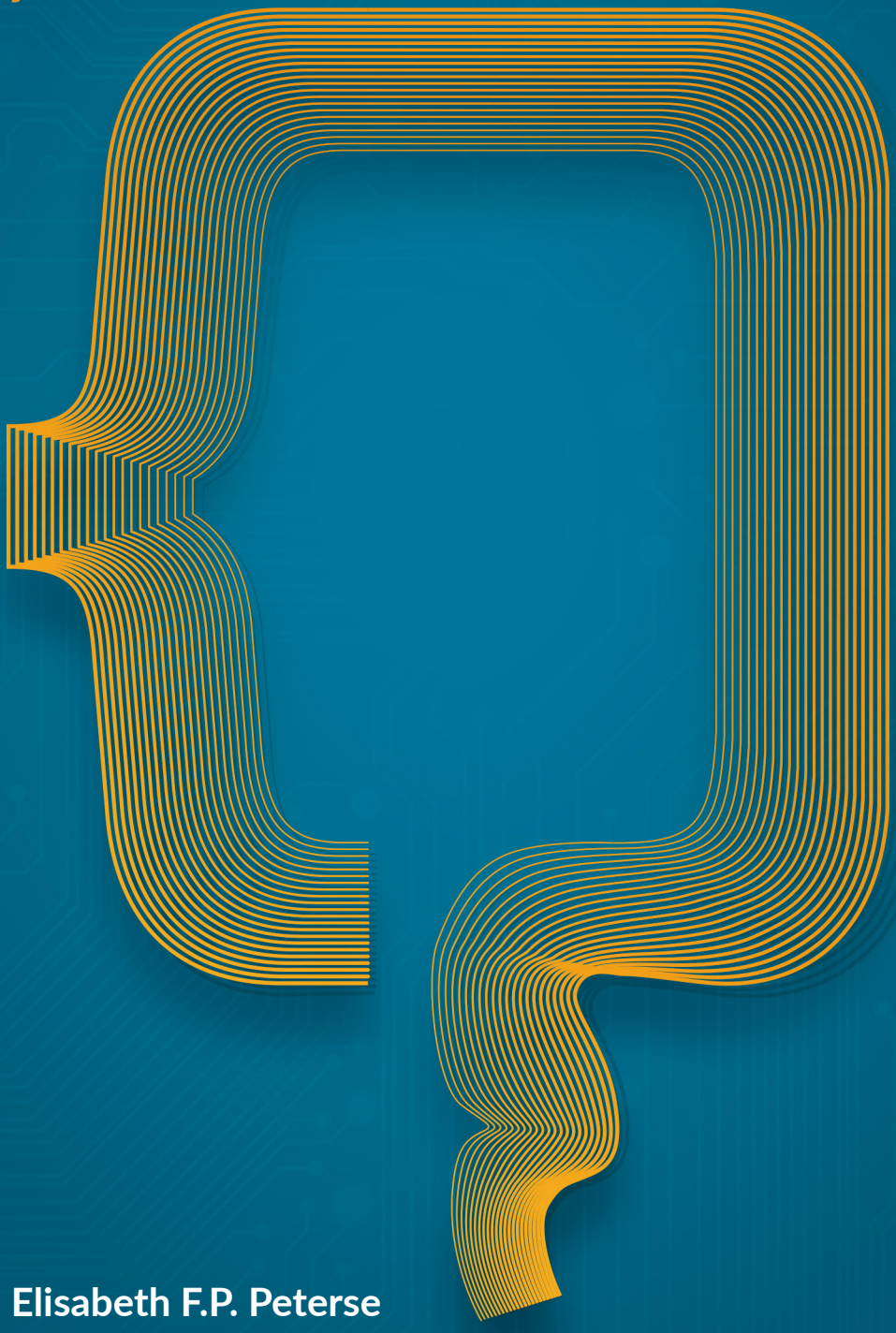
{ SIMULATING POPULATION-LEVEL EFFECTS OF COLORECTAL CANCER SCREENING POLICIES }



Elisabeth F.P. Peterse

Simulating Population-Level Effects of Colorectal Cancer Screening Policies

Elisabeth Francisca Patricia Peterse

Simulating Population-Level Effects of Colorectal Cancer Screening Policies
Elisabeth F. P. Peterse
Doctoral thesis, Erasmus University Rotterdam, the Netherlands

This thesis was financially supported by the Department of Public Health, Erasmus MC.

ISBN: 978-94-6332-731-8
Layout and printing: GVO drukkers & vormgevers
Cover design: RAUW Grafisch Design | Sem Henneman

©Elisabeth F. P. Peterse, 2021
All right reserved. No part of this thesis may be reproduced in any form, by print, photocopy, digital file, internet or any other means without permission from the author or the copyright-owning journals for previously published chapters.

Simulating Population-Level Effects of Colorectal Cancer Screening Policies

Simulatie van de effecten van darmkankerscreeningsbeleid op populatieniveau

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. F.A. van der Duijn Schouten

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on

Wednesday 20 January 2021 at 11.30 hrs
by

Elisabeth Francisca Patricia Peterse
born in Diessen, the Netherlands.

Erasmus University Rotterdam

Doctoral Committee:

Promotor:	prof. dr. H.J. de Koning
Other members:	prof. dr. P. Devilee prof. dr. B.W. Koes prof. dr. M.C.W. Spaander
Copromotors:	dr. I. Lansdorp – Vogelaar dr. R.G.S. Meester

Table of contents

Chapter 1

Introduction

Colorectal cancer

Colorectal cancer incidence

Colorectal cancer (CRC), including cancer of the colon and rectum, is a major public health concern for many countries worldwide. With an estimated 1.8 million new cases each year globally, it is the third most common malignancy in men and women combined.[1] Although CRC was primarily occurring in developed countries, incidence is rising rapidly in countries undergoing economic development, which can be explained by changes in diet and lifestyle.[2] Due to these changes in diet and lifestyle, and the increasing life expectancy, it is expected that CRC incidence will keep on increasing, with an estimated 2.2 million new cases globally in 2030.[2] The majority of studies presented in this thesis focus on the US. In the US, approximately 148 thousand individuals are projected to be diagnosed with CRC in 2020, accounting for 8.3% of all cancer diagnoses.[3] Approximately 4.2% of the population will be diagnosed with CRC at some point during their lifetime. The incidence and mortality of CRC increases with age (Figure 1.1), with the median age at diagnosis being 67 years in the US.[4]

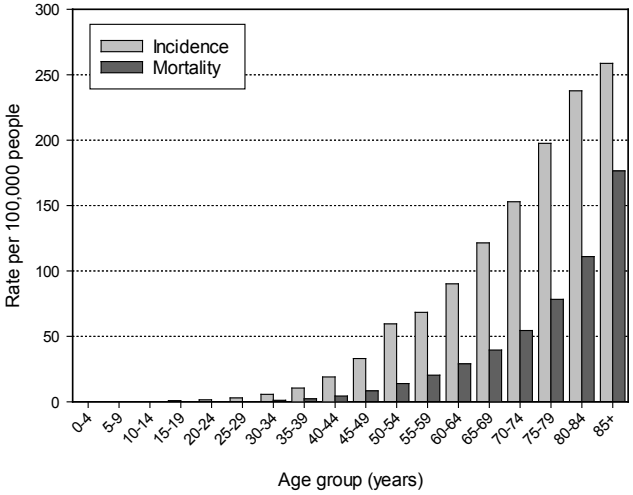


Figure 1.1: Colorectal cancer incidence and mortality rates per 100,000 individuals in the United States (2012-2016) by 5-year age groups.[5]

Colorectal cancer mortality and survival

CRC is not only a major cause of morbidity, but also of mortality. It is estimated that approximately 52 thousand individuals will die of CRC in the US in 2020. Off all cancer types, CRC is second only to lung cancer in terms of the numbers of cancer deaths in men and women combined.[3] Survival of CRC strongly depends on the stage of diagnosis (Figure 1.2A), which is determined by the Tumor-Node-Metastasis (TNM) classification.[6] In stage 0, the cancer cells have only invaded the mucosa (inner lining) of

the colon or rectum, and is therefore also called carcinoma in situ. In stage 1, the cancer cells also invaded the muscular layer of the colon or rectum. In stage 2, the cancer has grown passed the colon wall. When the cancer has invaded the local lymph nodes or has spread to other organs in the body such as the liver or lungs, it is classified as a stage 3 or stage 4 cancer, respectively. Symptomatically, the majority of CRCs are detected in stage 3 or 4 (**Figure 1.2B**). The later the disease is diagnosed, the more difficult it is to treat the disease. In the US, the 5-year relative survival of CRC ranges from 88% for stage 1 cancers to 13% for stage 4 cancers.[5]

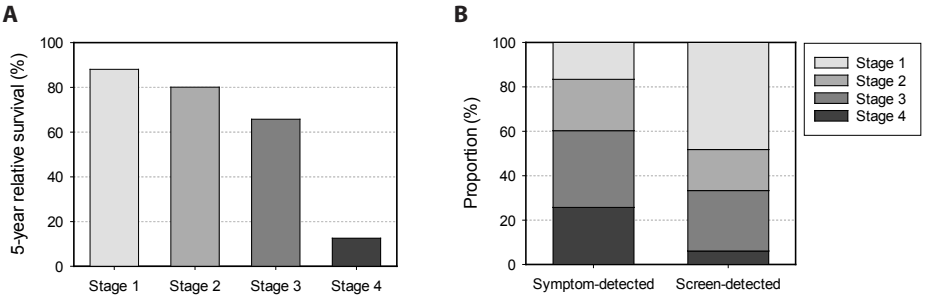


Figure 1.2: Colorectal survival by stage, and stage distribution upon diagnosis. **A:** 5-year relative survival by stage of colorectal cancer diagnosis in the United States, 2007-2013.[7] **B:** Stage distribution by symptom-detected and screen-detected colorectal cancers in the Netherlands, 2015, ages 60-75 years.[8]

Trends in colorectal cancer incidence and mortality

There is an alarming global increase in CRC incidence observed in individuals below age 50 years.[9-14] Although overall CRC incidence and mortality has declined for several decades in the US,[15] CRC incidence increased by over 25% since the mid-1990s in individuals below age 50 years.[15-21] Physicians have been called to look out for symptoms to enhance earlier diagnosis, but actual trends suggest that there is currently a shift toward later stage at diagnosis in those aged 40 through 49 compared to the 1990s.[22] Age-period-cohort modeling suggests that the increase in CRC cases observed in young adults is primarily driven by a cohort effect, where age-specific CRC risk for successive generations has been increasing compared to those born in the 1940s (**Figure 1.3**).[16] This implies that increasing incidence is not restricted to the young ages, but is carried forward with contemporary birth cohorts as they age. Compared with US citizens born in 1950, those born in 1990 have 2.4 times the risk to develop colon cancer, and 4.3 times the risk to develop rectal cancer (**Figure 1.3**).[16] Interestingly, for unknown reasons, the increase is stronger in rectal than in colon cancers in the US,[16] whereas in most of Europe, the increase is stronger in colon than in rectal cancers.[12] What is causing the troubling rise in CRC among young adults is currently unknown, which is therefore evaluated in many ongoing studies.

