Technical Report

Colorectal Cancer Screening: An Updated Decision Analysis for the U.S. Preventive Services Task Force

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Authors' Contributions

Drs. Zauber, Kuntz, and Lansdorp-Vogelaar contributed equally to this report.

Navigation

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Structured Abstract

Importance: The U.S. Preventive Services Task Force (USPSTF) is updating its 2016 recommendations for screening for colorectal cancer.

Objective: To provide the USPSTF updated model-based estimates of the benefits, burden, and harms of colorectal cancer screening strategies that vary by the ages to begin and end screening, screening modality, and screening interval. Analyses also identify strategies that may provide an efficient balance of the colonoscopy burden and the life-years gained (LYG) from screening.

Design: Comparative modeling using 3 microsimulation models that simulate outcomes with and without colorectal cancer screening in a hypothetical cohort of previously unscreened average-risk U.S. 40-year-olds with no prior colorectal cancer diagnosis.

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 (FIT-DNA), flexible sigmoidoscopy (SIG) alone or in conjunction with interval FIT, computed tomographic colonography (CTC), or colonoscopy. Screening intervals varied by modality. All persons with an abnormal non-colonoscopy screening test were assumed to undergo follow up colonoscopy. Full adherence with all screening, follow up, and surveillance procedures was assumed.

Main Outcome and Measures: Estimated LYG relative to no screening (benefit), lifetime number of colonoscopies (burden), lifetime number of complications from screening (harms), and balance of incremental burden and benefit (efficiency ratios). Efficient strategies were those that required fewer additional colonoscopies per LYG, relative to other strategies.

Results: Estimated LYG from screening 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. Forty-nine screening strategies were found to be efficient options by all 3 models; in 41 of these strategies, screening began at age 45. No single age to end screening was predominant among the efficient strategies, although the estimated increases in LYG from continuing screening after age 75 were generally small. With the exception of a 5-year interval for CTC, no screening interval was predominant among the efficient strategies for each modality. Among the screening strategies highlighted in the 2016 USPSTF colorectal cancer screening recommendations, lowering the age to begin screening from 50 to 45 was estimated to result in 22 to 27 additional LYG, 2 to 3 fewer colorectal cancer cases, and 0.9 to 1 fewer colorectal cancer death, but it was also estimated to result in 0.1 to 2 additional complications, 161 to 784 additional colonoscopies, and 0 (with colonoscopy) to 3553 additional non-colonoscopy tests over the lifetimes of 1000 persons (ranges are across screening strategies, based on mean estimates across the 3 models).

Sensitivity analyses indicated that there was little advantage to customizing screening by race and sex; the estimated numbers of LYG, colonoscopies, and complications were similar across race-sex groups, as were the efficient strategies and their ratios. Scenario analyses demonstrated that efficient strategies were similar across 3 scenarios for the population risk of colorectal cancer, including one in which the assumed risk increase was less conservative than the assumption for the base-case analysis.

The effect of imperfect adherence on outcomes was estimated by comparing strategies with different ages to begin screening (to examine delays in uptake) or with strategies with different screening intervals (to examine delays in rescreening). For example, the models estimated that extending the interval of repeat colonoscopy screening from 10 to 15 years would result in a loss of 22 to 38 life years per 1000, and extending the interval of FIT screening from annual to triennial testing would result in a loss of 28 to 41 life years per 1000.

Limitations: The models do not simulate the serrated polyp pathway to CRC. The models assume that the observed increase in colorectal cancer incidence among 20- to 44-year-olds in recent years is a cohort effect, and that the increase in risk will be carried forward as individuals age. They further assume that the increase in incidence is driven by an increased risk of developing adenomas, as opposed to faster or more frequent progression of adenomas to malignancy.

Conclusions: This comparative modeling study suggests that colorectal cancer screening may lead to sizable reductions in the lifetime risks of developing and dying from colorectal cancer. Many screening strategies are estimated to provide an efficient balance of the burden and benefit of screening; these strategies encompass a range of screening modalities, intervals, and ages. However, when the benefits of screening are measured by the number of LYG, most of the efficient screening strategies identified by all 3 models specified screening starting at age 45. Starting screening at age 45 was generally estimated to result in more LYG and fewer colorectal cancer cases and deaths than similar strategies with screening starting at age 50 or age 55, albeit with a higher lifetime burden of both colonoscopy and non-colonoscopy testing and slightly higher lifetime risks of complications.

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Chapter 1. Introduction

Although colorectal cancer mortality rates have declined 51 percent from 1975 to 2016,[1] colorectal cancer remains the second most common cause of cancer death in the United States (US) with 52,980 deaths expected in 2021.[2] Randomized trials have shown that screening reduces colorectal cancer incidence and mortality.[3-10] While these trials provide the highest quality evidence of screening effectiveness, it is not feasible for trials to examine the full range of potential screening programs. In this context, microsimulation modeling can be used to synthesize available information about screening to provide estimates of the risks, benefits, and burden of different screening strategies to reduce colorectal cancer incidence and mortality.

The US Preventive Services Task Force (USPSTF) first recommended colorectal cancer screening in 1996[11] with updated recommendations reported in 2002,[12] 2008,[13] and 2016.[14] The latter 2 updates considered outcomes of decision analyses conducted using colorectal cancer models funded by the Cancer Intervention and Surveillance Modeling Network (CISNET) to inform the ages to begin and end screening, intervals of screening, and screening modality.[15,16] Modeling input was most informative regarding the age to end routine colorectal cancer screening and the screening interval for recommended tests. In 2016 the USPSTF recommended that average-risk adults undergo screening for colorectal cancer from ages 50 to 75.[14] Screening strategies highlighted by the USPSTF included colonoscopy every 10 years, flexible sigmoidoscopy alone every 5 years, sigmoidoscopy every 10 years with annual fecal immunochemical testing (SIG+FIT), computed tomographic colonography (CTC) every 5 years, annual high-sensitivity guaiac-based fecal occult blood testing (HSgFOBT, i.e., Hemoccult SENSA® (Beckman Coulter; Brea, CA)), annual fecal immunochemical testing (FIT), or multitarget stool DNA testing (sDNA-FIT, i.e., Cologuard® (Exact Sciences Corporation; Madison, WI)) either annually or every 3 years.[14]

This decision analysis, with an accompanying systematic evidence review,[17] will be used by the USPSTF to update its 2016 colorectal cancer screening recommendations.[14]

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this decision analysis in conjunction with a systematic evidence review from the Kaiser Permanente Evidence-based Practice Center (EPC), to update its 2016 recommendation statement on colorectal cancer screening.[14] This decision analysis updates the prior analysis[16] of how the benefits, burden, and harms of colorectal cancer screening might vary by screening modality, screening interval, age to begin screening, and age to end screening. It incorporates recent evidence reporting increasing rates of colorectal cancer among recent birth cohorts[18] and evaluates whether the benefits, burden, and harms of screening might vary by race and sex.

Key Questions

The CISNET Colorectal Cancer Working Group, USPSTF members, EPC evidence review team, and Agency for Healthcare Research and Quality (AHRQ) Medical Officer defined the scope and key questions for the decision analysis. The key questions were:

1. How do the benefits, burden, and harms of screening average-risk, asymptomatic adults for colorectal cancer vary by screening modality, screening interval, age to begin screening, and age to end screening?
2. Which screening strategies are efficient in terms of the additional number of colonoscopies per life-year gained? Do the efficient strategies vary by race and sex?
3. Do the answers to key questions 1 and 2 change when efficiency is measured as the additional number of colonoscopies per quality-adjusted life-year gained? As the additional number of colonoscopies per colorectal cancer death averted?
4. Do the answers to key questions 1 and 2 change according to assumptions about the underlying risk of colorectal cancer?

In addition to analyses to address the key questions above, we performed sensitivity analysis to assess the effect of uncertainty in test characteristics. We also provide plausible ways to consider different types of non-adherence with the screening process (i.e., non-adherence with screening initiation, repeat screening, and follow-up of a positive non-colonoscopy screening test).

Overview of the Analysis

We used 3 independently-developed microsimulation models of colorectal cancer that are funded by the National Cancer Institute's CISNET consortium – Simulation Model of Colorectal Cancer (SimCRC), Colorectal Cancer Simulated Population model for Incidence and Natural history (CRC-SPIN), and Microsimulation Screening Analysis (MISCAN) for Colorectal Cancer – to estimate life-years gained, colorectal cancer incidence and mortality, number of screening tests required, and complications of screening for 239 (221 unique) colorectal cancer screening strategies that vary by screening modality, age to begin screening, age to end screening and

screening interval. Each of these strategies is simulated for 3 scenarios of population-level colorectal cancer risk.

Models

The microsimulation models used for this analysis have a long history of use in collaborative modeling analyses, including analyses to inform colorectal cancer screening National Coverage Determinations for the Centers for Medicare and Medicaid Services,[19-21] to inform screening recommendations by the American Cancer Society (ACS)[22,23] and the USPSTF,[15,16] as well as to guide screening programs in South Carolina.[24] Each model consists of a natural history component and a screening component. These components were described in detail in the 2016 report[25] and are briefly summarized below. Changes to the CRC-SPIN model are highlighted because that model has been revised since 2016.[26]

SimCRC was programmed in C++, CRC-SPIN in R, and MISCAN in Delphi.

Natural History Component

The 3 CISNET microsimulation* models describe the natural history of colorectal cancer in an unscreened population, based on the adenoma-carcinoma sequence.[27-29] Simulated persons begin in a disease-free "no lesion" state and may progress to an adenoma state, a preclinical colorectal cancer state, and a clinically detected colorectal cancer state, from which they may die from colorectal cancer (**Figure 1**). Persons may die from other causes at any time.

While the models have a similar natural history framework, they differ in the implementation of the framework. **Table 1** provides a brief comparison of the structure of the natural history components of the 3 models.

A key change from the 2016 decision analysis is that the code for the CRC-SPIN model has been rewritten, after which the model was recalibrated.[26] Compared with the previous version, the current version of CRC-SPIN (CRC-SPIN 2.0) simulates a longer sojourn time of preclinical colorectal cancer, more in line with the other 2 models, as described later in this report. CRC-SPIN was also revised to more accurately simulate the stage at clinical detection. No changes have been made to the SimCRC and MISCAN models since the 2016 report.

Adenoma Risk

In all 3 models, adenoma risk varies stochastically across individuals and by age and sex. All models allow multiple adenomas within individuals and none allow detectable adenomas in individuals <20 years of age. The risk of having an adenoma is derived to match the prevalence of adenomas by age from autopsy studies (**Figure 2**). None of the models allow regression of adenomas,[30-33] nor do they simulate the serrated polyp pathway to colorectal cancer.[34,35]

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* Microsimulation means that the models simulate outcomes for individual agents (i.e., individual hypothetical people).

Distribution of Adenomas in the Colon and Rectum

All models assign adenomas a location in the large intestine based on a multinomial distribution. SimCRC and CRC-SPIN inform these distributions using data on the location of adenomas from autopsy studies;[36-45] MISCAN assumes that the distribution of adenomas in the colon and rectum is the same as the distribution of clinically-detected colorectal cancer.[46] Consequently, the models differ in the estimated distribution of adenomas by location within the colon and rectum (**Figure 3**).

Adenoma Growth

All models allow adenoma growth to vary stochastically across individuals, and across adenomas within individuals. SimCRC and MISCAN define adenoma size categorically (1 to <6 mm, 6 to <10 mm, ≥10 mm) and do not explicitly specify a maximum size. CRC-SPIN simulates continuous adenoma size using a Richard's growth curve model,[47] with a minimum detectable size of 1 mm and maximum size of 50 mm. The models also differ in the estimated distribution of the size of the most advanced adenoma (**Figure 4**). For all models the estimated percentage of adenomas that are ≥10 mm increases with age.

Progression to Preclinical Colorectal Cancer

All models allow multiple preclinical cancers within individuals and allow the time from adenoma onset to progression to preclinical disease to vary stochastically across individuals and across adenomas within individuals. MISCAN and SimCRC do not allow progression to preclinical cancer in adenomas that are <6 mm. CRC-SPIN simulates progression rates that are a function of continuous size, with a very small (non-zero) probability of progression to preclinical cancer in adenomas <6 mm.

MISCAN specifies 2 types of adenomas: non-progressive adenomas, which have no potential of becoming cancerous, and progressive adenomas, which have this potential; the risk that an adenoma is progressive increases with age at initiation. The SimCRC and CRC-SPIN models do not explicitly model non-progressive adenomas; in these models, all adenomas have the potential to progress although most will not within a simulated individual's lifetime.

Progression to Clinically Detected Colorectal Cancer (Sojourn Time)

All models allow sojourn time (i.e., the time from preclinical cancer onset to cancer detection in the absence of screening) to vary stochastically across individuals. Mean sojourn time (for cancers that are ultimately diagnosed) ranges from 3.6 to 4.7 years across the 3 models (**Table 2**). All models assume that when 1 preclinical cancer is detected (either by symptoms or by screening), all are detected. Currently, none of the models explicitly simulate metachronous primary colorectal cancer after colorectal cancer detection. The impact of metachronous primary colorectal cancer is incorporated in rates of colorectal cancer relative survival after diagnosis.

Prior to age 75, the models reproduce age-specific colorectal cancer incidence rates (excluding carcinoid tumors and others that are not the primary target of colorectal cancer screening) from the Surveillance, Epidemiology, and End Results Program (SEER) from 1975-1979[46] – a period

with little to no colorectal cancer screening (**Figure 5**). At older ages SimCRC predicts incidence rates that are higher than those observed in SEER.

The models are calibrated to and generally replicate the stage distribution observed in SEER among a largely unscreened population (**Figure 6**).

Colorectal Cancer Death

For each simulated individual who is diagnosed with colorectal cancer, the models stochastically assign the age of colorectal cancer death using survival probabilities based on Cox proportional hazards models for relative (i.e., cause-specific) survival applied to SEER survival data for cases diagnosed from 1/1/1975 to 12/31/2003 with follow-up through 12/31/2010.[48] Time from colorectal cancer diagnosis to colorectal cancer death depends on year of diagnosis, stage, location (colon or rectum), age at diagnosis, sex, and (optionally) race. Rather than project continued improvements in relative survival for persons diagnosed after 2003 (the last diagnosis year included in the statistical analysis, due to a change in the cancer staging algorithm in 2004[49] and the dissemination of neoadjuvant chemotherapy for rectal cancer[50-52]), we fixed survival at rates estimated for cases diagnosed in 2003. None of the models allow colorectal cancer death during the lead time (i.e., the time between a screen-detected cancer and the time that the person would have been clinically detected). The age-specific colorectal cancer mortality rates estimated by the models are presented in **Figure 7**.

Non-Colorectal Cancer Death

All models stochastically assign each simulated individual's age of non-colorectal cancer death using all-cause mortality rates reported in the 2017 US life tables from the National Center for Health Statistics.[53] In the absence of screening, life expectancy at age 40 ranged from 40.2 to 40.3 years across models (when calibrated to colorectal cancer incidence rates from SEER for 1975-1979[46]), which is slightly less than the 40.7-year life expectancy from the 2017 US life table for the total population. This difference is expected, because colorectal cancer deaths were not removed from the all-cause mortality rates (i.e., the models treat all-cause mortality rates as non-colorectal cancer death rates).

Screening Component

All models have a screening component that allows the adenoma-carcinoma sequence to be interrupted through detection and removal of preclinical lesions. The screening components also allow for detection of preclinical cancer, potentially at an earlier stage. Each individual'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 individual's outcomes are known. The effectiveness of a screening strategy is simulated through a test's ability to detect lesions (that is, adenomas or preclinical colorectal cancer) (**Figure 1**). Once screening is introduced, a simulated person who has an underlying lesion has a chance of having it detected during a screening round depending on the sensitivity of the test for that lesion and, for endoscopic tests, whether the lesion is within the reach of the scope.

The models assume that all simulated people with an abnormal non-colonoscopy screening test undergo a follow-up colonoscopy; the person may be found to have 1 or more adenomas, which would be removed via polypectomy, or colorectal cancer. Screened persons without an underlying lesion can have a false-positive test result and undergo an unnecessary follow-up colonoscopy. Non-adenomatous polyps are not simulated explicitly, but their detection is reflected in false-positive rates of the direct visualization tests (colonoscopy, sigmoidoscopy, and CTC). Patient management following cancer detection is not explicitly simulated. Patients with a history of adenomas of any size are assumed to undergo surveillance with colonoscopy. The time to the next surveillance colonoscopy is simulated based on past findings. The models incorporate the risk of fatal and non-fatal complications from colonoscopy.

Model Calibration

Because the natural history of colorectal cancer is largely unobserved, there are limited data to directly inform the parameters of the natural history components of the models. Model parameter values for the natural history components were derived by calibration. Calibration is the process of selecting parameters so that model estimates closely match data from observational studies ("calibration data").[54]

All 3 natural history models are calibrated to SEER colorectal cancer incidence rates (excluding carcinoid tumors and others that are not the primary target of colorectal cancer screening) in 1975-1979[46] because this period represents colorectal cancer incidence in the US when there was little or no screening for the disease. All models incorporate information about adenoma prevalence from autopsy studies.[36-45] The SimCRC and MISCAN models are calibrated using findings from each study. The CRC-SPIN model incorporates this information by specifying prior distributions for adenoma risk parameters that are based on a meta-analysis of autopsy studies.[55]

Each model includes additional calibration data. SimCRC was calibrated to outcomes from autopsy studies that report the size distribution of adenomas[37-45] and the prevalence of preclinical colorectal cancer[38-45,56] (by age group and sex, when reported). MISCAN was calibrated to adenoma size distributions from colonoscopy studies,[57-59] stage-specific screen-detected and interval cancers from 3 large randomized FOBT trials,[60] and incidence reduction from the United Kingdom Flexible Sigmoidoscopy Screening (UKFSS) Trial.[7] CRC-SPIN was calibrated to adenoma prevalence by age and sex,[61] adenoma size,[58,62] and prevalence of preclinical colorectal cancer[57,63] reported in screening studies, and the proportion of adenomas that included colorectal cancer from a clinical series that reported adenoma-level data drawn from pathology records.[64]

Changes From the 2016 Decision Analysis

Increasing Population Risk of Colorectal Cancer

Since the mid-1990s, there have been steady increases in colorectal cancer incidence before age 50,[18,65-71] the age of screening initiation recommended by the USPSTF in 2016. Age-period-cohort modeling[18] suggests that the increase in colorectal cancer incidence in young adults is

primarily driven by a cohort effect, implying that increased risk observed before age 50 is carried forward as individuals age. Presumably this increase is not observed in colorectal cancer incidence rates among people aged ≥50 years because of the dissemination of screening.[72,73]

To estimate the effectiveness of screening in the context of increasing population risk, we modified the models to incorporate an increase in background risk. This increase in risk was estimated by the incidence rate ratio (IRR), which reflects the ratio of colorectal cancer incidence in among 20- to 44-year-olds in 2012-2016 (the most recent 5 years of data available from SEER) relative to colorectal cancer incidence among 20- to 44-year-olds in 1975-1979 (the years of SEER data used for model calibration). [Analyses of SEER data excluded carcinoid tumors and other cancers in the colon and rectum that are not the primary target of colorectal cancer screening; see **Appendix 1** for included histology codes.] While there is certainty that colorectal cancer incidence is higher among adults aged <50 years today vs 40 years ago (i.e., IRR>1), the extent of the increase is uncertain. The CISNET modeling group collaborated with USPSTF members and a leading expert on trends in cancer risk to obtain estimates of the magnitude of increasing risk for use in simulation models (see **Appendix 1** and **Table 3**).

In consultation with USPSTF members, we decided that base-case simulations used for the decision analysis would assume an IRR of 1.19 for increasing population risk models, and that this increase would be simulated as a cohort effect,[18] so that the relative increase in risk, which we assume is driven by an increase in adenoma risk, is applied throughout each simulated individuals' lifespan. Sensitivity analyses assume an IRR of 1.52 (the approximate upper bound of the 95% CI for the IRR estimated from age-period-cohort modeling of SEER incidence rates) and of 1 (no increase from the pre-screening era). These analyses were selected to capture the likely range of risk elevation.

Analyses by Race and Sex

An important addition to the current analysis compared with the 2016 analysis is the inclusion of analyses by race and sex. These analyses allow assessment of whether model results would potentially support differential screening recommendations by race and sex.

Prior to performing these analyses, we conducted a comprehensive review of the literature on race and colorectal cancer.[74] 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 adenoma risk and progression to colorectal cancer. This research found that Black-White differences in colorectal cancer incidence began only after the dissemination of screening, that there is strong evidence that Black adults are less likely to be screened for colorectal cancer than White adults, and that there is limited evidence for Black-White differences in findings at screening, including detection of adenomas, advanced adenomas, and cancer.[74] A recent study by Warren Andersen and colleagues[75] reporting the findings of over 47,000 individuals in the Southern Community Cohort Study (68% African American; 55% with household income <$15,000) found that the effect of screening on colorectal cancer incidence did not vary by race or household income, concluding that addressing the gap in screening use may reduce disparities in colorectal cancer outcomes.

Based on these studies, we assumed no Black-White differences in the risk of developing colorectal cancer, but we incorporated Black-White differences in all-cause mortality[53] and in stage-specific relative survival after diagnosis.[48] [For details on these data sources, see **Non-Colorectal Cancer Death** and **Colorectal Cancer Death**, respectively].

With respect to differences by sex, SimCRC has separately calibrated natural history models for men and women, based on sex-specific calibration targets for adenoma prevalence and size (when available)[36-45] and colorectal cancer incidence.[46] The CRC-SPIN model allows adenoma incidence and the probability of transition to preclinical cancer to vary by sex. The MISCAN model simulates sex differences in adenoma risk. All models incorporate race- and sex-specific all-cause mortality rates[53] and relative survival probabilities[48] after colorectal cancer diagnosis. In race- and sex-specific analyses, colorectal cancer incidence was simulated under the increasing population risk scenario (IRR = 1.19). We did not simulate race- and sex-specific increases in colorectal cancer incidence over time due to the wide and largely overlapping confidence intervals (CIs) for race- and sex-specific IRRs.

Model Validation

We have conducted a series of model comparisons (cross-validation) to better understand differences in outcomes across models.[76,77] As mentioned above, the models estimate similar adenoma prevalence (**Figure 2**), cancer incidence (**Figure 5**), and stage distribution (**Figure 6**). However, among colorectal cancer cases diagnosed in the absence of screening, the models estimate different mean times between adenoma formation and clinical colorectal cancer detection *for adenomas that progress to diagnosed colorectal cancer* ("dwell time," **Table 2**). Dwell time is unobservable and is an important driver of the simulated effectiveness of screening tests. The total time from adenoma formation to clinical cancer detection can be divided into 2 parts: the time from adenoma formation to onset of preclinical cancer ("adenoma dwell time"), and the time from preclinical cancer onset to clinical detection ("sojourn time"). While the models estimate similar mean sojourn time (3.6-4.7 years), they estimate different adenoma dwell times (12-25 years) and therefore different total dwell times (17-29 years). Estimated dwell times are shorter with MISCAN, due to the assumption that some adenomas are non-progressive (see **Progression to Preclinical Colorectal Cancer**).

External validation offers an opportunity to evaluate these dwell time assumptions. We externally validated all 3 models,[78] comparing their estimates to published 10-year results from the UKFSS Trial, a randomized controlled trial of 1-time sigmoidoscopy screening to reduce colorectal cancer mortality.[7] The MISCAN modeling group subsequently used these data for calibration and afterwards revalidated their model to the Norwegian Colorectal Cancer Prevention sigmoidoscopy study.[79] All models recently updated their validation against the 17-year outcomes of the UKFSS.[80] Validation focused on longer-term primary study outcomes: estimated hazard ratios of colorectal cancer incidence and mortality 17 years after screening in intervention versus control participants.[81] We also examined the ability of the models to estimate adenoma detection rates by location in the colon and rectum.[78] Point predictions were based on the mean across 2,000 simulated trials. We also compared the estimated and observed variability of outcomes based on 95% intervals estimated by the 2.5th and 97.5th percentiles across 2,000 simulated trials. We found that the 95% credible intervals from model estimates were similar in

width to reported 95% CIs and largely overlapped (**Figure 8**); this suggests that the models show a reasonable estimation of the effect of the intervention on CRC-specific incidence and mortality. Estimated adenoma detection rates at baseline sigmoidoscopy (UKFSS: 12.1%, 95% CI 11.8%-12.4%) were too low for SimCRC (8.8%, 95% credible interval 8.5%-9.0%) and too high for CRC-SPIN and MISCAN (13.3%, 95% credible interval 13.0%-13.6% and 27.7%, 95% credible interval 27.2%-28.2%, respectively). The CRC-SPIN modeling group subsequently incorporated UKFSS screen detection rates[63] into model calibration.

Colorectal Cancer Screening Strategies

In consultation with the USPSTF, we included the following screening modalities: HSgFOBT (i.e., Hemoccult SENSA (Beckman Coulter; Brea, CA)); a FIT representative of the OC-Sensor family of tests (Polymedco; Cortlandt, NY), with a cutoff of 20 µg of hemoglobin per g of feces; a stool DNA test with a FIT assay (sDNA-FIT), marketed as Cologuard (Exact Sciences Corporation; Madison, WI); sigmoidoscopy (without biopsy); SIG+FIT; colonoscopy; CTC; strategies with once-only colonoscopy then annual FIT; and strategies with annual FIT then 10-yearly colonoscopy (**Table 4**).

For each modality, we evaluated multiple screening intervals, referring to the time between subsequent screening tests for persons with a normal test result. Intervals were 1, 2, and 3 years for stool tests; 5 and 10 years for sigmoidoscopy and for CTC; and 5, 10, and 15 years for colonoscopy. For SIG+FIT, we simulated sigmoidoscopy at a 10-year interval with FIT at intervals of 1 or 2 years. We also simulated 1-time screens for sigmoidoscopy and colonoscopy.

For each combination of screening modality and interval, we evaluated ages to begin screening of 45, 50, and 55 and ages to end screening of 70, 75, 80, and 85. These ages were chosen to provide ranges around the recommended ages to begin (age 50) and end (age 75) screening from the 2016 USPSTF recommendations. The age at the last screening test for a particular strategy is not necessarily equal to the age to end screening, but rather it is a function of the age to begin and the screening interval. For example, colonoscopy every 10 years for age to begin 50 and age to end 75 results in 3 screening colonoscopies at ages 50, 60, and 70. We assume no screening occurs after the stopping age, but that colonoscopy surveillance of persons with a history of adenoma(s) is continued through at least age 85 (see **Surveillance** subsection below for more details).

In all, we evaluated 221 unique screening strategies (**Table 4**). Including duplicate strategies, the total number was 239. **Table 5** lists the non-unique strategies, that is, strategies with screening at the same ages despite different ages to end screening (e.g., “COL 50-80, 10” and “COL 50-85, 10”, both of which have screening colonoscopies at ages 50, 60, 70, and 80).

A comparison of the 2021 and 2016 CISNET colorectal cancer screening analyses is presented in **Table 6**.

Model Input Parameters

Operating Characteristics of Screening Tests

Test characteristics are based primarily on estimates from a systematic evidence review conducted by Lin et al.[17] for the USPSTF.

The sensitivity for direct visualization tests (colonoscopy, sigmoidoscopy, and CTC) is often reported on both a per-lesion and a per-person basis, whereas sensitivity estimates for stool-based tests are always per person. All 3 models specify lesion-level sensitivity for direct visualization tests so that simulated persons with multiple adenomas have a greater likelihood of an abnormal test than simulated persons with only 1 adenoma. For stool tests, CRC-SPIN specifies person-level sensitivity. SimCRC and MISCAN specify lesion-specific sensitivity values that are calibrated so that sensitivity estimates on a person-level match those observed in the selected studies. See **Appendix 2** for more information.

For all tests other than CTC, specificity in the models is defined as the probability of a normal test result among persons who do not have any adenomas or colorectal cancer. For CTC, we use a different definition for specificity to match the purpose of CTC for detecting adenomas ≥6 mm (see below for details). The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, which, in the case of sigmoidoscopy, leads to referral to colonoscopy.

Model inputs for sensitivity and specificity for each test are provided in **Table 7**. Additional information on the assumptions and sources for test characteristics is provided in **Appendix 2**.

It is important to note the findings of the systematic review for HSgFOBT. The EPC pooled the diagnostic accuracy from 2 studies[82,83] of the HSgFOBT Hemoccult SENSA. Both used colonoscopy as the reference standard and were deemed 'fair quality'. The 95% CIs for point estimates of the pooled sensitivity for advanced adenomas and for colorectal cancer were wide (0.01 to 0.22 and 0.46 to 0.90, respectively) and only 1 study[83] provided information on sensitivity for non-advanced adenomas and on test specificity using the definition required by the models (i.e., the probability of a normal test result among persons who do not have any adenomas or colorectal cancer). Given the uncertainty in the test performance characteristics, there is considerable uncertainty in model outcomes for HSgFOBT. As a result, decisions about this test should not be informed by the models. We include model findings for HSgFOBT strategies in **Appendix 4**, rather than with the main results.

Endoscopy Reach

We assume that 5% of persons undergoing colonoscopy have poor bowel preparation[84] and require 2 procedures to achieve complete visualization, and that the cecum is ultimately visualized in 95% of patients.[85] Reach of sigmoidoscopy was based on the UKFSS Trial,[63] with 76-88% of procedures reaching the junction of the sigmoid and descending colon.

Complications of Screening

Colonoscopy is the main source of reported harms (complications) from colorectal cancer screening. Harms could be from a screening or surveillance colonoscopy, or from a follow-up colonoscopy to evaluate a patient after an abnormal finding on another screening test. Fatal complications are extremely rare and affect life-years gained from screening. Non-fatal complications are more common, and affect quality of life (and costs, which are not explored in the decision analysis).

Colonoscopy

As noted by Lin et al.,[17] serious adverse events from colonoscopy in asymptomatic persons are relatively uncommon. In a population undergoing colonoscopy for screening, the risks of perforation and major bleeding were 3.3 per 10,000 (95% CI 2.2 to 4.3) and 14.9 per 10,000 (95% CI 9.0 to 20.8), respectively. Complication rates were higher in a population undergoing colonoscopy for either screening or diagnostic follow-up, with 4.8 (95% CI 3.8 to 5.7) perforations and 16.7 (95% CI 12.0 to 21.5) major bleeds per 10,000.

The risks of colonoscopy complications increase with age.[17] Age-specific estimates of the risk of non-fatal complications from colonoscopy used in the analysis are based on results from a study of adverse events (serious gastrointestinal events, other gastrointestinal events, and cardiovascular events) by age among Medicare beneficiaries undergoing outpatient colonoscopy (with or without polypectomy) relative to matched controls.[86] This study found no evidence of excess risk for complications when colonoscopies did not include polypectomy, and that the risks in therapeutic colonoscopies (i.e., those with polypectomy) increased exponentially with age (**Figure 9**). We assumed 2 fatal complications per 100,000 colonoscopies with polypectomy, based on the risk of perforation at age 65 and the risk of dying of a perforation reported by Gatto et al.[87]

Sigmoidoscopy

Lin et al.[17] identified several studies reporting the harms of sigmoidoscopy among the general population. However, none evaluated excess risks relative to a comparison group. As with colonoscopy, we assume risks of complications are conditional on polypectomy. Because we assume that polyps detected at sigmoidoscopy are not removed or biopsied during the procedure, we assumed that there is no risk of complications due to sigmoidoscopy, though complications could occur during colonoscopic follow-up of an abnormal sigmoidoscopy exam.

CTC

Lin et al.[17] found that perforation from CTC itself was rare, with 95% CIs of 0 to 2.9 per 10,000 procedures. Furthermore, these perforations were detected radiologically, so are not on par with serious harms of perforation with colonoscopy. We therefore assumed no complications from CTC, though complications could occur during colonoscopic follow-up of an abnormal CTC exam.

Because CTC is a radiologic procedure, it may increase the risk of radiation-induced cancers. The models do not account for these risks, although their risks have been estimated to be small relative to the potential reduction in colorectal cancer risk from CTC screening.[88]

CTC often leads to the detection of suspicious findings outside of the colon.[17] The models do not include the potential benefits or harms associated with the work-up and possible treatment of these extracolonic findings.

Stool Tests

Given their non-invasive nature, we assumed no direct harms from stool tests. We assumed complications could arise from colonoscopic follow-up of an abnormal stool test.

Surveillance

Simulated persons who have an abnormal screening test but have no adenomas or cancer at the follow-up colonoscopy return to their original screening modality and schedule 10 years after the normal follow-up colonoscopy. Simulated persons with adenomas detected at a screening or a follow-up colonoscopy are assumed to undergo surveillance with colonoscopy. The time to the next surveillance colonoscopy is simulated based on findings at prior colonoscopies, in accordance with the 2020 recommendations of the Multi-Society Task Force on Colorectal Cancer (MSTF).[89] These recommendations provide intervals for surveillance based on baseline findings and findings at the first surveillance colonoscopy. We assume the intervals provided by the MSTF can be more generally expressed as the intervals based on the most recent colonoscopy ("first-most-recent colonoscopy") and the colonoscopy prior to that ("second-most-recent colonoscopy") (**Table 8**). In situations where the MSTF provided a range rather than a single interval, we assumed that the shortest interval would be used in routine practice. Surveillance colonoscopy is assumed to continue through age 85, provided no adenomas or colorectal cancer are detected at the last surveillance colonoscopy (either at or before age 85). Otherwise surveillance was continued according to the clinical findings at the last colonoscopy until no adenomas are detected. For example, if a simulated person has no adenomas detected at a surveillance colonoscopy at age 83, they would stop surveillance because they would be >85-years-old at the next surveillance colonoscopy. However, if an adenoma ≥10 mm is detected at the surveillance colonoscopy at age 83, another surveillance colonoscopy would be performed at age 86, because the surveillance colonoscopy at or just prior to age 85 was abnormal; if the colonoscopy at age 86 is normal, then surveillance ends.

Adherence

In base-case analyses, we assumed perfect adherence to the screening process, including all screening, follow-up, and surveillance procedures, reflecting the goal of estimating the effect of screening among average-risk persons with full willingness to be screened for colorectal cancer.

Lin et al.[17] performed a robust review of the literature on adherence. None of the identified studies provide information on long-term adherence patterns required by the models. Given the limited evidence to inform long-term adherence patterns and the variability in estimates of short-term adherence rates, simulating the effect of imperfect adherence requires numerous

assumptions. As a result, uncertainty surrounding model outcomes with imperfect adherence would be high. We therefore did not perform a formal sensitivity analysis on adherence rates, but instead discuss the potential effect of delayed screening initiation, repeat screening less frequently than recommended, delayed or lack of follow-up colonoscopy, and earlier screening cessation than recommended by comparing outcomes across scenarios with perfect adherence but with screening at different ages and intervals. For example, if people start colonoscopy late and only do 1, then the estimated effect on outcomes can be seen through comparison of once-only colonoscopy at age 55 with the recommended colonoscopy strategy. Similarly, if people are non-adherent with annual FIT, the estimated effect can be seen by comparing outcomes with annual FIT vs with FIT every 2 or 3 years.

Quality of Life Assumptions

When calculating quality-adjusted life-years (QALYs), we accounted for preferences for a year of life varying by age, as well as utility losses associated with specific events (e.g., colonoscopy) or health states (e.g., time with CRC). The approach we used is similar to that used by the CISNET breast cancer group in their 2016 analysis for the USPSTF.[90]

Estimates of how preferences for a year of life vary according to age were obtained from the age-related utility weights from Hanmer et al.[91] We assumed no disutility from performing stool tests themselves, but for all tests, we accounted for the disutility associated with waiting for test results. Disutilities for colonoscopy were based on a study by Swan et al.[92] and were applied for a duration of 36 hours, based on a study by Jonas et al.[93] We assumed the same disutility for sigmoidoscopy and CTC as for colonoscopy, but for shorter time periods because the lack of sedation reduces the time to resolution of normal activities. See **Appendix 3** for more details on the inputs for QALY calculation.

Outcomes

The models estimated a number of outcomes for each screening strategy to capture the potential health effects and harms over a lifetime. Outcomes included the estimated numbers of stool tests, sigmoidoscopies, CTCs, colonoscopies by type (screening, follow-up, surveillance, or symptom diagnosis), normal and abnormal test results, complications, colorectal cancer cases, colorectal cancer deaths, complication-related deaths, overall life-years, and life-years with colorectal cancer by stage at diagnosis. To keep the tables of outputs manageable, not all outcomes are included in the summary tables provided in this report (e.g., colonoscopies were reported as screening vs other colonoscopies).

All model-estimated outcomes are presented for a cohort of average-risk US adults who are unscreened and free of diagnosed colorectal cancer at age 40.[†] Outcomes are tallied from age 40

[†] We chose a 40-year-old cohort to maintain consistency with the 2008 and 2016 decision analyses for colorectal cancer screening for the USPSTF. The initial decision to simulate a cohort of 40-year-olds was based on the fact that the 2008 decision analysis included strategies with screening starting at age 40.

to death and expressed per 1,000 persons at age 40. To facilitate interpretation of LYG, they are also expressed in terms of days of life gained per person.

Benefit

We considered estimated life-years gained (LYG) compared with no screening[‡] as the primary outcome for benefits of screening. A small fraction of those who are screened may experience a loss of life-years as a result of fatal complications; these losses are accounted for in the LYG for a given screening strategy.

Harms

We used the model-estimated lifetime number of required colonoscopies to represent the primary harms and burden of colorectal cancer screening. This metric includes colonoscopies for screening, follow-up, and surveillance, as well as colonoscopies for the diagnosis of symptomatic cancers (i.e., cancers detected outside of screening or surveillance). Because the number of colonoscopies does not fully capture the burden of colorectal cancer screening, we also report the number of screening tests by type and the number of complications.

Ratio of Harms (Burden) to Benefit

Ideally, all colorectal cancer screening strategies would be evaluated together in one comprehensive analysis comparing the model-estimated harms and benefits of screening. However, an analysis such as this would provide an incomplete picture of the tradeoffs across different screening modalities due to large differences in the number of non-colonoscopy tests (i.e., stool tests, sigmoidoscopies, and CTCs) across modalities. We therefore did not perform a comprehensive analysis of all strategies. Instead, we performed separate analyses by screening modality, as described in the sections that follow. Briefly, we first grouped together screening modalities with comparable non-colonoscopy burden to create "classes" of screening modalities. We then identified the subset of efficient screening strategies within each class, as described below.

Classes of Comparable Screening Modalities

We grouped FIT and sDNA-FIT together as exclusively stool-based screening modalities with comparable burden. (Model-estimated outcomes for stool-based modalities including HSgFOBT are included in **Appendix 4.**) The remaining modalities – SIG+FIT, sigmoidoscopy alone, CTC, and colonoscopy – each remained a unique screening class due to differences in bowel preparation, invasiveness, the need for sedation, and in the need for, type of, and number of non-colonoscopy tests. After this grouping, we were left with seven classes of screening modalities:

[‡] The number of life-years gained with a given strategy was calculated as the difference in model-estimated life expectancy between the strategy of interest and the no screening strategy.

stool-based modalities, SIG+FIT, sigmoidoscopy alone, CTC, colonoscopy alone, and strategies involving colonoscopy either preceded by or followed by annual FIT.

Efficient Strategies Within a Class of Screening Modality

Our goal was not to identify a "best" test or set of tests, but, as noted in Key Question 2, to identify efficient screening strategies within each class of screening modality. A strategy is efficient if no other strategy or combination of strategies within the class is estimated to provide more LYG with the same (or fewer) estimated number of colonoscopies. We first identified screening strategies that were estimated to require more colonoscopies and provide lower LYG than another strategy within the class; these strategies are strongly dominated and were deemed inefficient (**Figure 10**). For each of the remaining strategies within a class of screening modality we calculated the incremental number of lifetime colonoscopies (ΔCOL) and the incremental LYG (ΔLYG), relative to the next least effective strategy. We then calculated an "efficiency ratio," defined as the incremental number of colonoscopies required to achieve an additional LYG (ΔCOL/ΔLYG). In an approach that mirrors that of incremental cost-effectiveness analysis, strategies that were estimated to provide lower LYG than another and had a higher efficiency ratio were weakly dominated and deemed inefficient.

We then derived an "efficient frontier" for each class of screening modality, which is the line connecting efficient strategies when the strategies are plotted with the estimated number of colonoscopies on the horizontal axis and the estimated number of LYG on the vertical axis. The inverse of the slope of the efficient frontier between adjacent strategies is the efficiency ratio. It represents the number of additional colonoscopies required to increase LYG by 1. This ratio is akin to the incremental cost-effectiveness ratio in a cost-effectiveness analysis. As the efficient frontier gets flatter, the efficiency ratio increases, indicating diminishing returns from each additional colonoscopy performed.

There is no standard for determining the optimal point on the efficient frontier. In cost-effectiveness analysis, decision makers typically refer to estimates of the willingness to pay for a year of (quality-adjusted) life gained as a benchmark for deciding which of the efficient strategies provide good vs poor value.[94-96] There is no comparable metric in this setting, where efficiency is expressed as the number of additional colonoscopies per LYG. To aid in the interpretation of the tradeoff between life expectancy gains and colonoscopies across strategies within a class of screening modality, we also present the results as the number of additional days of life gained per additional colonoscopy performed (ΔDLG/ΔCOL) in a summary table provided in the **Discussion**. This metric is equivalent to the slope of the efficient frontier, but with the benefit of screening expressed in terms of days of life gained instead of years of life gained. It conveys the "bang" (additional days of life gained) for each additional colonoscopy "buck."

Lastly, because an inefficient strategy providing outcomes that are very similar to an efficient strategy may be a reasonable option for another reason[97] (e.g., for consistency of starting and stopping ages across screening modalities), we also identified "near-efficient" strategies, which we defined as a strategy within 3 days of life gained per person of the efficient frontier. There is no standard for what constitutes a reasonable number of days from the frontier for a strategy to be near efficient. We chose an absolute distance of 3 days per person, which, for the strategies highlighted by the USPSTF in 2016, is largely consistent with the relative measure that we used

in the 2016 decision analysis, namely LYG within 2% of the efficient frontier. Hereafter, we refer to efficient and near-efficient strategies as "efficient".

Scenario and Sensitivity Analyses

Many of the sensitivity and scenario analyses have been described above, although not in those terms. Through the use of 3 independently-developed models, the primary analysis includes a sensitivity analysis on model structure. We also evaluated outcomes for 2 scenarios of colorectal cancer risk (IRR of 1.52, and 1, see **Increasing Population Risk of Colorectal Cancer**), in addition to the scenario for the base-case analysis (IRR = 1.19). Additional analyses were stratified by race and sex (see **Analyses by Race and Sex**).

Two additional sensitivity analyses were performed. First, because there are multiple ways to express the benefit of screening, we presented results using 3 metrics: LYG (the metric for base-case analyses); quality-adjusted life-years gained (QALYG);[§] and colorectal cancer deaths averted.[**] Additional information on the calculation of quality-adjusted life-years is provided in **Appendix 3**. We assumed that a strategy within 3 quality-adjusted days of life gained per person of the efficient frontier is near efficient, which is similar to the approach used for LYG (i.e., within 3 days of life gained per person of the efficient frontier is near efficient). With the estimated number of colorectal cancer deaths averted as the measure of benefit, we assumed a dominated strategy within 0.75 deaths averted per 1,000 of the efficient frontier is near efficient.

Second, we performed a sensitivity analysis to evaluate the effect of uncertainty in the sensitivity of colonoscopy for detecting adenomas by size. Values for colonoscopy sensitivity (**Table 7**) were based on a 2019 systematic review and meta-analysis of tandem colonoscopy studies by Zhao et al.[98]

To keep the number of model simulations at a manageable number, in consultation with USPSTF members, analyses by race and sex and sensitivity analyses of colonoscopy sensitivity were limited to 1 risk scenario (IRR=1.19) and 2 screening modalities (colonoscopy and FIT). Even so, these additional analyses required 355 additional simulations for each model.

While not technically a sensitivity or scenario analysis, we also provided plausible ways to consider different types of non-adherence with the screening process. For example, estimated outcomes accounting for non-adherence with screening initiation can be calculated by a weighted average of estimated outcomes with a given screening strategy and with no screening. The effect of delayed screening initiation can be estimated by comparing output across strategies with

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[§] The number of quality-adjusted life-years gained with a given strategy was calculated as the difference in model-estimated quality-adjusted life expectancy between the strategy of interest and the no screening strategy.

[**] The estimated number of colorectal cancer deaths averted with a given strategy was calculated as the difference in the model-estimated number of colorectal cancer deaths with the no screening strategy and the strategy of interest.

different ages to begin screening. Similarly, the effect of non-adherence with repeat screening can be estimated by comparison of strategies with different screening intervals.

Expert Review and Public Comments

A draft version of this report was reviewed by content experts, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report when appropriate. Additionally, a draft of this report was posted for public comment on the USPSTF website from October 27, 2020, through November 23, 2020. Few comments were received during this public comment period; minor clarifications and editorial changes were made to the report based on these comments. While no changes were made to the model findings or to the conclusions, tables and figures were added to simplify comparison of outcomes by race and sex.

Chapter 3. Results

Benefits, Burden, and Harms of Screening

As noted in the Methods, primary analyses are based on models calibrated to reflect the increasing population risk of colorectal cancer (see **Appendix 1** for details). Screening strategies are referred to by *modality age to begin-age to end, interval*. For example, annual FIT from ages 55 to 70 is FIT 55-70, 1. The strategy combining sigmoidoscopy every 10 years with annual fecal immunochemical testing from ages 50 to 80 is SIG+FIT 50-80, 10_1.

Findings in the Absence of Screening

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. Models estimated that out of 1000 40-years-olds, 77 to 85 would be diagnosed with colorectal cancer in their lifetimes and 32 to 34 would die from the disease (**Figure 11**).

General Findings in the Presence of Screening

Model-estimated outcomes for HSgFOBT strategies, once-only colonoscopy strategies, once-only sigmoidoscopy strategies, and strategies with colonoscopy preceded by or followed by annual FIT are presented in **Appendix 4-8**; outcomes with these strategies are not discussed. Outcomes with all other screening strategies are shown in **Appendix 9**. Although the *absolute* estimates of the benefits, colonoscopy burden and harms of screening differed across models, *relative* estimates and rankings of screening strategies within each screening modality were consistent across models. Compared to no screening, all colorectal cancer screening strategies were estimated to yield substantial increases in life expectancy and substantial reductions in the lifetime number of colorectal cancer cases and deaths. Estimated LYG from screening ranged from 171 to 381 per 1000 40-year-olds (63 to 139 days of life gained per person); within each model, LYG were lowest with FIT 55-70, 3 and highest with COL 45-85, 5.

With screening, the estimated lifetime number of colorectal cancer cases diagnosed ranged from 9 to 65 per 1000 40-year-olds, and the estimated lifetime number of colorectal cancer deaths ranged from 2 to 20 per 1000, depending upon the screening strategy and model. Within each model, the estimated numbers of cases diagnosed and colorectal cancer deaths were generally lowest with COL 45-85, 5 and highest with FIT 55-70, 3. The estimated benefits of screening were generally highest with SimCRC and lowest with MISCAN, with results from CRC-SPIN falling in between.

The estimated lifetime number of colonoscopies – the primary measure of the burden of screening – ranged from 624 to 6817 per 1000 40-year-olds (<1 to nearly 7 per person) and were lowest with FIT 55-70, 3 and highest with COL 45-85, 5 across models. Harms from screening – the estimated number of colonoscopy complications – ranged from 5 to 22 per 1000 40-year-olds (**Appendix 9**). Fatal complications were rare, ranging from 4.2 to 23.1 per million 40-year-olds; the years of life lost from these deaths were accounted for in the estimation of the LYG from

screening. The strategies with the lowest and highest estimated number of total complications and of fatal complications generally tracked with the strategies with the lowest and highest estimated number of lifetime colonoscopies.

Efficient Strategies Within Each Class of Screening Modality

Efficiency ratios for the screening strategies highlighted by the USPSTF in 2016 are in **Table 9**. As a reminder, a strategy is efficient if no other strategy or combination of strategies within the class of screening modality is estimated to provide more life-years with the same (or fewer) number of colonoscopies. Efficiency ratios are calculated within a class of screening modality and can be interpreted as the number of additional colonoscopies required to achieve an additional LYG.

Colonoscopy

Of the 26 unique colonoscopy strategies, 11 were efficient with SimCRC, 12 with CRC-SPIN, and 17 with MISCAN (**Appendix Table 10.1**). Eleven strategies were efficient with all 3 models; 9 of the 11 were strategies with screening beginning at age 45. The MISCAN model estimated that several strategies with screening starting at age 50 or age 55 would also be efficient options (**Figure 12**). No single age to end screening or screening interval was predominant among efficient strategies. Among strategies that were efficient with all 3 models, strategies with screening ending at age 80 or 85 had efficiency ratios of ≥169 additional colonoscopies per LYG, and strategies with a 5-year interval had efficiency ratios ranging from 84 to >2000 (**Appendix Table 10.1**). Across the 3 models, estimated LYG per 1000 were lowest for COL 55-70, 15 (250 to 285 across models) and highest for COL 45-85, 5 (323 to 381 across models, **Figure 12**); the estimated number of complications for these strategies ranged from 13 to 14 per 1000 and from 20 to 22 per 1000, respectively (**Appendix Table 9.1**).

Stool Tests (FIT and sDNA-FIT)

Seventy-two strategies used stool testing (FIT or sDNA-FIT) alone. Of these, 21 were efficient with SimCRC, 21 with CRC-SPIN, and 32 with MISCAN; 16 strategies were efficient with all 3 models (**Appendix Table 10.2**). Efficient strategies with all 3 models were primarily those with screening beginning at age 45 (14 of 16 strategies) The MISCAN model again included several (17 out of 32) strategies with screening starting at age 50 or age 55 as efficient options (**Figure 13**).

With all 3 models, efficient stool testing strategies were primarily those with FIT as the stool test (**Figure 13**) (14 of 21 with SimCRC, 13 of 21 with CRC-SPIN; 27 of 32 with MISCAN); efficiency ratios were ≤43 additional colonoscopies per LYG across models for the efficient FIT strategies with all 3 models (**Appendix Table 10.2**). Annual and biennial sDNA-FIT strategies (with screening starting at age 45) were also efficient with all 3 models with efficiency ratios ranging from 26 to 375 additional colonoscopies per LYG. sDNA-FIT strategies with a 3-year interval were not efficient with any model.

Efficiency ratios for the subset of efficient FIT strategies with all 3 models with screening ending at age 85 ranged from 12 to 43 additional colonoscopies per LYG (**Appendix Table 10.2**). Across models, FIT 55-70, 3 yielded the fewest LYG (171 to 203 per 1000), and sDNA-FIT 45-85, 1 provided the most LYG (313 to 368 per 1000, **Figure 13**). The estimated number of complications for these strategies ranged from 5 to 7 per 1000 for FIT 55-70, 3 and from 14 to 16 per 1000 for sDNA-FIT 45-85, 1 (**Appendix Tables 9.2 and 9.3**).

Model findings for stool-based screening modalities including HSgFOBT are in **Appendix 4**.

Sigmoidoscopy

Of the 20 unique sigmoidoscopy strategies, 7 were efficient with SimCRC, 8 with CRC-SPIN, and 15 with MISCAN (**Appendix Table 10.3**). Seven strategies were efficient with all 3 models, and in all but 1 strategy screening began at age 45. With MISCAN, strategies with screening starting at age 50 were also efficient (**Figure 14**). All 4 ages to end screening and both screening intervals were included among the strategies that were efficient across all 3 models; efficiency ratios with screening to age 85 ranged from 78 to 98 additional colonoscopies per LYG and efficiency ratios for strategies with a 5-year screening interval ranged from 11 to 98 additional colonoscopies per LYG (**Appendix Table 10.3**). Across models, estimated LYG were lowest for SIG 55-70, 10 (range 204 to 210 per 1000) and highest with SIG 45-85, 5 (272 to 312 per 1000, **Figure 14**); the estimated number of complications for these 2 strategies ranged from 7 to 10 per 1000 and from 12 to 13 per 1000, respectively (**Appendix Table 9.4**).

SIG+FIT

Of the 24 SIG+FIT strategies evaluated, the number that were efficient was 10, 10, and 20 for the SimCRC, CRC-SPIN, and MISCAN models, respectively (**Appendix Table 10.4**). Ten strategies were efficient with all 3 models, and strategies with screening beginning at age 45 were predominant among them (8 of 10 strategies). As with other modalities, with MISCAN, strategies with screening starting at age 50 or 55 were also among those that were efficient (**Figure 15**, **Appendix Table 10.4**). Among strategies that were efficient with all 3 models, no single age to end screening or interval for FIT was predominant. Across the 3 models, SIG+FIT 55-70, 10_2 provided the fewest estimated LYG (241 to 266 per 1000) and SIG+FIT 45-85, 10_1 provided the most (309 to 367 per 1000, **Figure 15**); the estimated number of complications for these strategies ranged from 8 to 11 per 1000 and from 14 to 16 per 1000, respectively (**Appendix Table 9.5**).[††]

CTC

Findings with CTC were similar to those with sigmoidoscopy: of the 20 unique CTC strategies, 7 were efficient with SimCRC, 8 with CRC-SPIN, and 14 with MISCAN (**Appendix Table 10.5**).

[††] As a reminder, the intervals noted in the reference to the SIG+FIT strategies, 10_1 and 10_2, refer to the interval for SIG (10 years) and for FIT (either 1 or 2 years).

Five strategies were efficient with all 3 models, and all but 1 had screening beginning at age 45. The MISCAN model estimated that strategies with screening beginning at age 50 and 55 would also be efficient (**Figure 16**). Among strategies that were efficient with all 3 models, no 1 age to end screening emerged as efficient, but efficient strategies were generally those with a 5-year interval. Across models, CTC 55-70, 10 yielded the fewest estimated LYG (181 to 245 per 1000) and CTC 45-85, 5 provided the most (290 to 359 per 1000, **Figure 16**); the estimated number of complications for these strategies ranged from 7 to 9 per 1000 and from 12 to 15 per 1000, respectively (**Appendix Table 9.6**).

Scenario and Sensitivity Analyses

Findings by Race and Sex

As explained in **Analyses by Race and Sex**, the modeling analyses assumed no differences by race in the development of clinically-detected colorectal cancer in the absence of screening. This assumption was based on our review of the literature on race and colorectal cancer.[74] While the development of adenomas and their progression to colorectal cancer was not allowed to vary by race, the models incorporated Black-White differences in all-cause mortality[53] and in relative survival from colorectal cancer following diagnosis.[48]

Before presenting the detailed findings, we briefly describe the general implications of the assumption and inputs described above. All else being equal, higher all-cause mortality rates among simulated Black adults vs White adults results in a smaller proportion of an initial cohort of Black adults being alive at older ages when the risk of colorectal cancer diagnosis is highest (**Figure 5**). Accordingly, in the absence of screening, the models would estimate both a lower life expectancy and a lower lifetime risk of being diagnosed with colorectal cancer among an initial cohort of cancer-free Black adults than among an initial cohort of cancer-free White adults. In addition, the lower stage-specific colorectal cancer relative survival probabilities among Black adults vs White adults would result in a larger proportion of Black colorectal cancer patients dying from their cancer than White colorectal cancer patients. Whether the model-estimated lifetime number of colorectal cancer deaths is higher among an initial cohort of cancer-free Black adults than White adults depends only on whether the lower lifetime risk of colorectal cancer diagnosis among Black adults is offset by this group's worse survival following colorectal cancer diagnosis. Detailed model-estimated outcomes for each race and sex group compared with those estimated for the total population are described below.

Compared to the total population (model-estimated life expectancy 40.2 years), model-estimated life expectancy among unscreened 40-year-olds with no prior CRC diagnosis was 2 years higher for White females (42.2 years), similar for Black females (40.1 years), 2 years lower for White males (38.4 years), and 5 years lower for Black males (35.2 years). In the absence of screening, the model-estimated lifetime number of diagnosed colorectal cancer cases was higher for White males compared to the total population (86 vs 81 cases per 1000, respectively; estimates are the mean across the 3 models) and lower than the total population for the other groups (77, 73, and 70 cases per 1000 White females, Black males, and Black females, respectively, **Table 10**). For both sexes, model-estimated lifetime risk of colorectal cancer diagnosis was lower among Black vs White adults (73 vs 86 per 1000 males by race; 70 vs 77 per 1000 females by race).

The models estimated that the lower lifetime risk of colorectal cancer diagnosis among Black males vs White males in the absence of screening also led to a lower lifetime risk of colorectal cancer death (33 vs 35 per 1000, **Table 10**), despite the worse relative survival following CRC diagnosis in Black patients compared to White patients. The pattern was reversed for females by race: Black females were estimated to have lower lifetime risk of colorectal cancer diagnosis in the absence of screening but higher lifetime risk of colorectal cancer death (32 vs 31 per 1000). This implies that the lower estimated lifetime incidence in Black females vs White females was offset by the worse relative survival following colorectal cancer diagnosis in Black patients vs White patients. Compared to the total population, the lifetime risk of colorectal cancer death was estimated to be higher for White males than for the total population (35 vs 33 deaths per 1000), the same as the total population for Black males (33 per 1000), and lower than the total population for Black females and White females (32 and 31 per 1000, respectively).

Due to these differences in estimated lifetime risk of colorectal cancer death among Black adults vs White adults by sex in the absence of screening, estimated LYG from both colonoscopy and FIT were generally lower for Black males vs White males and generally similar for Black females vs White females (**Appendix Figures 11.1 and 11.2**). However, efficient strategies by race and sex were generally the same, and efficiency ratios were similar by race among each sex (**Tables 11 and 12**; **Appendix Tables 11.1 and 11.2**), suggesting that with equal access to quality care, the relative balance of the colonoscopy burden and the LYG from screening differs by sex but not by race. For example, across models, efficiency ratios for 10-yearly colonoscopy from age 45 to 75 ranged from 48 to 143 for White males, 46 to 142 for Black males, 57 to 100 for White females, and 51 to 93 for Black females. Among all 4 race-sex groups, efficient screening options for all 3 models were predominantly those beginning at age 45. Results for colonoscopy are described in more detail below, followed by those for FIT.

For colonoscopy screening, the SimCRC and CRC-SPIN models found that for each of the 4 race-sex groups, efficient strategies were the same as those for the population as a whole (**Appendix Tables 11.1a and 11.1b**). With MISCAN, differences in conclusions about efficiency only occurred for COL 55-85, 15, which was efficient among Black males and dominated in all other groups, including the total population (**Appendix Table 11.1c**). With SimCRC and MISCAN, efficiency ratios for a given colonoscopy strategy were generally lower for males than for females, while the opposite was true with CRC-SPIN. Across all 3 models, efficiency ratios were slightly lower for a given colonoscopy strategy for Black adults vs White adults by sex. For example, the efficiency ratio for COL 45-75, 10 was 52 vs 56 additional colonoscopies per LYG for Black vs White males and 66 vs 76 for Black vs White females (reported ratios are from SimCRC, **Appendix Table 11.1a**).

For FIT screening, efficient strategies with SimCRC were the same as those for the population as a whole (**Appendix Table 11.2a**). With CRC-SPIN and MISCAN, differences in efficiency across populations occurred almost exclusively in strategies with biennial and triennial screening (**Appendix Tables 11.2b and 11.2c**). With CRC-SPIN, strategies that were dominated among the total population and among White and Black males were efficient among White and Black females. No clear patterns were observed for changes in efficiency by race and sex with MISCAN. As with colonoscopy screening strategies, efficiency ratios for a given FIT strategy were generally the same as or lower for males than for females in SimCRC and MISCAN, while the opposite was true with CRC-SPIN. Across all 3 models, efficiency ratios for a given FIT

strategy were generally equal to or slightly lower for Black adults vs White adults by sex. For example, the efficiency ratio for FIT 45-80, 1 was 28 vs 32 additional colonoscopies per LYG for Black males vs White males and 21 vs 23 for Black females vs White females (reported ratios are from CRC-SPIN, **Appendix Tables 11.2b**).

Measure of the Benefit of Screening

QALYG

Estimated QALYG from screening ranged from 144 to 358 per 1000 40-year-olds, which is lower than the range for estimated LYG (171 to 381 per 1000, **Appendix Tables 9.1-9.8**). In general, we found a larger effect of quality-adjustment of LYG for strategies and models that estimated more colorectal cancer cases (i.e., stool-based strategies, compared with direct-visualization tests (colonoscopy, CTC, and sigmoidoscopy), and MISCAN, compared with SimCRC and CRC-SPIN), due to the relatively large decrement in quality of life associated with colorectal cancer (**Appendix Table 3.4** vs **Appendix Tables 3.2** and **3.3**).

Efficient strategies within each class of screening modality with estimated QALYG as the measure of benefit were nearly identical to those with estimated LYG (**Appendix Tables 12.1-12.5**; **Appendix Figures 12.1-12.5**). Estimated QALYG with a given screening strategy were lower than the estimated LYG, shifting the efficient frontier down. For each class of screening modality, efficient screening strategies continued to be primarily those with screening starting at age 45; MISCAN continued to find additional strategies with screening starting at age 50 or 55 to be efficient. Across classes of screening modalities and models, efficiency ratios were generally the same or higher with estimated QALYG vs estimated LYG as the measure of screening benefit, though the differences in efficiency ratios were small for most strategies (**Appendix Tables 12.1-12.5**). For example, with SIG 45-75, 5 efficiency ratios with LYG and QALYG were 20 and 23 with SimCRC, 27 and 31 with CRC-SPIN, and 19 and 23 with MISCAN (**Appendix Table 12.3**).

Colorectal Cancer Deaths Averted

The estimated number of colorectal cancer deaths averted ranged from 15 to 32 per 1000 (**Appendix Tables 9.1-9.8**). Within each class of screening modality, the ranking of strategies by the estimated number of colorectal cancer deaths averted differed from the ranking by the estimated number of LYG. As a result, the strategies deemed efficient changed when the estimated number of colorectal cancer deaths averted was used as the measure of the benefit of screening, instead of the estimated LYG (**Appendix Tables 13.1-13.5**; **Figures 17-21**). Efficient strategies included those with all 3 ages to begin screening, all 4 ages to end screening, and all simulated screening intervals. Incremental numbers of colonoscopies required to prevent an additional colorectal cancer death are presented in **Appendix Tables 13.6-13.10**.

Colonoscopy Strategies

The colonoscopy screening strategy with the fewest estimated colorectal cancer deaths averted varied across models (**Figure 17**): COL 55-70, 10 with SimCRC (27 estimated colorectal cancer deaths averted per 1000 40-year-olds); COL 55-70, 15 with CRC-SPIN (24 estimated colorectal

cancer deaths averted per 1000); and COL 45-70, 15 with MISCAN (22 estimated colorectal cancer deaths averted per 1000). The estimated number of colorectal cancer deaths averted was highest with COL 45-85, 5 with all 3 models (28 to 32 per 1000, **Appendix Table 9.1**). The number of efficient colonoscopy screening strategies was 16 with SimCRC, 15 with CRC-SPIN, and 23 with MISCAN; 13 strategies were efficient with all 3 models (**Appendix Table 13.6**). Compared to COL 55-70, 15, COL 50-70, 10 required 380 to 712 additional colonoscopies per additional colorectal cancer death averted. This number increased to over 3000 colonoscopies per additional colorectal cancer death averted for COL 45-85, 5 vs COL 45-80, 5.

Stool Tests

With SimCRC and CRC-SPIN, FIT 55-70, 3 was estimated to prevent the fewest colorectal cancer deaths (15 to 17 per 1000), while with MISCAN FIT 50-70, 3 was estimated to prevent the fewest (15 per 1000) (**Figure 18**). With all 3 models, sDNA-FIT 45-85, 1 was estimated to prevent the most colorectal cancer deaths (27 to 31 per 1000). The number of efficient stool test strategies was 24 with SimCRC, 40 with CRC-SPIN, and 23 with MISCAN; 18 strategies were efficient with all 3 models. For these strategies, the estimated number of additional colonoscopies per colorectal cancer death averted were 35 to 54 with FIT 55-75, 3; 317 to 531 with FIT 50-80, 1; and 783 to over 1200 with sDNA-FIT 45-85, 1 (**Appendix Table 13.7**). Efficient strategies with all 3 models included all ages to begin and end screening and screening intervals, but were primarily those with FIT, as opposed to sDNA-FIT. sDNA-FIT strategies with a 3-year interval were not efficient with 2 models and were efficient with CRC-SPIN (>300 additional colonoscopies per colorectal cancer death averted).

Other Modalities

For all but 1 other screening modality, the strategies estimated to yield the fewest and most colorectal cancer deaths averted did not vary across models. For sigmoidoscopy and CTC, screening from ages 55 to 70 every 10 years (SIG or CTC 55-70, 10) was estimated to yield the fewest colorectal cancer deaths averted (18 to 19 per 1000 with sigmoidoscopy (**Figure 19**); 16 to 22 with CTC (**Figure 21**)), and screening from ages 45 to 85 every 5 years (45-85, 5) was estimated to yield the most colorectal cancer deaths averted (23 to 27 with sigmoidoscopy; 25 to 31 with CTC). For SIG+FIT, screening from ages 55 to 70 with sigmoidoscopy every 10 years and biennial FIT (SIG+FIT 55-70, 10_2) was estimated to yield the fewest colorectal cancer deaths averted (22 to 24 per 1000 (**Figure 20**)) and screening from ages 45 to 85 with sigmoidoscopy every 10 years and annual FIT (SIG+FIT 45-85, 10_1) was estimated to yield the most (27 to 31 per 1000).

Efficient sigmoidoscopy (**Appendix Table 13.8**) and CTC (**Appendix Table 13.10**) strategies with all 3 models included all 3 ages to begin screening, all 4 ages to end screening, and both screening intervals. With SIG+FIT, no ages to begin or end screening or FIT interval were predominant among the efficient strategies with all 3 models (**Appendix Table 13.9**).

Population-Level Risk (IRR)

Estimated adenoma prevalence and colorectal cancer incidence when models were calibrated to achieve an IRR of 1.52 are presented in **Appendix 14**. Estimated adenoma prevalence and

colorectal cancer incidence were fairly similar with SimCRC and MISCAN: prevalence increased to a maximum of 63% to 65% by approximately age 85 (**Appendix Figure 14.6**) and the lifetime incidence of colorectal cancer was estimated at 103 to 105 cases per 1000 (**Appendix Figure 14.9**). With CRC-SPIN smaller changes in adenoma onset were needed to achieve an IRR of 1.52; estimated adenoma prevalence was at most 47% by age 79, and lifetime incidence of colorectal cancer was 91 cases per 1000. For all models, estimated adenoma prevalence was still within the range observed in autopsy studies.

Within each class of screening modality, efficient strategies, based on estimated life-years gained, were nearly identical across the 3 scenarios for colorectal cancer risk (**Appendix Tables 14.1-14.7**, **Figures 22-26**). Across all models, efficient strategies were generally those with screening beginning at age 45. Efficiency ratios generally decreased as risk increased. Changes for specific classes of modalities are highlighted below.

Colonoscopy

With SimCRC and CRC-SPIN the efficient colonoscopy screening strategies did not change across scenarios of population colorectal cancer risk (**Appendix Tables 14.1a**, **14.1b**; **Figures 22a**, **22b**). With MISCAN, COL 50-75, 5 was not efficient at the highest assumed increase in population risk (IRR = 1.52); it was dominated by COL 45-70, 5 but was efficient at lower risk (**Appendix Table 14.1c**; **Figure 22c**). As noted above, efficiency ratios generally fell as risk increased. For example, the efficiency ratio for COL 45-70, 10 fell from 39 to 58 across models with IRR = 1, to 34 to 45 across models with IRR = 1.19, and to 29 to 40 across models with IRR = 1.52, respectively.

Stool Tests

With all models, efficient stool strategies changed across scenarios of population colorectal cancer risk. For SimCRC, FIT 50-75, 3 was only efficient at IRR = 1, and sDNA-FIT 45-70, 1 was not efficient at IRR = 1.52 (**Appendix Table 14.2a**; **Figure 23a**). For CRC-SPIN, 4 strategies (FIT 55-75, 3; FIT 55-70, 2; FIT 50-75, 3; and FIT 50-70, 2) were only efficient at IRR = 1 (no increase in risk from 1975-1979 levels) (**Appendix Table 14.2b**; **Figure 23b**). For MISCAN, 3 FIT strategies that were efficient at IRR = 1 were not efficient at higher levels of colorectal cancer risk and an additional 5 strategies were efficient at only the two lower levels of risk (IRR = 1 and IRR = 1.19), including the 2016 USPSTF-highlighted FIT strategy (FIT 50-75, 1) (**Appendix Table 14.2c**; **Figure 23c**). The efficiency ratio for FIT 45-75, 1, for example, fell as risk increased: the range across models was 16 to 18 with IRR = 1, 15 to 16 with IRR = 1.19, and 13 to 15 with IRR = 1.52.

Sigmoidoscopy

With CRC-SPIN, efficient sigmoidoscopy strategies did not change across scenarios of population colorectal cancer risk (**Appendix Table 14.3b**; **Figure 24b**). With SimCRC, SIG 45-85, 10 was only efficient at IRR = 1 (**Appendix Table 14.3a**; **Figure 24a**). Similarly, with MISCAN, SIG 55-75, 10 and SIG 55-75, 5 were only efficient at IRR = 1 (**Appendix Table 14.3c**; **Figure 24c**), and SIG 45-85, 10 was only efficient with IRR = 1 and IRR = 1.19 but not IRR = 1.52. The efficiency ratio for SIG 45-75, 5, for example, fell as risk increased: the range

across models was 22 to 29 with IRR = 1, 19 to 27 with IRR = 1.19, and 16 to 24 with IRR = 1.52.

SIG+FIT

With SimCRC and CRC-SPIN, efficient SIG+FIT strategies did not change across scenarios of population colorectal cancer risk (**Appendix Tables 14.4a, 14.4b**; **Figures 25a, 25b**). With MISCAN, 2 strategies (SIG+FIT 55-75, 10_2 and SIG+FIT 55-80, 10_2) were not efficient at IRR = 1.52 (**Appendix Table 14.4c**; **Figure 25c**).

CTC

As with sigmoidoscopy strategies, efficient CTC strategies with CRC-SPIN did not change across scenarios of population colorectal cancer risk (**Appendix Table 14.5b**; **Figure 26b**). With SimCRC, CTC 45-85, 10 was only efficient at IRR = 1 (**Appendix Table 14.5a**; **Figure 26a**). With MISCAN, both CTC 55-75, 10 and CTC 45-75, 10 were only efficient at IRR = 1 (**Appendix Table 14.5c**; **Figure 26c**), and CTC 55-80, 5 was not efficient at IRR = 1.52. The efficiency ratio for CTC 45-75, 5, for example, fell as risk increased; the range across models was 12 to 22 with IRR = 1, 11 to 21 with IRR = 1.19, and 8 to 19 with IRR = 1.52.

Colonoscopy Sensitivity

Sensitivity analyses on colonoscopy sensitivity were performed only for colonoscopy modalities alone and FIT modalities alone. For colonoscopy strategies (**Appendix Table 15.1**), efficient strategies were unchanged across all models when alternative (lower) values for the sensitivity of colonoscopy (**Table 7**) were used. For efficient colonoscopy strategies with a 10- or 15-year screening interval, changes in efficiency ratios were small. For FIT (**Appendix Table 15.2**), efficient strategies were nearly identical with use of the alternative values for colonoscopy sensitivity; the exception was that with CRC-SPIN 1 additional strategy (FIT 55-75, 3) was included as efficient (**Appendix Table 15.2b**). All changes in efficiency ratios were small. Efficiency ratios generally decreased from the base-case estimates.

Potential Implications of Adherence

Because this analysis is meant to inform population guidelines, the analyses assumed perfect adherence to screening strategies, including receipt of all screening, follow-up (i.e., for abnormal non-colonoscopy screening tests), and surveillance tests in order to predict the maximum achievable benefit for each strategy. In practice, such high adherence is not observed.[17] Because of the complexities and uncertainties of long-term adherence rates, we did not simulate scenarios of imperfect adherence. Instead, we highlight the potential implications of non-adherence.

There are at least 3 different types of non-adherence associated with colorectal cancer screening: initial screening, repeat screening, and follow-up colonoscopy. Below, we discuss evidence available related to each type of screening failure, and plausible ways to consider the effect of non-adherence on outcomes.

Screening Initiation

Adherence to initial screening, also referred to as screening uptake, is arguably the most important type of adherence in terms of its effect on health benefits. Not initiating screening is equivalent to remaining unscreened, and results in no "screening" benefit. The effect of screening uptake on outcomes can be compared by taking a weighted average of estimated outcomes with a given screening strategy and with no screening.

The effect of delayed uptake (e.g., a person who is recommended to start screening at age 50 doesn't get her first screen until the age of 53 years) can be gleaned from the differences in estimated outcomes based on different start ages. For example, with annual FIT to age 75, delaying the start age from age 50 to age 55 could result in 3 to 6 additional diagnosed cases of colorectal cancer per 1000, 1 to 2 additional colorectal cancer deaths per 1000, and a loss of 28 to 41 LYG per 1000 (**Table 13**). Changes in outcomes with delayed screening uptake may be similar with colonoscopy screening every 10 years to age 75: a 5-year delay (i.e., starting at age 55 instead of 50) could result in 1 to 4 additional cases per 1000, 0.1 to 0.4 additional colorectal cancer deaths per 1000, and a loss of 22 to 38 LYG per 1000. Changes in outcomes associated with 5- and 10-year delays in screening initiation relative to colorectal cancer screening starting at age 45 are presented in **Appendix Table 16.1**.

Appendix G of the systematic evidence review reports wide ranges of the adherence to initial screening based on both US and non-US studies performed over the past 3 decades.[17] A population-based estimate from the Behavioral Risk Factor Surveillance System survey shows that 26% of the US population of screening age have never been screened, indicating an uptake of 74%.[99] For those who do initiate screening, the benefit depends on the adherence with repeat screening and follow-up colonoscopy (if applicable).

Repeat Screening

Once a first test is done, adherence to the recommended tests at each interval is necessary to achieve the full benefit of the screening strategy. The first screening test provides the greatest benefit compared with the magnitude of the benefit associated with subsequent screening (i.e., the estimated LYG moving from no screening to once-only colonoscopy is about 3 to 6 times greater than moving from once-only screening to twice-in-a-lifetime colonoscopy). If people do not get screened at the recommended interval but instead undergo delayed screening, the estimated benefit of that non-adherent schedule would be similar to a strategy with the same test but with a longer interval between tests. For example, it has been estimated that if, on average, 60% to 70% of people adhere with repeat screening tests, then the benefit would be similar to a doubling of the screening interval.[100,101]

We found that, for example, extending the interval for FIT 50-75 from 1 to 2 years could result in 9 to 11 additional diagnosed cases of colorectal cancer per 1000, 3 additional colorectal cancer deaths per 1000, and a loss of 33 to 37 LYG per 1000 (**Table 14**). When the interval is extended from 1 to 3 years, there could be as many as 14 to 19 additional diagnosed cases of colorectal cancer per 1000, 5 to 6 additional colorectal cancer deaths per 1000, and a loss of 60 to 65 LYG per 1000. For colonoscopy screening from ages 50 to 75, extending the interval from 10 to 15 years could result in 3 to 5 additional diagnosed cases of colorectal cancer per 1000, 1 to 2

additional colorectal cancer deaths per 1000, and a loss of 12 to 22 LYG per 1000. If the interval is extended such that only 1 colonoscopy is performed, the changes could be considerably larger: 15 to 22 additional diagnosed cases of colorectal cancer per 1000, 6 to 9 additional colorectal cancer deaths per 1000, and a loss of 53 to 87 LYG per 1000. Changes in outcomes associated with extending the screening interval for strategies with screening beginning at age 45 are presented in **Appendix Table 16.2**.

Appendix G of the systematic evidence review reports limited data on adherence with repeated tests in the short term.[17] One study found adherence over the subsequent 3 years after the initial FIT to be as high as 75.3% to 86.1%.[102]

Follow-Up Colonoscopy

Most tests other than colonoscopy require adherence with a colonoscopy following a positive screen in order for that screen to have any benefit. If a test is done that requires follow-up colonoscopy and the follow-up test is never done, then it is equivalent, benefit-wise, to the screening test not being done in the first place. This type of adherence impacts non-colonoscopy test strategies. Alternatively, the follow-up could just be delayed. For example, a delay of 1 year in getting a follow-up colonoscopy after a positive FIT is estimated to reduce life years gained by 2.0% to 9.5%.[103,104]

A recent systematic review reported adherence to follow-up colonoscopy of 80.4%.[105]

Much of the evidence on adherence assesses whether the test recommended at a particular time was performed at or near that time. If it was not performed at or near that time, then the alternative is either that the test was never performed again or that it was just delayed, which would have different implications. Very little information is available about screening behaviors needed for models to simulate the impact of these behaviors on efficacy. This information includes whether screening delays are clustered within individuals and how delays vary across screening tests.

Chapter 4. Discussion

The goal of this decision analysis was to estimate how the benefits, burden, and harms of screening average-risk, asymptomatic adults for colorectal cancer vary by class of screening modality, screening interval, age to begin screening, and age to end screening. The decision analysis examined a large number of screening strategies, with 8 screening modalities, 3 ages to begin screening, 4 ages to end screening, and multiple screening intervals. Analyses were also carried out under 3 assumptions about population risk of colorectal cancer, and they examined the sensitivity of results to reductions in the sensitivity of colonoscopy and the potential for targeted screening strategies based on race and sex.

This analysis is not intended for individual-level decision-making, which would consider information about personal risk and patient preferences that would likely affect screening behavior. Previous model-based analyses have evaluated screening strategies tailored to individuals at increased risk due to family history,[106] genetics,[107] and other reasons,[108] comorbidity status,[109] and screening history.[110]

Summary of Findings

Compared to no screening, all of the colorectal cancer screening strategies evaluated by the models were estimated to yield substantial increases in both life expectancy (171 to 381 LYG per 1000 40-year-olds) and quality-adjusted life expectancy (144 to 358 QALYG per 1000) and substantial reductions in the estimated lifetime number of colorectal cancer cases (16 to 74 cases averted per 1000) and colorectal cancer deaths (15 to 32 deaths averted per 1000).[⌗⌗] In consultation with USPSTF members, this report focuses on the estimated number of LYG as the primary measure of the benefit of screening, although numbers of other events are also provided. Across screening strategies estimated LYG from screening were lowest with FIT 55-70, 3 and highest with COL 45-85, 5. The estimated number of colonoscopies needed to achieve these benefits was generally lowest for FIT and highest for colonoscopy, and strategies with fewer colonoscopies also resulted in fewer harms from screening. Although non-colonoscopy screening modalities do not require screening colonoscopies, they still require colonoscopies for follow-up of positive tests, for surveillance, and for detection of colorectal cancer by symptoms. The estimated number of such colonoscopies varied by modality and ranged from 0.6 to 2.0 per person with FIT, 1.1 to 2.9 per person with sDNA-FIT, 0.9 to 2.2 per person with sigmoidoscopy, and 0.9 to 1.9 per person with CTC.

Efficient screening strategies within a class of screening modality are those that best balance the burden and benefits of screening, with burdens measured in terms of the estimated number of colonoscopies. This decision analysis focused on describing screening strategies that were efficient based on estimated LYG, and not on identifying a best set of strategies. Efficiency ratios were only used to compare strategies within a class of screening modality. Many screening

[⌗⌗] Ranges exclude HSgFOBT, once-only colonoscopy, once-only sigmoidoscopy, and colonoscopy preceded by and followed by annual FIT; estimated outcomes for these strategies are presented in **Appendixes 4-8**, respectively.

strategies were efficient across classes of screening modalities, and with some exceptions, results were similar across models. Across three scenarios for increasing population risk of colorectal cancer, most of the strategies that were efficient across all 3 models specified screening beginning at age 45.

Table 15 summarizes the strategies that were efficient across all 3 models with estimated LYG as the measure of the benefit of screening and IRR of 1.19. [Efficient strategies with estimated QALYG as the measure of benefit were nearly identical to those identified based on estimated LYG, and findings were generally robust across the 3 scenarios of population risk of colorectal cancer.] **Table 15** also includes the strategies highlighted by the USPSTF in 2016, for comparison. Summarizing across the 57 efficient strategies is challenging, but we offer some observations below.

The estimated numbers of colonoscopies and colonoscopy complications were highest with colonoscopy screening alone (as many as 6.5 to 6.8 lifetime colonoscopies per person). They were generally lowest with FIT (at most 1.8 to 2.0 colonoscopies per person), followed by CTC and sigmoidoscopy (at most 1.8 to 1.9 and 1.8 to 2.2 lifetime colonoscopies per person, respectively). Among the stool-based options, the estimated number of colonoscopies was higher with sDNA-FIT compared with FIT alone (at most 2.7 to 2.9 vs 1.8 to 2.0 colonoscopies per person). The risk of serious complications was generally low (at most 22 per 1000 with COL 45-85, 5). Even the most intensive sigmoidoscopy -alone strategy (SIG 45-85, 5) generally had lower estimated LYG and more estimated colorectal cancer deaths than efficient strategies with other classes of modalities. Estimated LYG and colorectal cancer deaths with SIG 45-85, 5 were comparable to those estimated for biennial FIT from age 45 to age 75, 80, or 85.

