40-year-old individuals will carry forward escalated disease risk as they age.

^b50/75/10 had an ER of 40.7; it was the strategy with the lowest ER among the strategies that met the life-year gained criterion.

suggested to start screening at age 40 years for all ER thresholds. Second, if the assumed higher CRC incidence was confined to ages <50 years, colonoscopy screening every 10 years from ages 50 to 75 years resulted in the lowest ER: 40.7. The model recommended starting screening at age 40 years by colonoscopy every 10 years with ER thresholds of 45 and 50. Finally, model-recommended strategies depended on the level of increase in CRC incidence. The start age for colonoscopy decreased as IRRs increased. With an ER threshold of 45, the optimal age to start screening remained at age 50 years for IRRs < 1.3, whereas the optimal age to start screening was decreased to age 40 years with an IRR of ≥ 1.7 . The first and second alternative assumption did not influence the stopping age nor the screening interval, but stopping age and/or interval were influenced by some of the more extreme IRRs.

DISCUSSION

The results of the current analyses suggest that screening initiation at age 45 years has a favorable balance between

screening benefits and burden based on the increase in CRC incidence in young adults. For current 40-year-olds, the model recommends screening every 10 years with colonoscopy, every year with FIT, every 5 years with SIG, or every 5 years with CTC from ages 45 to 75 years. The model-recommended start age depended on the ER threshold that was applied; when 50 colonoscopies per LYG was used as a threshold, the model recommended starting screening at age 40 years.

The results of the current study were sensitive for alternative assumptions regarding the magnitude and etiology of the increase in CRC incidence in young adults; however, the model recommended starting screening before age 50 years, often even at age 40 years, in the majority of alternative scenarios. Thus, the model recommendation of screening initiation at age 45 years appears robust and may even be conservative. Close monitoring of the developments in CRC incidence is required to inform future guidelines because incidence is increasing with each subsequent birth cohort.⁶

To our knowledge, the current study is the first study that incorporates the recent increase in CRC incidence, especially for rectal and distal colon cancer, in a decision-analytic modeling approach to assess CRC screening. Our estimated benefits of screening, which resulted in decreased incremental burden-to-benefit ratios, were much higher compared with the analysis performed to inform the USPSTF guidelines.¹⁴ For example, the LYG and ERs for screening every 10 years by colonoscopy from ages 50 to 75 years were 248 and 39 for the USPSTF analysis, versus 404 and 23 in this analysis. In addition, in contrast to the analysis performed for the USPSTF, SIG screening every 5 years was recommended by the model. This likely can be attributed to the higher percentage of tumors in the rectum and the distal colon. The only other difference between the current model and the one used for USPSTF was the update of the lifetable from 2009 to 2012, which did not meaningfully influence findings (data not shown).

The ER of colonoscopy screening every 10 years from ages 45 to 75 years in our analysis was 32, a lower ratio of incremental burden to benefit than the ER of the model-recommended colonoscopy strategy in the USPSTF analysis. In contrast to the USPSTF analysis, this analysis to inform the ACS was only performed by 1 of the 3 CISNET models. However, the other 2 CISNET models already suggested that starting screening at age 45 years was preferred in the analysis for the USPSTF, in which the higher risk was not incorporated, albeit with a 15-year interval for colonoscopy screening.¹⁴

Decision models are a useful tool with which to inform screening guidelines because they can extrapolate evidence and predict long-term outcomes of numerous screening strategies. Decision modeling is an important component within the context of all scientific evidence that is taken into consideration when screening guidelines are evaluated. Since the USPSTF recommendations, compelling empirical data from Siegel et al⁶ have demonstrated that the increase in CRC incidence is primarily the result of a strong birth cohort effect, which fueled debate regarding the age of screening initiation. This debate triggered reanalysis of the optimal age to begin and end screening and the screening interval that CISNET models performed earlier for the USPSTF. Taken together, empirical data and modeling now suggest that screening should be started at an earlier age for those at average risk of disease. Our model recommendation to start screening at age 45 years instead of age 50 years is driven solely by the assumed increase in CRC disease burden. A study by Murphy et al suggested that the increase in CRC incidence in younger ages is likely caused by an increase in colonoscopy use rather than an increase in disease burden, based in part on stable CRC mortality rates.²⁴ It is important to note that Murphy et al presented mortality data from 1992 through 2013 and did not systematically quantify recent trends. Race-specific examination of CRC mortality from 1970 to 2014 among individuals aged 20 to 49 years by Siegel et al demonstrated that although CRC mortality is decreasing in blacks, it actually is increasing in whites. Moreover, the trend is consistent with a cohort effect, with the increase beginning in 1995 for individuals aged 30 to 39 years and in 2005 for individuals aged 40 to 49 years, a decade later than the uptick in incidence for each age group.²⁵ Therefore, because the increase in incidence is accompanied by an increase in mortality, higher colonoscopy use in individuals aged <50 years does not appear to be the main driver of the increase in CRC incidence in young adults.