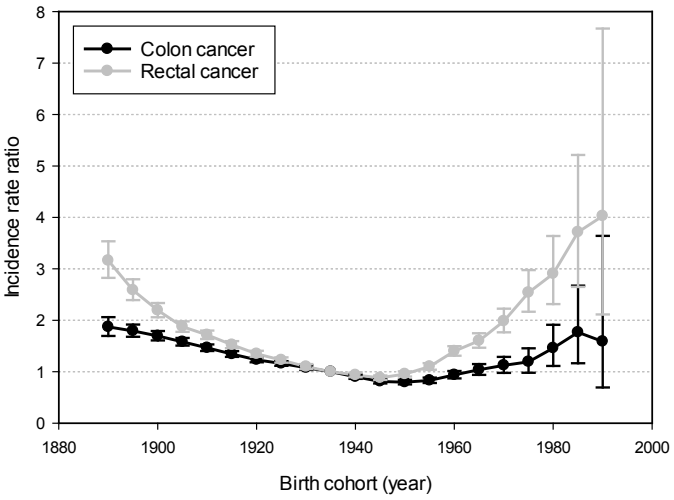


Figure 1.3: Incidence rate ratios by birth cohort compared to the 1935 birth cohort for colon and rectal cancer in the Unites States, obtained by age-period-cohort modeling.[16]

Risk factors for colorectal cancer

Risk factors for CRC can be divided into non-modifiable risk factors, modifiable risk factors and medical conditions (Table 1.1). In addition to age, important non-modifiable risk factors are sex, race/ethnicity, and family history. CRC incidence rates are approximately 30% higher in men compared to women, and rates in blacks are 20% higher than in whites and 50% higher than in Asians.[23] Underlying causes for the discrepancies in incidence rates by sex and ethnicity are not fully understood, but the discrepancies can be partly explained by a different exposure to modifiable risk factors. Alcohol consumption, obesity, red- and processed meat consumption, and smoking are modifiable risk factors that increase CRC risk. On the other hand, physical activity, aspirin and dairy- and milk consumption decrease CRC risk. Medical conditions that increase the risk of CRC are inflammatory bowel disease and diabetes, which have relative risks of 1.7 and 1.3, respectively.[23]

Familial colorectal cancer

Up to 30% of CRC cases have relatives that are affected by the disease. Only about 5% of all CRC cases have a hereditary cancer syndrome, caused by a well-characterized germline mutation in a high-penetrance gene.[35] Asymptomatic individuals with a hereditary cancer syndrome can be identified through a process called cascade testing: when a pathogenic germline mutation is identified in a CRC case, genetic testing can be extended to his/her relatives. Lynch syndrome, also called Hereditary Nonpolyposis Colorectal Cancer, is caused by a germline mutation in one of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2* or *EPCAM*). It is the most common familial syndrome, accounting for approximately 3% of all CRC cases.[36] Individuals with Lynch syndrome have an approximate 35% risk of developing CRC before the age of 70 years.[37] Another

hereditary syndrome is Familial Adenomatous Polyposis (FAP), which is characterized by germline mutations of the tumor suppressor gene *APC*. Patients with FAP typically present with hundreds to thousands adenomas, resulting in a lifetime risk to develop CRC of nearly 100%. It accounts for less than 1% of all CRC cases. Other, even more rare familial syndromes are familial CRC type X, MutYH-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome and PTEN hamartomatous syndrome.[35] Serrated polyposis syndrome, previously considered to be uncommon, is now known to be the most common polyposis syndrome.[38] However, the majority of patients have no family history of CRC. Patients present with numerous serrated polyps, which is the basis of their diagnosis as no genetic mutations have been identified.[38] Even family members of individuals diagnosed with CRC that do not have one of these syndromes have an increased risk to develop CRC, for whom risk depends on the number and the age of the affected relatives (Table 1.1).

Table 1.1: Risk factors for colorectal cancer.[23]

Risk factor	Relative risk	Source
Non-modifiable risk factors		
Age	Age specific (Figure 1.1)	USCSWG [5]
Sex		ACS [23]
Women	1	
Men	1.3	
Race		ACS [23]
Whites	1	
Blacks	1.2	
Asians	0.8	
Family history		
1 first-degree relative	2.2	Butterworth *et al*. [24]
Relative with diagnoses < age 45	3.9	Johns *et al*. [25]
≥2 relatives	4.0	Butterworth *et al*. [24]
Modifiable risk factors		
Alcohol consumption (daily average)		Bagnardi *et al*. [26]
2-3 drinks	1.2	
>3 drinks	1.4	
Obesity (body mass index ≥30 kg/m^2)	1.3	Ma *et al*. [27]
Red meat consumption (100g/day)	1.2	Chan *et al*. [28]
Processed meat consumption (50g/day)	1.2	Chan *et al*. [28]
Smoking (ever vs. never)	1.2	Botteri *et al*. [29]
Physical activity	0.7	Boyle *et al*. [30]
Dairy consumption (400g/day)	0.8	Aune *et al*. [31]
Milk consumption (200g/day)	0.9	Aune *et al*. [31]
Aspirin usage (>75mg/day)	0.8	Rothwell *et al*. [32]
Medical conditions		
Inflammatory bowel disease	1.7	Lutgens *et al*. [33]
Diabetes	1.3	Tsilidis *et al*. [34]

ACS - American Cancer Society; USCSWG - US Cancer Statistics Working Group

Colorectal carcinogenesis

Most CRCs originate from benign precursor lesions in the inner lining of the colon or rectum. Two carcinogenic pathways have been distinguished: the adenoma-carcinoma sequence and the serrated pathway. These multistep processes differ in histological, morphological and genetic changes that occur during carcinoma genesis (**Figure 1.4**). In the conventional pathway, which gives rise to the large majority of the CRCs, the benign precursor lesion is an adenomatous polyp, also called an adenoma. Approximately 30-50% of individuals develop one or more adenomas throughout their life, of which the large majority remains benign. However, when a small adenoma progresses, it grows in size and malignant potential. An adenoma that is larger than 10 mm in size has high-grade dysplasia or has a ≥ 25% villous histology component is called an advanced adenoma. Subsequently, these advanced adenomas can progress into Stage 1 to Stage 4 CRCs by acquiring several somatic mutations.[39] It has been estimated that the average time from adenoma onset to clinical diagnosis of the cancer is approximately 20 years.[40]

The second pathway, the serrated pathway, may account for up to one-third of all CRCs.[41] Sessile serrated lesions (which can progress to cancer), can originate directly from normal mucosa or originate via a precursor lesion called the hyperplastic polyp. The hyperplastic polyp is characterized histologically by a serrated (or saw-toothed) appearance of the crypt epithelium.[41] These lesions tend to have a flatter shape than conventional adenomas, and have a mucus cap, making them harder to detect endoscopically. There is great uncertainty regarding the progression risk of sessile serrated lesions. They were barely reported before the 4th WHO classification of tumors was released in 2010.[42] Consequently, the natural history of sessile serrated lesions remains largely to be discovered. Initially, they were believed to have a larger malignant potential compared to adenomatous polyp.[43-45] However, reports of increased risk may be due to the misclassification of sessile serrated lesions and the higher endoscopic miss rate of these lesions compared to adenomatous polyps.[46-48]

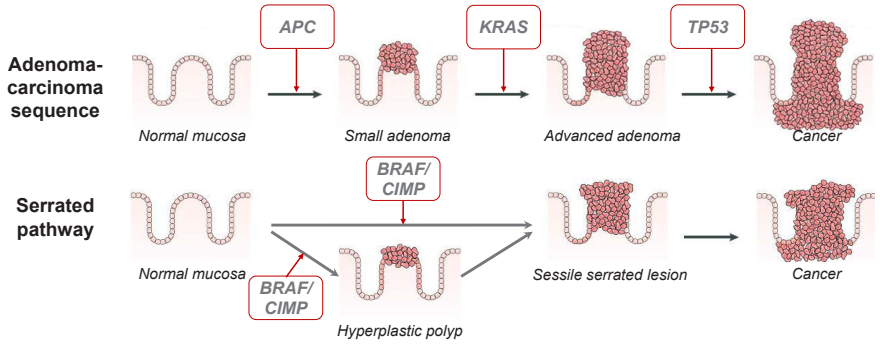


Figure 1.4: Schematic overview of the colorectal carcinogenic pathways, [39,41,49] adapted from Keum *et al.*[50]

APC, KRAS, TP53, BRAF, MLH1 - somatic mutations; CIMP - CPG island methylator phenotype; MSI - microsatellite instability

Colorectal cancer screening

Principle of screening

With screening, an apparently healthy, asymptomatic population is systematically tested for disease or for risk factors associated with the disease. The aim of screening is to detect the disease in an earlier stage, providing the opportunity to act earlier. As survival for cancers is often better when diagnosed in an earlier stage, screening is a suitable method to decrease cancer morbidity and mortality. CRC is a very good candidate for screening due to its occurrence of a benign precursor lesion, the relative long period between disease onset and malignancy,[40] and its good prognosis when diagnosed in an early stage (**Figure 1.2A**). CRC screening decreases CRC mortality in two ways: it improves the survival of CRC cases by earlier diagnosis, and it can prevent CRC cases by the removal of adenomas (CRC precursor lesions). Evidence for the effectiveness of CRC screening comes from studies showing a CRC stage shift (**Figure 1.2B**),[8] numerous clinical trials,[51-62] and observational studies.[63-66]

Colorectal cancer screening tests

Many different CRC screening tests have been developed. They can be divided into three groups. The first group consists of the direct visualization tests, namely colonoscopy, flexible sigmoidoscopy, computed tomographic colonography (CTC) and capsule endoscopy. All these visualization tests require cleansing of the colorectum by taking medication that empties the bowel. When this bowel preparation is successful, the inside of the colon and the rectum can be examined. A colonoscopy is a procedure that enables visual inspection of the inside of the colon using a flexible tube with a small camera at its tip. Individuals are usually sedated when undergoing this procedure. Most lesions detected can be removed immediately, but large lesions require surgical removal.[67] A flexible sigmoidoscopy resembles a colonoscopy, but only examines the lower part of the colon (rectum and sigmoid). Sedation is less frequently used as with colonoscopy, and it requires less heavy bowel preparation.[68] With a CTC, the colon and rectum are examined using a low dose CT scan.[69] Capsule endoscopy is a recently developed CRC screening test, in which a capsule, the size of the vitamin pill, is swallowed.[70] The capsule contains two cameras, which capture images when travelling through the digestive tract. These images are wirelessly transmitted to a computer and reviewed by an examiner.

The second group are the stool-based tests. This group consists of the guaiac-based fecal occult blood test (gFOBT), the fecal immunochemical test (FIT) and the multitarget stool DNA (FIT-DNA) test. All these tests aim to detect small amounts of blood in the stool that are not visible to the naked eye, which can be an early sign of CRC. All these tests are non-invasive and can be performed at home. For the gFOBT test, participants have to smear multiple small amounts of stool on a card, collected from multiple bowel movements.[56] For the FIT, a mascara stick-like probe is used to scrape the stool surface of a single bowel movement, which is than inserted back into the sampling bottle and send to a laboratory for analysis. A benefit of the FIT compared to the gFOBT is that it can quantify the amount of blood detected in the stool, allowing health care providers to select a cut-off based on the desired balance between test sensitivity and specificity.[71] The

FIT-DNA test does not only detect blood in the stool, but also detects DNA markers of colorectal neoplasia.[72] It requires participants to collect an entire stool sample at home, and send it to the laboratory for evaluation.