With the exception of colonoscopy strategies with a 5-year screening interval, for each colonoscopy screening strategy that was efficient with all 3 models there is generally a strategy from each class of modality (potentially with the exception of sigmoidoscopy alone) that yields similar estimated LYG, colorectal cancer deaths, and/or number of complications. For example, strategies with similar estimated LYG and colorectal cancer deaths per 1000 as COL 45-70, 10 (292 to 361 LYG; 4-10 colorectal cancer deaths) include:

- FIT 45-75, 1 (291 to 348 LYG; 6-10 colorectal cancer deaths);
- FIT 45-80, 1 (300 to 355 LYG; 5-9 colorectal cancer deaths);
- SIG+FIT 45-75, 10_2 (294 to 354 LYG; 5 to 9 colorectal cancer deaths);
- SIG+FIT 45-80, 10_2 (296 to 357 LYG; 4 to 9 colorectal cancer deaths);
- SIG+FIT 45-85, 10_2 (298 to 358 LYG; 4 to 8 colorectal cancer deaths);
- SIG+FIT 45-75, 10_1 (304 to 363 LYG; 4 to 9 colorectal cancer deaths);
- CTC 45-80, 5 (288 to 358 LYG; 4 to 9 colorectal cancer deaths);
- CTC 45-85, 5 (290 to 359 LYG; 4 to 9 colorectal cancer deaths).

A similar exercise can be undertaken for other strategies that are of particular interest.

Finally, the majority of efficient strategies with all 3 models were those with screening starting at age 45 (41/49). With the exception of the efficient FIT strategies, the efficiency ratio generally increased sharply among strategies in which screening continues beyond age 75 (assuming full adherence with prior screening), indicating an increasing number of colonoscopies is needed for

a limited increase in LYG. For colonoscopy, there is a sharp increase in efficiency ratio with strategies involving 5-yearly screening, while with stool-based screening the efficiency ratio almost quadruples for strategies involving sDNA-FIT. An alternative way to present the results is in terms of the additional days of life gained per additional colonoscopy performed. Compared to the next-best option, an estimated 8 to 11 additional days of life are gained per additional colonoscopy performed with COL 45-70, 10, and an estimated 3 to 7 days are gained per additional colonoscopy performed with COL 45-75, 10. The estimated number of additional days gained per additional colonoscopy approaches 0 with COL 45-85, 10, or when the colonoscopy screening interval is every 5 years.

Scenario analyses examined whether the balance of colonoscopy burden and LYG from screening differed by race and sex. As noted in **Analyses by Race and Sex**, the analyses were limited to Black and White race and assumed racial differences in only all-cause mortality[53] and in survival from colorectal cancer following diagnosis.[48] Despite the assumption that the risk of developing adenomas and their progression to colorectal cancer in the absence of screening was the same among Black adults and White adults, the models did not estimate the same lifetime risk of colorectal cancer diagnosis by race. Due to higher age-specific rates of death among Black adults compared to White adults,[53] the models estimated that a smaller proportion of an initial cohort of 40-year-old Black adults would be alive at older ages where the risk of colorectal cancer diagnosis is highest, and therefore the estimated lifetime risk of colorectal cancer diagnosis was lower among a cohort of Black adults compared to a cohort of White adults by sex (**Table 10**). Among Black males, this lower estimated lifetime incidence of colorectal cancer compared to White males also resulted in a lower estimated lifetime risk of colorectal cancer death, despite the higher risk of dying from colorectal cancer among Black colorectal cancer patients compared to White colorectal cancer patients.[48] Among Black females, the lower estimated lifetime incidence of colorectal cancer was offset by the higher risk of colorectal cancer death among Black colorectal cancer patients compared with White colorectal cancer patients, resulting in a slightly higher estimated lifetime risk of colorectal cancer death among a cohort of Black females compared to a cohort of White females.

Despite these differences in the absence of screening, the models estimated that there was little advantage to customizing screening by race and sex; while the estimated LYG from screening were lower for Black males compared with White males (but similar for Black females and White females), efficient strategies identified for each race-sex group were generally the same as those for the population as a whole (**Appendix Figures 11.1 and 11.2**), and efficiency ratios were similar by race for each sex (**Tables 11-12**). As noted in **Analyses by Race and Sex**, while access to screening is thought to be the largest driver of Black-White differences in colorectal cancer incidence, differences in biology[111,112] and/or risk factors[113,114] may also contribute. In that event, it is possible that efficient strategies and their efficiency ratios would vary by race.

The model finding that, in the absence of screening, the incidence of colorectal cancer is lower in Black adults than in White adults may appear to be inconsistent with SEER data that show higher incidence of colorectal cancer among Black adults.[115] However, SEER data are in the presence of screening, while the model estimates are in the absence of screening. It is important to consider historical disadvantages of Black adults especially as it relates to receipt of medical care. Black adults are less likely to be up-to-date with colorectal cancer screening recommendations, to

undergo follow-up colonoscopy after a positive non-colonoscopy screening test, and to be screened by endoscopists with higher adenoma detection rates.[74]

Similar to the finding that efficient strategies were similar by race and sex, scenario analyses demonstrated that efficient strategies were similar across 3 scenarios for population risk of colorectal cancer, including one in which the assumed risk increase is less conservative than the assumption for the base-case analysis. However, at the highest level of risk increase evaluated (IRR of 1.52), efficiency ratios were generally lower than for the base-case analysis, indicating that at this rate of risk increase, more intensive strategies could result in a similar balance between colonoscopy burden and LYG as less intensive strategies in the base-case.

Based on sensitivity analysis, we did not find evidence that reduced sensitivity of colonoscopy would result in different efficient colonoscopy and FIT strategies.

Across the 3 models, the estimated benefits and colonoscopy burden of screening were generally highest with SimCRC and lowest with MISCAN, with results from CRC-SPIN falling in between. The SimCRC and CRC-SPIN models estimated that most (and often, nearly all) of the efficient strategies would begin at age 45. While the strategies starting at age 45 that were efficient with SimCRC and CRC-SPIN were generally also efficient with MISCAN, MISCAN found strategies with screening beginning at age 50 or even at age 55 were also efficient. Based on prior extensive work to understand the differences in the models,[76,77] we believe that differences in outcomes across models are primarily attributable to differences in adenoma dwell times. As explained in the section "**Natural History Component**", MISCAN simulates a shorter adenoma dwell time than the SimCRC and CRC-SPIN models (**Table 2**), which arises from the assumption that some adenomas are non-progressive. The probability that an adenoma in MISCAN is progressive increases with the age at adenoma initiation (see **Progression to Preclinical Colorectal Cancer**). CRC-SPIN also allows the risk of adenoma progression to be a function of the age at adenoma initiation, but all adenomas in CRC-SPIN have the potential to progress. In SimCRC, the risk of progression is based on the current age, not the age at adenoma initiation, and as with CRC-SPIN, all adenomas have the potential to progress. We suspect that the smaller incremental estimated benefit from a first screen with adenoma removal at age 45 compared to a first screen with adenoma removal at age 50 in MISCAN compared to the other 2 models is attributable to MISCAN's assumption that an adenoma that forms between ages 45 and 50 is more likely to be progressive and has a higher risk of progression than an adenoma that forms before age 45.

Unlike the age to begin screening, there were no consistent patterns across models in the age to end screening. For colonoscopy screening, efficiency ratios were relatively high when screening was extended to age 80 or 85 (>169 additional colonoscopies per LYG; **Table 15**), assuming full adherence with prior screening; efficiency ratios were considerably lower for the efficient FIT strategies with all 3 models with screening to age 85 (< 43 additional colonoscopies per LYG). With sigmoidoscopy and CTC strategies, the efficiency ratio increased substantially when an additional screening colonoscopy was performed at age 85 (**Table 15**).

Two models (SimCRC and CRC-SPIN) found that the screening strategies highlighted by the

USPSTF in 2016 were not among the efficient options at any IRR[§§] (see **Table 9** for IRR = 1.19; the efficiency of these strategies with IRR = 1 and IRR = 1.52 can be gleaned from **Appendix Tables 14.1-14.7**). With MISCAN, all strategies highlighted by the USPSTF in 2016 were efficient options in this analysis with IRR = 1 and IRR = 1.19, with the exception of the 2 highlighted sDNA-FIT strategies; these strategies were not efficient at any of the 3 IRRs with any model. Additionally, at IRR = 1.52, FIT 50-75, 1 was no longer an efficient option with MISCAN. As summarized in **Table 15**, in the current analysis, many strategies within each class of screening modality were efficient with all 3 models; across classes of modalities, 49 strategies were efficient with all 3 models. [Note that the strategies highlighted by the USPSTF in 2016 were generally only efficient in the 2016 analysis when strategies with screening beginning at age 45 were removed from consideration – see Knudsen et al.[16] for details. Even then, the USPSTF-highlighted strategy of sDNA-FIT every 3 years was not efficient with any of the models.]

Estimation of the tradeoffs involved with starting screening at age 45 vs age 50 is challenging because multiple strategies with screening starting at age 45 are efficient (**Table 15**). **Figure 27** and **Tables 16-22** show the changes in model-estimated outcomes for the strategies highlighted by the USPSTF in 2016 if screening were to begin at age 45 instead of age 50, and **Tables 16-22** compare these changes with those from the 2016 decision analysis. Despite different assumptions about colorectal cancer risk (IRR = 1.19 vs IRR = 1), and the use of different all-cause mortality rates, different surveillance intervals, and a different version of CRC-SPIN model, the changes in model-estimated outcomes between screening at age 45 vs age 50 were similar in the current and the 2016 decision analyses. The outcomes for each screening strategy highlighted by the USPSTF in 2016 are summarized below. *All outcomes are expressed per 1000 40-year-olds.*

Colonoscopy Every 10 Years to Age 75

For colonoscopy every 10 years to age 75, lowering the age to begin screening from 50 to 45 was estimated to prevent 2 to 4 diagnosed cases of colorectal cancer and 1 to 2 colorectal cancer deaths and yield 16 to 34 additional LYG. However, it is also estimated to require 756 to 800 additional colonoscopies and result in 2 additional complications (**Table 16**).

Annual FIT to Age 75

Screening with annual FIT from ages 45 to 75 instead of from ages 50 to 75 was estimated to prevent 1 to 4 cases of diagnosed colorectal cancer and approximately 1 colorectal cancer death, and yield 17 to 33 additional LYG. It was also estimated to require 3387 to 3520 additional FITs and 175 to 205 additional colonoscopies and result in <1 additional complication (**Table 17**).

[§§] These strategies were not efficient with SimCRC or CRC-SPIN in 2016 when strategies with screening beginning at age 45 were included in the analysis; with the exception of sDNA-FIT 50-75, 3, all recommended strategies in 2016 were efficient in all 3 models when strategies starting at age 45 were eliminated from the analysis.

Annual sDNA-FIT to Age 75

For annual sDNA-FIT to age 75, lowering the age to begin screening from 50 to 45 was estimated to prevent 1 to 4 diagnosed cases of colorectal cancer and approximately 1 colorectal cancer death. It was estimated to result in 16 to 33 additional LYG. The estimated number of additional tests were as follows: 2361 to 2425 additional sDNA-FITs and 305 to 322 additional colonoscopies. It was estimated to result in <1 additional complication (**Table 18**).

Triennial sDNA-FIT to Age 75

For sDNA-FIT every 3 years to age 75, lowering the age to begin screening from 50 to 45 was estimated to prevent 1 to 4 diagnosed cases of colorectal cancer and approximately 1 colorectal cancer death, and to yield 16 to 31 additional LYG. It was estimated to require 1166 to 1201 additional sDNA-FITs and 177 to 196 additional colonoscopies and result in <1 additional complication (**Table 19**).

Sigmoidoscopy Every 5 Years to Age 75

Lowering the age to begin 5-yearly FIT screening from age 50 to age 45 (with screening ending at age 75) was estimated to result in 1 to 3 fewer cases of diagnosed colorectal cancer, approximately 1 fewer colorectal cancer death, and 13 to 30 additional LYG. It was estimated to require 743 to 801 additional sigmoidoscopies and 170 to 192 additional colonoscopies, and result in <1 additional complication (**Table 20**).

Sigmoidoscopy Every 10 Years With Annual FIT to Age 75

For the USPSTF-highlighted strategy combining sigmoidoscopy every 10 years and annual FIT to age 75, the estimated benefits of lowering the age to begin screening from age 50 to age 45 were as follows: 2 to 4 fewer diagnosed cases of colorectal cancer; about 1 fewer colorectal cancer death; and 17 to 33 additional LYG. The estimated burdens and harms associated with this change were: 458 to 493 additional sigmoidoscopies; 3018 to 3112 additional FITs; 263 to 284 additional colonoscopies; and <1 additional complication (**Table 21**).

CTC Every 5 Years to Age 75

For CTC every 5 years to age 75, lowering the ages to begin screening from age 50 to age 45 was estimated to avert 1 to 3 diagnosed colorectal cancer cases and about 1 colorectal cancer death, yielding an estimated 14 to 31 additional LYG. It was estimated to require 798 to 806 additional CTCs and 153 to 165 additional colonoscopies and result in approximately 1 additional complication (**Table 22**).

Caution Regarding the Interpretation of Findings

It is important to remember that, with the exception of colonoscopy, all screening modalities involve additional screening procedures, some of which result in the referral to colonoscopy.

These additional non-colonoscopy screening procedures represent a screening burden and are not accounted for in the assessment of efficiency, which measures burden only in terms of the estimated number of colonoscopies. When comparing efficiency ratios across classes of modalities, it would not be appropriate to assume a colonoscopy strategy and a non-colonoscopy strategy with the same efficiency ratios are equivalent. An equivalent non-colonoscopy strategy would have a lower efficiency ratio (i.e., to account for the increased burden). How much lower is a matter of judgement.

Comparison With the 2016 Decision Analysis

A key change from the 2016 decision analysis of colorectal cancer screening for the USPSTF to the current decision analysis is the assumption of increasing population risk of colorectal cancer in the current base-case analysis (IRR of 1.19) vs stable population risk in the 2016 analysis (IRR of 1). However, as shown in **Figures 22-26**, efficient strategies were similar across risk scenarios, as were efficiency ratios (**Appendix Tables 14.1-14.7)**. The systematic evidence review found few new studies informing test performance characteristics,[17] so inputs for test sensitivity and specificity were similar to those in the prior analysis. It is therefore not surprising that the findings from this decision analyses are similar to those of the 2016 decision analysis for the USPSTF. In both the current and the 2016 decision analyses, all 3 models found that when the estimated number of LYG is used as the measure of screening benefit (estimated number of LYG was the only measure of benefit used in the 2016 analysis), efficient strategies were primarily those with screening beginning at age 45. In 2016, there was limited evidence to support screening before age 50. While data on the yield of screening among asymptomatic adults aged 45 to 49 remain sparse,[116-118] there is now clearer evidence that colorectal cancer incidence in the US is increasing before age 50,[18,65-71] and that this increase is likely a cohort effect that will be carried forward with each generation as they age.[18]

As in 2016, the models continue to differ in terms of the magnitude of the estimated benefit from starting screening at age 45 instead of at age 50; estimated benefits from starting at age 45 are greater with SimCRC and CRC-SPIN than with MISCAN. In 2016 we used an algorithm to select sets of recommendable strategies from the efficient options for each class of screening modality. Doing so made it relatively easy to identify and quantify the differences in estimated outcomes across strategies with different ages to begin and end screening. Because recommending strategies is the role of the USPSTF, current analyses identify the efficient options with each class of modality but do not include further analyses to identify "model-recommendable" strategies. In addition, the current analysis compares a much larger number of strategies than the 2016 report, and each can be evaluated on several dimensions (i.e., estimated life expectancy, colorectal cancer deaths averted, numbers of colonoscopies and harms). This makes it difficult to identify and communicate key differences between strategies.

As in 2016, we found that efficient stool testing strategies are generally those that involve FIT (11/16 efficient stool-based strategies across all three models, **Table 15**). While annual sDNA-FIT (referred to as "FIT-DNA" in the 2016 analyses) strategies are also among the efficient strategies, the estimated efficiency ratios for those strategies are high compared to those of FIT. The sensitivity of sDNA-FIT for adenomas by size and for colorectal cancer is higher than that of FIT (**Table 7**). As a result, annual sDNA-FIT is estimated to yield more LYG and to prevent

more colorectal cancer deaths than annual FIT. However, sDNA-FIT has lower specificity than FIT, so the additional estimated LYG with sDNA-FIT come with more colonoscopies − colonoscopies for follow-up of true-positive and of false-positive sDNA-FITs, and colonoscopies for surveillance of persons with detected adenomas. The high efficiency ratios for sDNA-FIT strategies imply that the estimated LYG from the superior sensitivity of sDNA-FIT are small relative to the large increase in the estimated colonoscopies due to the lower specificity. sDNA-FIT strategies with a 3-year interval are not efficient; this finding indicates that repeated FIT screening may be more effective than 3-yearly sDNA-FIT while requiring fewer colonoscopies. This finding is the same as in the 2016 decision analysis.

In both the current and the 2016 decision analyses, we found that older ages to end screening could be supported for stool tests. For example, in the current analyses, efficiency ratios for annual FIT strategies with screening from age 45 increased slowly as the age to end screening was extended from age 75 to age 80 and to age 85 (efficiency ratios 15-16, 14-27, and 19-43 additional colonoscopies per LYG, respectively, **Appendix Table 10.2**); for comparison, efficiency ratios for 10-yearly colonoscopy strategies with screening from age 45 often more than doubled as the age of the last scheduled screening colonoscopy increased from 65, to 75, to 85 (efficiency ratios 34-45, 52-112, and 227-828 additional colonoscopies per LYG, respectively, **Appendix Table 10.1**). Note that strategies with annual FIT from ages 50 to 80 or 85 were dominated with SimCRC and CRC-SPIN but not with MISCAN, and with colonoscopy, strategies with 10-yearly screening from age 50 to age 80, which is the same as to age 85, were also dominated with SimCRC and CRC-SPIN but not with MISCAN. It is important to remember that the FIT strategies require FITs that are not accounted for in the efficiency assessment.

As in the 2016 decision analysis, estimated outcomes from the SimCRC and CRC-SPIN models were very similar. All 3 models estimated similar relative performance across screening strategies. In some cases, findings differed for the MISCAN model, which posits a shorter adenoma dwell time (**Table 2**).

The models continued to differ regarding COL 45-75, 15. A key finding from the 2016 decision analysis was that with 2 models (SimCRC and CRC-SPIN) COL 45-75, 15 was an efficient screening strategy that had estimated LYG slightly higher than the estimated LYG with COL 50-75, 10, while with MISCAN, COL 45-75, 15 was strongly dominated by COL 50-75, 10, that is, it was estimated to provide fewer LYG and require more colonoscopies (see **Figure 10** for an example). This finding is the same in the current decision analysis (**Figure 12**). However, in the current decision analysis, both strongly- and weakly-dominated strategies may be deemed near efficient, provided they meet the benefit criterion (e.g., within 3 days of life gained per person of the efficient frontier); with MISCAN, the COL 45-75, 15 is strongly dominated and has estimated LYG within 3 days per person of the efficient frontier, so is near efficient. In the 2016 analysis, only weakly dominated strategies were eligible for near-efficient status and as a result, COL 45-75, 15 was not included as a near-efficient option with MISCAN.

Finally, in both analyses, we found that efficiency ratios for strategies with colonoscopy screening every 5 years were generally high (≥84 additional colonoscopies per LYG, **Appendix Table 10.1**), as were efficiency ratios for strategies with annual sDNA-FIT, relative to screening with annual FIT (**Appendix Table 10.2**).

For outcomes assessed in both the 2016 and the current decision analysis, there were no major differences in findings.

Comparison With Decision Analysis for the ACS

The ACS requested 2 decision analyses from CISNET to evaluate the age to begin colorectal cancer screening for their 2018 colorectal cancer screening guidelines. These analyses focused on the rising colorectal cancer incidence observed in recent birth cohorts (performed by MISCAN)[22] and on analyses by race and sex (performed by MISCAN and SimCRC).[22,23] Citing the studies by Siegel et al.[18,119] and the CISNET decision analyses,[22,23] the ACS gave a qualified recommendation that average-risk adults, regardless of sex or race, begin screening for colorectal cancer at age 45 years.[120] The current analysis, based on all 3 CISNET models, similarly finds that beginning screening at age 45 years provides an efficient balance of the estimated colonoscopies required (a measure of the burden of screening that correlates with harms) and LYG, for the asymptomatic average-risk population as a whole and by race and sex.

While analyses reached similar conclusions, there are several noteworthy differences (summarized in **Appendix 17**). First, there is uncertainty about how much risk has increased, and the ACS and USPSTF analyses made different assumptions that were incorporated into model calibration to colorectal cancer incidence. Due to differences in SEER case selection (i.e., exclusions or inclusion of carcinoid tumors and others that are not the primary target of colorectal cancer screening) and in methods for estimating the increase in risk (see **Appendix 1**), the USPSTF analyses use a lower elevation in risk (IRR of 1.19 in base-case analyses, vs 1.59 in the ACS analyses), and this resulted in a lower estimated absolute benefit of screening. However, the strategies with screening beginning at age 45 were predominant among the efficient strategies in both the current USPSTF and the ACS analyses. Additionally, in sensitivity analyses we found that efficient screening strategies and efficiency ratios were robust to a wide range of assumptions about the magnitude of the increase in colorectal cancer risk. For example, 10-yearly colonoscopy screening from ages 45 to 75 years (COL 45-75, 10), compared to 10-yearly colonoscopy from ages 50 to 75 years (COL 50-70, 1), was estimated to result in 34, 32 and 16 additional LYG and 798, 800 and 756 additional colonoscopies per 1000 unscreened 40-year-olds for SimCRC, CRC-SPIN and MISCAN, respectively. In the analysis for the ACS,[22] MISCAN estimated a difference of 25 LYG and 810 colonoscopies, resulting in a slightly more favorable balance between the burden and benefits of screening initiation at age 45 years than MISCAN's current estimate. However, the current analysis demonstrates that MISCAN is the most conservative model when estimating the burden-to-benefit ratio of screening initiation at age 45 years (**Tables 16-22**).

Second, the differences in outcomes by race and sex in this analysis were smaller than in the ACS analysis.[2] These differences can be explained by the assumptions about the underlying risk of colorectal cancer by race across the two analyses. While both the ACS and USPSTF analyses incorporated sex- and race-specific estimates of relative survival after diagnosis with colorectal cancer[48] and sex- and race-specific all-cause mortality rates,[53] only the analyses for the ACS allowed for a difference by race in the underlying risk of developing colorectal cancer. As noted in the section **Analyses by Race and Sex**, we reviewed the literature on race and colorectal cancer immediately prior to performing this analysis for the USPSTF. We concluded that the

primary driver of differences in colorectal cancer incidence and mortality by race is access to screening and subsequent care, rather than biological differences in natural history,[74] and therefore did not allow for differential risk of adenoma onset or colorectal cancer incidence by race in the USPSTF analyses. The model-estimated outcomes from the USPSTF analysis likely better reflect the benefits, harms, and burden of colorectal cancer screening by race and sex. Still findings are in line, because the race-specific analysis for ACS incorporating the increase in CRC risk also showed that efficient screening recommendations were similar for different races and hence the ACS did not issue differential screening recommendations by race.[120]

Third, more screening strategies were evaluated in the USPSTF analysis; the hybrid strategies (screen first with FIT, then change to COL, and vice-versa), once-only strategies, and strategies that end screening at age 70 years were not included in the analyses for the ACS. Furthermore, the USPSTF analysis included strategies with screening starting at ages 45, 50, and 55 years, whereas the comparable analysis for the ACS evaluated start ages of 40, 45, and 50 years.[22] The set of strategies considered affects estimated efficiency ratios for a given modality, and several of the strategies included in the USPSTF, but not ACS analyses were efficient options. For example, a strategy included in the USPSTF analysis that was found to be efficient with all 3 models is colonoscopy screening at ages 45, 55 and 65 years (COL 45-70, 10). This strategy was not included in the ACS analysis. As a result, the efficiency ratios for 10-yearly colonoscopy screening from ages 45 to 75 years (COL 45-75, 10) were higher in the current analysis, as the estimated LYG and number of colonoscopies were being compared to a different strategy (10-yearly colonoscopy screening from ages 45 to 70 years in current analysis vs 10-yearly colonoscopy screening from ages 50 to 75 years in ACS analysis).

Strengths of the Modeling

Although randomized controlled trials are the gold standard for determining the effectiveness of screening, they have their limitations. They are expensive and time consuming and therefore limited in the number of strategies that can be evaluated. Decision models provide a useful tool to extrapolate evidence from randomized trials and project outcomes of screening strategies that vary by age to begin, age to end and interval of screening, as well as explore new evidence on the natural history such as the increase in cancers observed among recent birth cohorts. The microsimulation models synthesize available evidence about the natural history of developing adenomas and subsequent progression to colorectal cancer and incorporate the evidence available from randomized trials to determine the effect of alternative screening strategies on colorectal cancer incidence and mortality.

We used 3 distinct simulation models to estimate benefits, burden, and harms of alternative screening strategies. Each model is based on different assumptions about the adenoma-carcinoma sequence, though all are calibrated to similar data on adenoma prevalence and cancer incidence,[76] with the latter excluding carcinoid tumors and others in the colon and rectum that are not the primary target of colorectal cancer screening. The models have a range of differences (e.g., in dwell times, size and location of adenomas, progressive vs non-progressive adenomas, continuous vs categorical adenoma size), which provide a range of estimated outcomes that reflect a sensitivity analysis of the different underlying model assumptions. The similar relative estimated outcomes across classes of screening modalities and similar rankings of strategies

within classes of screening modalities across the 3 models demonstrate the robustness of the findings. Differences in relative estimations of screening effectiveness are most influenced by the dwell times associated with each model. Longer dwell times correspond to longer periods of time during which screening can identify and remove preclinical lesions (adenomas and preclinical colorectal cancer). Differences in the estimated distribution of adenomas by location (**Figure 3**) have the biggest effect on the model-estimated effectiveness of strategies involving sigmoidoscopy alone. For example, with MISCAN, 63% of adenomas are estimated to be within reach of the sigmoidoscope, and the sigmoidoscopy strategy highlighted by the USPSTF in 2016 (**Table 20**) is estimated to yield 90% of the estimated LYG from the USPSTF-highlighted colonoscopy strategy (**Table 14**). The estimated proportion of adenomas within reach of the sigmoidoscope is lower with SimCRC and CRC-SPIN (38% and 45%, respectively), as are the relative estimated LYG of the highlighted sigmoidoscopy strategy compared to the highlighted colonoscopy strategy in 2016 (83% for both models).

Limitations of the Modeling

Despite the strengths of modeling, some limitations are noteworthy.

We did not include some tests that have been used for colorectal cancer screening. One such test is the low-sensitivity fecal occult blood test, Hemoccult II® (Beckman Coulter; Brea, CA), which, in consultation with USPSTF members, we excluded due to the availability of similar tests with better sensitivity. [Hemoccult II was also excluded from the 2016 decision analysis.] For HSgFOBT (a similar test with better sensitivity) we only present results in **Appendix 4** due to the high degree of uncertainty in its test characteristics and the fact that FIT is easier to administer and has better test characteristics.[17] In addition, we did not evaluate the blood-based methylated septin 9 DNA test, which has only been FDA-approved for individuals not willing to do any of the USPSTF-recommended CRC screening tests, or tests with very limited evidence among screening populations (i.e., magnetic resonance colonography and capsule colonoscopy). For tests that we did simulate, we did not carry out a complete examination of the variability and uncertainty in test characteristics, though the accompanying systematic review indicated that there was little to no evidence about the ability of screening tests to detect small (<6 mm) adenomas), and limited information about the sensitivity of tests to detect preclinical colorectal cancers.[17] If the findings for the sensitivity analysis on colonoscopy test characteristics hold for other classes of screening modalities, then the effect of uncertainty in test characteristics on model results is likely to be modest.

Although the modeled results provide a lifetime framework for evaluating benefits, burden, and harms from a program of screening, much of the empiric data on sensitivity and specificity of screening tests are based on a single round of screening with relatively short periods of follow-up. Currently, there only is long-term evidence for Hemoccult II and sigmoidoscopy, which the models have shown to successfully reproduce.[60,78,79] However, outcomes for repeat rounds of FIT and HSgFOBT have only been reported in a few small studies; these studies suggest that test performance in repeat screening is not independent as assumed in the current analysis.[121,122] Future larger studies are needed to confirm these findings so they can be used to inform model assumptions and inputs. An analysis using the MISCAN model previously showed that the effect of assuming correlation of outcomes in repeat screening rounds is likely to be modest.[121]

The models simulate the adenoma-carcinoma sequence using the size of adenomas as an indicator for advanced adenomas. The models do not explicitly simulate adenoma histology. Given the high correlation between adenoma size and histology,[123,124] the effect of this assumption is likely small. Additionally, the models do not simulate the serrated polyp pathway,[34,35] in part due to insufficient evidence on the prevalence of serrated polyps by age and location, their malignant potential, and the ability of screening tests to detect them. A modeling study by Greuter et al.[125] assessed the effect of the serrated polyp pathway on screening effectiveness and found very little difference in results between a model assuming 0% vs 30% of cancers arise from this pathway. Analyses with an expanded version of the MISCAN model that included a first exploratory serrated polyp pathway also showed that inclusion of the serrated pathway had limited effect on the optimal screening strategies.[106] More information is needed to fully incorporate this pathway into the models.

We assumed that the current generation of 40-year-olds will carry forward the same elevated disease risk as they age, and that the increase in colorectal cancer incidence is caused by an increase in adenoma risk. Although the increasing background risk is likely a cohort effect that will be carried forward with this generation as they age,[18] it is unlikely that it will be observed in colorectal cancer incidence data, especially at ages ≥55 years, because it is counteracted by the increased uptake of screening. Furthermore, it is not known whether the increase in colorectal cancer incidence is caused by an increase in adenoma risk, a faster adenoma progression to malignancy, or some combination of the two. The effects of each of these assumptions were evaluated in MISCAN's analysis for the ACS;[22] the model recommendation of screening initiation at age 45 years was robust. Future research is needed to determine the cause and carcinogenic pathway of the increase in colorectal cancer incidence.

In analyses by race and sex we assumed that the natural history of colorectal cancer does not vary by race. This assumption was based on a comprehensive review of the literature that found that the primary driver of differential risks by race is access to care, not biological differences in natural history.[74] This assumption is also supported by the recently-published findings from the Southern Community Cohort Study[75] (see the section **Analyses by Race and Sex** for more details on the findings of these studies). While differences in biology[111,112] and/or risk factors[113,114] may also contribute to Black-White differences in colorectal cancer incidence and mortality rates, mounting evidence suggests that the magnitude is likely small relative to the role of access to screening[126-128] and treatment.[129,130]

We expressed results using 3 different metrics of efficiency, differing with respect to the measure of benefit. When the estimated number of LYG (or QALYG) is used as a measure of benefit, screening strategies beginning at age 45 years mostly dominate the efficient frontiers, whereas when using the estimated number of deaths averted, strategies that begin screening at ages 50 or 55 years are also efficient. The advantage of using the estimated number of deaths averted as the measure of benefit is that patients and clinicians find it easier to interpret.[131] However, this measure does not tell us how premature the avoided death would have been.[132] Using estimated LYG as a measure of benefit accounts for a larger gain in life expectancy from, for example, preventing a colorectal cancer death in a 45-year-old individual compared to a 75-year-old individual. To provide guidance with interpretation, we also expressed the LYG from each screening strategy in terms of the estimated number of days of life gained per person.

We did not perform analyses to identify the optimal ages to begin and end screening among all possible ages to begin and end. In consultation with Task Force members, analyses were limited to 3 ages to being screening (45, 50, and 55) and 4 ages to end screening (70, 75, 80, and 85). It is possible that strategies with screening starting prior to age 45 would also be efficient options. Analysis performed by MISCAN for the 2018 ACS colorectal cancer screening recommendations included strategies with screening beginning at age 40, 45, and 50.[22] Although screening strategies starting at age 40 were efficient, there were diminishing returns from lowering the age to begin screening, and the estimated benefits of starting at age 40 rather than at age 45 were small. For example, for colonoscopy strategies that involve 4 screening colonoscopies at 10-year intervals (i.e., COL 40-70, 10; COL 45-75, 10, and COL 50-80, 10), starting at age 45 rather than at age 50 were estimated to increase LYG by 5%, whereas starting at age 40 instead of at age 45 was estimated to increase LYG by 2%.

We did not perform a comprehensive analysis directly comparing all available screening strategies. Cost-effectiveness analysis would be a way to perform such a comprehensive analysis, however cost analysis is not part of the USPSTF evaluation. As there is no consensus on the appropriate metric to assess efficiency when costs are not considered, we used the estimated number of required colonoscopies as a proxy for harms and burden of screening. Because of the required cathartic preparation and its invasive nature, colonoscopy is likely to contribute most to the burden and harms of screening. However, not all components of screening burden and/or harm are captured this way. For example, many patients may also consider collecting feces for stool testing or undergoing a sigmoidoscopy to be burdensome. Furthermore, CTC, like colonoscopy, generally requires cathartic bowel preparation and is associated with radiation exposure. Because of this, we estimated the relative efficiency of strategies *within* a class of screening modalities; we did not estimate relative efficiency *across* classes of modalities. A comprehensive analysis comparing all tests based on the estimated number of required colonoscopies would penalize colonoscopy strategies compared to strategies with other screening modalities. Future measures need to be developed that can provide a common denominator for resources other than costs that would make comparison of screening strategies across tests more informative.

Additionally, as alluded to in the limitations described above, there is uncertainty in many model inputs and assumptions, from natural history and changes in colorectal cancer risk over time to test characteristics and their correlation. Additional uncertainty not focused on here surrounds assumptions for risks of fatal and non-fatal complications, endoscopy reach, surveillance intervals (the MSTF provides ranges, rather than a single interval), and utility weights for health states. Furthermore, we did not account for increasing colonoscopy quality over time, via increasing emphasis among the gastrointestinal endoscopy community on improving adenoma detection rates,[133-139] which have been shown to inversely correlate with both interval colorectal cancer cases[133-135,137,140] and interval colorectal cancer deaths.[134,137] Similarly, we were unable to account for possible improvements in relative survival following colorectal cancer diagnosis after 2003, due to changes in the staging algorithm used by the SEER Program[49] and in the use of neoadjuvant chemotherapy over time.[50-52] We also did not perform a probabilistic sensitivity analysis (PSA) to characterize the simultaneous effect of all uncertain model parameters on the findings; high-performance computing resources would be required to perform a PSA for models of this level of complexity and an analysis of this magnitude. Instead, the effect of uncertainty in model structure and natural history parameters are explored through the use of 3 independently-

developed models, and sensitivity analysis on other key assumptions and parameters (IRR, colonoscopy sensitivity) are explored in sensitivity analysis.

Finally, it is important to remember that models only approximate reality. The models used in this report have been extensively calibrated and validated and are able to approximate observed outcomes. However, as mentioned above, there remains uncertainty about the accuracy of screening tests, which use colonoscopy as the reference standard, and the true natural history of colorectal cancer, which cannot be directly observed. In addition, simulations evaluate screening regimens that patients are unlikely to follow exactly (e.g., most patients opting for annual FIT will not be screened at exact one-year intervals). The intent of these analyses was to compare the estimated benefits (i.e., efficacy), harms, burden, and efficiency of different screening regimens, it was not to estimate the effectiveness of regimens in real-world settings. These 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, decisions that would otherwise be left to individual judgement, as that information cannot feasibly be obtained from clinical studies. Modeling studies are no substitute for empirical evidence. Instead they synthesize, build from, and extend empirical evidence to provide insights into questions about screening practices.

Conclusion

This decision analysis suggests that colorectal cancer screening may lead to sizable reductions in the lifetime risks of developing and dying from the disease and may increase population life expectancy. The models suggest that many screening strategies may provide an efficient balance of the burden and benefits of screening; these strategies encompass a range of screening modalities, intervals, and ages. However, when the benefits of screening are measured by the estimated number of LYG, most of the efficient screening strategies identified by all 3 models specified screening starting at age 45. Starting screening at age 45 was generally estimated to result in more LYG and QALYG and fewer colorectal cancer cases and deaths than similar strategies with screening starting at age 50 or age 55, albeit with a higher burden of both colonoscopy and non-colonoscopy testing and slightly higher risks of complications.

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Table 1. Comparison of Natural History Model Structures

Property	SimCRC	CRC-SPIN	MISCAN
Adenoma risk			
Mechanism	Logistic function	Poisson process	Poisson process
Risk varies:			
Randomly across individuals	Yes	Yes	Yes
Systematically with age and sex	Yes	Yes	Yes
Adenoma growth			
Mechanism	Time in each size category	Growth curve	Time in each size category
Size modeled as continuous	No	Yes	No
Risk varies:			
Randomly across individuals	Yes	Yes	Yes
Systematically with location	Yes*	Yes*	No
Transition times correlated across size categories	No	Yes	Yes
Transition to preclinical CRC			
Mechanism	Logistic function	Adenoma size at transition	Overall transition probability
Risk varies:			
Randomly across adenomas by size within individuals	Yes	Yes	No†
Systematically with:			
Sex	Yes	Yes	No
Age	Yes	Yes‖	Yes‡
Adenoma size	No	Yes	Yes
Location	Yes*	Yes*	No
Transition times correlated across preclinical stages	No	Not applicable	Yes
Transition to clinical CRC			
Mechanism	Time to transition	Time to transition	Time to transition
Transition times:			
Vary randomly across CRCs within individuals	Yes	Yes	Yes
Vary systematically with:			
Sex	No	No	Yes
Location	Yes§	Yes§	Yes§
Correlated with duration of preclinical CRC	No	No	Yes

* Varies by proximal colon, distal colon, and rectum for SimCRC and by colon and rectum for CRC-SPIN.
† The probability of transition is 0 for all non-progressive adenomas and for adenomas <6 mm, 0.3 for progressive adenomas 6 to <10 mm, and 1 for progressive adenomas ≥10 mm.
‡ The probability that an adenoma is progressive depends on age at adenoma initiation.
‖ Depends on age at adenoma initiation.
§ Varies by proximal colon, distal colon, and rectum for SimCRC and MISCAN and by colon and rectum for CRC-SPIN.

Table 2. Estimated Dwell Times Among Colorectal Cancer Cases: Mean (Interquartile Ranges) in Years Across Simulated Individuals, by Model

Dwell time component	SimCRC	CRC-SPIN	MISCAN
Adenoma onset to preclinical colorectal cancer onset (adenoma dwell time)	21.2 (12-29)	25.4 (16-33)	12.5 (4-18)
Preclinical colorectal cancer onset to colorectal cancer diagnosis (sojourn time)	4.0 (2-5)	3.6 (2-5)	4.7 (1-7)
Adenoma onset to colorectal cancer diagnosis (total dwell time)	25.2 (15-33)	29.0 (20-37)	17.2 (9-24)

Note: Dwell time is calculated for diagnosed colorectal cancers and is defined as the time from adenoma onset to symptom-detection of colorectal cancer in the absence of screening.

Table 3. Age-Adjusted Rates of Colorectal Cancer Among 20- to 44-Year-Olds by Period of Diagnosis (1975-1979 and 2012-2016) From the Surveillance, Epidemiology, and End Results Program, With and Without Adjustment for Delays in Reporting

Delay-adjustment status/ Period of diagnosis	Cases per 100,000 (95% CI)	Incidence rate ratio (95% CI)
With delay adjustment		
1975-1979	4.92 (4.74, 5.12)	--
2012-2016	6.15 (5.98, 6.32)	1.25 (1.19, 1.31)
Without delay adjustment		
1975-1979	4.94 (4.68, 5.21)	--
2012-2016	6.06 (5.84, 6.29)	1.23 (1.15, 1.31)

Table 4. Screening Strategies Evaluated by the Models

Modality	Age to begin screening, y	Age to end screening*, y	Screening interval, y	Number of (unique) runs
Strategies with once-only screening†				
COL	45, 50, 55, 60, 65	--	Once only	5 (5)
SIG	45, 50, 55, 60, 65	--	Once only	5 (5)
Strategies with repeated screening using the same modality/modalities				
COL	45, 50, 55	70, 75, 80, 85	5, 10, 15	36 (26)
CTC	45, 50, 55	70, 75, 80, 85	5, 10	24 (20)
SIG	45, 50, 55	70, 75, 80, 85	5, 10	24 (20)
FIT	45, 50, 55	70, 75, 80, 85	1, 2, 3	36 (36)
HSgFOBT†	45, 50, 55	70, 75, 80, 85	1, 2, 3	36 (36)
sDNA-FIT	45, 50, 55	70, 75, 80, 85	1, 2, 3	36 (36)
SIG + FIT‡	45, 50, 55	70, 75, 80, 85	10 (SIG) + 1 (FIT), 10 (SIG) + 2 (FIT)	24 (24)
Strategies with screening using different modalities by age†				
Annual FIT 45-49y then COL	50 (COL)	70, 80 (COL)	10 (COL)	2 (2)
Annual FIT 50-54y then COL	55 (COL)	75, 85 (COL)	10 (COL)	2 (2)
COL at 45y then FIT	55 (FIT)	70, 75, 80, 85 (FIT)	1 (FIT)	4 (4)
COL at 50y then FIT	60 (FIT)	70, 75, 80, 85 (FIT)	1 (FIT)	4 (4)
Additional strategy				
No screening	--	--	--	1 (1)
TOTAL NUMBER OF STRATEGIES FOR BASE-CASE ANALYSIS				**239 (221)**

FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; HSgFOBT – high sensitivity guaiac-based fecal occult blood test (i.e., Hemoccult SENSA); sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test, i.e., Cologuard); SIG – sigmoidoscopy without biopsy; CTC – computed tomographic colonography; COL – colonoscopy.

* Age to end screening is the last age at which screening happens; screening may happen during this age but no later.

† Outcomes are included in **Appendix 4** (HSgFOBT), **Appendix 5** (once-only colonoscopy), **Appendix 6** (once-only sigmoidoscopy), **Appendix 7** (annual FIT then 10-yearly COL), and **Appendix 8** (once-only COL, then annual FIT).

‡ If performed at the same time, assume FIT is performed first, and SIG is only performed if FIT is negative. If FIT is positive, skip the SIG and go directly to colonoscopy.

Table 5. Strategies With Screening at the Same Ages Despite Different Ages to End Screening

Modality/ screening ages (y)	Age to begin-age to end, interval (y)		
	Strategy	**Equivalent strategy 1**	**Equivalent strategy 2**
Colonoscopy/sigmoidoscopy/CT colonography			
45, 55, 65, 75	45-75, 10	45-80, 10	--
50, 60, 70	50-70, 10	50-75, 10	--
50, 60, 70, 80	50-80, 10	50-85, 10	--
55, 65, 75	55-75, 10	55-80, 10	--
Colonoscopy			
45, 60, 75	45-75, 15	45-80, 15	45-85, 15
50, 65	50-70, 15	50-75, 15	--
50, 65, 80	50-80, 15	50-85, 15	--
55, 70	55-70, 15	55-75, 15	55-80, 15

Note: Table 4 notes that there are 239 screening strategies but only 221 unique strategies, therefore 18 strategies are effectively equivalent to another strategy with a different age to end screening. These equivalent strategies are listed here. For example, colonoscopy from ages 50-75 every 10 years and from 50-70 every 10 years both involved colonoscopy screening at ages 50, 60, and 70.

Table 6. Comparison of the 2021 and 2016 CISNET CRC Screening Analyses for the USPSTF

Characteristic	2021 analysis	2016 analysis
Simulation models	SimCRC, CRC-SPIN, MISCAN	SimCRC, CRC-SPIN, MISCAN
Cohort of interest	US average-risk 40-year-olds*	US average-risk 40-year-olds*
US life table (for other-cause mortality rates)	2017	2009
CRC incidence	Models calibrated to incidence rate ratio from SEER for 20- to 44-year-olds in 2012-2016 vs 1975-1979	Models calibrated to rates from 1975-1979 SEER data
CRC relative survival	SEER (1975-2003)†	SEER (1975-2003)†
Age to begin screening (y)	45, 50, 55	45, 50, 55
Age to end screening (y)	70, 75, 80, 85	75, 80, 85
Stool based screening modalities (intervals (y))	HSgFOBT (1, 2, 3)‡	HSgFOBT (1, 2, 3)
	FIT (1, 2, 3)	FIT (1, 2, 3)
	sDNA-FIT (1, 2, 3)	sDNA-FIT (1, 3, 5)
Other screening modalities (intervals (y))	COL (5, 10, 15)	COL (5, 10, 15)
	SIG (5, 10)	SIG (5, 10)
	SIG + FIT (10_1, 10_2)	SIG + FIT (5_2, 5_3, 10_1, 10_2)
	Not simulated	SIG + HSgFOBT (5_2, 5_3, 10_1, 10_2)
	CTC (5, 10)	CTC (5, 10)
	Once-only COL to FIT (1)	Not simulated
	Five years of FIT (1) to COL (10)	Not simulated
Management of persons with a false-positive non-colonoscopy test§	Resume screening with original modality and schedule 10 years after the false-positive test	Resume screening with original modality and schedule 10 years after the false-positive test
Age to end surveillance	85, assuming the last surveillance colonoscopy detected no adenomas	85, assuming the last surveillance colonoscopy detected no adenomas
Adherence with all procedures	100%	100%

COL – colonoscopy; CRC – colorectal cancer; CTC – computed tomographic colonography; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); HSgFOBT – high sensitivity guaiac-based fecal occult blood test; SEER – Surveillance, Epidemiology and End Results Program; SIG – sigmoidoscopy.

* Previously unscreened for colorectal cancer and free of diagnosed colorectal cancer.

† CRC relative survival estimates from models fit to SEER data from 1975-2003 that predict stage-specific survival as a function of age at diagnosis, time since diagnosis, diagnosis year, sex, and (optionally) race.[48] Rather than project continued improvements in relative survival for persons diagnosed after 2003 (the last year of diagnosis included in the statistical analysis), we fixed survival at rates predicted for cases diagnosed in 2003.

‡ Due to uncertainty in the test performance characteristics of HSgFOBT, outcomes with this modality are included in **Appendix 4**.

§ A positive non-colonoscopy test but no adenomas or CRC detected at follow-up colonoscopy.

Table 7. Screening Test Characteristics Used in the Analysis

Test characteristic	Base-case value	Source	Value in sensitivity analysis	Source
HSgFOBT (per person)		Lin, 2021[17]	Not varied	Not applicable
Specificity	0.97			
Sensitivity for adenomas 1 to <6 mm Sensitivity for adenomas 6 to <10 mm	0.05*			
Sensitivity for adenomas ≥10 mm	0.11†			
Sensitivity for colorectal cancer	0.68			
FIT (per person)		Lin, 2021[17]	Not varied	Not applicable
Specificity	0.97			
Sensitivity for adenomas 1 to <6 mm Sensitivity for adenomas 6 to <10 mm	0.07*			
Sensitivity for adenomas ≥10 mm	0.22†			
Sensitivity for colorectal cancer	0.74			
sDNA-FIT (per person)		Lin, 2021[17]	Not varied	Not applicable
Specificity	0.91			
Sensitivity for adenomas 1 to <6 mm Sensitivity for adenomas 6 to <10 mm	0.15*			
Sensitivity for adenomas ≥10 mm	0.42†			
Sensitivity for colorectal cancer	0.94			
Colonoscopy (within reach, per lesion)‡				
Specificity	0.86§	Schroy, 2013[141]	Not varied	Not applicable
Sensitivity for adenomas 1 to <6 mm	0.75	van Rijn, 2006[142]	0.69	Zhao, 2019[98]
Sensitivity for adenomas 6 to <10 mm	0.85	van Rijn, 2006[142]	0.81	Zhao, 2019[98]
Sensitivity for adenomas ≥10 mm	0.95	van Rijn, 2006[142]	0.91	Zhao, 2019[98]
Sensitivity for colorectal cancer	0.95	By assumption‖	Not varied	Not applicable
SIG (within reach, per lesion)			Not varied	Not applicable
Specificity	0.87§	Weissfeld, 2005[143]		
Sensitivity for adenomas 1 to <6 mm	0.75	By assumption¶		
Sensitivity for adenomas 6 to <10 mm	0.85	By assumption¶		
Sensitivity for adenomas ≥10 mm	0.95	By assumption¶		
Sensitivity for colorectal cancer	0.95	By assumption¶		
CTC (per lesion)		Johnson, 2008[144]	Not varied	Not applicable
Specificity	0.88**			
Sensitivity for adenomas 1 to <6 mm	--			
Sensitivity for adenomas 6 to <10 mm	0.57			
Sensitivity for adenomas ≥10 mm	0.84			
Sensitivity for colorectal cancer	0.84‖			

CTC – computed tomographic colonography; FIT – fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); HSgFOBT – high sensitivity guaiac-based fecal occult blood test; SIG – sigmoidoscopy; -- indicates sensitivity is not provided because adenoma size is smaller than the referral threshold for a colonoscopy of 6 mm.

Note: For all tests other than CTC, specificity is defined as the probability of a normal test result among persons who do not have any adenomas or colorectal cancer. The specificity of CTC is explained below.

* Sensitivity for persons with non-advanced adenomas. For persons with 1 to <6 mm adenomas, sensitivity is assumed to equal to the positivity rate in persons without adenomas. The sensitivity for persons with 6 to <10 mm adenomas was chosen such that the weighted-average sensitivity for persons with 1 to < 6 mm and with 6 to <10 mm adenoma(s) is equal to the sensitivity for non-advanced adenomas.

† Sensitivity for persons with advanced adenomas (i.e., adenomas ≥10 mm and/or adenomas with advanced histology); the studies cited did not provide sensitivity for ≥10 mm adenomas separately from advanced adenomas.

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

§ The lack of specificity with endoscopy reflects the 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.

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

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

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

Table 8. Surveillance Intervals Used in the Analysis

Finding at second-most recent colonoscopy*†	Finding at first-most recent colonoscopy*†	Interval‡ to next colonoscopy, y
No prior colonoscopy	Normal colonoscopy	See note below§
	1-2 adenomas <10 mm	7
	3-4 adenomas <10 mm	3
	5-10 adenomas <10 mm or any adenoma ≥10 mm	3
	> 10 adenomas	1
Normal colonoscopy	Normal colonoscopy	10
	1-2 adenomas <10 mm	7
	3-4 adenomas <10 mm	3
	5-10 adenomas <10 mm or any adenoma ≥10 mm	3
	> 10 adenomas	1
1-2 adenomas <10 mm	Normal colonoscopy	10
	1-2 adenomas <10 mm	7
	3-4 adenomas <10 mm	3
	5-10 adenomas <10 mm or any adenoma ≥10 mm	3
	> 10 adenomas	1
3-4 adenomas <10 mm	Normal colonoscopy	10
	1-2 adenomas <10 mm	7
	3-4 adenomas <10 mm	3
	5-10 adenomas <10 mm or any adenoma ≥10 mm	3
	> 10 adenomas	1
5-10 adenomas <10 mm or any adenoma ≥10 mm	Normal colonoscopy	5
	1-2 adenomas <10 mm	5
	3-4 adenomas <10 mm	3
	5-10 adenomas <10 mm or any adenoma ≥10 mm	3
	> 10 adenomas	1
> 10 adenomas of any size	Normal colonoscopy	5
	1-2 adenomas <10 mm	5
	3-4 adenomas <10 mm	3
	5-10 adenomas <10 mm or any adenoma ≥10 mm	3
	>10 adenomas	1

Note: Intervals are based on surveillance recommendations for individuals with a personal history of adenomas from the Multi-Society Task Force on Colorectal Cancer.[89]

* A normal colonoscopy is one in which no adenomas, sessile-serrated polyps (not currently simulated), or colorectal cancer is detected.

† This table omits the case where colorectal cancer is detected at a screening, follow-up, or surveillance colonoscopy because the CISNET colorectal cancer models do not simulate detailed events following colorectal cancer diagnosis.

‡ The Multi-Society Task Force provides a range for some intervals (e.g., the interval for 3-4 adenomas <10 mm is 3-5 years). In such cases, we selected the shortest interval provided.

§ A person whose first screening or follow-up colonoscopy is normal does not enter surveillance but instead resumes screening with the original modality 10 years after the normal colonoscopy. The exception to the 10-year waiting period is when the first colonoscopy is a screening colonoscopy with an *x*-year interval, where $x > 10$. In that case, the next colonoscopy is in *x* years.

Table 9. Efficient Frontier Status and Efficiency Ratios (i.e., Number of Additional Colonoscopies per Additional Life-Year Gained) for Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016, by Model

	Efficient frontier status (efficiency ratio*), by model		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
COL 50-75, 10	Dominated	Dominated	Efficient (ER = 28)
SIG 50-75, 5	Dominated	Dominated	Near efficient‡ (ER = 19)
SIG+FIT 50-75, 10_1	Dominated	Dominated	Near efficient‡ (ER = 18)
CTC 50-75, 5	Dominated	Dominated	Efficient (ER = 9)
FIT 50-75, 1†	Dominated	Dominated	Near efficient‡ (ER = 29)
sDNA-FIT 50-75, 1†	Dominated	Dominated	Dominated
sDNA-FIT 50-75, 3†	Dominated	Dominated	Dominated

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); ER = efficiency ratio.*

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

* Expressed as the number of additional colonoscopies per additional life-year gained.

† For FIT and sDNA-FIT, efficient frontier status and efficiency ratio did not change with inclusion of HSgFOBT. HSgFOBT was highlighted by the USPSTF in 2016 but is not included in this table.

‡ Dominated strategy with ≤3 days of life gained per person of the efficient frontier.

Table 10. Model-Estimated Lifetime Outcomes for a Cohort of 40-Year-Olds in the Absence of Colorectal Cancer Screening

	Life Expectancy (y)				Colorectal Cancer Cases per 1000				Colorectal Cancer Deaths per 1000			
Population	**SimCRC**	**CRC-SPIN**	**MISCAN**	**Mean***	**SimCRC**	**CRC-SPIN**	**MISCAN**	**Mean***	**SimCRC**	**CRC-SPIN**	**MISCAN**	**Mean***
Total population	40.2	40.2	40.2	40.2	85	77	81	81	34	32	34	33
White males	38.4	38.4	38.4	38.4	92	80	87	86	37	33	36	35
Black males	35.2	35.2	35.2	35.2	78	68	74	73	35	31	34	33
White females	42.2	42.2	42.2	42.2	78	74	77	77	31	30	32	31
Black females	40.1	40.1	40.1	40.1	72	68	71	70	32	31	33	32

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
* Mean outcome across the SimCRC, CRC-SPIN, and MISCAN models.

Table 11. Estimated Range of Outcomes Over the Lifetime of a Cohort of 40-Year-Olds Across the SimCRC, CRC-SPIN, and MISCAN Models With No Screening and With Efficient Colonoscopy Screening Strategies Among the Total Population and by Race and Sex

	Range of outcomes across models, by population group																								
	Colonoscopies per 1000					Colorectal cancer cases per 1000					Colorectal cancer deaths per 1000					Days of life gained per person					Efficiency ratio (Δ COL / Δ LYG)				
Strategy	**TP**	**WM**	**BM**	**WF**	**BF**	**TP**	**WM**	**BM**	**WF**	**BF**	**TP**	**WM**	**BM**	**WF**	**BF**	**TP**	**WM**	**BM**	**WF**	**BF**	**TP**	**WM**	**BM**	**WF**	**BF**
No screening	77-85	80-92	68-78	74-78	68-72	77-85	80-92	68-78	74-78	68-72	32-34	33-37	31-35	30-32	31-33	0	0	0	0	0					
COL 55-70, 15	2532-2630	2560-2658	2320-2411	2522-2647	2387-2503	21-40	21-44	19-39	21-38	19-35	7-11	7-12	8-12	7-10	7-11	91-104	92-106	81-96	89-98	88-99	--	--	--	--	--
COL 50-70, 15	2734-2868	2788-2929	2575-2704	2695-2855	2580-2728	18-40	17-44	15-38	19-38	17-35	6-11	6-12	6-12	6-10	7-11	96-116	98-119	87-108	94-110	93-111	6*-18	7-17	8-18	5*-17	6*-18
COL 45-70, 15	2829-3006	2903-3104	2732-2916	2768-2966	2678-2862	18-41	16-45	14-39	19-39	18-36	6-12	6-13	5-13	6-11	7-12	97-123	99-125	89-115	93-116	93-118	6-85*	7-52*	8-45*	5-26*	5-280*
COL 45-75, 15	3463-3558	3475-3620	3199-3340	3472-3567	3311-3404	14-37	13-41	12-36	15-35	14-33	4-10	4-10	4-11	4-9	4-10	103-129	104-131	93-120	99-122	99-124	38*-59*	35*-70*	33*-72*	44*-55*	40*-50*
COL 45-70, 10	3679-3782	3714-3865	3483-3623	3661-3788	3532-3650	13-37	12-40	11-35	15-35	14-32	4-10	4-10	4-10	4-9	5-10	107-132	109-134	98-123	103-125	103-127	34-45	33-49	32-49	38-55	35-50
COL 45-75, 10	4212-4300	4180-4306	3865-3988	4268-4318	4080-4129	12-34	11-38	10-33	12-32	11-30	3-8	4-9	4-9	3-8	3-8	110-135	112-137	100-126	106-128	106-130	52-112	48-143	46-142	57-100	51-93
COL 45-85, 10	4449-4566	4341-4504	3994-4136	4572-4653	4343-4419	11-34	11-38	10-33	12-32	11-30	3-8	3-9	3-9	2-7	3-8	110-135	112-137	100-126	107-128	107-130	227*-828*	228*-870*	187*-395*	270*-574*	219*-416*
COL 45-70, 5	5626-5789	5456-5689	5129-5347	5802-5917	5596-5710	10-32	10-35	9-30	11-30	10-28	3-8	3-8	3-8	2-7	3-8	116-138	118-140	106-129	112-130	112-133	84-180*	74-187	74-203	95-206	92-185*
COL 45-75, 5	6016-6235	5764-6060	5384-5653	6270-6444	6020-6186	10-31	9-34	8-30	9-29	9-27	3-7	3-8	3-8	2-7	2-7	117-139	119-141	107-130	113-131	113-134	116-344	110-450	103-414	129-322	115-299
COL 45-80, 5	6320-6581	5989-6333	5560-5867	6649-6866	6354-6558	9-30	9-33	8-29	9-28	8-26	2-7	3-7	3-8	2-6	2-7	118-139	119-141	108-130	114-131	114-134	169-736	163-1030	145-843	210-680	175-605
COL 45-85, 5	6516-6817	6122-6506	5660-5997	6909-7167	6579-6819	9-30	9-33	8-29	9-28	8-26	2-7	3-7	3-8	2-6	2-7	118-139	119-141	108-130	114-132	114-134	926-2190	934-8876	724-4827	1100-3557	863-1813

TP – total population; WM – White males; BM – Black males; WF – White females; BF – Black females; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

* Near efficient.

Table 12. Estimated Range of Outcomes Over the Lifetime of a Cohort of 40-Year-Olds Across the SimCRC, CRC-SPIN, and MISCAN Models With No Screening and With Efficient FIT Strategies Among the Total Population and by Race and Sex

	Range of outcomes across models, by population group																								
	Colonoscopies per 1000					Colorectal cancer cases per 1000					Colorectal cancer deaths per 1000					Days of life gained per person					Efficiency ratio (Δ COL / Δ LYG)				
Strategy	**TP**	**WM**	**BM**	**WF**	**BF**	**TP**	**WM**	**BM**	**WF**	**BF**	**TP**	**WM**	**BM**	**WF**	**BF**	**TP**	**WM**	**BM**	**WF**	**BF**	**TP**	**WM**	**BM**	**WF**	**BF**
No screening	77-85	80-92	68-78	74-78	68-72	77-85	80-92	68-78	74-78	68-72	32-34	33-37	31-35	30-32	31-33	0	0	0	0	0					
FIT 55-70, 3	624-754	687-845	607-747	566-668	529-624	47-65	47-70	42-61	46-62	43-57	17-20	17-20	16-20	15-18	17-19	63-74	64-77	55-67	61-70	59-67	--	--	--	--	--
FIT 50-70, 3	691-858	760-968	682-869	627-754	591-708	43-64	43-69	37-60	43-61	40-56	15-20	15-20	15-20	14-18	16-19	67-84	69-88	60-77	66-80	63-78	2-6*	3-10*	3-7*	2-6*	2-6*
FIT 45-70, 3	810-1007	886-1137	801-1027	739-883	699-834	38-62	38-67	33-58	39-59	36-55	13-18	13-19	12-19	13-17	14-18	75-97	77-100	67-90	73-92	70-90	3-6*	4-6*	4-6*	3-7*	3-7*
FIT 45-75, 3	917-1110	1000-1243	894-1114	842-984	793-926	36-60	35-65	31-57	36-57	34-53	11-16	11-16	11-16	10-14	11-16	82-104	84-108	73-96	80-99	78-97	5-7*	6-9*	6-9*	5-9*	5-10*
FIT 45-80, 3	971-1163	1054-1294	937-1154	896-1039	840-974	35-60	34-65	30-57	35-56	33-52	10-14	10-15	11-15	9-13	10-14	85-107	87-110	75-98	83-102	80-99	6-8*	6-10*	6-10*	7-7	7-7*
FIT 45-75, 2	1147-1361	1239-1512	1113-1360	1063-1219	1001-1149	29-55	28-60	25-52	30-52	28-48	9-13	8-13	8-14	8-12	9-13	93-116	96-119	84-107	91-109	88-108	7-9	7-11	7-11	8-8	7-10*
FIT 45-80, 2	1220-1426	1307-1574	1170-1409	1138-1289	1068-1211	28-54	27-59	24-52	28-51	26-47	7-12	7-12	8-13	6-11	8-12	96-119	98-122	86-109	94-112	91-111	8-12	8-19*	8-16*	8-13	8-14*
FIT 45-85, 2	1288-1492	1358-1632	1209-1453	1218-1363	1138-1275	27-54	26-59	24-52	28-51	26-47	6-11	6-11	7-12	5-10	7-11	98-120	100-123	87-110	96-114	93-112	12-25*	13-22*	11-19*	12-21*	11-17*
FIT 45-75, 1	1602-1824	1702-1990	1540-1805	1513-1670	1431-1581	20-46	19-50	17-44	21-44	20-40	6-10	6-11	6-11	5-10	6-11	106-127	109-131	97-119	103-120	101-120	15*-16	14*-20	13*-22	15-17	14-15
FIT 45-80, 1	1710-1923	1791-2080	1614-1876	1633-1780	1538-1678	19-45	18-49	16-43	20-42	19-39	5-9	5-9	5-10	4-8	5-9	110-129	112-133	99-120	106-122	105-123	14-27	14-32	13-28	15-23	13-21
FIT 45-85, 1	1769-1990	1841-2136	1652-1919	1717-1859	1611-1747	19-44	18-49	16-43	19-41	18-38	4-8	4-9	5-9	3-7	4-8	111-130	113-133	100-121	108-123	106-123	19-43	20-63	17-52	20-42	17-35

TP – total population; WM – White males; BM – Black males; WF – White females; BF – Black females; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

* Near efficient.

Table 13. Illustration of the Estimated Changes in Outcomes From Adherence to Screening Initiation for Sample Strategies With Screening Beginning at Age 50, by Model*

Strategy by model	Outcomes and change in outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Colonoscopy (COL)										
SimCRC										
COL 50-75, 10	0	0	0	3414	13	18	5	335	314	122
Delay start by 5y	0	0	0	-262	+2	+4	+1	-38	-38	-14
CRC-SPIN										
COL 50-75, 10	0	0	0	3500	15	15	5	308	291	112
Delay start by 5y	0	0	0	-285	+1	+3	+1	-30	-30	-11
MISCAN										
COL 50-75, 10	0	0	0	3476	14	36	9	286	257	104
Delay start by 5y	0	0	0	-296	+1	+1	+0.4	-22	-21	-8
Sigmoidoscopy (SIG)										
SimCRC										
SIG 50-75, 5	0	4058	0	1544	10	29	9	279	260	102
Delay start by 5y	0	-755	0	-187	-0.2	+5	+2	-37	-36	-14
CRC-SPIN										
SIG 50-75, 5	0	4134	0	1510	11	26	9	256	241	94
Delay start by 5y	0	-770	0	-185	-0.4	+4	+1	-27	-27	-10
MISCAN										
SIG 50-75, 5	0	3646	0	1927	12	40	11	256	229	93
Delay start by 5y	0	-686	0	-215	-0.1	+2	+0.9	-22	-21	-8
Sigmoidoscopy plus interval fecal immunochemical testing (SIG+FIT)										
SimCRC										
SIG+FIT 50-75, 10_1	13537	2099	0	1840	11	22	6	330	306	121
Delay start by 5y	-2885	-269	0	-190	+0.4	+5	+2	-40	-39	-15
CRC-SPIN										
SIG+FIT 50-75, 10_1	13305	2067	0	1973	13	18	6	301	282	110
Delay start by 5y	-2828	-257	0	-232	-0.2	+4	+1	-31	-31	-12

Table 13. Illustration of the Estimated Changes in Outcomes From Adherence to Repeat Screening for Sample Strategies With Screening Beginning at Age 50, by Model*

MISCAN										
SIG+FIT 50-75, 10_1	12357	1900	0	2048	12	39	10	287	255	105
Delay start by 5y	-2732	-169	0	-177	+0.6	+1	+0.6	-24	-22	-9
Computed tomographic colonography (CTC)										
SimCRC										
CTC 50-75, 5	0	0	4006	1624	11	21	6	325	302	119
Delay start by 5y	0	0	-760	-177	-0.2	+5	+2	-41	-40	-15
CRC-SPIN										
CTC 50-75, 5	0	0	4088	1626	12	20	7	287	270	105
Delay start by 5y	0	0	-768	-186	-0.4	+4	+1	-30	-30	-11
MISCAN										
CTC 50-75, 5	0	0	4075	1519	10	43	11	268	238	98
Delay start by 5y	0	0	-766	-169	-0.2	+2	+1	-24	-23	-9
Fecal immunochemical testing (FIT)										
SimCRC										
FIT 50-75, 1	16160	0	0	1423	9	30	7	316	289	115
Delay start by 5y	-3370	0	0	-191	-0.3	+6	+2	-41	-40	-15
CRC-SPIN										
FIT 50-75, 1	15562	0	0	1619	12	23	7	285	266	104
Delay start by 5y	-3221	0	0	-225	-0.6	+5	+2	-35	-34	-13
MISCAN										
FIT 50-75, 1	16097	0	0	1445	10	47	11	274	240	100
Delay start by 5y	-3340	0	0	-193	-0.3	+3	+1	-28	-26	-10
Multitarget stool DNA test (sDNA-FIT), 1-year interval										
SimCRC										
sDNA-FIT 50-75, 1	11463	0	0	2156	11	22	6	330	305	121
Delay start by 5y	-2291	0	0	-307	-0.2	+5	+2	-41	-40	-15
CRC-SPIN										
sDNA-FIT 50-75, 1	11132	0	0	2295	14	18	6	301	281	110
Delay start by 5y	-2222	0	0	-331	-0.5	+5	+2	-33	-33	-12

Table 13. Illustration of the Estimated Changes in Outcomes From Adherence to Repeat Screening for Sample Strategies With Screening Beginning at Age 50, by Model*

MISCAN										
sDNA-FIT 50-75, 1	11315	0	0	2211	12	39	9	290	257	106
Delay start by 5y	-2225	0	0	-314	-0.2	+2	+1	-27	-25	-10
Multitarget stool DNA test (sDNA-FIT), 3-year interval										
SimCRC										
sDNA-FIT 50-75, 3	6074	0	0	1405	9	34	8	304	278	111
Delay start by 5y	-1344	0	0	-218	-0.5	+6	+2	-43	-41	-16
CRC-SPIN										
sDNA-FIT 50-75, 3	5939	0	0	1576	12	26	8	271	253	99
Delay start by 5y	-1306	0	0	-244	-0.8	+5	+2	-35	-34	-13
MISCAN										
sDNA-FIT 50-75, 3	6006	0	0	1449	9	50	12	257	223	94
Delay start by 5y	-1321	0	0	-218	-0.5	+3	+1	-28	-26	-10

CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** These strategies were selected for illustration purposes. Inclusion in this table should not be interpreted as endorsement of these strategies.

† Includes deaths from complications of screening.

Table 14. Illustration of the Estimated Changes in Outcomes From Adherence to Repeat Screening for Sample Strategies With Screening Beginning at Age 50, by Model*

Strategy by model	Outcomes and change in outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Colonoscopy (COL)										
SimCRC										
COL 50-75, 10	0	0	0	3414	13	18	5	335	314	122
Increase interval to 15y	0	0	0	-680	-2	+5	+2	-17	-16	-6
Once-only	0	0	0	-1695	-6	+22	+9	-79	-73	-29
CRC-SPIN										
COL 50-75, 10	0	0	0	3500	15	15	5	308	291	112
Increase interval to 15y	0	0	0	-676	-2	+3	+1	-12	-11	-4
Once-only	0	0	0	-1621	-6	+15	+6	-53	-50	-20
MISCAN										
COL 50-75, 10	0	0	0	3476	14	36	9	286	257	104
Increase interval to 15y	0	0	0	-608	-1	+4	+2	-22	-20	-8
Once-only	0	0	0	-1535	-5	+16	+9	-87	-77	-32
Sigmoidoscopy (SIG)										
SimCRC										
SIG 50-75, 5	0	4058	0	1544	10	29	9	279	260	102
Increase interval to 10y	0	-1593	0	-407	-2	+8	+3	-32	-30	-12
Once-only	0	-3087	0	-1001	-6	+32	+14	-129	-120	-47
CRC-SPIN										
SIG 50-75, 5	0	4134	0	1510	11	26	9	256	241	94
Increase interval to 10y	0	-1680	0	-294	-1	+4	+2	-16	-15	-6
Once-only	0	-3162	0	-816	-5	+21	+9	-83	-77	-30
MISCAN										
SIG 50-75, 5	0	3646	0	1927	12	40	11	256	229	93
Increase interval to 10y	0	-1349	0	-346	-1	+4	+2	-23	-21	-8
Once-only	0	-2675	0	-1030	-6	+21	+12	-119	-105	-43
Sigmoidoscopy plus interval fecal immunochemical testing (SIG+FIT)										
SimCRC										

Table 14. Illustration of the Estimated Changes in Outcomes From Adherence to Repeat Screening for Sample Strategies With Screening Beginning at Age 50, by Model*

SIG+FIT 50-75, 10_1	13537	2099	0	1840	11	22	6	330	306	121
Increase FIT interval to 2y	-5605	+97	0	-261	-1	+4	+1	-11	-11	-4
CRC-SPIN										
SIG+FIT 50-75, 10_1	13305	2067	0	1973	13	18	6	301	282	110
Increase FIT interval to 2y	-5462	+96	0	-265	-0.9	+3	+1	-10	-9	-4
MISCAN										
SIG+FIT 50-75, 10_1	12357	1900	0	2048	12	39	10	287	255	105
Increase FIT interval to 2y	-5180	+138	0	-181	-0.5	+2	+0.7	-10	-10	-4
Computed tomographic colonography (CTC)										
SimCRC										
CTC 50-75, 5	0	0	4006	1624	11	21	6	325	302	119
Increase interval to 10y	0	0	-1566	-396	-2	+8	+3	-30	-28	-11
CRC-SPIN										
CTC 50-75, 5	0	0	4088	1626	12	20	7	287	270	105
Increase interval to 10y	0	0	-1626	-366	-2	+6	+3	-28	-25	-10
MISCAN										
CTC 50-75, 5	0	0	4075	1519	10	43	11	268	238	98
Increase interval to 10y	0	0	-1622	-382	-2	+9	+4	-49	-46	-18
Fecal immunochemical testing (FIT)										
SimCRC										
FIT 50-75, 1	16160	0	0	1423	9	30	7	316	289	115
Increase interval to 2y	-6714	0	0	-417	-2	+11	+3	-33	-33	-12
Increase interval to 3y	-9215	0	0	-609	-3	+19	+6	-60	-60	-22
CRC-SPIN										
FIT 50-75, 1	15562	0	0	1619	12	23	7	285	266	104
Increase interval to 2y	-6357	0	0	-426	-2	+9	+3	-37	-35	-13
Increase interval to 3y	-8745	0	0	-638	-3	+16	+6	-65	-62	-24
MISCAN										
FIT 50-75, 1	16097	0	0	1445	10	47	11	274	240	100
Increase interval to 2y	-6703	0	0	-407	-2	+9	+3	-37	-36	-13
Increase interval to 3y	-9192	0	0	-598	-3	+14	+5	-65	-63	-24

Table 14. Illustration of the Estimated Changes in Outcomes From Adherence to Repeat Screening for Sample Strategies With Screening Beginning at Age 50, by Model*

Multitarget stool DNA testing (sDNA-FIT)										
SimCRC										
sDNA-FIT 50-75, 1	11463	0	0	2156	11	22	6	330	305	121
Increase interval to 2y	-3735	0	0	-498	-2	+6	+1	-13	-13	-5
Increase interval to 3y	-5389	0	0	-752	-2	+11	+3	-26	-27	-10
CRC-SPIN										
sDNA-FIT 50-75, 1	11132	0	0	2295	14	18	6	301	281	110
Increase interval to 2y	-3607	0	0	-474	-1	+4	+1	-14	-14	-5
Increase interval to 3y	-5194	0	0	-720	-2	+8	+3	-30	-28	-11
MISCAN										
sDNA-FIT 50-75, 1	11315	0	0	2211	12	39	9	290	257	106
Increase interval to 2y	-3672	0	0	-502	-2	+6	+1	-16	-16	-6
Increase interval to 3y	-5309	0	0	-761	-3	+11	+3	-33	-34	-12

CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** These strategies were selected for illustration purposes. Inclusion in this table should not be interpreted as endorsement of these strategies.

† Includes deaths from complications of screening.

Table 15. Estimated Outcomes for Strategies That Were Efficient With SimCRC, CRC-SPIN, and MISCAN With Estimated Life-Years Gained as the Measure of Screening Benefit

Class of modality	Unique strategies simulated, N	Efficient strategies with all models[†]		Range of outcomes per 1000 across models								Efficiency ratio (Δ COL / Δ LYG)[§]	Alternative ratio (Δ DLG / Δ COL)[§]
		N	Strategy	COLs	Non-COL tests[‡]	Compli-cations	CRC cases	CRC deaths	LYG	QALYG	DLG		
Colonoscopy	26	11	COL 55-70, 15	2532-2630	0	13-14	21-40	7-11	250-285	223-265	91-104	--	--
			COL 50-70, 15	2734-2868	0	11-13	18-40	6-11	264-318	237-298	96-116	6*-18	21-61*
			COL 45-70, 15	2829-3006	0	10-12	18-41	6-12	265-336	240-316	97-123	6-85*	4*-63
			COL 45-75, 15	3463-3558	0	15-16	14-37	4-10	281-352	253-331	103-129	38*-59*	6*-10*
			COL 45-70, 10	3679-3782	0	12-14	13-37	4-10	292-361	265-340	107-132	34-45	8-11
			COL 45-75, 10	4212-4300	0	15-17	12-34	3-8	301-369	272-347	110-135	52-112	3-7
			COL 45-85, 10	4449-4566	0	17-19	11-34	3-8	302-370	273-347	110-135	227*-828*	0*-2*
			COL 45-70, 5	5626-5789	0	15-17	10-32	3-8	318-377	288-355	116-138	84-180*	2*-4
			COL 45-75, 5	6016-6235	0	17-19	10-31	3-7	321-380	291-357	117-139	116-344	1-3
			COL 45-80, 5	6320-6581	0	19-20	9-30	2-7	323-381	293-358	118-139	169-736	0-2
			COL 45-85, 5	6516-6817	0	20-22	9-30	2-7	323-381	293-358	118-139	926-2190	0-0
COL strategy highlighted in 2016			COL 50-75, 10	3414-3500	0	13-15	15-36	5-9	286-335	257-314	104-122	D, D, 28	D, D, 13
FIT or sDNA-FIT	72	16	FIT 55-70, 3	624-754	4637-4710	5-7	47-65	17-20	171-203	144-181	63-74	--	--
			FIT 50-70, 3	691-858	5663-5757	5-7	43-64	15-20	184-231	156-208	67-84	2-6*	65*-155
			FIT 45-70, 3	810-1007	7299-7435	6-8	38-62	13-18	205-266	175-241	75-97	3-6*	59*-106
			FIT 45-75, 3	917-1110	8300-8475	7-9	36-60	11-16	226-286	192-258	82-104	5-7*	49*-68
			FIT 45-80, 3	971-1163	8866-9043	8-10	35-60	10-14	233-293	198-264	85-107	6-8*	44*-59
			FIT 45-75, 2	1147-1361	11420-11731	8-11	29-55	9-13	256-318	221-289	93-116	7-9	39-50
			FIT 45-80, 2	1220-1426	12249-12576	9-12	28-54	7-12	264-325	227-295	96-119	8-12	29-47
			FIT 45-85, 2	1288-1492	13160-13487	10-13	27-54	6-11	269-329	231-298	98-120	12-25*	14*-31
			FIT 45-75, 1	1602-1824	18950-19680	10-13	20-46	6-10	291-348	256-321	106-127	15*-16	22-25*
			FIT 45-80, 1	1710-1923	20622-21368	11-14	19-45	5-9	300-355	263-326	110-129	14-27	13-27
			FIT 45-85, 1	1769-1990	21850-22567	12-15	19-44	4-8	303-356	266-328	111-130	19-43	8-19
			sDNA-FIT 45-80, 2	2012-2181	9928-10167	11-14	18-43	5-9	298-356	262-329	109-130	26*-176*	2*-14*
			sDNA-FIT 45-85, 2	2114-2275	10620-10828	13-15	17-42	4-8	301-358	265-330	110-131	69*-375*	1*-5*
			sDNA-FIT 45-75, 1	2462-2617	13494-13888	12-14	15-38	4-9	306-363	272-337	112-133	53-251*	1*-7
			sDNA-FIT 45-80, 1	2614-2758	14608-14966	13-15	14-37	4-8	311-367	277-340	114-134	62-104*	4*-6
			sDNA-FIT 45-85, 1	2713-2856	15424-15721	14-16	14-36	3-8	313-368	278-341	114-134	94-111	3-4
FIT and sDNA-FIT strategies highlighted in 2016			sDNA-FIT 50-75, 3	1405-1576	5939-6074	9-12	26-50	8-12	257-304	223-278	94-111	D, D, D	D, D, D
			FIT 50-75, 1	1423-1619	15562-16160	9-12	23-47	7-11	274-316	240-289	100-115	D, D, 29*	D, D, 13*
			sDNA-FIT 50-75, 1	2156-2295	11132-11463	11-14	18-39	6-9	290-330	257-305	106-121	D, D, D	D, D, D
SIG	20	7	SIG 55-70, 10	907-1340	1623-1708	7-10	35-48	13-16	204-210	182-197	74-77	--	--
			SIG 45-70, 10	1155-1635	2480-2622	7-10	29-45	11-14	234-262	210-246	85-96	4-73*	5*-86
			SIG 45-75, 10	1360-1800	2946-3173	9-12	26-43	9-12	245-278	220-260	90-101	13*-18	21-27*
			SIG 45-70, 5	1586-2020	4013-4446	9-11	25-40	9-12	263-302	237-284	96-110	11-20	18-34
			SIG 45-75, 5	1680-2119	4389-4935	10-12	24-39	8-11	269-309	241-289	98-113	19-27	13-19
			SIG 45-80, 5	1749-2196	4681-5326	11-13	23-38	7-10	271-311	244-291	99-114	29-49	7-12
			SIG 45-85, 5	1793-2235	4877-5602	12-13	23-38	7-10	272-312	244-292	99-114	78-98	4-5
SIG strategy highlighted in 2016			SIG 50-75, 5	1510-1927	3646-4134	10-12	26-40	9-11	256-279	229-260	93-102	D, D, 19*	D, D, 19*
SIG+FIT	24	10	SIG+FIT 55-70, 10_2	1230-1547	6084-6685	8-11	27-45	9-13	241-266	213-245	88-97	--	--

Table 15. Estimated Outcomes for Strategies That Were Efficient With SimCRC, CRC-SPIN, and MISCAN With Estimated Life-Years Gained as the Measure of Screening Benefit and IRR of 1.19

Class of modality	Unique strategies simulated, N	Efficient strategies with all models† N	Strategy	Range of outcomes per 1000 across models: COLs	Non-COL tests‡	Compli-cations	CRC cases	CRC deaths	LYG	QALYG	DLG	Efficiency ratio (Δ COL / Δ LYG)§	Alternative ratio (Δ DLG / Δ COL)§
			SIG+FIT 50-70, 10_2	1512-1835	8519-9277	9-12	22-42	7-11	274-314	243-291	100-115	6*-9	42-63*
			SIG+FIT 45-70, 10_2	1617-1947	10174-11005	9-12	20-42	7-11	280-340	250-316	102-124	5-24*	15*-70
			SIG+FIT 45-75, 10_2	1835-2130	11710-12693	11-13	18-39	5-9	294-354	262-329	108-129	15-22	17-24
			SIG+FIT 45-80, 10_2	1889-2154	12266-13375	11-14	17-39	4-9	296-357	264-331	108-130	15-25	15-24
			SIG+FIT 45-70, 10_1	1903-2148	15867-17141	10-13	17-40	6-10	292-353	261-329	107-129	19*-88*	4*-20*
			SIG+FIT 45-85, 10_2	1988-2235	13131-14286	13-15	17-39	4-8	298-358	265-332	109-131	38*-78*	5*-10*
			SIG+FIT 45-75, 10_1	2102-2331	17858-19217	11-14	15-37	4-9	304-363	272-338	111-133	22*-34	11-17*
			SIG+FIT 45-80, 10_1	2203-2379	19076-20649	12-15	15-37	4-8	307-366	274-340	112-134	21-53	7-17
			SIG+FIT 45-85, 10_1	2293-2463	20204-21763	14-16	14-37	3-8	309-367	275-341	113-134	46-81	5-8
SIG+FIT strategy highlighted in 2016			SIG+FIT 50-75, 10_1	1840-2048	14257-15636	11-13	18-39	6-10	287-330	255-306	105-121	D, D, 18*	D, D, 21*
CTC	20	5	CTC 55-70, 10	939-1029	1695-1705	7-9	32-57	12-19	181-245	159-227	66-90	--	--
			CTC 45-70, 5	1569-1677	4372-4436	9-11	20-45	6-12	271-348	241-326	99-127	11-21*	17*-33
			CTC 45-75, 5	1672-1791	4804-4893	10-13	18-42	5-11	283-355	251-332	103-130	11-21	17-33
			CTC 45-80, 5	1744-1882	5131-5254	11-14	17-40	4-9	288-358	256-335	105-131	13-38	10-28
			CTC 45-85, 5	1790-1939	5348-5504	12-15	17-40	4-9	290-359	257-335	106-131	32-104	4-12
CTC strategy highlighted in 2016			CTC 50-75, 5	1519-1626	4006-4088	10-12	20-43	6-11	268-325	238-302	98-119	D, D, 9	D, D, 41
Total	**162**	**49**											

Note: For comparison purposes, the strategies highlighted in the 2016 USPSTF recommendations are included (in gray) even though they are not efficient in all 3 models. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – range across models of days of life gained per person, compared with no screening; D – dominated; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

* Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

† For comparison purposes, the strategies highlighted by the USPSTF in 2016) are included even though they are not efficient in all 3 models.