The current study has several limitations. First, it is not known whether the increase in CRC incidence is caused by an increase in the number of adenomas, a faster adenoma progression to malignancy, or some combination of the 2. We found that under both assumption of a higher adenoma onset as well as faster adenoma progression, screening initiation before age 50 years was optimal and therefore also would be expected for the combination of assumptions. Future research is needed to determine the cause and carcinogenic pathway of the increase in CRC. Second, it is not certain that the current 40-year-olds will carry forward the same escalated disease risk as

they age. Therefore, we evaluated the extreme, namely that they would return to levels for 1975-1979 levels, in a sensitivity analysis. Although this impacted the predicted benefits of screening, this only further lowered the recommended starting age to 40 years when an ER threshold of 45 incremental colonoscopies per LYG was applied. Third, we used the number of LYG and the number of colonoscopies to measure the benefits and the burden, respectively. Therefore, the burden of tests other than colonoscopies was not considered, which made direct comparison of all strategies not possible. Fourth, to the best of our knowledge, there is no commonly accepted threshold for the incremental number of colonoscopies per LYG. For the USPSTF analysis, 39 was considered an acceptable ratio for our model.¹⁴ Because it is recommended to evaluate multiple willingness-to-pay thresholds,²² we evaluated ER thresholds of 40, 45, and 50. Although these thresholds are subjective and do influence our model recommendations, the ER for screening initiation at age 45 years was 32 in this analysis, and therefore was superior to the ER accepted by the USPSTF.¹⁴ Fifth, similar to the assumptions in our analysis for the USPSTF,¹⁴ we assumed perfect adherence to all screening, diagnostic follow-up, and surveillance tests for the purpose of comparing the performance of individual tests under ideal assumptions. Therefore, the model predicted the maximum achievable benefit for all screening strategies. In reality, the current percentage of being up to date with screening is 61.1%,²⁶ and the adherence to diagnostic follow-up and surveillance is approximately 80%.^{27,28} This suggests that the model-predicted benefits will not be achieved. However, guidelines are optimally based on the full potential of benefit that would accrue under complete adherence to recommendations because assuming realistic adherence might result in recommending more frequent screenings as the model then compensates for the substantial percentage of the population that does not participate in every recommended screening. For individuals who do adhere to the recommendations, this actually would result in overscreening associated with unnecessary burden. Furthermore, public health organizations will always seek to increase adherence to recommendations. Sixth, the lack of empirical data regarding the performance of CRC screening tests in adults aged 45 to 49 years means that we assumed that these tests would perform equally well in this age group compared with adults aged 50 to 54 years. In fact, apart from a lower prevalence of disease, there is little reason to expect that performance would differ. In the case of visual tests, lesions of interest should have similar visibility. Tests for occult blood have

been shown to perform differently by age, but the difference in characteristics is small at younger ages. Harms associated with colonoscopy should be lower given the observation that harms increase with increasing age. Finally, we did not tailor recommendations to population characteristics, whereas further personalization of screening may improve the balance of burden to benefit. In the accompanying article, Meester et al have demonstrated that when incidence is updated in race- and sex-specific analyses, screening is recommended from age 45 years for all race and gender combinations.²⁹

A well-established decision-analytic modeling approach that incorporates the increase in CRC incidence among those of younger ages suggests that screening from ages 45 to 75 years is recommended for the current generation of 40-year-olds. Colonoscopy screening every 10 years, annual FIT screening, SIG screening every 5 years, and CTC screening every 5 years are screening strategies with similar benefits and acceptable colonoscopy burdens. If the gradual increase in CRC incidence in more recent birth cohorts continues, even earlier start ages for screening should be considered in the future.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Elisabeth F.P. Peterse: Formal analysis, investigation, data curation, methodology, software, visualization, and writing—original draft. **Reinier G.S. Meester:** Formal analysis, validation, methodology, software, visualization, and writing—original draft. **Rebecca L. Siegel:** Data curation and methodology. **Jennifer C. Chen:** Data curation and project administration. **Andrea Dwyer:** Conceptualization. **Dennis J. Ahnen:** Conceptualization. **Robert A. Smith:**

Conceptualization and supervision. **Ann G. Zauber:** Conceptualization, supervision, and methodology. **Iris Lansdorp-Vogelaar:** Supervision, methodology, software, and writing—original draft.

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