The third group are the liquid biopsies. The methylated *SEPT9* DNA plasma assay is the only test in this group that has been FDA approved, but it can only be used for individuals that are not willing to do any of the tests described above. It evaluates whether there is DNA in the blood plasma in which the *SEPT9* gene promoter has been methylated, which is a biomarker for CRC. Furthermore, a urine-based test is being developed, which analyses metabolomics biomarkers by using liquid chromatography-mass spectrometry.[73]

All CRC screening tests have different trade-offs in terms of test accuracy, burden and cost. All positive non-colonoscopy tests must be followed by a colonoscopy for diagnosis and lesion removal. Screening is not simply having individuals take a test, but involves a multistep process of identifying eligible individuals, testing individuals, giving individuals a diagnostic follow-up if needed, and giving individuals the proper treatment and/or surveillance.[74] All these steps are essential components of a successful screening program.

The downside of colorectal cancer screening

Similar to any other cancer screening program, CRC screening does not solely have positive effects. In addition to the costs, CRC screening comes with significant harms and burdens. Harms of CRC screening are, for example, the detection of lesions that would have never been diagnosed without screening (= overdiagnosis). Furthermore, colonoscopy can result in substantial complications, such as major bleeding.[75] Although fatal complications of colonoscopy are rare,[75] they cannot be ignored. No single CRC screening test is perfect, resulting in false-positives (unnecessary follow-up, anxiety and stress), and false-negatives (false reassurance, potentially delaying clinical diagnosis). Although the burden of CRC screening depends on which screening test is being used, no CRC screening test is without any discomfort or disgust. Particularly the bowel preparation needed for the direct visualization test is a substantial burden for individuals, as well as the procedures themselves. In addition, CRC screening is a financial burden, not just to the health care system, but potentially also to the individual. Although CRC screening is recommended by expert panels,[76-78] it is essential that every individual makes an informed decision regarding CRC screening.[79]

Guidelines for colorectal cancer screening in the United States

CRC screening was introduced in the US almost four decades ago, even before the first randomized controlled trials demonstrated its effectiveness. The US has opportunistic CRC screening, which implies that the opportunity for screening results from an individual's request or health care providers who choose to recommend it.[80] In contrast, other countries such as the Netherlands, have implemented organized screening programs, in which invitations are send out directly from central registries.[71] In countries with an organized screening program, the decision about who should be screened and

which screening test should be used is made on a national or regional level. In the US, it is the responsibility of the physician to discuss CRC screening options with their patients. Several organizations, such as the US Preventive Services Task Force (USPSTF), the US Multi-Society Task Force (USMSTF) and the American Cancer Society (ACS), make recommendations about CRC screening that intend to guide physicians.[76,78,81] Although these recommendations largely align, there are some differences (**Table 1.2**). An important difference is the recommend ages at which screening is supposed to commence. Although all three organizations strongly recommend screening between ages 50 and 75 years, the USMSTF and the ACS recommend screening from ages 45 to 50 years for African Americans and for all races/ethnicities, respectively. Furthermore, the USMSTF ranked the recommended screening strategies, whereas the other organization did not.

Table 1.2: Overview of US colorectal cancer screening recommendations issued by the US Preventive Services Task Force, US Multi-society Task Force and American Cancer Society.

	US Preventive Services Task Force	**US Multi-Society Task Force**	**American Cancer Society**
Year latest issue	2016	2017	2018
Ages (years)	50 to 75	Blacks: 45 to 75 Others: 50 to 75	Strong: 50 to 75 Qualified: 45 to 50
Screening strategies	• 10-yearly colonoscopy • 5-yearly CTC • 5-yearly SIG • 1or3-yearly FIT-DNA • Annual FIT • Annual HS-gFOBT • 10-yearly SIG & annual FIT	Tier 1 • 10-yearly colonoscopy • Annual FIT Tier 2 • 5-yearly CTC • 3-yearly FIT-DNA • 5/10-yearly SIG Tier 3 • 5-yearly Capsule endoscopy	• 10-yearly colonoscopy • 5-yearly CTC • 5-yearly SIG • 3-yearly FIT-DNA • Annual FIT • Annual HS-gFOBT
Source	Bibbins-Domingo *et al.*[76]	Rex *et al.* [81]	Wolf *et al.* [78]

CTC - computed tomographic colonography; FIT - fecal immunochemical test; FIT-DNA - multitarget stool DNA test; HS-gFOBT - high-sensitivity guaiac-based fecal occult blood test; SIG - flexible sigmoidoscopy

Colorectal cancer screening utilization in the United States

As there is no central registry in the US to monitor CRC screening, national CRC screening parameters are based on self-reported estimates from surveys. The Behavioral Risk Factor Surveillance Survey (BRFSS) estimated that 67.3% of the population between ages 50 to 75 years is currently up to date with CRC screening, and 74% have ever participated in screening.[82] Estimates from the National Health interview Survey are approximately 8 percentage point lower, reflecting the uncertainty in what true participation rates are.[83] It is noteworthy that screening participation rates vary greatly by state – the reported percentage up to date ranges from 58.5% in New Mexico to 75.9% in Maine in BRFSS data.[82] Among the individuals up to date with CRC screening

in 2015, 96% reported receiving an endoscopy within the last 10 years, whereas 12% reported having received a FIT or gFOBT in the past year.[15] Although these data are not test-specific, it is known that sigmoidoscopy use has dropped to 2.5% for individuals ages 50 and above, and gFOBT has largely been replaced by FIT.[23] Therefore, colonoscopy is by far the most common CRC screening test in the US, followed by FIT.[23]

Once a first CRC screening test is done, continued adherence to the recommended test after a specified interval is necessary to achieve the full benefit of a screening strategy. Very little information is available about screening participation over multiple rounds of screening in the US. Furthermore, there are no national estimates of adherence to diagnostic colonoscopy follow-up and compliance to surveillance guidelines. A recent international systematic review reported an adherence rate to follow-up diagnostic colonoscopy of 80.4%;[84] US estimates of adherence to surveillance colonoscopies range from 60% to 85% .[85-87] In 2014, a large national collaboration of more than 1,700 public, private, and voluntary organizations called the National colorectal cancer roundtable launched the "80% by 2018" initiative, which aimed to increase CRC screening participation to 80% in 2018.[88] They now updated their goal to "80% in Every Community" and continue working to reduce barriers to screening.

Microsimulation modeling to inform colorectal cancer screening policies

The need for modeling

Randomized controlled trials (RCTs) are considered the highest level of evidence,[89] and are crucial for evaluating the effectiveness of CRC screening. However, not every question regarding CRC screening policies can be addressed by RCTs, because of five reasons. First, RCTs are very expensive and time-consuming studies. This is why, for several of the CRC screening tests described above, a RCT demonstrating long-term reductions in CRC incidence and mortality has not been performed. Second, RCTs can only evaluate a few intervention strategies at the same time, as the number of individuals needed in each arm to reach statistical significance is substantial. Third, RCTs usually have a limited follow-up time. Therefore, they do not provide evidence for lifetime benefits, harms and costs of CRC screening, which are needed to determine the cost-effectiveness of a screening program.[90,91] Fourth, RCTs are performed within a specific context. Important parameters that drive the effectiveness of screening programs can be very different from setting to setting. For example, approximately 60% in the US are screened by means of a colonoscopy, whereas in a Dutch clinical trial only 22% of individuals were willing to participate in colonoscopy screening.[92] This implies than RCTs performed in a specific setting may not be representative for another setting. Finally, RCTs cannot directly be used to predict the health care resources needed on a national level. Capacity estimates are essential when planning the implementation of a CRC screening program or when changing an existing CRC program.

To address these issues, mathematical models have been developed. These models can be used to extrapolate results from RCTs to new time periods, populations or regions. The lifetime benefits, harms and burden of hundreds of screening strategies can be analyzed within a short timeframe. Therefore, models are a useful tool to inform screening policies.[93]

The Microsimulation Screening Analysis – Colon model

One of the mathematical models developed to guide CRC screening policies is the Microsimulation Screening Analysis Colon model (MISCAN-Colon). MISCAN-Colon was developed in 1998 by the department of Public Health of the Erasmus University Medical Center in Rotterdam, the Netherlands.[94] It was partly based on earlier versions of MISCAN that were generated for other cancers.[95] It has been used to inform CRC screening policies in multiple countries, among which the Netherlands and the US.[93,96-99] Figure 1.5 illustrates the model inputs, modules and outputs; a detailed description of the model can be found in the Model Appendix.

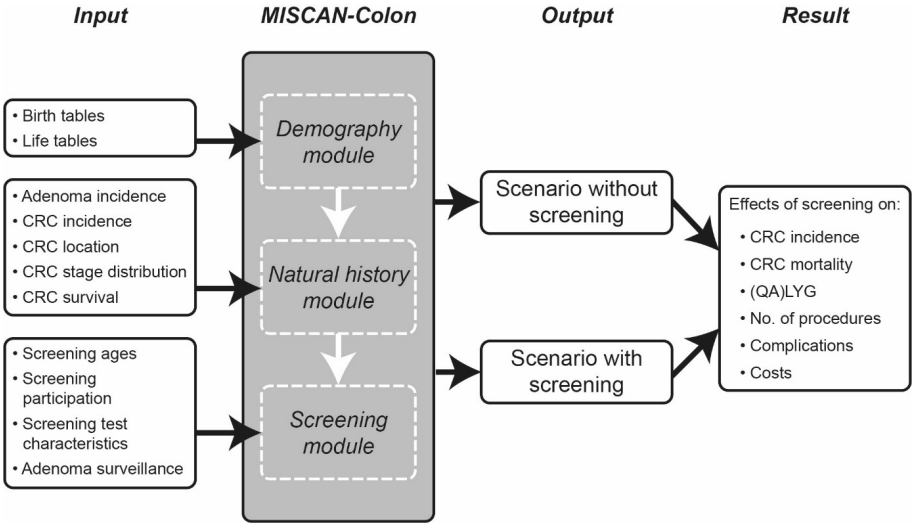


Figure 1.5: Overview of the Microsimulation Screening Analysis Colon model. The MISCAN-colon model consists of the demography -, natural history - and screening module, which require country-specific model inputs. By comparing a scenario with screening to a scenario without screening, the effects of screening can be quantified.
CRC - colorectal cancer; MISCAN-Colon - microsimulation screening analysis colon; (QA)LYG - (quality-adjusted) life-years gained

In short, a hypothetical cohort of individuals is generated by the model resembling a real target population in terms of the life expectancy and occurrence of CRC. The lives of these hypothetical individuals are simulated one by one, hence the term microsimulation. The simulated individuals move subsequently through the three

different model modules (**Figure 1.5**). In the demography module, individuals get a date of birth and a date of death in the absence of CRC, based on the birth tables and life tables entered in the model. In the natural history module, individuals can develop one or multiple adenomas, which may or may not progress to cancer. When individuals develop CRC, a date of death by CRC is generated based on CRC survival rates entered in the model. Only if the date of CRC death generated in the natural history module is earlier than the date of death generated in the demography module, individuals die of the disease instead of from competing conditions. In the screening module, individuals are offered screening, which may or may not detect adenomas and CRC depending on the assumed screening ages, participation, and test characteristics. We run the model twice with the same individuals; once in the presence of screening and once in the absence screening. By comparing all individual life histories of both simulations, the benefits, harms and burdens of CRC screening can be quantified on a population level.