‡ For SIG+FIT, this is the sum of the 2 tests. Numbers of each test can be found in **Appendix Table 9.5**.

§ The strategies highlighted by the USPSTF in 2016 were not efficient in all 3 models. For these strategies, the efficiency ratio and alternative ratio columns indicate whether the 2016 highlighted strategy was dominated and not near efficient (D) or if efficient, the efficiency ratio (or alternative ratio) in the SimCRC, CRC-SPIN, and MISCAN models, respectively. For all other strategies, these columns indicate the range of efficiency ratios/alternative ratios across the 3 models.

Table 16. Estimated Outcomes From the Current Analysis and From the 2016 Analysis* for the Colonoscopy Screening Strategy Highlighted by the USPSTF in 2016 and for the Same Strategy But With Screening Beginning at Age 45 Instead of Age 50

Strategy by model	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Colonoscopy every 10 years to age 75 – current analysis										
SimCRC										
COL 50-75, 10	0	0	0	3414	13	18	5	335	314	122
COL 45-75, 10	0	0	0	4212	16	14	3	369	347	135
Difference‡	**0**	**0**	**0**	**+798**	**+2**	**-4**	**-2**	**+34**	**+33**	**+12**
CRC-SPIN										
COL 50-75, 10	0	0	0	3500	15	15	5	308	291	112
COL 45-75, 10	0	0	0	4300	17	12	4	340	321	124
Difference‡	**0**	**0**	**0**	**+800**	**+2**	**-3**	**-1**	**+32**	**+30**	**+12**
MISCAN										
COL 50-75, 10	0	0	0	3476	14	36	9	286	257	104
COL 45-75, 10	0	0	0	4232	15	34	8	301	272	110
Difference‡	**0**	**0**	**0**	**+756**	**+2**	**-2**	**-1**	**+16**	**+15**	**+6**
Colonoscopy every 10 years to age 75 – 2016 analysis										
SimCRC										
COL 50-70, 10	0	0	0	4007	14	13	4	275	255	100
COL 45-75, 10	0	0	0	4853	16	9	2	303	281	110
Difference‡	**0**	**0**	**0**	**+846**	**+2**	**-4**	**-1**	**+28**	**+26**	**+10**
CRC-SPIN										
COL 50-70, 10	0	0	0	4049	15	9	3	270	257	98
COL 45-75, 10	0	0	0	4906	17	6	2	289	276	106
Difference‡	**0**	**0**	**0**	**+856**	**+2**	**-3**	**-1**	**+19**	**+18**	**+7**
MISCAN										
COL 50-70, 10	0	0	0	4101	15	25	6	248	222	90
COL 45-75, 10	0	0	0	4928	16	23	5	262	236	96
Difference‡	**0**	**0**	**0**	**+827**	**+1**	**-2**	**-0.8**	**+15**	**+14**	**+5**

SIG = sigmoidoscopy; CTC – computed tomographic colonography; COL – colonoscopy; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

***** The current and 2016 decision analyses make different assumptions about CRC risk (IRR 1.19 vs 1) and use different all-cause mortality rates, different surveillance intervals, and a different version of CRC-SPIN model.

† Includes deaths from complications of screening.

‡ Due to rounding, reported difference may not match calculated difference.

Table 17. Estimated Outcomes From the Current Analysis and From the 2016 Analysis* for the FIT Screening Strategy Highlighted by the USPSTF in 2016 and for the Same Strategy But With Screening Beginning at Age 45 Instead of Age 50

Strategy by model	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Annual fecal immunochemical testing to age 75 – current analysis										
SimCRC										
FIT 50-75, 1	16160	0	0	1423	9	30	7	316	289	115
FIT 45-75, 1	19680	0	0	1602	10	26	6	348	321	127
Difference‡	**+3520**	**0**	**0**	**+179**	**+0.2**	**-4**	**-1**	**+33**	**+32**	**+12**
CRC-SPIN										
FIT 50-75, 1	15562	0	0	1619	12	23	7	285	266	104
FIT 45-75, 1	18950	0	0	1824	13	20	6	314	293	115
Difference‡	**+3387**	**0**	**0**	**+205**	**+0.4**	**-3**	**-1**	**+29**	**+28**	**+11**
MISCAN										
FIT 50-75, 1	16097	0	0	1445	10	47	11	274	240	100
FIT 45-75, 1	19607	0	0	1620	10	46	10	291	256	106
Difference‡	**+3510**	**0**	**0**	**+175**	**+0.2**	**-1**	**-0.6**	**+17**	**+16**	**+6**
Annual fecal immunochemical testing to age 75 – 2016 analysis										
SimCRC										
FIT 50-75, 1	15778	0	0	1739	10	23	5	260	240	95
FIT 45-75, 1	19196	0	0	1979	10	20	4	287	267	105
Difference‡	**+3418**	**0**	**0**	**+239**	**+0.2**	**-3**	**-1**	**+27**	**+27**	**+10**
CRC-SPIN										
FIT 50-75, 1	15444	0	0	1899	11	20	5	244	231	89
FIT 45-75, 1	18733	0	0	2163	11	17	4	263	250	96
Difference‡	**+3289**	**0**	**0**	**+263**	**+0.2**	**-3**	**-0.8**	**+19**	**+19**	**+7**
MISCAN										
FIT 50-75, 1	15843	0	0	1757	10	35	8	231	205	84
FIT 45-75, 1	19256	0	0	1995	10	34	7	247	221	90
Difference‡	**+3413**	**0**	**0**	**+238**	**+0.2**	**-2**	**-0.7**	**+16**	**+16**	**+6**

FIT – fecal immunochemical testing with a cutoff for positivity of 20 μg of hemoglobin per g of feces; SIG = sigmoidoscopy; CTC – computed tomographic colonography; COL – colonoscopy; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

***** The current and 2016 decision analyses make different assumptions about CRC risk (IRR 1.19 vs 1) and use different all-cause mortality rates, different surveillance intervals, and a different version of CRC-SPIN model.

† Includes deaths from complications of screening.

‡ Due to rounding, reported difference may not match calculated difference.

Table 18. Estimated Outcomes From the Current Analysis and From the 2016 Analysis* for the Annual sDNA-FIT Screening Strategy Highlighted by the USPSTF in 2016 and for the Same Strategy But With Screening Beginning at Age 45 Instead of Age 50

Strategy by model	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Annual multitarget stool DNA testing to age 75 – current analysis										
SimCRC										
sDNA-FIT 50-75, 1	11463	0	0	2156	11	22	6	330	305	121
sDNA-FIT 45-75, 1	13888	0	0	2462	12	19	4	363	337	133
Difference‡	**+2425**	**0**	**0**	**+305**	**+0.2**	**-4**	**-1**	**+33**	**+32**	**+12**
CRC-SPIN										
sDNA-FIT 50-75, 1	11132	0	0	2295	14	18	6	301	281	110
sDNA-FIT 45-75, 1	13494	0	0	2617	14	15	5	331	309	121
Difference‡	**+2361**	**0**	**0**	**+322**	**+0.4**	**-3**	**-1**	**+30**	**+28**	**+11**
MISCAN										
sDNA-FIT 50-75, 1	11315	0	0	2211	12	39	9	290	257	106
sDNA-FIT 45-75, 1	13698	0	0	2515	12	38	9	306	272	112
Difference‡	**+2383**	**0**	**0**	**+305**	**+0.2**	**-1**	**-0.6**	**+16**	**+15**	**+6**
Annual multitarget stool DNA testing to age 75 – 2016 analysis										
SimCRC										
sDNA-FIT 50-75, 1	11041	0	0	2601	12	17	4	271	252	99
sDNA-FIT 45-75, 1	13372	0	0	2978	12	14	3	298	278	109
Difference‡	**+2331**	**0**	**0**	**+378**	**+0.2**	**-3**	**-1**	**+26**	**+26**	**+10**
CRC-SPIN										
sDNA-FIT 50-75, 1	10745	0	0	2729	13	13	4	261	249	95
sDNA-FIT 45-75, 1	12989	0	0	3122	13	11	3	279	267	102
Difference‡	**+2244**	**0**	**0**	**+393**	**+0.2**	**-2**	**-0.7**	**+18**	**+18**	**+7**
MISCAN										
sDNA-FIT 50-75, 1	11025	0	0	2662	12	28	6	246	222	90
sDNA-FIT 45-75, 1	13328	0	0	3044	12	27	6	261	236	95
Difference‡	**+2303**	**0**	**0**	**+382**	**+0.2**	**-1**	**-0.6**	**+15**	**+14**	**+5**

sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG = sigmoidoscopy; CTC – computed tomographic colonography; COL – colonoscopy; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

* The current and 2016 decision analyses make different assumptions about CRC risk (IRR 1.19 vs 1) and use different all-cause mortality rates, different surveillance intervals, and a different version of CRC-SPIN model.

† Includes deaths from complications of screening.

‡ Due to rounding, reported difference may not match calculated difference.

Table 19. Estimated Outcomes From the Current Analysis and From the 2016 Analysis* for the Triennial sDNA-FIT Screening Strategy Highlighted by the USPSTF in 2016 and for the Same Strategy But With Screening Beginning at Age 45 Instead of Age 50

Strategy by model	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Triennial multitarget stool DNA testing to age 75 – current analysis										
SimCRC										
sDNA-FIT 50-75, 3	6074	0	0	1405	9	34	8	304	278	111
sDNA-FIT 45-75, 3	7274	0	0	1582	9	30	7	335	308	122
Difference‡	**+1201**	**0**	**0**	**+177**	**+0.2**	**-4**	**-1**	**+31**	**+30**	**+11**
CRC-SPIN										
sDNA-FIT 50-75, 3	5939	0	0	1576	12	26	8	271	253	99
sDNA-FIT 45-75, 3	7105	0	0	1772	12	23	7	301	281	110
Difference‡	**+1166**	**0**	**0**	**+196**	**+0.4**	**-3**	**-1**	**+30**	**+28**	**+11**
MISCAN										
sDNA-FIT 50-75, 3	6006	0	0	1449	9	50	12	257	223	94
sDNA-FIT 45-75, 3	7204	0	0	1629	10	49	12	273	239	100
Difference‡	**+1199**	**0**	**0**	**+179**	**+0.2**	**-1**	**-0.6**	**+16**	**+15**	**+6**
Triennial multitarget stool DNA testing to age 75 – 2016 analysis										
SimCRC										
sDNA-FIT 50-75, 3	5990	0	0	1701	9	26	6	250	229	91
sDNA-FIT 45-75, 3	7158	0	0	1928	9	23	5	274	254	100
Difference‡	**+1168**	**0**	**0**	**+226**	**+0.2**	**-3**	**-1**	**+25**	**+24**	**+9**
CRC-SPIN										
sDNA-FIT 50-75, 3	5927	0	0	1827	10	23	7	226	215	83
sDNA-FIT 45-75, 3	7061	0	0	2073	10	20	6	244	232	89
Difference‡	**+1134**	**0**	**0**	**+245**	**+0.2**	**-3**	**-0.8**	**+18**	**+18**	**+6**
MISCAN										
sDNA-FIT 50-75, 3	5779	0	0	1714	9	38	9	215	190	79
sDNA-FIT 45-75, 3	7086	0	0	1965	10	36	8	231	205	84
Difference‡	**+1308**	**0**	**0**	**+251**	**+0.4**	**-2**	**-0.9**	**+16**	**+15**	**+6**

sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG = sigmoidoscopy; CTC – computed tomographic colonography; COL – colonoscopy; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

* The current and 2016 decision analyses make different assumptions about CRC risk (IRR 1.19 vs 1) and use different all-cause mortality rates, different surveillance intervals, and a different version of CRC-SPIN model.

† Includes deaths from complications of screening.

‡ Due to rounding, reported difference may not match calculated difference.

Table 20. Estimated Outcomes From the Current Analysis and From the 2016 Analysis* for the SIG Screening Strategy Highlighted by the USPSTF in 2016 and for the Same Strategy But With Screening Beginning at Age 45 Instead of Age 50

Strategy by model	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Sigmoidoscopy every 5 years to age 75 – current analysis										
SimCRC										
SIG 50-75, 5	0	4058	0	1544	10	29	9	279	260	102
SIG 45-75, 5	0	4846	0	1720	10	25	8	309	289	113
Difference‡	**0**	**+788**	**0**	**+176**	**+0.1**	**-3**	**-1**	**+30**	**+29**	**+11**
CRC-SPIN										
SIG 50-75, 5	0	4134	0	1510	11	26	9	256	241	94
SIG 45-75, 5	0	4935	0	1680	12	24	9	280	264	102
Difference‡	**0**	**+801**	**0**	**+170**	**+0.2**	**-2**	**-0.9**	**+24**	**+22**	**+9**
MISCAN										
SIG 50-75, 5	0	3646	0	1927	12	40	11	256	229	93
SIG 45-75, 5	0	4389	0	2119	12	39	11	269	241	98
Difference‡	**0**	**+743**	**0**	**+192**	**0**	**-1**	**-0.4**	**+13**	**+12**	**+5**
Sigmoidoscopy every 5 years to age 75 – 2016 analysis										
SimCRC										
SIG 50-75, 5	0	4111	0	1820	10	23	7	227	207	83
SIG 45-75, 5	0	4912	0	2039	11	20	6	251	230	91
Difference‡	**0**	**+800**	**0**	**+219**	**+0.2**	**-3**	**-1**	**+24**	**+23**	**+9**
CRC-SPIN										
SIG 50-75, 5	0	4298	0	1493	9	30	10	181	169	66
SIG 45-75, 5	0	5128	0	1669	9	28	10	193	180	70
Difference‡	**0**	**+830**	**0**	**+176**	**+0.1**	**-1**	**-0.4**	**+12**	**+11**	**+4**
MISCAN										
SIG 50-75, 5	0	3807	0	2287	12	29	8	221	196	81
SIG 45-75, 5	0	4572	0	2533	12	28	7	234	207	85
Difference‡	**0**	**+765**	**0**	**+246**	**+0.2**	**-1**	**-0.5**	**+12**	**+11**	**+5**

SIG - sigmoidoscopy; CTC – computed tomographic colonography; COL – colonoscopy; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

* The current and 2016 decision analyses make different assumptions about CRC risk (IRR 1.19 vs 1) and use different all-cause mortality rates, different surveillance intervals, and a different version of CRC-SPIN model.

† Includes deaths from complications of screening.

‡ Due to rounding, reported difference may not match calculated difference.

Table 21. Estimated Outcomes From the Current Analysis and From the 2016 Analysis* for the SIG+FIT Screening Strategy Highlighted by the USPSTF in 2016 and for the Same Strategy But With Screening Beginning at Age 45 Instead of Age 50

Strategy by model	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Sigmoidoscopy every 10 years with annual fecal immunochemical testing to age 75 – current analysis										
SimCRC										
SIG+FIT 50-75, 10_1	13537	2099	0	1840	11	22	6	330	306	121
SIG+FIT 45-75, 10_1	16648	2568	0	2102	11	18	4	363	338	133
Difference‡	**+3112**	**+469**	**0**	**+263**	**+0.6**	**-4**	**-1**	**+33**	**+32**	**+12**
CRC-SPIN										
SIG+FIT 50-75, 10_1	13305	2067	0	1973	13	18	6	301	282	110
SIG+FIT 45-75, 10_1	16322	2525	0	2237	14	15	5	330	309	120
Difference‡	**+3018**	**+458**	**0**	**+265**	**+0.5**	**-3**	**-1**	**+29**	**+27**	**+11**
MISCAN										
SIG+FIT 50-75, 10_1	12357	1900	0	2048	12	39	10	287	255	105
SIG+FIT 45-75, 10_1	15466	2393	0	2331	13	37	9	304	272	111
Difference‡	**+3109**	**+493**	**0**	**+284**	**+0.8**	**-2**	**-0.9**	**+17**	**+17**	**+6**
Sigmoidoscopy every 10 years with annual fecal immunochemical testing to age 75 – 2016 analysis										
SimCRC										
SIG+FIT 50-75, 10_1	13393	2097	0	2248	11	17	4	270	250	99
SIG+FIT 45-75, 10_1	16427	2553	0	2560	12	13	3	298	276	109
Difference‡	**+3034**	**+456**	**0**	**+312**	**+0.4**	**-3**	**-1**	**+28**	**+27**	**+10**
CRC-SPIN										
SIG+FIT 50-75, 10_1	13404	2079	0	2289	12	15	4	256	242	93
SIG+FIT 45-75, 10_1	16356	2523	0	2606	12	12	3	274	260	100
Difference‡	**+2952**	**+444**	**0**	**+317**	**+0.3**	**-3**	**-0.8**	**+18**	**+18**	**+7**
MISCAN										
SIG+FIT 50-75, 10_1	12642	1903	0	2490	12	28	6	246	220	90
SIG+FIT 45-75, 10_1	15711	2397	0	2826	13	26	5	262	235	96
Difference‡	**+3069**	**+494**	**0**	**+336**	**+0.6**	**-2**	**-0.8**	**+16**	**+15**	**+6**

SIG = sigmoidoscopy; FIT –fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; CTC – computed tomographic colonography; COL – colonoscopy; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

* The current and 2016 decision analyses make different assumptions about CRC risk (IRR 1.19 vs 1) and use different all-cause mortality rates, different surveillance intervals, and a different version of CRC-SPIN model.

† Includes deaths from complications of screening.

‡ Due to rounding, reported difference may not match calculated difference.

Table 22. Estimated Outcomes From the Current Analysis and From the 2016 Analysis for the CTC Screening Strategy Highlighted by the USPSTF in 2016 and for the Same Strategy But With Screening Beginning at Age 45 Instead of Age 50

Strategy by model	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Computed tomographic colonography every 5 years to age 75 – current analysis										
SimCRC										
CTC 50-75, 5	0	0	4006	1624	11	21	6	325	302	119
CTC 45-75, 5	0	0	4804	1788	11	18	5	355	332	130
Difference‡	**0**	**0**	**+798**	**+164**	**+0.1**	**-3**	**-1**	**+31**	**+30**	**+11**
CRC-SPIN										
CTC 50-75, 5	0	0	4088	1626	12	20	7	287	270	105
CTC 45-75, 5	0	0	4893	1791	13	18	6	313	294	114
Difference‡	**0**	**0**	**+805**	**+165**	**+0.2**	**-2**	**-1**	**+26**	**+24**	**+9**
MISCAN										
CTC 50-75, 5	0	0	4075	1519	10	43	11	268	238	98
CTC 45-75, 5	0	0	4881	1672	10	42	11	283	251	103
Difference‡	**0**	**0**	**+806**	**+153**	**+0.1**	**-1**	**-0.5**	**+14**	**+14**	**+5**
Computed tomographic colonography every 5 years to age 75 – 2016 analysis										
SimCRC										
CTC 50-75, 5	0	0	4069	1927	11	16	4	265	241	97
CTC 45-75, 5	0	0	4879	2133	11	13	3	290	265	106
Difference‡	**0**	**0**	**+811**	**+206**	**+0.2**	**-3**	**-1**	**+25**	**+24**	**+9**
CRC-SPIN										
CTC 50-75, 5	0	0	4254	1654	10	16	5	248	232	91
CTC 45-75, 5	0	0	5106	1807	10	14	4	264	246	96
Difference‡	**0**	**0**	**+852**	**+153**	**+0.1**	**-2**	**-0.5**	**+15**	**+14**	**+6**
MISCAN										
CTC 50-75, 5	0	0	4171	1743	10	33	8	226	196	82
CTC 45-75, 5	0	0	4990	1933	10	32	7	239	207	87
Difference‡	**0**	**0**	**+819**	**+190**	**+0.2**	**-1**	**-0.5**	**+14**	**+12**	**+5**

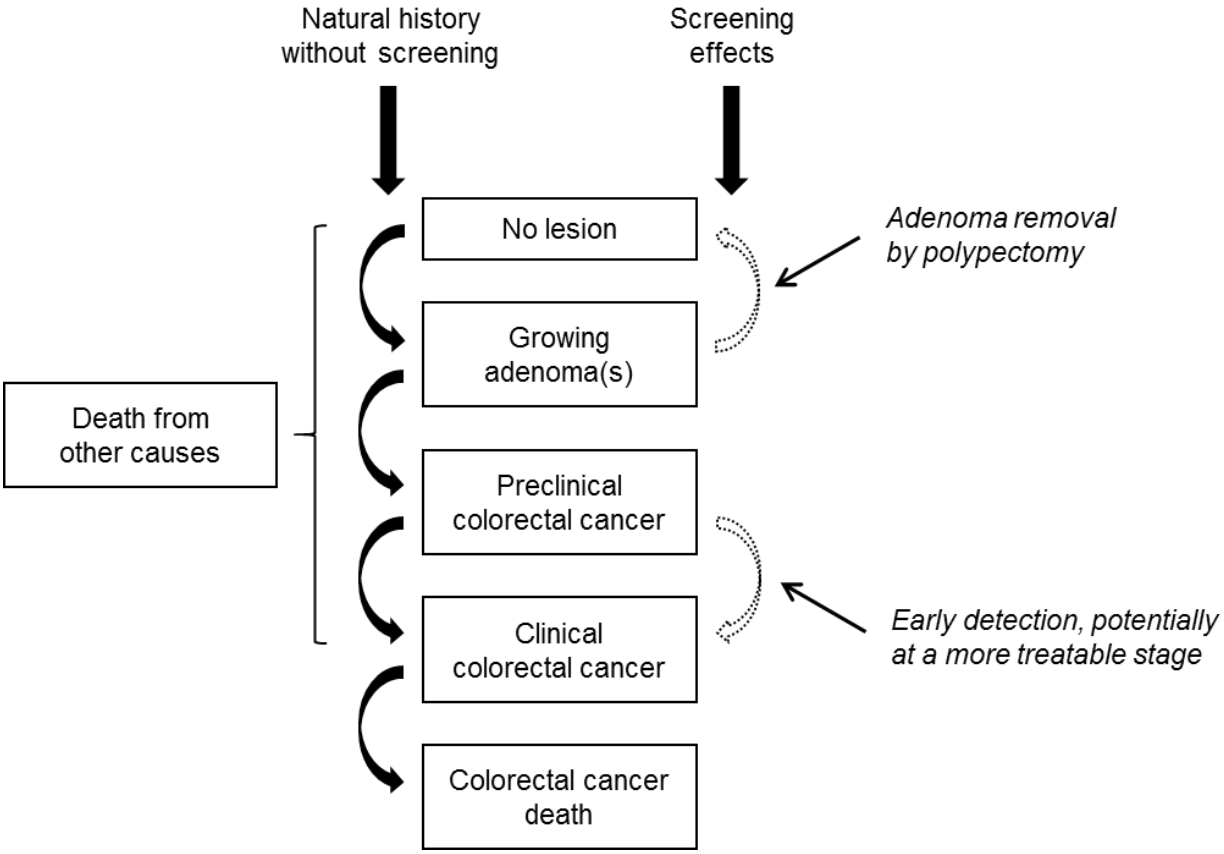
CTC – computed tomographic colonography; SIG = sigmoidoscopy; COL – colonoscopy; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

* The current and 2016 decision analyses make different assumptions about CRC risk (IRR 1.19 vs 1) and use different all-cause mortality rates, different surveillance intervals, and a different version of CRC-SPIN model.

† Includes deaths from complications of screening.

‡ Due to rounding, reported difference may not match calculated difference.

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



Note: The opportunity to intervene in the natural history through screening (adenoma detection and removal, and early detection) is noted by the dotted lines. Screening can either remove a precancerous lesion (i.e., 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.

Figure 2. Prevalence of Adenomas by Age From Autopsy Studies and as Estimated by the Original Models Calibrated to (Among Others) Colorectal Cancer Incidence Data From the Surveillance, Epidemiology, and End Results Program for 1975-1979

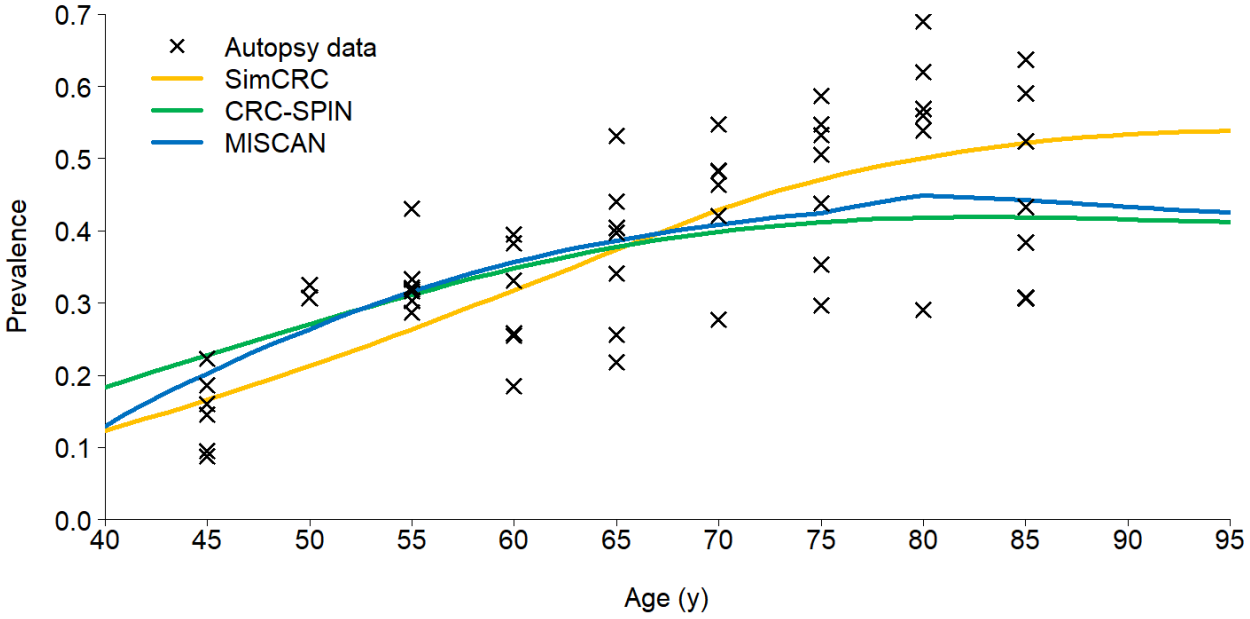


Figure 3. Model-Estimated Distribution of Adenomas by Location (Including Proportion in the Distal Colon or Rectum) Among Persons Aged 40 and Older

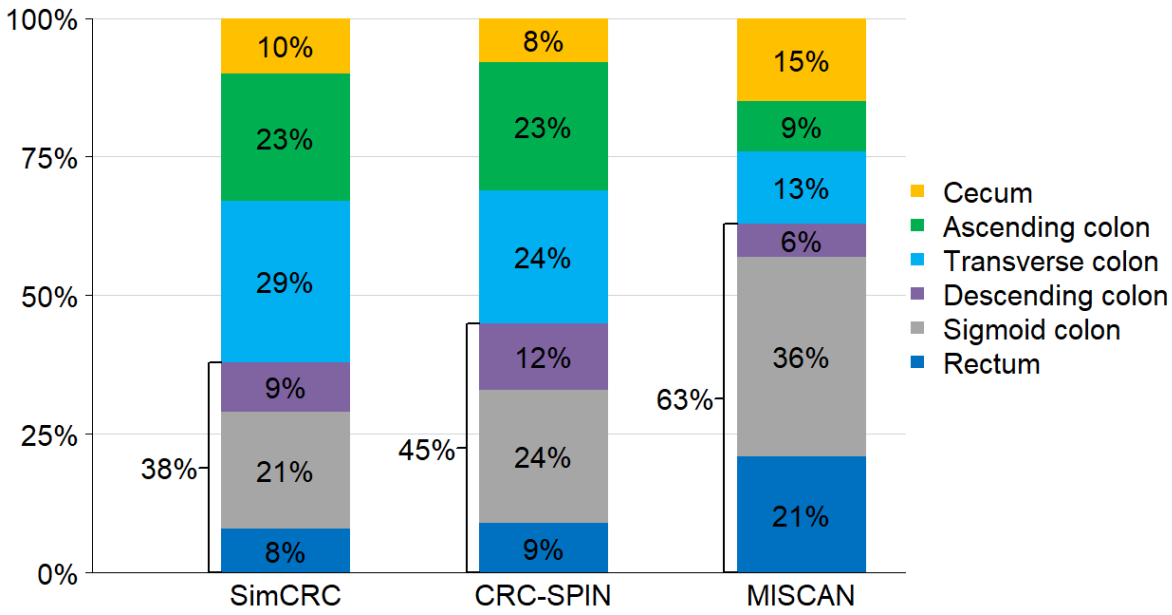
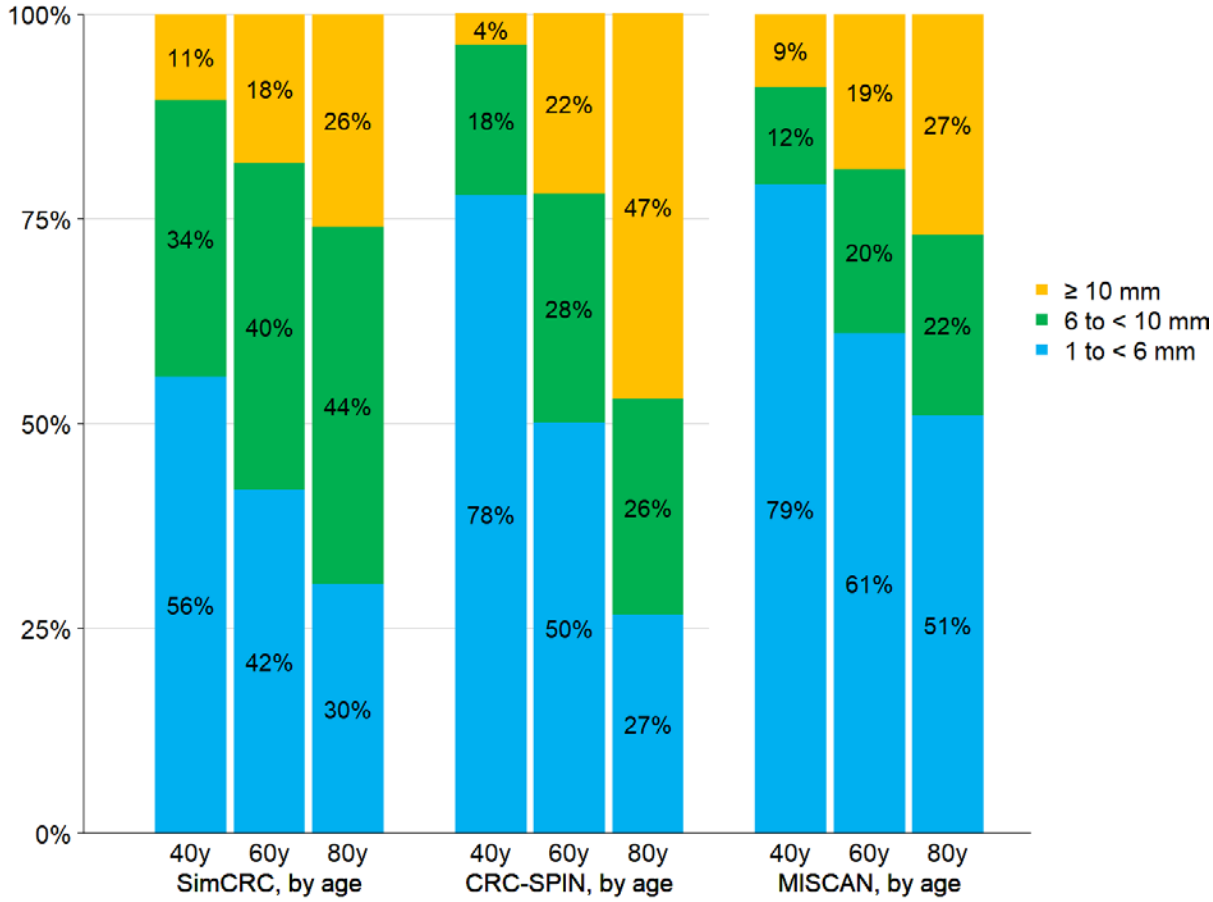
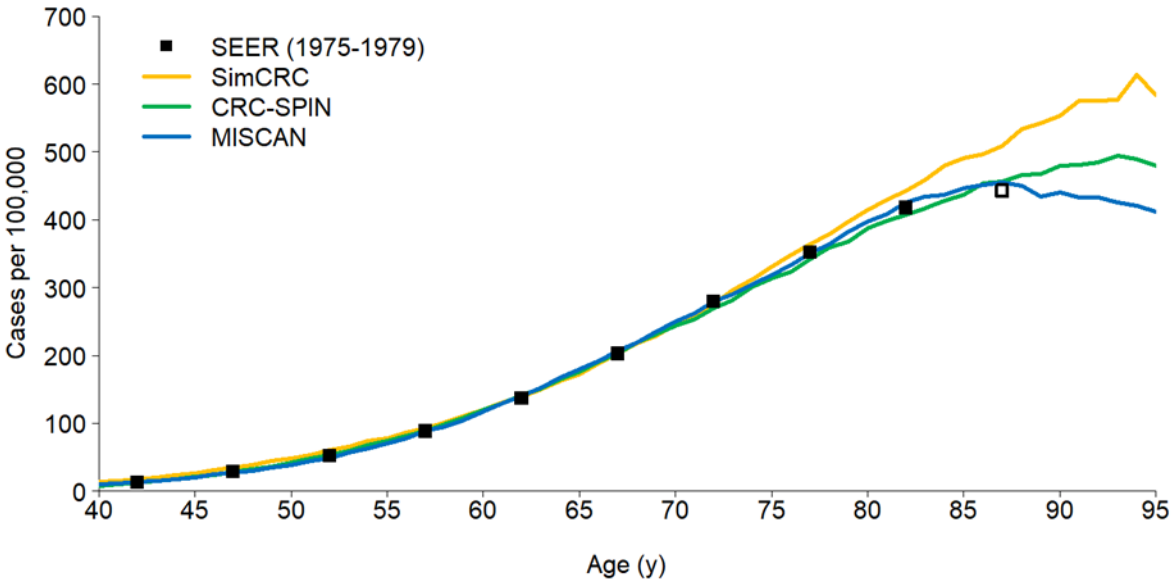


Figure 4. Model-Estimated Distribution of Adenomas by Size of the Most Advanced Adenoma Among Persons Aged 40 and Older, by Age



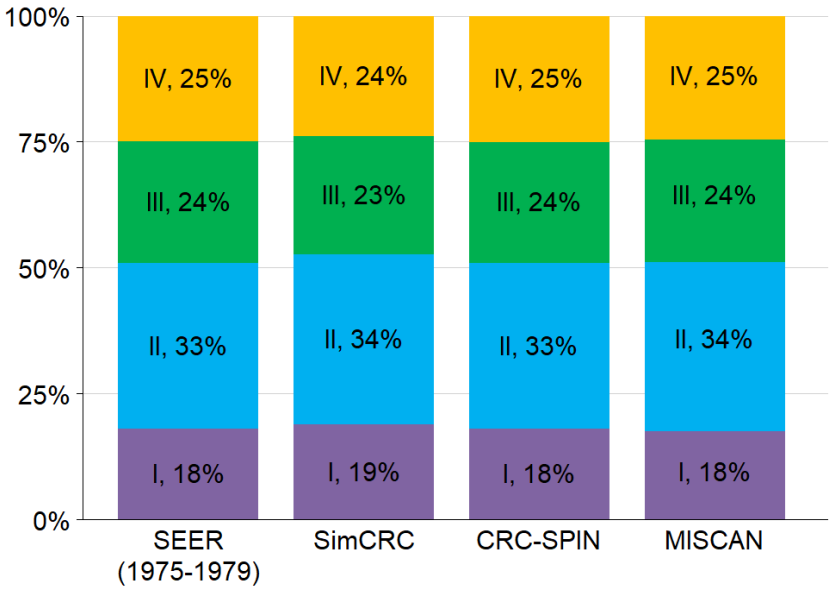
Note: Distributions are from the original models calibrated to (among others) colorectal cancer incidence data from the Surveillance, Epidemiology, and End Results Program for 1975-1979.

Figure 5. Estimated Colorectal Cancer Cases per 100,000 Persons by Age and Model for Models Calibrated to Incidence Rates From the Surveillance, Epidemiology, and End Results (SEER) Program for 1975-1979*



* This period was chosen because incidence rates at that time are likely to reflect those among a largely unscreened population. Note that open symbols indicate incidence rates for the 85+ age group (plotted at age 87 for convenience).

Figure 6. Model-Estimated Distribution of the Stage of Colorectal Cancer at Diagnosis Among Persons Aged 40 and Older*



Note: Stage distributions are from the original models calibrated to (among others) colorectal cancer incidence data from the Surveillance, Epidemiology and End Results Program for 1975-1979.

* Distributions may not sum to 100% due to rounding.

Figure 7. Estimated Colorectal Cancer Deaths per 100,000 Persons by Age for Models Calibrated to Colorectal Cancer Incidence Rates From the Surveillance, Epidemiology, and End Results Program for 1975-1979

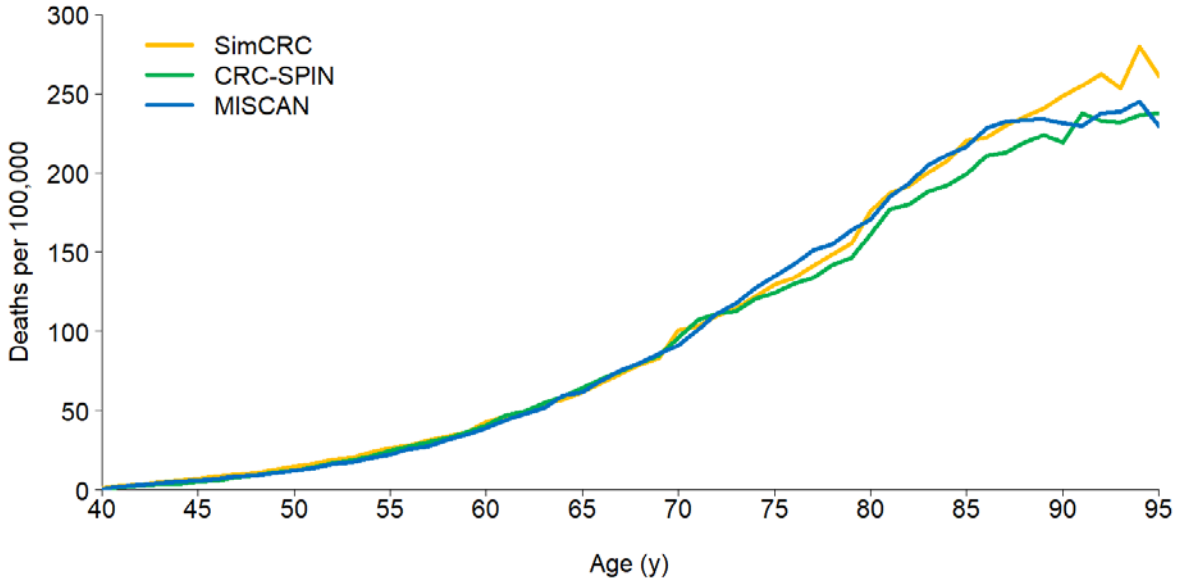
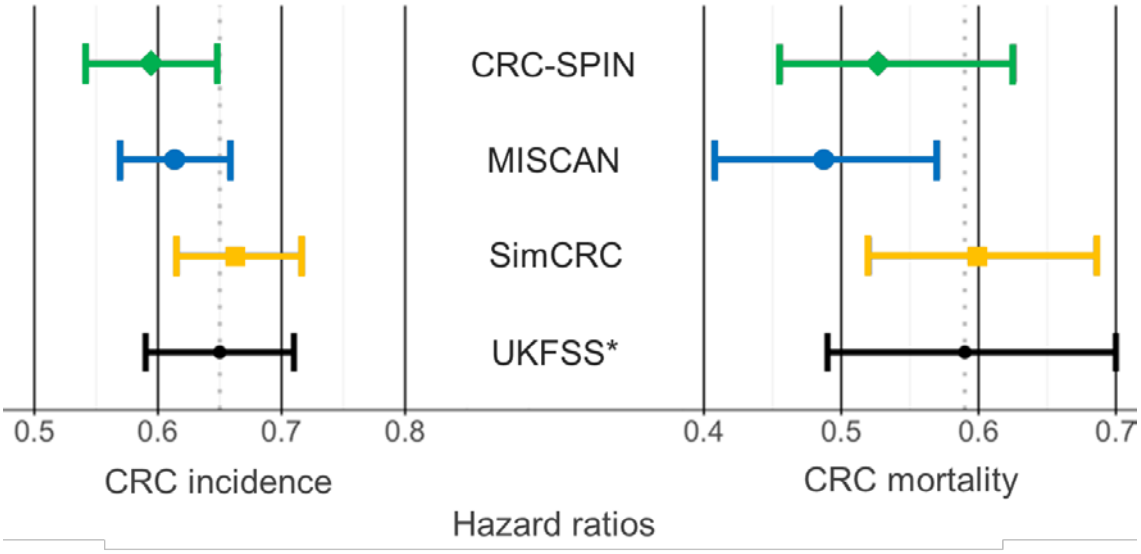
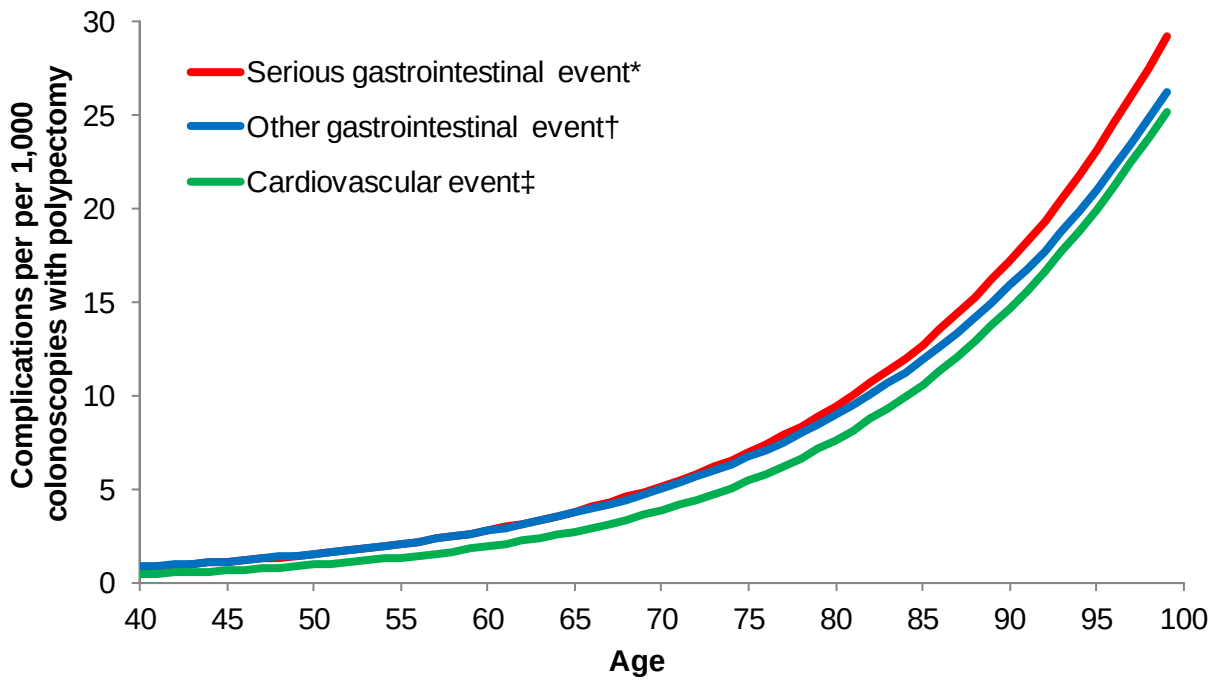


Figure 8. Model Validation Based on Estimated Hazard Ratios for Colorectal Cancer Incidence and Mortality After 17 Years of Follow-up Among the Intervention Group Compared With the Control Group of the UK Flexible Sigmoidoscopy Screening Trial (UKFSS)



* Hazard ratios and confidence intervals are from the per-protocol analysis.[81]

Figure 9. Age-Specific Excess Risks of Complications From Colonoscopy With Polypectomy Relative to Colonoscopies Without Polypectomy as Estimated by Van Hees et al[73]



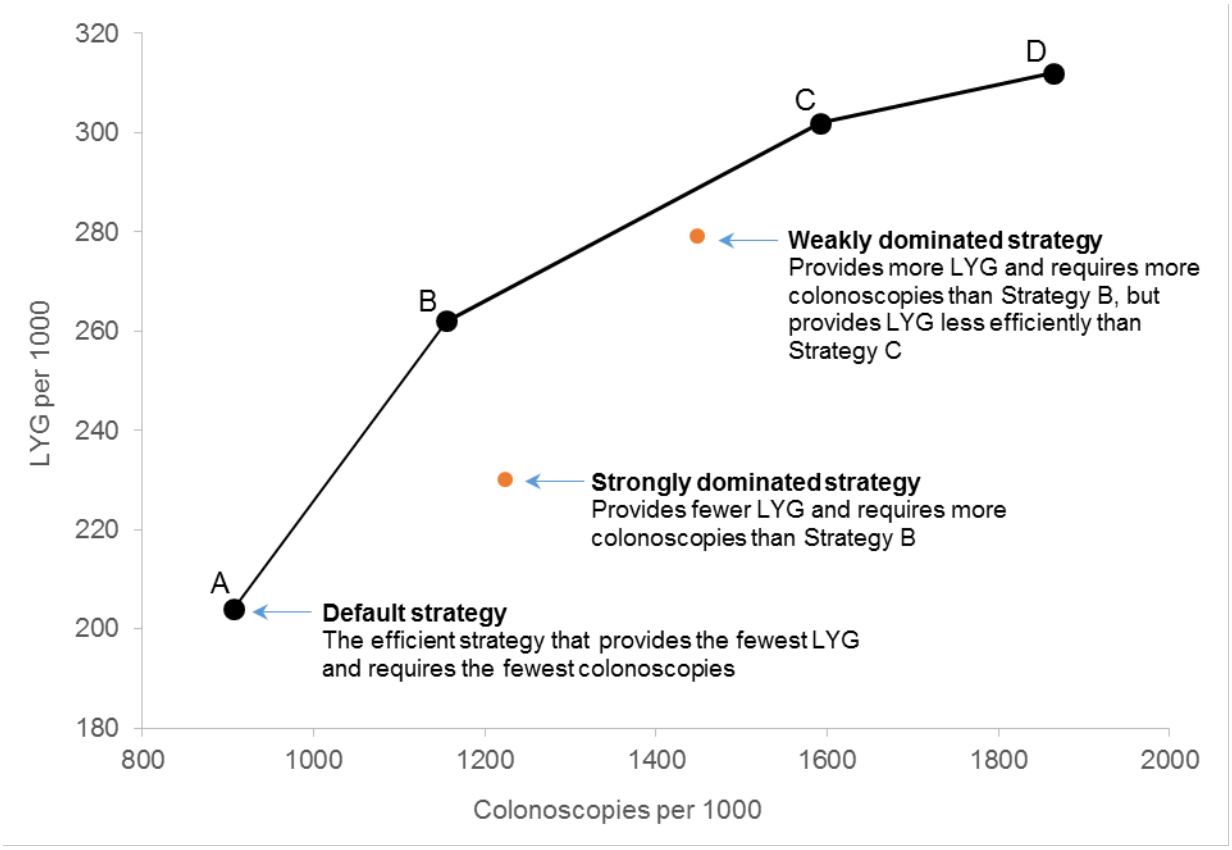
Note: Complications include serious gastrointestinal events, other gastrointestinal events, and cardiovascular events.

* Perforations, gastrointestinal bleeding, or transfusions. Excess risk per colonoscopy with polypectomy = 1/[exp(9.27953 − 0.06105 × Age) + 1] − 1/[exp(10.78719 − 0.06105 × Age) + 1].

† Paralytic ileus, nausea and vomiting, dehydration, abdominal pain. Excess risk per colonoscopy with polypectomy = 1/[exp(8.81404 − 0.05903 × Age) + 1] − 1/[exp(9.61197 − 0.05903 × Age) + 1].

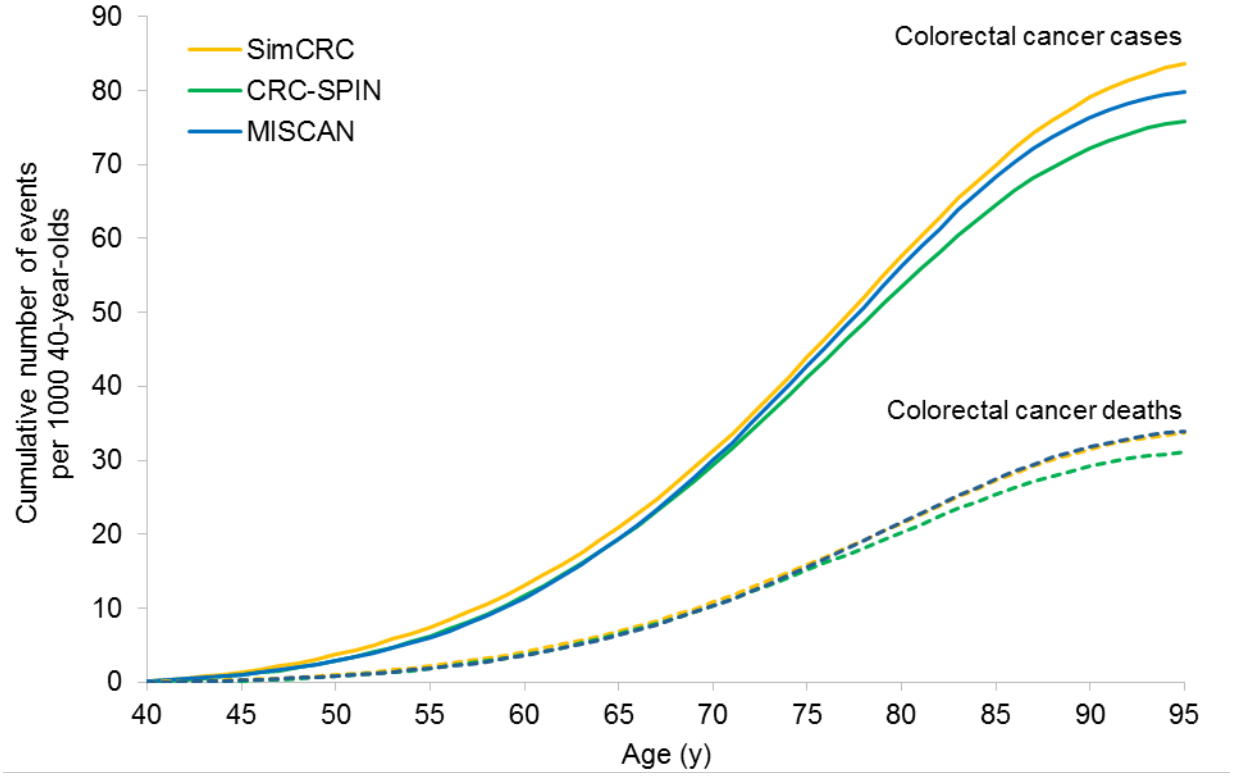
‡ Myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock. Excess risk per colonoscopy with polypectomy = 1/[exp(9.09053 − 0.07056 × Age) + 1] − 1/[exp(9.38297 − 0.07056 × Age) + 1]

Figure 10. Illustration of Efficient, Strongly Dominated and Weakly Dominated Strategies



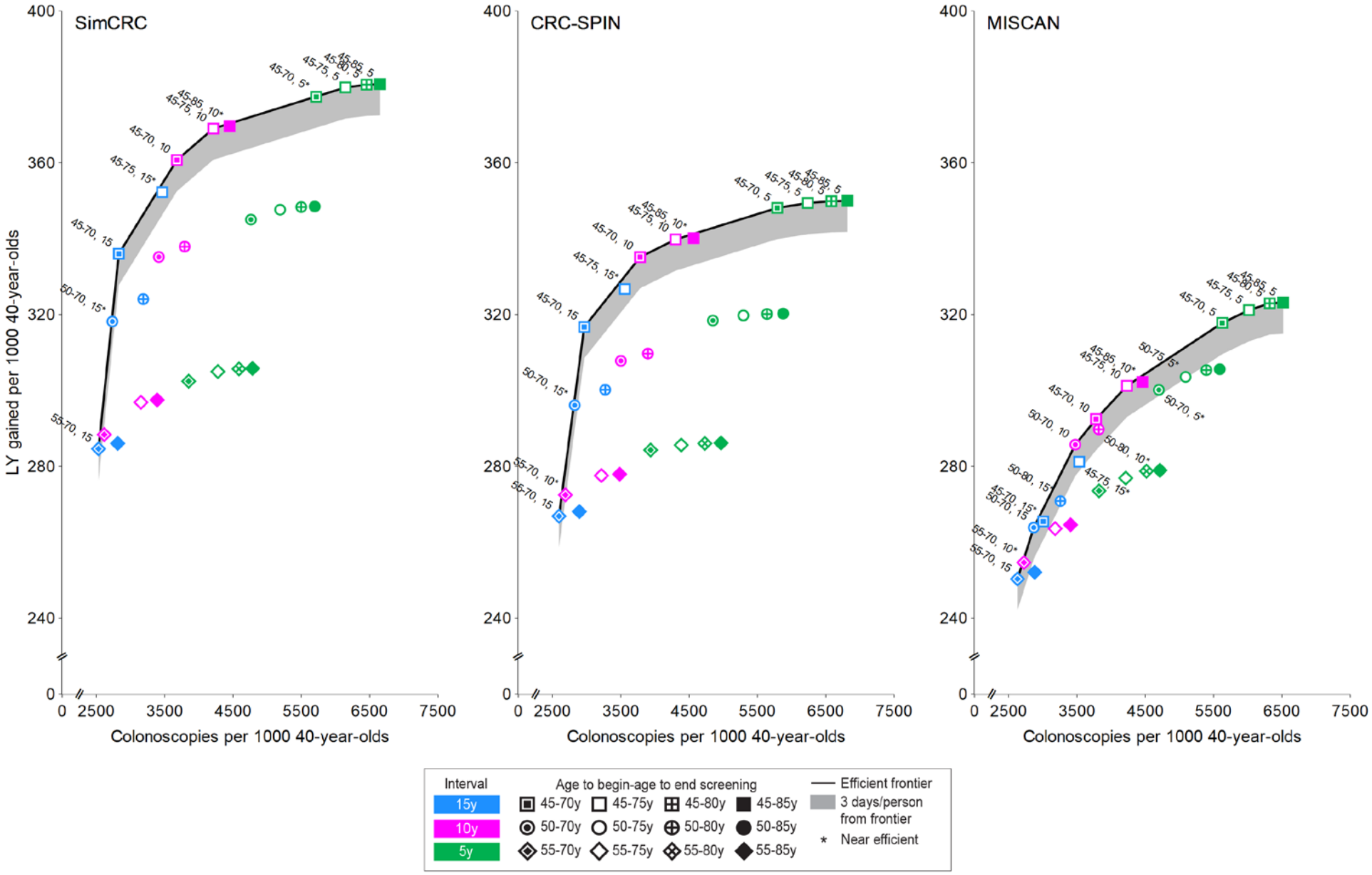
Note: Strategies A, B, C, and D are efficient. The line connecting the efficient strategies is the *efficient frontier*. The inverse of the slope of the efficient frontier between 2 adjacent efficient strategies is the *efficiency ratio*. A steep efficient frontier implies a big increase in LYG from the additional colonoscopies (i.e., a low efficiency ratio); a flat efficient frontier implies a small increase in LYG from the additional colonoscopies (i.e., a high efficiency ratio).

Figure 11. Estimated Cumulative Number of Colorectal Cancer Cases and of Colorectal Cancer Deaths per 1,000 Persons From Age 40 to Age 95 in the Absence of Screening, by Model



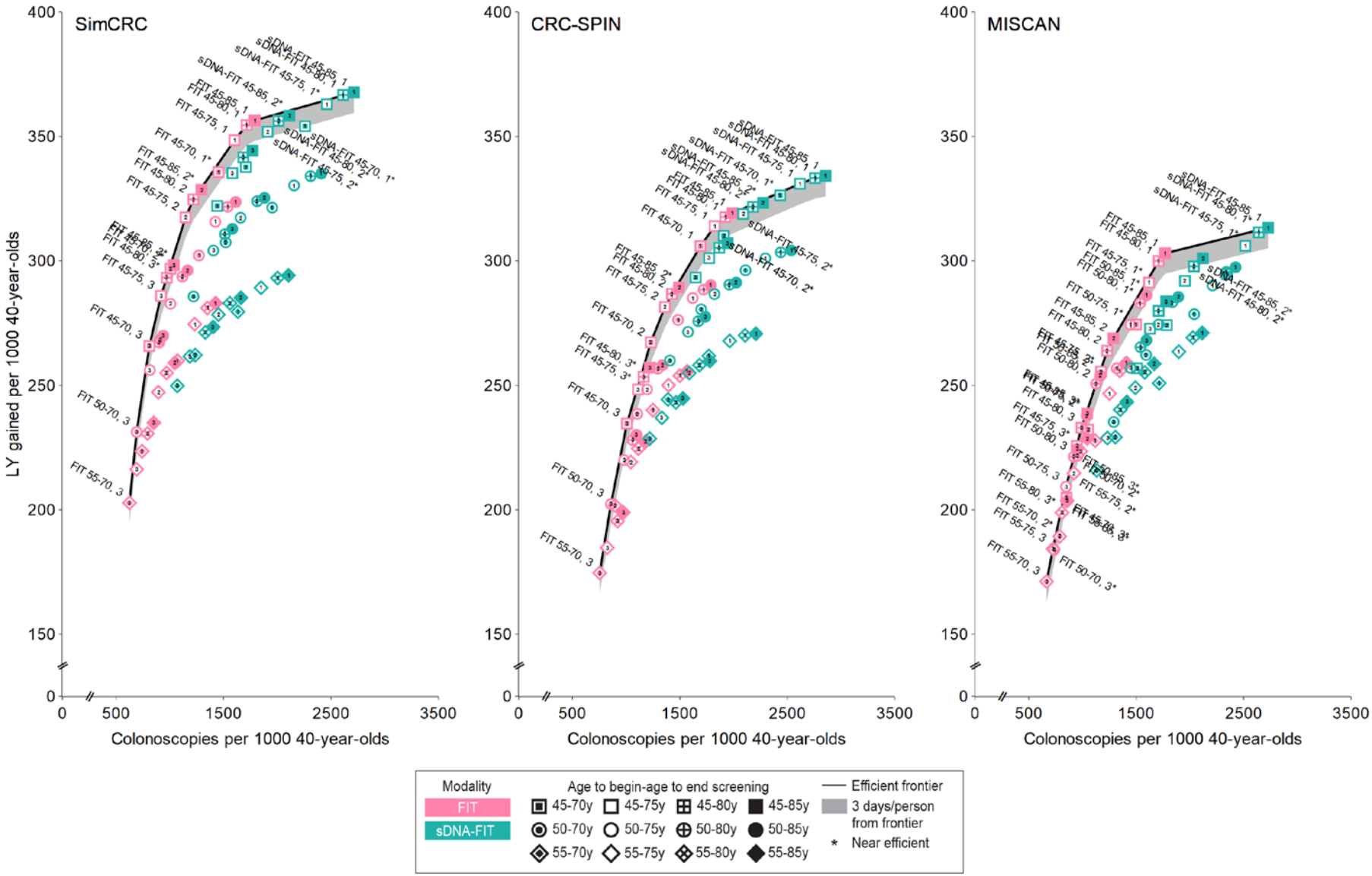
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 12. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies, by Model



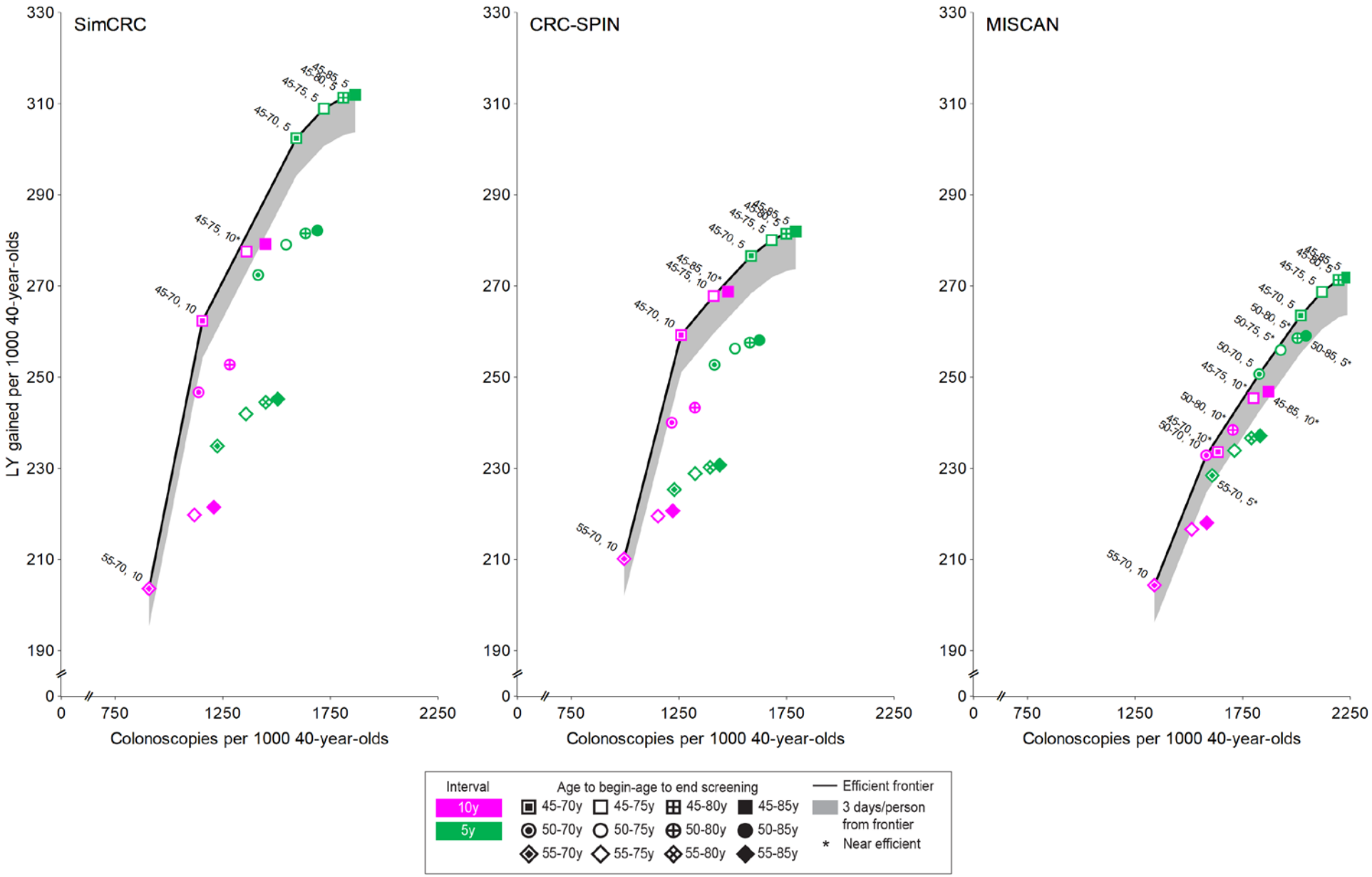
Note: Here, color indicates modality; screening interval (1, 2, or 3y) is noted on each symbol. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 13. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for FIT and sDNA-FIT Screening Strategies, by Model



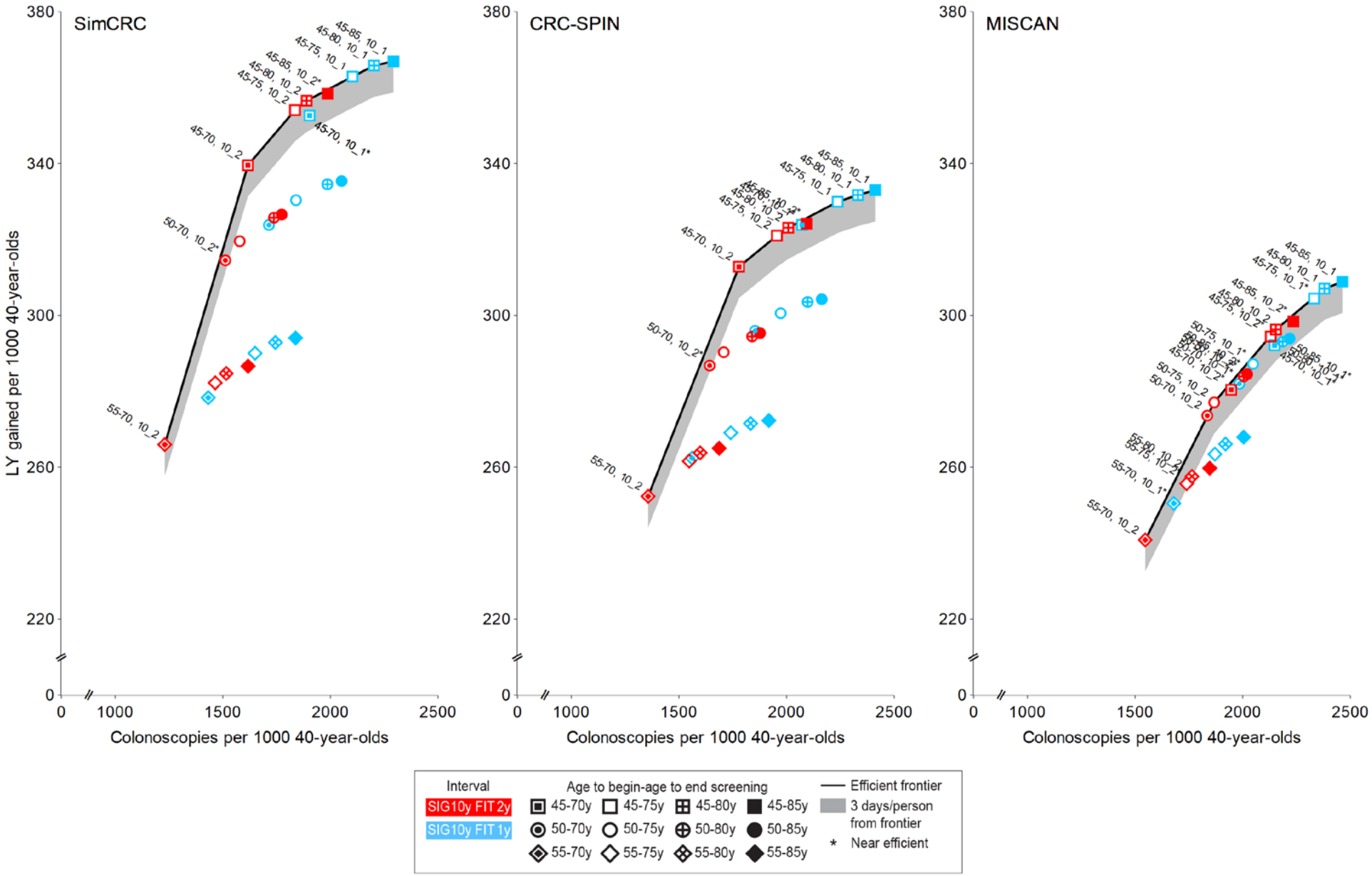
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 14. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Strategies, by Model



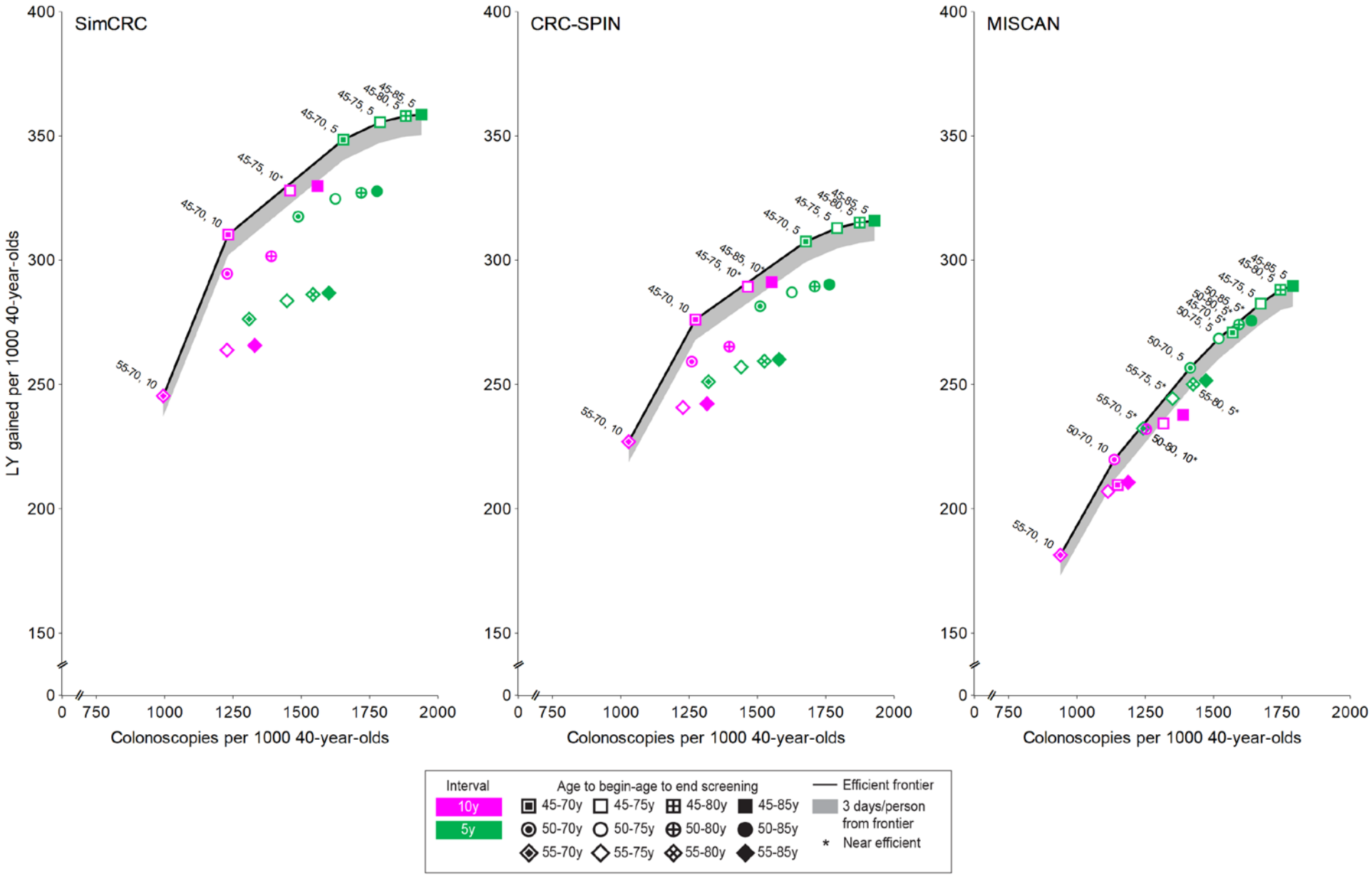
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 15. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies, by Model



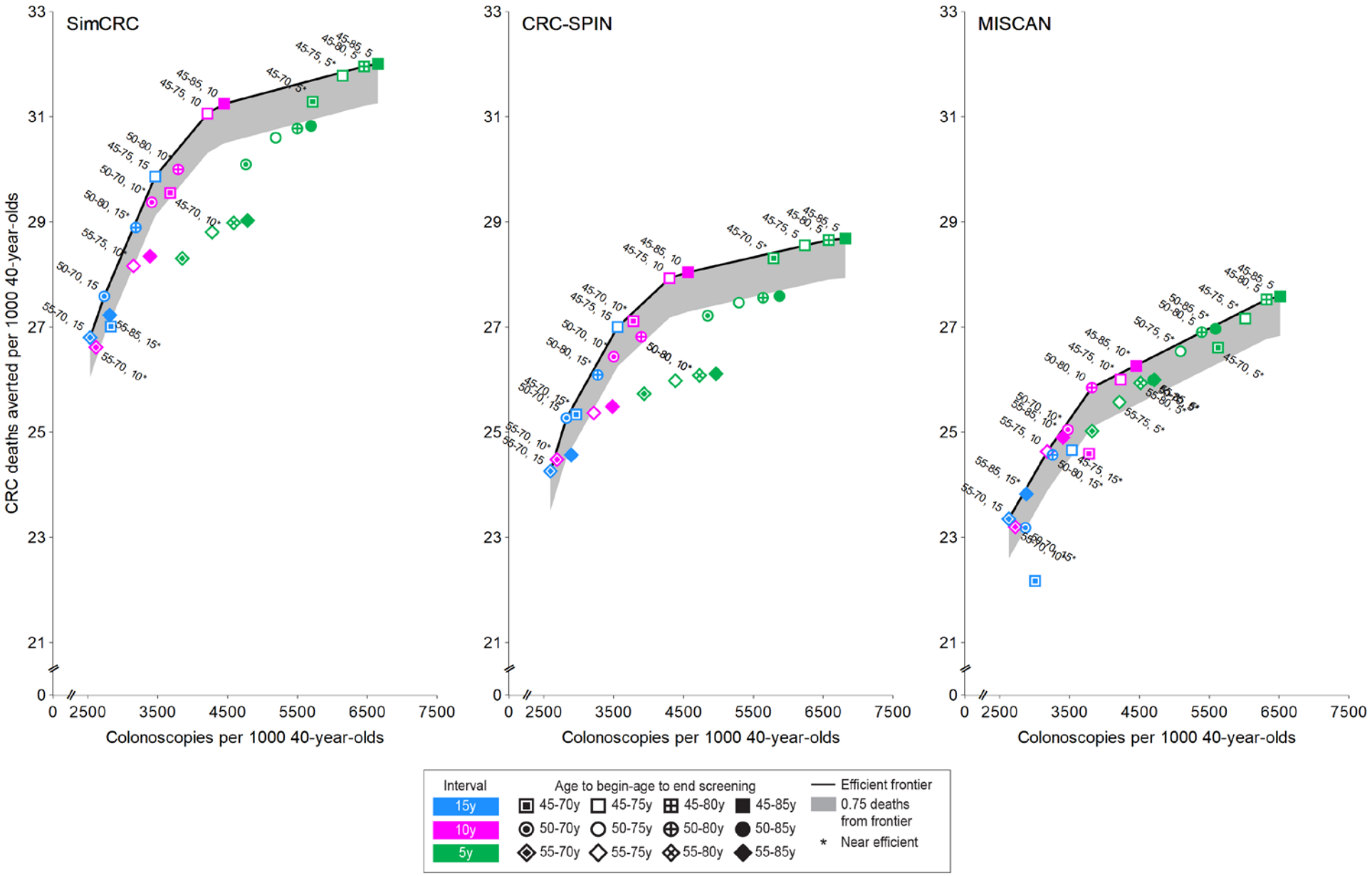
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 16. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Computed Tomographic Colonography Screening Strategies, by Model



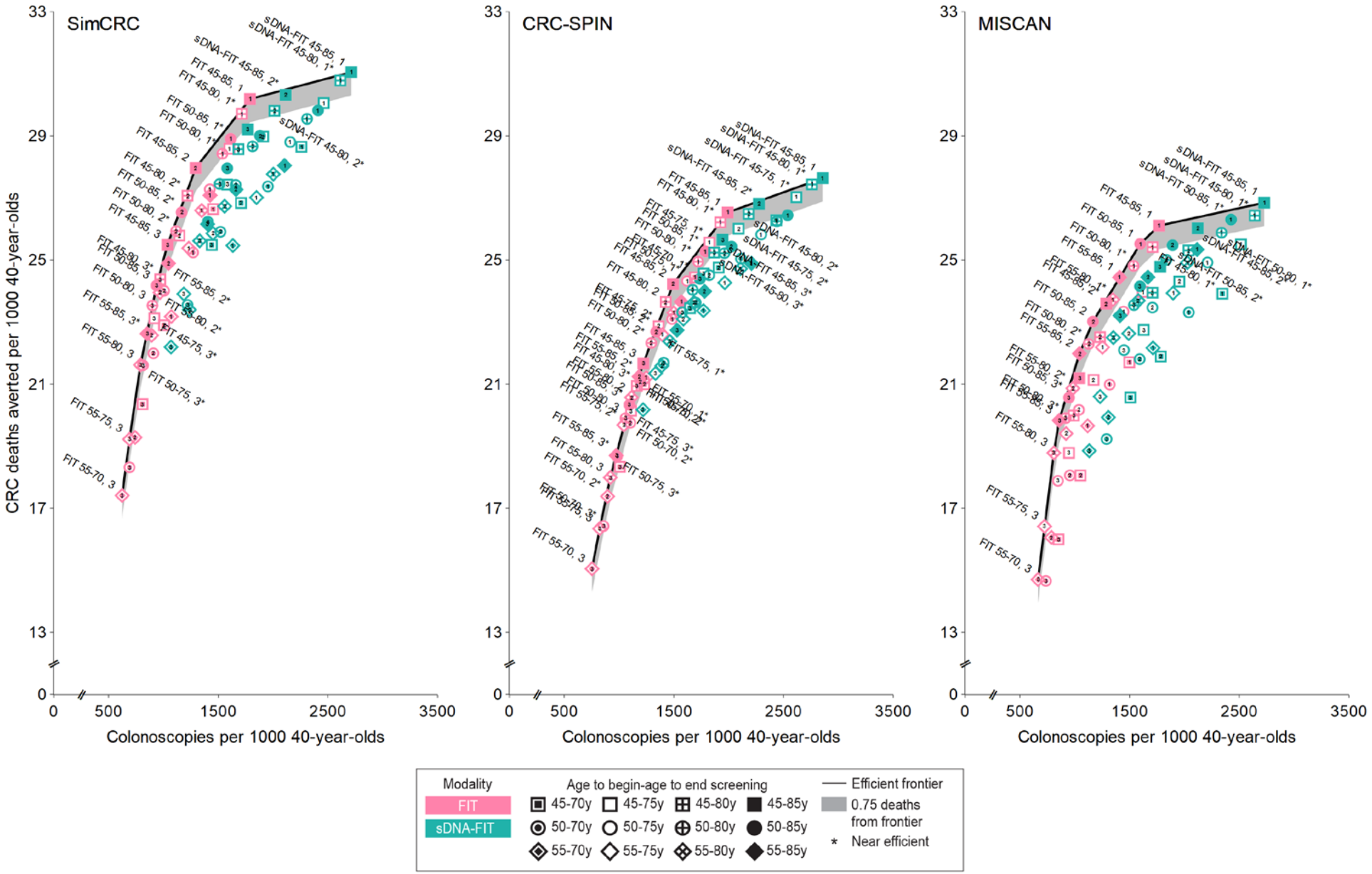
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 17. Estimated Colonoscopies and Colorectal Cancer Deaths Averted for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies, by Model



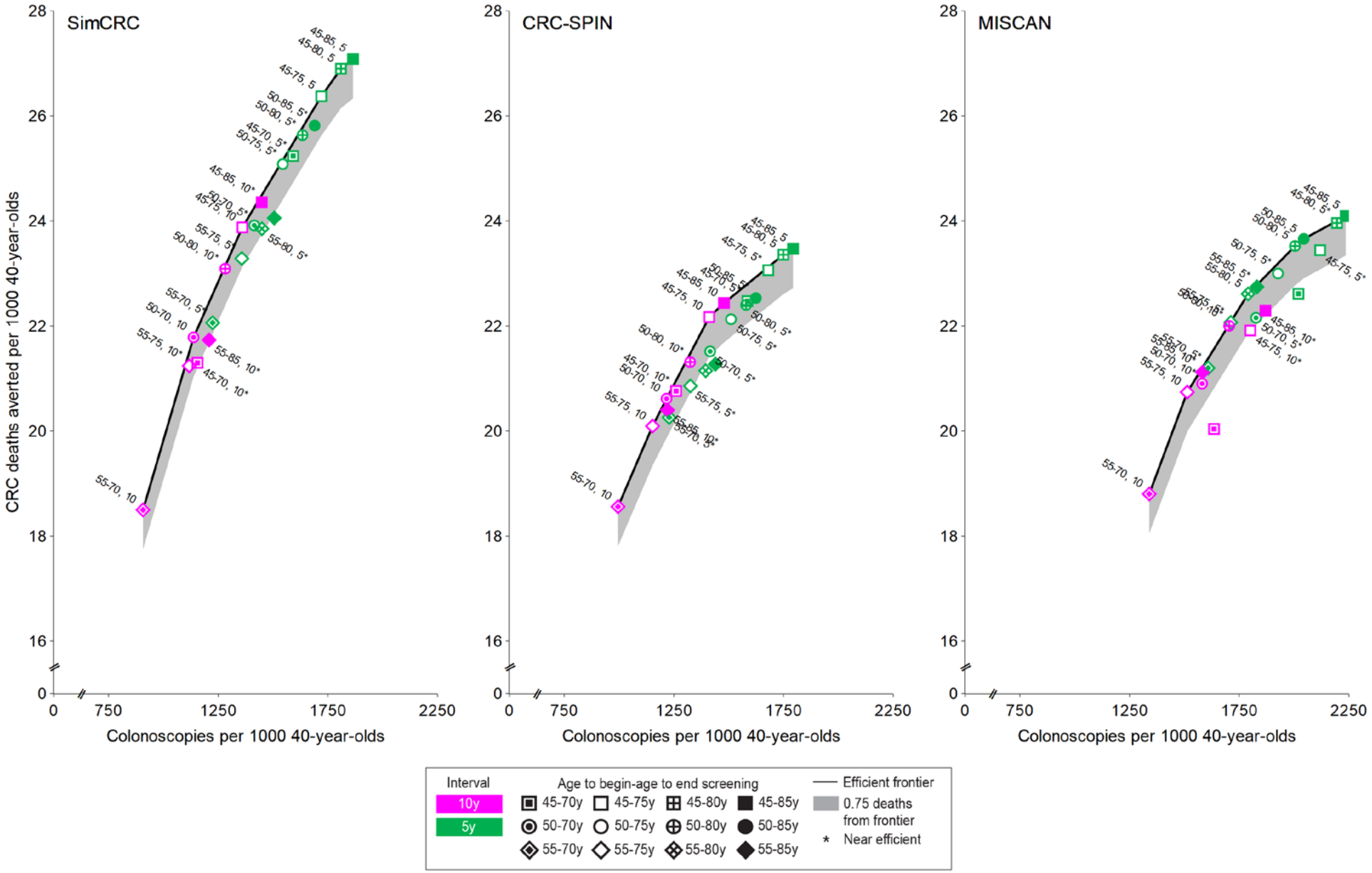
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 18. Estimated Colonoscopies and Colorectal Cancer Deaths Averted for a Cohort of 40-Year-Olds for FIT and sDNA-FIT Screening Strategies, by Model



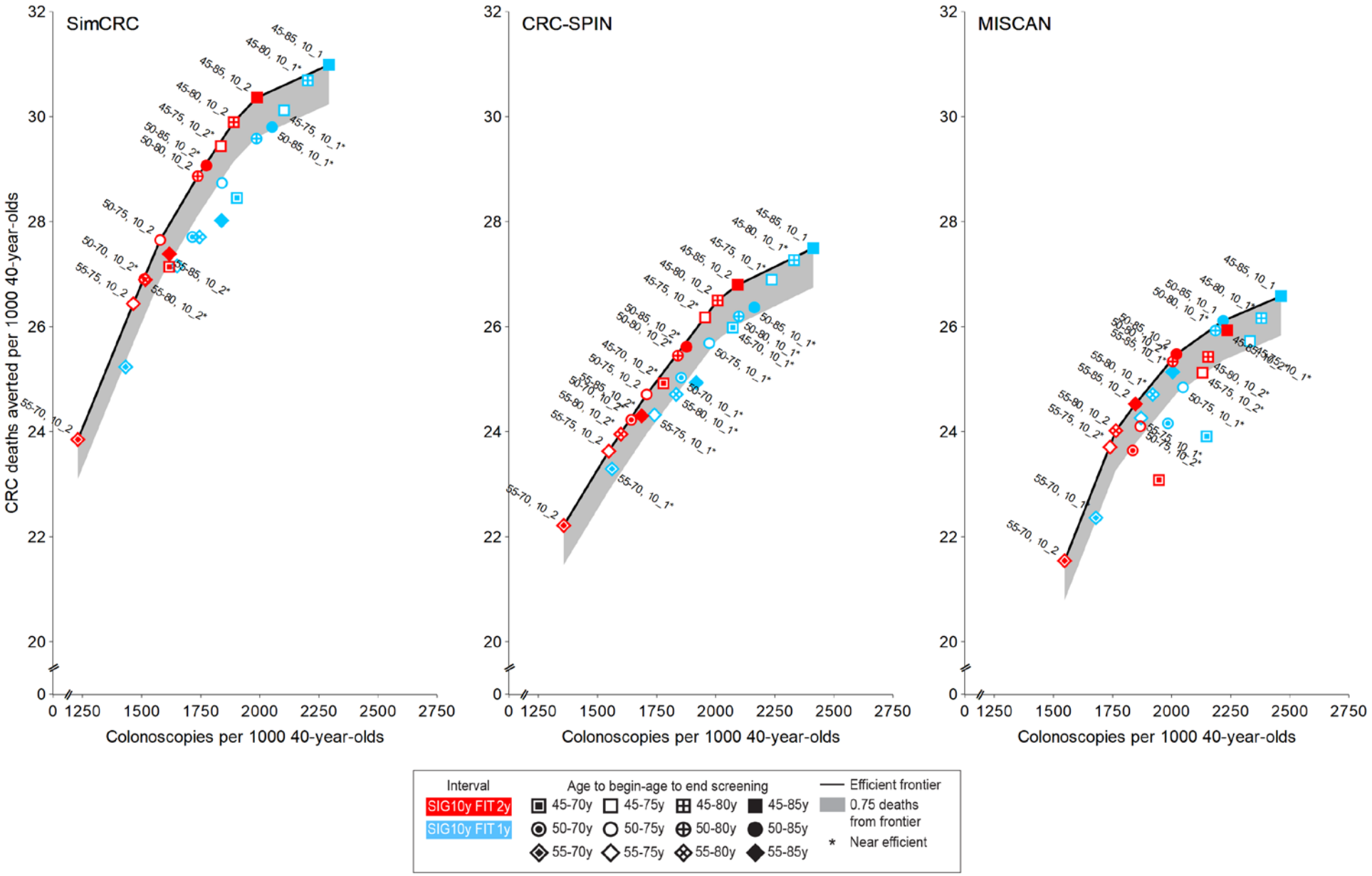
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 19. Estimated Colonoscopies and Colorectal Cancer Deaths Averted for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Strategies, by Model



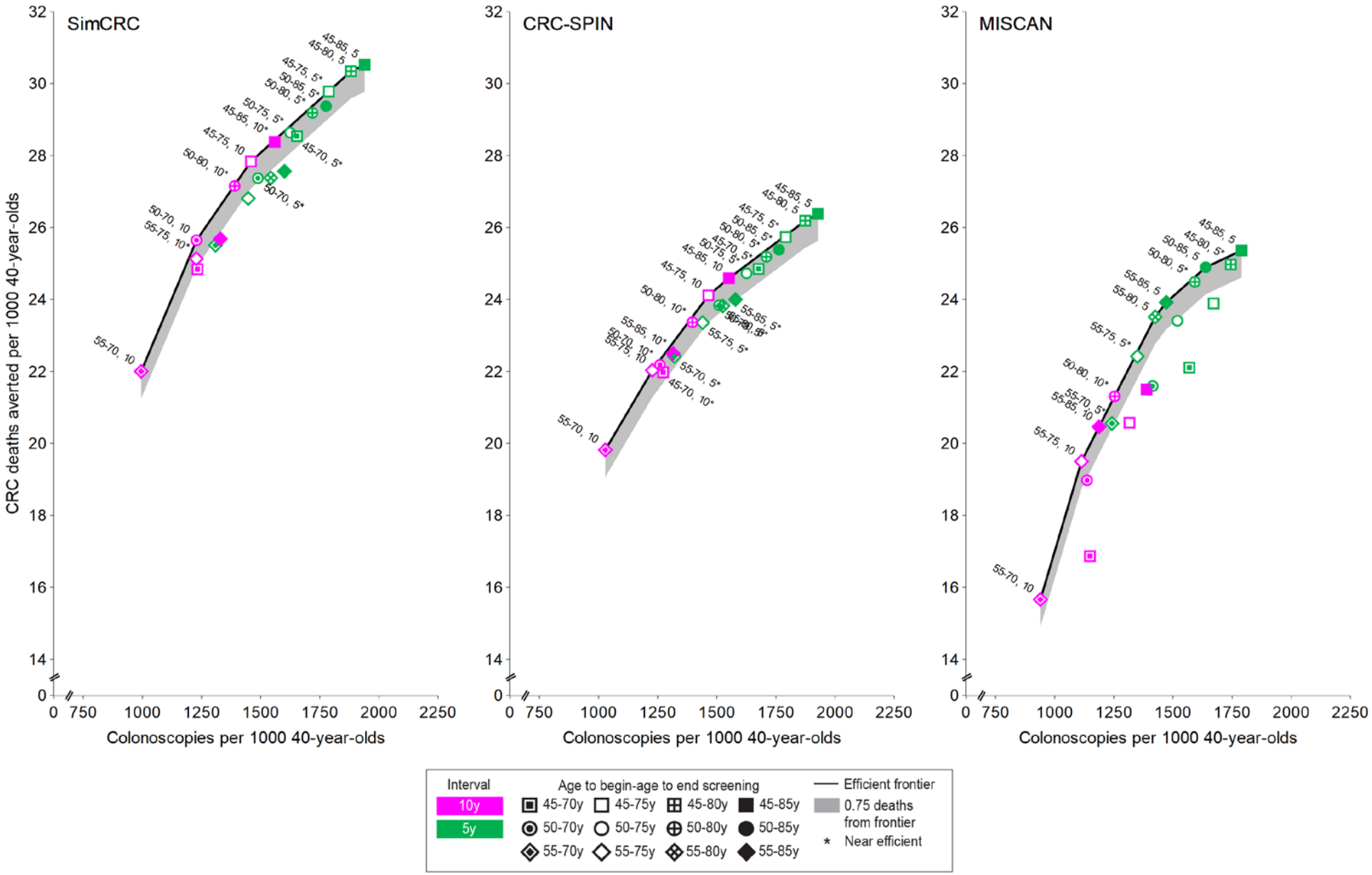
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 20. Estimated Colonoscopies and Colorectal Cancer Deaths Averted for a Cohort of 40-Year-Olds for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies, by Model



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 21. Estimated Colonoscopies and Colorectal Cancer Deaths Averted for a Cohort of 40-Year-Olds for Computed Tomographic Colonography Screening Strategies, by Model



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Figure 22a. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies, by Risk Scenario: SimCRC

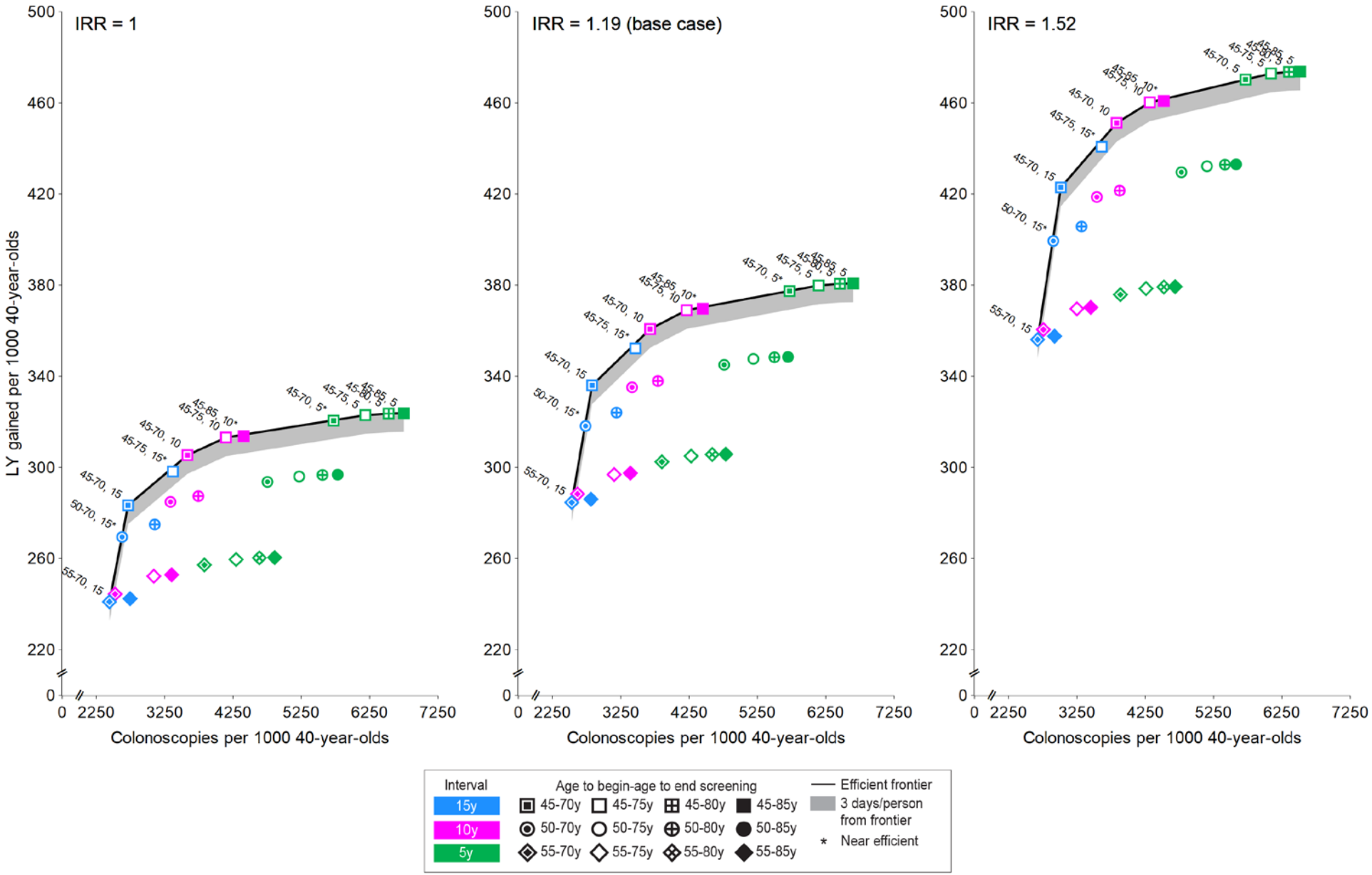


Figure 22b. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies, by Risk Scenario: CRC-SPIN

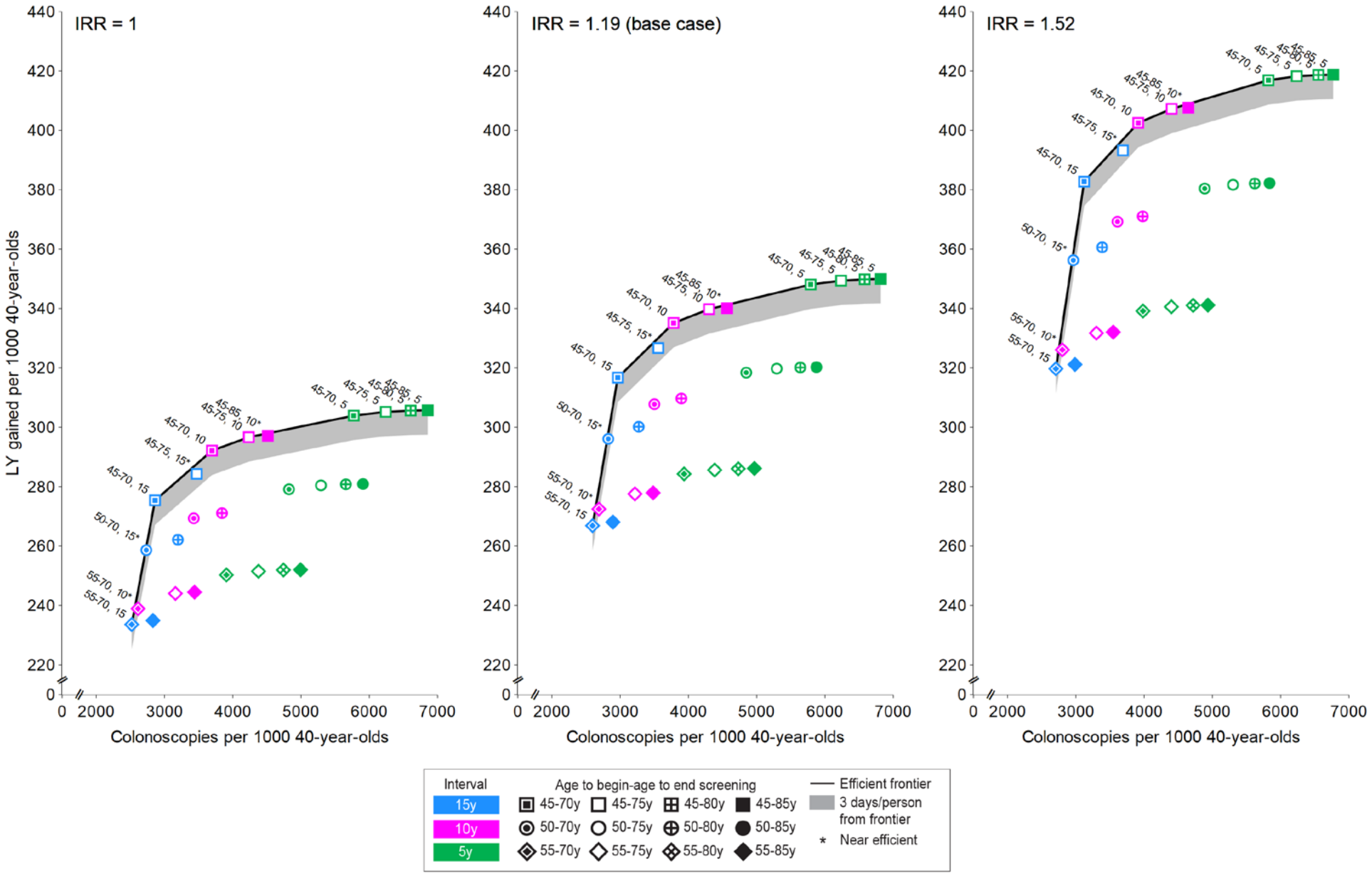


Figure 22c. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies, by Risk Scenario: MISCAN

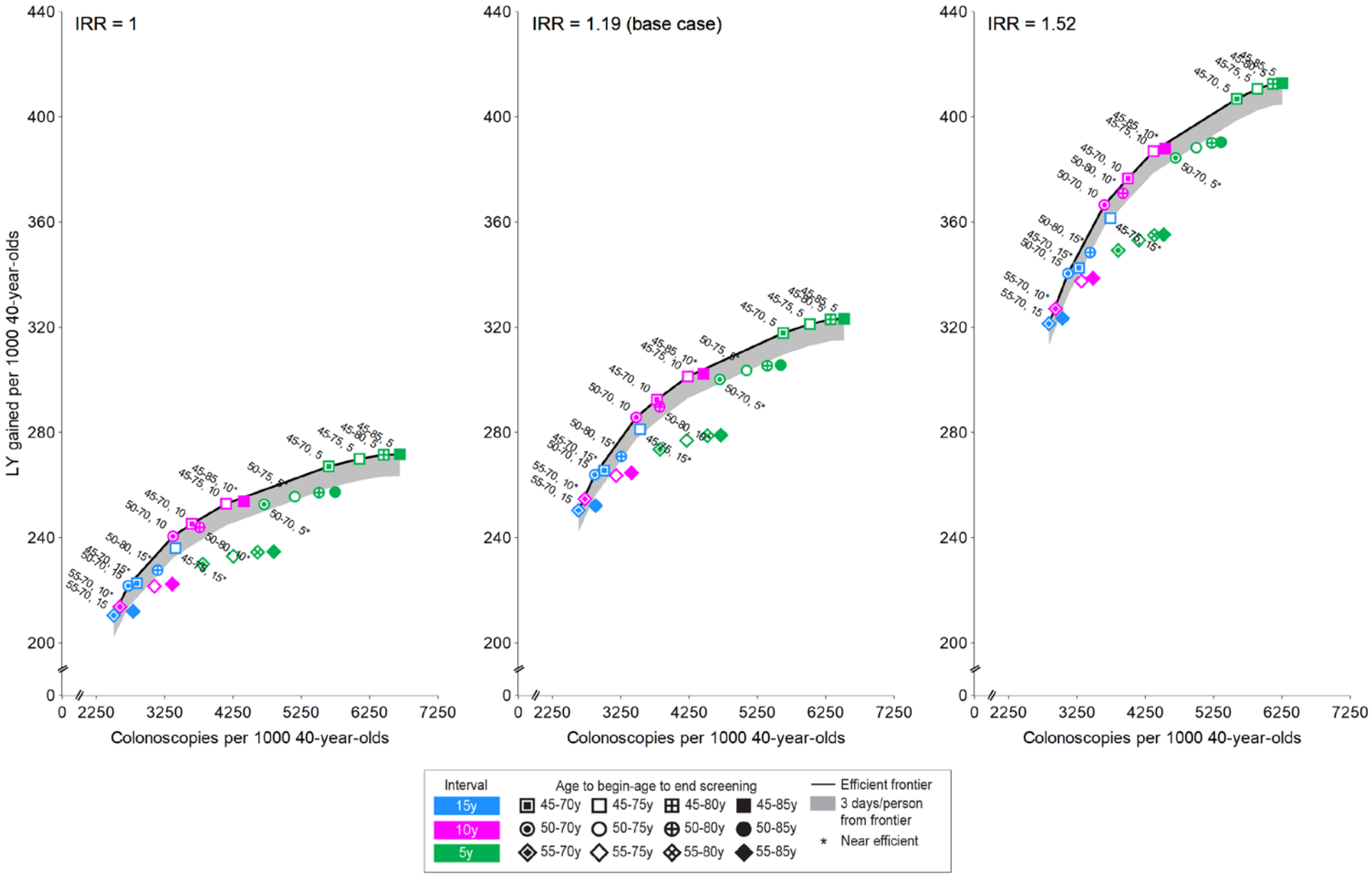


Figure 23a. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for FIT and sDNA-FIT Screening Strategies, by Risk Scenario: SimCRC

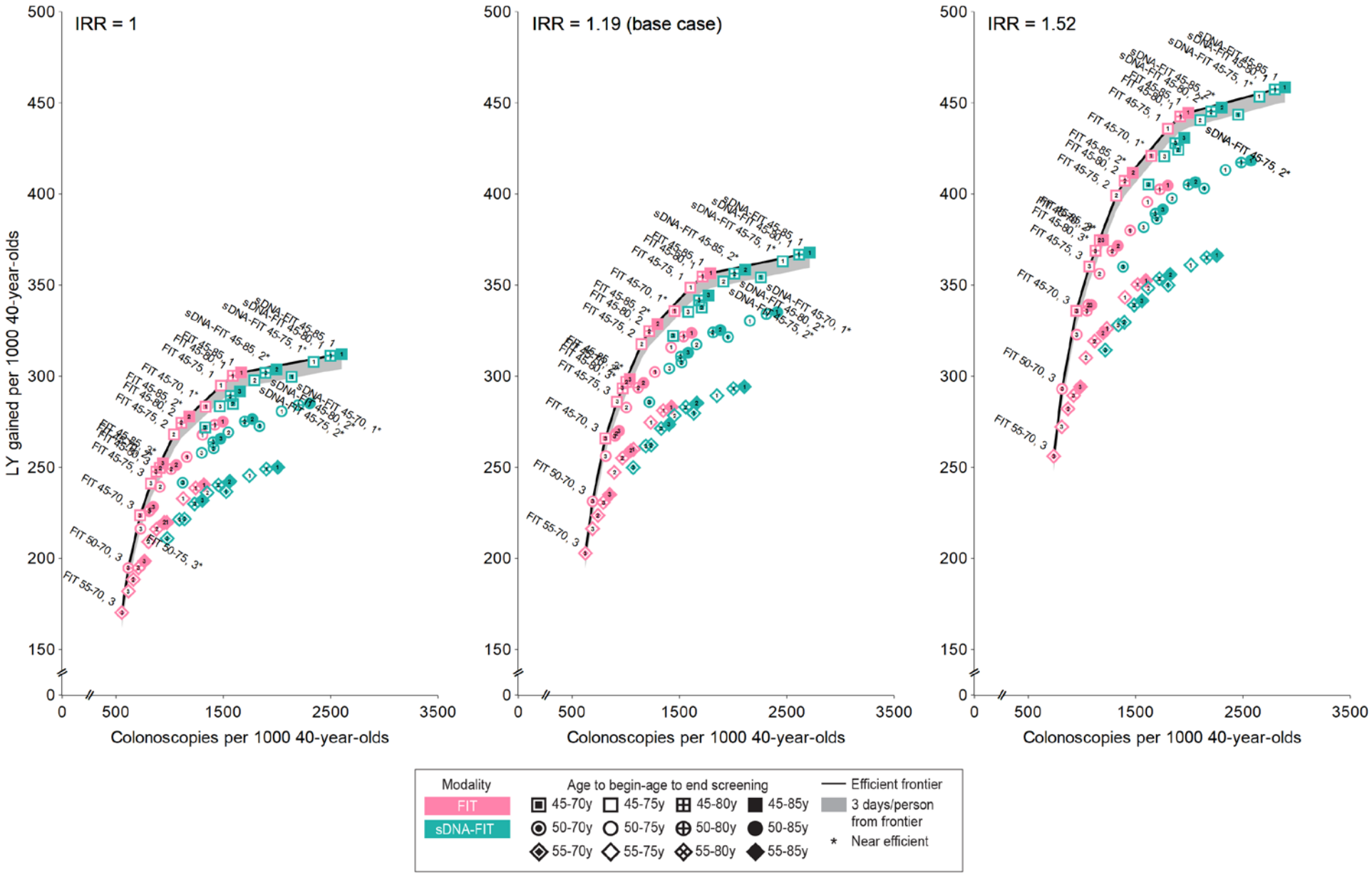


Figure 23b. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for FIT and sDNA-FIT Screening Strategies, by Risk Scenario: CRC-SPIN

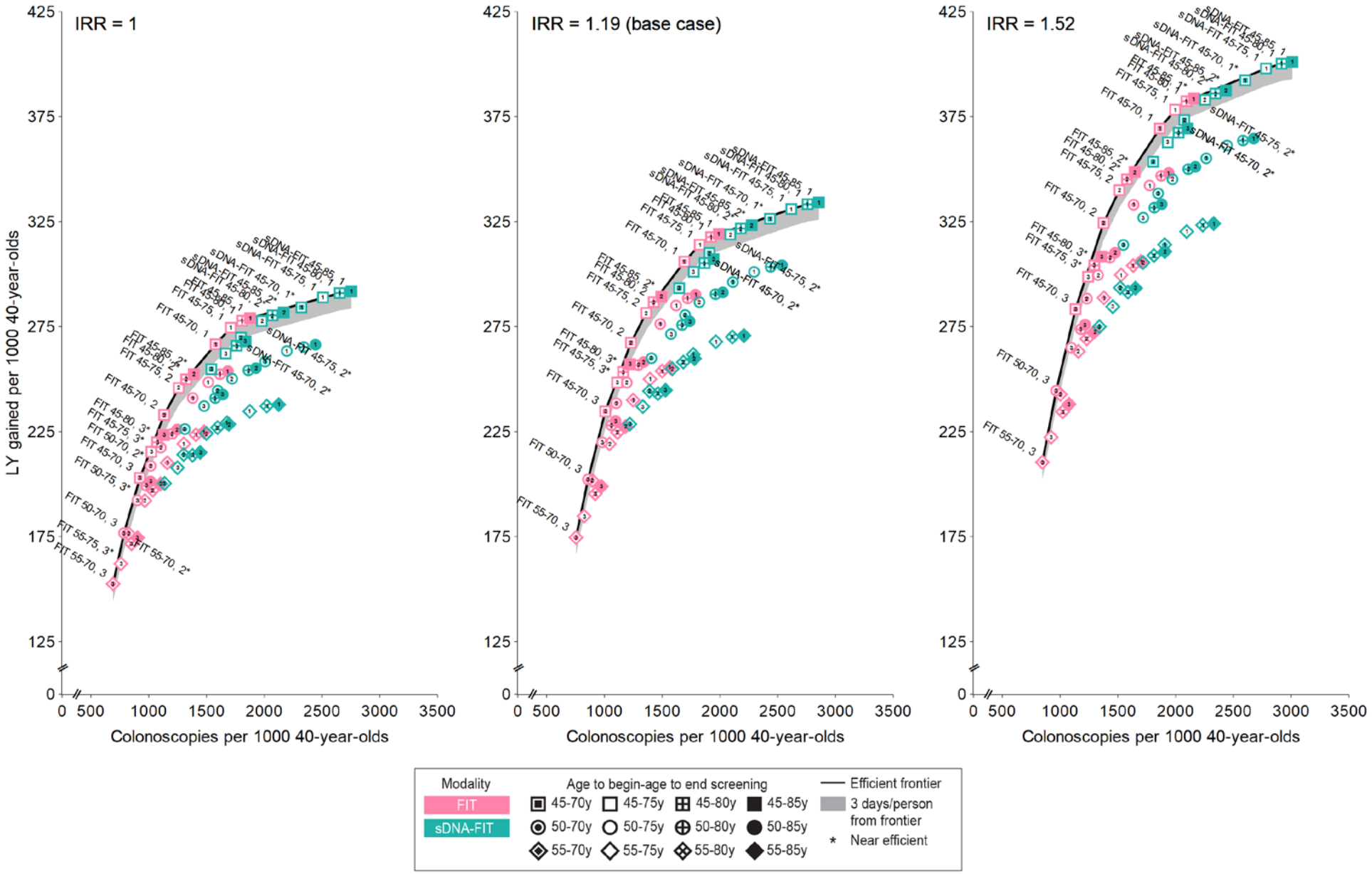


Figure 23c. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for FIT and sDNA-FIT Screening Strategies, by Risk Scenario: MISCAN

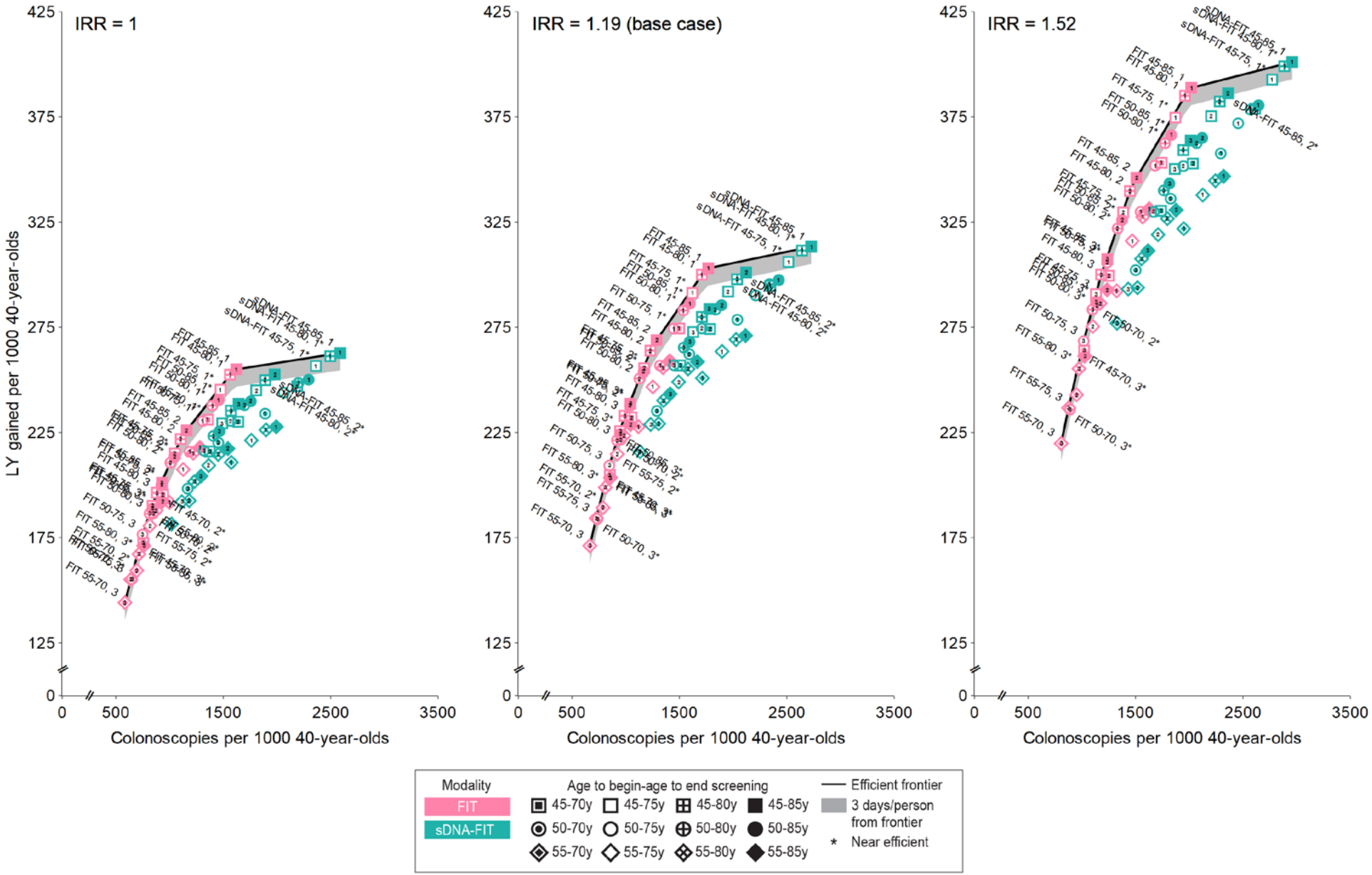


Figure 24a. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Strategies, by Risk Scenario: SimCRC

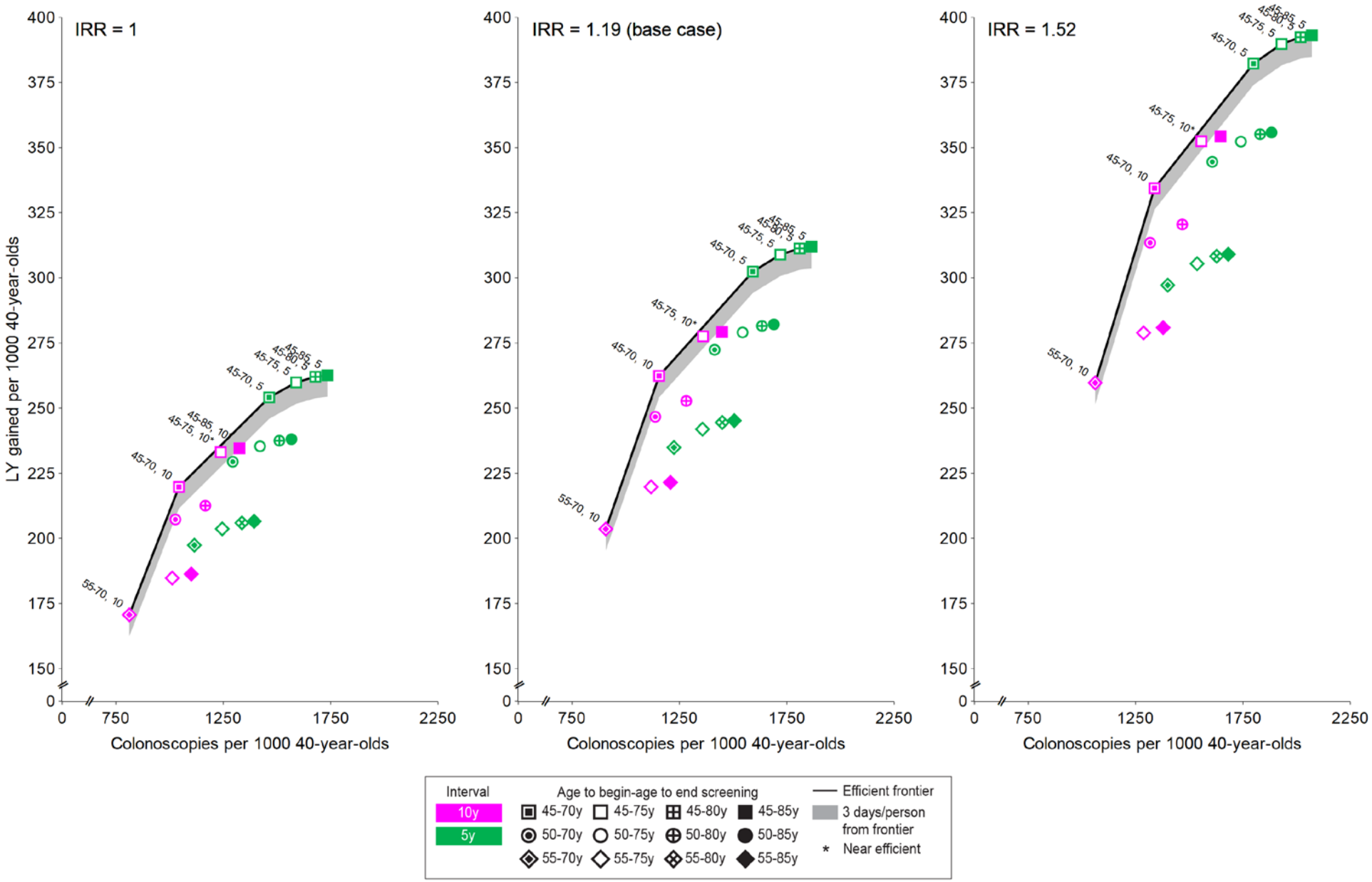


Figure 24b. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Strategies, by Risk Scenario: CRC-SPIN

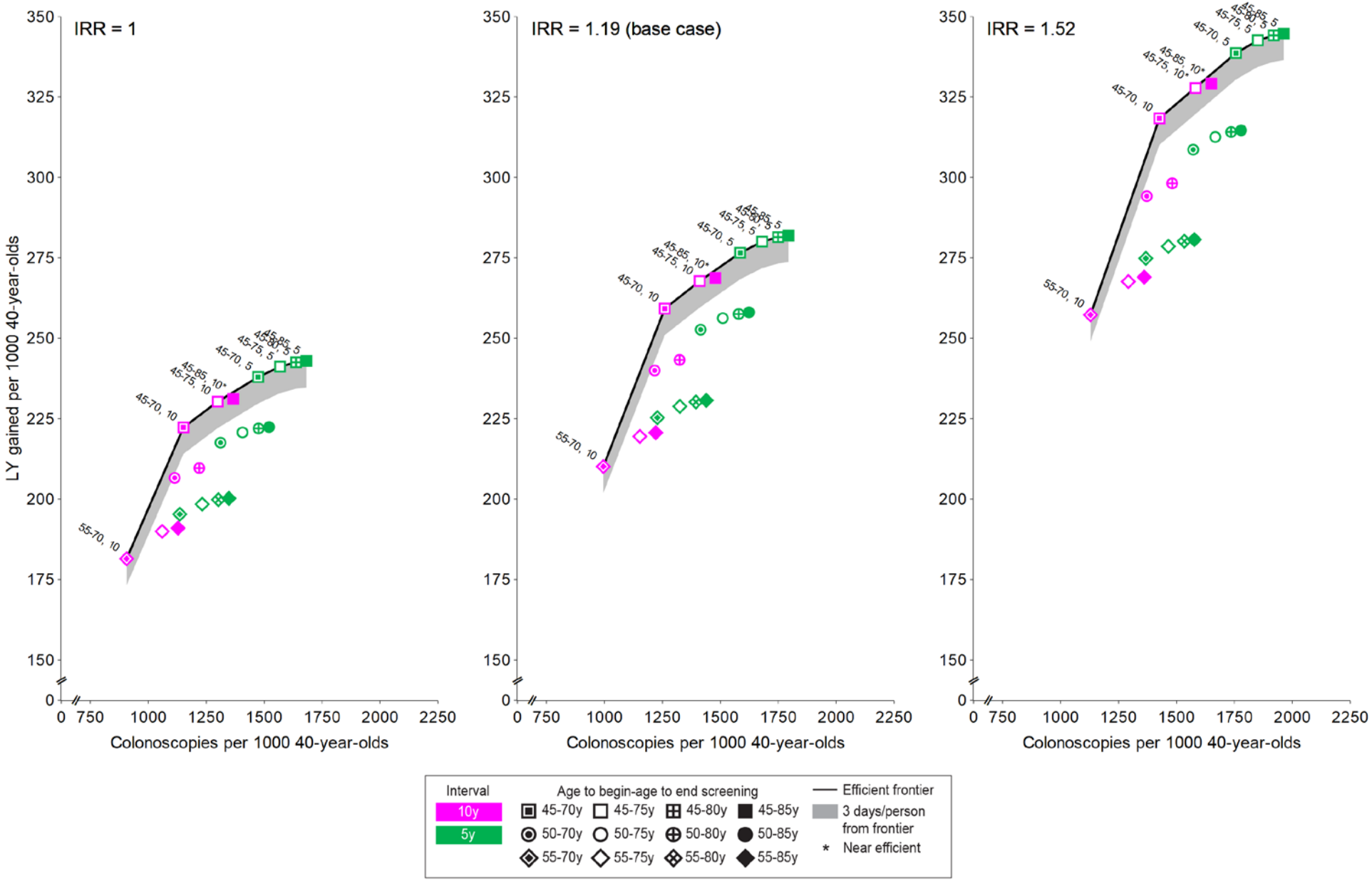


Figure 24c. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Strategies, by Risk Scenario: MISCAN

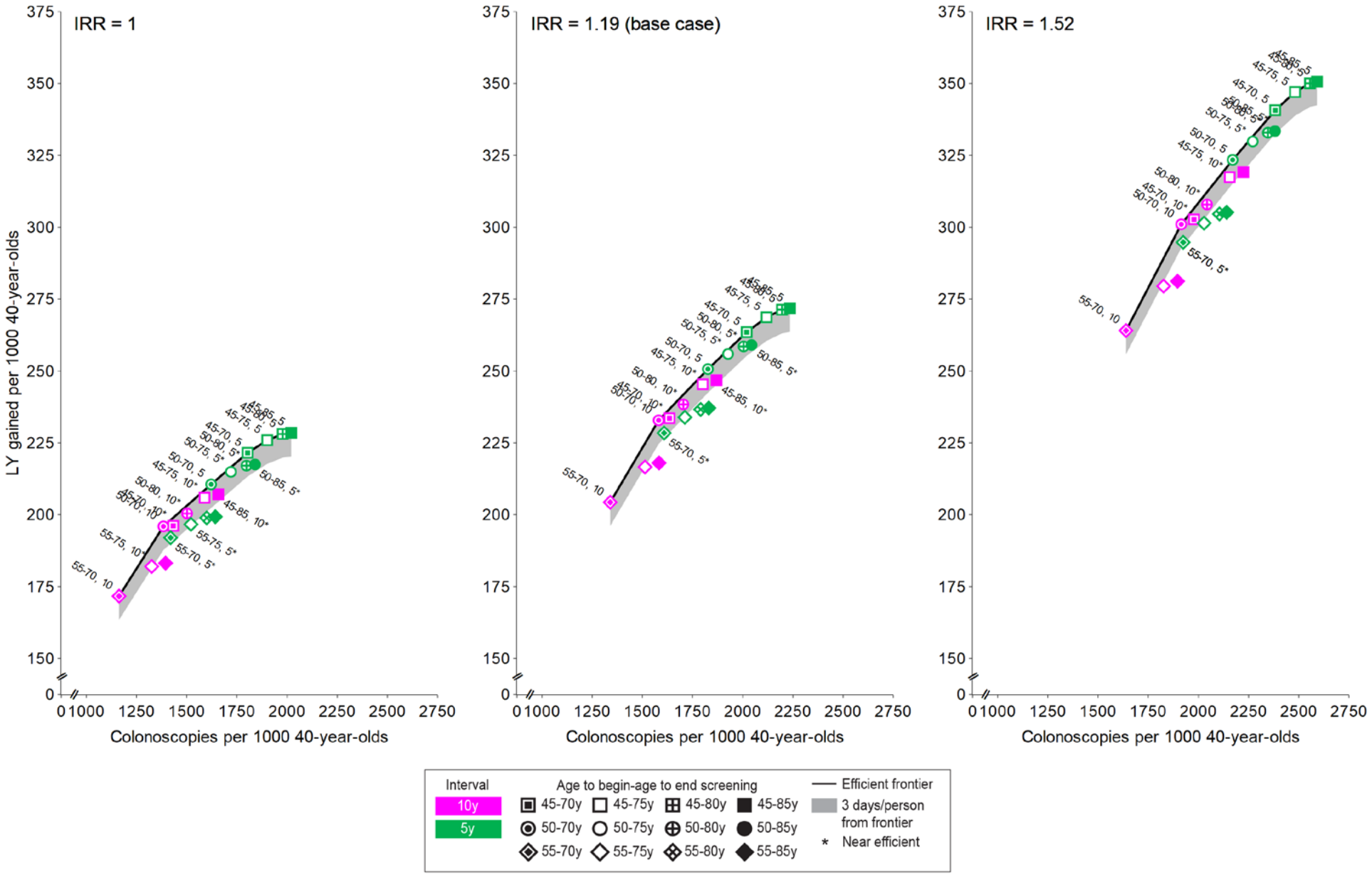


Figure 25a. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies, by Risk Scenario: SimCRC

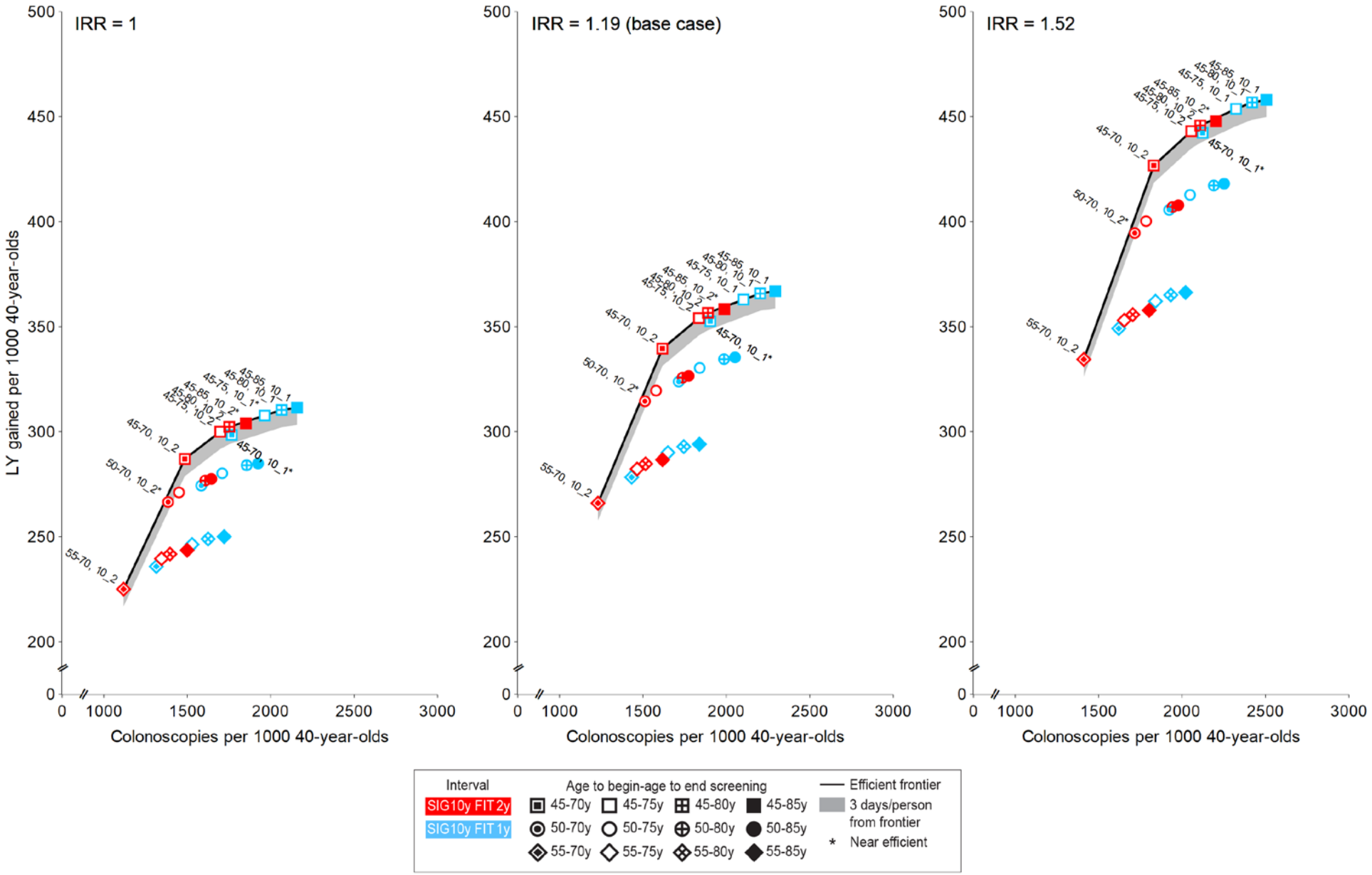


Figure 25b. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies, by Risk Scenario: CRC-SPIN

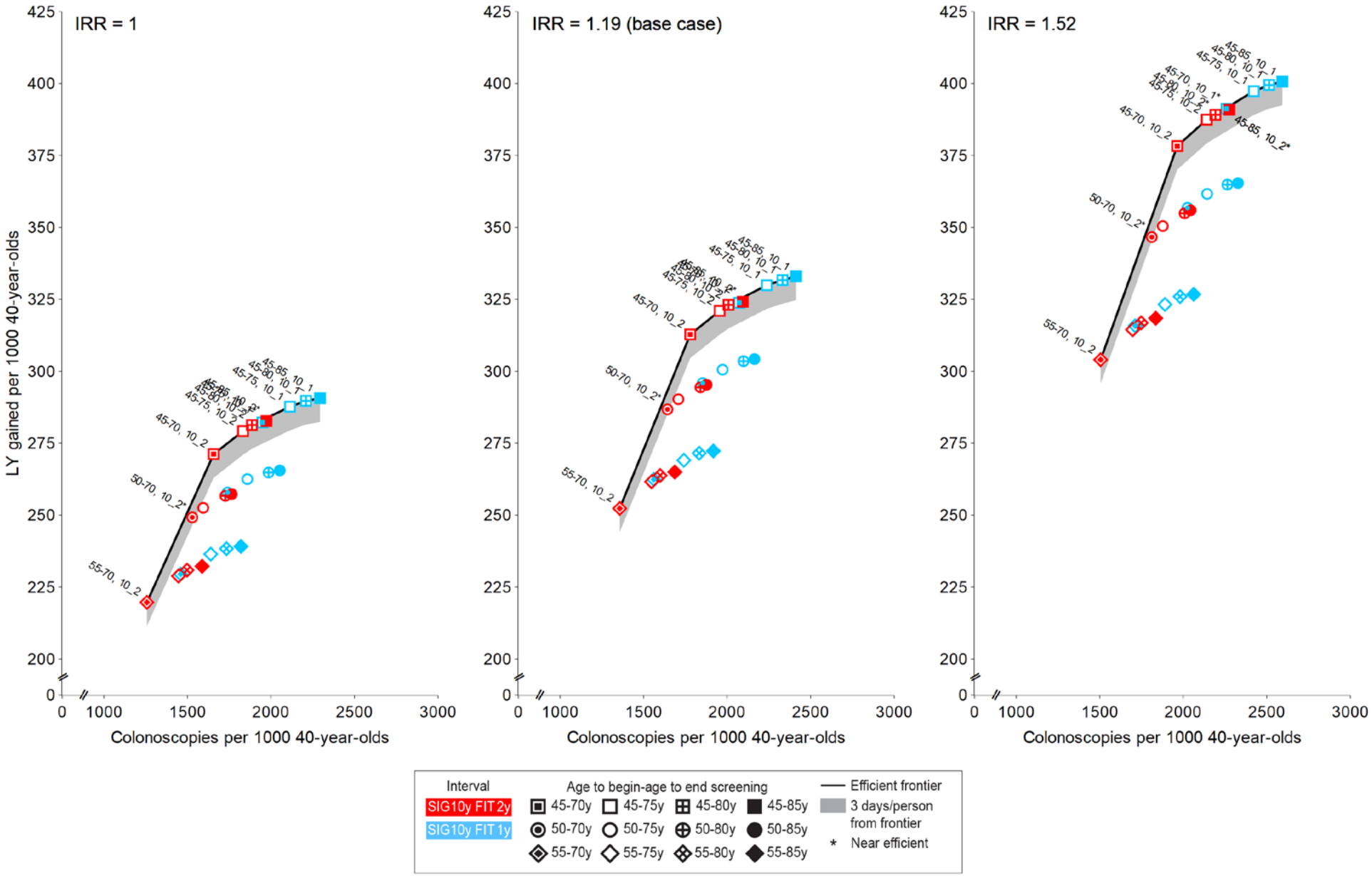


Figure 25c. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies, by Risk Scenario: MISCAN

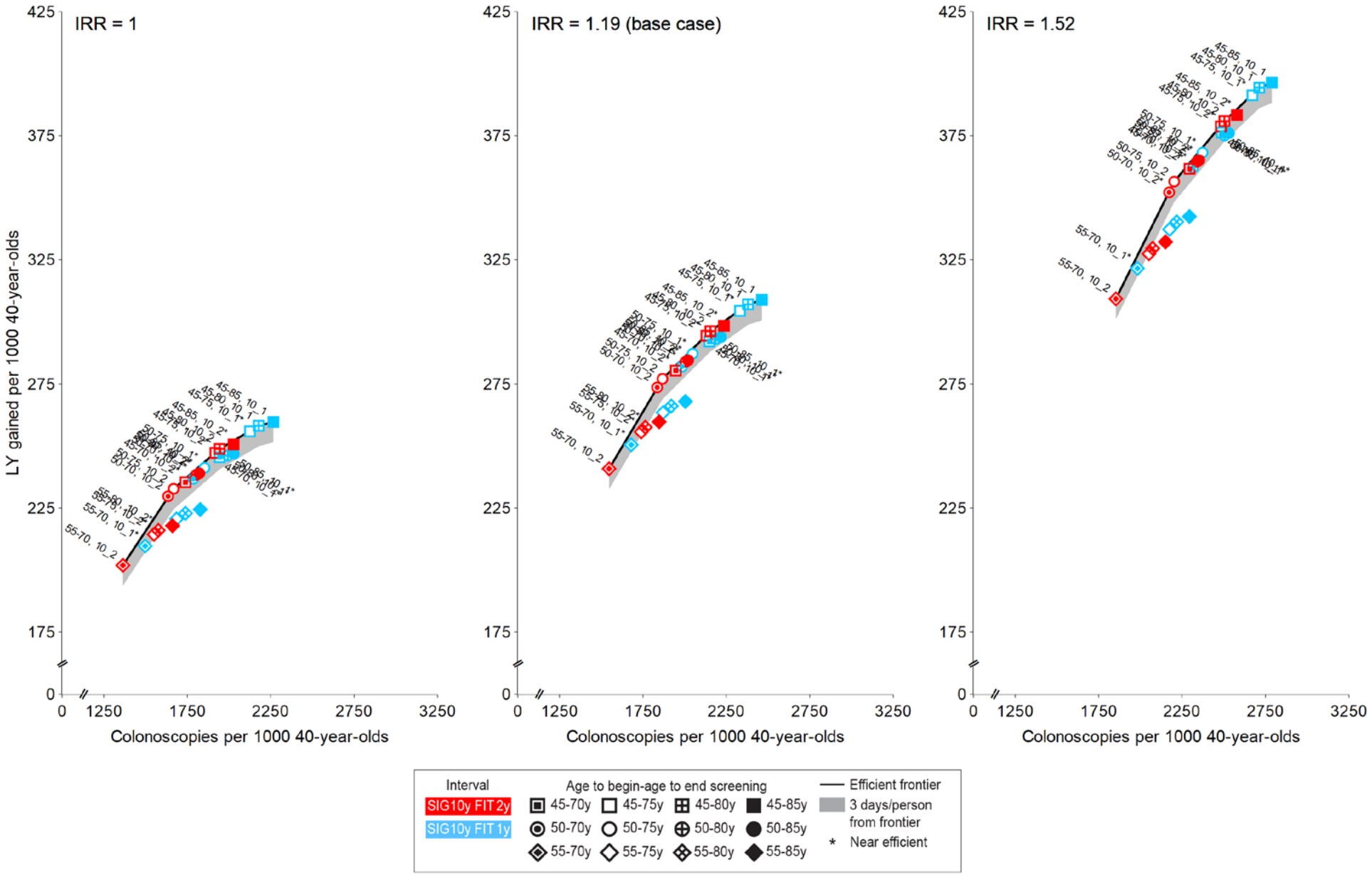


Figure 26a. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Computed Tomographic Colonography Screening Strategies, by Risk Scenario: SimCRC

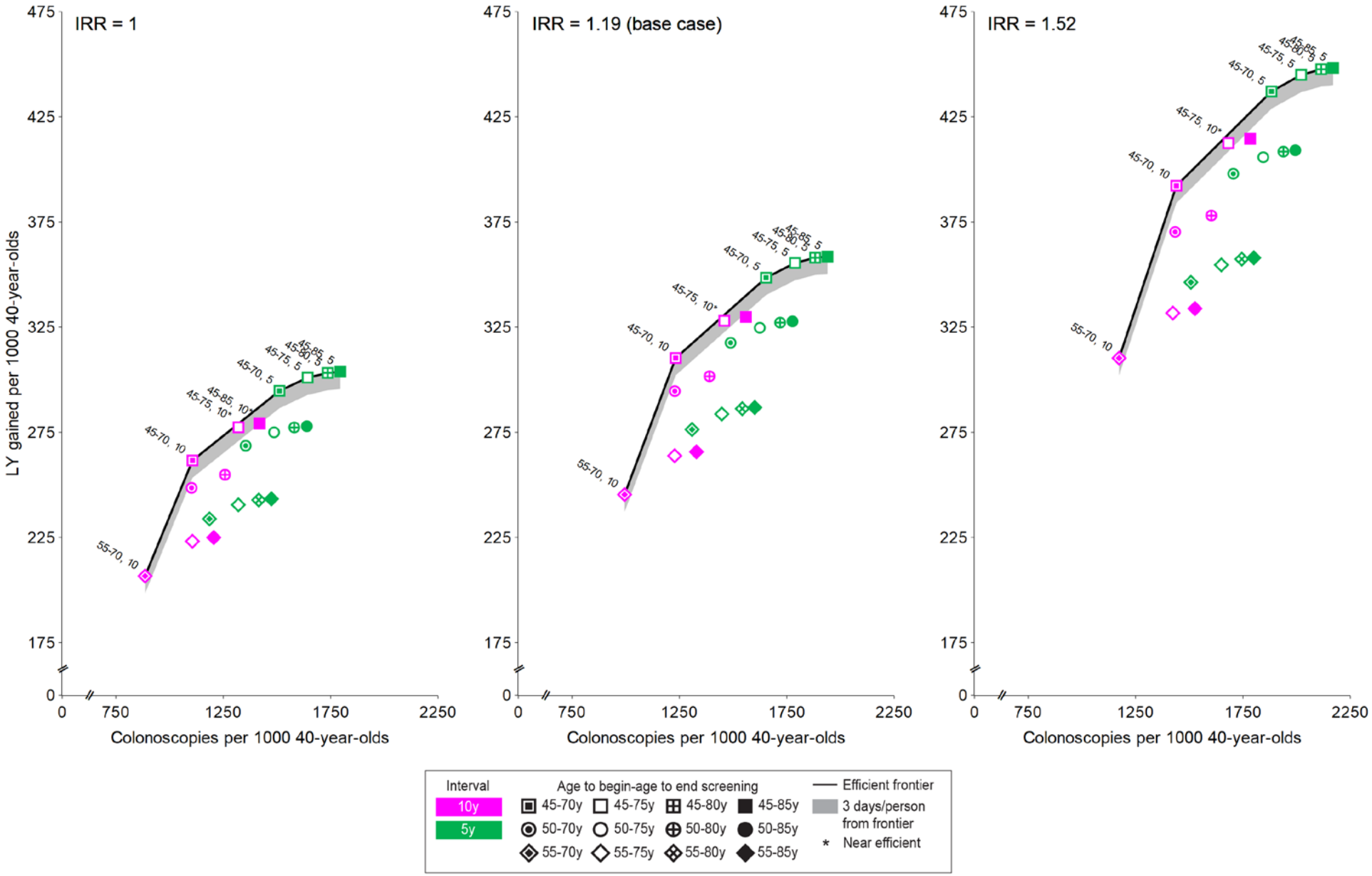


Figure 26b. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Computed Tomographic Colonography Screening Strategies, by Risk Scenario: CRC-SPIN

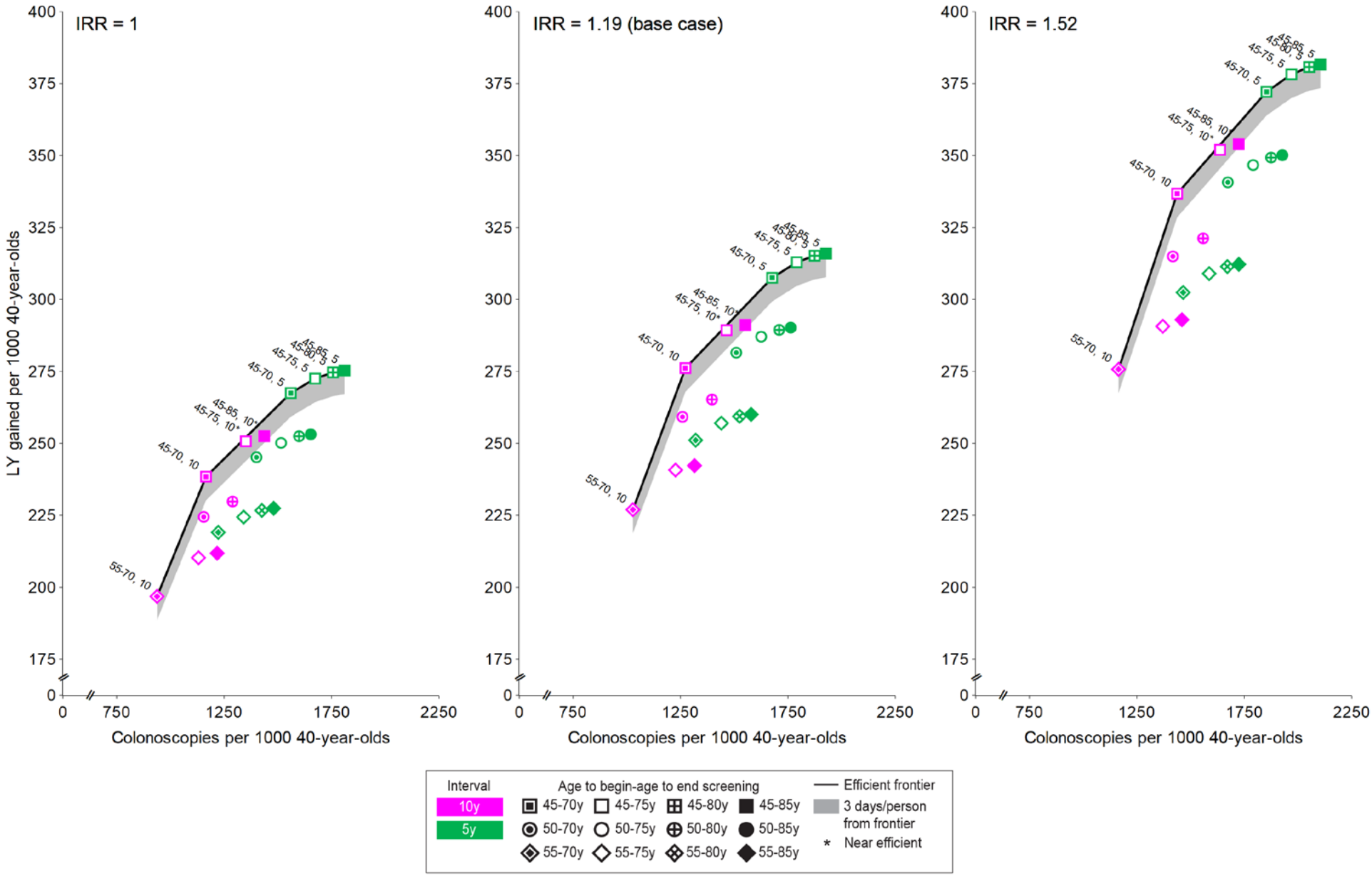


Figure 26c. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Computed Tomographic Colonography Screening Strategies, by Risk Scenario: MISCAN

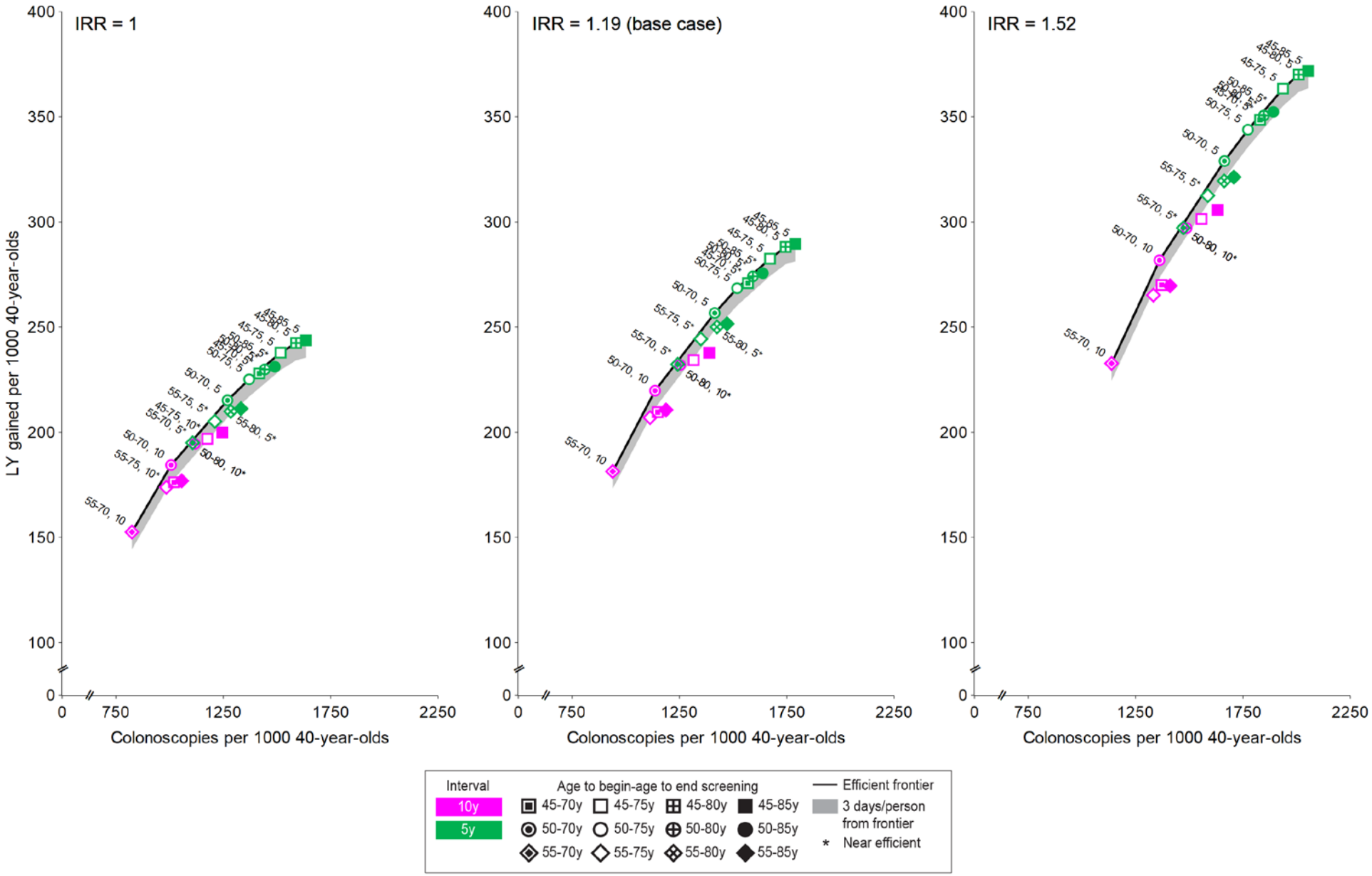


Figure 27. Estimated Benefits, Harms and Burden of Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016 (With Screening From Ages 50 to 75 Years) and the Change in Outcomes When Screening Is Started at Age 45 Instead of At Age 50

[A] Benefit: Life-years gained per 1000 individuals screened*

Screening Modality and Frequency	Life-Years Gained if Start Screening at Age 50				Additional Life-Years Gained if Start Screening at Age 45			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT 1y	316	285	274	292	+33	+29	+17	+26
HSgFOBT 1y†‡	297	261	258	272	+33	+29	+17	+26
sDNA-FIT 1y	330	301	290	307	+33	+30	+16	+26
sDNA-FIT 3y‡	304	271	257	278	+31	+30	+16	+25
Direct visualization tests								
COL 10y	335	308	286	310	+34	+32	+16	+27
CTC 5y	325	287	268	293	+31	+26	+14	+24
SIG 5y	279	256	256	264	+30	+24	+13	+22
SIG 10y + FIT 1y	330	301	287	306	+33	+29	+17	+26

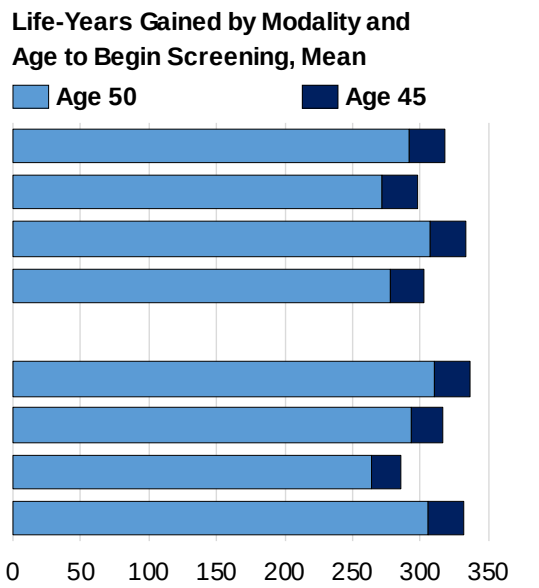


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Figure 27. Estimated Benefits, Harms and Burden of Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016 (With Screening From Ages 50 to 75 Years) and the Change in Outcomes When Screening Is Started at Age 45 Instead of At Age 50

[B] Benefit: CRC cases averted per 1000 individuals screened*

Screening Modality and Frequency	CRC Cases Averted if Start Screening at Age 50				Additional CRC Cases Averted if Start Screening at Age 45			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT 1y	55	53	33	47	+4	+3	+1	+3
HSgFOBT 1y†‡	44	45	27	39	+4	+4	+2	+3
sDNA-FIT 1y	63	59	41	54	+4	+3	+1	+3
sDNA-FIT 3y‡	51	51	31	44	+4	+3	+1	+3
Direct visualization tests								
COL 10y	67	62	45	58	+4	+3	+2	+3
CTC 5y	64	57	38	53	+3	+2	+1	+2
SIG 5y	56	51	41	49	+3	+2	+1	+2
SIG 10y + FIT 1y	63	59	41	54	+4	+3	+2	+3

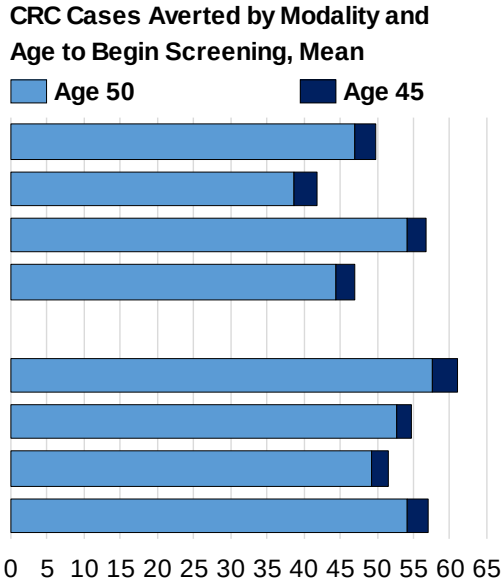

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Figure 27. Estimated Benefits, Harms and Burden of Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016 (With Screening From Ages 50 to 75 Years) and the Change in Outcomes When Screening Is Started at Age 45 Instead of At Age 50

[C] Benefit: CRC deaths averted per 1000 individuals screened*

Screening Modality and Frequency	CRC Deaths Averted if Start Screening at Age 50				Additional CRC Deaths Averted if Start Screening at Age 45			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT 1y	27	24	23	25	+1	+1	+0.6	+1
HSgFOBT 1y†‡	25	22	22	23	+1	+1	+0.7	+1
sDNA-FIT 1y	29	26	25	27	+1	+1	+0.6	+1
sDNA-FIT 3y‡	26	23	22	24	+1	+1	+0.6	+1
Direct visualization tests								
COL 10y	29	26	25	27	+2	+1	+1	+1
CTC 5y	29	25	23	26	+1	+1	+0.5	+0.9
SIG 5y	25	22	23	23	+1	+0.9	+0.4	+0.9
SIG 10y + FIT 1y	29	26	25	26	+1	+1	+0.9	+1

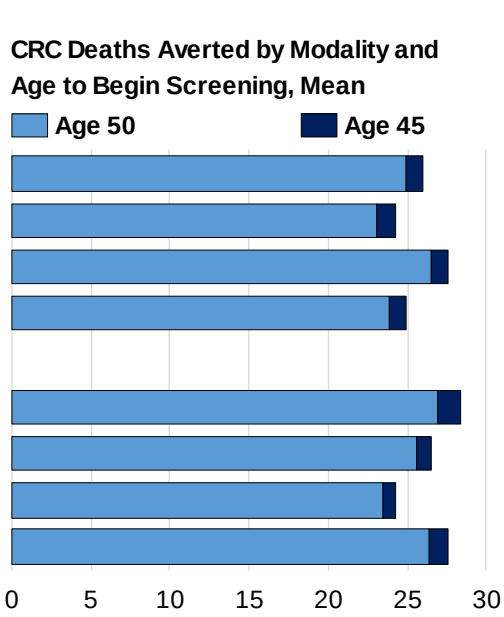

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Figure 27. Estimated Benefits, Harms and Burden of Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016 (With Screening From Ages 50 to 75 Years) and the Change in Outcomes When Screening Is Started at Age 45 Instead of At Age 50

[D] Harms: Complications (gastrointestinal and cardiovascular) of CRC screening and follow-up procedures per 1000 individuals screened*

Screening Modality and Frequency	Complications if Start Screening at Age 50				Additional Complications if Start Screening at Age 45			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT 1y	9	12	10	10	+0.2	+0.4	+0.2	+0.2
HSgFOBT 1y†‡	9	11	9	9	+0.2	+0.5	+0.2	+0.3
sDNA-FIT 1y	11	14	12	12	+0.2	+0.4	+0.2	+0.2
sDNA-FIT 3y‡	9	12	9	10	+0.2	+0.4	+0.2	+0.3
Direct visualization tests								
COL 10y	13	15	14	14	+2	+2	+2	+2
CTC 5y	11	12	10	11	+0.1	+0.2	+0.1	+0.2
SIG 5y	10	11	12	11	+0.1	+0.2	+0.05	+0.1
SIG 10y + FIT 1y	11	13	12	12	+0.6	+0.5	+0.8	+0.6

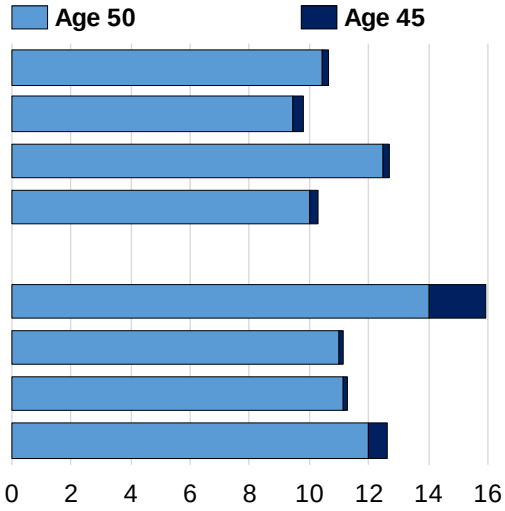

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Figure 27. Estimated Benefits, Harms and Burden of Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016 (With Screening From Ages 50 to 75 Years) and the Change in Outcomes When Screening Is Started at Age 45 Instead of At Age 50

[E] Burden: Lifetime number of colonoscopies per 1000 individuals screened*

Screening Modality and Frequency	Lifetime No. of Colonoscopies if Start Screening at Age 50				Additional Colonoscopies if Start Screening at Age 45			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT 1y	1423	1619	1445	1496	+179	+205	+175	+186
HSgFOBT 1y†‡	1285	1431	1324	1347	+179	+206	+181	+188
sDNA-FIT 1y	2156	2295	2211	2221	+305	+322	+305	+311
sDNA-FIT 3y‡	1405	1576	1449	1477	+177	+196	+179	+184
Direct visualization tests								
COL 10y	3414	3500	3476	3464	+798	+800	+756	+784
CTC 5y	1624	1626	1519	1590	+164	+165	+153	+161
SIG 5y	1544	1510	1927	1660	+176	+170	+192	+179
SIG 10y + FIT 1y	1840	1973	2048	1953	+263	+265	+284	+270

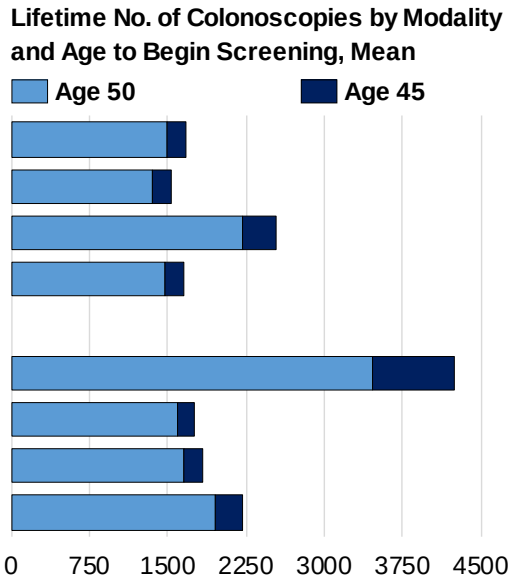

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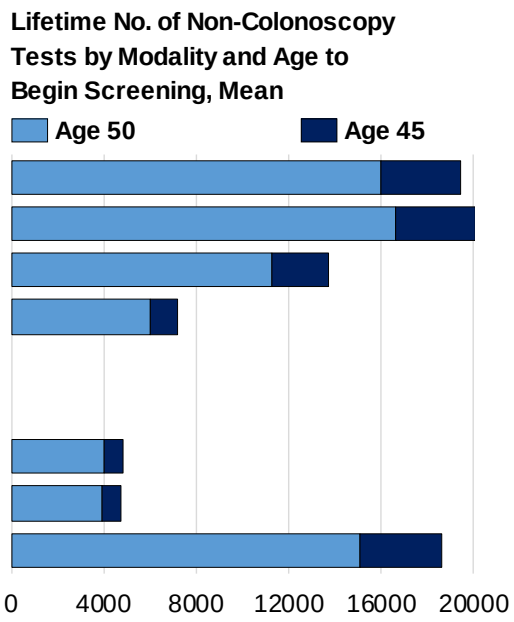
Figure 27. Estimated Benefits, Harms and Burden of Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016 (With Screening From Ages 50 to 75 Years) and the Change in Outcomes When Screening Is Started at Age 45 Instead of At Age 50

[F] Burden: Lifetime number of other (non-colonoscopy) tests[§] per 1000 individuals screened*

Screening Modality and Frequency	Lifetime No. of Non-Colonoscopy Tests if Start Screening at Age 50				Additional Non-Colonoscopy Tests if Start Screening at Age 45			
	SimCRC	CRC-SPIN	MISCAN	Mean	SimCRC	CRC-SPIN	MISCAN	Mean
Stool tests								
FIT 1y	16160	15562	16097	15940	+3520	+3387	+3510	+3472
HSgFOBT 1y[†‡]	16703	16386	16641	16577	+3547	+3443	+3512	+3501
sDNA-FIT 1y	11463	11132	11315	11303	+2425	+2361	+2383	+2390
sDNA-FIT 3y[‡]	6074	5939	6006	6006	+1201	+1166	+1199	+1188
Direct visualization tests								
COL 10y	0	0	0	0	----------	No change		----------
CTC 5y	4006	4088	4075	4056	+798	+805	+806	+803
SIG 5y	4058	4134	3646	3946	+788	+801	+743	+777
SIG 10y + FIT 1y	15636	15371	14257	15088	+3581	+3476	+3602	+3553



FIT indicates fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; HSgFOBT, high sensitivity guaiac-based fecal occult blood test; sDNA-FIT, multitarget stool DNA test (stool DNA test with a fecal immunochemical test); CTC, computed tomographic colonography; SIG, flexible sigmoidoscopy; CRC, colorectal cancer.

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

* Outcomes are expressed per 1000 40-year-olds who start screening at age 45 or at age 50.

† Due to imprecision in sensitivity and specificity, there is considerable uncertainty in model outcomes for HSgFOBT strategies. See **Appendix 4** for details.

‡ Compared to other options for stool-based screening, these strategies do not provide an efficient balance of the burden (i.e., lifetime number of colonoscopies) vs the benefit (life-years gained) of screening.

§ Other (non-colonoscopy) tests include FIT, HSgFOBT, sDNA-FIT, CTC, SIG.