Research and outline of this thesis

The aim of this thesis is to advise CRC screening programs using microsimulation modeling. The remainder of this thesis is divided in three parts. In **Part I**, optimal CRC screening strategies are determined, given recent trends in CRC incidence. In **Part II**, the cost-effectiveness of several interventions that aim to improve CRC screening participation is explored. **Part III** focusses on the cost-effectiveness of screening for, and subsequently clinical management of, individuals diagnosed with Lynch syndrome. The research questions addressed in each of these parts are listed below.

Part I. Informing screening guidelines

- Does the optimal screening strategy for the general population change when incorporating contemporary trends in CRC incidence? (**Chapter 2**)
- What is the potential benefit and burden from earlier screening for black men and women versus whites? (**Chapter 3**)
- How do the rising CRC incidence and the increasing CRC treatment costs impact the optimal screening strategy from a cost-effectiveness perspective? (**Chapter 4**)

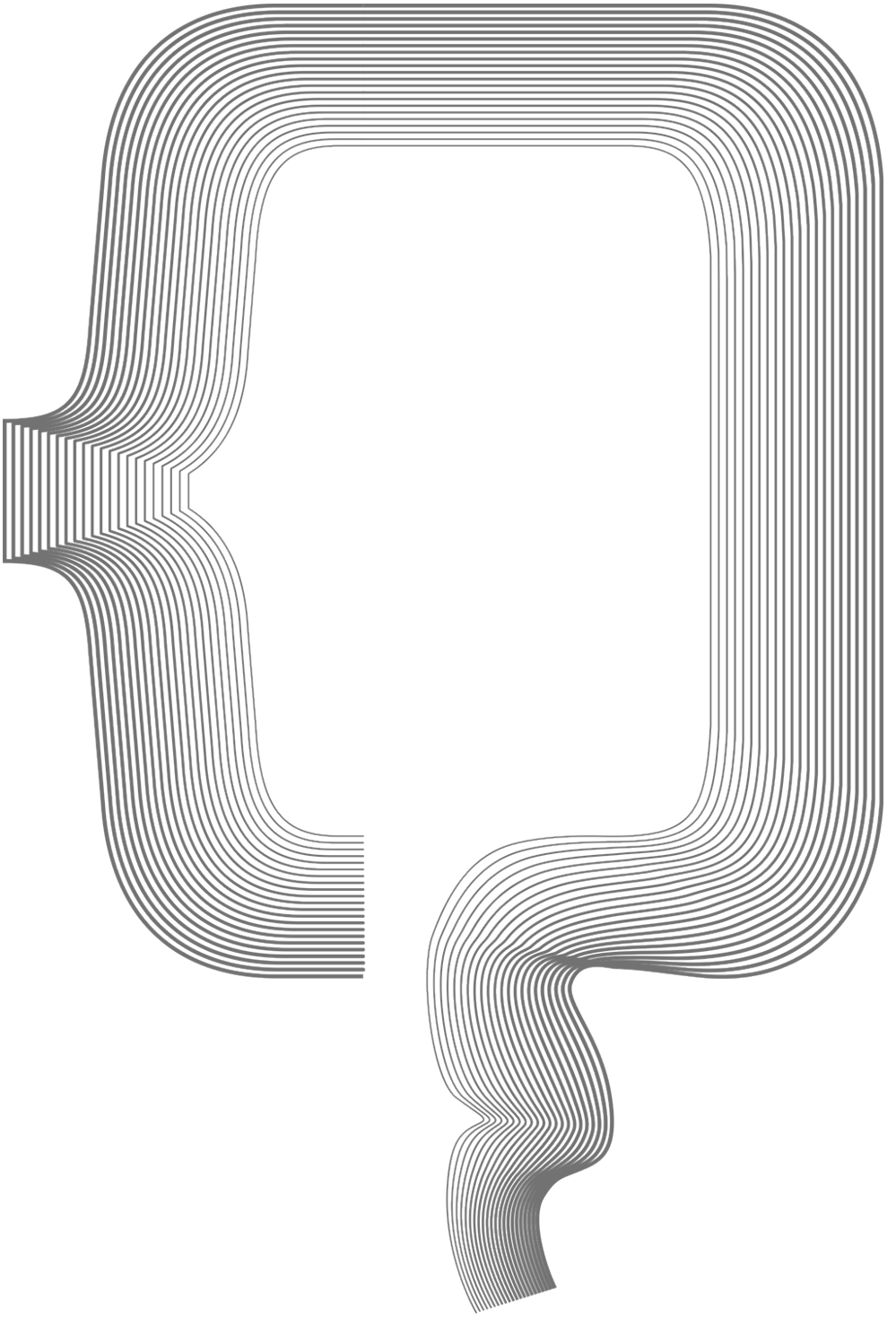
Part II. Interventions to improve adherence

- Under what circumstances is waiving all coinsurance for CRC screening in Medicare beneficiaries cost-effective? (**Chapter 5**)
- For individuals who are unwilling to undergo FIT or colonoscopy screening, which screening strategy is a cost-effective alternative? (**Chapter 6**)
- What are the optimal screening strategies for women willing to obtain some, but not all, US Preventive Services Task Force (USPSTF)-recommended screenings? (**Chapter 7**)
- Would it be cost-effective to include the FIT kit in the screening invitation letter in France? (**Chapter 8**)

Part III. Screening and subsequent steps for Lynch syndrome patients

- Is it cost-effective to screen CRC cases for Lynch syndrome, and what is the optimal surveillance interval for first-degree relatives identified through cascade testing? (**Chapter 9**)
- What are the optimal age thresholds for offering prophylactic hysterectomy to asymptomatic women identified with Lynch syndrome from a cost-effectiveness perspective? (**Chapter 10**)

The thesis directly informs screening programs in the US (Chapters 2-7, 10), France (Chapter 8) and Canada (Chapter 9), but is informative for policy makers across the globe. It ends with a general discussion (**Chapter 11**) in which the above research questions are answered, and future directions are discussed.



Part I

Informing screening guidelines

Chapter 2

The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: Microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline

Elisabeth F.P. Peterse, Reinier G.S. Meester, Rebecca L. Siegel, Jennifer C. Chen, Andrea Dwyer, Dennis J. Ahnen, Robert A. Smith, Ann G. Zauber & Iris Lansdorp-Vogelaar

Cancer (2018), 124: 2964-2971.

Abstract

Background

In 2016, the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model was used to inform the US Preventive Services Task Force colorectal cancer (CRC) screening guidelines. In this study, 1 of 2 microsimulation analyses to inform the update of the American Cancer Society CRC screening guideline, the authors re-evaluated the optimal screening strategies in light of the increase in CRC diagnosed in young adults.

Methods

The authors adjusted the MISCAN-Colon model to reflect the higher CRC incidence in young adults, who were assumed to carry forward escalated disease risk as they age. Life-years gained (LYG; benefit), the number of colonoscopies (COL; burden) and the ratios of incremental burden to benefit (efficiency ratio [ER] = ΔCOL/ΔLYG) were projected for different screening strategies. Strategies differed with respect to test modality, ages to start (40 years, 45 years, and 50 years) and ages to stop (75 years, 80 years, and 85 years) screening, and screening intervals (depending on screening modality). The authors then determined the model-recommended strategies in a similar way as was done for the US Preventive Services Task Force, using ER thresholds in accordance with the previously accepted ER of 39.

Results

Because of the higher CRC incidence, model-predicted LYG from screening increased compared with the previous analyses. Consequently, the balance of burden to benefit of screening improved and now 10-yearly colonoscopy screening starting at age 45 years resulted in an ER of 32. Other recommended strategies included fecal immunochemical testing annually, flexible sigmoidoscopy screening every 5 years, and computed tomographic colonography every 5 years.

Conclusions

This decision-analysis suggests that in light of the increase in CRC incidence among young adults, screening may be offered earlier than has previously been recommended.

Introduction

It is estimated that in 2018, > 50,000 colorectal cancer (CRC) deaths will occur in the United States,[100] making CRC the second most common cause of cancer death in men and women combined.[15] CRC death often can be prevented by CRC screening,[51] which is recommended from ages 50 years to 75 years by the US Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS).[76,101] For the population as a whole, CRC incidence and mortality have been declining for several decades, much of which is attributed to an increase in CRC screening uptake.[15] However, in adults aged <50 years among whom screening currently is not routinely recommended for those at average risk, CRC incidence has been increasing since the mid-1990s.[16-21] Based on national data, CRC now is the most commonly diagnosed cancer and the most common cause of cancer death in American men aged <50 years.[39,40]

In the recently updated USPSTF guidelines,[76] screening was recommended to begin at age 50 years, despite the fact that 2 of 3 colorectal microsimulation models of the Cancer Intervention and Surveillance Modeling Network (CISNET) suggested that starting screening at age 45 years provided a more favorable balance between the benefits and burden of screening compared with starting at age 50 years.[96] As described in the USPSTF recommendation statement, reasons for not lowering the recommended age to start screening were the lack of agreement between all 3 CISNET models and the limited empirical data related to screening before age 50 years.[76] However, accumulating evidence has demonstrated a persistent increase in CRC incidence in adults aged <50 years.[15,16] Although the elevated background risk likely will be carried forward with these generations as they age due to the cohort effect, [6] it is unlikely that it will be observed in CRC incidence data for those aged ≥55 years because it is counteracted by the increased uptake of screening in those ages.

The CISNET microsimulation models that were used to inform the 2016 USPSTF CRC screening guidelines were calibrated to CRC incidence rates from the Surveillance, Epidemiology, and End Results (SEER) program registries during 1975 through 1979.[96] This time frame was chosen because there was little CRC screening in this period. As a result, these models did not account for the recent increase in CRC incidence in individuals aged <50 years. Therefore, at the request of the ACS, we re-evaluated the optimal age to start screening, age to stop screening, and the screening interval incorporating contemporary trends in young adults to inform the update of the ACS CRC screening guideline.