We considered several incidence rate ratio (IRR) estimates, which we used to characterize observed increases in colorectal cancer risk in adults 50 and younger. A key issue was that a simple IRR estimate, based on comparison of age-adjusted colorectal cancer incidence from SEER[115,145] among current 20- to 44-year-olds (i.e., diagnosed in 2012 to 2016) relative to 20 to 44-year-olds diagnosed in 1975-1979 (a time period corresponding with the years of SEER data used for initial model calibration) resulted in IRR estimates that were lower than IRR estimates reported by Siegel et al.[18]

IRR estimates based directly on SEER data, described in section **A1.1**, ranged from 1.23 (95% confidence interval [CI] 1.15 to 1.31) to 1.25 (95% CI 1.19 to 1.31), depending on whether or not rates were delay-adjusted.[146,147] [Note that the initial analysis, based on non delay-adjusted SEER incidence rates, yielded an IRR of 1.19. We later modified the inclusion criteria for the analysis, yielding the estimates reported above.[***] Because this initial estimate was within the 95% confidence intervals reported above for the final estimates, we continued to use IRR of 1.19 in the simulations.] In contrast, Siegel and colleagues estimated age-period-cohort (APC) models using SEER data from 1974 to 2013. The analysis included all tumors recorded in SEER as occurring in the colon or rectum (excluding the appendix) regardless of histology and included all persons aged 20 and older. From these models, they estimate IRRs for colon and rectal cancer for individuals born around 1990 relative to those born around 1950, obtaining estimates of 2.40 for colon cancer (95% CI 1.11 to 5.19) and 4.32 for rectal cancer (95% CI 2.19 to 8.51). We note the high degree of uncertainty in these estimates.

Because of differences in estimated IRRs obtained from analysis of SEER rates and published estimates from APC models, the CISNET Colorectal Cancer Working Group requested that Rebecca Siegel, MPH, of the American Cancer Society fit APC models to SEER data, restricted to 20- to 44-year-olds, to estimate IRRs comparing persons born in 1977 (i.e., 40-year-olds in 2017) vs 1937 (i.e., 40-year-olds in 1977, the midpoint of the years of data the models were initially calibrated to). Consistent with assumptions made for simple SEER comparisons, these analyses excluded carcinoid tumors and other neuroendocrine carcinomas appearing in the colon or rectum[71] and included SEER data through 2016. The revised IRR was 1.37 (95% CI 1.22 to 1.54). Details of Ms. Siegel's analysis and the differences between her analysis for the CISNET Colorectal Cancer Working Group and her published paper are described in section **A1.2**.

There are several reasons for uncertainty in estimated IRRs that capture population-level increases in colorectal cancer risk, which we outline below.

- First, in APC models, *age effects* capture the increasing colorectal cancer risk that is reflected in the increases in colorectal cancer incidence with age, which the CISNET models simulate as an increase in adenoma prevalence and in the probability of adenoma transition to cancer with age; *period effects* capture the effect of changes in medical

[***] The initial analysis included only the following reporting sources: "Hospital inpatient"; "Laboratory only"; "Physician's office/private medical practitioner"; or "Nursing/convalescent home/hospice". The final analysis also included the following reporting sources: "Radiation treatment centers or medical oncology centers" and "Other hospital outpatient units/surgery centers". In both the initial and final SEER analyses, cases with reporting source coded as "Autopsy only" or "Death certificate only" were excluded.

practice, such as the dissemination of screening and the increased use of endoscopic follow-up, over time and can also capture changes in risk, for example, such as changes in diet and exercise or environmental exposures (e.g., antibiotics); *cohort effects* capture changes in risk across generations (e.g., smoking rates).[148] It is difficult to tease apart period and cohort effects because the time scales of age, period, and cohort effects are linearly dependent. In other words, *age + year of birth = year of diagnosis, i.e., age + cohort = period.* APC models are not identifiable without adding constraints to the age, period, and cohort effects, and different constraints can lead to different conclusions, especially about cohort effects.[148]

- Second, there is some uncertainty about which types of cancers to include as colorectal cancers. CISNET modelers focus on specific disease etiology and so include only cancers of the large intestine with histology indicative of colorectal cancer (see **Appendix Table 1.1** for the histology codes included as colorectal cancer). In contrast, original analyses by Siegel and colleagues included cancers with a primary location in the large intestine, regardless of histology. This includes cancers with histology coded as "8240: carcinoid tumors, NOS" and "8246: neuroendocrine carcinoma". Carcinoid cancers are a type of neuroendocrine cancer that occur throughout the body and have a somewhat different etiology than colorectal cancer. Neuroendocrine tumors are rare, though their incidence has increased in the last 15 years.[149]
- Third, the different modeling approaches each compared slightly different cohorts.
- Finally, IRR estimates are uncertain because even with rising rates, colorectal cancer remains relatively rare before age 50.

A1.1 Specifications for SEER*Stat Incidence Analyses

Appendix Tables 1.1 and **1.2** detail the SEER*Stat analyses for estimation of age-adjusted colorectal cancer incidence rates among current 20- to 44-year-olds (i.e., cases diagnosed in 2012-2016) vs the incidence rate among 20 to 44-year-olds in 1975-1979, a period corresponding with the years of data used for initial calibration of the SimCRC, CRC-SPIN, and MISCAN models. Analyses were performed with and without use of delay-adjusted rates.

A1.2. Information on APC Models by Siegel

Rebecca Siegel, MPH, of the American Cancer Society, carried out specific analyses for the CISNET Colorectal Cancer Working Group to inform increased risk assumptions. Ms. Siegel's published analysis[18] was based on all colorectal cancers in the 9 oldest SEER areas that were diagnosed in adults 20 years and older from 1974 through 2013 (the latest SEER data available at the time). Analyses carried out for CISNET include SEER data up through 2016. Ms. Siegel carried out a series of analyses in response to CISNET queries.

First, APC models were used to estimate IRRs comparing CRC incidence in persons born in 1975 vs 1935 based on SEER data (IRR=1.59).[18,22]

Next, to rule out that possibility that screening is not adequately accounted for by the model, SEER data were restricted to cancers diagnosed at ages 20 to 44 (IRR=1.52).

Finally, APC-modeled IRRs were generated based on the same case selection criteria used for simple IRR estimates (shown in **Appendix Table 1.1**). This case definition excludes colorectal cancer cases diagnosed at autopsy or death certificate only (these cases were included in the published analysis), second (or later) primaries, and cancers located in the colon and rectum that do not have histology indicative of colorectal cancer (the published analysis included all cancers in the colon and rectum including, for example, carcinoid tumors and other neuroendocrine carcinomas). The resulting rate ratio for 20- to 44-year-olds diagnosed in 1977 vs in 1937 is 1.37 (95% CI 1.22-1.54) (**Appendix Figure 1.1**).

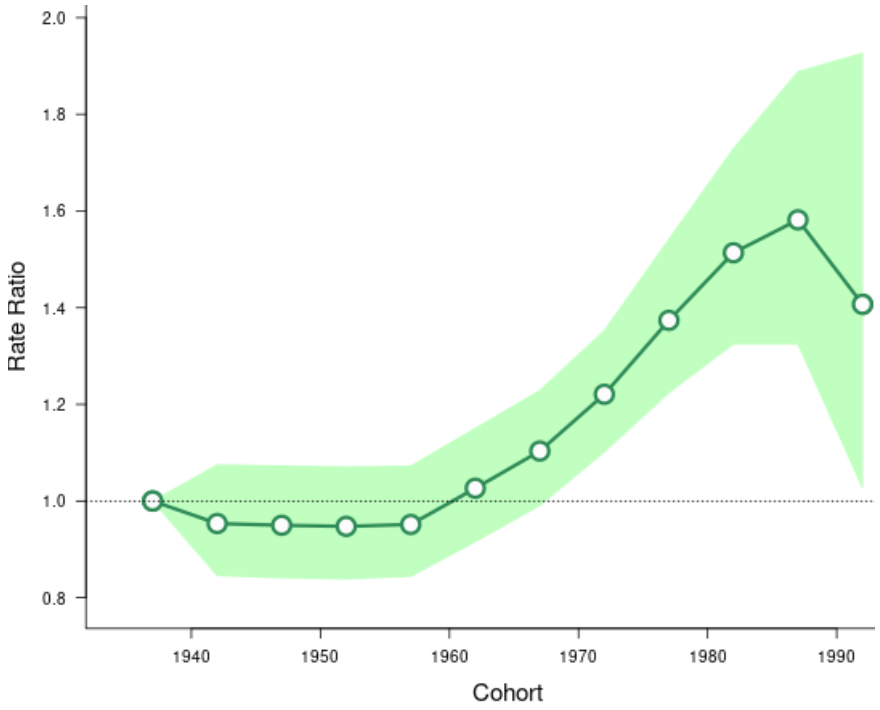
Appendix Table 1.1. SEER*Stat 8.3.6 Rate Session Using Delay-Adjusted Rates

Tab	Variables/options
Data	Incidence – SEER 9 Reg Research Data with Delay-Adjustment, Malignant Only, Nov 2018 Sub (1975-2016) <Katrina/Rita Population Adjustment> Age variable: Age recode with <1 year olds
Statistic	Rates (age-adjusted), include rate ratios with 95% CI Standard population: 2000 US STD Population (19 age groups - Census P25-1130) Select "Include Rate Ratios on Last Row Variable Groupings"
Selection	Other.Type of Reporting Source: Unselect 'Autopsy only' and 'Death certificate only' Site and Morphology.ICD-O-3 Hist/behav = { '8000/3: Neoplasm, malignant', '8001/3: Tumor cells, malignant', '8010/3: Carcinoma, NOS', '8020/3: Carcinoma, undifferentiated, NOS', '8021/3: Carcinoma, anaplastic, NOS', '8022/3: Pleomorphic carcinoma', '8140/3: Adenocarcinoma, NOS', '8141/3: Scirrhous adenocarcinoma', '8144/3: Adenocarcinoma, intestinal type', '8145/3: Carcinoma, diffuse type', '8210/3: Adenocarcinoma in adenomatous polyp', '8211/3: Tubular adenocarcinoma', '8213/3: Serrated adenocarcinoma', '8220/3: Adenocarcinoma in adenomatous polyposis coli', '8221/3: Adenocarcinoma in multiple adenomatous polyps', '8230/3: Solid carcinoma, NOS', '8255/3: Adenocarcinoma with mixed subtypes', '8260/3: Papillary adenocarcinoma, NOS', '8261/3: Adenocarcinoma in villous adenoma', '8262/3: Villous adenocarcinoma', '8263/3: Adenocarcinoma in tubulovillous adenoma', '8480/3: Mucinous adenocarcinoma', '8481/3: Mucin-producing adenocarcinoma', '8490/3: Signet ring cell carcinoma', '8560/3: Adenosquamous carcinoma', '8570/3: Adenocarcinoma with squamous metaplasia', '8574/3: Adenocarcinoma with neuroendocrine differentiation'} Multiple Primary Fields.Sequence number = {One primary only, 1st of 2 or more primaries} Site and Morphology.Site recode ICD-O-3/WHO 2008 = {Cecum, Ascending Colon, Hepatic Flexure, Transverse Colon, Splenic Flexure, Descending Colon, Sigmoid Colon, Large Intestine NOS, Rectum and Rectosigmoid Junction} Required Delay Fields.Delay site = {'Colon and Rectum'} Age at Diagnosis.Age recode with <1 year olds = {'20-24 years','25-29 years','30-34 years','35-39 years','40-44 years'} Race, Sex, Year Dx, Registry, County.Year of diagnosis = {'1975','1976','1977','1978','1979','2012','2013','2014','2015','2016'}
Table	Year of Diagnosis: {1975-1979, 2012-2016}

Appendix Table 1.2. SEER*Stat 8.3.6 Rate Session Using Non-Delay-Adjusted Rates

Tab	Variables/options
Data	Incidence – SEER 9 Reg Research Data, Nov 2018 Sub (1975-2016) <Katrina/Rita Population Adjustment> Age variable: Age recode with <1 year olds
Statistic	Rates (age-adjusted), include rate ratios with 95% CI Standard population: 2000 US STD Population (19 age groups - Census P25-1130) Select "Include Rate Ratios on Last Row Variable Groupings"
Selection	Other.Type of Reporting Source: Unselect 'Autopsy only' and 'Death certificate only' Site and Morphology.ICD-O-3 Hist/behav = { '8000/3: Neoplasm, malignant', '8001/3: Tumor cells, malignant', '8010/3: Carcinoma, NOS', '8020/3: Carcinoma, undifferentiated, NOS', '8021/3: Carcinoma, anaplastic, NOS', '8022/3: Pleomorphic carcinoma', '8140/3: Adenocarcinoma, NOS', '8141/3: Scirrhous adenocarcinoma', '8144/3: Adenocarcinoma, intestinal type', '8145/3: Carcinoma, diffuse type', '8210/3: Adenocarcinoma in adenomatous polyp', '8211/3: Tubular adenocarcinoma', '8213/3: Serrated adenocarcinoma', '8220/3: Adenocarcinoma in adenomatous polyposis coli', '8221/3: Adenocarcinoma in multiple adenomatous polyps', '8230/3: Solid carcinoma, NOS', '8255/3: Adenocarcinoma with mixed subtypes', '8260/3: Papillary adenocarcinoma, NOS', '8261/3: Adenocarcinoma in villous adenoma', '8262/3: Villous adenocarcinoma', '8263/3: Adenocarcinoma in tubulovillous adenoma', '8480/3: Mucinous adenocarcinoma', '8481/3: Mucin-producing adenocarcinoma', '8490/3: Signet ring cell carcinoma', '8560/3: Adenosquamous carcinoma', '8570/3: Adenocarcinoma with squamous metaplasia', '8574/3: Adenocarcinoma with neuroendocrine differentiation'} Multiple Primary Fields.Sequence number = {One primary only, 1st of 2 or more primaries} Site and Morphology.Site recode ICD-O-3/WHO 2008 = {Cecum, Ascending Colon, Hepatic Flexure, Transverse Colon, Splenic Flexure, Descending Colon, Sigmoid Colon, Large Intestine NOS, Rectum and Rectosigmoid Junction} Age at Diagnosis.Age recode with <1 year olds = {'20-24 years','25-29 years','30-34 years','35-39 years','40-44 years'} Race, Sex, Year Dx, Registry, County.Year of diagnosis = {'1975','1976','1977','1978','1979','2012','2013','2014','2015','2016'}
Table	Year of Diagnosis: {1975-1979, 2012-2016}

Appendix Figure 1.1. Incidence Rate Ratio and 95% Confidence Interval by Birth Cohort From an Age-Period-Cohort Model Fit to Colorectal Cancer Incidence Rates Among 20- to 44-Year-Olds in SEER



As noted in the section "**Model Input Parameters**", test characteristics are based primarily on estimates from a systematic evidence review conducted by Lin et al.[17] for the USPSTF. Below we provide additional information on the inputs for each screening modality.

Colonoscopy

The EPC identified no new studies reporting test performance characteristics for colonoscopy.[17] We therefore used the same test characteristics as in the 2016 decision analysis[16] (**Table 7**); per-lesion colonoscopy sensitivity for adenomas by size category was based on a meta-analysis of tandem colonoscopy studies.[142] Test specificity was based a screening study of colonoscopy in the Boston University catchment area.[141]

Sigmoidoscopy

The EPC found no studies evaluating the test performance of sigmoidoscopy.[17] As in the 2016 decision analysis,[16] we assumed that sigmoidoscopy had the same sensitivity as colonoscopy *within the reach of the endoscope* (**Table 7**). We assumed that neither biopsies nor polypectomy would be performed during sigmoidoscopy and that persons with any lesion visualized at sigmoidoscopy were deemed positive and referred for follow-up colonoscopy. This is similar to the sigmoidoscopy approach used in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in which biopsy and polypectomy were not routinely performed.[143] Test specificity was based on data from the PLCO Trial.[143]

CTC

The systematic evidence review reported pooled estimates of the per-person sensitivity and specificity of CTC for adenomas by size (adenomas ≥10 mm; adenomas ≥6 mm). However, the models require *lesion*-based sensitivity *separately* for adenomas 6 to <10 mm and for adenomas ≥10 mm. We therefore used the same test characteristics as in the 2016 decision analysis, which were based on test performance data from the American College of Radiology Imaging Network National CT Colonography Trial.[144] (**Table 7**).

Stool Tests

The EPC provided pooled estimates of the per-person test sensitivity and specificity for each of the 3 stool tests (FIT, sDNA-FIT, HSgFOBT).[17] We assumed that sensitivity for adenomas ≥10 mm was equal to the sensitivity for advanced adenomas, a category that includes any adenoma ≥10 mm in size, an adenoma containing high-grade dysplasia or villous histology, and, depending on the study, sessile serrated lesions. Similarly, we assumed that the sensitivity for 1 to <10 mm adenomas was equal to the sensitivity for non-advanced adenomas. In all models, specificity is for any adenoma or cancer.

All 3 models made adjustments to the pooled person-based sensitivity estimates from the EPC. SimCRC and MISCAN derived lesion-based sensitivities that match the pooled person-based

sensitivity estimates. Doing so allowed the probability of a positive test to increase with the number of adenomas a person has. For preclinical cancers and for adenomas ≥10 mm, SimCRC and MISCAN simulated stool tests (and follow-up colonoscopies) under different values for lesion-based sensitivity for the size category of interest to identify the value at which the person-based sensitivity generated by the model matched the corresponding person-based sensitivity from the EPC's pooled analysis. These models assumed that 1 to <6 mm adenomas do not bleed, which implies that the sensitivity of the stool tests for adenomas of this size is 0 (individuals with 1 to <6 mm adenomas are allowed to have a positive test via the sensitivity for co-occurring adenomas ≥6 mm, or by the test's false-positive rate). They then derived the person-based sensitivity for a 6 to <10 mm adenoma such that the person-based sensitivity for lesions 1 to <10 mm was equal to the pooled person-based sensitivity for 1 to <10 mm adenomas from the EPC. The resulting lesion-based sensitivity estimates are in **Appendix Table 2.1**.

CRC-SPIN applied person-based sensitivity estimates. Unlike SimCRC and MISCAN, CRC-SPIN allows 1 to <6 mm adenomas to bleed, assuming that the overall sensitivity for persons with these adenomas as the most-advanced finding is 1 to 2 percentage points higher than the test's false positive rate. CRC-SPIN then determined the sensitivity for persons with 6 to <10 mm adenomas as the most advanced finding such that the weighted-average sensitivity for 1 to <6 mm adenomas and 6 to <10 mm adenomas was equal to that of 1 to <10 mm adenomas, with weights based on CRC-SPIN's underlying distribution of the size of the most advanced adenoma across these categories. The resulting person-based sensitivity estimates are in **Appendix Table 2.2**.

Additional information for each of the 3 stool tests is provided below.

FIT: Test characteristics for FIT are for the OC-Sensor family of FITs at a cutoff of 20 µg of hemoglobin per g of feces.

sDNA-FIT: Test characteristics for sDNA-FIT are for Cologuard.

HSgFOBT: Test characteristics for HSgFOBT are for Hemoccult SENSA. As noted in the section "**Model input parameters**", there is considerable uncertainty in test performance characteristics for Hemoccult SENSA and therefore in model outcomes for strategies using this modality. Decisions about this test should not be informed by the models. We include model findings for HSgFOBT strategies in **Appendix 4**, rather than with the main results.

Appendix Table 2.1. Per-Lesion Test Sensitivity for Stool Tests Used in the SimCRC and MISCAN Models

Model/ stool test	Per-lesion sensitivity*			
	Adenoma 1 to <6 mm†	Adenoma 6 to <10 mm	Adenoma ≥10 mm	Preclinical colorectal cancer‡
SimCRC				
HSgFOBT	0	0.035	0.061	0.658
FIT	0	0.060	0.161	0.710
sDNA-FIT	0	0.103	0.307	0.922
MISCAN				
HSgFOBT	0	0.056	0.056	0.569 / 0.860
FIT	0	0.113	0.147	0.630 / 0.888
sDNA-FIT	0	0.183	0.295	0.895 / 0.975

FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; HSgFOBT – high sensitivity guaiac-based fecal occult blood test; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test)

* Estimates were derived by calibrating to the person-based sensitivities in **Table 7**.

† SimCRC and MISCAN assume 1 to <6 mm adenomas do not bleed and therefore cannot cause a positive stool test.

‡ For SimCRC, the value is the sensitivity for any preclinical cancer. For MISCAN, the first value is the sensitivity for a preclinical cancer while at an earlier stage than it would have been diagnosed in the absence of screening, and the second value is the sensitivity at the stage it would have been diagnosed in the absence of screening.

Appendix Table 2.2. Per-Person Test Sensitivity for Stool Tests Used in the CRC-SPIN Model

Stool test	Per-person sensitivity*			
	Adenoma 1 to <6 mm†	Adenoma 6 to <10 mm	Adenoma ≥10 mm	Preclinical colorectal cancer‡
HSgFOBT	0.04	0.09	0.11	0.68
FIT	0.05	0.15	0.22	0.74
sDNA-FIT	0.11	0.31	0.42	0.94

FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; HSgFOBT – high sensitivity guaiac-based fecal occult blood test; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test)

* Estimates were derived by calibrating model outcomes to the per-person sensitivities given in **Table 7**.

† CRC-SPIN assumes that the overall sensitivity for detecting persons with at most 1 to <6 mm adenoma(s) is 1 (HSgFOBT) to 2 (FIT, sDNA-FIT) percentage points higher than the false-positive rate of the test.

To calculate quality-adjusted life-years (QALYs), we assign quality-of-life weights for each year of life that accounts for population health by age, as well as utility losses associated with specific events (e.g. colonoscopy) or health states (e.g., time with colorectal cancer). The approach is similar to that used by the breast cancer CISNET group in their 2016 analysis for the USPSTF.[90]

Utilities Associated With Aging

We obtained estimates of the age-related utility weights from Hanmer et al.,[91] who reported mean EQ-5D US values for men and women in deciles of age from age 20 to age 89 years. To extrapolate utilities within each 10-year age group (for ages 40 and older) we used data from the 2017 US life table on the mean age by sex and 10-year age group. We then fit a line to predict weights at each age within the age groups and smoothed it to eliminate discontinuities. We extrapolated to estimate risk from age 90 to 99. Finally, we calculated a weighted-average age-specific weight using data from the 2017 US life table on the proportion of the population that is female. This step was necessary because the output template did not stratify by sex. **Appendix Table 3.1** contains the resulting age-specific weights used in the analysis.

Utility Losses Associated With Screening, Complications, and Cancer Care

Appendix Table 3.2 contains the assumptions for the utility losses associated with each test. Estimates on the disutility of the screening test included those associated with the test itself, and those related to fear or anxiety while waiting for the test result and while waiting for a follow-up colonoscopy after a positive test. A study by Jonas et al.[93] was used to derive estimates of the time spent on the different procedures. As this study only captures colonoscopy, time estimates for the other tests were adjusted based on patient information sheets and expert opinion. A study by Swan et al.[92] was used for the disutility of a colonoscopy. Due to the lack of data, we assumed that, apart from the shorter procedure times of CTC and SIG, the disutility values of CTC and SIG are equal to those of colonoscopy. For the stool-based tests, we assumed no disutility for performing the test itself. A study by Kirkegaard et al.[150] and the 2016 USPSTF analysis from the breast cancer CISNET group,[90] were used to derive estimates for the disutility related to fear or anxiety while waiting for test results. Additional details on the derivation of these utility losses are in the section "**Additional details on the disutility of the screening tests**" below.

Appendix Table 3.3 contains the assumptions for the utility loss associated with complications. **Appendix Table 3.4** contains the assumptions for the utility losses associated with cancer care by stage at diagnosis and phase of care.

Calculation of QALYs

Using the values in **Appendix Tables 3.1-3.4**, we calculate QALYs as follows:

$$QALY = \text{sum}_i\ (ly\_pop_i * age\_wt_i$$
$$- \text{sum}_{j,k}\ (ly\_crc_{i,j,k} * age\_wt_i * utility\_loss\_crc_{j,k})$$

– sum_l ($n\_fit_{i,l}$ * age_wt_i * $utility\_loss\_fit_l$)
– sum_l ($n\_sen_{i,l}$ * age_wt_i * $utility\_loss\_sen_l$)
– sum_l ($n\_pos\_sdnafit_{i,l}$ * age_wt_i * $utility\_loss\_sdnafit_l$)
– sum_l ($n\_pos\_sig_{i,l}$ * age_wt_i * $utility\_loss\_sig_l$)
– sum_l ($n\_ctc_{i,l}$ * age_wt_i * $utility\_loss\_ctc_l$)
– sum_l (($n\_screencol_{i,l}$ + $n\_followupcol_{i,l}$ + $n\_survcol_{i,l}$) * age_wt_i * $utility\_loss\_col_l$)
– $\text{sum}_{i,j}$ ($n\_clin\_crc_{i,j}$ * age_wt_i * $utility\_loss\_symptom\_diagnosis$)
– $n\_col\_complication\_cardio_i$ * age_wt_i * $utility\_loss\_complication\_cardio$
– $n\_col\_complication\_seriousGI_i$ * age_wt_i * $utility\_loss\_complication\_seriousGI$
– $n\_col\_complication\_otherGI_i$ * age_wt_i * $utility\_loss\_complication\_otherGI$)

where *i* is age, *j* is stage at diagnosis, *k* is phase of care, and *l* is test result (positive vs negative).

Additional Details on the Disutility of the Screening Tests

Estimates on the disutility of the screening test included those associated with the test itself, and those related to fear or anxiety while waiting for the test result and while waiting for a follow-up colonoscopy after a positive test.

Assumptions for Utility Losses Associated With the Screening Tests Themselves

The disutility associated with a screening test depends on the time spent on a screening test and the disutility experienced during this time. **Appendix Tables 3.5-3.9** contain the assumptions for time spent on the screening tests. **Appendix Table 3.10** contains the disutility experienced while undergoing the screening test and the total utility losses associated with the screening tests themselves.

Data from the Centers for Medicare and Medicaid Services suggest that 22% of SIG claims are accompanied by a claim for anesthesia services provided by an anesthesiology professional. We therefore assumed the total time spent on sigmoidoscopy (**Appendix Table 3.9**) is the weighted average of the procedures with (22%, **Appendix Table 3.8**) and without (78%, **Appendix Table 3.7**) sedation.

Assumptions for Utility Losses Associated With Fear or Anxiety

Appendix Table 3.11 and **Appendix Table 3.12** contain the utility losses associated with fear or anxiety while waiting for the test result and while waiting for a follow-up colonoscopy after a positive test, respectively.

Appendix Table 3.1. General Health Utility Weights by Age

Age	Utility	Age	Utility	Age	Utility
40	0.888522	60	0.835435	80	0.763673
41	0.885463	61	0.833031	81	0.759805
42	0.882405	62	0.830623	82	0.755897
43	0.879346	63	0.828212	83	0.751944
44	0.876288	64	0.825797	84	0.747941
45	0.873460	65	0.822419	85	0.743880
46	0.870845	66	0.818415	86	0.739750
47	0.868229	67	0.814408	87	0.735546
48	0.865613	68	0.810398	88	0.731258
49	0.862996	69	0.806386	89	0.726879
50	0.860377	70	0.802370	90	0.722403
51	0.857758	71	0.798351	91	0.717824
52	0.855138	72	0.794328	92	0.713137
53	0.852516	73	0.790300	93	0.708341
54	0.849893	74	0.786267	94	0.703433
55	0.847402	75	0.782535	95	0.698415
56	0.845015	76	0.778817	96	0.693291
57	0.842624	77	0.775075	97	0.688068
58	0.840231	78	0.771305	98	0.682755
59	0.837835	79	0.767506	99	0.677363

Appendix Table 3.2. Assumptions for Utility Losses Associated With Each Screening Test

Test type	Utility loss when abnormal	Utility loss when normal
FIT	0.001330	0.000063
sDNA-FIT	0.001394	0.000127
HSgFOBT	0.001330	0.000063
SIG	0.001415	0.000147
CTC	0.001559	0.000292
COL with adenoma polypectomy	0.001401	
COL without adenoma polypectomy	0.000496	
COL for symptomatic cancer diagnosis	0.001401	

COL – colonoscopy; CTC – computed tomography colonography; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; HSgFOBT – high sensitivity guaiac-based fecal occult blood test; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG – sigmoidoscopy

Appendix Table 3.3. Assumptions for Utility Losses Associated With Complications

Complications	Utility loss	Rationale [expert opinion]
Fatal perforation	0	Patient dies
Serious gastrointestinal event	0.005479	4 days at 0.5 utility
Other gastrointestinal event	0.002740	2 days at 0.5 utility
Cardiovascular event	0.004795	3.5 days at 0.5 utility

Appendix Table 3.4. Utility Losses Associated With Cancer Care by Stage at Diagnosis and Phase of Care

	Utility loss [source: Ness et al.[151]]			
Phase of cancer care	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial phase	0.12	0.18	0.24	0.70
Continuing phase	0.05	0.05	0.24	0.70
Terminal phase, death CRC	0.70	0.70	0.70	0.70
Terminal phase, death other causes	0.05	0.05	0.24	0.70

CRC – colorectal cancer

Appendix Table 3.5. Time Spent on Colonoscopy, Based on Jonas et al[91]

Colonoscopy component	Patient time (in hours)	Assumptions
Bowel preparation	16.70	
Travel to	0.42	
Waiting/preparing	1.40	
Sedation	0.20	Assume always used
Procedure	0.33	
Onsite recovery	0.78	
Travel home	0.58	
Recovery to routine	15.80	
Total	**36.22**	

Appendix Table 3.6. Time Spent on Computed Tomography Colonography (CTC)

CTC component	Patient time (in hours)	Assumptions
Bowel preparation	16.70	Same as colonoscopy
Travel to	0.42	Same as colonoscopy
Waiting/preparing	1.40	Same as colonoscopy
Sedation	0.00	No sedation
Procedure	0.25	75% of colonoscopy (generally ~15 min[152])
Onsite recovery	0.00	No on-site recovery
Travel home	0.58	Same as colonoscopy
Recovery to routine	0.00	Immediately back to routine
Total	**19.35**	

Appendix Table 3.7. Time Spent on Sigmoidoscopy Without Sedation

Sigmoidoscopy component	Patient time (in hours)	Assumptions
Bowel preparation	1.50	2 hrs. according to Capital Digestive Group,[153] 1 h according to Forest Canyon Endoscopy[154]
Travel to	0.42	Same as colonoscopy
Waiting/preparing	0.70	50% of colonoscopy
Sedation	0.00	No sedation
Procedure	0.33	20 minutes according to Walter Reed's info
Onsite recovery	0.39	50% of colonoscopy, due to no sedation
Travel home	0.58	Same as colonoscopy
Recovery to routine	3.95	25% of colonoscopy, due to no sedation
Total	**7.88**	

Appendix Table 3.8. Time Spent on Sigmoidoscopy With Sedation

Sigmoidoscopy component	Patient time (in hours)	Assumptions
Bowel preparation	1.50	2 hrs. according to Capital Digestive Group,[153] 1 h according to Forest Canyon Endoscopy [154]
Travel to	0.42	Same as colonoscopy
Waiting/preparing	1.40	Same as colonoscopy
Sedation	0.20	Same as colonoscopy
Procedure	0.33	20 minutes according to Walter Reed's info
Onsite recovery	0.78	Same as colonoscopy, due to sedation
Travel home	0.58	Same as colonoscopy
Recovery to routine	15.80	Same as colonoscopy
Total	**21.02**	

Appendix Table 3.9. Time Spent on Sigmoidoscopy, Averaged Over Procedures With and Without Sedation

Sigmoidoscopy component	Patient time (in hours)
Bowel preparation	1.50
Travel to	0.42
Waiting/preparing	0.85
Sedation	0.04
Procedure	0.33
Onsite recovery	0.48
Travel home	0.58
Recovery to routine	6.56
Total	**10.77**

Appendix Table 3.10. Assumptions for Utility Losses Associated With the Screening Tests Themselves

Screening modality	Disutility	Source	Time the disutility applies in hours*	Utility loss per event
Colonoscopy (regardless of type)	0.12	Swan et al. [92]	36.22	0.000496
CTC	0.12	Same as colonoscopy	19.4	0.000265
SIG	0.12	Same as colonoscopy	10.8	0.000147
FIT	0	Expert opinion	-	0
sDNA-FIT	0	Expert opinion	-	0
HSgFOBT	0	Expert opinion	-	0

COL – colonoscopy; CTC – computed tomography colonography; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; HSgFOBT – high sensitivity guaiac-based fecal occult blood test; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG – sigmoidoscopy
* See **Appendix Tables 3.5-3.9**.

Appendix Table 3.11. Assumptions for Utility Losses Associated With Waiting for the Test Result

Screening modality	Disutility	Source	Time the disutility applies in days*	Utility loss per event
COL without polypectomy	0	Immediate results	0	0
COL with polypectomy	0.033036	Expert opinion, same as waiting for follow-up COL after a positive FIT	10	0.000905
SIG	0	Immediate results (no biopsy or polypectomy)	0	0
CTC	0.003304	Expert opinion, 10% of waiting for a follow-up COL after a positive FIT	3	0.000027
FIT			7	0.000063
sDNA-FIT			14	0.000127
HSgFOBT			7	0.000063

COL – colonoscopy; CTC – computed tomography colonography; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; HSgFOBT – high sensitivity guaiac-based fecal occult blood test; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG – sigmoidoscopy

* Time estimates are based on expert opinion.

Appendix Table 3.12. Assumptions for Utility Losses Associated With Waiting for a Follow-Up Colonoscopy

Screening modality	Disutility	Source	Time the disutility applies in days*	Utility loss per event
CTC	0.033036	12.5% are very worried.[150] Assuming they experience half of the utility decrement as for a positive mammography as reported by Mandelblatt[90]	14	0.001267
SIG				
FIT				
sDNA-FIT				
HSgFOBT				

COL – colonoscopy; CTC – computed tomography colonography; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; HSgFOBT – high sensitivity guaiac-based fecal occult blood test; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG – sigmoidoscopy
* Time estimates are based on expert opinion.

As noted in the section "**Model Input Parameters**" there is considerable uncertainty in the diagnostic accuracy of the HSgFOBT Hemoccult SENSA.[82,83] As a result, model outcomes for HSgFOBT should be interpreted with caution and decisions about this test should not be informed by modeling. Outcomes for HSgFOBT strategies using the pooled estimates of test sensitivity and specificity from Lin et al.[17] are presented in **Appendix Table 4.1**. Colonoscopies and life-years gained for stool-based modalities are in **Appendix Figure 4.1** and efficient stool-based strategies with inclusion of HSgFOBT strategies are in **Appendix Table 4.2**.

When HSgFOBT is evaluated together with FIT and sDNA-FIT, all 3 models find that HSgFOBT strategies with a 3-year interval are efficient but they are estimated to provide the lowest LYG relative to the other efficient stool-based modalities (**Appendix Figure 4.1**). With MISCAN, a small number of HSgFOBT strategies with shorter screening intervals are also efficient.

Appendix Table 4.1a. Estimated Outcomes for HSgFOBT Strategies: SimCRC

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	85	85	2	85	34	0	0	0
HSgFOBT 45-70, 1	18001	0	0	0	1321	1321	8	40	10	314	285	115
HSgFOBT 45-70, 2	10362	0	0	0	857	857	6	54	15	262	234	96
HSgFOBT 45-70, 3	7560	0	0	0	668	668	5	61	18	225	200	82
HSgFOBT 45-75, 1	20251	0	0	0	1464	1464	9	36	8	330	299	121
HSgFOBT 45-75, 2	12025	0	0	0	982	982	7	51	12	286	255	105
HSgFOBT 45-75, 3	8651	0	0	0	758	758	6	58	15	248	218	91
HSgFOBT 45-80, 1	22037	0	0	0	1573	1573	10	35	6	338	306	124
HSgFOBT 45-80, 2	12922	0	0	0	1047	1047	8	50	10	296	262	108
HSgFOBT 45-80, 3	9247	0	0	0	803	803	6	58	13	256	225	94
HSgFOBT 45-85, 1	23312	0	0	0	1646	1646	11	35	5	341	308	125
HSgFOBT 45-85, 2	13898	0	0	0	1116	1116	9	50	9	301	266	110
HSgFOBT 45-85, 3	9983	0	0	0	860	860	7	59	12	263	229	96
HSgFOBT 50-70, 1	14431	0	0	0	1138	1138	7	44	11	280	253	102
HSgFOBT 50-70, 2	8582	0	0	0	762	762	6	57	16	235	209	86
HSgFOBT 50-70, 3	5855	0	0	0	560	560	4	64	20	193	170	71
HSgFOBT 50-75, 1	16703	0	0	0	1285	1285	9	41	9	297	268	109
HSgFOBT 50-75, 2	9702	0	0	0	848	848	6	54	13	252	223	92
HSgFOBT 50-75, 3	7096	0	0	0	662	662	5	61	16	220	193	81
HSgFOBT 50-80, 1	18502	0	0	0	1397	1397	10	39	7	306	274	112
HSgFOBT 50-80, 2	11055	0	0	0	947	947	8	53	11	266	234	97
HSgFOBT 50-80, 3	7988	0	0	0	736	736	6	61	14	234	203	85
HSgFOBT 50-85, 1	19784	0	0	0	1471	1471	11	39	7	309	276	113
HSgFOBT 50-85, 2	11710	0	0	0	994	994	9	53	10	270	237	99
HSgFOBT 50-85, 3	8426	0	0	0	769	769	7	61	13	237	205	87
HSgFOBT 55-70, 1	10967	0	0	0	940	940	7	50	14	238	212	87
HSgFOBT 55-70, 2	6246	0	0	0	608	608	5	62	18	192	169	70
HSgFOBT 55-70, 3	4800	0	0	0	498	498	4	67	20	170	148	62
HSgFOBT 55-75, 1	13284	0	0	0	1095	1095	8	46	11	257	229	94
HSgFOBT 55-75, 2	7949	0	0	0	741	741	6	58	15	220	193	80
HSgFOBT 55-75, 3	5468	0	0	0	553	553	5	65	19	184	159	67
HSgFOBT 55-80, 1	15106	0	0	0	1210	1210	10	45	9	266	236	97
HSgFOBT 55-80, 2	8862	0	0	0	810	810	7	57	13	231	200	84
HSgFOBT 55-80, 3	6495	0	0	0	638	638	6	64	16	201	173	73
HSgFOBT 55-85, 1	16399	0	0	0	1286	1286	11	44	9	269	239	98
HSgFOBT 55-85, 2	9852	0	0	0	880	880	8	58	12	236	205	86
HSgFOBT 55-85, 3	7147	0	0	0	689	689	7	65	15	207	177	75

HSgFOBT – high sensitivity guaiac-based fecal occult blood test; COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 4.1b. Estimated Outcomes for HSgFOBT Strategies: CRC-SPIN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	77	77	2	77	32	0	0	0
HSgFOBT 45-70, 1	17621	0	0	0	1505	1505	10	30	10	280	260	102
HSgFOBT 45-70, 2	10237	0	0	0	1002	1002	8	43	15	224	206	82
HSgFOBT 45-70, 3	7501	0	0	0	782	782	6	50	18	183	168	67
HSgFOBT 45-75, 1	19829	0	0	0	1637	1637	11	28	8	290	269	106
HSgFOBT 45-75, 2	11876	0	0	0	1122	1122	9	40	12	242	222	88
HSgFOBT 45-75, 3	8576	0	0	0	871	871	7	48	16	199	182	73
HSgFOBT 45-80, 1	21617	0	0	0	1736	1736	12	26	7	296	274	108
HSgFOBT 45-80, 2	12769	0	0	0	1184	1184	10	39	11	248	227	91
HSgFOBT 45-80, 3	9175	0	0	0	915	915	8	47	15	206	188	75
HSgFOBT 45-85, 1	22930	0	0	0	1803	1803	13	26	7	299	276	109
HSgFOBT 45-85, 2	13757	0	0	0	1246	1246	11	39	11	253	231	92
HSgFOBT 45-85, 3	9918	0	0	0	967	967	9	47	14	211	192	77
HSgFOBT 50-70, 1	14154	0	0	0	1293	1293	10	34	11	249	230	91
HSgFOBT 50-70, 2	8495	0	0	0	878	878	7	47	16	195	179	71
HSgFOBT 50-70, 3	5820	0	0	0	649	649	6	55	20	155	142	57
HSgFOBT 50-75, 1	16386	0	0	0	1431	1431	11	32	10	261	241	95
HSgFOBT 50-75, 2	9601	0	0	0	962	962	8	44	14	208	191	76
HSgFOBT 50-75, 3	7051	0	0	0	752	752	7	52	17	175	159	64
HSgFOBT 50-80, 1	18188	0	0	0	1532	1532	12	30	9	267	246	98
HSgFOBT 50-80, 2	10952	0	0	0	1056	1056	9	43	13	219	200	80
HSgFOBT 50-80, 3	7937	0	0	0	821	821	8	50	16	185	168	68
HSgFOBT 50-85, 1	19508	0	0	0	1601	1601	13	30	8	270	248	99
HSgFOBT 50-85, 2	11616	0	0	0	1099	1099	10	43	12	222	202	81
HSgFOBT 50-85, 3	8386	0	0	0	852	852	8	50	15	188	170	69
HSgFOBT 55-70, 1	10797	0	0	0	1058	1058	9	41	13	211	194	77
HSgFOBT 55-70, 2	6202	0	0	0	689	689	6	53	18	161	146	59
HSgFOBT 55-70, 3	4779	0	0	0	561	561	5	58	21	133	120	48
HSgFOBT 55-75, 1	13077	0	0	0	1206	1206	10	37	11	226	207	83
HSgFOBT 55-75, 2	7890	0	0	0	824	824	8	49	16	183	165	67
HSgFOBT 55-75, 3	5447	0	0	0	617	617	6	56	19	143	130	52
HSgFOBT 55-80, 1	14902	0	0	0	1314	1314	11	36	10	233	213	85
HSgFOBT 55-80, 2	8803	0	0	0	890	890	9	48	14	191	172	70
HSgFOBT 55-80, 3	6476	0	0	0	699	699	7	55	18	156	140	57
HSgFOBT 55-85, 1	16233	0	0	0	1384	1384	12	36	10	236	215	86
HSgFOBT 55-85, 2	9809	0	0	0	956	956	10	48	13	196	176	72
HSgFOBT 55-85, 3	7132	0	0	0	747	747	8	54	17	161	144	59

HSgFOBT – high sensitivity guaiac-based fecal occult blood test; COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 4.1c. Estimated Outcomes for HSgFOBT Strategies: MISCAN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	81	81	2	81	34	0	0	0
HSgFOBT 45-70, 1	17953	0	0	0	1380	1380	8	55	14	257	222	94
HSgFOBT 45-70, 2	10347	0	0	0	900	900	6	64	19	206	175	75
HSgFOBT 45-70, 3	7548	0	0	0	699	699	5	68	21	176	147	64
HSgFOBT 45-75, 1	20153	0	0	0	1505	1505	9	53	12	275	238	100
HSgFOBT 45-75, 2	11984	0	0	0	1014	1014	7	62	15	230	194	84
HSgFOBT 45-75, 3	8632	0	0	0	785	785	6	67	18	197	163	72
HSgFOBT 45-80, 1	21913	0	0	0	1596	1596	10	52	10	285	245	104
HSgFOBT 45-80, 2	12868	0	0	0	1071	1071	8	62	14	239	201	87
HSgFOBT 45-80, 3	9212	0	0	0	823	823	6	67	17	204	168	75
HSgFOBT 45-85, 1	23187	0	0	0	1656	1656	11	52	9	288	248	105
HSgFOBT 45-85, 2	13836	0	0	0	1128	1128	9	63	13	245	205	89
HSgFOBT 45-85, 3	9944	0	0	0	872	872	7	68	16	211	173	77
HSgFOBT 50-70, 1	14409	0	0	0	1194	1194	8	56	15	238	205	87
HSgFOBT 50-70, 2	8571	0	0	0	801	801	6	65	19	195	164	71
HSgFOBT 50-70, 3	5849	0	0	0	590	590	5	70	22	156	129	57
HSgFOBT 50-75, 1	16641	0	0	0	1324	1324	9	54	12	258	221	94
HSgFOBT 50-75, 2	9677	0	0	0	880	880	7	64	16	212	177	78
HSgFOBT 50-75, 3	7077	0	0	0	687	687	6	68	19	181	148	66
HSgFOBT 50-80, 1	18420	0	0	0	1418	1418	10	53	11	268	229	98
HSgFOBT 50-80, 2	11015	0	0	0	967	967	8	63	14	226	188	83
HSgFOBT 50-80, 3	7965	0	0	0	753	753	7	69	17	194	158	71
HSgFOBT 50-85, 1	19705	0	0	0	1480	1480	11	53	10	271	231	99
HSgFOBT 50-85, 2	11666	0	0	0	1005	1005	8	64	13	230	190	84
HSgFOBT 50-85, 3	8395	0	0	0	780	780	7	69	16	197	160	72
HSgFOBT 55-70, 1	10977	0	0	0	986	986	7	59	16	209	178	76
HSgFOBT 55-70, 2	6249	0	0	0	639	639	5	68	21	163	135	60
HSgFOBT 55-70, 3	4802	0	0	0	522	522	5	71	22	144	118	53
HSgFOBT 55-75, 1	13269	0	0	0	1126	1126	9	57	14	230	195	84
HSgFOBT 55-75, 2	7938	0	0	0	764	764	7	66	17	190	157	69
HSgFOBT 55-75, 3	5460	0	0	0	574	574	5	70	21	158	128	58
HSgFOBT 55-80, 1	15081	0	0	0	1225	1225	10	56	12	241	203	88
HSgFOBT 55-80, 2	8846	0	0	0	825	825	7	66	16	200	164	73
HSgFOBT 55-80, 3	6481	0	0	0	650	650	6	70	18	173	139	63
HSgFOBT 55-85, 1	16384	0	0	0	1289	1289	11	56	11	245	206	89
HSgFOBT 55-85, 2	9835	0	0	0	886	886	8	66	14	206	168	75
HSgFOBT 55-85, 3	7134	0	0	0	696	696	7	71	17	178	142	65

HSgFOBT – high sensitivity guaiac-based fecal occult blood test; COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 4.2. Efficient Stool-Based Screening Strategies (FIT, sDNA-FIT, HSgFOBT), by Model

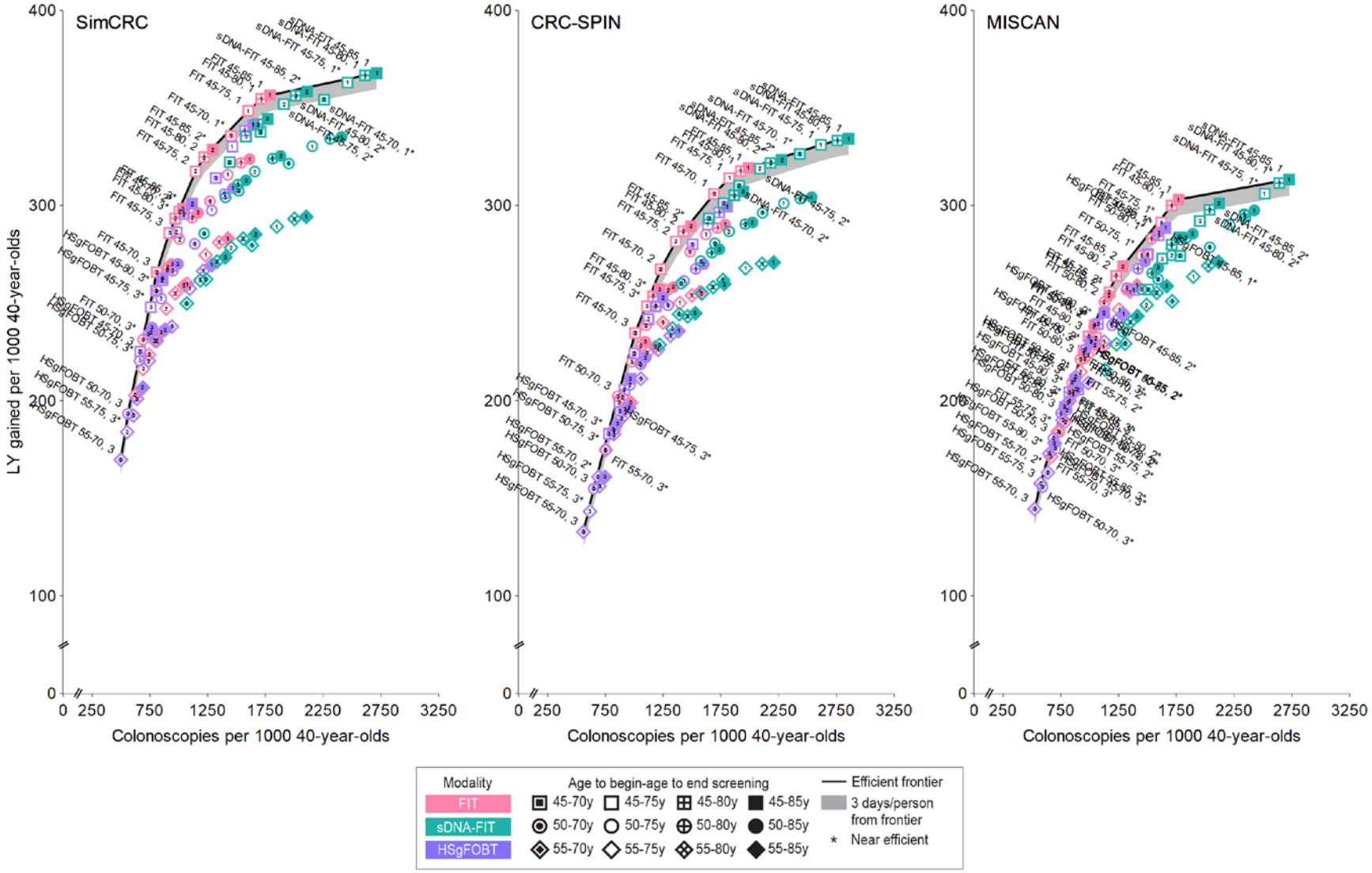
	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
HSgFOBT 55-70, 3	--	--	--
HSgFOBT 55-75, 3	4*	5*	4
HSgFOBT 50-70, 3	3	4	6*
HSgFOBT 55-70, 2	Dominated	7*	12*
FIT 55-70, 3	Dominated	5*	7*
HSgFOBT 55-80, 3	Dominated	Dominated	5*
HSgFOBT 50-75, 3	4*	5*	5
HSgFOBT 45-70, 3	3	5*	7*
HSgFOBT 55-85, 3	Dominated	Dominated	6*
FIT 55-75, 3	Dominated	Dominated	11*
FIT 50-70, 3	4*	4	15*
HSgFOBT 50-80, 3	Dominated	Dominated	5
HSgFOBT 55-75, 2	Dominated	Dominated	8*
HSgFOBT 45-75, 3	4*	5*	10*
HSgFOBT 50-70, 2	Dominated	Dominated	27*
HSgFOBT 50-85, 3	Dominated	Dominated	8*
FIT 55-80, 3	Dominated	Dominated	11*
HSgFOBT 45-80, 3	4*	Dominated	7*
FIT 45-70, 3	3	5	9*
HSgFOBT 55-80, 2	Dominated	Dominated	11*
FIT 50-75, 3	Dominated	Dominated	6*
HSgFOBT 50-75, 2	Dominated	Dominated	7*
FIT 55-85, 3	Dominated	Dominated	11*
HSgFOBT 45-85, 3	Dominated	Dominated	7*
FIT 55-75, 2	Dominated	Dominated	8*
FIT 50-80, 3	Dominated	Dominated	6
FIT 50-70, 2	Dominated	Dominated	94*
FIT 45-75, 3	5	7*	7*
FIT 50-85, 3	Dominated	Dominated	10*
HSgFOBT 50-80, 2	Dominated	Dominated	9*
FIT 45-80, 3	7*	8*	6
HSgFOBT 45-75, 2	Dominated	Dominated	11*
HSgFOBT 50-85, 2	Dominated	Dominated	10*
FIT 45-70, 2	8*	7	Dominated
FIT 50-75, 2	Dominated	Dominated	10*
FIT 45-85, 3	10*	Dominated	9*
HSgFOBT 45-80, 2	Dominated	Dominated	13*
HSgFOBT 45-85, 2	Dominated	Dominated	11*

Appendix Table 4.2. Efficient Stool-Based Screening Strategies (FIT, sDNA-FIT, HSgFOBT), by Model

FIT 50-80, 2	Dominated	Dominated	8
FIT 45-75, 2	7	9	9*
FIT 50-85, 2	Dominated	Dominated	12*
FIT 45-80, 2	10	12	8
FIT 45-85, 2	19*	25*	12
FIT 50-75, 1	Dominated	Dominated	29*
FIT 45-70, 1	21*	14	Dominated
FIT 50-80, 1	Dominated	Dominated	18*
HSgFOBT 45-80, 1	Dominated	Dominated	19*
FIT 45-75, 1	16	16	15*
FIT 50-85, 1	Dominated	Dominated	18*
HSgFOBT 45-85, 1	Dominated	Dominated	19*
sDNA-FIT 45-70, 2	Dominated	52*	Dominated
FIT 45-80, 1	19	27	14
FIT 45-85, 1	39	43	19
sDNA-FIT 45-75, 2	91*	135*	Dominated
sDNA-FIT 45-80, 2	176*	75*	26*
sDNA-FIT 45-85, 2	175*	69*	375*
sDNA-FIT 45-70, 1	116*	62*	Dominated
sDNA-FIT 45-75, 1	103*	53	251*
sDNA-FIT 45-80, 1	81	62	104*
sDNA-FIT 45-85, 1	95	111	94

Note: Strategies that were dominated in all 3 models are not shown.
COL – colonoscopy; LYG – life-years gained compared with no screening; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Figure 4.1. Estimated Colonoscopies and Life-Years Gained (Compared With No Screening) for a Cohort of 40-Year-Olds for Stool-Based Screening Strategies (FIT, sDNA-FIT, and HSgFOBT), by Model



Note: Color indicates modality; screening interval (1, 2, or 3y) is noted on each symbol. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Table 5.1. Estimated Outcomes for Once-Only Colonoscopy Screening Strategies by Model

Model/ Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
SimCRC												
No screening	0	0	0	0	85	85	2	85	34	0	0	0
COL at 45	0	0	0	1037	649	1686	6	45	17	246	233	90
COL at 50	0	0	0	1019	700	1720	7	40	14	256	241	94
COL at 55	0	0	0	991	730	1721	8	37	13	248	232	91
COL at 60	0	0	0	950	691	1640	9	38	13	219	203	80
COL at 65	0	0	0	893	654	1547	11	43	14	177	161	64
CRC-SPIN												
No screening	0	0	0	0	77	77	2	77	32	0	0	0
COL at 45	0	0	0	1038	845	1882	8	33	13	255	242	93
COL at 50	0	0	0	1020	859	1879	9	30	11	254	241	93
COL at 55	0	0	0	992	838	1830	10	29	11	243	229	89
COL at 60	0	0	0	951	751	1702	11	31	12	206	194	75
COL at 65	0	0	0	895	663	1557	11	36	13	167	155	61
MISCAN												
No screening	0	0	0	0	81	81	2	81	34	0	0	0
COL at 45	0	0	0	1038	822	1860	7	58	22	168	153	61
COL at 50	0	0	0	1020	921	1941	8	52	18	199	180	73
COL at 55	0	0	0	992	941	1933	10	48	16	212	190	77
COL at 60	0	0	0	951	855	1806	11	47	15	204	180	74
COL at 65	0	0	0	895	758	1653	12	49	16	171	149	62

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 5.2. Efficient Once-Only Colonoscopy Screening Strategies, by Model

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
COL at 65	--	--	--
COL at 60	2*	4*	5
COL at 45	2	4	Dominated
COL at 50	3	4*	Dominated
COL at 55	Dominated	4	15

COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 5.3. Efficient Colonoscopy Screening Strategies Including Once-Only Strategies, by Model

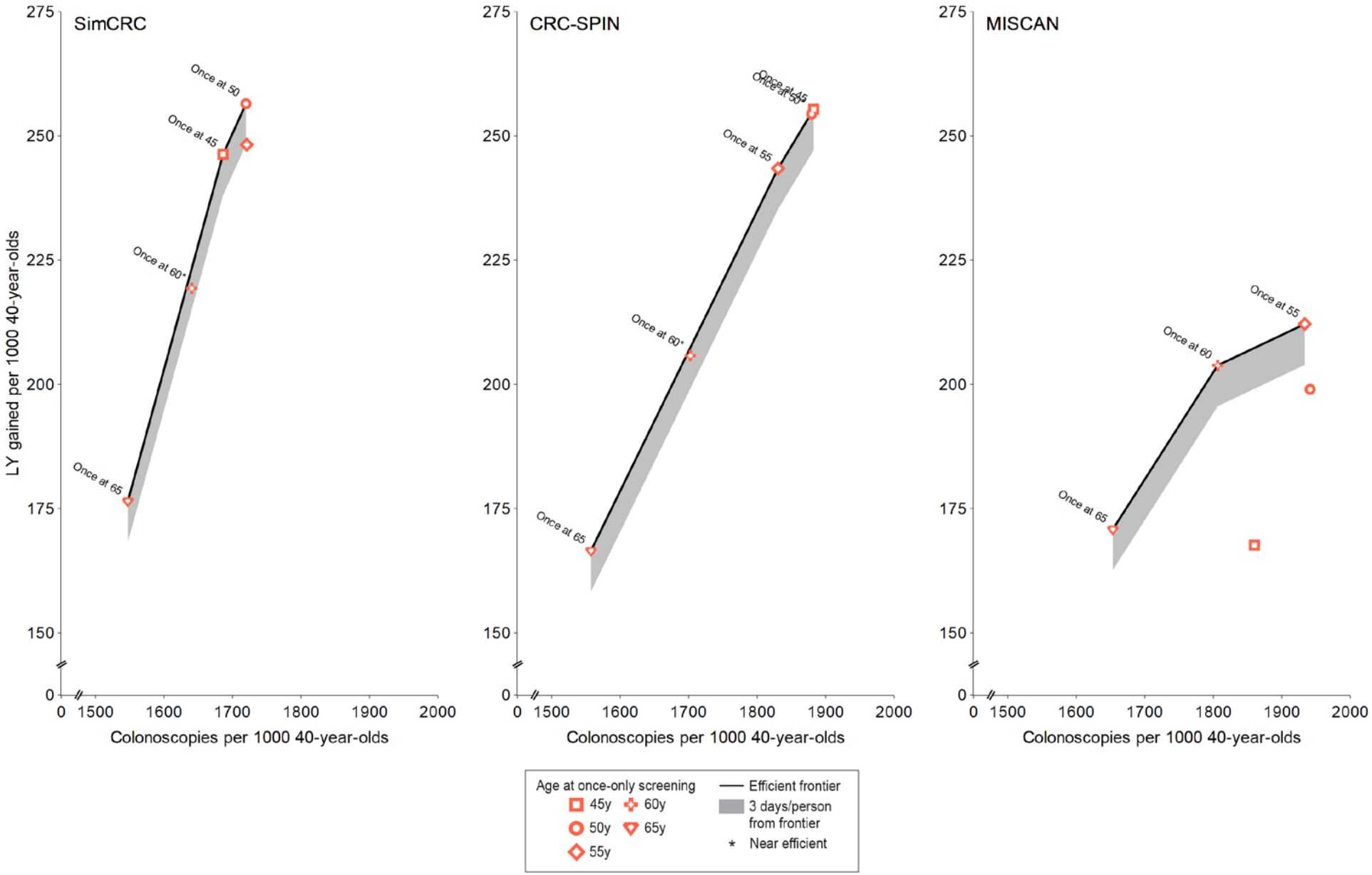
Strategy	Efficiency ratio (Δ COL / Δ LYG)		
	SimCRC	CRC-SPIN	MISCAN
COL at 65	--	--	--
COL at 60	2*	4*	5
COL at 45	2	4	Dominated
COL at 50	3	4*	Dominated
COL at 55	Dominated	4	15
COL 55-70, 15	Dominated	Dominated	18*
COL 55-70, 10	Dominated	Dominated	19*
COL 50-70, 15	Dominated	Dominated	18
COL 45-70, 15	14	18	85*
COL 50-80, 15	Dominated	Dominated	56*
COL 50-70, 10	Dominated	Dominated	28
COL 45-75, 15	39*	59*	38*
COL 45-70, 10	34	44	45
COL 50-80, 10	Dominated	Dominated	86*
COL 45-75, 10	64	112	52
COL 45-85, 10	394*	828*	227*
COL 50-70, 5	Dominated	Dominated	120*
COL 50-75, 5	Dominated	Dominated	367*
COL 45-70, 5	180*	179	84
COL 45-75, 5	178	344	116
COL 45-80, 5	428	736	169
COL 45-85, 5	1445	2190	926

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

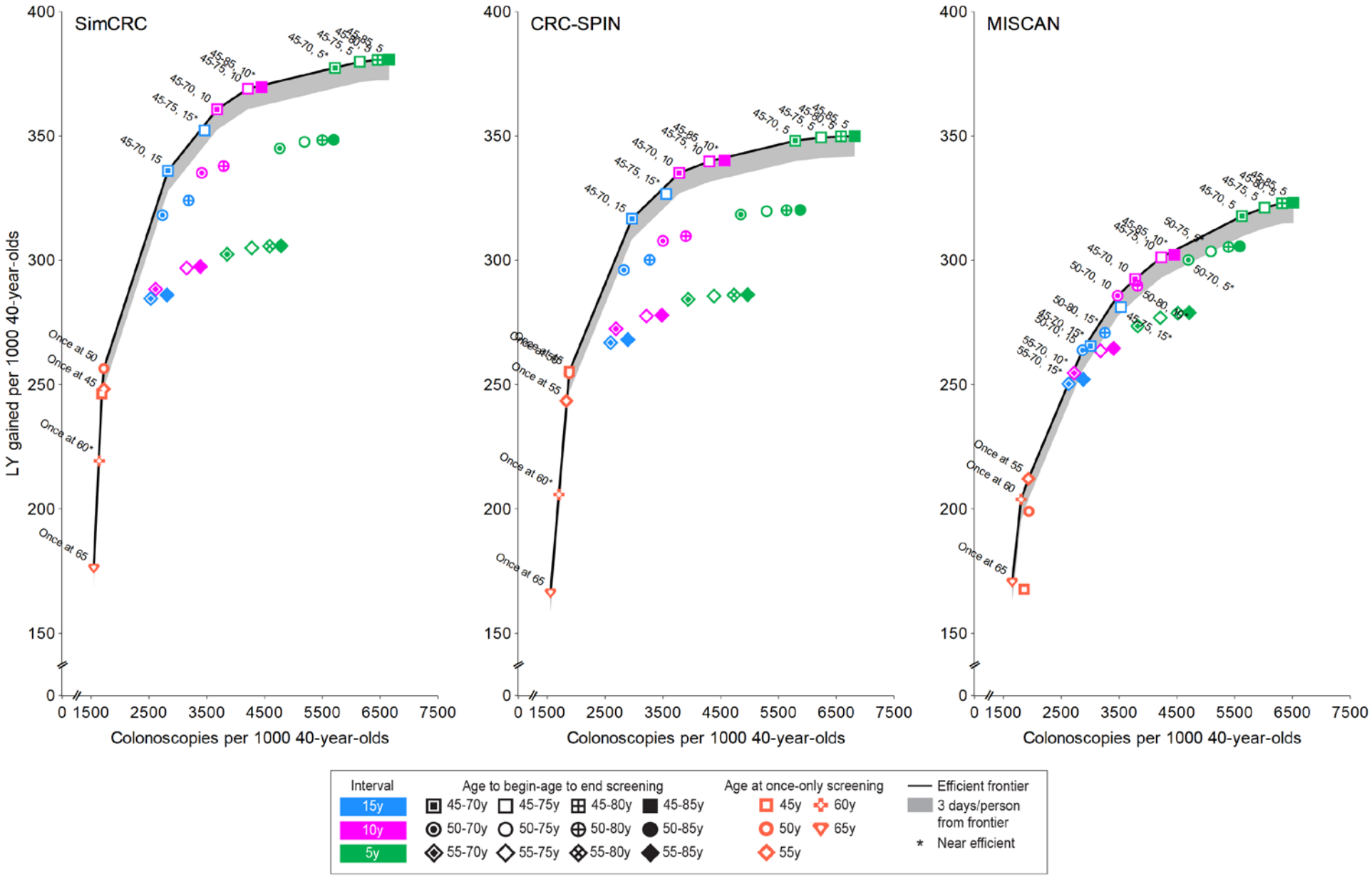
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Figure 5.1. Estimated Colonoscopies and Life-Years Gained (Compared With No Screening) for a Cohort of 40-Year-Olds for Once-Only Colonoscopy Screening Strategies, by Model



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 5.2. Estimated Colonoscopies and Life-Years Gained (Compared With No Screening) for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies Including Once-Only Strategies, by Model



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Table 6.1. Estimated Outcomes for Once-Only Sigmoidoscopy Strategies by Model

Model/ Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
SimCRC												
No screening	0	0	0	0	85	85	2	85	34	0	0	0
SIG at 45	0	988	0	0	500	500	3	64	25	138	131	51
SIG at 50	0	971	0	0	543	543	4	61	23	150	141	55
SIG at 55	0	944	0	0	579	579	4	58	22	151	141	55
SIG at 60	0	905	0	0	587	587	5	57	21	140	129	51
SIG at 65	0	851	0	0	588	588	6	58	21	117	107	43
CRC-SPIN												
No screening	0	0	0	0	77	77	2	77	32	0	0	0
SIG at 45	0	988	0	0	651	651	5	51	20	165	157	60
SIG at 50	0	971	0	0	695	695	6	47	18	174	165	63
SIG at 55	0	945	0	0	711	711	7	44	17	174	164	64
SIG at 60	0	906	0	0	690	690	7	44	17	151	142	55
SIG at 65	0	852	0	0	646	646	7	47	18	126	117	46
MISCAN												
No screening	0	0	0	0	81	81	2	81	34	0	0	0
SIG at 45	0	988	0	0	769	769	5	66	26	107	97	39
SIG at 50	0	971	0	0	896	896	6	61	23	137	124	50
SIG at 55	0	945	0	0	966	966	7	57	21	155	138	56
SIG at 60	0	906	0	0	955	955	8	55	20	156	138	57
SIG at 65	0	852	0	0	906	906	9	56	20	136	117	50

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 6.2. Efficient Once-Only Sigmoidoscopy Screening Strategies, by Model

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
SIG at 45	--	<1	--
SIG at 50	4	5	4*
SIG at 55	21	34	Dominated
SIG at 60	Dominated	Dominated	4
SIG at 65	Dominated	--	5*

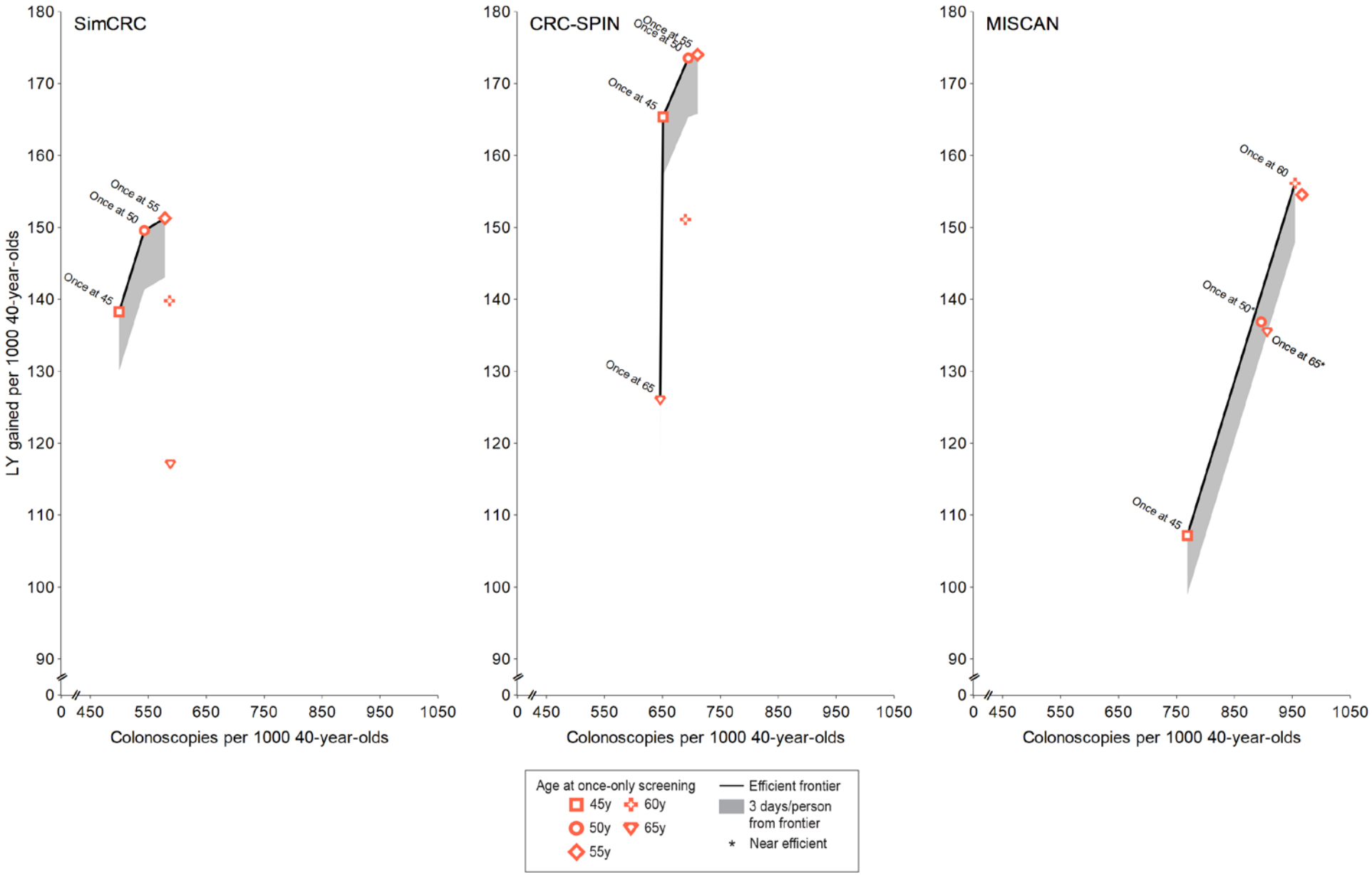
COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 6.3. Efficient Sigmoidoscopy Screening Strategies Including Once-Only Strategies, by Model

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
SIG at 45	--	<1	--
SIG at 50	4	5	4*
SIG at 55	21*	34*	4*
SIG at 60	Dominated	Dominated	4
SIG at 65	Dominated	--	5*
SIG 55-70, 10	Dominated	Dominated	8
SIG 50-70, 10	Dominated	Dominated	8
SIG 45-70, 10	5	7	73*
SIG 55-70, 5	Dominated	Dominated	11*
SIG 50-80, 10	Dominated	Dominated	22*
SIG 45-75, 10	13*	18	18*
SIG 50-70, 5	Dominated	Dominated	14
SIG 45-85, 10	Dominated	68*	21*
SIG 50-75, 5	Dominated	Dominated	19*
SIG 45-70, 5	11	20	15
SIG 50-80, 5	Dominated	Dominated	23*
SIG 50-85, 5	Dominated	Dominated	26*
SIG 45-75, 5	20	27	19
SIG 45-80, 5	38	49	29
SIG 45-85, 5	89	98	78

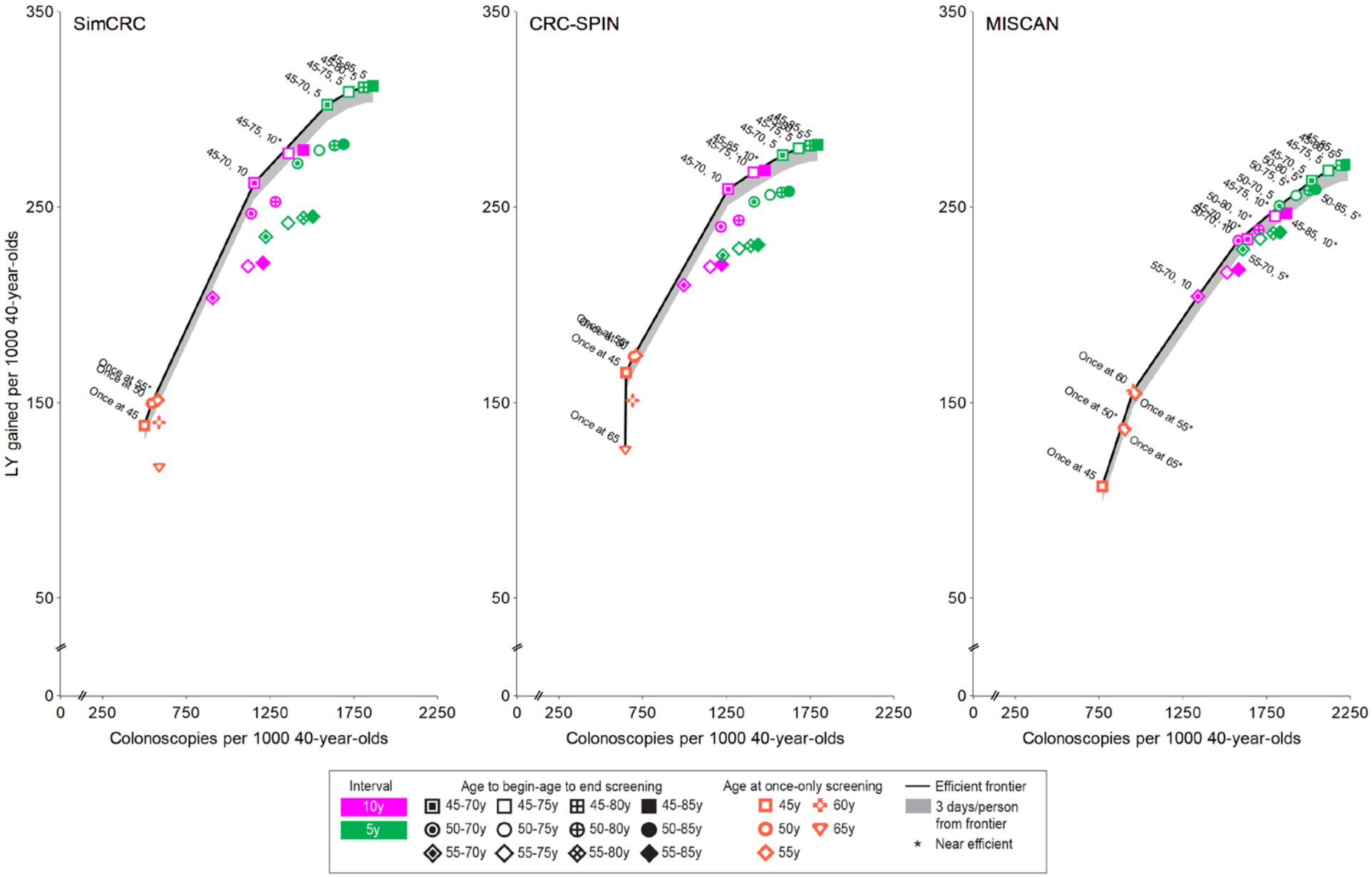
Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Figure 6.1. Estimated Colonoscopies and Life-Years Gained (Compared With No Screening) for a Cohort of 40-Year-Olds for Once-Only Sigmoidoscopy Strategies, by Model



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 6.2. Estimated Colonoscopies and Life-Years Gained (Compared With No Screening) for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Including Once-Only Strategies, by Model



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Table 7.1. Estimated Outcomes for 5 Years of Annual FIT Followed by 10-Yearly Colonoscopy Screening Strategies, by Model

Model/ Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
SimCRC												
No screening	0	0	0	0	85	85	2	85	34	0	0	0
Annual FIT from 45 to 49, followed by												
COL 50-70, 10	4541	0	0	2177	1281	3458	13	17	4	361	338	132
COL 50-80, 10	4541	0	0	2521	1329	3850	16	15	3	365	341	133
Annual FIT from 50 to 54, followed by												
COL 55-75, 10	4411	0	0	1945	1252	3197	15	20	5	331	307	121
COL 55-85, 10	4411	0	0	2174	1273	3447	18	19	5	331	308	121
CRC-SPIN												
No screening	0	0	0	0	77	77	2	77	32	0	0	0
Annual FIT from 45 to 49, followed by												
COL 50-70, 10	4492	0	0	2143	1418	3561	15	14	4	330	311	121
COL 50-80, 10	4492	0	0	2519	1447	3967	18	13	4	332	313	121
Annual FIT from 50 to 54, followed by												
COL 55-75, 10	4352	0	0	1936	1346	3282	16	16	5	302	283	110
COL 55-85, 10	4352	0	0	2200	1359	3559	18	16	5	302	284	110
MISCAN												
No screening	0	0	0	0	81	81	2	81	34	0	0	0
Annual FIT from 45 to 49, followed by												
COL 50-70, 10	4555	0	0	2063	1454	3517	14	36	9	300	270	110
COL 50-80, 10	4555	0	0	2387	1483	3870	16	34	8	305	274	111
Annual FIT from 50 to 54, followed by												
COL 55-75, 10	4419	0	0	1840	1385	3224	15	36	9	288	257	105
COL 55-85, 10	4419	0	0	2064	1396	3460	17	36	9	289	258	106

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 7.2. Efficient Strategies With 5 Years of Annual FIT Followed by 10-Yearly Colonoscopy With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by Model

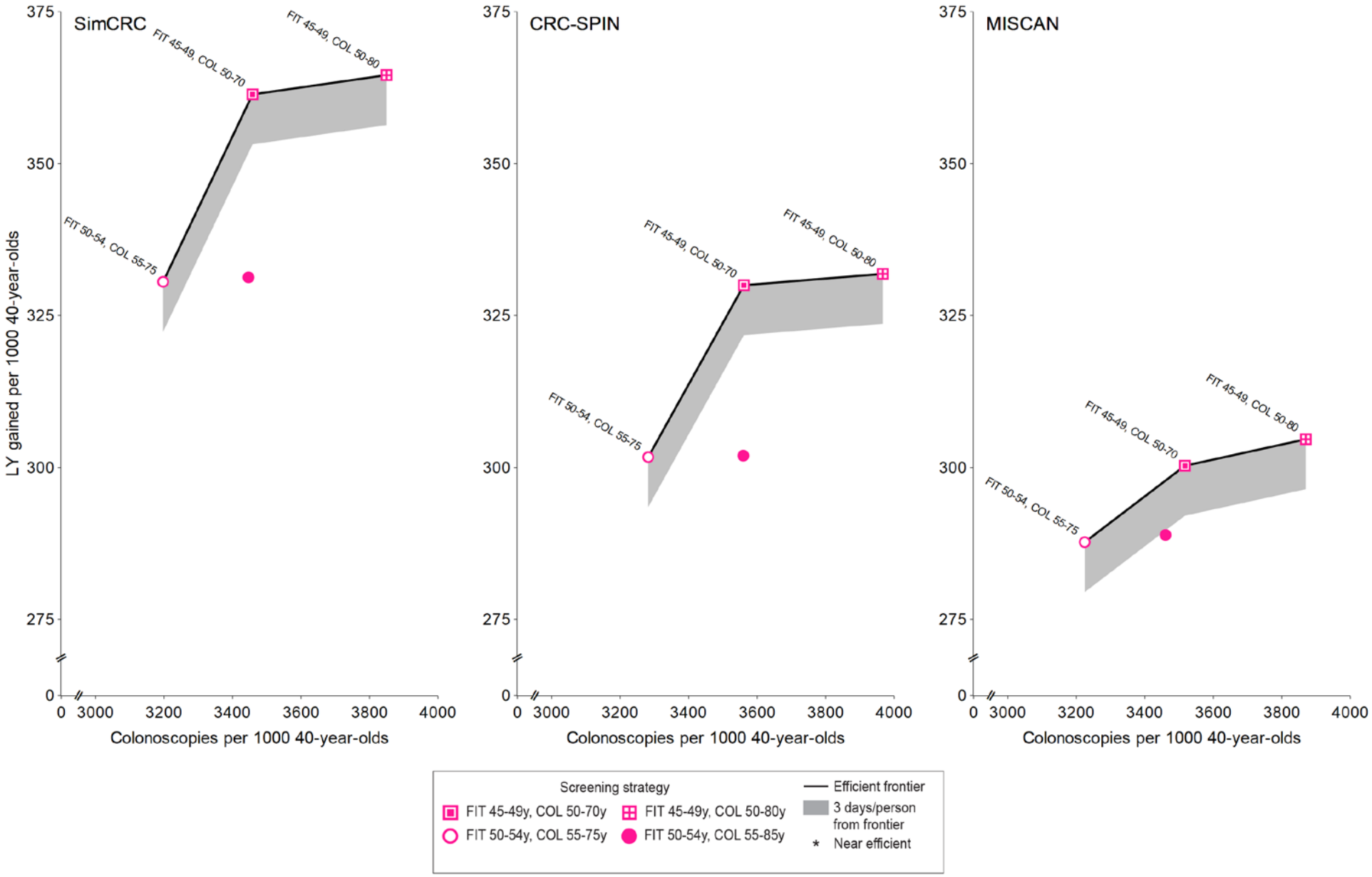
	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
FIT 50-54, 1; COL 55-75, 10	--	--	--
FIT 45-49, 1; COL 50-70, 10	8	10	23
FIT 45-49, 1; COL 50-80, 10	123	216	81

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Figure 7.1. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Screening Strategies With 5 Years of Annual FIT Followed by 10-Yearly Colonoscopy, by Model



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Table 8.1. Estimated Outcomes for Once-Only Colonoscopy Followed by Annual FIT Screening Strategies, by Model

Model/ Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
SimCRC												
No screening	0	0	0	0	85	85	2	85	34	0	0	0
COL at 45 followed by												
FIT 55-70, 1	9554	0	0	1037	1274	2311	9	26	7	345	323	126
FIT 55-75, 1	11649	0	0	1037	1413	2451	10	22	5	357	333	130
FIT 55-80, 1	13309	0	0	1037	1521	2559	11	21	4	362	338	132
FIT 55-85, 1	14491	0	0	1037	1593	2631	13	20	4	364	339	133
COL at 50, followed by												
FIT 60-70, 1	6319	0	0	1019	1109	2128	9	28	8	316	295	115
FIT 60-75, 1	8372	0	0	1019	1243	2262	10	25	6	327	304	119
FIT 60-80, 1	10021	0	0	1019	1348	2367	11	23	5	332	309	121
FIT 60-85, 1	11196	0	0	1019	1420	2439	13	23	5	334	310	122
CRC-SPIN												
No screening	0	0	0	0	77	77	2	77	32	0	0	0
COL at 45, followed by												
FIT 55-70, 1	9192	0	0	1038	1481	2518	12	19	6	322	304	118
FIT 55-75, 1	11233	0	0	1038	1603	2641	13	17	5	329	309	120
FIT 55-80, 1	12888	0	0	1038	1698	2736	14	16	5	332	312	121
FIT 55-85, 1	14106	0	0	1038	1763	2801	15	15	4	334	313	122
COL at 50, followed by												
FIT 60-70, 1	6143	0	0	1020	1279	2299	12	20	7	294	278	107
FIT 60-75, 1	8153	0	0	1020	1398	2418	13	19	6	301	283	110
FIT 60-80, 1	9805	0	0	1020	1491	2511	14	18	6	304	286	111
FIT 60-85, 1	11020	0	0	1020	1556	2576	15	17	5	305	287	111
MISCAN												
No screening	0	0	0	0	81	81	2	81	34	0	0	0
COL at 45, followed by												
FIT 55-70, 1	8674	0	0	1038	1368	2406	9	46	13	272	242	99
FIT 55-75, 1	10765	0	0	1038	1480	2518	10	44	11	288	256	105
FIT 55-80, 1	12481	0	0	1038	1566	2603	11	42	9	297	263	108
FIT 55-85, 1	13768	0	0	1038	1626	2664	12	42	9	301	266	110
COL at 50, followed by												
FIT 60-70, 1	5459	0	0	1020	1235	2255	10	46	13	259	231	95
FIT 60-75, 1	7462	0	0	1020	1337	2357	11	44	11	274	243	100
FIT 60-80, 1	9140	0	0	1020	1418	2438	11	42	10	282	250	103
FIT 60-85, 1	10404	0	0	1020	1475	2495	12	42	9	285	252	104

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 8.2. Efficient Once-Only Colonoscopy Followed by Annual FIT Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by Model

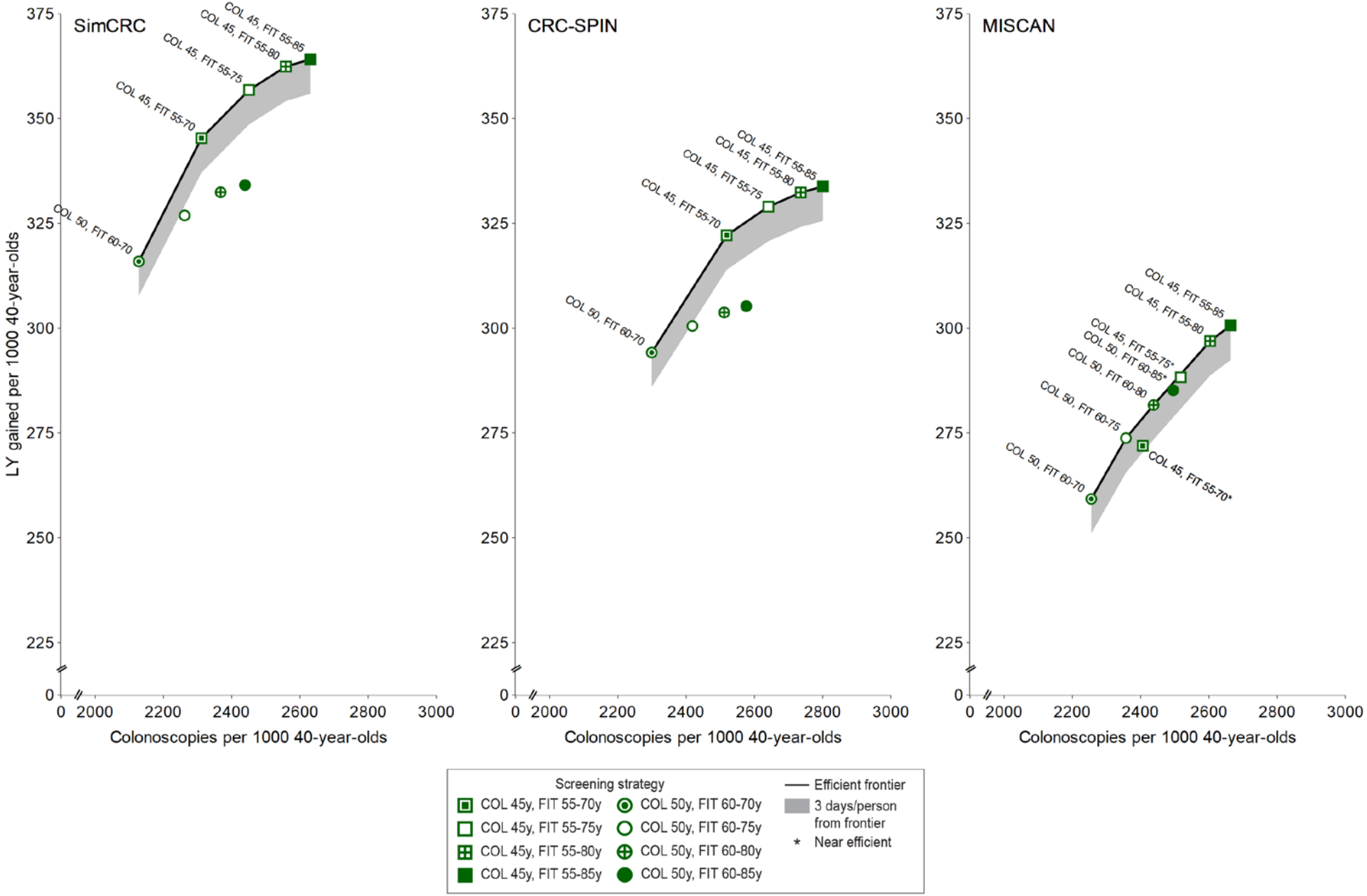
	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
COL at 50; FIT 60-70, 1	--	--	--
COL at 50; FIT 60-75, 1	Dominated	Dominated	7
COL at 45; FIT 55-70, 1	6	8	12*
COL at 50; FIT 60-80, 1	Dominated	Dominated	10
COL at 50; FIT 60-85, 1	Dominated	Dominated	16*
COL at 45; FIT 55-75, 1	12	18	12*
COL at 45; FIT 55-80, 1	19	28	11
COL at 45; FIT 55-85, 1	41	46	16

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Figure 8.1. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds for Screening Strategies With Once-Only Colonoscopy Followed by Annual FIT, by Model



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Table 9.1a. Estimated Outcomes for Colonoscopy Screening Strategies: SimCRC

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	85	85	2	85	34	0	0	0
COL 45-70, 5	0	0	0	4436	1282	5718	15	12	3	377	355	138
COL 45-70, 10	0	0	0	2537	1142	3679	12	17	5	361	340	132
COL 45-70, 15	0	0	0	1846	983	2829	10	24	7	336	316	123
COL 45-75, 5	0	0	0	4826	1319	6145	17	11	3	380	357	139
COL 45-75, 10	0	0	0	2987	1225	4212	16	14	3	369	347	135
COL 45-75, 15	0	0	0	2351	1112	3463	15	18	4	352	331	129
COL 45-80, 5	0	0	0	5115	1339	6454	19	11	2	381	358	139
COL 45-80, 10	0	0	0	2987	1225	4212	16	14	3	369	347	135
COL 45-80, 15	0	0	0	2351	1112	3463	15	18	4	352	331	129
COL 45-85, 5	0	0	0	5304	1347	6652	21	10	2	381	358	139
COL 45-85, 10	0	0	0	3205	1244	4449	18	14	3	370	347	135
COL 45-85, 15	0	0	0	2351	1112	3463	15	18	4	352	331	129
COL 50-70, 5	0	0	0	3583	1179	4762	15	16	4	345	323	126
COL 50-70, 10	0	0	0	2343	1072	3414	13	18	5	335	314	122
COL 50-70, 15	0	0	0	1742	992	2734	11	23	7	318	298	116
COL 50-75, 5	0	0	0	3973	1216	5189	17	15	4	348	326	127
COL 50-75, 10	0	0	0	2343	1072	3414	13	18	5	335	314	122
COL 50-75, 15	0	0	0	1742	992	2734	11	23	7	318	298	116
COL 50-80, 5	0	0	0	4262	1236	5498	19	14	4	348	326	127
COL 50-80, 10	0	0	0	2676	1116	3792	16	17	4	338	316	123
COL 50-80, 15	0	0	0	2123	1064	3186	16	21	5	324	303	118
COL 50-85, 5	0	0	0	4451	1244	5696	20	14	3	348	326	127
COL 50-85, 10	0	0	0	2676	1116	3792	16	17	4	338	316	123
COL 50-85, 15	0	0	0	2123	1064	3186	16	21	5	324	303	118
COL 55-70, 5	0	0	0	2792	1059	3851	14	21	6	302	282	110
COL 55-70, 10	0	0	0	1666	949	2615	12	26	8	288	269	105
COL 55-70, 15	0	0	0	1617	915	2532	13	26	8	285	265	104
COL 55-75, 5	0	0	0	3182	1096	4279	16	20	5	305	284	111
COL 55-75, 10	0	0	0	2118	1034	3152	15	22	6	297	276	108
COL 55-75, 15	0	0	0	1617	915	2532	13	26	8	285	265	104
COL 55-80, 5	0	0	0	3471	1116	4587	18	19	5	306	284	112
COL 55-80, 10	0	0	0	2118	1034	3152	15	22	6	297	276	108
COL 55-80, 15	0	0	0	1617	915	2532	13	26	8	285	265	104
COL 55-85, 5	0	0	0	3661	1124	4785	20	19	5	306	284	112
COL 55-85, 10	0	0	0	2337	1053	3389	18	22	6	297	277	109
COL 55-85, 15	0	0	0	1866	947	2812	16	25	7	286	266	104

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.1b. Estimated Outcomes for Colonoscopy Screening Strategies: CRC-SPIN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	77	77	2	77	32	0	0	0
COL 45-70, 5	0	0	0	4379	1410	5789	17	10	3	348	328	127
COL 45-70, 10	0	0	0	2506	1276	3782	14	13	4	335	317	122
COL 45-70, 15	0	0	0	1827	1138	2965	12	18	6	317	300	116
COL 45-75, 5	0	0	0	4804	1431	6235	19	10	3	349	329	128
COL 45-75, 10	0	0	0	2976	1324	4300	17	12	4	340	321	124
COL 45-75, 15	0	0	0	2339	1218	3558	16	14	5	327	309	119
COL 45-80, 5	0	0	0	5138	1443	6581	20	9	3	350	330	128
COL 45-80, 10	0	0	0	2976	1324	4300	17	12	4	340	321	124
COL 45-80, 15	0	0	0	2339	1218	3558	16	14	5	327	309	119
COL 45-85, 5	0	0	0	5369	1448	6817	22	9	3	350	330	128
COL 45-85, 10	0	0	0	3230	1336	4566	19	11	4	340	321	124
COL 45-85, 15	0	0	0	2339	1218	3558	16	14	5	327	309	119
COL 50-70, 5	0	0	0	3571	1276	4847	17	13	4	318	300	116
COL 50-70, 10	0	0	0	2337	1163	3500	15	15	5	308	291	112
COL 50-70, 15	0	0	0	1732	1093	2825	13	18	6	296	280	108
COL 50-75, 5	0	0	0	3996	1297	5293	18	12	4	320	301	117
COL 50-75, 10	0	0	0	2337	1163	3500	15	15	5	308	291	112
COL 50-75, 15	0	0	0	1732	1093	2825	13	18	6	296	280	108
COL 50-80, 5	0	0	0	4329	1310	5639	20	12	4	320	302	117
COL 50-80, 10	0	0	0	2705	1191	3896	18	14	5	310	293	113
COL 50-80, 15	0	0	0	2133	1139	3272	17	16	5	300	284	110
COL 50-85, 5	0	0	0	4560	1315	5875	22	12	4	320	302	117
COL 50-85, 10	0	0	0	2705	1191	3896	18	14	5	310	293	113
COL 50-85, 15	0	0	0	2133	1139	3272	17	16	5	300	284	110
COL 55-70, 5	0	0	0	2815	1121	3936	16	17	6	284	267	104
COL 55-70, 10	0	0	0	1668	1021	2689	14	20	7	272	256	100
COL 55-70, 15	0	0	0	1619	976	2595	14	21	7	267	251	97
COL 55-75, 5	0	0	0	3241	1143	4384	18	16	6	286	268	104
COL 55-75, 10	0	0	0	2142	1073	3216	16	18	6	278	261	101
COL 55-75, 15	0	0	0	1619	976	2595	14	21	7	267	251	97
COL 55-80, 5	0	0	0	3574	1155	4729	19	16	5	286	268	104
COL 55-80, 10	0	0	0	2142	1073	3216	16	18	6	278	261	101
COL 55-80, 15	0	0	0	1619	976	2595	14	21	7	267	251	97
COL 55-85, 5	0	0	0	3805	1160	4966	21	16	5	286	268	105
COL 55-85, 10	0	0	0	2396	1086	3482	18	18	6	278	261	102
COL 55-85, 15	0	0	0	1896	997	2893	17	20	7	268	252	98

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.1c. Estimated Outcomes for Colonoscopy Screening Strategies: MISCAN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	81	81	2	81	34	0	0	0
COL 45-70, 5	0	0	0	4147	1479	5626	16	32	8	318	288	116
COL 45-70, 10	0	0	0	2428	1351	3779	13	37	10	292	265	107
COL 45-70, 15	0	0	0	1805	1201	3006	11	41	12	265	240	97
COL 45-75, 5	0	0	0	4518	1498	6016	17	31	7	321	291	117
COL 45-75, 10	0	0	0	2837	1395	4232	15	34	8	301	272	110
COL 45-75, 15	0	0	0	2256	1276	3532	15	37	10	281	253	103
COL 45-80, 5	0	0	0	4808	1512	6320	19	30	7	323	293	118
COL 45-80, 10	0	0	0	2837	1395	4232	15	34	8	301	272	110
COL 45-80, 15	0	0	0	2256	1276	3532	15	37	10	281	253	103
COL 45-85, 5	0	0	0	5001	1515	6516	20	30	7	323	293	118
COL 45-85, 10	0	0	0	3053	1404	4457	17	34	8	302	273	110
COL 45-85, 15	0	0	0	2256	1276	3532	15	37	10	281	253	103
COL 50-70, 5	0	0	0	3341	1357	4698	15	33	8	300	271	110
COL 50-70, 10	0	0	0	2224	1252	3476	14	36	9	286	257	104
COL 50-70, 15	0	0	0	1685	1184	2868	13	40	11	264	237	96
COL 50-75, 5	0	0	0	3713	1376	5089	17	32	8	304	274	111
COL 50-75, 10	0	0	0	2224	1252	3476	14	36	9	286	257	104
COL 50-75, 15	0	0	0	1685	1184	2868	13	40	11	264	237	96
COL 50-80, 5	0	0	0	4002	1390	5393	18	32	8	305	275	112
COL 50-80, 10	0	0	0	2540	1279	3819	16	35	9	290	260	106
COL 50-80, 15	0	0	0	2031	1226	3257	16	38	10	271	242	99
COL 50-85, 5	0	0	0	4196	1393	5589	20	32	7	306	275	112
COL 50-85, 10	0	0	0	2540	1279	3819	16	35	9	290	260	106
COL 50-85, 15	0	0	0	2031	1226	3257	16	38	10	271	242	99
COL 55-70, 5	0	0	0	2618	1204	3822	15	36	9	274	245	100
COL 55-70, 10	0	0	0	1602	1122	2724	13	40	11	255	228	93
COL 55-70, 15	0	0	0	1556	1074	2630	13	40	11	250	223	91
COL 55-75, 5	0	0	0	2990	1223	4213	16	35	9	277	248	101
COL 55-75, 10	0	0	0	2014	1167	3180	15	37	10	264	235	96
COL 55-75, 15	0	0	0	1556	1074	2630	13	40	11	250	223	91
COL 55-80, 5	0	0	0	3279	1238	4517	18	34	8	279	249	102
COL 55-80, 10	0	0	0	2014	1167	3180	15	37	10	264	235	96
COL 55-80, 15	0	0	0	1556	1074	2630	13	40	11	250	223	91
COL 55-85, 5	0	0	0	3473	1240	4713	19	34	8	279	250	102
COL 55-85, 10	0	0	0	2229	1176	3406	17	37	10	265	236	97
COL 55-85, 15	0	0	0	1791	1090	2881	16	40	11	252	224	92

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.2a. Estimated Outcomes for FIT Strategies: SimCRC

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	85	85	2	85	34	0	0	0
FIT 45-70, 1	17539	0	0	0	1453	1453	8	30	8	336	310	123
FIT 45-70, 2	10148	0	0	0	1006	1006	6	42	11	297	271	108
FIT 45-70, 3	7435	0	0	0	810	810	6	49	14	266	241	97
FIT 45-75, 1	19680	0	0	0	1602	1602	10	26	6	348	321	127
FIT 45-75, 2	11731	0	0	0	1147	1147	8	38	9	318	289	116
FIT 45-75, 3	8475	0	0	0	917	917	7	46	11	286	258	104
FIT 45-80, 1	21368	0	0	0	1715	1715	11	25	5	355	326	129
FIT 45-80, 2	12576	0	0	0	1220	1220	9	36	7	325	295	119
FIT 45-80, 3	9043	0	0	0	971	971	8	44	10	293	264	107
FIT 45-85, 1	22567	0	0	0	1790	1790	12	24	4	356	328	130
FIT 45-85, 2	13487	0	0	0	1294	1294	10	36	6	329	298	120
FIT 45-85, 3	9734	0	0	0	1037	1037	9	44	9	298	267	109
FIT 50-70, 1	14004	0	0	0	1271	1271	8	34	9	302	277	110
FIT 50-70, 2	8382	0	0	0	909	909	6	45	12	268	244	98
FIT 50-70, 3	5757	0	0	0	691	691	5	53	16	231	208	84
FIT 50-75, 1	16160	0	0	0	1423	1423	9	30	7	316	289	115
FIT 50-75, 2	9446	0	0	0	1006	1006	7	42	10	283	256	103
FIT 50-75, 3	6945	0	0	0	814	814	6	49	13	256	230	94
FIT 50-80, 1	17856	0	0	0	1538	1538	11	28	6	322	294	118
FIT 50-80, 2	10719	0	0	0	1116	1116	9	40	8	294	265	107
FIT 50-80, 3	7785	0	0	0	900	900	8	47	11	267	238	98
FIT 50-85, 1	19059	0	0	0	1613	1613	12	28	5	324	296	118
FIT 50-85, 2	11329	0	0	0	1166	1166	10	39	8	296	267	108
FIT 50-85, 3	8199	0	0	0	939	939	8	47	10	270	240	99
FIT 55-70, 1	10601	0	0	0	1072	1072	8	40	11	260	236	95
FIT 55-70, 2	6100	0	0	0	742	742	6	51	15	223	201	82
FIT 55-70, 3	4710	0	0	0	624	624	5	56	17	203	181	74
FIT 55-75, 1	12790	0	0	0	1232	1232	9	36	9	275	249	100
FIT 55-75, 2	7715	0	0	0	893	893	7	46	12	247	221	90
FIT 55-75, 3	5351	0	0	0	691	691	6	54	15	216	192	79
FIT 55-80, 1	14502	0	0	0	1349	1349	11	34	8	281	255	103
FIT 55-80, 2	8573	0	0	0	970	970	8	45	10	255	228	93
FIT 55-80, 3	6324	0	0	0	791	791	7	52	13	231	204	84
FIT 55-85, 1	15711	0	0	0	1426	1426	12	33	7	283	256	103
FIT 55-85, 2	9494	0	0	0	1046	1046	10	44	9	259	231	95
FIT 55-85, 3	6931	0	0	0	851	851	9	52	12	235	207	86

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.2b. Estimated Outcomes for FIT Strategies: CRC-SPIN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	77	77	2	77	32	0	0	0
FIT 45-70, 1	16882	0	0	0	1692	1692	12	22	7	306	286	112
FIT 45-70, 2	9891	0	0	0	1230	1230	9	32	11	267	249	98
FIT 45-70, 3	7299	0	0	0	1007	1007	8	38	13	235	218	86
FIT 45-75, 1	18950	0	0	0	1824	1824	13	20	6	314	293	115
FIT 45-75, 2	11420	0	0	0	1361	1361	11	29	9	281	262	103
FIT 45-75, 3	8300	0	0	0	1110	1110	9	36	11	248	230	91
FIT 45-80, 1	20622	0	0	0	1923	1923	14	19	5	318	296	116
FIT 45-80, 2	12249	0	0	0	1426	1426	12	28	8	287	266	105
FIT 45-80, 3	8866	0	0	0	1163	1163	10	35	11	253	235	93
FIT 45-85, 1	21850	0	0	0	1990	1990	15	19	5	319	298	117
FIT 45-85, 2	13160	0	0	0	1492	1492	13	27	7	289	268	106
FIT 45-85, 3	9551	0	0	0	1222	1222	11	34	10	257	238	94
FIT 50-70, 1	13481	0	0	0	1483	1483	11	26	8	276	258	101
FIT 50-70, 2	8177	0	0	0	1102	1102	9	35	12	239	222	87
FIT 50-70, 3	5663	0	0	0	858	858	7	43	15	202	188	74
FIT 50-75, 1	15562	0	0	0	1619	1619	12	23	7	285	266	104
FIT 50-75, 2	9206	0	0	0	1194	1194	10	33	10	248	231	91
FIT 50-75, 3	6818	0	0	0	981	981	9	39	13	220	203	80
FIT 50-80, 1	17240	0	0	0	1721	1721	13	22	7	288	268	105
FIT 50-80, 2	10454	0	0	0	1294	1294	11	31	9	257	238	94
FIT 50-80, 3	7634	0	0	0	1059	1059	10	38	12	228	210	83
FIT 50-85, 1	18471	0	0	0	1788	1788	14	22	6	290	270	106
FIT 50-85, 2	11065	0	0	0	1339	1339	12	30	9	258	239	94
FIT 50-85, 3	8055	0	0	0	1096	1096	11	37	11	230	212	84
FIT 55-70, 1	10229	0	0	0	1249	1249	10	31	10	240	222	88
FIT 55-70, 2	5974	0	0	0	896	896	8	41	14	202	186	74
FIT 55-70, 3	4637	0	0	0	754	754	7	47	17	175	161	64
FIT 55-75, 1	12342	0	0	0	1394	1394	12	28	9	250	231	91
FIT 55-75, 2	7539	0	0	0	1043	1043	10	37	12	219	201	80
FIT 55-75, 3	5270	0	0	0	824	824	8	45	15	185	170	67
FIT 55-80, 1	14032	0	0	0	1499	1499	13	27	8	254	235	93
FIT 55-80, 2	8381	0	0	0	1114	1114	11	36	11	225	206	82
FIT 55-80, 3	6226	0	0	0	920	920	9	42	14	195	179	71
FIT 55-85, 1	15273	0	0	0	1568	1568	14	27	8	256	236	93
FIT 55-85, 2	9304	0	0	0	1182	1182	12	36	10	227	208	83
FIT 55-85, 3	6824	0	0	0	973	973	10	42	13	199	181	73

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.2c. Estimated Outcomes for FIT Strategies: MISCAN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	81	81	2	81	34	0	0	0
FIT 45-70, 1	17494	0	0	0	1498	1498	9	49	13	274	242	100
FIT 45-70, 2	10116	0	0	0	1052	1052	7	58	16	232	201	85
FIT 45-70, 3	7409	0	0	0	852	852	6	62	18	205	175	75
FIT 45-75, 1	19607	0	0	0	1620	1620	10	46	10	291	256	106
FIT 45-75, 2	11672	0	0	0	1172	1172	8	55	13	256	221	93
FIT 45-75, 3	8437	0	0	0	948	948	7	60	16	226	192	82
FIT 45-80, 1	21300	0	0	0	1710	1710	11	45	9	300	263	110
FIT 45-80, 2	12509	0	0	0	1230	1230	9	54	12	264	227	96
FIT 45-80, 3	8991	0	0	0	991	991	8	60	14	233	198	85
FIT 45-85, 1	22527	0	0	0	1769	1769	12	44	8	303	266	111
FIT 45-85, 2	13423	0	0	0	1288	1288	10	54	11	269	231	98
FIT 45-85, 3	9679	0	0	0	1043	1043	9	60	13	239	202	87
FIT 50-70, 1	13963	0	0	0	1319	1319	9	50	13	257	225	94
FIT 50-70, 2	8347	0	0	0	956	956	7	58	16	222	191	81
FIT 50-70, 3	5736	0	0	0	737	737	6	64	20	184	156	67
FIT 50-75, 1	16097	0	0	0	1445	1445	10	47	11	274	240	100
FIT 50-75, 2	9395	0	0	0	1038	1038	8	56	14	238	204	87
FIT 50-75, 3	6905	0	0	0	847	847	7	61	17	209	177	76
FIT 50-80, 1	17802	0	0	0	1537	1537	11	46	10	283	247	103
FIT 50-80, 2	10658	0	0	0	1127	1127	9	55	12	251	214	92
FIT 50-80, 3	7740	0	0	0	919	919	8	61	15	221	186	81
FIT 50-85, 1	19037	0	0	0	1597	1597	11	45	9	286	249	105
FIT 50-85, 2	11272	0	0	0	1166	1166	10	55	11	254	216	93
FIT 50-85, 3	8148	0	0	0	948	948	8	61	14	224	188	82
FIT 55-70, 1	10580	0	0	0	1118	1118	8	53	15	228	198	83
FIT 55-70, 2	6080	0	0	0	788	788	6	61	18	189	161	69
FIT 55-70, 3	4696	0	0	0	665	665	6	65	20	171	144	63
FIT 55-75, 1	12758	0	0	0	1253	1253	9	50	12	247	214	90
FIT 55-75, 2	7677	0	0	0	921	921	8	58	15	215	182	78
FIT 55-75, 3	5325	0	0	0	725	725	6	63	18	184	154	67
FIT 55-80, 1	14485	0	0	0	1348	1348	10	48	11	256	221	93
FIT 55-80, 2	8530	0	0	0	983	983	8	57	14	223	189	82
FIT 55-80, 3	6288	0	0	0	810	810	7	62	16	199	165	73
FIT 55-85, 1	15731	0	0	0	1410	1410	11	48	10	259	224	95
FIT 55-85, 2	9459	0	0	0	1044	1044	9	57	12	229	193	84
FIT 55-85, 3	6897	0	0	0	858	858	8	63	15	204	169	74

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.3a. Estimated Outcomes for sDNA-FIT Strategies: SimCRC

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	85	85	2	85	34	0	0	0
sDNA-FIT 45-70, 1	12498	0	0	0	2258	2258	10	22	6	354	329	129
sDNA-FIT 45-70, 2	8354	0	0	0	1708	1708	9	28	7	338	313	123
sDNA-FIT 45-70, 3	6548	0	0	0	1442	1442	8	33	9	322	297	118
sDNA-FIT 45-75, 1	13888	0	0	0	2462	2462	12	19	4	363	337	133
sDNA-FIT 45-75, 2	9543	0	0	0	1910	1910	10	24	5	352	325	129
sDNA-FIT 45-75, 3	7274	0	0	0	1582	1582	9	30	7	335	308	122
sDNA-FIT 45-80, 1	14966	0	0	0	2614	2614	13	17	4	367	340	134
sDNA-FIT 45-80, 2	10167	0	0	0	2012	2012	11	23	5	356	329	130
sDNA-FIT 45-80, 3	7852	0	0	0	1684	1684	10	28	6	342	313	125
sDNA-FIT 45-85, 1	15721	0	0	0	2713	2713	14	17	3	368	341	134
sDNA-FIT 45-85, 2	10828	0	0	0	2114	2114	13	22	4	358	330	131
sDNA-FIT 45-85, 3	8347	0	0	0	1770	1770	12	28	5	344	315	126
sDNA-FIT 50-70, 1	10087	0	0	0	1953	1953	10	25	7	321	298	117
sDNA-FIT 50-70, 2	6929	0	0	0	1520	1520	9	31	8	307	283	112
sDNA-FIT 50-70, 3	5122	0	0	0	1221	1221	7	38	11	286	262	104
sDNA-FIT 50-75, 1	11463	0	0	0	2156	2156	11	22	6	330	305	121
sDNA-FIT 50-75, 2	7728	0	0	0	1659	1659	10	29	7	317	292	116
sDNA-FIT 50-75, 3	6074	0	0	0	1405	1405	9	34	8	304	278	111
sDNA-FIT 50-80, 1	12548	0	0	0	2310	2310	13	21	5	334	308	122
sDNA-FIT 50-80, 2	8668	0	0	0	1813	1813	12	26	6	324	297	118
sDNA-FIT 50-80, 3	6652	0	0	0	1513	1513	10	32	7	311	283	113
sDNA-FIT 50-85, 1	13305	0	0	0	2410	2410	14	20	4	335	309	122
sDNA-FIT 50-85, 2	9110	0	0	0	1881	1881	13	26	5	325	298	119
sDNA-FIT 50-85, 3	7066	0	0	0	1582	1582	11	32	6	313	285	114
sDNA-FIT 55-70, 1	7737	0	0	0	1633	1633	10	31	9	280	257	102
sDNA-FIT 55-70, 2	5122	0	0	0	1237	1237	8	38	11	262	240	96
sDNA-FIT 55-70, 3	4121	0	0	0	1070	1070	7	42	12	250	227	91
sDNA-FIT 55-75, 1	9171	0	0	0	1849	1849	11	28	7	289	265	106
sDNA-FIT 55-75, 2	6340	0	0	0	1452	1452	10	33	8	278	254	102
sDNA-FIT 55-75, 3	4730	0	0	0	1187	1187	8	39	10	262	237	96
sDNA-FIT 55-80, 1	10246	0	0	0	2002	2002	13	26	7	293	269	107
sDNA-FIT 55-80, 2	6973	0	0	0	1558	1558	11	32	8	283	258	103
sDNA-FIT 55-80, 3	5493	0	0	0	1331	1331	10	37	9	271	245	99
sDNA-FIT 55-85, 1	11009	0	0	0	2104	2104	14	26	6	294	269	107
sDNA-FIT 55-85, 2	7641	0	0	0	1662	1662	13	31	7	285	259	104
sDNA-FIT 55-85, 3	5905	0	0	0	1403	1403	11	37	8	273	247	100

COL – colonoscopy; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.3b. Estimated Outcomes for sDNA-FIT Strategies: CRC-SPIN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	77	77	2	77	32	0	0	0
sDNA-FIT 45-70, 1	12107	0	0	0	2433	2433	13	17	5	326	305	119
sDNA-FIT 45-70, 2	8128	0	0	0	1908	1908	12	21	7	310	290	113
sDNA-FIT 45-70, 3	6400	0	0	0	1647	1647	11	25	8	293	274	107
sDNA-FIT 45-75, 1	13494	0	0	0	2617	2617	14	15	5	331	309	121
sDNA-FIT 45-75, 2	9298	0	0	0	2089	2089	13	19	6	319	298	116
sDNA-FIT 45-75, 3	7105	0	0	0	1772	1772	12	23	7	301	281	110
sDNA-FIT 45-80, 1	14608	0	0	0	2758	2758	15	14	4	333	311	122
sDNA-FIT 45-80, 2	9928	0	0	0	2181	2181	14	18	5	322	300	118
sDNA-FIT 45-80, 3	7688	0	0	0	1866	1866	13	21	6	305	285	111
sDNA-FIT 45-85, 1	15424	0	0	0	2856	2856	16	14	4	334	312	122
sDNA-FIT 45-85, 2	10620	0	0	0	2275	2275	15	17	5	323	301	118
sDNA-FIT 45-85, 3	8193	0	0	0	1944	1944	14	21	6	307	286	112
sDNA-FIT 50-70, 1	9760	0	0	0	2111	2111	13	19	7	296	277	108
sDNA-FIT 50-70, 2	6740	0	0	0	1698	1698	12	24	8	281	262	102
sDNA-FIT 50-70, 3	5011	0	0	0	1407	1407	10	29	10	260	243	95
sDNA-FIT 50-75, 1	11132	0	0	0	2295	2295	14	18	6	301	281	110
sDNA-FIT 50-75, 2	7525	0	0	0	1822	1822	13	22	7	287	268	105
sDNA-FIT 50-75, 3	5939	0	0	0	1576	1576	12	26	8	271	253	99
sDNA-FIT 50-80, 1	12255	0	0	0	2438	2438	15	17	5	303	283	111
sDNA-FIT 50-80, 2	8474	0	0	0	1961	1961	14	21	6	290	271	106
sDNA-FIT 50-80, 3	6510	0	0	0	1672	1672	13	25	8	276	257	101
sDNA-FIT 50-85, 1	13073	0	0	0	2537	2537	16	17	5	304	284	111
sDNA-FIT 50-85, 2	8937	0	0	0	2025	2025	15	20	6	291	272	106
sDNA-FIT 50-85, 3	6941	0	0	0	1737	1737	14	24	7	278	258	101
sDNA-FIT 55-70, 1	7485	0	0	0	1769	1769	12	24	8	262	244	96
sDNA-FIT 55-70, 2	4987	0	0	0	1390	1390	11	30	10	244	227	89
sDNA-FIT 55-70, 3	4029	0	0	0	1219	1219	10	33	11	229	212	83
sDNA-FIT 55-75, 1	8911	0	0	0	1964	1964	13	22	7	268	249	98
sDNA-FIT 55-75, 2	6183	0	0	0	1587	1587	12	27	8	255	236	93
sDNA-FIT 55-75, 3	4633	0	0	0	1332	1332	11	31	10	237	219	87
sDNA-FIT 55-80, 1	10021	0	0	0	2107	2107	15	21	7	270	251	99
sDNA-FIT 55-80, 2	6820	0	0	0	1683	1683	13	26	8	258	239	94
sDNA-FIT 55-80, 3	5391	0	0	0	1463	1463	12	29	9	243	225	89
sDNA-FIT 55-85, 1	10845	0	0	0	2207	2207	16	21	7	271	251	99
sDNA-FIT 55-85, 2	7517	0	0	0	1779	1779	14	25	8	260	240	95
sDNA-FIT 55-85, 3	5809	0	0	0	1529	1529	13	29	9	245	226	89

COL – colonoscopy; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.3c. Estimated Outcomes for sDNA-FIT Strategies: MISCAN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	81	81	2	81	34	0	0	0
sDNA-FIT 45-70, 1	12364	0	0	0	2346	2346	11	41	10	295	263	108
sDNA-FIT 45-70, 2	8285	0	0	0	1785	1785	9	47	13	274	243	100
sDNA-FIT 45-70, 3	6493	0	0	0	1507	1507	9	51	14	257	225	94
sDNA-FIT 45-75, 1	13698	0	0	0	2515	2515	12	38	9	306	272	112
sDNA-FIT 45-75, 2	9435	0	0	0	1954	1954	11	44	10	292	258	107
sDNA-FIT 45-75, 3	7204	0	0	0	1629	1629	10	49	12	273	239	100
sDNA-FIT 45-80, 1	14753	0	0	0	2641	2641	13	37	8	311	277	114
sDNA-FIT 45-80, 2	10046	0	0	0	2037	2037	12	43	9	298	262	109
sDNA-FIT 45-80, 3	7760	0	0	0	1709	1709	10	48	10	280	244	102
sDNA-FIT 45-85, 1	15513	0	0	0	2727	2727	14	36	8	313	278	114
sDNA-FIT 45-85, 2	10707	0	0	0	2121	2121	13	42	8	301	265	110
sDNA-FIT 45-85, 3	8255	0	0	0	1780	1780	11	47	10	284	247	104
sDNA-FIT 50-70, 1	9988	0	0	0	2040	2040	11	42	11	279	247	102
sDNA-FIT 50-70, 2	6868	0	0	0	1592	1592	9	48	13	262	230	96
sDNA-FIT 50-70, 3	5080	0	0	0	1291	1291	8	53	15	235	205	86
sDNA-FIT 50-75, 1	11315	0	0	0	2211	2211	12	39	9	290	257	106
sDNA-FIT 50-75, 2	7642	0	0	0	1708	1708	10	46	11	274	241	100
sDNA-FIT 50-75, 3	6006	0	0	0	1449	1449	9	50	12	257	223	94
sDNA-FIT 50-80, 1	12379	0	0	0	2339	2339	13	38	9	296	261	108
sDNA-FIT 50-80, 2	8565	0	0	0	1836	1836	12	44	9	283	248	104
sDNA-FIT 50-80, 3	6579	0	0	0	1540	1540	10	49	11	265	230	97
sDNA-FIT 50-85, 1	13142	0	0	0	2425	2425	14	38	8	297	263	109
sDNA-FIT 50-85, 2	9009	0	0	0	1892	1892	12	44	9	286	250	104
sDNA-FIT 50-85, 3	6984	0	0	0	1595	1595	11	49	10	268	232	98
sDNA-FIT 55-70, 1	7698	0	0	0	1714	1714	11	45	12	251	221	92
sDNA-FIT 55-70, 2	5092	0	0	0	1306	1306	9	51	14	229	200	84
sDNA-FIT 55-70, 3	4099	0	0	0	1133	1133	8	55	16	216	186	79
sDNA-FIT 55-75, 1	9090	0	0	0	1897	1897	12	42	10	264	232	96
sDNA-FIT 55-75, 2	6283	0	0	0	1492	1492	10	48	12	249	217	91
sDNA-FIT 55-75, 3	4684	0	0	0	1232	1232	9	53	14	229	197	84
sDNA-FIT 55-80, 1	10153	0	0	0	2027	2027	13	40	9	269	236	98
sDNA-FIT 55-80, 2	6907	0	0	0	1580	1580	11	46	11	255	222	93
sDNA-FIT 55-80, 3	5436	0	0	0	1352	1352	10	51	12	240	206	88
sDNA-FIT 55-85, 1	10924	0	0	0	2115	2115	14	40	9	271	238	99
sDNA-FIT 55-85, 2	7580	0	0	0	1667	1667	12	46	10	259	224	94
sDNA-FIT 55-85, 3	5853	0	0	0	1413	1413	11	51	11	243	209	89

COL – colonoscopy; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.4a. Estimated Outcomes for Sigmoidoscopy Strategies: SimCRC

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	85	85	2	85	34	0	0	0
SIG 45-70, 5	0	4402	0	0	1592	1592	9	28	9	302	284	110
SIG 45-70, 10	0	2622	0	0	1155	1155	7	37	13	262	246	96
SIG 45-75, 5	0	4846	0	0	1720	1720	10	25	8	309	289	113
SIG 45-75, 10	0	3173	0	0	1360	1360	9	32	10	278	260	101
SIG 45-80, 5	0	5185	0	0	1809	1809	11	24	7	311	291	114
SIG 45-80, 10	0	3173	0	0	1360	1360	9	32	10	278	260	101
SIG 45-85, 5	0	5414	0	0	1864	1864	12	24	7	312	292	114
SIG 45-85, 10	0	3463	0	0	1449	1449	11	32	10	279	261	102
SIG 50-70, 5	0	3611	0	0	1414	1414	9	31	10	272	254	99
SIG 50-70, 10	0	2465	0	0	1138	1138	8	37	13	247	230	90
SIG 50-75, 5	0	4058	0	0	1544	1544	10	29	9	279	260	102
SIG 50-75, 10	0	2465	0	0	1138	1138	8	37	13	247	230	90
SIG 50-80, 5	0	4399	0	0	1634	1634	11	28	9	282	262	103
SIG 50-80, 10	0	2894	0	0	1282	1282	10	34	11	253	235	92
SIG 50-85, 5	0	4629	0	0	1690	1690	12	28	8	282	263	103
SIG 50-85, 10	0	2894	0	0	1282	1282	10	34	11	253	235	92
SIG 55-70, 5	0	2851	0	0	1224	1224	8	36	12	235	218	86
SIG 55-70, 10	0	1708	0	0	907	907	7	45	16	204	189	74
SIG 55-75, 5	0	3302	0	0	1357	1357	10	34	11	242	224	88
SIG 55-75, 10	0	2267	0	0	1118	1118	9	39	13	220	203	80
SIG 55-80, 5	0	3647	0	0	1449	1449	11	33	10	244	226	89
SIG 55-80, 10	0	2267	0	0	1118	1118	9	39	13	220	203	80
SIG 55-85, 5	0	3878	0	0	1505	1505	12	32	10	245	227	90
SIG 55-85, 10	0	2559	0	0	1208	1208	11	39	13	221	205	81

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.4b. Estimated Outcomes for Sigmoidoscopy Strategies: CRC-SPIN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	77	77	2	77	32	0	0	0
SIG 45-70, 5	0	4446	0	0	1586	1586	11	25	9	277	261	101
SIG 45-70, 10	0	2604	0	0	1260	1260	9	29	11	259	245	95
SIG 45-75, 5	0	4935	0	0	1680	1680	12	24	9	280	264	102
SIG 45-75, 10	0	3169	0	0	1411	1411	11	26	9	268	252	98
SIG 45-80, 5	0	5326	0	0	1749	1749	12	23	8	281	265	103
SIG 45-80, 10	0	3169	0	0	1411	1411	11	26	9	268	252	98
SIG 45-85, 5	0	5602	0	0	1793	1793	13	23	8	282	265	103
SIG 45-85, 10	0	3487	0	0	1479	1479	12	26	9	269	253	98
SIG 50-70, 5	0	3644	0	0	1415	1415	10	27	10	253	238	92
SIG 50-70, 10	0	2454	0	0	1217	1217	10	29	11	240	227	88
SIG 50-75, 5	0	4134	0	0	1510	1510	11	26	9	256	241	94
SIG 50-75, 10	0	2454	0	0	1217	1217	10	29	11	240	227	88
SIG 50-80, 5	0	4525	0	0	1579	1579	12	25	9	258	243	94
SIG 50-80, 10	0	2906	0	0	1324	1324	12	28	10	243	230	89
SIG 50-85, 5	0	4801	0	0	1624	1624	13	25	9	258	243	94
SIG 50-85, 10	0	2906	0	0	1324	1324	12	28	10	243	230	89
SIG 55-70, 5	0	2873	0	0	1228	1228	10	31	11	225	211	82
SIG 55-70, 10	0	1699	0	0	995	995	9	35	13	210	197	77
SIG 55-75, 5	0	3364	0	0	1325	1325	11	29	11	229	214	84
SIG 55-75, 10	0	2268	0	0	1153	1153	11	31	11	219	206	80
SIG 55-80, 5	0	3756	0	0	1395	1395	12	29	10	230	216	84
SIG 55-80, 10	0	2268	0	0	1153	1153	11	31	11	219	206	80
SIG 55-85, 5	0	4032	0	0	1439	1439	13	28	10	231	216	84
SIG 55-85, 10	0	2587	0	0	1221	1221	12	31	11	221	207	81

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.4c. Estimated Outcomes for Sigmoidoscopy Strategies: MISCAN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	81	81	2	81	34	0	0	0
SIG 45-70, 5	0	4013	0	0	2020	2020	11	40	12	263	237	96
SIG 45-70, 10	0	2480	0	0	1635	1635	10	45	14	234	210	85
SIG 45-75, 5	0	4389	0	0	2119	2119	12	39	11	269	241	98
SIG 45-75, 10	0	2946	0	0	1800	1800	12	43	12	245	220	90
SIG 45-80, 5	0	4681	0	0	2196	2196	13	38	10	271	244	99
SIG 45-80, 10	0	2946	0	0	1800	1800	12	43	12	245	220	90
SIG 45-85, 5	0	4877	0	0	2235	2235	13	38	10	272	244	99
SIG 45-85, 10	0	3193	0	0	1869	1869	13	42	12	247	221	90
SIG 50-70, 5	0	3268	0	0	1826	1826	11	41	12	251	225	92
SIG 50-70, 10	0	2297	0	0	1581	1581	10	44	14	233	208	85
SIG 50-75, 5	0	3646	0	0	1927	1927	12	40	11	256	229	93
SIG 50-75, 10	0	2297	0	0	1581	1581	10	44	14	233	208	85
SIG 50-80, 5	0	3939	0	0	2004	2004	13	39	11	259	231	94
SIG 50-80, 10	0	2660	0	0	1704	1704	12	43	12	238	212	87
SIG 50-85, 5	0	4136	0	0	2044	2044	13	39	11	259	231	95
SIG 50-85, 10	0	2660	0	0	1704	1704	12	43	12	238	212	87
SIG 55-70, 5	0	2578	0	0	1608	1608	11	43	13	228	203	83
SIG 55-70, 10	0	1623	0	0	1340	1340	10	48	16	204	182	75
SIG 55-75, 5	0	2960	0	0	1711	1711	12	42	12	234	208	85
SIG 55-75, 10	0	2094	0	0	1513	1513	11	45	14	217	192	79
SIG 55-80, 5	0	3255	0	0	1790	1790	13	41	12	237	210	86
SIG 55-80, 10	0	2094	0	0	1513	1513	11	45	14	217	192	79
SIG 55-85, 5	0	3453	0	0	1831	1831	13	41	12	237	210	87
SIG 55-85, 10	0	2343	0	0	1583	1583	13	45	13	218	193	80

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.5a. Estimated Outcomes for 10-Yearly Sigmoidoscopy Plus Interval FIT Strategies: SimCRC

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	85	85	2	85	34	0	0	0
SIG+FIT 45-70, 10_1	14876	2264	0	0	1903	1903	10	22	6	353	329	129
SIG+FIT 45-70, 10_2	8643	2362	0	0	1617	1617	9	26	7	340	316	124
SIG+FIT 45-75, 10_1	16648	2568	0	0	2102	2102	11	18	4	363	338	133
SIG+FIT 45-75, 10_2	9936	2757	0	0	1835	1835	11	22	5	354	329	129
SIG+FIT 45-80, 10_1	17986	2664	0	0	2203	2203	12	17	4	366	340	134
SIG+FIT 45-80, 10_2	10569	2806	0	0	1889	1889	11	21	4	357	331	130
SIG+FIT 45-85, 10_1	18952	2812	0	0	2293	2293	14	17	3	367	341	134
SIG+FIT 45-85, 10_2	11283	3003	0	0	1988	1988	13	20	4	358	332	131
SIG+FIT 50-70, 10_1	11821	2005	0	0	1714	1714	10	24	7	324	301	118
SIG+FIT 50-70, 10_2	7125	2152	0	0	1512	1512	9	27	7	314	291	115
SIG+FIT 50-75, 10_1	13537	2099	0	0	1840	1840	11	22	6	330	306	121
SIG+FIT 50-75, 10_2	7932	2196	0	0	1579	1579	10	26	7	320	296	117
SIG+FIT 50-80, 10_1	14921	2331	0	0	1986	1986	13	21	5	335	310	122
SIG+FIT 50-80, 10_2	8949	2498	0	0	1738	1738	12	24	5	326	301	119
SIG+FIT 50-85, 10_1	15864	2398	0	0	2052	2052	13	20	5	335	310	122
SIG+FIT 50-85, 10_2	9398	2532	0	0	1774	1774	12	24	5	327	301	119
SIG+FIT 55-70, 10_1	8842	1498	0	0	1432	1432	9	31	9	278	257	102
SIG+FIT 55-70, 10_2	5139	1547	0	0	1230	1230	8	35	10	266	245	97
SIG+FIT 55-75, 10_1	10651	1830	0	0	1650	1650	11	27	7	290	267	106
SIG+FIT 55-75, 10_2	6459	1962	0	0	1465	1465	11	30	8	282	259	103
SIG+FIT 55-80, 10_1	11994	1903	0	0	1745	1745	12	26	7	293	269	107
SIG+FIT 55-80, 10_2	7095	1997	0	0	1516	1516	11	29	7	285	261	104
SIG+FIT 55-85, 10_1	12970	2060	0	0	1838	1838	14	26	6	294	270	107
SIG+FIT 55-85, 10_2	7817	2200	0	0	1617	1617	13	29	7	287	262	105

COL – colonoscopy; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.5b. Estimated Outcomes for 10-Yearly Sigmoidoscopy Plus Interval FIT Strategies: CRC-SPIN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	77	77	2	77	32	0	0	0
SIG+FIT 45-70, 10_1	14529	2219	0	0	2072	2072	13	17	6	324	304	118
SIG+FIT 45-70, 10_2	8503	2318	0	0	1779	1779	12	20	7	313	294	114
SIG+FIT 45-75, 10_1	16322	2525	0	0	2237	2237	14	15	5	330	309	120
SIG+FIT 45-75, 10_2	9813	2717	0	0	1955	1955	13	18	5	321	301	117
SIG+FIT 45-80, 10_1	17752	2628	0	0	2331	2331	15	15	4	332	311	121
SIG+FIT 45-80, 10_2	10493	2770	0	0	2008	2008	14	17	5	323	303	118
SIG+FIT 45-85, 10_1	18818	2791	0	0	2413	2413	16	14	4	333	312	122
SIG+FIT 45-85, 10_2	11272	2985	0	0	2094	2094	15	17	5	324	304	118
SIG+FIT 50-70, 10_1	11534	1967	0	0	1854	1854	13	19	7	296	278	108
SIG+FIT 50-70, 10_2	7006	2115	0	0	1643	1643	12	22	7	287	269	105
SIG+FIT 50-75, 10_1	13305	2067	0	0	1973	1973	13	18	6	301	282	110
SIG+FIT 50-75, 10_2	7842	2163	0	0	1708	1708	12	21	7	290	272	106
SIG+FIT 50-80, 10_1	14761	2310	0	0	2098	2098	15	17	5	304	284	111
SIG+FIT 50-80, 10_2	8909	2479	0	0	1840	1840	14	19	6	294	276	108
SIG+FIT 50-85, 10_1	15814	2386	0	0	2163	2163	15	17	5	304	285	111
SIG+FIT 50-85, 10_2	9411	2518	0	0	1877	1877	14	19	6	295	277	108
SIG+FIT 55-70, 10_1	8652	1475	0	0	1561	1561	12	24	8	262	245	96
SIG+FIT 55-70, 10_2	5065	1523	0	0	1357	1357	11	27	9	252	236	92
SIG+FIT 55-75, 10_1	10476	1809	0	0	1741	1741	13	22	7	269	251	98
SIG+FIT 55-75, 10_2	6396	1942	0	0	1548	1548	13	24	8	262	244	96
SIG+FIT 55-80, 10_1	11917	1891	0	0	1833	1833	14	21	7	272	253	99
SIG+FIT 55-80, 10_2	7079	1981	0	0	1599	1599	13	24	8	264	246	96
SIG+FIT 55-85, 10_1	12987	2062	0	0	1918	1918	15	21	7	272	253	99
SIG+FIT 55-85, 10_2	7866	2202	0	0	1687	1687	14	23	7	265	246	97

COL – colonoscopy; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.5c. Estimated Outcomes for 10-Yearly Sigmoidoscopy Plus Interval FIT Strategies: MISCAN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	81	81	2	81	34	0	0	0
SIG+FIT 45-70, 10_1	13812	2055	0	0	2148	2148	11	40	10	292	261	107
SIG+FIT 45-70, 10_2	7965	2209	0	0	1947	1947	11	42	11	280	250	102
SIG+FIT 45-75, 10_1	15466	2393	0	0	2331	2331	13	37	9	304	272	111
SIG+FIT 45-75, 10_2	9117	2593	0	0	2130	2130	12	39	9	294	262	108
SIG+FIT 45-80, 10_1	16683	2393	0	0	2379	2379	13	37	8	307	274	112
SIG+FIT 45-80, 10_2	9673	2593	0	0	2154	2154	12	39	9	296	264	108
SIG+FIT 45-85, 10_1	17634	2570	0	0	2463	2463	14	37	8	309	275	113
SIG+FIT 45-85, 10_2	10336	2795	0	0	2235	2235	14	39	8	298	265	109
SIG+FIT 50-70, 10_1	10831	1900	0	0	1984	1984	11	40	10	282	251	103
SIG+FIT 50-70, 10_2	6482	2038	0	0	1835	1835	11	42	11	274	243	100
SIG+FIT 50-75, 10_1	12357	1900	0	0	2048	2048	12	39	10	287	255	105
SIG+FIT 50-75, 10_2	7177	2038	0	0	1867	1867	11	41	10	277	246	101
SIG+FIT 50-80, 10_1	13676	2161	0	0	2185	2185	13	38	8	293	260	107
SIG+FIT 50-80, 10_2	8098	2335	0	0	2005	2005	13	40	9	284	251	104
SIG+FIT 50-85, 10_1	14548	2161	0	0	2218	2218	14	38	8	294	260	107
SIG+FIT 50-85, 10_2	8496	2335	0	0	2021	2021	13	40	9	284	251	104
SIG+FIT 55-70, 10_1	7944	1389	0	0	1680	1680	11	43	12	250	222	91
SIG+FIT 55-70, 10_2	4622	1462	0	0	1547	1547	10	45	13	241	213	88
SIG+FIT 55-75, 10_1	9625	1730	0	0	1871	1871	12	40	10	263	233	96
SIG+FIT 55-75, 10_2	5792	1851	0	0	1739	1739	12	42	11	256	225	93
SIG+FIT 55-80, 10_1	10851	1730	0	0	1920	1920	13	40	10	266	235	97
SIG+FIT 55-80, 10_2	6351	1851	0	0	1764	1764	12	42	10	258	227	94
SIG+FIT 55-85, 10_1	11807	1908	0	0	2004	2004	14	40	9	268	236	98
SIG+FIT 55-85, 10_2	7018	2054	0	0	1847	1847	14	42	10	260	228	95

COL – colonoscopy; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.6a. Estimated Outcomes for Computed Tomographic Colonography Strategies: SimCRC

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	85	85	2	85	34	0	0	0
CTC 45-70, 5	0	0	4372	0	1653	1653	9	21	6	348	326	127
CTC 45-70, 10	0	0	2605	0	1233	1233	8	31	9	310	290	113
CTC 45-75, 5	0	0	4804	0	1788	1788	11	18	5	355	332	130
CTC 45-75, 10	0	0	3141	0	1459	1459	10	24	6	328	306	120
CTC 45-80, 5	0	0	5131	0	1882	1882	12	17	4	358	335	131
CTC 45-80, 10	0	0	3141	0	1459	1459	10	24	6	328	306	120
CTC 45-85, 5	0	0	5348	0	1939	1939	13	17	4	359	335	131
CTC 45-85, 10	0	0	3416	0	1559	1559	12	24	6	330	307	120
CTC 50-70, 5	0	0	3573	0	1488	1488	9	24	7	318	296	116
CTC 50-70, 10	0	0	2440	0	1229	1229	8	29	9	295	274	108
CTC 50-75, 5	0	0	4006	0	1624	1624	11	21	6	325	302	119
CTC 50-75, 10	0	0	2440	0	1229	1229	8	29	9	295	274	108
CTC 50-80, 5	0	0	4334	0	1719	1719	12	20	5	327	304	119
CTC 50-80, 10	0	0	2852	0	1390	1390	11	27	7	302	280	110
CTC 50-85, 5	0	0	4551	0	1776	1776	13	20	5	328	305	120
CTC 50-85, 10	0	0	2852	0	1390	1390	11	27	7	302	280	110
CTC 55-70, 5	0	0	2810	0	1309	1309	9	29	9	276	256	101
CTC 55-70, 10	0	0	1695	0	995	995	7	38	12	245	227	90
CTC 55-75, 5	0	0	3246	0	1447	1447	11	26	7	284	263	104
CTC 55-75, 10	0	0	2235	0	1228	1228	10	31	9	264	243	96
CTC 55-80, 5	0	0	3574	0	1543	1543	12	25	7	286	265	105
CTC 55-80, 10	0	0	2235	0	1228	1228	10	31	9	264	243	96
CTC 55-85, 5	0	0	3792	0	1601	1601	13	25	7	287	265	105
CTC 55-85, 10	0	0	2512	0	1329	1329	12	31	9	266	245	97

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.6b. Estimated Outcomes for Computed Tomographic Colonography Strategies: CRC-SPIN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	77	77	2	77	32	0	0	0
CTC 45-70, 5	0	0	4432	0	1677	1677	11	20	7	308	289	112
CTC 45-70, 10	0	0	2621	0	1273	1273	10	27	10	276	260	101
CTC 45-75, 5	0	0	4893	0	1791	1791	13	18	6	313	294	114
CTC 45-75, 10	0	0	3179	0	1465	1465	12	22	7	289	272	106
CTC 45-80, 5	0	0	5254	0	1874	1874	14	17	5	315	296	115
CTC 45-80, 10	0	0	3179	0	1465	1465	12	22	7	289	272	106
CTC 45-85, 5	0	0	5504	0	1927	1927	15	17	5	316	296	115
CTC 45-85, 10	0	0	3483	0	1551	1551	14	21	7	291	273	106
CTC 50-70, 5	0	0	3625	0	1510	1510	11	22	8	281	265	103
CTC 50-70, 10	0	0	2462	0	1259	1259	10	26	9	259	244	95
CTC 50-75, 5	0	0	4088	0	1626	1626	12	20	7	287	270	105
CTC 50-75, 10	0	0	2462	0	1259	1259	10	26	9	259	244	95
CTC 50-80, 5	0	0	4450	0	1709	1709	13	19	6	289	272	106
CTC 50-80, 10	0	0	2903	0	1397	1397	12	23	8	265	250	97
CTC 50-85, 5	0	0	4700	0	1763	1763	14	19	6	290	272	106
CTC 50-85, 10	0	0	2903	0	1397	1397	12	23	8	265	250	97
CTC 55-70, 5	0	0	2854	0	1321	1321	11	26	9	251	235	92
CTC 55-70, 10	0	0	1705	0	1029	1029	9	32	12	227	213	83
CTC 55-75, 5	0	0	3320	0	1440	1440	12	24	8	257	240	94
CTC 55-75, 10	0	0	2267	0	1227	1227	11	27	10	241	225	88
CTC 55-80, 5	0	0	3683	0	1525	1525	13	23	8	259	242	95
CTC 55-80, 10	0	0	2267	0	1227	1227	11	27	10	241	225	88
CTC 55-85, 5	0	0	3934	0	1579	1579	14	23	8	260	242	95
CTC 55-85, 10	0	0	2572	0	1315	1315	13	27	9	242	226	88

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 9.6c. Estimated Outcomes for Computed Tomographic Colonography Strategies: MISCAN

Strategy	Outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer											
	Stool tests	SIGs	CTCs	Screening COLs	Other COLs*	Total COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
No screening	0	0	0	0	81	81	2	81	34	0	0	0
CTC 45-70, 5	0	0	4436	0	1569	1569	9	45	12	271	241	99
CTC 45-70, 10	0	0	2622	0	1149	1149	7	55	18	210	185	77
CTC 45-75, 5	0	0	4881	0	1672	1672	10	42	11	283	251	103
CTC 45-75, 10	0	0	3164	0	1316	1316	9	50	14	234	205	86
CTC 45-80, 5	0	0	5227	0	1744	1744	11	40	9	288	256	105
CTC 45-80, 10	0	0	3164	0	1316	1316	9	50	14	234	205	86
CTC 45-85, 5	0	0	5464	0	1790	1790	12	40	9	290	257	106
CTC 45-85, 10	0	0	3455	0	1389	1389	11	50	13	238	208	87
CTC 50-70, 5	0	0	3627	0	1414	1414	9	46	13	257	227	94
CTC 50-70, 10	0	0	2453	0	1137	1137	8	52	15	220	192	80
CTC 50-75, 5	0	0	4075	0	1519	1519	10	43	11	268	238	98
CTC 50-75, 10	0	0	2453	0	1137	1137	8	52	15	220	192	80
CTC 50-80, 5	0	0	4422	0	1592	1592	11	42	10	274	242	100
CTC 50-80, 10	0	0	2878	0	1253	1253	10	50	13	232	202	85
CTC 50-85, 5	0	0	4660	0	1638	1638	12	41	10	276	243	101
CTC 50-85, 10	0	0	2878	0	1253	1253	10	50	13	232	202	85
CTC 55-70, 5	0	0	2857	0	1242	1242	9	48	14	232	204	85
CTC 55-70, 10	0	0	1701	0	939	939	7	57	19	181	159	66
CTC 55-75, 5	0	0	3309	0	1350	1350	10	45	12	244	215	89
CTC 55-75, 10	0	0	2250	0	1113	1113	9	52	15	207	180	76
CTC 55-80, 5	0	0	3660	0	1425	1425	11	43	11	250	220	91
CTC 55-80, 10	0	0	2250	0	1113	1113	9	52	15	207	180	76
CTC 55-85, 5	0	0	3899	0	1472	1472	12	43	10	252	221	92
CTC 55-85, 10	0	0	2543	0	1187	1187	10	51	14	211	182	77

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

***** Colonoscopies for follow-up, surveillance, and symptom diagnosis

† Includes deaths from complications of screening

Appendix Table 10.1. Efficient Colonoscopy Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by Model

The tables that follow show the efficiency ratios that correspond with the efficient frontiers in **Figures 12-16**.

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
COL 55-70, 15	--	--	--
COL 55-70, 10	Dominated	17*	22*
COL 50-70, 15	6*	8*	18
COL 45-70, 15	6	7	85*
COL 50-80, 15	Dominated	Dominated	56*
COL 50-70, 10	Dominated	Dominated	28
COL 45-75, 15	39*	59*	38*
COL 45-70, 10	34	44	45
COL 50-80, 10	Dominated	Dominated	86*
COL 45-75, 10	64	112	52
COL 45-85, 10	394*	828*	227*
COL 50-70, 5	Dominated	Dominated	120*
COL 50-75, 5	Dominated	Dominated	367*
COL 45-70, 5	180*	179	84
COL 45-75, 5	178	344	116
COL 45-80, 5	428	736	169
COL 45-85, 5	1445	2190	926

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 10.2. Efficient FIT and sDNA-FIT Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
FIT 55-70, 3	--	--	--
FIT 55-75, 3	Dominated	Dominated	5
FIT 50-70, 3	2	4	6*
FIT 55-70, 2	Dominated	Dominated	13*
FIT 55-80, 3	Dominated	Dominated	6*
FIT 45-70, 3	3	5	6*
FIT 50-75, 3	Dominated	Dominated	5
FIT 55-85, 3	Dominated	Dominated	7*
FIT 55-75, 2	Dominated	Dominated	14*
FIT 50-80, 3	Dominated	Dominated	6
FIT 50-70, 2	Dominated	Dominated	94*
FIT 45-75, 3	5	7*	7*
FIT 50-85, 3	Dominated	Dominated	10*
FIT 45-80, 3	7*	8*	6
FIT 45-70, 2	8*	7	Dominated
FIT 50-75, 2	Dominated	Dominated	10*
FIT 45-85, 3	10*	Dominated	9*
FIT 50-80, 2	Dominated	Dominated	8
FIT 45-75, 2	7	9	9*
FIT 50-85, 2	Dominated	Dominated	12*
FIT 45-80, 2	10	12	8
FIT 45-85, 2	19*	25*	12
FIT 50-75, 1	Dominated	Dominated	29*
FIT 45-70, 1	21*	14	Dominated
FIT 50-80, 1	Dominated	Dominated	18*
FIT 45-75, 1	16	16	15*
FIT 50-85, 1	Dominated	Dominated	18*
sDNA-FIT 45-70, 2	Dominated	52*	Dominated
FIT 45-80, 1	19	27	14
FIT 45-85, 1	39	43	19
sDNA-FIT 45-75, 2	91*	135*	Dominated
sDNA-FIT 45-80, 2	176*	75*	26*
sDNA-FIT 45-85, 2	175*	69*	375*
sDNA-FIT 45-70, 1	116*	62*	Dominated
sDNA-FIT 45-75, 1	103*	53	251*
sDNA-FIT 45-80, 1	81	62	104*
sDNA-FIT 45-85, 1	95	111	94

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; FIT – fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 10.3. Efficient Sigmoidoscopy Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
SIG 55-70, 10	--	--	--
SIG 50-70, 10	Dominated	Dominated	8
SIG 45-70, 10	4	5	73*
SIG 55-70, 5	Dominated	Dominated	11*
SIG 50-80, 10	Dominated	Dominated	22*
SIG 45-75, 10	13*	18	18*
SIG 50-70, 5	Dominated	Dominated	14
SIG 45-85, 10	Dominated	68*	21*
SIG 50-75, 5	Dominated	Dominated	19*
SIG 45-70, 5	11	20	15
SIG 50-80, 5	Dominated	Dominated	23*
SIG 50-85, 5	Dominated	Dominated	26*
SIG 45-75, 5	20	27	19
SIG 45-80, 5	38	49	29
SIG 45-85, 5	89	98	78

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 10.4. Efficient 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
SIG+FIT 55-70, 10_2	--	--	--
SIG+FIT 55-70, 10_1	Dominated	Dominated	14*
SIG+FIT 55-75, 10_2	Dominated	Dominated	13*
SIG+FIT 50-70, 10_2	6*	8*	9
SIG+FIT 55-80, 10_2	Dominated	Dominated	13*
SIG+FIT 50-75, 10_2	Dominated	Dominated	9
SIG+FIT 45-70, 10_2	5	7	24*
SIG+FIT 50-70, 10_1	Dominated	Dominated	24*
SIG+FIT 50-80, 10_2	Dominated	Dominated	20*
SIG+FIT 50-85, 10_2	Dominated	Dominated	21*
SIG+FIT 45-75, 10_2	15	22	15*
SIG+FIT 50-75, 10_1	Dominated	Dominated	18*
SIG+FIT 45-80, 10_2	22	25	15
SIG+FIT 45-70, 10_1	22*	88*	19*
SIG+FIT 50-80, 10_1	Dominated	Dominated	20*
SIG+FIT 45-85, 10_2	54*	78*	38*
SIG+FIT 50-85, 10_1	Dominated	Dominated	21*
SIG+FIT 45-75, 10_1	34	34	22*
SIG+FIT 45-80, 10_1	35	53	21
SIG+FIT 45-85, 10_1	81	64	46

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 10.5. Efficient Computed Tomographic Colonography Screening Strategies, With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
CTC 55-70, 10	--	--	--
CTC 50-70, 10	Dominated	Dominated	5
CTC 45-70, 10	4	5	Dominated
CTC 55-70, 5	Dominated	Dominated	8*
CTC 50-80, 10	Dominated	Dominated	10*
CTC 55-75, 5	Dominated	Dominated	9*
CTC 45-75, 10	13*	15*	Dominated
CTC 50-70, 5	Dominated	Dominated	8
CTC 55-80, 5	Dominated	Dominated	10*
CTC 45-85, 10	Dominated	19*	Dominated
CTC 50-75, 5	Dominated	Dominated	9
CTC 45-70, 5	11	13	21*
CTC 50-80, 5	Dominated	Dominated	13*
CTC 50-85, 5	Dominated	Dominated	17*
CTC 45-75, 5	19	21	11
CTC 45-80, 5	38	37	13
CTC 45-85, 5	104	73	32

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
COL – colonoscopy; LYG – life-years gained compared with no screening; CTC – computed tomographic colonography; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 11.1a. Efficient Colonoscopy Screening Strategies for the Total Population and by Race and Sex: SimCRC

Strategy	Efficiency ratio (Δ COL / Δ LYG)				
	Total population	White males	Black males	White females	Black females
COL 55-70, 15	--	--	--	--	--
COL 50-70, 15	6*	7	8	5*	6*
COL 45-70, 15	6	7	8	5	5
COL 45-75, 15	39*	35*	33*	45*	40*
COL 45-70, 10	34	33	32	38	35
COL 45-75, 10	64	56	52	76	66
COL 45-85, 10	394*	336*	257*	453*	360*
COL 45-70, 5	180*	166*	156*	206	185*
COL 45-75, 5	178	161	151	208	183
COL 45-80, 5	428	363	294	541	425
COL 45-85, 5	1445	1239	880	1735	1323

Note: Strategies that were dominated in all groups are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 11.1b. Efficient Colonoscopy Screening Strategies for the Total Population and by Race and Sex: CRC-SPIN

Strategy	Efficiency ratio (Δ COL / Δ LYG)				
	Total population	White males	Black males	White females	Black females
COL 55-70, 15	--	--	--	--	--
COL 55-70, 10	17*	19*	24*	15*	15*
COL 50-70, 15	8*	8*	9*	7*	8*
COL 45-70, 15	7	8	9	7	8
COL 45-75, 15	59*	70*	72*	55*	50*
COL 45-70, 10	44	49	49	42	41
COL 45-75, 10	112	143	142	100	93
COL 45-85, 10	828*	870*	395*	574*	416*
COL 45-70, 5	179	187	203	160	154
COL 45-75, 5	344	450	414	322	299
COL 45-80, 5	736	1030	843	680	605
COL 45-85, 5	2190	8876	4827	3557	1813

Note: Strategies that were dominated in all groups are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 11.1c. Efficient Colonoscopy Screening Strategies for the Total Population and by Race and Sex: MISCAN

Strategy	Efficiency ratio (Δ COL / Δ LYG)				
	Total population	White males	Black males	White females	Black females
COL 55-70, 15	--	--	--	--	--
COL 55-70, 10	22*	19*	24*	21*	24*
COL 50-70, 15	18	17	18	17	18
COL 55-85, 15	Dominated	Dominated	117*	Dominated	Dominated
COL 45-70, 15	85*	52*	45*	26*	280*
COL 50-80, 15	56*	55*	49*	64*	55*
COL 50-70, 10	28	26	26	31	30
COL 45-75, 15	38*	36*	34*	44*	40*
COL 45-70, 10	45	37	39	55	50
COL 50-80, 10	86*	84*	75*	100*	86*
COL 45-75, 10	52	48	46	57	51
COL 45-85, 10	227*	228*	187*	270*	219*
COL 50-70, 5	120*	125*	145*	122*	118*
COL 50-75, 5	367*	633*	1825*	322*	334*
COL 45-70, 5	84	74	74	95	92
COL 45-75, 5	116	110	103	129	115
COL 45-80, 5	169	163	145	210	175
COL 45-85, 5	926	934	724	1100	863

Note: Strategies that were dominated in all groups are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 11.2a. Efficient FIT Screening Strategies for the Total Population and by Race and Sex: SimCRC

Strategy	Efficiency ratio (Δ COL / Δ LYG)				
	Total population	White males	Black males	White females	Black females
FIT 55-70, 3	--	--	--	--	--
FIT 50-70, 3	2	3	3	2	2
FIT 45-70, 3	3	4	4	3	3
FIT 45-75, 3	5	6	6	5	5
FIT 45-80, 3	7*	8*	7*	7	7*
FIT 45-70, 2	8*	8*	7*	18*	7*
FIT 45-85, 3	10*	10*	9*	13*	9*
FIT 45-75, 2	7	7	7	8	7
FIT 45-80, 2	10	10	10	11	10
FIT 45-85, 2	19*	19*	17*	20*	17*
FIT 45-70, 1	21*	23*	17*	25*	17*
FIT 45-75, 1	16	17	14	17	14
FIT 45-80, 1	19	18	17	20	18
FIT 45-85, 1	39	40	33	41	35

Note: Strategies that were dominated in all groups are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

FIT – fecal immunochemical test fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 11.2b. Efficient FIT Screening Strategies for the Total Population and by Race and Sex: CRC-SPIN

Strategy	Efficiency ratio (Δ COL / Δ LYG)				
	Total population	White males	Black males	White females	Black females
FIT 55-70, 3	--	--	--	--	--
FIT 55-75, 3	Dominated	Dominated	8*	Dominated	6*
FIT 50-70, 3	4	4	4	4	4
FIT 55-70, 2	Dominated	Dominated	Dominated	28*	18*
FIT 50-75, 3	Dominated	Dominated	Dominated	6*	6*
FIT 45-70, 3	5	5	5	4	4
FIT 50-70, 2	Dominated	Dominated	Dominated	12*	12*
FIT 45-75, 3	7*	9*	9*	7*	6*
FIT 45-80, 3	8*	10*	10*	7*	7*
FIT 45-70, 2	7	7	7	6	6
FIT 45-75, 2	9	11	11	8	8
FIT 45-80, 2	12	19*	16*	13	14*
FIT 45-85, 2	25*	22*	19*	21*	15*
FIT 45-70, 1	14	14	13	14	12
FIT 45-75, 1	16	20	22	15	15
FIT 45-80, 1	27	32	28	23	21
FIT 45-85, 1	43	63	52	42	33

Note: Strategies that were dominated in all groups are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

FIT – fecal immunochemical test fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 11.2c. Efficient FIT Screening Strategies for the Total Population and by Race and Sex: MISCAN

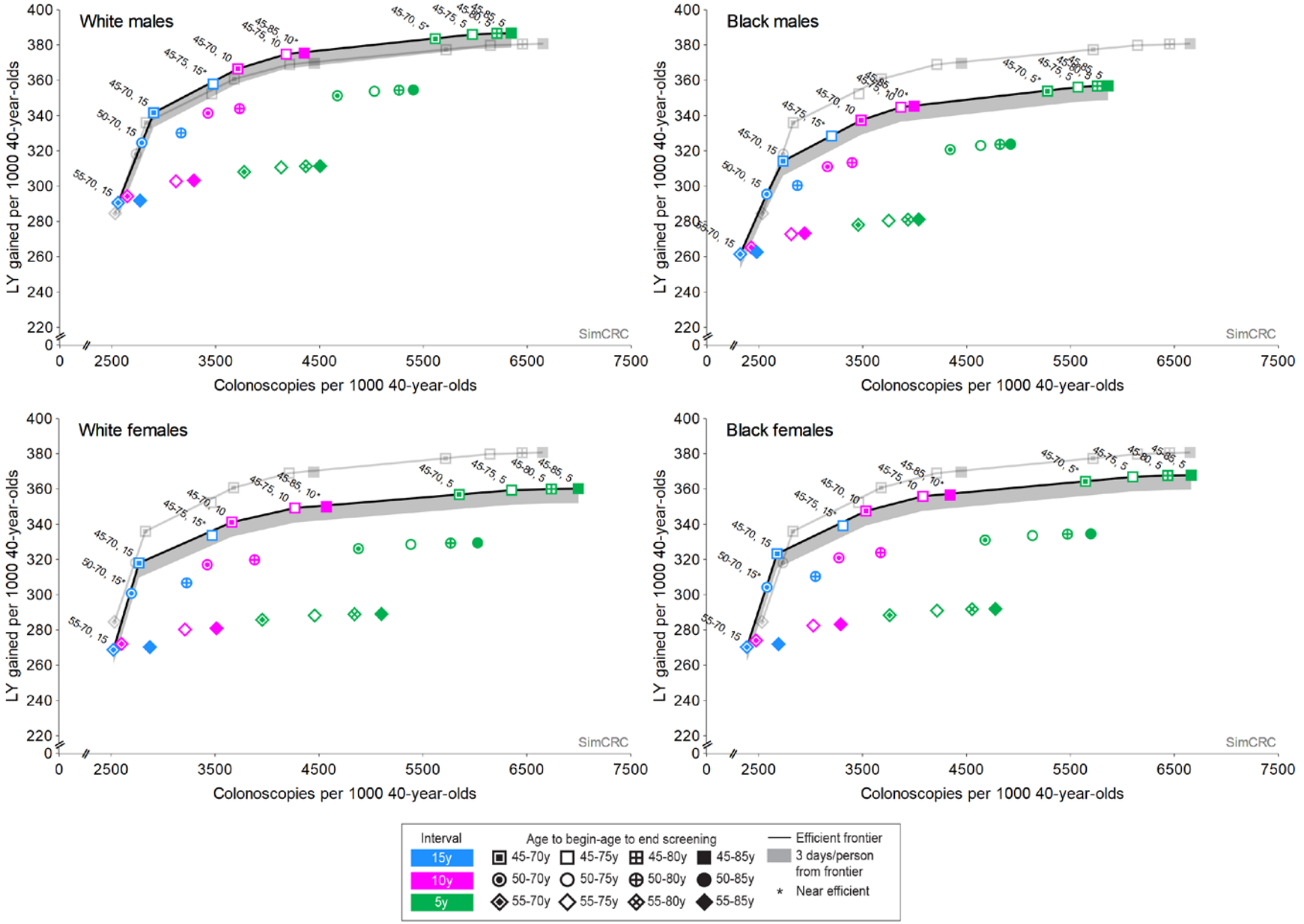
Strategy	Efficiency ratio (Δ COL / Δ LYG)				
	Total population	White males	Black males	White females	Black females
FIT 55-70, 3	--	--	--	--	--
FIT 55-75, 3	5	5	5	5	4
FIT 50-70, 3	6*	10*	7*	6*	6*
FIT 55-70, 2	13*	Dominated	11*	15*	12*
FIT 55-80, 3	6*	6*	6*	6*	5*
FIT 50-75, 3	5	5	5	5	5
FIT 45-70, 3	6*	6*	6*	7*	7*
FIT 55-85, 3	7*	Dominated	7*	7*	6*
FIT 50-80, 3	6	6*	6	6	5
FIT 55-75, 2	14*	Dominated	22*	14*	11*
FIT 45-75, 3	7*	6	6*	9*	10*
FIT 50-85, 3	10*	7*	10*	10*	9*
FIT 50-70, 2	94*	9*	13*	10*	9*
FIT 55-80, 2	Dominated	Dominated	310*	28*	22*
FIT 45-80, 3	6	6	6	7	7
FIT 50-75, 2	10*	12*	10*	11*	9*
FIT 45-85, 3	9*	10*	9*	9*	8*
FIT 45-70, 2	Dominated	30*	18*	Dominated	Dominated
FIT 50-80, 2	8	9*	8*	8*	7
FIT 50-85, 2	12*	9*	8*	9*	11*
FIT 45-75, 2	9*	8*	8*	8*	10*
FIT 45-80, 2	8	8	8	8	8
FIT 45-85, 2	12	13	11	12	11
FIT 50-75, 1	29*	33*	24*	36*	25*
FIT 45-70, 1	Dominated	Dominated	21*	Dominated	Dominated
FIT 50-80, 1	18*	20*	17*	19*	16*
FIT 50-85, 1	18*	20*	17*	19*	16*
FIT 45-75, 1	15*	14*	13*	16*	14*
FIT 45-80, 1	14	14	13	15	13
FIT 45-85, 1	19	20	17	20	17

Note: Strategies that were dominated in all groups are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

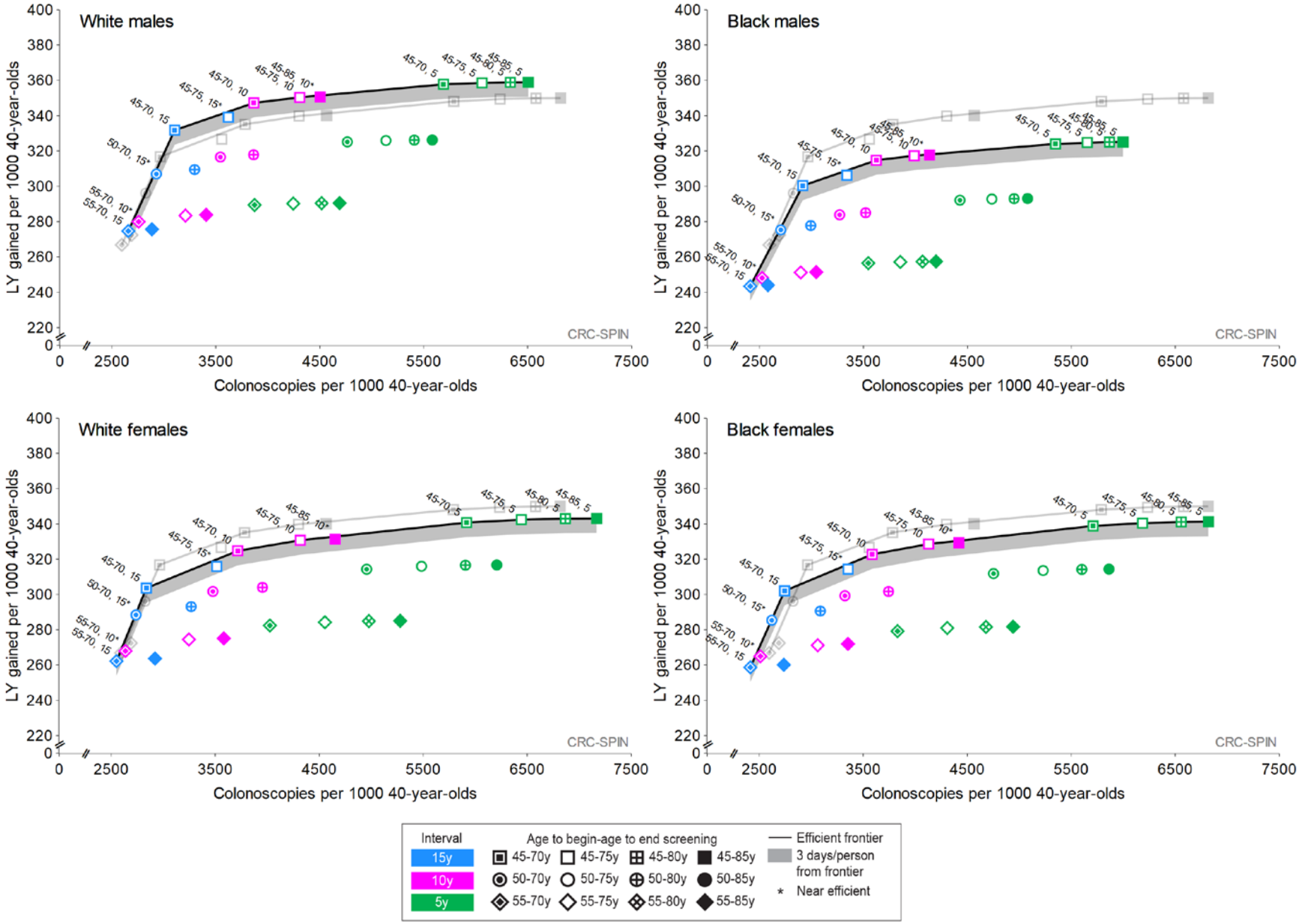
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Figure 11.1a. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds by Race and Sex for Colonoscopy Screening Strategies: SimCRC