Materials and methods

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model to evaluate the optimal age to start screening, age to stop screening, and screening interval. First, we adjusted the model to reflect the increased CRC incidence in more recent birth cohorts. Second, the benefits and harms of the different screening strategies

were predicted. Third, the balance between the benefits and the burden of screening was used to select model-recommended strategies. The methods used for these steps are described in the section below. Analyses were similar to those performed to inform USPSTF guideline recommendations (see **Supplementary Table A2.1** for a summary of all differences).[96]

MISCAN-Colon

The MISCAN-Colon model used in this study was developed by the Department of Public Health within Erasmus University Medical Center in Rotterdam, the Netherlands, and has been described in detail elsewhere (**Model Appendix**).[102,103] It is part of CISNET, a consortium of cancer decision modelers sponsored by the National Cancer Institute (NCI). In brief, the model generates, with random variation, the individual life histories for a large cohort to simulate the US population in terms of life expectancy and cancer risk. Each simulated person ages over time and may develop ≥1 adenomas that can progress from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm) in size. Some adenomas develop into preclinical cancer, which may progress through stages I to IV. During each disease transition point, CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the location of the cancer, and the person's age. Some simulated life histories are altered by screening through the detection and removal of adenomas or diagnosing CRC in an earlier stage, resulting in a better prognosis. Screening also results in high rates of detection and removal (overtreatment) of polyps, the majority of which would not progress to invasive disease, and may result in fatal complications from colonoscopy with polypectomy,[102,104,105] all of which are considered in the model.

Model incorporation of increase in CRC incidence

The original MISCAN-Colon model was calibrated to CRC incidence in 1975-1979. To incorporate the increased CRC incidence in recent birth cohorts, we adjusted the model based on the observed increase since that period as estimated by Siegel et al.[16] Age-period-cohort modeling of SEER data performed by Siegel et al revealed that the increase in CRC incidence currently is confined to ages <55 years and primarily is the result of a strong birth cohort effect that began in those born in the 1950s. Consequently, these and subsequent generations will carry forward escalated disease risk as they age.[16] Affected cohorts are only now reaching the age to initiate screening, which will likely somewhat counteract the trend. In our analyses, we simulated a cohort of adults aged 40 years in 2015, and assumed that this cohort had a 1.591-fold increased CRC incidence across all ages compared with the original model. This incidence multiplier was based on the incidence rate ratio (IRR) for CRC of the 1935 birth cohort (those aged 40 years in 1975) compared with the 1975 birth cohort (those aged 40 years in 2015).[106] In accordance with the data, we assumed that the increase in CRC incidence was mostly confined to an increase in tumors in the rectum and the distal colon.[16] In the base case analysis, we assumed that the increase in CRC incidence was caused by a higher prevalence of adenomas. In a sensitivity analysis, we explored how our results differed with the alternative assumption of stable adenoma prevalence, but faster progression to malignancy.

Screening strategies

Six screening modalities were evaluated: 1) colonoscopy; 2) fecal immunochemical testing (FIT); 3) high-sensitivity guaiac-based fecal occult blood testing (HSgFOBT); 4) multitarget stool DNA testing (FIT-DNA); 5) flexible sigmoidoscopy (SIG); and 6) computed tomographic colonography (CTC). Multiple ages to begin and stop screening and multiple screening intervals were evaluated for each modality (**Table 2.1**). Test characteristics are described by Knudsen et al,[96] and are presented in **Supplementary Table A2.2**. A 40-year-old US cohort free of CRC was simulated, thereby only evaluating the effect of the different screening strategies in a population of individuals to whom the screening guidelines for average-risk individuals apply. These 40-year-olds were assumed to have a 100% adherence to screening, follow-up, and surveillance.[107]

The benefit of screening was measured by the number of life-years gained (LYG) from the screening strategy, and corrected for life-years lost due to screening complications. The number of required colonoscopies was used as a measure of the aggregate burden of screening, and included colonoscopies for screening, follow-up, surveillance, and the diagnosis of symptomatic cancer. Because this measure of burden does not capture the burden of other screening modalities, direct comparisons of the benefit and burden across screening strategies were limited to those with similar noncolonoscopy burden. Therefore, only the stool-based tests were grouped, which resulted in 4 classes of screening modalities: 1) colonoscopy; 2) stool-based modalities (FIT, HSgFOBT, and FIT-DNA); 3) SIG; and 4) CTC.

Table 2.1: Screening strategies evaluated by the microsimulation model

Screening Modality	Age to start screening (years)	Age to stop screening (years)	Screening interval (years)	No. of (unique) strategies [a]
No screening				1 (1)
Colonoscopy	40,45,50	75,80,85	5,10,15	27 (20)
Stool-based tests				
– Fecal immunochemical test	40,45,50	75,80,85	1,2,3	27 (27)
– High-sensitivity guaiac-based fecal occult blood test	40,45,50	75,80,85	1,2,3	27 (27)
– Multitarget stool DNA test	40,45,50	75,80,85	1,3,5	27 (27)
Flexible sigmoidoscopy	40,45,50	75,80,85	5,10	18 (15)
Computed tomographic colonography	40,45,50	75,80,85	5,10	18 (15)
Total				**145 (132)**

[a] The number of unique strategies excluded the strategies that overlap (eg, COL every 10 years from ages 50-80 years and from ages 50-85 years both include colonoscopies at age 50, 60, 70, and 80 years, and thus are not unique strategies).

Efficient and near-efficient screening strategies

The LYG and colonoscopy burden were plotted for each screening strategy by class of screening modalities. Strategies providing the largest incremental increase in LYG per additional colonoscopy were connected, thereby composing the efficient frontier. All strategies on the efficient frontier were considered efficient screening options,[108] whereas others fell below the frontier and were dominated. Weakly dominated strategies that had LYG within 98% of the efficient frontier were defined as near-efficient; other strategies below the efficient frontier were considered inefficient. For efficient and near-efficient strategies, the incremental number of colonoscopies (ΔCOL), the incremental number of LYG (ΔLYG), and the efficiency ratio (ER) (ΔCOL/ΔLYG) relative to the next less effective efficient strategy were calculated.

Model-recommended screening strategies

A predefined algorithm was used to select model-recommended screening strategies (**Figure 2.1**).[96] First, the efficient frontier for the colonoscopy strategies was generated (step 1), after which a benchmark colonoscopy screening strategy was selected that 1) was an efficient or near-efficient colonoscopy screening strategy, 2) had LYG no less than the previously recommended colonoscopy every 10 years from ages 50 to 75 years, and 3) had an efficiency ratio (ER = ΔCOL/ΔLYG) of ≤ 40, 45, or 50 incremental colonoscopies per LYG (step 2). We decided to evaluate different ER thresholds in liaison with recommendations for cost-effectiveness analysis, for which it is recommended to evaluate multiple willingness-to-pay thresholds.[109] We analyzed ER thresholds of 40, 45, and 50, in accordance with the efficiency ratio for the MISCAN-Colon model in the USPSTF analyses, in which 39 was considered an acceptable number of colonoscopies per LYG and 114 was not, suggesting the threshold of an acceptable number of colonoscopies per LYG was in-between those values.[96] Next, the start age and stop age of screening were fixed at those of the colonoscopy benchmark strategy (step 3), because different start ages and stop ages for different screening modalities are not easy to implement in practice because this may complicate the communication between physicians and patients. Simplifying a regimen has been shown to be an important intervention to increase patient adherence,[110] and therefore recommending different start ages or stop ages for the different screening modalities may result in lower participation. For the noncolonoscopy screening modalities, within-class efficient frontiers were created, with the same start age and stop age as the benchmark colonoscopy strategy (step 4), and selected were 1) efficient or near-efficient strategies that 2) had at least 90% of the LYG compared with the benchmark colonoscopy strategy and 3) had ERs lower than the benchmark colonoscopy strategy (step 5). Among all strategies within a class of screening modality fulfilling all the above criteria, only the most effective strategies were recommended by the model (step 6).

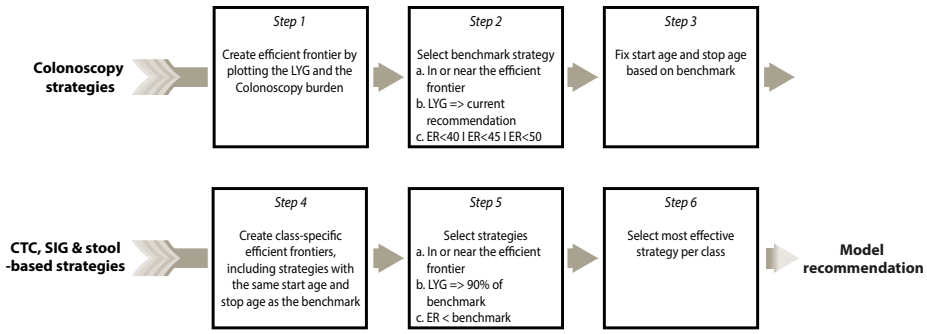


Figure 2.1: Algorithm used to select model-recommended strategies. LYG indicates life-years gained (current recommendation is colonoscopy screening from ages 50 to 75 years every 10 years); ER, efficiency ratio. The ER is calculated as and is an incremental burden-to-benefits ratio. Threshold ERs of 40, 45, and 50 colonoscopies per LYG were evaluated. The stool-based strategies (fecal immunochemical test, high-sensitivity guaiac-based fecal occult blood test, and multitarget stool DNA test) were combined into 1 class because they have a similar noncolonoscopy burden.
CTC - computed tomographic colonography; SIG - flexible sigmoidoscopy.

Assumptions evaluated in the sensitivity analyses

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

Results

A total of 132 unique screening strategies were evaluated (**Table 2.1**). The CRC deaths averted per 1000 40-year-olds ranged from 25 for triennial HSgFOBT from ages 50 to 75 years to 40 for colonoscopy every 5 years from ages 40 to 85 years (**Supplementary Table A2.3**). The lifetime number of colonoscopies per 1000 40-year-olds, used as a measure of burden, ranged from 1433 for triennial FIT screening from ages 50 to 75 years to 8671 for colonoscopy every 5 years from ages 40 to 85 years, whereas the number of LYG compared with no screening, used to measure benefit, ranged from 284 for triennial HSgFOBT from ages 50 to 75 years to 475 for colonoscopy every 5 years from ages 40 to 85 years (**see Supplemenatry Table A2.3**).

Efficient and near-efficient screening strategies

The LYG compared with the number of colonoscopies required and the efficient frontier for the colonoscopy strategies are presented in Figure 2.2. Nine efficient and 5 near-efficient (LYG within 98% of the efficient frontier) colonoscopy strategies were identified, in which the ERs (incremental burden-to-benefits ratios) for the colonoscopy strategies ranged from 11 colonoscopies per LYG for screening every 15 years from ages 50 to 75 years to 569 for colonoscopy screening every 5 years from ages 40 to 85 years (see Supplementary Table A2.4). The current colonoscopy screening recommendation (screening every 10 years from ages 50-75 years) was 1 of the 9 efficient strategies and had an ER of 23. The plots of the other screening modalities can be found in Supplementary Figures A2.1 to A2.3. Twenty-two of 25 stool-based strategies in or near the efficient frontier were FIT strategies, demonstrating that FIT screening largely dominated the other stool-based strategies (Supplementary Figure A2.1).