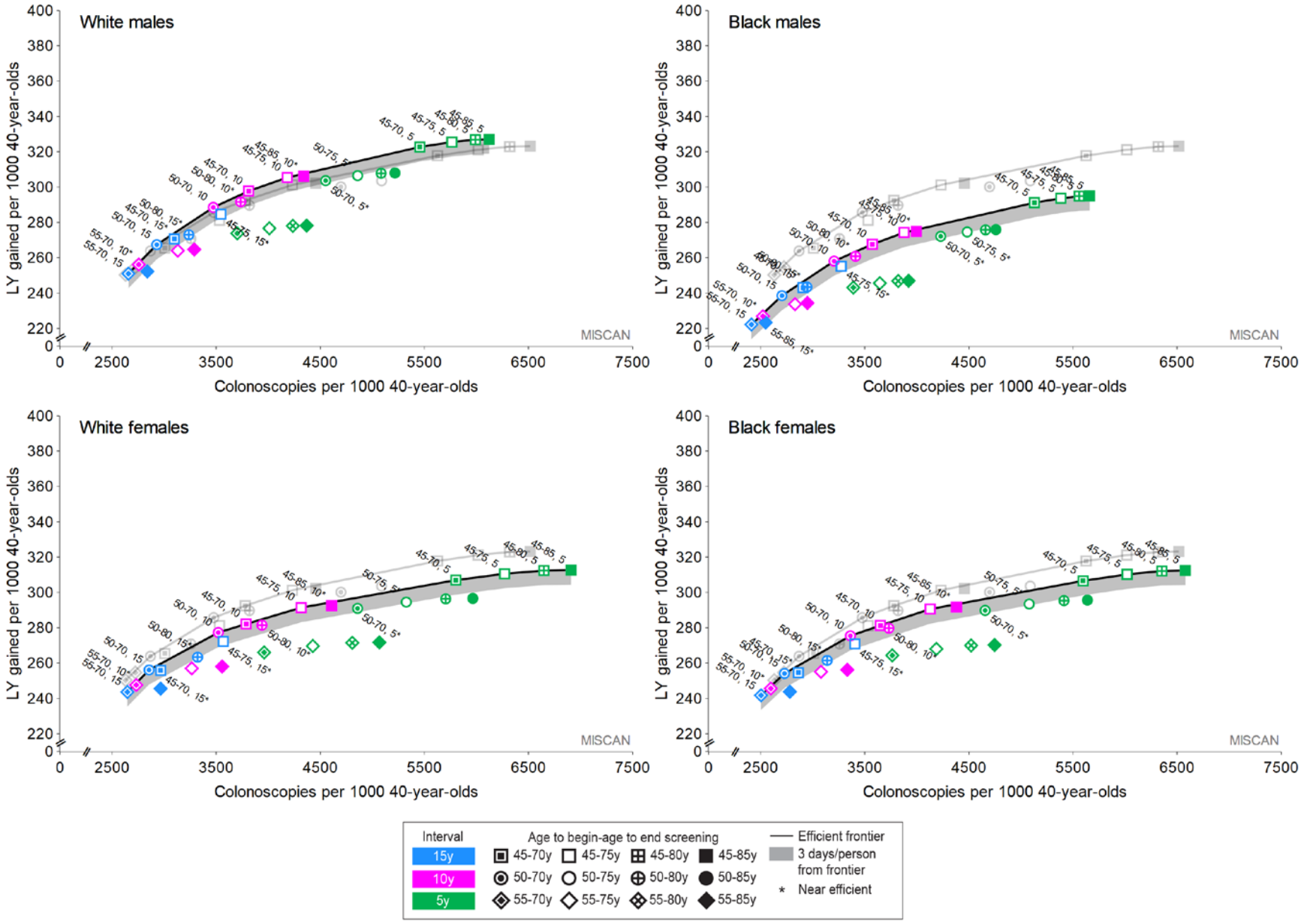
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 11.1b. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds by Race and Sex for Colonoscopy Screening Strategies: CRC-SPIN



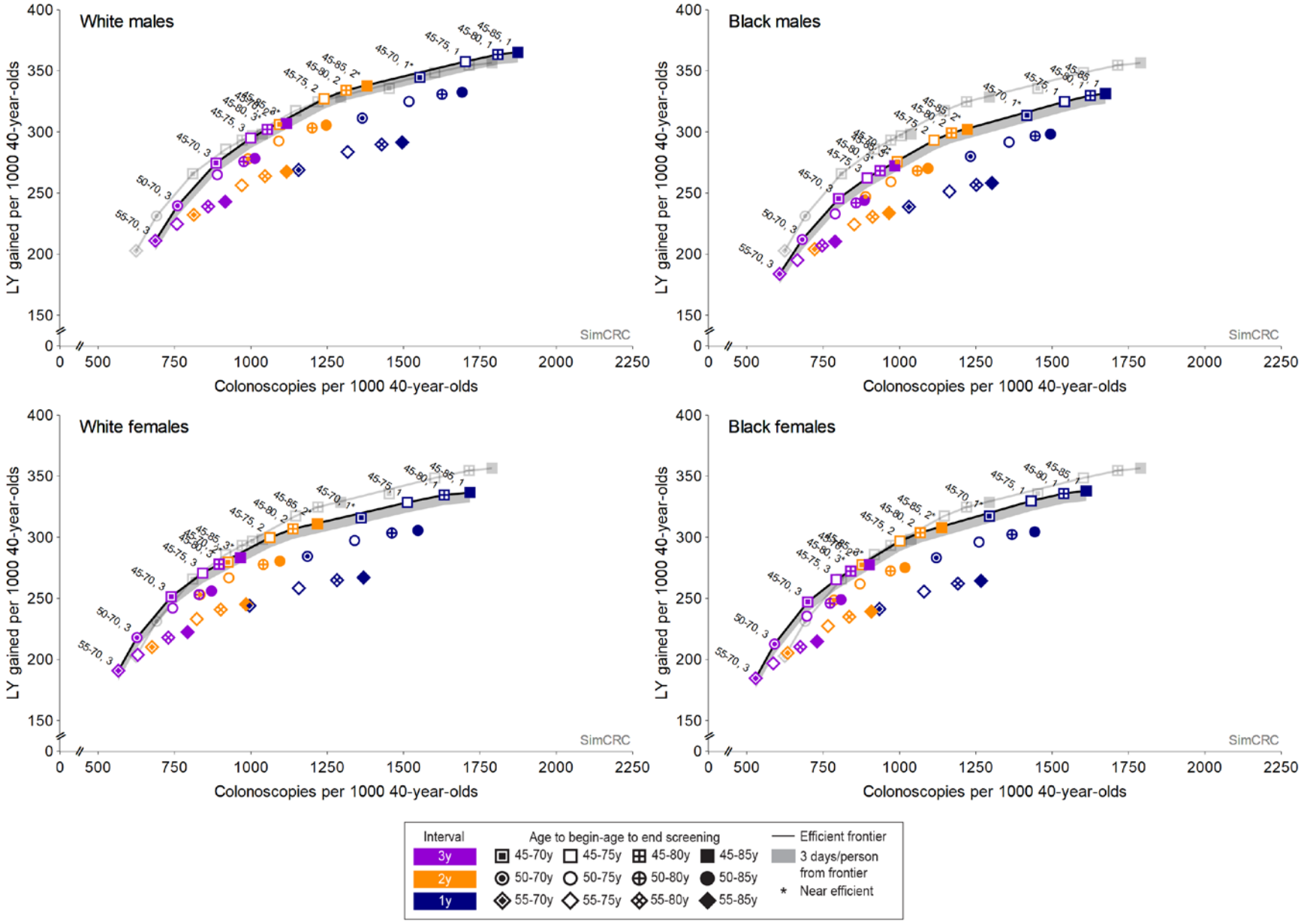
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 11.1c. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds by Race and Sex for Colonoscopy Screening Strategies: MISCAN



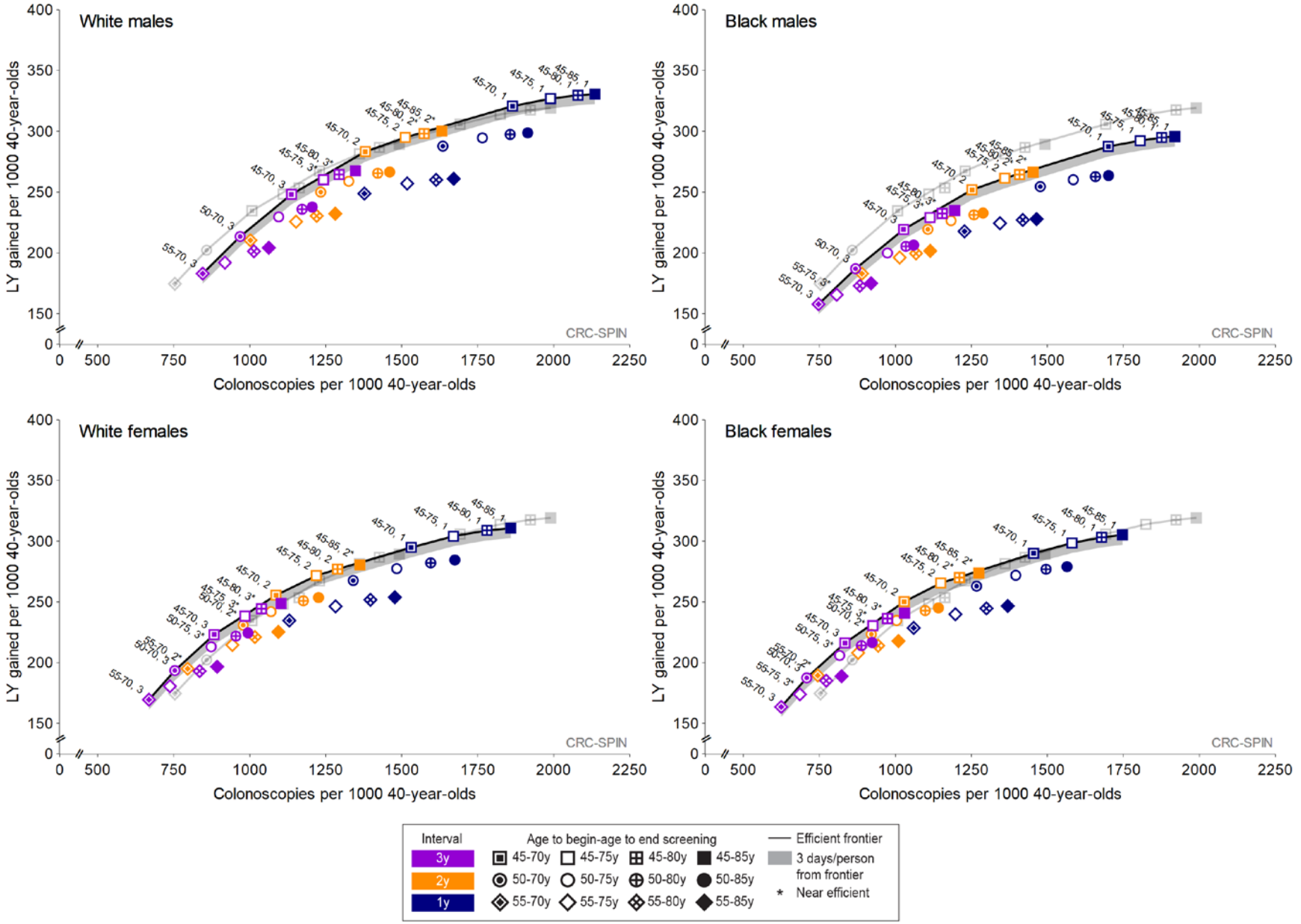
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 11.2a. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds by Race and Sex for FIT Screening Strategies: SimCRC



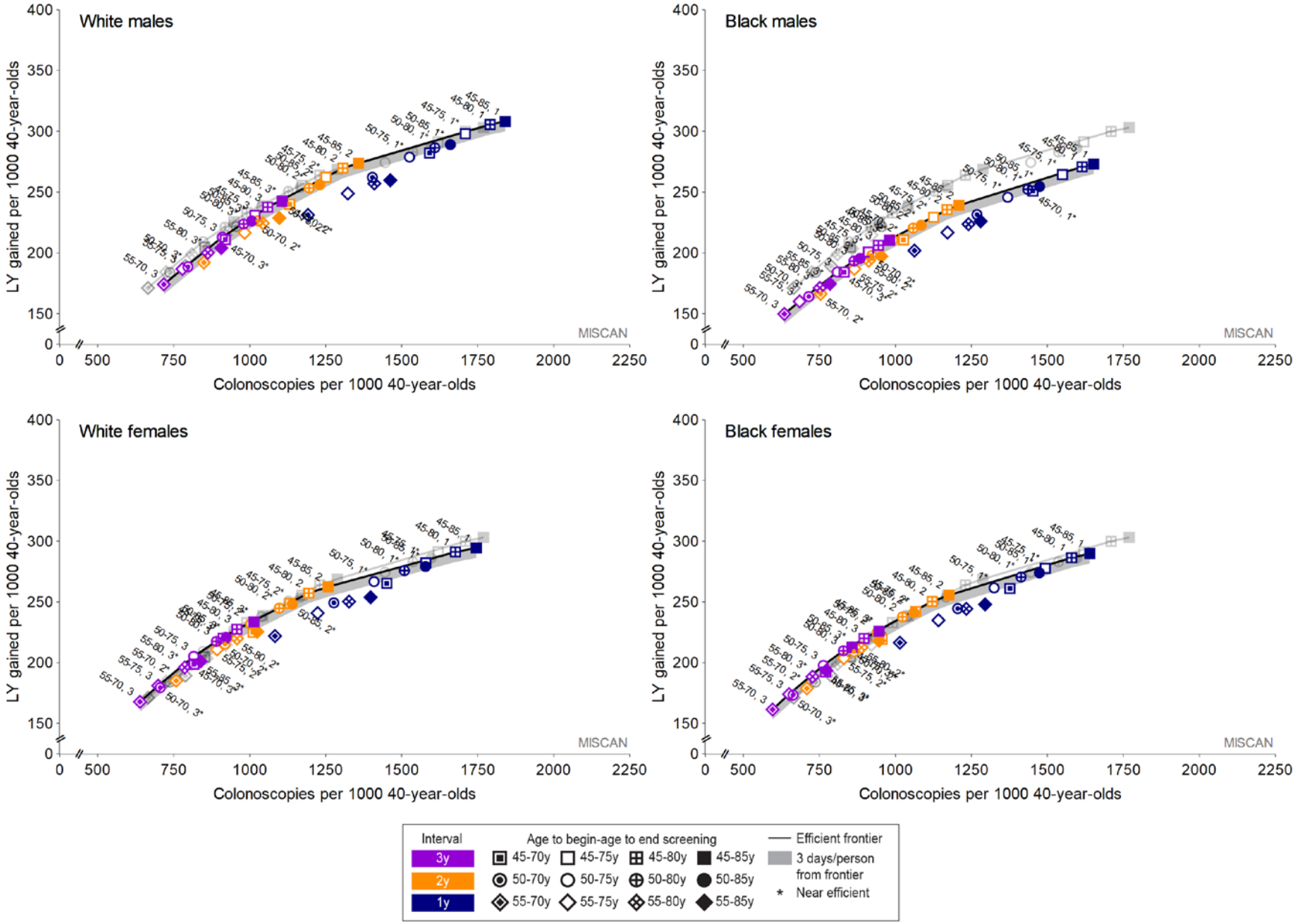
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 11.2b. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds by Race and Sex for FIT Screening Strategies: CRC-SPIN



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 11.2c. Estimated Colonoscopies and Life-Years Gained for a Cohort of 40-Year-Olds by Race and Sex for FIT Screening Strategies: MISCAN



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Table 12.1. Efficient Colonoscopy Screening Strategies, by Model and Benefit Variable (LYG, QALYG)

Strategy	Efficiency ratio, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG
COL 55-70, 15	--	--	--	--	--	--
COL 55-70, 10	Dominated	Dominated	17*	18*	22*	19*
COL 50-70, 15	6*	6*	8*	8*	18	17
COL 45-70, 15	6	6	7	8	85*	46*
COL 50-80, 15	Dominated	Dominated	Dominated	Dominated	56*	71*
COL 50-70, 10	Dominated	Dominated	Dominated	Dominated	28	30
COL 45-75, 15	39*	44*	59*	66*	38*	41*
COL 45-70, 10	34	36	44	48	45	38
COL 50-80, 10	Dominated	Dominated	Dominated	Dominated	86*	107*
COL 45-75, 10	64	72	112	127	52	61
COL 45-85, 10	394*	627*	828*	1470*	227*	352*
COL 50-70, 5	Dominated	Dominated	Dominated	Dominated	120*	151*
COL 50-75, 5	Dominated	Dominated	Dominated	Dominated	367*	Dominated
COL 45-70, 5	180*	184	179	198	84	86
COL 45-75, 5	178	198	344	447	116	137
COL 45-80, 5	428	585	736	1388	169	211
COL 45-85, 5	1445	7114	2190	Dominated	926	2285

Note: Strategies that were dominated with both measures across all 3 models are not shown. Conclusions about efficiency and efficiency ratios were similar across the two measures of the benefit of screening. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
COL – colonoscopy; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest LYG/QALYG).
* Near efficient (i.e., within 3 (quality-adjusted) days of life gained per person of the efficient frontier).

Appendix Table 13.7. Efficient FIT and sDNA-FIT Strategies, by Model and Benefit Variable (LYG, QALYG)

Strategy	Efficiency ratio, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG
FIT 55-70, 3	--	--	--	--	--	--
FIT 55-75, 3	Dominated	Dominated	Dominated	Dominated	5	6*
FIT 50-70, 3	2	2	4	4	6*	6*
FIT 55-70, 2	Dominated	Dominated	Dominated	Dominated	13*	7*
FIT 55-80, 3	Dominated	Dominated	Dominated	Dominated	6*	7*
FIT 45-70, 3	3	4	5	5	6*	6*
FIT 50-75, 3	Dominated	Dominated	Dominated	Dominated	5	5
FIT 55-85, 3	Dominated	Dominated	Dominated	Dominated	7*	Dominated
FIT 55-75, 2	Dominated	Dominated	Dominated	Dominated	14*	14*
FIT 50-80, 3	Dominated	Dominated	Dominated	Dominated	6	8*
FIT 50-70, 2	Dominated	Dominated	Dominated	Dominated	94*	8*
FIT 45-75, 3	5	6	7*	8*	7*	7
FIT 50-85, 3	Dominated	Dominated	Dominated	Dominated	10*	9*
FIT 55-80, 2	Dominated	Dominated	Dominated	Dominated	Dominated	11*
FIT 45-80, 3	7*	9*	8*	9*	6	8
FIT 45-70, 2	8*	7	7	7	Dominated	16*
FIT 50-75, 2	Dominated	Dominated	Dominated	Dominated	10*	8
FIT 45-85, 3	10*	13*	Dominated	Dominated	9*	13*
FIT 50-80, 2	Dominated	Dominated	Dominated	Dominated	8	9*
FIT 45-75, 2	7	8	9	11	9*	8
FIT 50-85, 2	Dominated	Dominated	Dominated	Dominated	12*	10*
FIT 45-80, 2	10	13	12	15*	8	9
FIT 45-85, 2	19*	26*	25*	20*	12	16*
FIT 50-75, 1	Dominated	Dominated	Dominated	Dominated	29*	17*
FIT 45-70, 1	21*	15*	14	13	Dominated	18*
FIT 50-80, 1	Dominated	Dominated	Dominated	Dominated	18*	15*
FIT 45-75, 1	16	14	16	19	15*	13*
FIT 50-85, 1	Dominated	Dominated	Dominated	Dominated	18*	16*
sDNA-FIT 45-70, 2	Dominated	Dominated	52*	55*	Dominated	Dominated

Appendix Table 13.7. Efficient FIT and sDNA-FIT Strategies, by Model and Benefit Variable (LYG, QALYG)

Strategy	Efficiency ratio, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG
FIT 45-80, 1	19	22	27	32	14	13
FIT 45-85, 1	39	53	43	55*	19	25
sDNA-FIT 45-75, 2	91*	78*	135*	112*	Dominated	Dominated
sDNA-FIT 45-80, 2	176*	203*	75*	68*	26*	23*
sDNA-FIT 45-85, 2	175*	123*	69*	71*	375*	237*
sDNA-FIT 45-70, 1	116*	291*	62*	57*	Dominated	Dominated
sDNA-FIT 45-75, 1	103*	72*	53	53	251*	110*
sDNA-FIT 45-80, 1	81	67	62	79	104*	78*
sDNA-FIT 45-85, 1	95	140	111	190	94	76

Note: Strategies that were dominated with both measures across all 3 models are not shown. Conclusions about efficiency and efficiency ratios were similar across the two measures of the benefit of screening. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest LYG/QALYG).

***** Near efficient (i.e., within 3 (quality-adjusted) days of life gained per person of the efficient frontier).

Appendix Table 12.3. Efficient Sigmoidoscopy Strategies, by Model and Benefit Variable (LYG, QALYG)

Strategy	Efficiency ratio, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG
SIG 55-70, 10	--	--	--	--	--	--
SIG 50-70, 10	Dominated	Dominated	Dominated	Dominated	8	9
SIG 45-70, 10	4	4	5	6	73*	24*
SIG 55-70, 5	Dominated	Dominated	Dominated	Dominated	11*	13*
SIG 50-80, 10	Dominated	Dominated	Dominated	Dominated	22*	28*
SIG 45-75, 10	13*	15*	18	20	18*	18*
SIG 50-70, 5	Dominated	Dominated	Dominated	Dominated	14	15
SIG 45-85, 10	Dominated	Dominated	68*	91*	21*	22*
SIG 50-75, 5	Dominated	Dominated	Dominated	Dominated	19*	23*
SIG 45-70, 5	11	12	20	21	15	15
SIG 50-80, 5	Dominated	Dominated	Dominated	Dominated	23*	28*
SIG 50-85, 5	Dominated	Dominated	Dominated	Dominated	26*	32*
SIG 45-75, 5	20	23	27	31	19	23
SIG 45-80, 5	38	46	49	60	29	38
SIG 45-85, 5	89	141	98	141	78	134

Note: Strategies that were dominated with both measures across all 3 models are not shown. Conclusions about efficiency and efficiency ratios were similar across the two measures of the benefit of screening. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
COL – colonoscopy; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; SIG – sigmoidoscopy; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest LYG/QALYG).
***** Near efficient (i.e., within 3 (quality-adjusted) days of life gained per person of the efficient frontier).

Appendix Table 12.4. Efficient 10-Yearly Sigmoidoscopy Plus Interval FIT Strategies, by Model and Benefit Variable (LYG, QALYG)

Strategy	Efficiency ratio, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG
SIG+FIT 55-70, 10_2	--	--	--	--	--	--
SIG+FIT 55-70, 10_1	Dominated	Dominated	Dominated	Dominated	14*	15*
SIG+FIT 55-75, 10_2	Dominated	Dominated	Dominated	Dominated	13*	16*
SIG+FIT 50-70, 10_2	6*	6*	8*	8*	9	10
SIG+FIT 55-80, 10_2	Dominated	Dominated	Dominated	Dominated	13*	Dominated
SIG+FIT 50-75, 10_2	Dominated	Dominated	Dominated	Dominated	9	12
SIG+FIT 45-70, 10_2	5	5	7	7	24*	16*
SIG+FIT 50-70, 10_1	Dominated	Dominated	Dominated	Dominated	24*	22*
SIG+FIT 50-80, 10_2	Dominated	Dominated	Dominated	Dominated	20*	25*
SIG+FIT 50-85, 10_2	Dominated	Dominated	Dominated	Dominated	21*	26*
SIG+FIT 45-75, 10_2	15	17	22	24	15*	16
SIG+FIT 50-75, 10_1	Dominated	Dominated	Dominated	Dominated	18*	19*
SIG+FIT 45-80, 10_2	22	27	25	31	15	17
SIG+FIT 45-70, 10_1	22*	23*	88*	49*	19*	18*
SIG+FIT 50-80, 10_1	Dominated	Dominated	Dominated	Dominated	20*	22*
SIG+FIT 45-85, 10_2	54*	75*	78*	106*	38*	54*
SIG+FIT 50-85, 10_1	Dominated	Dominated	Dominated	Dominated	21*	24*
SIG+FIT 45-75, 10_1	34	31	34	35	22*	22
SIG+FIT 45-80, 10_1	35	42	53	69	21	24
SIG+FIT 45-85, 10_1	81	116	64	89	46	65

Note: Strategies that were dominated with both measures across all 3 models are not shown. Conclusions about efficiency and efficiency ratios were similar across the two measures of the benefit of screening. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest LYG/QALYG).

***** Near efficient (i.e., within 3 (quality-adjusted) days of life gained per person of the efficient frontier).

Appendix Table 12.5. Efficient 10-Yearly Computed Tomographic Colonography Strategies, by Model and Benefit Variable (LYG, QALYG)

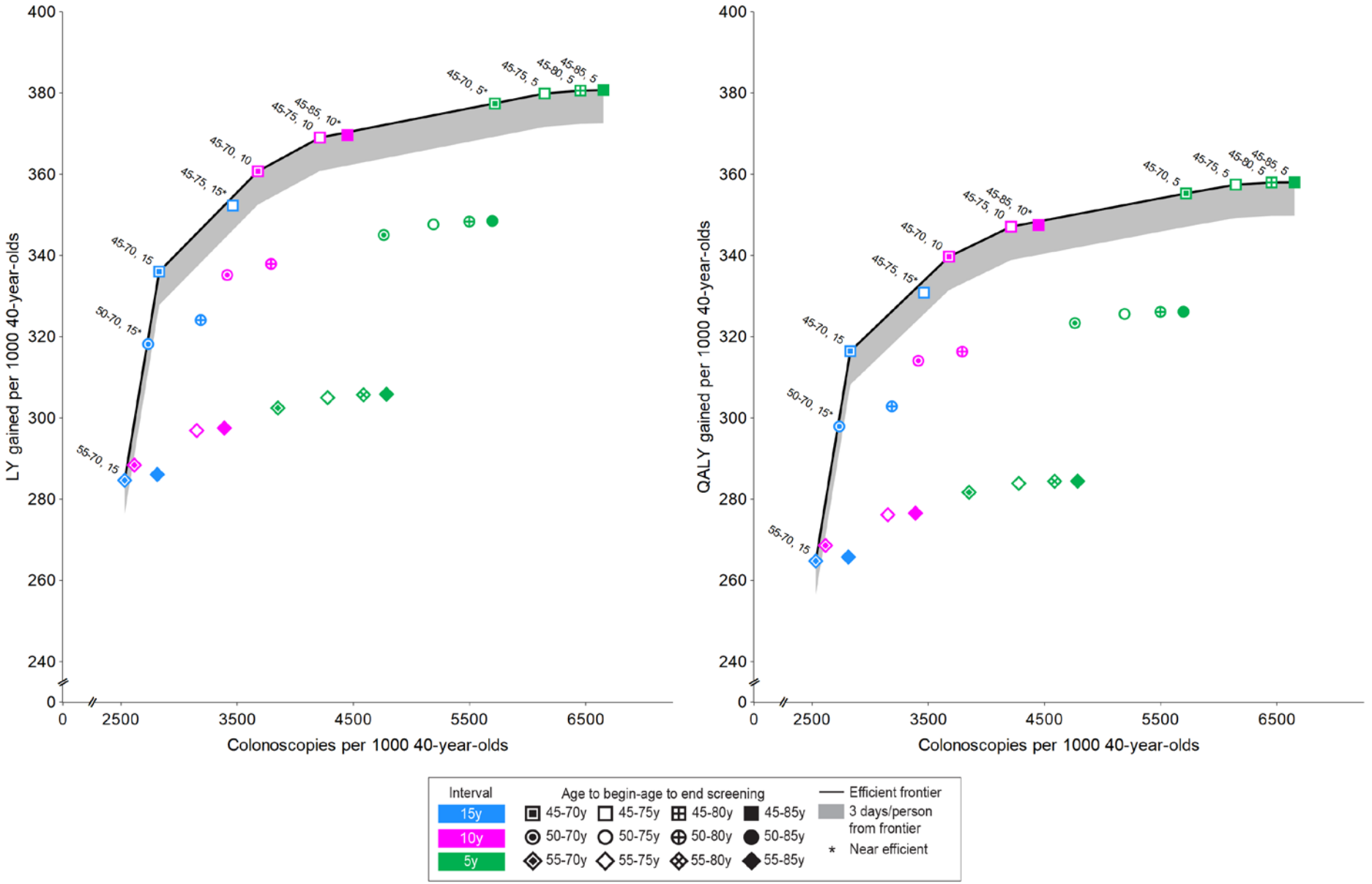
Strategy	Efficiency ratio, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG	Δ COL / Δ LYG	Δ COL / Δ QALYG
CTC 55-70, 10	--	--	--	--	--	--
CTC 55-75, 10	Dominated	Dominated	Dominated	Dominated	Dominated	8*
CTC 50-70, 10	Dominated	Dominated	Dominated	Dominated	5	6
CTC 45-70, 10	4	4	5	5	Dominated	Dominated
CTC 55-70, 5	Dominated	Dominated	Dominated	Dominated	8*	8*
CTC 50-80, 10	Dominated	Dominated	Dominated	Dominated	10*	12*
CTC 55-75, 5	Dominated	Dominated	Dominated	Dominated	9*	9*
CTC 45-75, 10	13*	15*	15*	16*	Dominated	Dominated
CTC 50-70, 5	Dominated	Dominated	Dominated	Dominated	8	8
CTC 55-80, 5	Dominated	Dominated	Dominated	Dominated	10*	Dominated
CTC 45-85, 10	Dominated	Dominated	19*	21*	Dominated	Dominated
CTC 50-75, 5	Dominated	Dominated	Dominated	Dominated	9	10
CTC 45-70, 5	11	12	13	14	21*	14*
CTC 50-80, 5	Dominated	Dominated	Dominated	Dominated	13*	16*
CTC 50-85, 5	Dominated	Dominated	Dominated	Dominated	17*	21*
CTC 45-75, 5	19	22	21	24	11	11
CTC 45-80, 5	38	46	37	45	13	16
CTC 45-85, 5	104	165	73	103	32	43

Note: Strategies that were dominated with both measures across all 3 models are not shown. Conclusions about efficiency and efficiency ratios were similar across the two measures of the benefit of screening. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; CTC – computed tomographic colonography; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest LYG/QALYG).

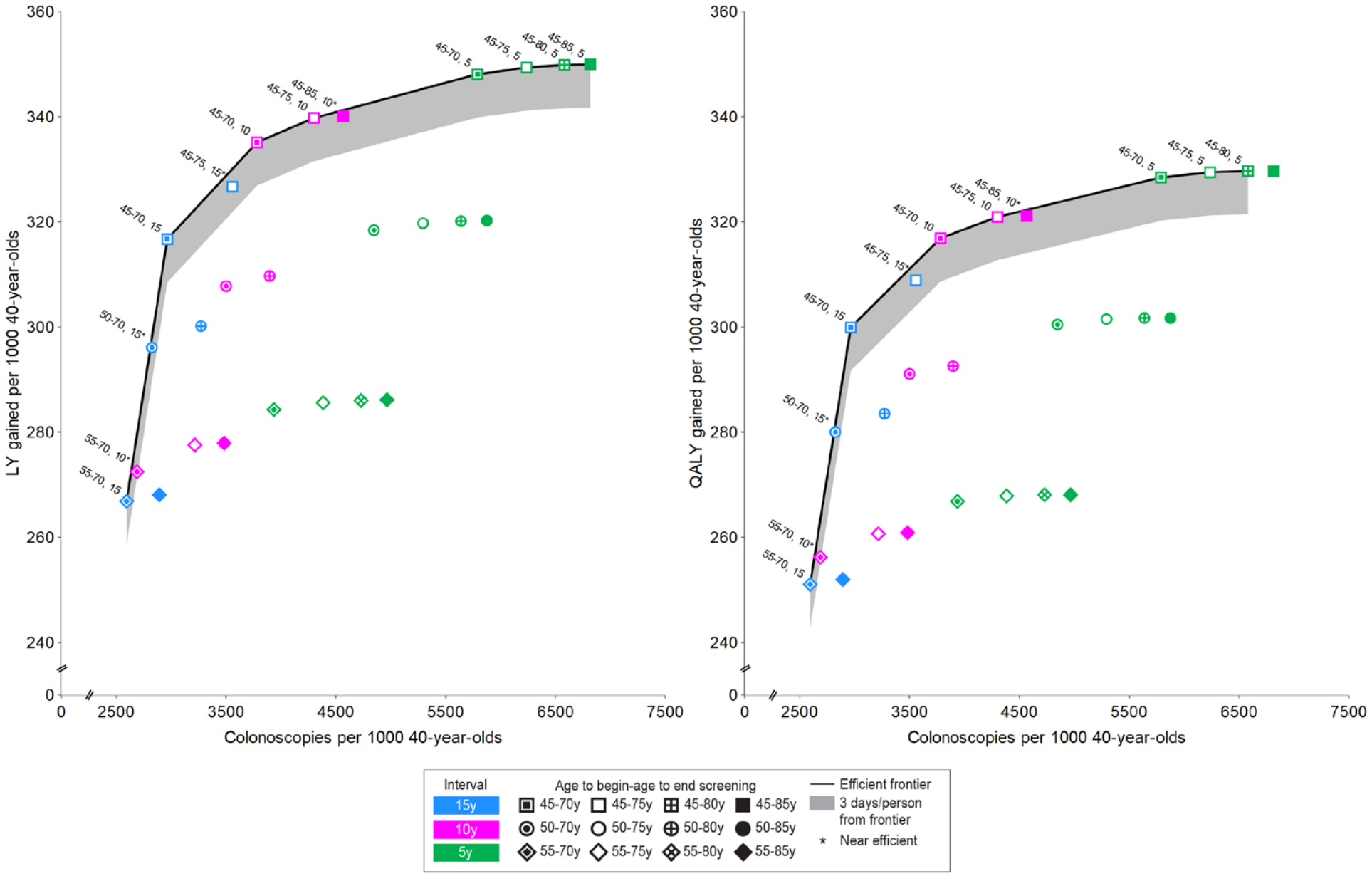
***** Near efficient (i.e., within 3 (quality-adjusted) days of life gained per person of the efficient frontier).

Appendix Figure 12.1a. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies: SimCRC



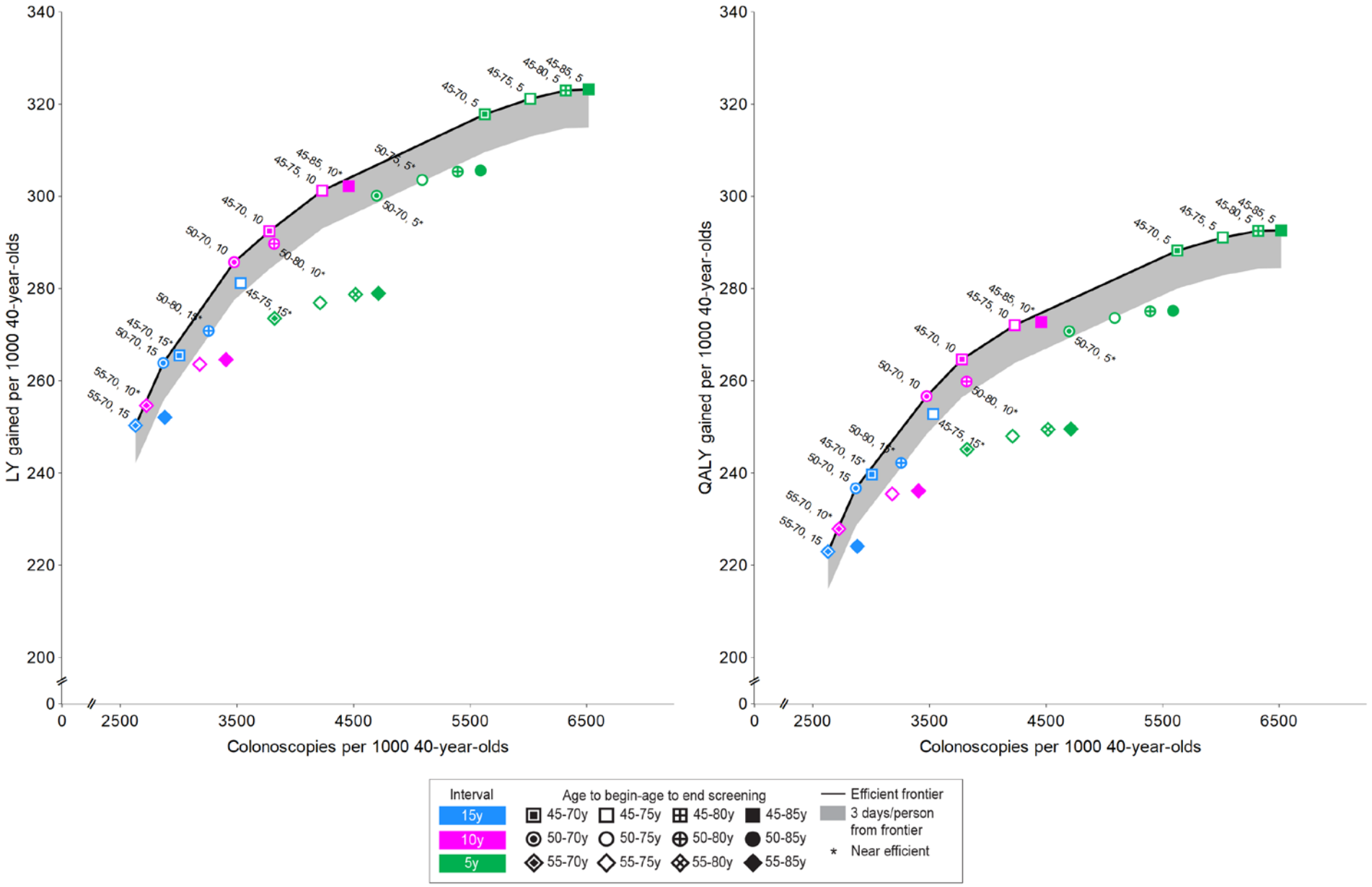
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.1b. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies: CRC-SPIN



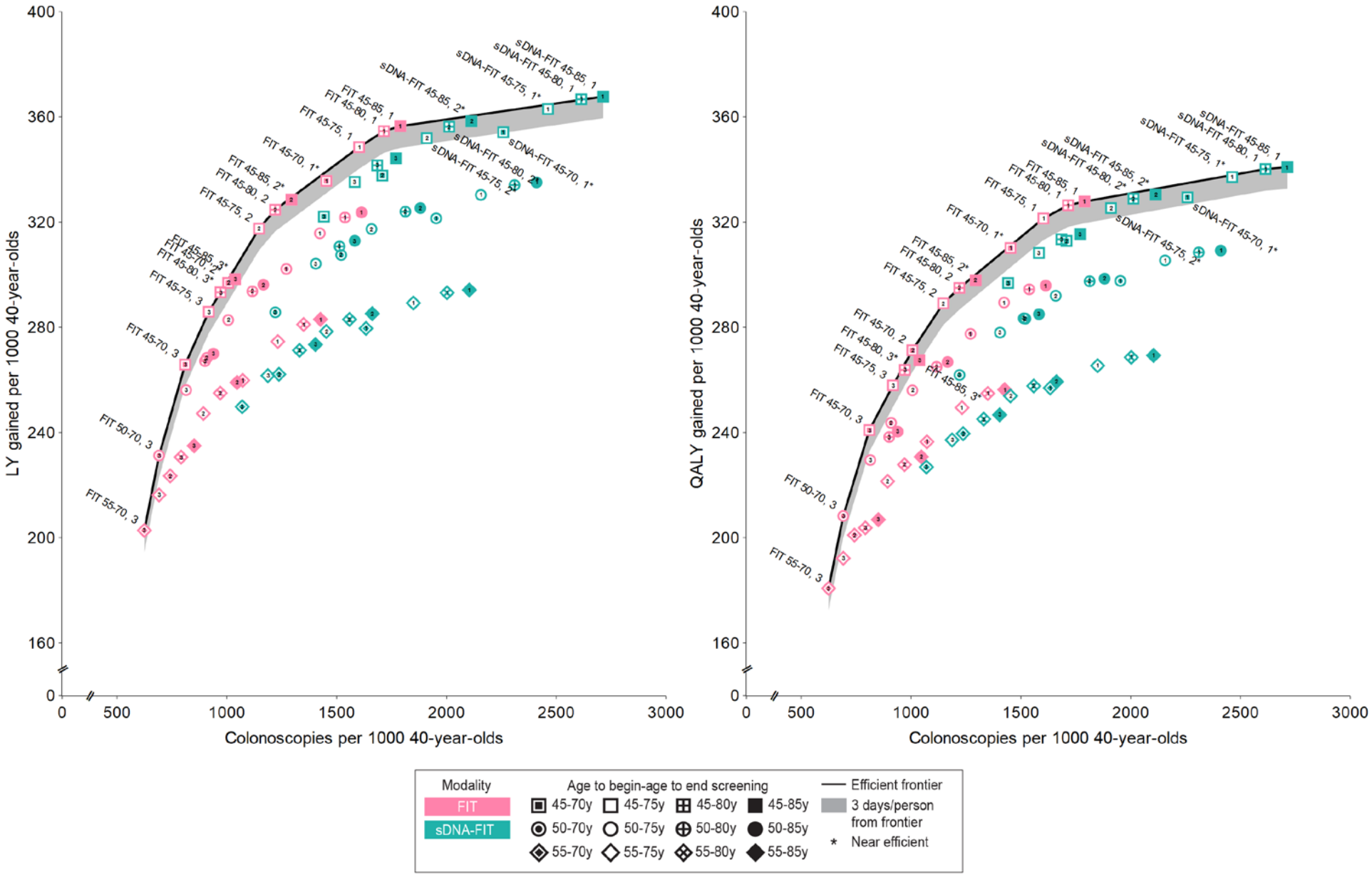
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.1c. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Colonoscopy Screening Strategies: MISCAN



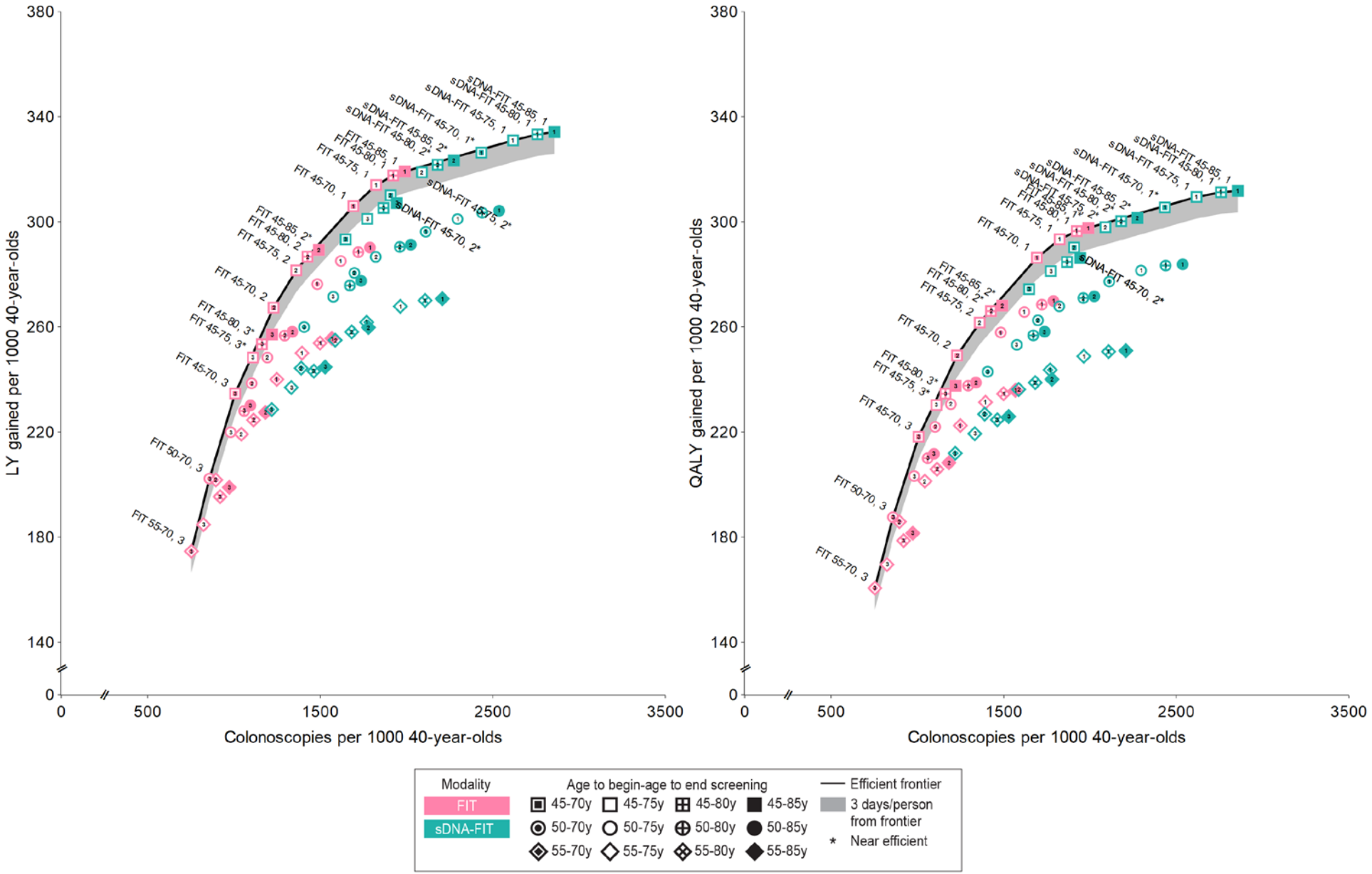
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.2a. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for FIT and sDNA-FIT Screening Strategies: SimCRC



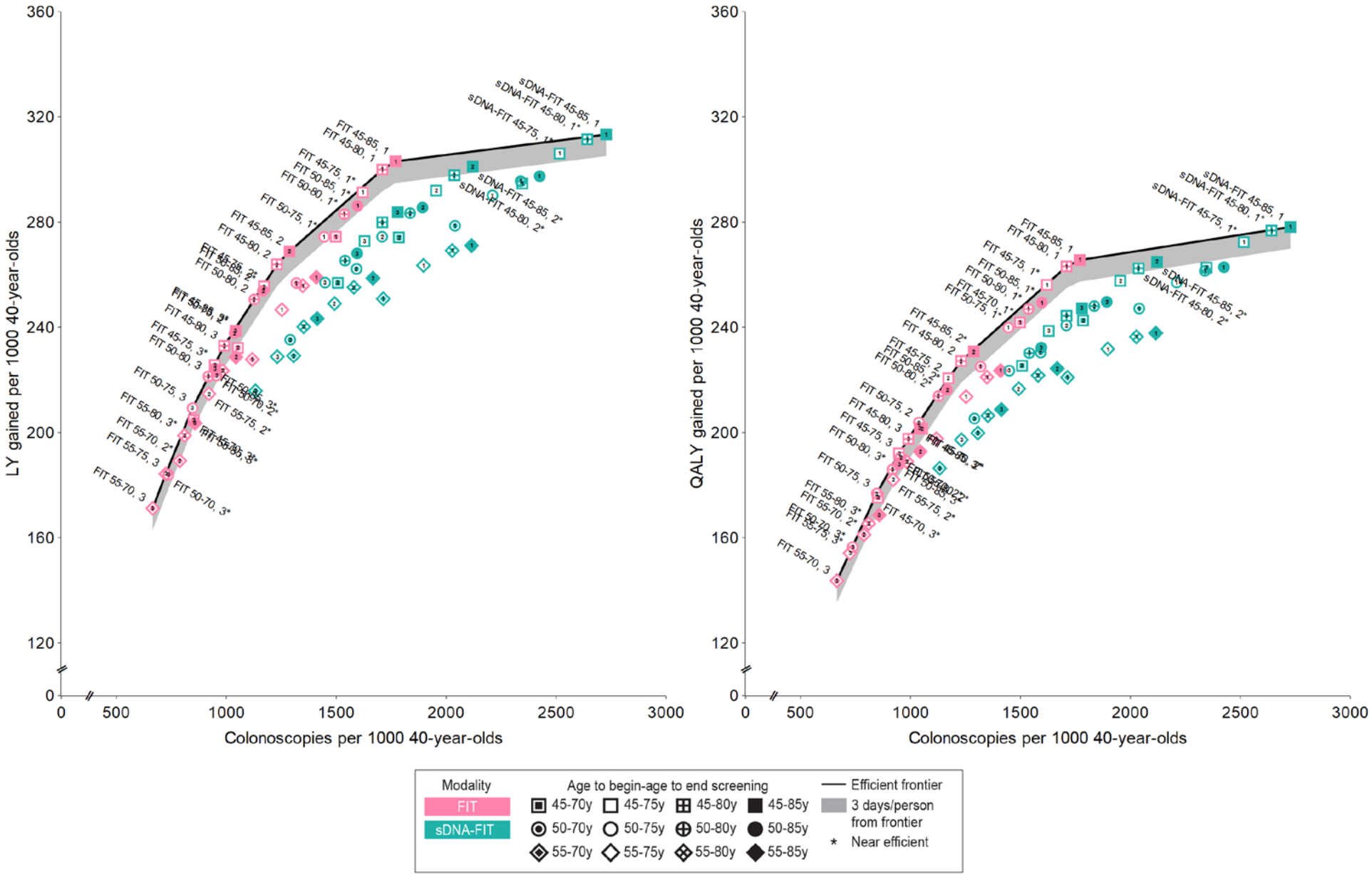
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.2b. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for FIT and sDNA-FIT Screening Strategies: CRC-SPIN



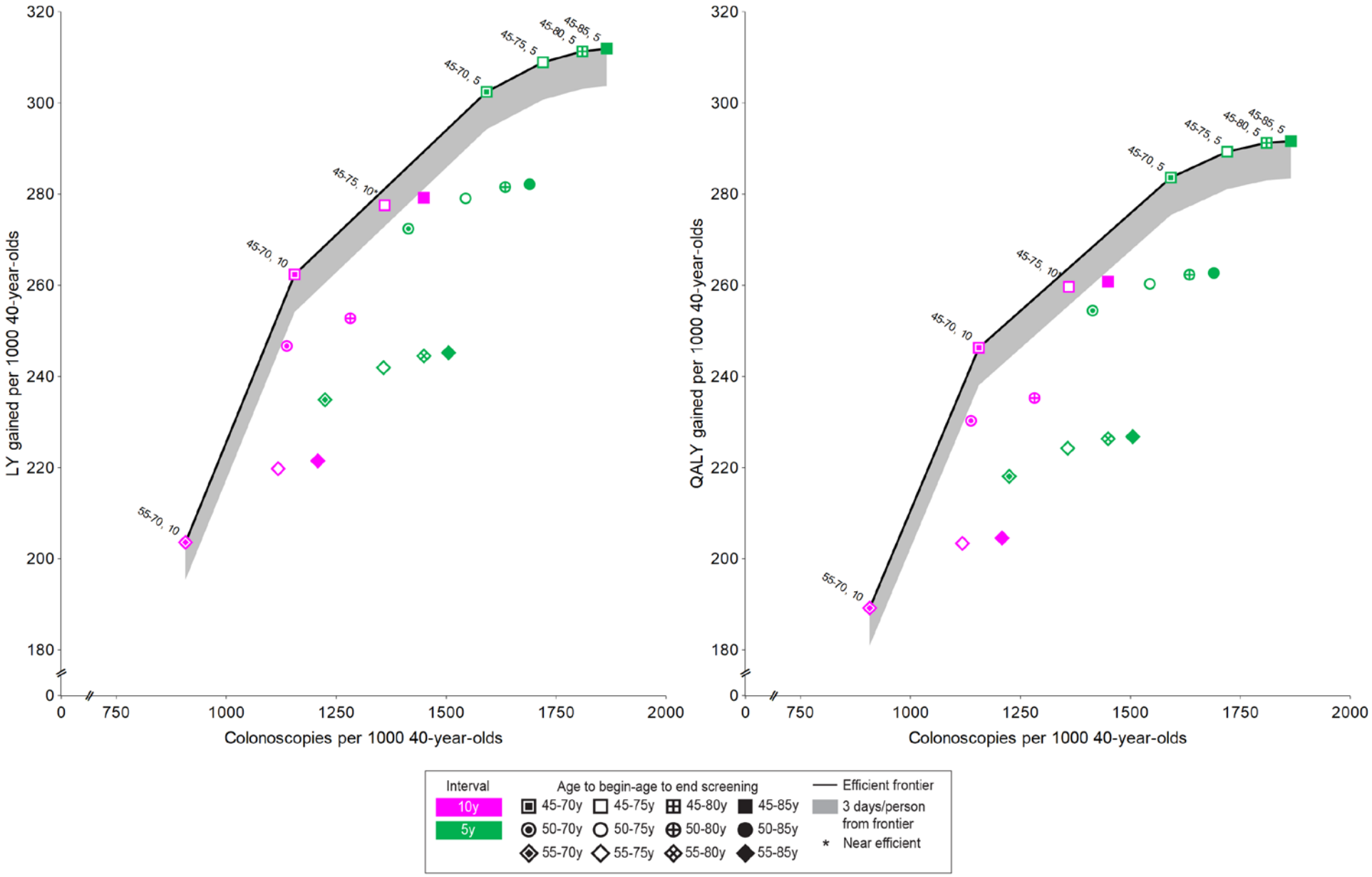
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.2c. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for FIT and sDNA-FIT Screening Strategies: MISCAN



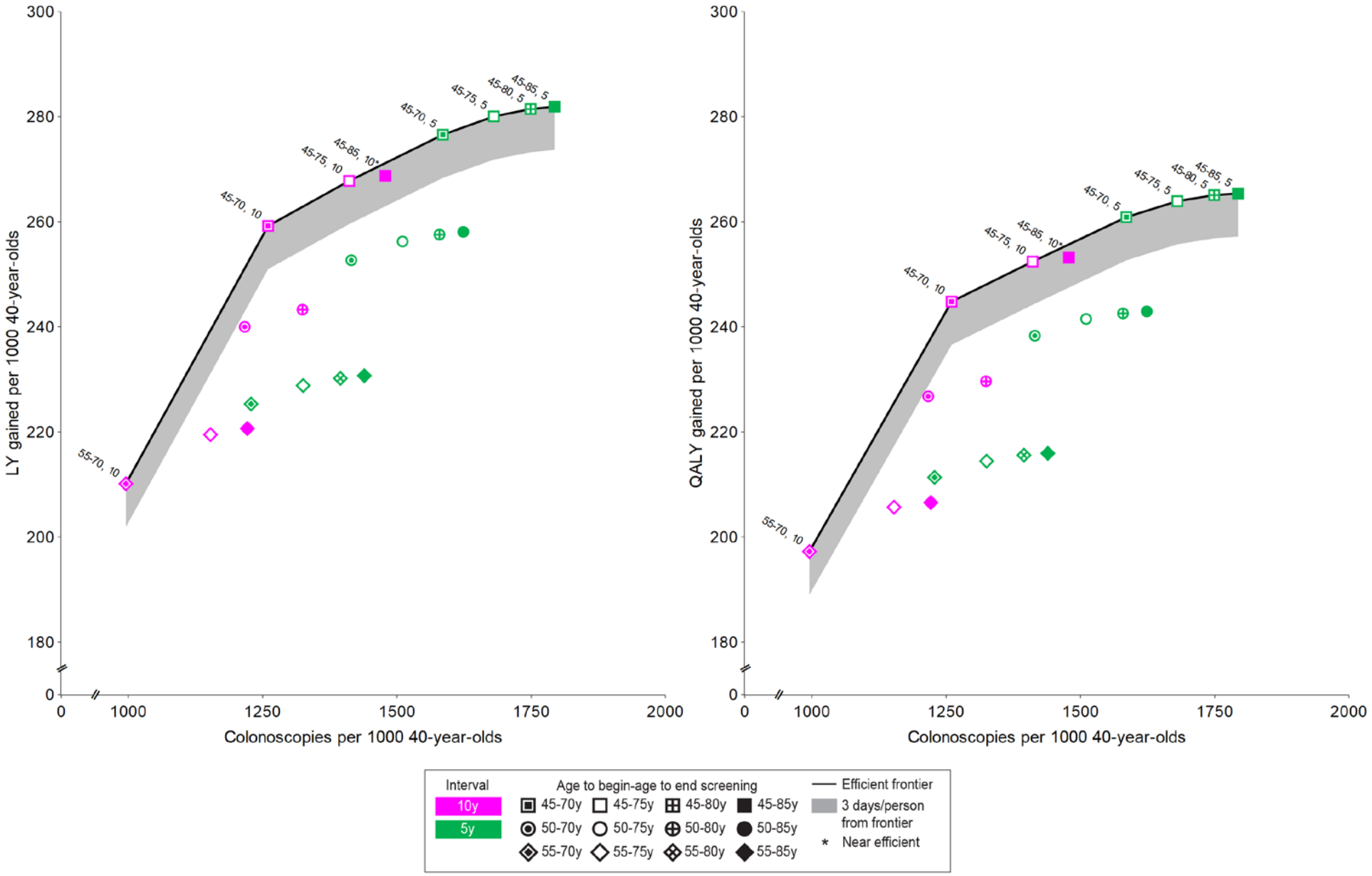
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.3a. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Strategies: SimCRC



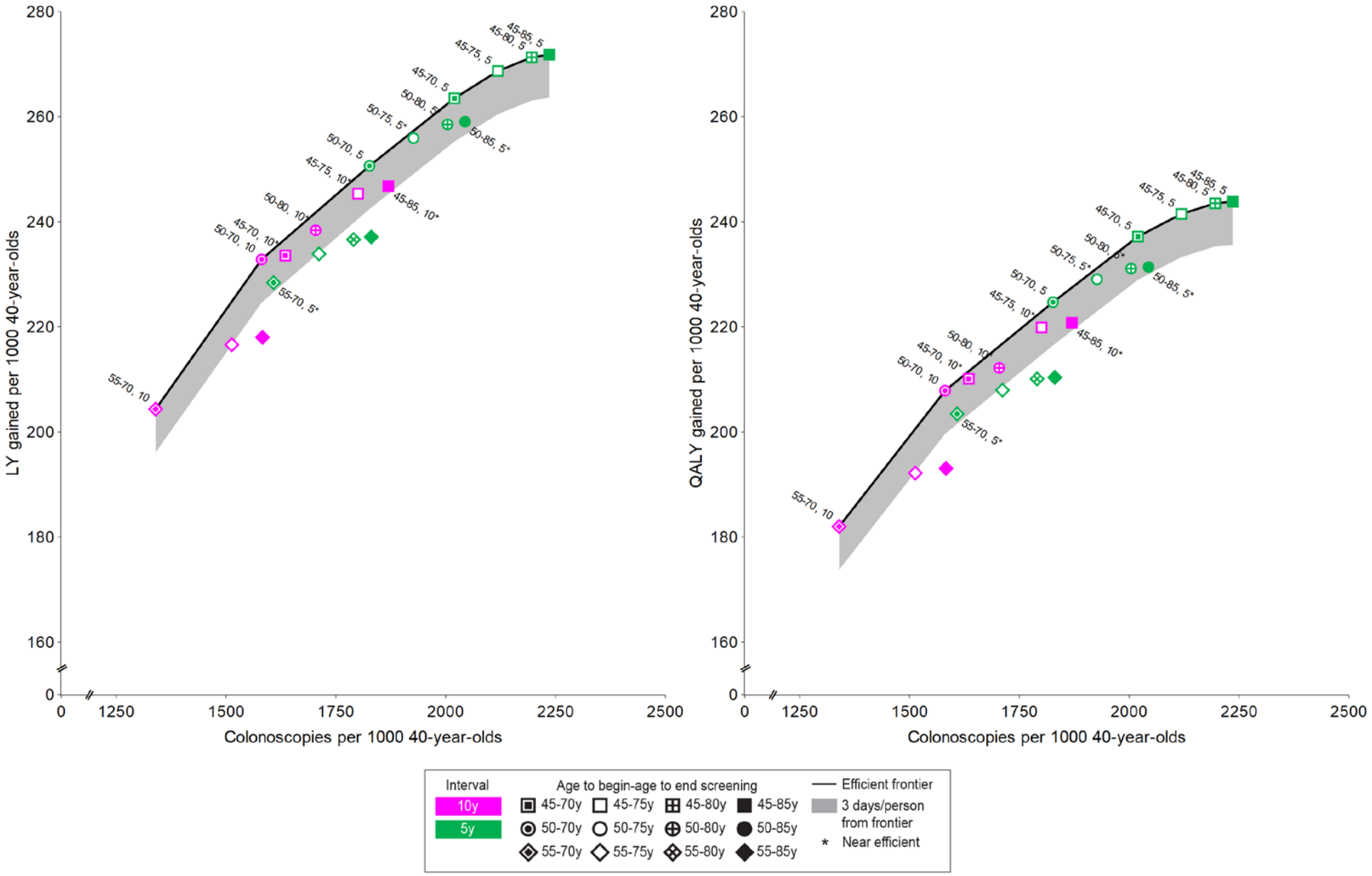
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.3b. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Strategies: CRC-SPIN



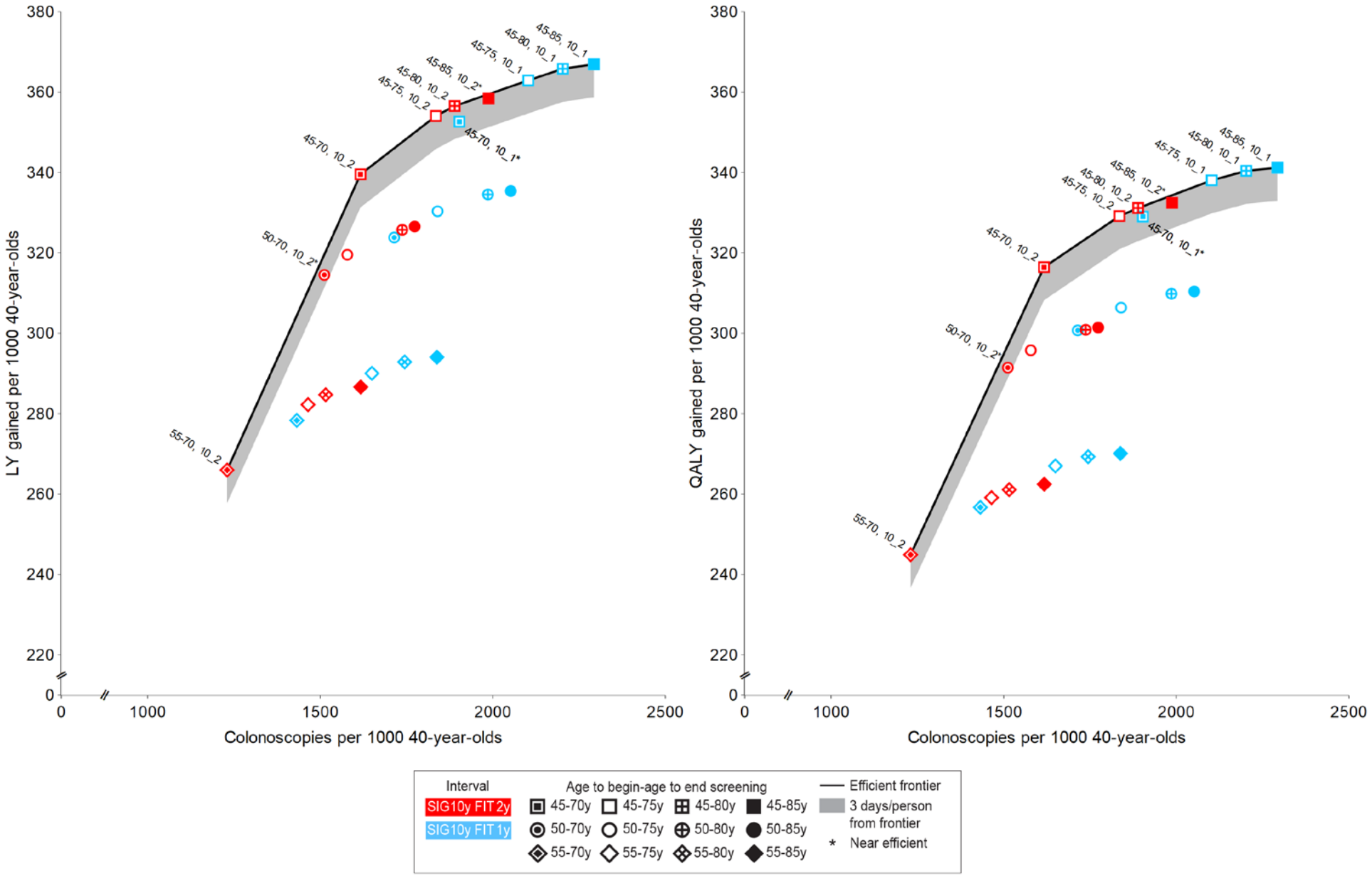
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.3c. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Sigmoidoscopy Screening Strategies: MISCAN



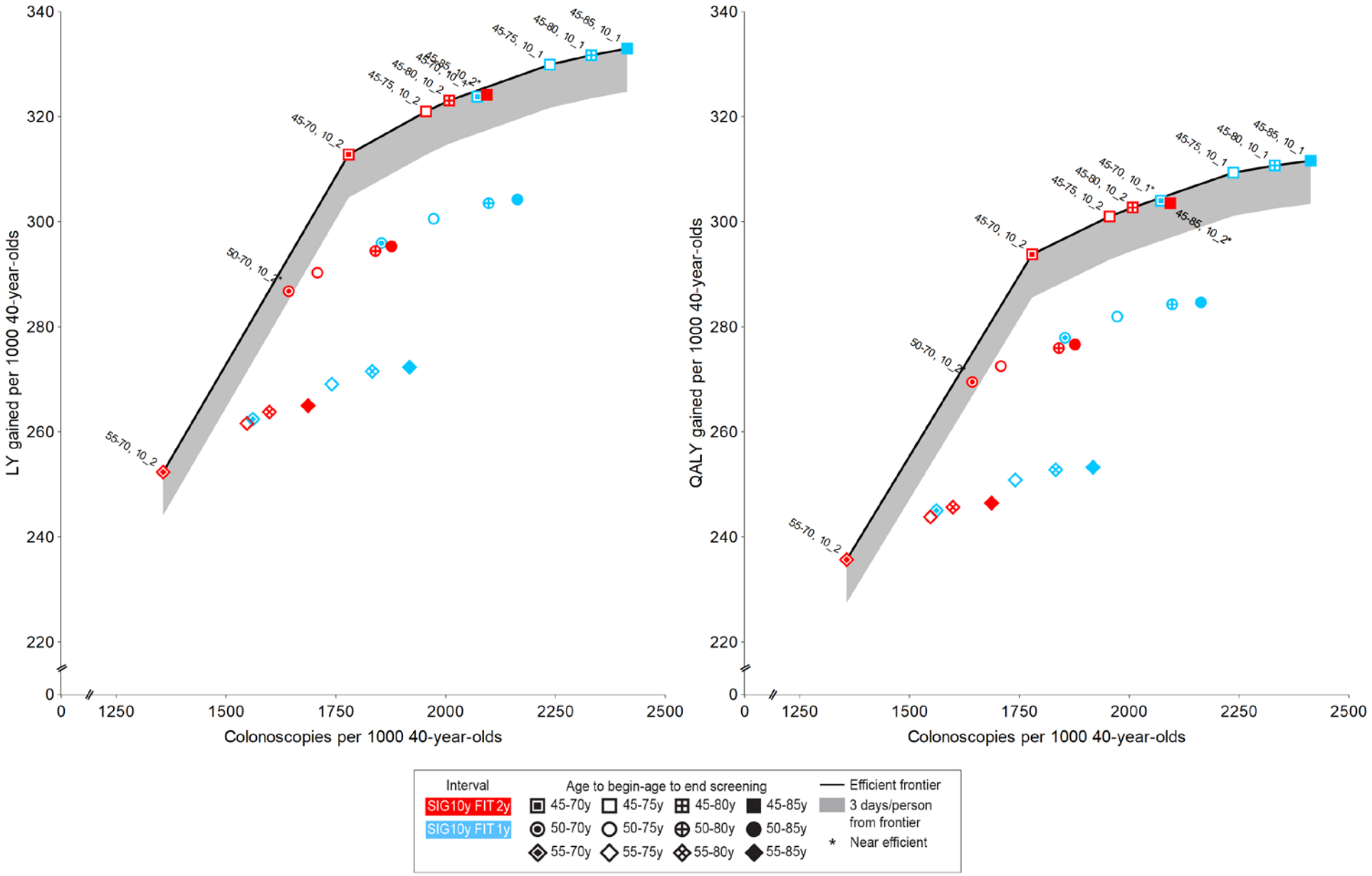
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.4a. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies: SimCRC



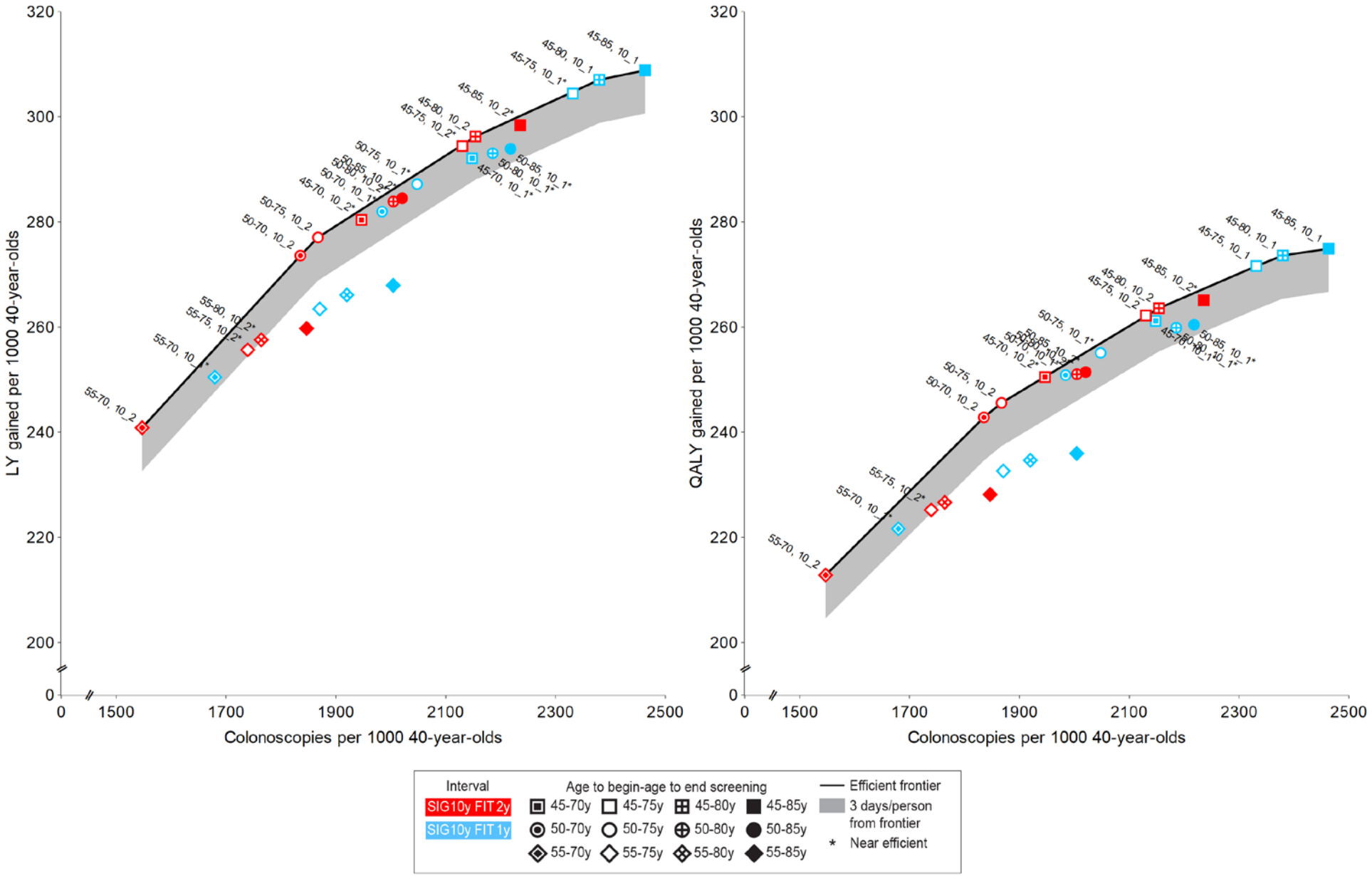
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.4b. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies: CRC-SPIN



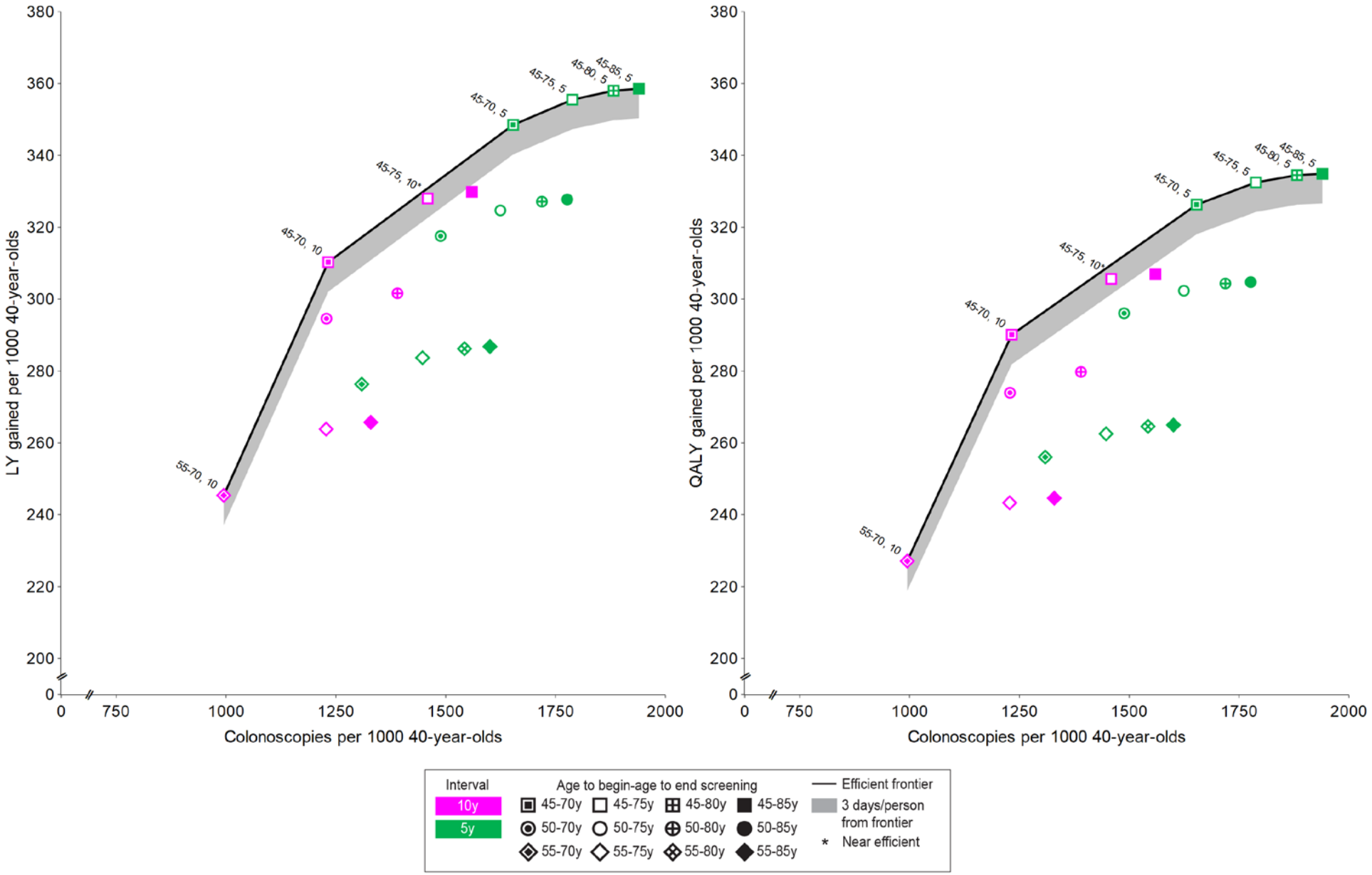
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.4c. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies: MISCAN



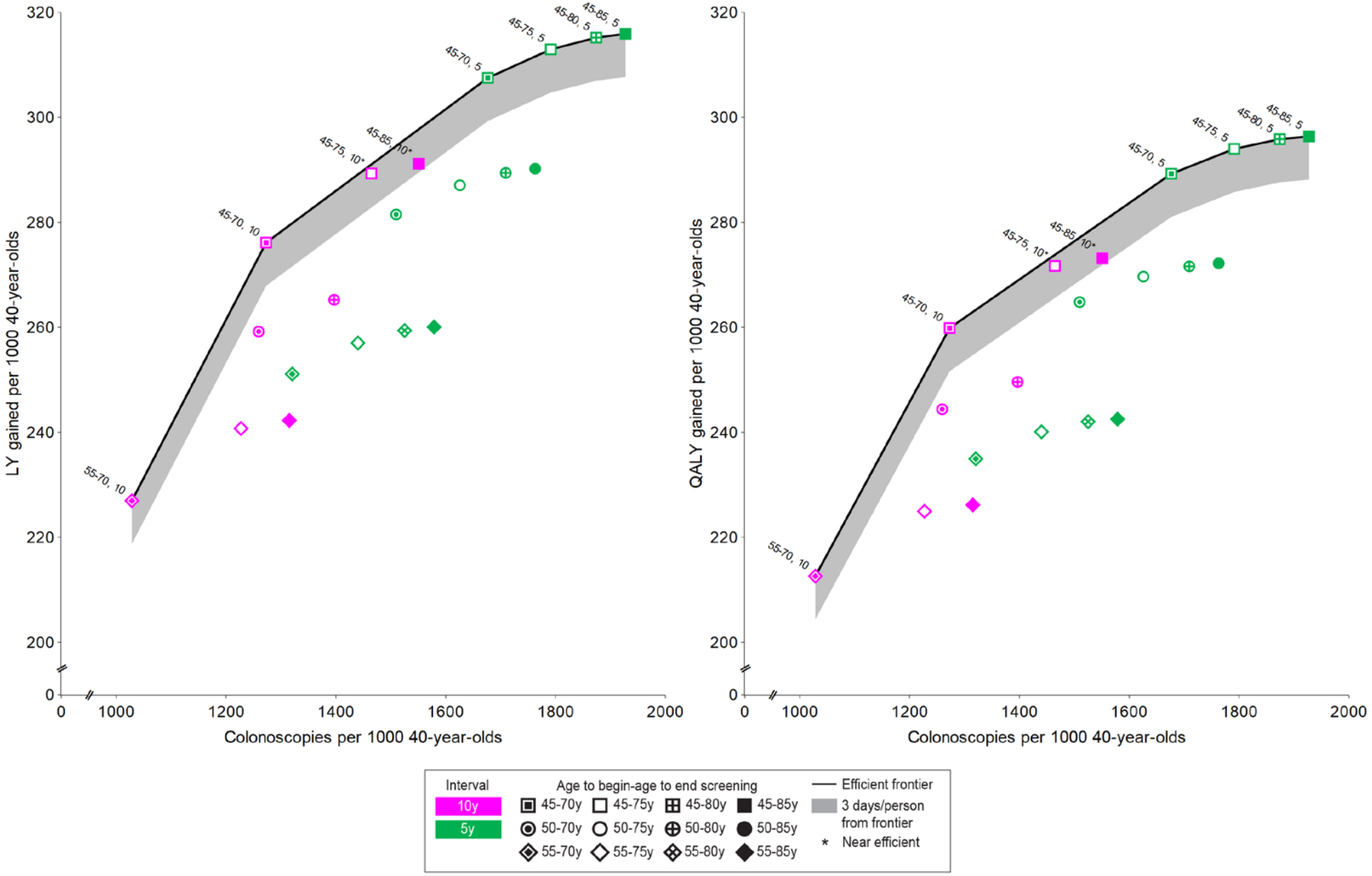
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.5a. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Computed Tomographic Colonography Screening Strategies: SimCRC



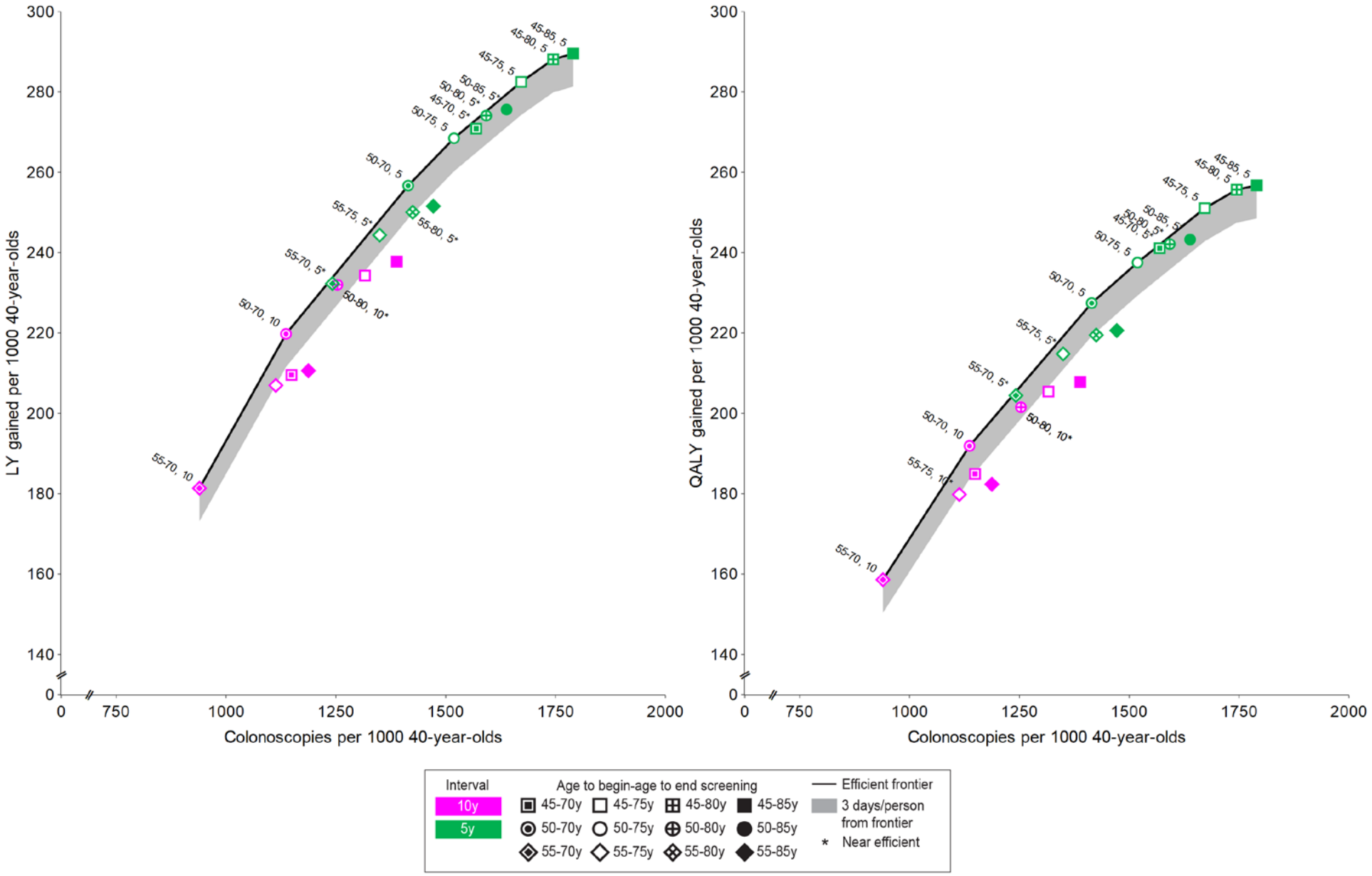
Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.5b. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Computed Tomographic Colonography Screening Strategies: CRC-SPIN



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Figure 12.5c. Estimated Colonoscopies vs. Life-Years Gained and vs. Quality-Adjusted Life-Years Gained for a Cohort of 40-Year-Olds for Computed Tomographic Colonography Screening Strategies: MISCAN



Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

Appendix Table 13.1. Efficient Frontier Status for Colonoscopy Screening Strategies, According to Whether Life-Years Gained or the Number of Colorectal Cancer Deaths Averted Are Used for the Benefit of Screening

	Efficient frontier status, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
Strategy	LYG	CRC deaths averted	LYG	CRC deaths averted	LYG	CRC deaths averted
COL 55-70, 15	E	E	E	E	E	E
COL 55-70, 10	--	NE	NE	NE	NE	NE
COL 50-70, 15	NE	E	NE	E	E	NE
COL 55-85, 15	--	NE	--	--	--	NE
COL 45-70, 15	E	--	E	NE	NE	--
COL 55-75, 10	--	NE	--	--	--	E
COL 50-80, 15	--	NE	--	NE	NE	NE
COL 55-85, 10	--	--	--	--	--	NE
COL 50-70, 10	--	NE	--	NE	E	NE
COL 45-75, 15	NE	E	NE	E	NE	NE
COL 45-70, 10	E	NE	E	NE	E	--
COL 50-80, 10	--	NE	--	NE	NE	E
COL 45-75, 10	E	E	E	E	E	NE
COL 55-75, 5	--	--	--	--	--	NE
COL 45-85, 10	NE	E	NE	E	NE	NE
COL 55-80, 5	--	--	--	--	--	NE
COL 50-70, 5	--	--	--	--	NE	NE
COL 55-85, 5	--	--	--	--	--	NE
COL 50-75, 5	--	--	--	--	NE	NE
COL 50-80, 5	--	--	--	--	--	E
COL 50-85, 5	--	--	--	--	--	NE
COL 45-70, 5	NE	NE	E	NE	E	NE
COL 45-75, 5	E	NE	E	E	E	NE
COL 45-80, 5	E	E	E	E	E	E
COL 45-85, 5	E	E	E	E	E	E

Note: Strategies that were dominated with both measures across all models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
COL – colonoscopy; E – strategy is efficient; NE – strategy is near efficient; -- indicates strategy is dominated and does not meet the criteria for near efficiency.