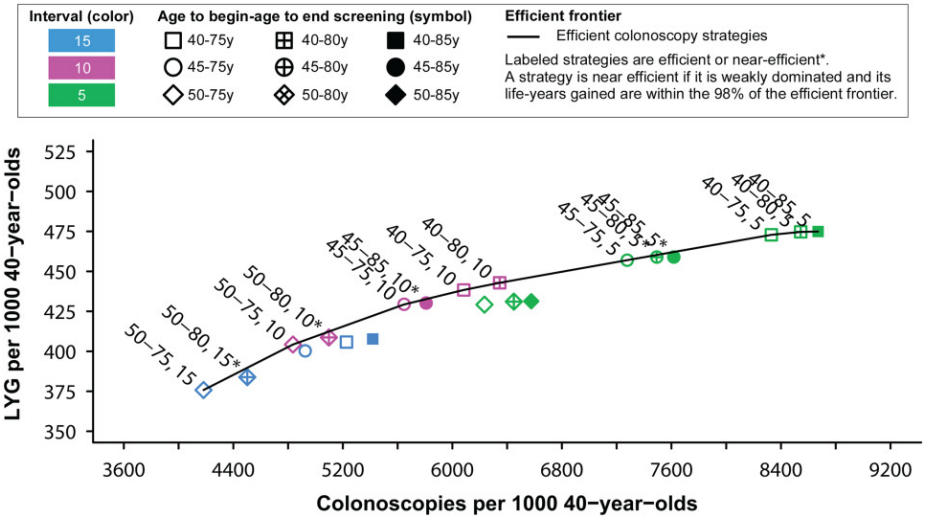


Figure 2.2: Lifetime number of colonoscopies and life-years gained (LYG) for colonoscopy screening strategies.

Model-recommended strategies

The colonoscopy strategy recommended by the model was screening every 10 years from ages 45 to 75 years with an ER of 32 incremental colonoscopies per LYG (Table 2.2). This strategy was selected because it was on the efficient frontier and had the highest number of LYG among the strategies with ERs <40 and 45. Compared with the current recommendation (screening every 10 years from ages 50-75 years), this strategy resulted in 25 (+6.2%) additional LYG accompanied by an increase in 810 (+17%) colonoscopies per 1000 40-year-olds.

Table 2.2: Outcomes for screening strategies with similar age to start and age to stop screening as the selected benchmark colonoscopy strategy

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

COL - colonoscopy; Dom. - Dominated; FIT - Fecal immunochemical test; HSgFOBT - High-sensitivity guaiac-based fecal occult blood test; FIT-DNA - Multitarget stool DNA test; SIG - Flexible sigmoidoscopy; CTC - Computed tomographic colonography; LYG - Life-years gained; CRC - Colorectal cancer; ER - Efficiency ratio

[a] In the absence of screening, the model predicted 45 CRC Deaths.

[b] calculated as $\frac{\text{incremental colonoscopies w.r.t. previous efficient strategy}}{\text{incremental LYG w.r.t. previous efficient strategy}}$. It is an incremental burden-to-benefits ratio.

[c] A strategy can only be recommended by the model if it has an efficiency ratio lower than the efficiency ratio of the benchmark strategy (colonoscopy every 10 years from ages 45 to 75 years).

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

[e] This strategy was selected by the model when an efficiency ratio threshold of 40 or 45 incremental colonoscopies per LYG was applied.

Class-specific efficient frontiers for strategies other than colonoscopy were created, including only those strategies with the same start age and stop age as the benchmark colonoscopy strategy (Table 2.2). Per screening class, 1 screening strategy was in or near the efficient frontier, had an ER smaller than the benchmark colonoscopy strategy, and had at least 90% of the LYG from the benchmark strategy, thereby fulfilling the criteria to be recommended by the model. In addition to colonoscopy screening every 10 years, our model recommended FIT screening annually, SIG every 5 years, and CTC every 5 years from ages 45 to 75 years (Table 2.2).

With an ER threshold of 50, screening was recommended from ages 40 to 75 years by colonoscopy every 10 years, FIT every year, SIG every 5 years, and CTC every 5 years (Supplemenatry Table A2.5). Irrespective of the ER threshold, no HSgFOBT and FIT-DNA strategies were recommended. HSgFOBT strategies were not on the efficient frontier and for the few efficient FIT-DNA strategies that were, the ER was higher than the colonoscopy benchmark.

Table 2.3: Model-recommended colonoscopy strategies under alternative model assumptions evaluated in the sensitivity analyses

	Recommended colonoscopy strategies (start age / end age / interval)		
Scenario	**ER < 40**	**ER < 45**	**ER < 50**
Base case[a]	45/75/10	45/75/10	40/75/10
Faster adenoma progression	40/75/10	40/75/10	40/75/10
Higher incidence only below age 50	50/75/10[b]	40/75/10	40/75/10
Different incidence rate ratios			
1.2	50/75/10	50/75/10	40/75/10
1.3	50/75/10	45/75/10	40/75/10
1.4	45/75/10	45/75/10	40/75/10
1.5	45/75/10	45/75/10	40/75/10
1.6	45/75/10	45/75/10	40/75/10
1.7	45/75/10	40/75/10	40/75/10
1.8	45/75/10	40/75/10	40/75/10
1.9	45/75/10	40/75/10	40/80/10
2.0	40/75/10	40/80/10	45/75/5
2.1	40/75/10	45/75/5	40/75/5
2.2	40/80/10	45/75/5	40/75/5
2.3	40/80/10	40/75/5	40/75/5
2.4	45/75/5	40/75/5	40/75/5

Colonoscopy strategies are described by: Age to start screening/Age to stop screening/ screening interval. Efficiency Ratio (ER) thresholds of 40, 45 and 50 colonoscopies per life-year gained were evaluated.

[a] In our Base-Case analyses, we assumed an Incidence Rate Ratio of 1.591 and we assumed that the higher incidence was caused by an increase in adenoma onset instead of faster adenoma progression. Furthermore, we assumed that the current generation of 40-year-olds will carry forward escalated disease risk as they age.

[b] 50-75-10 had an ER of 40.7; it was the strategy with the lowest ER among the strategies that met the LYG criterion.

Sensitivity analyses

As shown in **Table 2.3**, alternative assumptions that were explored in the sensitivity analyses influenced the model recommendations. First, when the increased CRC incidence was incorporated as faster adenoma progression to malignancy rather than higher adenoma onset, the model suggested to start screening at age 40 years for all ER thresholds. Second, if the assumed higher CRC incidence was confined to ages <50 years, colonoscopy screening every 10 years from ages 50 to 75 years resulted in the lowest ER: 40.7. The model recommended starting screening at age 40 years by colonoscopy every 10 years with ER thresholds of 45 and 50. Finally, model-recommended strategies depended on the level of increase in CRC incidence. The start age for colonoscopy decreased as IRRs increased. With an ER threshold of 45, the optimal age to start screening remained at age 50 years for IRRs < 1.3, whereas the optimal age to start screening was decreased to age 40 years with an IRR of ≥1.7. The first and second alternative assumption did not influence the stopping age nor the screening interval, but stopping age and/or interval were influenced by some of the more extreme IRRs.

Discussion

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

The results of the current study were sensitive for alternative assumptions regarding the magnitude and etiology of the increase in CRC incidence in young adults; however, the model recommended starting screening before age 50 years, often even at age 40 years, in the majority of alternative scenarios. Thus, the model recommendation of screening initiation at age 45 years appears robust and may even be conservative. Close monitoring of the developments in CRC incidence is required to inform future guidelines because incidence is increasing with each subsequent birth cohort.[16]

To our knowledge, the current study is the first study that incorporates the recent increase in CRC incidence, especially for rectal and distal colon cancer, in a decision-analytic modeling approach to assess CRC screening. Our estimated benefits of screening, which resulted in decreased incremental burden-to-benefit ratios, were much higher compared with the analysis performed to inform the USPSTF guidelines.[96] For example, the LYG and ERs for screening every 10 years by colonoscopy from ages 50 to 75 years were 248 and 39 for the USPSTF analysis, versus 404 and 23 in this analysis. In addition, in contrast to the analysis performed for the USPSTF, SIG screening every 5 years was recommended by the model. This likely can be attributed to the higher percentage of tumors in the rectum and the distal colon. The only other difference between the current

model and the one used for USPSTF was the update of the lifetable from 2009 to 2012, which did not meaningfully influence findings (data not shown).

The ER of colonoscopy screening every 10 years from ages 45 to 75 years in our analysis was 32, a lower ratio of incremental burden to benefit than the ER of the model-recommended colonoscopy strategy in the USPSTF analysis. In contrast to the USPSTF analysis, this analysis to inform the ACS was only performed by 1 of the 3 CISNET models. However, the other 2 CISNET models already suggested that starting screening at age 45 years was preferred in the analysis for the USPSTF, in which the higher risk was not incorporated, albeit with a 15-year interval for colonoscopy screening.[96]

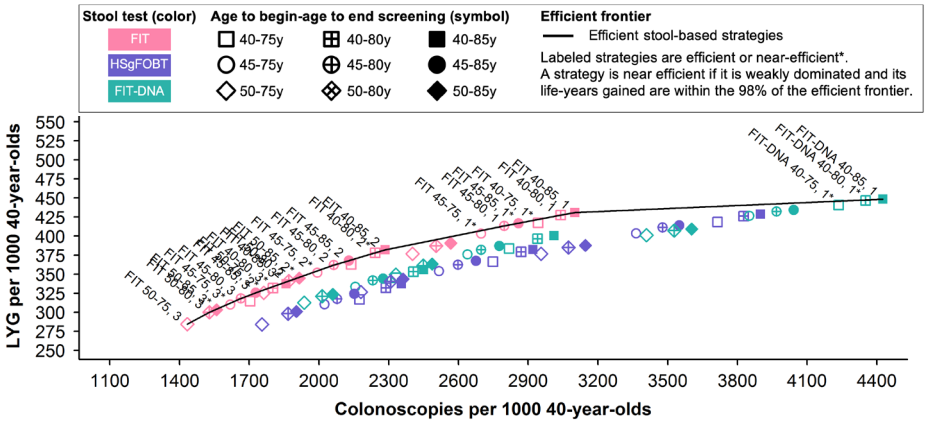
Decision models are a useful tool with which to inform screening guidelines because they can extrapolate evidence and predict long-term outcomes of numerous screening strategies. Decision modeling is an important component within the context of all scientific evidence that is taken into consideration when screening guidelines are evaluated. Since the USPSTF recommendations, compelling empirical data from Siegel et al [16] have demonstrated that the increase in CRC incidence is primarily the result of a strong birth cohort effect, which fueled debate regarding the age of screening initiation. This debate triggered reanalysis of the optimal age to begin and end screening and the screening interval that CISNET models performed earlier for the USPSTF. Taken together, empirical data and modeling now suggest that screening should be started at an earlier age for those at average risk of disease. Our model recommendation to start screening at age 45 years instead of age 50 years is driven solely by the assumed increase in CRC disease burden. A study by Murphy et al suggested that the increase in CRC incidence in younger ages is likely caused by an increase in colonoscopy use rather than an increase in disease burden, based in part on stable CRC mortality rates.[111] It is important to note that Murphy et al presented mortality data from 1992 through 2013 and did not systematically quantify recent trends. Race-specific examination of CRC mortality from 1970 to 2014 among individuals aged 20 to 49 years by Siegel et al demonstrated that although CRC mortality is decreasing in blacks, it actually is increasing in whites. Moreover, the trend is consistent with a cohort effect, with the increase beginning in 1995 for individuals aged 30 to 39 years and in 2005 for individuals aged 40 to 49 years, a decade later than the uptick in incidence for each age group.[112] Therefore, because the increase in incidence is accompanied by an increase in mortality, higher colonoscopy use in individuals aged <50 years does not appear to be the main driver of the increase in CRC incidence in young adults.