Appendix Table 13.2. Efficient Frontier Status for FIT and sDNA-FIT Screening Strategies, According to Whether Life-Years Gained or the Number of Colorectal Cancer Deaths Averted Are Used for the Benefit of Screening

	Efficient frontier status, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
Strategy	LYG	CRC deaths averted	LYG	CRC deaths averted	LYG	CRC deaths averted
FIT 55-70, 3	E	E	E	E	E	E
FIT 55-75, 3	--	E	--	E	E	E
FIT 50-70, 3	E	--	E	NE	NE	--
FIT 55-70, 2	--	--	--	NE	NE	--
FIT 55-80, 3	--	E	--	E	NE	E
FIT 45-70, 3	E	--	E	--	NE	--
FIT 50-75, 3	--	NE	--	NE	E	--
FIT 55-85, 3	--	NE	--	NE	NE	E
FIT 55-75, 2	--	--	--	NE	NE	--
FIT 50-80, 3	--	E	--	E	E	NE
FIT 50-70, 2	--	--	--	NE	NE	--
FIT 45-75, 3	E	NE	NE	NE	NE	--
FIT 50-85, 3	--	E	--	NE	NE	NE
FIT 55-80, 2	--	NE	--	E	--	NE
FIT 45-80, 3	NE	NE	NE	NE	E	--
FIT 45-70, 2	NE	--	E	NE	--	--
FIT 50-75, 2	--	--	--	NE	NE	--
FIT 45-85, 3	NE	E	--	E	NE	--
FIT 55-85, 2	--	NE	--	NE	--	E
FIT 55-70, 1	--	--	--	NE	--	--
FIT 50-80, 2	--	NE	--	NE	E	NE
FIT 45-75, 2	E	--	E	NE	NE	--
FIT 50-85, 2	--	NE	--	NE	NE	E
FIT 45-80, 2	E	NE	E	E	E	--
FIT 55-75, 1	--	--	--	NE	--	--
FIT 45-85, 2	NE	E	NE	E	E	NE
FIT 55-80, 1	--	--	--	--	--	NE
FIT 50-75, 1	--	--	--	NE	NE	--
FIT 55-85, 1	--	--	--	--	--	E
FIT 45-70, 1	NE	--	E	NE	--	--
FIT 50-80, 1	--	NE	--	NE	NE	NE
FIT 45-75, 1	E	--	E	NE	NE	--
FIT 50-85, 1	--	NE	--	NE	NE	E
sDNA-FIT 45-80, 3	--	--	--	NE	--	--
sDNA-FIT 45-70, 2	--	--	NE	--	--	--
FIT 45-80, 1	E	NE	E	NE	E	NE
sDNA-FIT 45-85, 3	--	--	--	NE	--	--

Appendix Table 13.7. Efficient FIT and sDNA-FIT Strategies, by Model and Benefit Variable (LYG, QALYG)

FIT 45-85, 1	E	E	E	E	E	E
sDNA-FIT 50-85, 2	--	--	--	--	--	NE
sDNA-FIT 45-75, 2	NE	--	NE	NE	--	--
sDNA-FIT 45-80, 2	NE	NE	NE	NE	NE	--
sDNA-FIT 45-85, 2	NE	NE	NE	NE	NE	NE
sDNA-FIT 45-70, 1	NE	--	NE	--	--	--
sDNA-FIT 50-80, 1	--	--	--	--	--	NE
sDNA-FIT 50-85, 1	--	--	--	--	--	NE
sDNA-FIT 45-75, 1	NE	--	E	NE	NE	--
sDNA-FIT 45-80, 1	E	NE	E	NE	NE	NE
sDNA-FIT 45-85, 1	E	E	E	E	E	E

Note: Strategies that were dominated with both measures across all models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); E – strategy is efficient; NE – strategy is near efficient; -- indicates strategy is dominated and does not meet the criteria for near efficiency.

Appendix Table 13.3. Efficient Frontier Status for 10-Yearly Sigmoidoscopy Screening Strategies, According to Whether Life-Years Gained or the Number of Colorectal Cancer Deaths Averted Are Used for the Benefit of Screening

	Efficient frontier status, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
Strategy	LYG	CRC deaths averted	LYG	CRC deaths averted	LYG	CRC deaths averted
SIG 55-70, 10	E	E	E	E	E	E
SIG 55-75, 10	--	NE	--	E	--	E
SIG 50-70, 10	--	E	--	E	E	NE
SIG 45-70, 10	E	NE	E	NE	NE	--
SIG 55-85, 10	--	NE	--	NE	--	NE
SIG 55-70, 5	--	NE	--	NE	NE	NE
SIG 50-80, 10	--	NE	--	NE	NE	NE
SIG 55-75, 5	--	NE	--	NE	--	NE
SIG 45-75, 10	NE	E	E	E	NE	NE
SIG 50-70, 5	--	NE	--	NE	E	NE
SIG 45-85, 10	--	NE	NE	E	NE	NE
SIG 55-80, 5	--	NE	--	--	--	E
SIG 55-85, 5	--	--	--	--	--	NE
SIG 50-75, 5	--	NE	--	NE	NE	NE
SIG 45-70, 5	E	NE	E	NE	E	--
SIG 50-80, 5	--	NE	--	NE	NE	E
SIG 50-85, 5	--	NE	--	NE	NE	E
SIG 45-75, 5	E	E	E	NE	E	NE
SIG 45-80, 5	E	E	E	E	E	NE
SIG 45-85, 5	E	E	E	E	E	E

Note: Strategies that were dominated with both measures across all models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
SIG – sigmoidoscopy; E – strategy is efficient; NE – strategy is near efficient; -- indicates strategy is dominated and does not meet the criteria for near efficiency.

Appendix Table 13.4. Efficient Frontier Status for 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies, According to Whether Life-Years Gained or the Number of Colorectal Cancer Deaths Averted Are Used for the Benefit of Screening

	Efficient frontier status, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
Strategy	LYG	CRC deaths averted	LYG	CRC deaths averted	LYG	CRC deaths averted
SIG+FIT 55-70, 10_2	E	E	E	E	E	E
SIG+FIT 55-70, 10_1	--	--	--	NE	NE	NE
SIG+FIT 55-75, 10_2	--	E	--	E	NE	NE
SIG+FIT 50-70, 10_2	NE	NE	NE	NE	E	--
SIG+FIT 55-80, 10_2	--	NE	--	NE	NE	E
SIG+FIT 50-75, 10_2	--	E	--	E	E	NE
SIG+FIT 45-70, 10_2	E	--	E	NE	NE	--
SIG+FIT 55-85, 10_2	--	NE	--	NE	--	E
SIG+FIT 55-75, 10_1	--	--	--	NE	--	NE
SIG+FIT 50-70, 10_1	--	--	--	NE	NE	--
SIG+FIT 50-80, 10_2	--	E	--	NE	NE	NE
SIG+FIT 55-80, 10_1	--	--	--	NE	--	NE
SIG+FIT 50-85, 10_2	--	NE	--	NE	NE	E
SIG+FIT 45-75, 10_2	E	NE	E	NE	NE	NE
SIG+FIT 55-85, 10_1	--	--	--	--	--	NE
SIG+FIT 50-75, 10_1	--	--	--	NE	NE	NE
SIG+FIT 45-80, 10_2	E	E	E	E	E	NE
SIG+FIT 45-70, 10_1	NE	--	NE	NE	NE	--
SIG+FIT 50-80, 10_1	--	--	--	NE	NE	NE
SIG+FIT 45-85, 10_2	NE	E	NE	E	NE	NE
SIG+FIT 50-85, 10_1	--	NE	--	NE	NE	E
SIG+FIT 45-75, 10_1	E	NE	E	NE	NE	NE
SIG+FIT 45-80, 10_1	E	NE	E	NE	E	NE
SIG+FIT 45-85, 10_1	E	E	E	E	E	E

Note: Strategies that were dominated with both measures across all models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; E – strategy is efficient; NE – strategy is near efficient; -- indicates strategy is dominated and does not meet the criteria for near efficiency.

Appendix Table 13.5. Efficient Frontier Status for Computed Tomographic Colonography Screening Strategies, According to Whether Life-Years Gained or the Number of Colorectal Cancer Deaths Averted Are Used for the Benefit of Screening

	Efficient frontier status, by model and benefit variable					
	SimCRC		CRC-SPIN		MISCAN	
Strategy	LYG	CRC deaths averted	LYG	CRC deaths averted	LYG	CRC deaths averted
CTC 55-70, 10	E	E	E	E	E	E
CTC 55-75, 10	--	NE	--	E	--	E
CTC 50-70, 10	--	E	--	NE	E	--
CTC 45-70, 10	E	--	E	NE	--	--
CTC 55-70, 5	--	--	--	NE	NE	NE
CTC 55-85, 10	--	--	--	NE	--	E
CTC 50-80, 10	--	NE	--	NE	NE	NE
CTC 55-75, 5	--	--	--	NE	NE	NE
CTC 45-75, 10	NE	E	NE	E	--	--
CTC 50-70, 5	--	NE	--	NE	E	--
CTC 55-80, 5	--	--	--	NE	NE	E
CTC 45-85, 10	--	NE	NE	E	--	--
CTC 55-85, 5	--	--	--	NE	--	E
CTC 50-75, 5	--	NE	--	NE	E	--
CTC 45-70, 5	E	NE	E	NE	NE	--
CTC 50-80, 5	--	NE	--	NE	NE	NE
CTC 50-85, 5	--	NE	--	NE	NE	E
CTC 45-75, 5	E	NE	E	NE	E	--
CTC 45-80, 5	E	E	E	E	E	NE
CTC 45-85, 5	E	E	E	E	E	E

Note: Strategies that were dominated with both measures across all models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.
CTC – computed tomographic colonography; E – strategy is efficient; NE – strategy is near efficient; -- indicates strategy is dominated and does not meet the criteria for near efficiency.

Appendix Table 13.6. Efficient Colonoscopy Screening Strategies With the Estimated Number of Colorectal Cancer Deaths Averted as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ CRC deaths averted)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
COL 55-70, 15	--	--	--
COL 55-70, 10	N/A*	423*	N/A*
COL 50-70, 15	258	227	N/A*
COL 55-85, 15	659*	Dominated	529*
COL 45-70, 15	Dominated	2115*	Dominated
COL 55-75, 10	725*	Dominated	429
COL 50-80, 15	346*	545*	515*
COL 55-85, 10	Dominated	Dominated	844*
COL 50-70, 10	380*	579*	712*
COL 45-75, 15	320	423	13793*
COL 45-70, 10	480*	2029*	Dominated
COL 50-80, 10	2418*	693*	526
COL 45-75, 10	625	801	2712*
COL 55-75, 5	Dominated	Dominated	1099*
COL 45-85, 10	1277	2341	1539*
COL 55-80, 5	Dominated	Dominated	7788*
COL 50-70, 5	Dominated	Dominated	6254*
COL 55-85, 5	Dominated	Dominated	5972*
COL 50-75, 5	Dominated	Dominated	1838*
COL 50-80, 5	Dominated	Dominated	1489
COL 50-85, 5	Dominated	Dominated	3178*
COL 45-70, 5	31880*	4594*	2374*
COL 45-75, 5	3172*	3258	2431*
COL 45-80, 5	2817	3392	1495
COL 45-85, 5	4268	8623	3351

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; CRC – colorectal cancer; N/A – not applicable; the efficiency ratio cannot be calculated because there is no efficient strategy with fewer colorectal cancer deaths averted; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and averting the fewest colorectal cancer deaths).

* Near efficient (i.e., within 0.75 colorectal cancer deaths averted per 1000 of the efficient frontier).

Appendix Table 13.7. Efficient Sigmoidoscopy Strategies With the Estimated Number of Colorectal Cancer Deaths Averted as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ CRC deaths averted)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
FIT 55-70, 3	--	--	--
FIT 55-75, 3	37	54	35
FIT 50-70, 3	Dominated	425*	Dominated
FIT 55-70, 2	Dominated	69*	Dominated
FIT 55-80, 3	42	58	36
FIT 50-75, 3	52*	89*	Dominated
FIT 55-85, 3	59*	75*	46
FIT 55-75, 2	Dominated	73*	Dominated
FIT 50-80, 3	57	73	826*
FIT 50-70, 2	Dominated	104*	Dominated
FIT 45-75, 3	84*	216*	Dominated
FIT 50-85, 3	59	85*	123*
FIT 55-80, 2	166*	82	122*
FIT 45-80, 3	167*	133*	Dominated
FIT 45-70, 2	Dominated	272*	Dominated
FIT 50-75, 2	Dominated	159*	Dominated
FIT 45-85, 3	75	99	Dominated
FIT 55-85, 2	151*	102*	86
FIT 55-70, 1	Dominated	210*	Dominated
FIT 50-80, 2	178*	110*	271*
FIT 45-75, 2	Dominated	116*	Dominated
FIT 50-85, 2	123*	115*	119
FIT 45-80, 2	115*	103	Dominated
FIT 55-75, 1	Dominated	186*	Dominated
FIT 45-85, 2	104	113	210*
FIT 55-80, 1	Dominated	Dominated	257*
FIT 50-75, 1	Dominated	1296*	Dominated
FIT 55-85, 1	Dominated	Dominated	171
FIT 45-70, 1	Dominated	934*	Dominated
FIT 50-80, 1	531*	317*	344*
FIT 45-75, 1	Dominated	249*	Dominated
FIT 50-85, 1	339*	282*	174
sDNA-FIT 45-80, 3	Dominated	369*	Dominated
FIT 45-80, 1	241*	217*	308*
sDNA-FIT 45-85, 3	Dominated	317*	Dominated
FIT 45-85, 1	223	216	294
sDNA-FIT 50-85, 2	Dominated	Dominated	466*
sDNA-FIT 45-75, 2	Dominated	335*	Dominated
sDNA-FIT 45-80, 2	390*	305*	Dominated
sDNA-FIT 45-85, 2	2427*	1019*	1049*

Appendix Table 13.7. Efficient FIT and sDNA-FIT Strategies, by Model and Benefit Variable (LYG, QALYG)

sDNA-FIT 50-80, 1	Dominated	Dominated	2068*
sDNA-FIT 50-85, 1	Dominated	Dominated	3337*
sDNA-FIT 45-75, 1	Dominated	1276*	Dominated
sDNA-FIT 45-80, 1	1384*	851*	2699*
sDNA-FIT 45-85, 1	1066	783	1295

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; CRC – colorectal cancer; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and averting the fewest colorectal cancer deaths).

***** Near efficient (i.e., within 0.75 colorectal cancer deaths averted per 1000 of the efficient frontier).

Appendix Table 13.8. Efficient Sigmoidoscopy Strategies With the Estimated Number of Colorectal Cancer Deaths Averted as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ CRC deaths averted)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
SIG 55-70, 10	--	--	--
SIG 55-75, 10	77*	103	89
SIG 50-70, 10	70	122	419*
SIG 45-70, 10	89*	301*	Dominated
SIG 55-85, 10	93*	226*	184*
SIG 55-70, 5	313*	460*	207*
SIG 50-80, 10	110*	154*	151*
SIG 55-75, 5	146*	448*	149*
SIG 45-75, 10	106	125	245*
SIG 50-70, 5	1415*	220*	221*
SIG 45-85, 10	185*	252	229*
SIG 55-80, 5	151*	Dominated	148
SIG 55-85, 5	Dominated	Dominated	301*
SIG 50-75, 5	153*	194*	350*
SIG 45-70, 5	171*	2946*	Dominated
SIG 50-80, 5	156*	726*	235
SIG 50-85, 5	170*	1530*	294
SIG 45-75, 5	144	323*	395*
SIG 45-80, 5	171	294	500*
SIG 45-85, 5	297	396	440

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; CRC – colorectal cancer; SIG – sigmoidoscopy; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and averting the fewest colorectal cancer deaths).

***** Near efficient (i.e., within 0.75 colorectal cancer deaths averted per 1000 of the efficient frontier).

Appendix Table 13.9. Efficient 10-Yearly Sigmoidoscopy Plus Interval FIT Strategies With the Estimated Number of Colorectal Cancer Deaths Averted as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ CRC deaths averted)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
SIG+FIT 55-70, 10_2	--	--	--
SIG+FIT 55-70, 10_1	Dominated	189*	162*
SIG+FIT 55-75, 10_2	91	135	89*
SIG+FIT 50-70, 10_2	101*	159*	Dominated
SIG+FIT 55-80, 10_2	112*	158*	88
SIG+FIT 50-75, 10_2	94	148	1234*
SIG+FIT 45-70, 10_2	Dominated	337*	Dominated
SIG+FIT 55-85, 10_2	161*	207*	162
SIG+FIT 55-75, 10_1	Dominated	279*	438*
SIG+FIT 50-70, 10_1	Dominated	458*	Dominated
SIG+FIT 50-80, 10_2	131	179*	195*
SIG+FIT 55-80, 10_1	Dominated	156027*	405*
SIG+FIT 50-85, 10_2	179*	186*	183
SIG+FIT 45-75, 10_2	170*	169*	475*
SIG+FIT 55-85, 10_1	Dominated	Dominated	258*
SIG+FIT 50-75, 10_1	Dominated	271*	634*
SIG+FIT 45-80, 10_2	147	168	342*
SIG+FIT 45-70, 10_1	Dominated	286*	Dominated
SIG+FIT 50-80, 10_1	Dominated	262*	369*
SIG+FIT 45-85, 10_2	211	290	476*
SIG+FIT 50-85, 10_1	336*	275*	312
SIG+FIT 45-75, 10_1	950*	1456*	1256*
SIG+FIT 45-80, 10_1	658*	504*	3232*
SIG+FIT 45-85, 10_1	488	455	522

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; CRC – colorectal cancer; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and averting the fewest colorectal cancer deaths).

***** Near efficient (i.e., within 0.75 colorectal cancer deaths averted per 1000 of the efficient frontier).

Appendix Table 13.10. Efficient Computed Tomographic Colonography Strategies With the Estimated Number of Colorectal Cancer Deaths Averted as the Measure of the Benefit of Screening, by Model

	Efficiency ratio (Δ COL / Δ CRC deaths averted)		
Strategy	**SimCRC**	**CRC-SPIN**	**MISCAN**
CTC 55-70, 10	--	--	--
CTC 55-75, 10	74*	90	45
CTC 50-70, 10	64	209*	Dominated
CTC 45-70, 10	Dominated	113*	Dominated
CTC 55-70, 5	Dominated	240*	587*
CTC 55-85, 10	Dominated	188*	77
CTC 50-80, 10	107*	127*	78*
CTC 55-75, 5	Dominated	161*	83*
CTC 45-75, 10	105	114	Dominated
CTC 50-70, 5	151*	156*	Dominated
CTC 55-80, 5	Dominated	167*	78
CTC 45-85, 10	186*	182	Dominated
CTC 55-85, 5	Dominated	178*	116
CTC 50-75, 5	207*	549*	Dominated
CTC 45-70, 5	276*	483*	Dominated
CTC 50-80, 5	193*	266*	212*
CTC 50-85, 5	207*	267*	171
CTC 45-75, 5	169*	210*	Dominated
CTC 45-80, 5	169	202	1355*
CTC 45-85, 5	324	281	325

Note: Strategies that were dominated in all 3 models are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

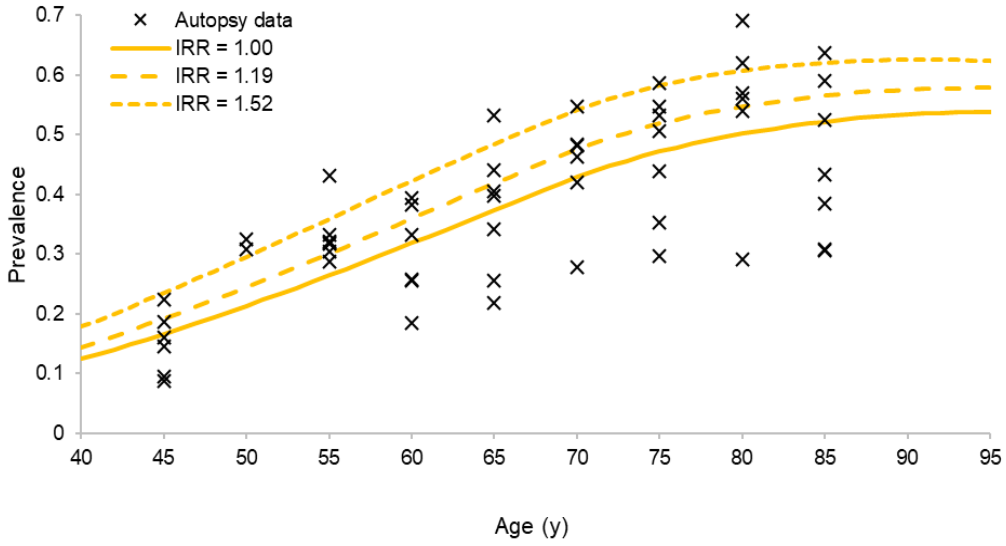
COL – colonoscopy; CRC – colorectal cancer; CTC – computed tomographic colonography; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and averting the fewest colorectal cancer deaths).

***** Near efficient (i.e., within 0.75 colorectal cancer deaths averted per 1000 of the efficient frontier).

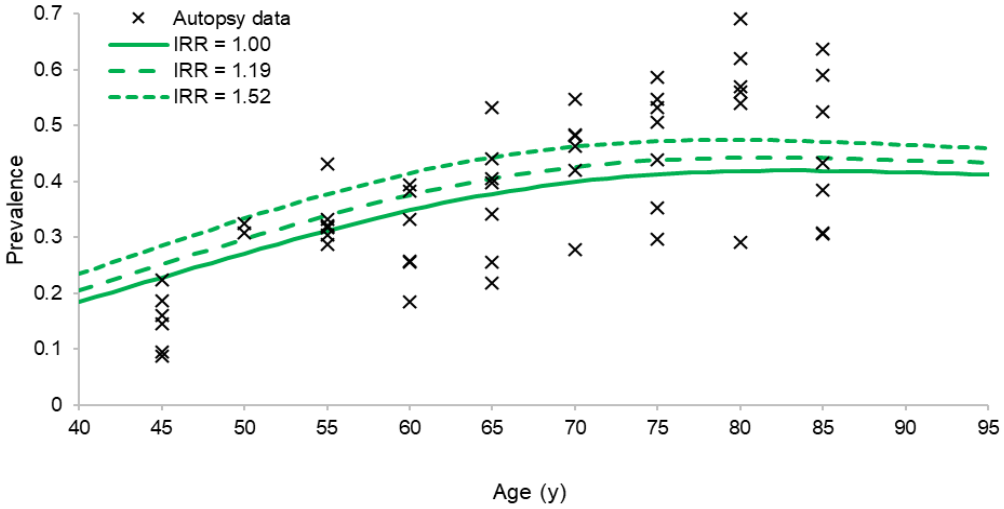
Appendix Figure 14.1 Prevalence of Adenomas by Age From Autopsy Studies and as Estimated by SimCRC, by Risk Scenario

Models were calibrated to 3 scenarios for colorectal cancer risk: IRR of 1.19 (base-case analysis), IRR of 1 (sensitivity analysis using original models calibrated to SEER data from 1975-1979), and IRR 1.52 (sensitivity analysis with higher increase in population risk). Increased colorectal cancer risk was simulated via increased risk of adenoma onset.

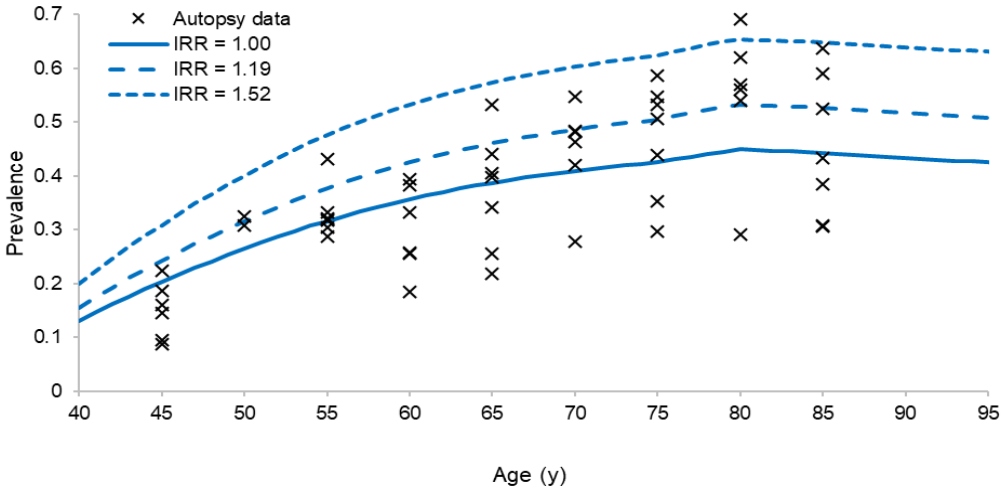
Estimated adenoma prevalence for these scenarios is shown in **Appendix Figure 14.1** for SimCRC, **Appendix Figure 14.2** for CRC-SPIN, and **Appendix Figure 14.3** for MISCAN.



Appendix Figure 14.2 Prevalence of Adenomas by Age From Autopsy Studies and as Estimated by CRC-SPIN, by Risk Scenario

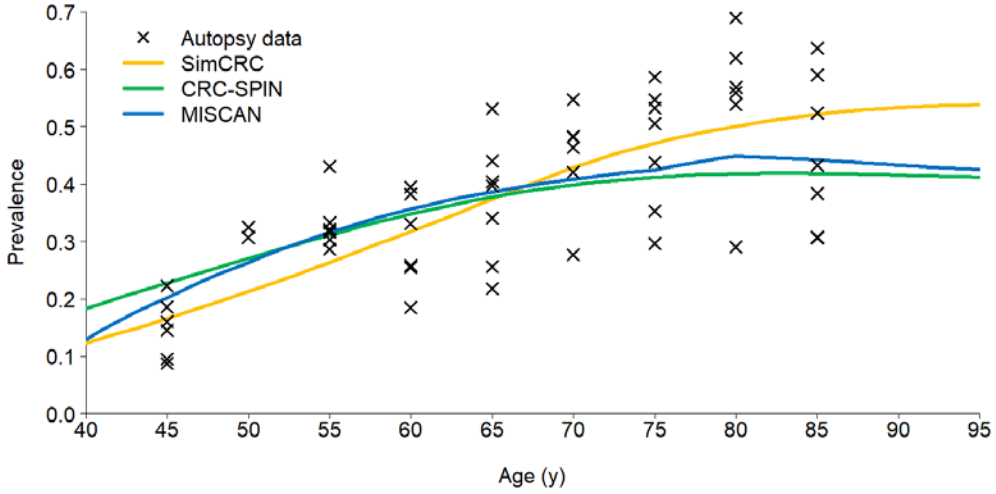


Appendix Figure 14.3 Prevalence of Adenomas by Age From Autopsy Studies and as Estimated by MISCAN, by Risk Scenario

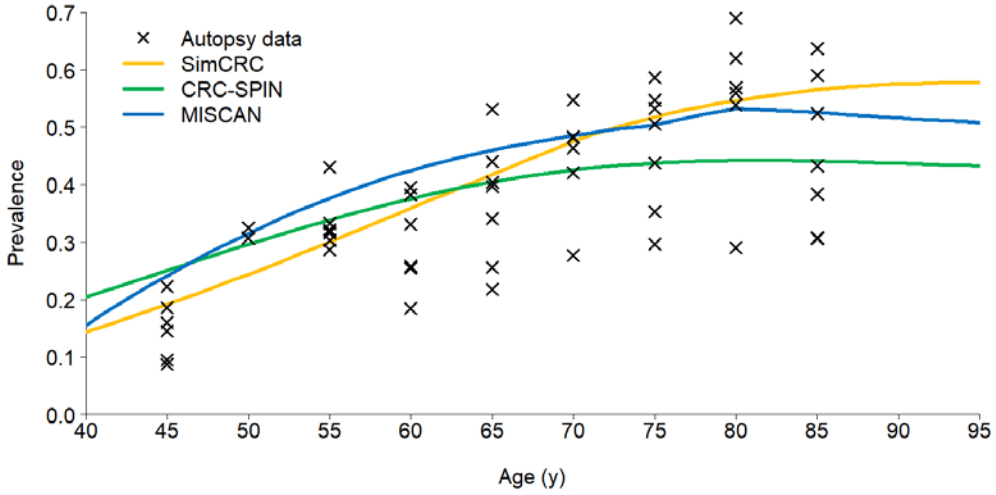


Appendix Figure 14.4 Prevalence of Adenomas by Age From Autopsy Studies and as Estimated by Models Calibrated to an IRR of 1, by Model

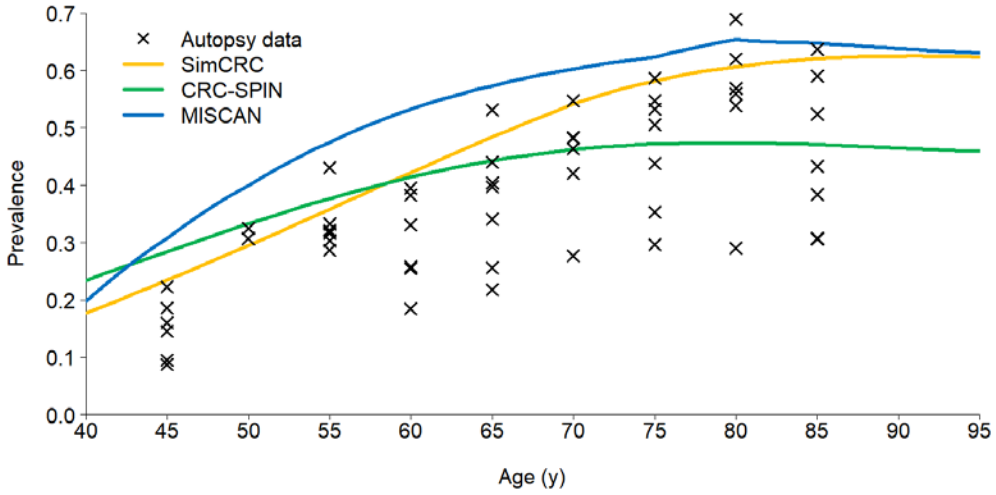
We also compare estimated prevalence across models for a given risk scenario. For the original models (IRR of 1), the comparison is in **Figure 2** but is repeated here for convenience (**Appendix Figure 14.4**); comparisons across models for IRR of 1.19 and 1.52 are in **Appendix Figures 14.5 and 14.6** below.



Appendix Figure 14.5 Prevalence of Adenomas by Age From Autopsy Studies and as Estimated by Models Calibrated to an IRR of 1.19, by Model

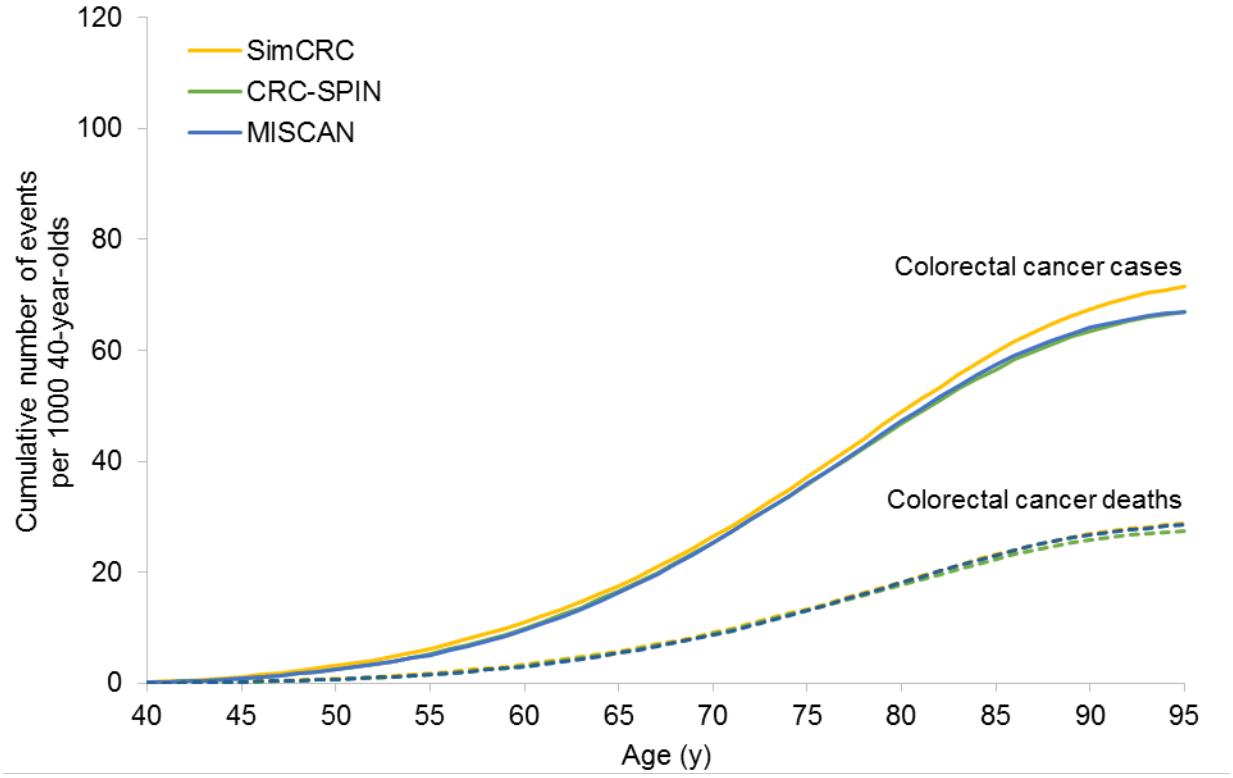


Appendix Figure 14.6 Prevalence of Adenomas by Age From Autopsy Studies and as Estimated by Models Calibrated to an IRR of 1.52, by Model

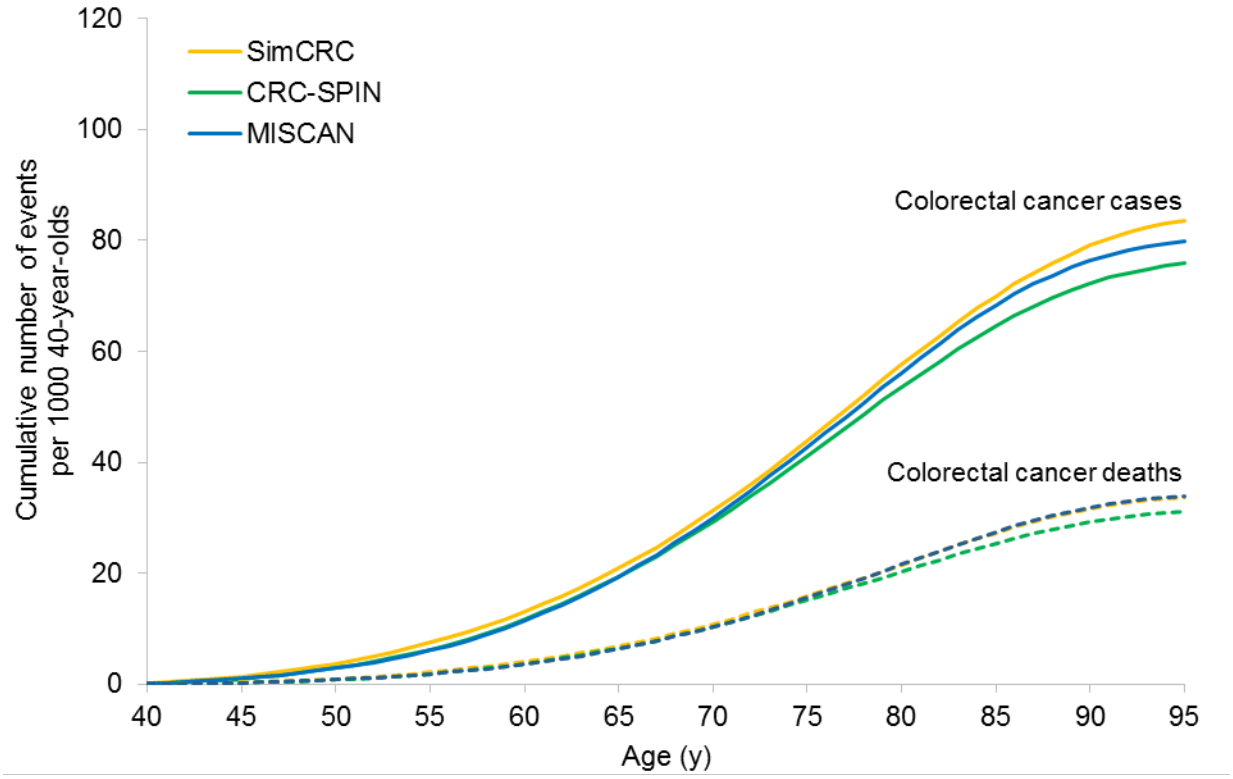


Appendix Figure 14.7 Estimated Cumulative Number of Colorectal Cancer Cases and of Colorectal Cancer Deaths per 1,000 Persons From Age 40 to Age 95 in the Absence of Screening, by Model Assuming IRR = 1

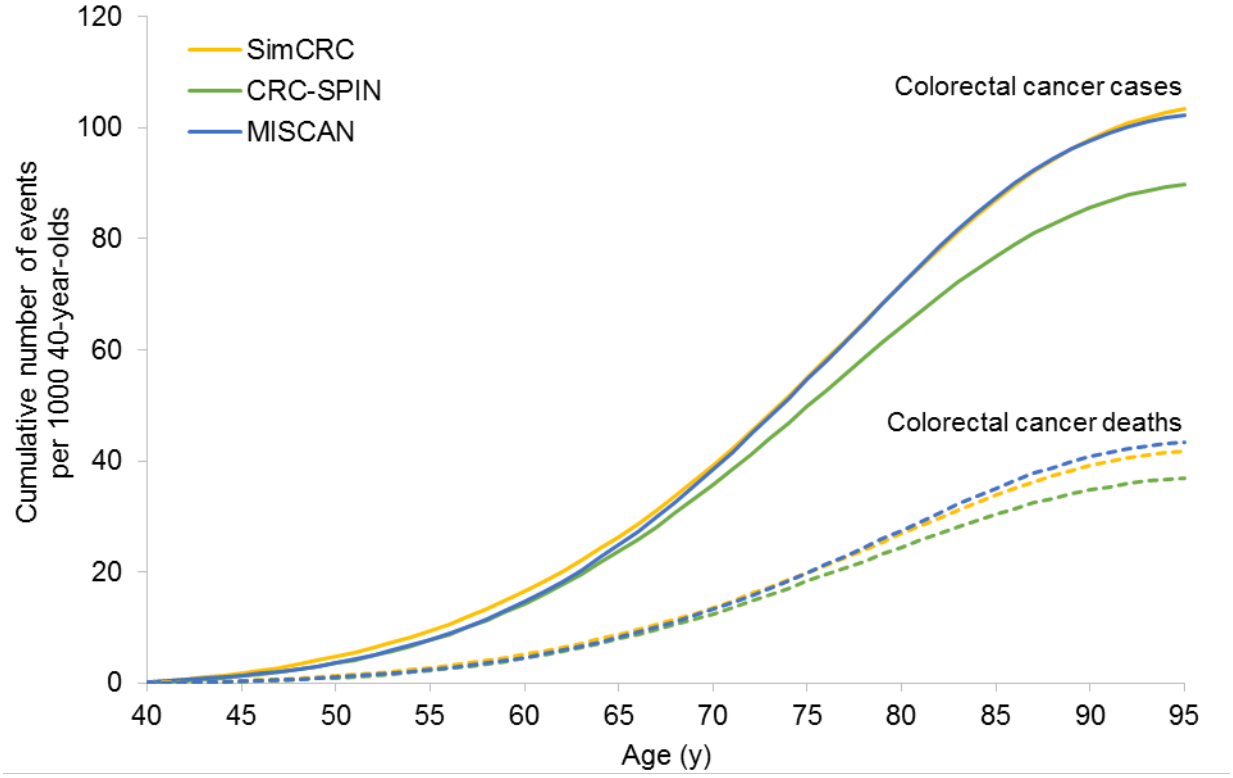
Finally, we also show how the estimated cumulative probability of being diagnosed with colorectal cancer and of dying from colorectal cancer from age 40 to age 95 in the absence of screening compares across models by risk scenario. For the original models (IRR of 1), the comparison is in **Figure 11** but is repeated here for convenience (**Appendix Figure 14.7**); comparisons across models for IRR of 1.19 and 1.52 are in **Appendix Figures 14.8 and 14.9** below.



Appendix Figure 14.8 Estimated Cumulative Number of Colorectal Cancer Cases and of Colorectal Cancer Deaths per 1,000 Persons From Age 40 to Age 95 in the Absence of Screening, by Model Assuming IRR = 1.19



Appendix Figure 14.9 Estimated Cumulative Number of Colorectal Cancer Cases and of Colorectal Cancer Deaths per 1,000 Persons From Age 40 to Age 95 in the Absence of Screening, by Model Assuming IRR = 1.52



Appendix Table 14.1a. Efficient Colonoscopy Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for SimCRC

Appendix Tables 14.1-14.7 show efficient screening strategies with estimated LYG as the measure of the benefit of screening, by IRR for each class of screening modality and model.

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
COL 55-70, 15	--	--	--
COL 50-70, 15	7*	6*	5*
COL 45-70, 15	6	6	5
COL 45-75, 15	44*	39*	33*
COL 45-70, 10	39	34	29
COL 45-75, 10	73	64	54
COL 45-85, 10	427*	394*	337*
COL 45-70, 5	213*	180*	140
COL 45-75, 5	208	178	141
COL 45-80, 5	496	428	376
COL 45-85, 5	1614	1445	1181

Note: Strategies that were dominated in all 3 risk scenarios are not shown.
COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.1b. Efficient Colonoscopy Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for CRC-SPIN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
COL 55-70, 15	--	--	-
COL 55-70, 10	17*	17*	15*
COL 50-70, 15	9*	8*	7*
COL 45-70, 15	8	7	7
COL 45-75, 15	68*	59*	54*
COL 45-70, 10	50	44	40
COL 45-75, 10	120	112	103
COL 45-85, 10	588*	828*	646*
COL 45-70, 5	211	179	147
COL 45-75, 5	367	344	306
COL 45-80, 5	860	736	768
COL 45-85, 5	2637	2190	2558

Note: Strategies that were dominated in all 3 risk scenarios are not shown.
COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.1c. Efficient Colonoscopy Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for MISCAN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
COL 55-70, 15	--	--	--
COL 55-70, 10	28*	22*	17*
COL 50-70, 15	19	18	15
COL 45-70, 15	126*	85*	77*
COL 50-80, 15	73*	56*	40*
COL 50-70, 10	35	28	20
COL 45-75, 15	48*	38*	30*
COL 45-70, 10	58	45	34
COL 50-80, 10	113*	86*	61*
COL 45-75, 10	65	52	36
COL 45-85, 10	314*	227*	160*
COL 50-70, 5	142*	120*	89*
COL 50-75, 5	373*	367*	Dominated
COL 45-70, 5	106	84	61
COL 45-75, 5	155	116	79
COL 45-80, 5	234	169	119
COL 45-85, 5	1245	926	585

Note: Strategies that were dominated in all 3 risk scenarios are not shown.
COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.2a. Efficient FIT and sDNA-FIT Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for SimCRC

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
FIT 55-70, 3	--	--	--
FIT 50-70, 3	3	2	2
FIT 45-70, 3	4	3	3
FIT 50-75, 3	5*	Dominated	Dominated
FIT 45-75, 3	6	5	5
FIT 45-80, 3	8	7*	7*
FIT 45-70, 2	15*	8*	7*
FIT 45-85, 3	14*	10*	9*
FIT 45-75, 2	8	7	6
FIT 45-80, 2	11	10	9
FIT 45-85, 2	20*	19*	18*
FIT 45-70, 1	25*	21*	18*
FIT 45-75, 1	18	16	14
FIT 45-80, 1	20	19	17
FIT 45-85, 1	44	39	36
sDNA-FIT 45-75, 2	104*	91*	64*
sDNA-FIT 45-80, 2	199*	176*	285*
sDNA-FIT 45-85, 2	190*	175*	106*
sDNA-FIT 45-70, 1	134*	116*	Dominated
sDNA-FIT 45-75, 1	117*	103*	75*
sDNA-FIT 45-80, 1	91	81	63
sDNA-FIT 45-85, 1	108	95	87

Note: Strategies that were dominated in all 3 risk scenarios are not shown.
COL – colonoscopy; LYG – life-years gained compared with no screening; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.2b. Efficient FIT and sDNA-FIT Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for CRC-SPIN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
FIT 55-70, 3	--	--	--
FIT 55-75, 3	7*	Dominated	Dominated
FIT 50-70, 3	4	4	4
FIT 55-70, 2	5*	Dominated	Dominated
FIT 50-75, 3	8*	Dominated	Dominated
FIT 45-70, 3	5	5	4
FIT 50-70, 2	16*	Dominated	Dominated
FIT 45-75, 3	8*	7*	7*
FIT 45-80, 3	9*	8*	8*
FIT 45-70, 2	7	7	6
FIT 45-75, 2	10	9	9
FIT 45-80, 2	16*	12	13*
FIT 45-85, 2	20*	25*	15*
FIT 45-70, 1	15	14	12
FIT 45-75, 1	17	16	15
sDNA-FIT 45-70, 2	69*	52*	53*
FIT 45-80, 1	30	27	24
FIT 45-85, 1	54	43	52*
sDNA-FIT 45-75, 2	83*	135*	253*
sDNA-FIT 45-80, 2	151*	75*	69*
sDNA-FIT 45-85, 2	107*	69*	67*
sDNA-FIT 45-70, 1	87*	62*	51*
sDNA-FIT 45-75, 1	64	53	44
sDNA-FIT 45-80, 1	69	62	60
sDNA-FIT 45-85, 1	131	111	101

Note: Strategies that were dominated in all 3 risk scenarios are not shown.
COL – colonoscopy; LYG – life-years gained compared with no screening; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.2c. Efficient FIT and sDNA-FIT Screening Strategies with Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for MISCAN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
FIT 55-70, 3	--	--	--
FIT 55-75, 3	5	5	4
FIT 50-70, 3	42*	6*	5*
FIT 55-70, 2	13*	13*	Dominated
FIT 55-80, 3	6*	6*	5*
FIT 50-75, 3	5	5	4
FIT 45-70, 3	7*	6*	5*
FIT 55-85, 3	8*	7*	Dominated
FIT 50-80, 3	7	6	5*
FIT 55-75, 2	16*	14*	Dominated
FIT 50-85, 3	11*	10*	6*
FIT 45-75, 3	7*	7*	5
FIT 50-70, 2	211*	94*	7*
FIT 55-80, 2	40*	Dominated	Dominated
FIT 45-80, 3	7	6	5
FIT 50-75, 2	11*	10*	10*
FIT 45-85, 3	10*	9*	8*
FIT 45-70, 2	14*	Dominated	Dominated
FIT 50-80, 2	9*	8	7*
FIT 50-85, 2	10*	12*	8*
FIT 45-75, 2	9*	9*	7*
FIT 45-80, 2	9	8	7
FIT 45-85, 2	14	12	10
FIT 50-75, 1	33*	29*	Dominated
FIT 45-70, 1	38*	Dominated	Dominated
FIT 50-80, 1	20*	18*	16*
FIT 50-85, 1	21*	18*	16*
FIT 45-75, 1	16*	15*	13*
FIT 45-80, 1	15	14	12
FIT 45-85, 1	23	19	15
sDNA-FIT 45-80, 2	31*	26*	Dominated
sDNA-FIT 45-85, 2	2580*	375*	350*
sDNA-FIT 45-75, 1	460*	251*	191*
sDNA-FIT 45-80, 1	141*	104*	85*
sDNA-FIT 45-85, 1	125	94	76

Note: Strategies that were dominated in all 3 risk scenarios are not shown.
COL – colonoscopy; LYG – life-years gained compared with no screening; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; sDNA-FIT – multitarget stool DNA test (stool DNA test with a fecal immunochemical test); -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.3a. Efficient Sigmoidoscopy Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for SimCRC

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
SIG 55-70, 10	--	--	--
SIG 45-70, 10	5	4	4
SIG 45-75, 10	15*	13*	12*
SIG 45-85, 10	19*	Dominated	Dominated
SIG 45-70, 5	12	11	10
SIG 45-75, 5	22	20	17
SIG 45-80, 5	41	38	34
SIG 45-85, 5	98	89	78

Note: Strategies that were dominated in all 3 risk scenarios are not shown.

COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

* Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.3b. Efficient Sigmoidoscopy Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for CRC-SPIN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
SIG 55-70, 10	--	--	--
SIG 45-70, 10	6	5	5
SIG 45-75, 10	18	18	17*
SIG 45-85, 10	74*	68*	21*
SIG 45-70, 5	23	20	16
SIG 45-75, 5	29	27	24
SIG 45-80, 5	51	49	45
SIG 45-85, 5	113	98	77

Note: Strategies that were dominated in all 3 risk scenarios are not shown.

COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.3c. Efficient Sigmoidoscopy Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for MISCAN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
SIG 55-70, 10	--	--	--
SIG 55-75, 10	16*	Dominated	Dominated
SIG 50-70, 10	9	8	7
SIG 55-70, 5	13*	11*	9*
SIG 45-70, 10	263*	73*	37*
SIG 50-80, 10	26*	22*	19*
SIG 55-75, 5	193*	Dominated	Dominated
SIG 45-75, 10	21*	18*	15*
SIG 50-70, 5	16	14	11
SIG 45-85, 10	25*	21*	Dominated
SIG 50-75, 5	23*	19*	16*
SIG 50-80, 5	27*	23*	19*
SIG 45-70, 5	17	15	12
SIG 50-85, 5	32*	26*	21*
SIG 45-75, 5	22	19	16
SIG 45-80, 5	36	29	24
SIG 45-85, 5	101	78	64

Note: Strategies that were dominated in all 3 risk scenarios are not shown.

COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.4a. Efficient 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for SimCRC

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
SIG+FIT 55-70, 10_2	--	--	--
SIG+FIT 50-70, 10_2	6*	6*	5*
SIG+FIT 45-70, 10_2	6	5	5
SIG+FIT 45-75, 10_2	16	15	14
SIG+FIT 45-80, 10_2	24	22	20
SIG+FIT 45-70, 10_1	25*	22*	19*
SIG+FIT 45-85, 10_2	58*	54*	48*
SIG+FIT 45-75, 10_1	39*	34	27
SIG+FIT 45-80, 10_1	39	35	32
SIG+FIT 45-85, 10_1	87	81	70

Note: Strategies that were dominated in all 3 risk scenarios are not shown.

COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.4b. Efficient 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for CRC-SPIN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
SIG+FIT 55-70, 10_2	--	--	--
SIG+FIT 50-70, 10_2	9*	8*	7*
SIG+FIT 45-70, 10_2	8	7	6
SIG+FIT 45-75, 10_2	22	22	19
SIG+FIT 45-80, 10_2	25	25	31*
SIG+FIT 45-70, 10_1	71*	88*	31*
SIG+FIT 45-85, 10_2	63*	78*	40*
SIG+FIT 45-75, 10_1	36	34	29
SIG+FIT 45-80, 10_1	47	53	42
SIG+FIT 45-85, 10_1	93	64	68

Note: Strategies that were dominated in all 3 risk scenarios are not shown.

COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.4c. Efficient 10-Yearly Sigmoidoscopy Plus Interval FIT Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for MISCAN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
SIG+FIT 55-70, 10_2	--	--	--
SIG+FIT 55-70, 10_1	17*	14*	11*
SIG+FIT 55-75, 10_2	15*	13*	Dominated
SIG+FIT 55-80, 10_2	15*	13*	Dominated
SIG+FIT 50-70, 10_2	10	9	7*
SIG+FIT 50-75, 10_2	11	9	7
SIG+FIT 45-70, 10_2	27*	24*	18*
SIG+FIT 50-70, 10_1	29*	24*	20*
SIG+FIT 50-80, 10_2	24*	20*	17*
SIG+FIT 50-85, 10_2	25*	21*	17*
SIG+FIT 50-75, 10_1	22*	18*	15*
SIG+FIT 45-75, 10_2	17*	15*	13*
SIG+FIT 45-80, 10_2	17	15	12
SIG+FIT 45-70, 10_1	22*	19*	14*
SIG+FIT 50-80, 10_1	24*	20*	16*
SIG+FIT 45-85, 10_2	45*	38*	31*
SIG+FIT 50-85, 10_1	26*	21*	17*
SIG+FIT 45-75, 10_1	26*	22*	16*
SIG+FIT 45-80, 10_1	25	21	16
SIG+FIT 45-85, 10_1	57	46	36

Note: Strategies that were dominated in all 3 risk scenarios are not shown.

COL – colonoscopy; LYG – life-years gained compared with no screening; SIG – sigmoidoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.5a. Efficient Computed Tomographic Colonography Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for SimCRC

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
CTC 55-70, 10	--	--	--
CTC 45-70, 10	4	4	3
CTC 45-75, 10	14*	13*	12*
CTC 45-85, 10	18*	Dominated	Dominated
CTC 45-70, 5	12	11	10
CTC 45-75, 5	21	19	18
CTC 45-80, 5	42	38	35
CTC 45-85, 5	102	104	85

Note: Strategies that were dominated in all 3 risk scenarios are not shown.

COL – colonoscopy; LYG – life-years gained compared with no screening; CTC – computed tomographic colonography; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.5b. Efficient Computed Tomographic Colonography Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for CRC-SPIN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
CTC 55-70, 10	--	--	--
CTC 45-70, 10	5	5	4
CTC 45-75, 10	15*	15*	13*
CTC 45-85, 10	19*	19*	17*
CTC 45-70, 5	14	13	12
CTC 45-75, 5	22	21	19
CTC 45-80, 5	39	37	32
CTC 45-85, 5	79	73	63

Note: Strategies that were dominated in all 3 risk scenarios are not shown.

COL – colonoscopy; LYG – life-years gained compared with no screening; CTC – computed tomographic colonography; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 14.5c. Efficient Computed Tomographic Colonography Screening Strategies With Estimated Life-Years Gained as the Measure of the Benefit of Screening, by IRR for MISCAN

	Efficiency ratio (Δ COL / Δ LYG)		
Strategy	**IRR = 1.0**	**IRR = 1.19**	**IRR = 1.52**
CTC 55-70, 10	--	--	--
CTC 55-75, 10	8*	Dominated	Dominated
CTC 50-70, 10	6	5	5
CTC 55-70, 5	9*	8*	7*
CTC 50-80, 10	11*	10*	8*
CTC 45-75, 10	14*	Dominated	Dominated
CTC 55-75, 5	10*	9*	7*
CTC 50-70, 5	9	8	6
CTC 55-80, 5	11*	10*	Dominated
CTC 50-75, 5	10	9	7
CTC 45-70, 5	17*	21*	12*
CTC 50-80, 5	16*	13*	11*
CTC 50-85, 5	20*	17*	14*
CTC 45-75, 5	12	11	8
CTC 45-80, 5	16	13	11
CTC 45-85, 5	37	32	25

Note: Strategies that were dominated in all 3 risk scenarios are not shown.
COL – colonoscopy; LYG – life-years gained compared with no screening; CTC – computed tomographic colonography; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).
***** Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

Appendix Table 15.1a. Efficient Colonoscopy Screening Strategies, by Values for Colonoscopy Sensitivity for SimCRC

	Efficiency ratio (Δ COL / Δ LYG), by values of COL sensitivity	
Strategy	**Base-case analysis**	**Sensitivity analysis†**
COL 55-70, 15	--	--
COL 50-70, 15	6*	6*
COL 45-70, 15	6	6
COL 45-75, 15	39*	38*
COL 45-70, 10	34	32
COL 45-75, 10	64	62
COL 45-85, 10	394*	357*
COL 45-70, 5	180*	141
COL 45-75, 5	178	161
COL 45-80, 5	428	398
COL 45-85, 5	1445	1324

Note: Strategies that were dominated in both scenarios are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

* Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

† Refer to **Table 7** for values used in the sensitivity analysis.

Appendix Table 15.1b. Efficient Colonoscopy Screening Strategies, by Values for Colonoscopy Sensitivity for CRC-SPIN

	Efficiency ratio (Δ COL / Δ LYG), by values of COL sensitivity	
Strategy	**Base-case analysis**	**Sensitivity analysis†**
COL 55-70, 15	--	--
COL 55-70, 10	17*	16*
COL 50-70, 15	8*	8*
COL 45-70, 15	7	7
COL 45-75, 15	59*	60*
COL 45-70, 10	44	44
COL 45-75, 10	112	108
COL 45-85, 10	828*	813*
COL 45-70, 5	179	161
COL 45-75, 5	344	349
COL 45-80, 5	736	663
COL 45-85, 5	2190	3491

Note: Strategies that were dominated in both scenarios are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

* Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

† Refer to **Table 7** for values used in the sensitivity analysis.

Appendix Table 15.1c. Efficient Colonoscopy Screening Strategies, by Values for Colonoscopy Sensitivity for MISCAN

	Efficiency ratio (Δ COL / Δ LYG), by values of COL sensitivity	
Strategy	**Base-case analysis**	**Sensitivity analysis†**
COL 55-70, 15	--	--
COL 55-70, 10	22*	21*
COL 50-70, 15	18	19
COL 45-70, 15	85*	169*
COL 50-80, 15	56*	54*
COL 50-70, 10	28	27
COL 45-75, 15	38*	39*
COL 45-70, 10	45	51*
COL 50-80, 10	86*	83*
COL 45-75, 10	52	50
COL 45-85, 10	227*	216*
COL 50-70, 5	120*	681*
COL 50-75, 5	367*	205*
COL 45-70, 5	84	79
COL 45-75, 5	116	111
COL 45-80, 5	169	166
COL 45-85, 5	926	822

Note: Strategies that were dominated in both scenarios are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

* Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

† Refer to **Table 7** for values used in the sensitivity analysis.

Appendix Table 15.2a. Efficient FIT Screening Strategies, by Values for Colonoscopy Sensitivity for SimCRC

	Efficiency ratio (Δ COL / Δ LYG), by values of COL sensitivity	
Strategy	**Base-case analysis**	**Sensitivity analysis†**
FIT 55-70, 3	--	--
FIT 50-70, 3	2	2
FIT 45-70, 3	3	3
FIT 45-75, 3	5	5
FIT 45-80, 3	7*	7
FIT 45-70, 2	8*	12*
FIT 45-85, 3	10*	13*
FIT 45-75, 2	7	7
FIT 45-80, 2	10	10
FIT 45-85, 2	19*	19*
FIT 45-70, 1	21*	24*
FIT 45-75, 1	16	17
FIT 45-80, 1	19	18
FIT 45-85, 1	39	38

Note: Strategies that were dominated in both scenarios are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

* Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

† Refer to **Table 7** for values used in the sensitivity analysis.

Appendix Table 15.2b. Efficient FIT Screening Strategies, by Values for Colonoscopy Sensitivity for CRC-SPIN

	Efficiency ratio (Δ COL / Δ LYG), by values of COL sensitivity	
Strategy	**Base-case analysis**	**Sensitivity analysis†**
FIT 55-70, 3	--	--
FIT 55-75, 3	Dominated	7*
FIT 50-70, 3	4	4
FIT 45-70, 3	5	5
FIT 45-75, 3	7*	8*
FIT 45-80, 3	8*	8*
FIT 45-70, 2	7	7
FIT 45-75, 2	9	10
FIT 45-80, 2	12	13
FIT 45-85, 2	25*	23*
FIT 45-70, 1	14	14
FIT 45-75, 1	16	16
FIT 45-80, 1	27	25
FIT 45-85, 1	43	45

Note: Strategies that were dominated in both scenarios are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

* Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

† Refer to **Table 7** for values used in the sensitivity analysis.

Appendix Table 15.2c. Efficient FIT Screening Strategies, by Values for Colonoscopy Sensitivity for MISCAN

	Efficiency ratio (Δ COL / Δ LYG), by values of COL sensitivity	
Strategy	**Base-case analysis**	**Sensitivity analysis†**
FIT 55-70, 3	--	--
FIT 55-75, 3	5	5
FIT 50-70, 3	6*	6*
FIT 55-70, 2	13*	14*
FIT 55-80, 3	6*	6*
FIT 50-75, 3	5	5
FIT 45-70, 3	6*	6*
FIT 55-85, 3	7*	7*
FIT 50-80, 3	6	6
FIT 55-75, 2	14*	14*
FIT 45-75, 3	7*	7*
FIT 50-85, 3	10*	10*
FIT 50-70, 2	94*	9*
FIT 45-80, 3	6	6
FIT 50-75, 2	10*	10*
FIT 45-85, 3	9*	9*
FIT 50-80, 2	8	8
FIT 50-85, 2	12*	12*
FIT 45-75, 2	9*	10*
FIT 45-80, 2	8	8
FIT 45-85, 2	12	12
FIT 50-75, 1	29*	32*
FIT 50-80, 1	18*	18*
FIT 50-85, 1	18*	18*
FIT 45-75, 1	15*	15*
FIT 45-80, 1	14	14
FIT 45-85, 1	19	19

Note: Strategies that were dominated in both scenarios are not shown. Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; LYG – life-years gained compared with no screening; -- indicates the default strategy (i.e., the strategy requiring the fewest colonoscopies and providing the fewest life-years gained).

* Near efficient (i.e., within 3 days of life gained per person of the efficient frontier).

† Refer to **Table 7** for values used in the sensitivity analysis.

Appendix Table 16.1. Illustration of the Changes in Estimated Outcomes From Adherence to Screening Initiation for Sample Strategies With Screening Beginning at Age 45, by Model*

The potential changes in outcomes with delayed screening initiation and with extended intervals (representing delays in repeat screening) are presented in **Tables 13 and 14**, relative to strategies with screening beginning at age 50. **Appendix Tables 16.1 and 16.2** show the changes for the same strategies, but with screening beginning at age 45.

Strategy by model	Outcomes and change in outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Colonoscopy (COL)										
SimCRC										
COL 45-75, 10	0	0	0	4212	16	14	3	369	347	135
Delay start by 5y	0	0	0	-798	-2	+4	+2	-34	-33	-12
Delay start by 10y	0	0	0	-1060	0	+8	+3	-72	-71	-26
CRC-SPIN										
COL 45-75, 10	0	0	0	4300	17	12	4	340	321	124
Delay start by 5y	0	0	0	-800	-2	+3	+1	-32	-30	-12
Delay start by 10y	0	0	0	-1085	-1	+7	+3	-62	-60	-23
MISCAN										
COL 45-75, 10	0	0	0	4232	15	34	8	301	272	110
Delay start by 5y	0	0	0	-756	-2	+2	+1	-16	-15	-6
Delay start by 10y	0	0	0	-1051	0	+3	+1	-38	-37	-14
Sigmoidoscopy (SIG)										
SimCRC										
SIG 45-75, 5	0	4846	0	1720	10	25	8	309	289	113
Delay start by 5y	0	-788	0	-176	0	+3	+1	-30	-29	-11
Delay start by 10y	0	-1543	0	-362	0	+8	+3	-67	-65	-24
CRC-SPIN										
SIG 45-75, 5	0	4935	0	1680	12	24	9	280	264	102
Delay start by 5y	0	-801	0	-170	0	+2	+1	-24	-22	-9
Delay start by 10y	0	-1571	0	-355	-1	+6	+2	-51	-49	-19
MISCAN										
SIG 45-75, 5	0	4389	0	2119	12	39	11	269	241	98
Delay start by 5y	0	-743	0	-192	0	+1	0	-13	-12	-5
Delay start by 10y	0	-1429	0	-407	0	+3	+1	-35	-34	-13

Appendix Table 16.1. Illustration of the Changes in Estimated Outcomes From Adherence to Screening Initiation for Sample Strategies With Screening Beginning at Age 45, by Model*

Sigmoidoscopy with interval fecal immunochemical testing (SIG+FIT)										
SimCRC										
SIG+FIT 45-75, 10_1	16648	2568	0	2102	11	18	4	363	338	133
Delay start by 5y	-3112	-469	0	-263	-1	+4	+1	-33	-32	-12
Delay start by 10y	-5997	-738	0	-453	0	+8	+3	-73	-71	-27
CRC-SPIN										
SIG+FIT 45-75, 10_1	16322	2525	0	2237	14	15	5	330	309	120
Delay start by 5y	-3018	-458	0	-265	0	+3	+1	-29	-27	-11
Delay start by 10y	-5846	-716	0	-496	-1	+7	+3	-61	-59	-22
MISCAN										
SIG+FIT 45-75, 10_1	15466	2393	0	2331	13	37	9	304	272	111
Delay start by 5y	-3109	-493	0	-284	-1	+2	+1	-17	-17	-6
Delay start by 10y	-5841	-662	0	-461	0	+3	+1	-41	-39	-15
Computed tomographic colonography (CTC)										
SimCRC										
CTC 45-75, 5	0	0	4804	1788	11	18	5	355	332	130
Delay start by 5y	0	0	-798	-164	0	+3	+1	-31	-30	-11
Delay start by 10y	0	0	-1559	-341	0	+8	+3	-72	-70	-26
CRC-SPIN										
CTC 45-75, 5	0	0	4893	1791	13	18	6	313	294	114
Delay start by 5y	0	0	-805	-165	0	+2	+1	-26	-24	-9
Delay start by 10y	0	0	-1573	-351	-1	+6	+2	-56	-54	-20
MISCAN										
CTC 45-75, 5	0	0	4881	1672	10	42	11	283	251	103
Delay start by 5y	0	0	-806	-153	0	+1	+0	-14	-14	-5
Delay start by 10y	0	0	-1572	-322	0	+3	+1	-38	-36	-14
Fecal immunochemical testing (FIT)										
SimCRC										
FIT 45-75, 1	19680	0	0	1602	10	26	6	348	321	127
Delay start by 5y	-3520	0	0	-179	0	+4	+1	-33	-32	-12
Delay start by 10y	-6889	0	0	-370	0	+9	+3	-74	-72	-27

Appendix Table 16.1. Illustration of the Changes in Estimated Outcomes From Adherence to Screening Initiation for Sample Strategies With Screening Beginning at Age 45, by Model*

CRC-SPIN										
FIT 45-75, 1	18950	0	0	1824	13	20	6	314	293	115
Delay start by 5y	-3387	0	0	-205	0	+3	+1	-29	-28	-11
Delay start by 10y	-6608	0	0	-430	-1	+8	+3	-64	-62	-23
MISCAN										
FIT 45-75, 1	19607	0	0	1620	10	46	10	291	256	106
Delay start by 5y	-3510	0	0	-175	0	+1	+1	-17	-16	-6
Delay start by 10y	-6849	0	0	-367	0	+4	+2	-45	-43	-16
Multitarget stool DNA test (sDNA-FIT), 1-year interval										
SimCRC										
sDNA-FIT 45-75, 1	13888	0	0	2462	12	19	4	363	337	133
Delay start by 5y	-2425	0	0	-305	0	+4	+1	-33	-32	-12
Delay start by 10y	-4717	0	0	-613	0	+9	+3	-74	-72	-27
CRC-SPIN										
sDNA-FIT 45-75, 1	13494	0	0	2617	14	15	5	331	309	121
Delay start by 5y	-2361	0	0	-322	0	+3	+1	-30	-28	-11
Delay start by 10y	-4583	0	0	-653	-1	+7	+3	-63	-61	-23
MISCAN										
sDNA-FIT 45-75, 1	13698	0	0	2515	12	38	9	306	272	112
Delay start by 5y	-2383	0	0	-305	0	+1	+1	-16	-15	-6
Delay start by 10y	-4608	0	0	-618	0	+4	+2	-43	-41	-16
Multitarget stool DNA test (sDNA-FIT), 3-year interval										
SimCRC										
sDNA-FIT 45-75, 3	7274	0	0	1582	9	30	7	335	308	122
Delay start by 5y	-1201	0	0	-177	0	+4	+1	-31	-30	-11
Delay start by 10y	-2545	0	0	-395	-1	+9	+4	-74	-71	-27
CRC-SPIN										
sDNA-FIT 45-75, 3	7105	0	0	1772	12	23	7	301	281	110
Delay start by 5y	-1166	0	0	-196	0	+3	+1	-30	-28	-11
Delay start by 10y	-2471	0	0	-440	-1	+9	+3	-64	-62	-23

Appendix Table 16.1. Illustration of the Changes in Estimated Outcomes From Adherence to Screening Initiation for Sample Strategies With Screening Beginning at Age 45, by Model*

MISCAN										
sDNA-FIT 45-75, 3	7204	0	0	1629	10	49	12	273	239	100
Delay start by 5y	-1199	0	0	-179	0	+1	+1	-16	-15	-6
Delay start by 10y	-2520	0	0	-397	-1	+4	+2	-44	-41	-16

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

***** These strategies were selected for illustration purposes. Inclusion in this table should not be interpreted as endorsement of these strategies.

† Includes deaths from complications of screening.

Appendix Table 16.2. Illustration of the Changes in Estimated Outcomes From Adherence to Repeat Screening for Sample Strategies With Screening Beginning at Age 45, by Model*

Strategy by model	Outcomes and change in outcomes per 1000 unscreened 40-year-olds free from diagnosed colorectal cancer									
	Stool tests	SIGs	CTCs	COLs	Compli-cations	CRC cases	CRC deaths†	LYG	QALYG	DLG
Colonoscopy (COL)										
SimCRC										
COL 45-75, 10	0	0	0	4212	16	14	3	369	347	135
Increase interval to 15y	0	0	0	-749	-1	+4	+1	-17	-16	-6
Once-only	0	0	0	-2526	-10	+32	+13	-123	-114	-45
CRC-SPIN										
COL 45-75, 10	0	0	0	4300	17	12	4	340	321	124
Increase interval to 15y	0	0	0	-743	-1	+2	+1	-13	-12	-5
Once-only	0	0	0	-2418	-8	+22	+9	-84	-79	-31
MISCAN										
COL 45-75, 10	0	0	0	4232	15	34	8	301	272	110
Increase interval to 15y	0	0	0	-699	-1	+3	+1	-20	-19	-7
Once-only	0	0	0	-2372	-9	+24	+13	-134	-119	-49
Sigmoidoscopy (SIG)										
SimCRC										
SIG 45-75, 5	0	4846	0	1720	10	25	8	309	289	113
Increase interval to 10y	0	-1672	0	-360	-1	+7	+2	-31	-30	-11
Once-only	0	-3858	0	-1220	-7	+39	+17	-171	-158	-62
CRC-SPIN										
SIG 45-75, 5	0	4935	0	1680	12	24	9	280	264	102
Increase interval to 10y	0	-1765	0	-269	0	+2	+1	-12	-12	-4
Once-only	0	-3946	0	-1029	-6	+27	+12	-115	-107	-42
MISCAN										
SIG 45-75, 5	0	4389	0	2119	12	39	11	269	241	98
Increase interval to 10y	0	-1443	0	-318	0	+4	+2	-23	-22	-9
Once-only	0	-3400	0	-1350	-7	+27	+15	-162	-144	-59

Appendix Table 16.2. Illustration of the Changes in Estimated Outcomes From Adherence to Repeat Screening for Sample Strategies With Screening Beginning at Age 45, by Model*

Sigmoidoscopy with interval fecal immunochemical testing (SIG+FIT)										
SimCRC										
SIG+FIT 45-75, 10_1	16648	2568	0	2102	11	18	4	363	338	133
Increase FIT interval to 2y	-6712	+189	0	-267	-1	+3	+1	-9	-9	-3
CRC-SPIN										
SIG+FIT 45-75, 10_1	16322	2525	0	2237	14	15	5	330	309	120
Increase FIT interval to 2y	-6509	+192	0	-282	-1	+2	+1	-9	-8	-3
MISCAN										
SIG+FIT 45-75, 10_1	15466	2393	0	2331	13	37	9	304	272	111
Increase FIT interval to 2y	-6348	+200	0	-201	0	+2	+1	-10	-9	-4
Computed tomographic colonography (CTC)										
SimCRC										
CTC 45-75, 5	0	0	4804	1788	11	18	5	355	332	130
Increase interval to 10y	0	0	-1664	-329	-1	+6	+2	-27	-27	-10
CRC-SPIN										
CTC 45-75, 5	0	0	4893	1791	13	18	6	313	294	114
Increase interval to 10y	0	0	-1714	-327	-1	+4	+2	-24	-22	-9
MISCAN										
CTC 45-75, 5	0	0	4881	1672	10	42	11	283	251	103
Increase interval to 10y	0	0	-1717	-356	-1	+8	+3	-48	-46	-18
Fecal immunochemical testing (FIT)										
SimCRC										
FIT 45-75, 1	19680	0	0	1602	10	26	6	348	321	127
Increase interval to 2y	-7949	0	0	-455	-2	+11	+3	-31	-32	-11
Increase interval to 3y	-11205	0	0	-685	-3	+19	+5	-63	-63	-23
CRC-SPIN										
FIT 45-75, 1	18950	0	0	1824	13	20	6	314	293	115
Increase interval to 2y	-7530	0	0	-463	-2	+8	+3	-33	-32	-12
Increase interval to 3y	-10650	0	0	-714	-3	+15	+5	-66	-63	-24

Appendix Table 16.2. Illustration of the Changes in Estimated Outcomes From Adherence to Repeat Screening for Sample Strategies With Screening Beginning at Age 45, by Model*

MISCAN										
FIT 45-75, 1	19607	0	0	1620	10	46	10	291	256	106
Increase interval to 2y	-7935	0	0	-448	-2	+9	+3	-36	-36	-13
Increase interval to 3y	-11170	0	0	-672	-3	+14	+5	-66	-64	-24
Multitarget stool DNA test (sDNA-FIT)										
SimCRC										
sDNA-FIT 45-75, 1	13888	0	0	2462	12	19	4	363	337	133
Increase interval to 2y	-4345	0	0	-552	-1	+6	+1	-11	-12	-4
Increase interval to 3y	-6614	0	0	-880	-2	+11	+3	-28	-29	-10
CRC-SPIN										
sDNA-FIT 45-75, 1	13494	0	0	2617	14	15	5	331	309	121
Increase interval to 2y	-4196	0	0	-528	-1	+4	+1	-12	-12	-4
Increase interval to 3y	-6389	0	0	-845	-2	+8	+2	-30	-28	-11
MISCAN										
sDNA-FIT 45-75, 1	13698	0	0	2515	12	38	9	306	272	112
Increase interval to 2y	-4263	0	0	-561	-1	+5	+1	-14	-15	-5
Increase interval to 3y	-6494	0	0	-887	-2	+10	+3	-33	-34	-12

Note: Analyses assume an increased population risk of colorectal cancer based on an incidence rate ratio comparing colorectal cancer incidence among 20- to 44-year-olds in 2012-2016 vs 1975-1979 of 1.19.

COL – colonoscopy; SIG – sigmoidoscopy; CTC – computed tomographic colonography; CRC – colorectal cancer; LYG – life-years gained compared with no screening; QALYG – quality-adjusted life-years gained compared with no screening; DLG – days of life gained per person, compared with no screening.

***** These strategies were selected for illustration purposes. Inclusion in this table should not be interpreted as endorsement of these strategies.

† Includes deaths from complications of screening.

Appendix Table 17.1. Summary of Differences Between Base-Case Analyses for the 2021 Decision Analysis for the USPSTF and for the 2018 Decision Analyses for the ACS[27,28]

Characteristics	2021 USPSTF analysis	2018 ACS analysis I[22]	2018 ACS analysis II[23]
Simulation models	MISCAN, SimCRC and CRC-SPIN	MISCAN	MISCAN and SimCRC
Cohort of interest	All 40-year-old adults at average risk of CRC	All 40-year-old adults at average risk of CRC	Race- and sex-specific 40-year-old adults at average risk of CRC
US life table (for other-cause mortality rates)	2017	2013	2013
CRC incidence	Models calibrated to incidence rate ratio from SEER for 20- to 44-year-olds in 2012-2016 vs 1975-1979 (IRR = 1.19)	Models calibrated to results from age-period-cohort modeling (IRR = 1.59)	1. Models calibrated to race- and sex-specific incidence in SEER 1975-1979 (SimCRC) and SEER 1990-1994 (MISCAN) 2. Race- and sex-specific results from age-period-cohort modeling
CRC localization	Models calibrated to localization in SEER 1975-1979	Models calibrated to localization in SEER 1975 birth cohort	1. Models calibrated to same sources as CRC risk 2. Models calibrated to localization in SEER 1975 birth cohort
Evaluated screening modalities	Single, hybrid and once-only test strategies	Single test strategies only	Single test strategies only
Age to begin screening (y)	45, 50, 55	40, 45, 50	45, 50, 55
Age to end screening (y)	70, 75, 80, 85	75, 80, 85	75, 80, 85
Selection of model-recommendable strategies (Yes/No)	No	Yes	Yes