The current study has several limitations. First, it is not known whether the increase in CRC incidence is caused by an increase in the number of adenomas, a faster adenoma progression to malignancy, or some combination of the 2. We found that under both assumption of a higher adenoma onset as well as faster adenoma progression, screening initiation before age 50 years was optimal and therefore also would be expected for the combination of assumptions. Future research is needed to determine the cause and carcinogenic pathway of the increase in CRC. Second, it is not certain that the current 40-year-olds will carry forward the same escalated disease risk as they age. Therefore, we evaluated the extreme, namely that they would return to levels for 1975-1979 levels,

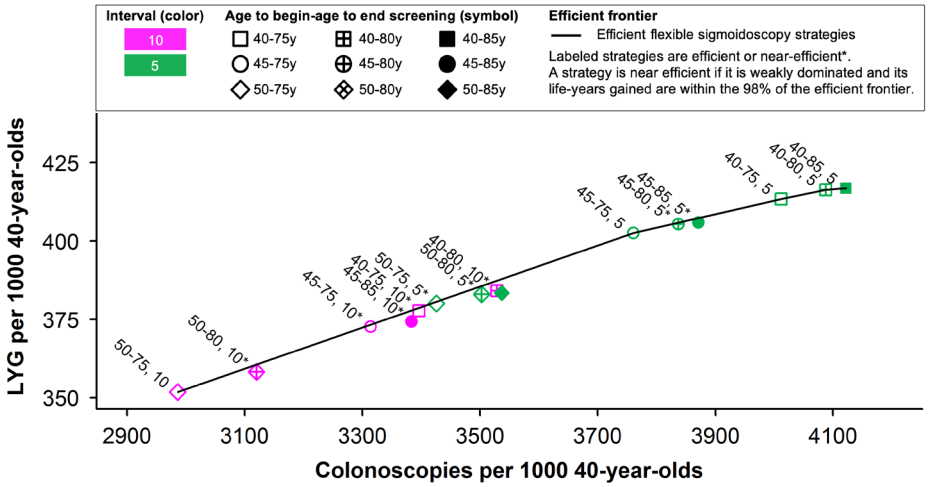
in a sensitivity analysis. Although this impacted the predicted benefits of screening, this only further lowered the recommended starting age to 40 years when an ER threshold of 45 incremental colonoscopies per LYG was applied. Third, we used the number of LYG and the number of colonoscopies to measure the benefits and the burden, respectively. Therefore, the burden of tests other than colonoscopies was not considered, which made direct comparison of all strategies not possible. Fourth, to the best of our knowledge, there is no commonly accepted threshold for the incremental number of colonoscopies per LYG. For the USPSTF analysis, 39 was considered an acceptable ratio for our model.[96] Because it is recommended to evaluate multiple willingness-to-pay thresholds,[109] we evaluated ER thresholds of 40, 45, and 50. Although these thresholds are subjective and do influence our model recommendations, the ER for screening initiation at age 45 years was 32 in this analysis, and therefore was superior to the ER accepted by the USPSTF.[96] Fifth, similar to the assumptions in our analysis for the USPSTF,[96] we assumed perfect adherence to all screening, diagnostic follow-up, and surveillance tests for the purpose of comparing the performance of individual tests under ideal assumptions. Therefore, the model predicted the maximum achievable benefit for all screening strategies. In reality, the current percentage of being up to date with screening is 61.1%,[113] and the adherence to diagnostic follow-up and surveillance is approximately 80%.[55,114]This suggests that the model-predicted benefits will not be achieved. However, guidelines are optimally based on the full potential of benefit that would accrue under complete adherence to recommendations because assuming realistic adherence might result in recommending more frequent screenings as the model then compensates for the substantial percentage of the population that does not participate in every recommended screening. For individuals who do adhere to the recommendations, this actually would result in overscreening associated with unnecessary burden. Furthermore, public health organizations will always seek to increase adherence to recommendations. Sixth, the lack of empirical data regarding the performance of CRC screening tests in adults aged 45 to 49 years means that we assumed that these tests would perform equally well in this age group compared with adults aged 50 to 54 years. In fact, apart from a lower prevalence of disease, there is little reason to expect that performance would differ. In the case of visual tests, lesions of interest should have similar visibility. Tests for occult blood have been shown to perform differently by age, but the difference in characteristics is small at younger ages. Harms associated with colonoscopy should be lower given the observation that harms increase with increasing age. Finally, we did not tailor recommendations to population characteristics, whereas further personalization of screening may improve the balance of burden to benefit. In the accompanying article, Meester et al [98] have demonstrated that when incidence is updated in race- and sex-specific analyses, screening is recommended from age 45 years for all race and gender combinations.

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

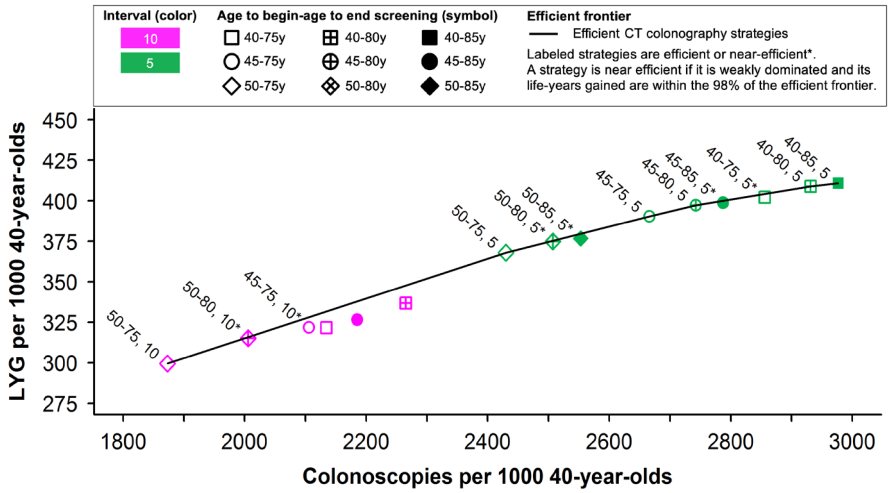
Appendix



Supplementary Figure A2.1: Lifetime number of colonoscopies and life-years gained for stool-based screening strategies.



Supplementary Figure A2.2: Lifetime number of colonoscopies and life-years gained for flexible sigmoidoscopy screening strategies.



Supplementary Figure A2.3: Lifetime number of colonoscopies and life-years gained for computed tomographic colonography strategies.

Supplementary Table A2.1: Summary of differences between this analysis and our previous analysis for the US Preventive Services Task Force.

	ACS analysis	USPSTF analysis
Data source, life expectancy	2013 U.S. lifetables	2009 U.S. lifetables
Data source, CRC risk	Elevated risk based on trends in incidence under age 40	SEER 1975-1979
Data source, CRC location	SEER 1975 birth cohort	SEER 1975-1979
Evaluated tests	Single test strategies only	Single- and hybrid test strategies
Evaluated start ages	Start ages 40, 45 and 50	Start ages 45, 50 and 55
Decision criterion for selection of model-recommendable strategies, efficiency	Re-assessed for classes of screening modality other than colonoscopy after selecting age to start and stop	Assessed among start ages 50 and 55 and stop ages 75, 80 and 85 for all screening modalities
Decision criterion for selection of model-recommendable strategies, incremental burden-to-benefit	An acceptance threshold of maximum 40, 45 or 50 colonoscopies per LYG was applied for colonoscopy-based screening strategies	No specified acceptance threshold was applied, but the number effectively accepted by the Task Force was 39-65 across models in that study.

Supplementary Table A2.2: Per lesion screening test sensitivities used in the analysis.

Test characteristic	Colonoscopy [a] (within reach)	FIT	HSgFOBT	FIT-DNA	SIG (within reach)	CTC
Sensitivity for adenomas ≤5 mm, %	75	0 [e]	0 [e]	0 [e]	75	
Sensitivity for adenomas 6–9 mm, %	85	11.4	4.29	22	85	57
Sensitivity for adenomas ≥10 mm, %	95	15.9	14.7	28.4	95	84
Sensitivity for CRC, %	95	88.6/62.6 [f]	85.9/56.8 [f]	96.7/86.4 [f]	95	84
Specificity, %	86 [b]	96.4	92.5	89.8	87 [b]	88 [g]
Reach, %	95 [c]	100	100	100	76 [c]	100
Risk of fatal complications, %	0.01 [d]	0	0	0	0 [d]	0

CTC - computed tomographic colonography; FIT - fecal immunochemical test ; FIT-DNA - multitarget stool DNA test; SIG - flexible sigmoidoscopy; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test. [a] It was assumed that the same test characteristics for screening colonoscopies applied to colonoscopies for diagnostic follow-up or for surveillance.

[b] The lack of specificity with endoscopy reflects the detection of nonadenomatous polyps, which, in the case of flexible sigmoidoscopy, may lead to unnecessary diagnostic colonoscopy, and in the case of colonoscopy, leads to unnecessary polypectomy, which is associated with an increased risk of colonoscopy complications.

[c] 95% of the colonoscopies reached the end of the colorectum (cecum); for the remainder 5% the endpoint was distributed between the cecum and rectum. With flexible sigmoidoscopy, 76% reached the end the sigmoid colon; 14% had an endpoint between the beginning and the end of the sigmoid colon; 12% had an endpoint between the beginning and end of the descending colon.

[d] Case fatality was derived by combining the overall perforation rate from Warren and colleagues with mortality given perforation (0.0519) in Gatto and colleagues. Flexible sigmoidoscopy was modeled without biopsy or polypectomy of detected lesions, and was therefore assumed to have 0 mortality risk.

[e] It was assumed that 1–5 mm adenomas do not bleed and therefore cannot cause a positive stool test.

[f] "Short" before clinical diagnosis / "Long" before clinical diagnosis.

[g] 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.

Supplementary Table A2.3: Lifetime number of screening tests, life-years gained, CRC Cases and CRC Deaths per 1000 40-year-olds for all evaluated screening strategies

Modality	Start age	End age	Inter-val	Stool tests	SIGs	CTCs	Colonos-copies[a]	LYG	CRC cases	CRC deaths[b]
No Screening		-	-	-	-	-	108	-	108	45
COL	40	75	5	0	0	0	8330	473	30	6
COL	40	75	10	0	0	0	6083	438	37	8
COL	40	75	15	0	0	0	5226	406	41	10
COL	40	80	5	0	0	0	8544	475	30	5
COL	40	80	10	0	0	0	6345	443	35	7
COL	40	80	15	0	0	0	5226	406	41	10
COL	40	85	5	0	0	0	8671	475	30	5
COL	40	85	10	0	0	0	6345	443	35	7
COL	40	85	15	0	0	0	5418	408	41	9
COL	45	75	5	0	0	0	7277	457	32	6
COL	45	75	10	0	0	0	5646	429	36	8
COL	45	75	15	0	0	0	4923	400	41	10
COL	45	80	5	0	0	0	7492	459	31	6
COL	45	80	10	0	0	0	5646	429	36	8
COL	45	80	15	0	0	0	4923	400	41	10
COL	45	85	5	0	0	0	7619	459	31	6
COL	45	85	10	0	0	0	5806	430	36	8
COL	45	85	15	0	0	0	4923	400	41	10
COL	50	75	5	0	0	0	6234	429	34	7
COL	50	75	10	0	0	0	4836	404	39	9
COL	50	75	15	0	0	0	4183	376	45	12
COL	50	80	5	0	0	0	6449	431	33	7
COL	50	80	10	0	0	0	5098	409	38	8
COL	50	80	15	0	0	0	4502	384	43	10
COL	50	85	5	0	0	0	6576	431	33	7
COL	50	85	10	0	0	0	5098	409	38	8
COL	50	85	15	0	0	0	4502	384	43	10
FIT	40	75	1	21262	0	0	2942	417	52	11
FIT	40	75	2	12800	0	0	2139	363	66	15
FIT	40	75	3	9162	0	0	1704	314	74	19
FIT	40	80	1	22578	0	0	3040	427	50	9
FIT	40	80	2	13843	0	0	2242	378	64	13
FIT	40	80	3	9971	0	0	1802	332	73	17
FIT	40	85	1	23492	0	0	3101	431	50	8
FIT	40	85	2	14331	0	0	2285	382	64	12
FIT	40	85	3	10504	0	0	1858	338	73	15
FIT	45	75	1	17835	0	0	2698	403	54	11
FIT	45	75	2	10973	0	0	1994	352	67	16
FIT	45	75	3	8038	0	0	1619	310	75	19
FIT	45	80	1	19157	0	0	2797	413	52	10
FIT	45	80	2	11672	0	0	2064	362	65	14

table continues

Modality	Start age	End age	Interval	Stool tests	SIGs	CTCs	Colonoscopies[a]	LYG	CRC cases	CRC deaths[b]
FIT	45	80	3	8434	0	0	1665	318	74	17
FIT	45	85	1	20074	0	0	2858	417	51	9
FIT	45	85	2	12407	0	0	2129	368	65	13
FIT	45	85	3	9016	0	0	1728	325	74	16
FIT	50	75	1	14610	0	0	2402	377	56	12
FIT	50	75	2	8839	0	0	1762	325	69	17
FIT	50	75	3	6522	0	0	1433	284	77	20
FIT	50	80	1	15948	0	0	2504	387	54	11
FIT	50	80	2	9900	0	0	1870	341	67	14
FIT	50	80	3	7298	0	0	1529	300	76	18
FIT	50	85	1	16872	0	0	2567	391	54	10
FIT	50	85	2	10394	0	0	1915	345	67	13
FIT	50	85	3	7580	0	0	1560	303	76	17
HSgFOBT	40	75	1	17001	0	0	3714	418	49	10
HSgFOBT	40	75	2	11348	0	0	2749	366	62	15
HSgFOBT	40	75	3	8410	0	0	2174	317	71	19
HSgFOBT	40	80	1	17955	0	0	3827	426	48	9
HSgFOBT	40	80	2	12213	0	0	2869	379	61	13
HSgFOBT	40	80	3	9121	0	0	2288	332	70	16
HSgFOBT	40	85	1	18610	0	0	3898	429	47	8
HSgFOBT	40	85	2	12612	0	0	2920	382	61	12
HSgFOBT	40	85	3	9585	0	0	2354	337	70	15
HSgFOBT	45	75	1	14366	0	0	3364	403	51	11
HSgFOBT	45	75	2	9776	0	0	2516	354	63	15
HSgFOBT	45	75	3	7405	0	0	2024	310	72	18
HSgFOBT	45	80	1	15326	0	0	3479	411	49	10
HSgFOBT	45	80	2	10357	0	0	2598	362	62	13
HSgFOBT	45	80	3	7754	0	0	2078	318	72	17
HSgFOBT	45	85	1	15983	0	0	3550	414	49	9
HSgFOBT	45	85	2	10960	0	0	2676	367	62	12
HSgFOBT	45	85	3	8263	0	0	2152	324	72	16
HSgFOBT	50	75	1	11925	0	0	2956	377	53	12
HSgFOBT	50	75	2	7965	0	0	2181	327	67	16
HSgFOBT	50	75	3	6061	0	0	1755	284	75	20
HSgFOBT	50	80	1	12899	0	0	3073	385	52	11
HSgFOBT	50	80	2	8853	0	0	2309	340	65	14
HSgFOBT	50	80	3	6749	0	0	1867	298	74	18
HSgFOBT	50	85	1	13563	0	0	3146	388	52	10
HSgFOBT	50	85	2	9260	0	0	2362	344	65	13
HSgFOBT	50	85	3	6996	0	0	1903	301	74	17
FIT-DNA	40	75	1	14326	0	0	4235	441	41	9
FIT-DNA	40	75	3	7608	0	0	2818	383	57	13
FIT-DNA	40	75	5	5793	0	0	2332	345	66	16
FIT-DNA	40	80	1	15086	0	0	4351	447	40	8
FIT-DNA	40	80	3	8193	0	0	2941	396	55	11

table continues

Modality	Start age	End age	Interval	Stool tests	SIGs	CTCs	Colonoscopies[a]	LYG	CRC cases	CRC deaths[b]
FIT-DNA	40	80	5	6113	0	0	2406	353	65	14
FIT-DNA	40	85	1	15609	0	0	4426	449	39	7
FIT-DNA	40	85	3	8572	0	0	3011	400	55	10
FIT-DNA	40	85	5	6324	0	0	2450	356	65	14
FIT-DNA	45	75	1	12019	0	0	3851	426	42	9
FIT-DNA	45	75	3	6644	0	0	2640	376	57	13
FIT-DNA	45	75	5	4949	0	0	2157	333	67	16
FIT-DNA	45	80	1	12780	0	0	3968	432	41	8
FIT-DNA	45	80	3	6930	0	0	2698	382	56	12
FIT-DNA	45	80	5	5271	0	0	2231	342	66	15
FIT-DNA	45	85	1	13302	0	0	4042	434	40	8
FIT-DNA	45	85	3	7344	0	0	2776	387	56	11
FIT-DNA	45	85	5	5483	0	0	2276	344	66	14
FIT-DNA	50	75	1	9887	0	0	3409	401	45	10
FIT-DNA	50	75	3	5422	0	0	2331	350	60	15
FIT-DNA	50	75	5	4147	0	0	1937	312	69	17
FIT-DNA	50	80	1	10659	0	0	3528	407	43	9
FIT-DNA	50	80	3	5982	0	0	2449	361	58	13
FIT-DNA	50	80	5	4473	0	0	2014	321	68	16
FIT-DNA	50	85	1	11184	0	0	3603	409	43	9
FIT-DNA	50	85	3	6182	0	0	2487	363	58	12
FIT-DNA	50	85	5	4686	0	0	2059	323	68	15
SIG	40	75	5	0	4631	0	4012	413	40	10
SIG	40	75	10	0	2992	0	3396	378	46	12
SIG	40	80	5	0	4837	0	4088	416	39	9
SIG	40	80	10	0	3260	0	3529	384	45	11
SIG	40	85	5	0	4967	0	4122	417	39	9
SIG	40	85	10	0	3260	0	3529	384	45	11
SIG	45	75	5	0	3865	0	3761	403	41	10
SIG	45	75	10	0	2691	0	3314	373	46	12
SIG	45	80	5	0	4070	0	3837	405	40	10
SIG	45	80	10	0	2691	0	3314	373	46	12
SIG	45	85	5	0	4201	0	3871	406	40	9
SIG	45	85	10	0	2866	0	3384	374	46	12
SIG	50	75	5	0	3181	0	3426	380	43	11
SIG	50	75	10	0	2119	0	2986	352	49	13
SIG	50	80	5	0	3388	0	3503	383	42	10
SIG	50	80	10	0	2388	0	3120	358	47	12
SIG	50	85	5	0	3519	0	3537	383	42	10
SIG	50	85	10	0	2388	0	3120	358	47	12
CTC	40	75	5	0	0	5458	2856	402	49	11
CTC	40	75	10	0	0	3311	2134	322	63	18
CTC	40	80	5	0	0	5742	2931	409	47	10
CTC	40	80	10	0	0	3675	2265	337	60	15
CTC	40	85	5	0	0	5928	2977	411	47	10

table continues

Modality	Start age	End age	Interval	Stool tests	SIGs	CTCs	Colonoscopies[a]	LYG	CRC cases	CRC deaths[b]
CTC	40	85	10	0	0	3675	2265	337	60	15
CTC	45	75	5	0	0	4630	2666	390	50	12
CTC	45	75	10	0	0	3045	2106	322	62	17
CTC	45	80	5	0	0	4915	2742	397	48	10
CTC	45	80	10	0	0	3045	2106	322	62	17
CTC	45	85	5	0	0	5102	2788	399	48	10
CTC	45	85	10	0	0	3286	2185	327	61	15
CTC	50	75	5	0	0	3850	2430	368	52	13
CTC	50	75	10	0	0	2374	1873	300	65	19
CTC	50	80	5	0	0	4137	2507	375	50	11
CTC	50	80	10	0	0	2741	2006	315	62	16
CTC	50	85	5	0	0	4325	2553	377	49	11
CTC	50	85	10	0	0	2741	2006	315	62	16

COL - Colonoscopy; FIT - Fecal immunochemical test; HSgFOBT - High-sensitivity guaiac-based fecal occult blood test; SIG - Flexible sigmoidoscopy; CTC - Computed tomographic colonography; LYG - Life-years gained; CRC - Colorectal cancer

[a] Total number of colonoscopies performed per 1000 40-year olds, including diagnostic colonoscopies and potential surveillance colonoscopies after adenoma removal.

[b] This includes the number of deaths due to fatal complications.

Supplementary Table A2.4: Lifetime number of screening tests and life-years gained per 1000 40-year-olds for all efficient and near-efficient screening strategies within each class.[a]

Modality, and age to start, age to stop, interval (years)	Stool tests	SIGs	CTCs	Colonos-copies [b]	LYG	CRC deaths averted	ER [c]	Near-efficient [d]
COL 50-75-15	0	0	0	4183	376	34	11	
COL 50-80-15	0	0	0	4502	384	35	40	*
COL 50-75-10	0	0	0	4836	404	36	23	
COL 50-80-10	0	0	0	5098	409	37	60	*
COL 45-75-10	0	0	0	5646	429	37	32	
COL 45-85-10	0	0	0	5806	430	38	156	*
COL 40-75-10	0	0	0	6083	438	37	48	
COL 40-80-10	0	0	0	6345	443	38	59	
COL 45-75-5	0	0	0	7277	457	39	66	
COL 45-80-5	0	0	0	7492	459	39	113	*
COL 45-85-5	0	0	0	7619	459	40	162	*
COL 40-75-5	0	0	0	8330	473	40	66	
COL 40-80-5	0	0	0	8544	475	40	117	
COL 40-85-5	0	0	0	8671	475	40	569	
FIT 50-75-3	6522	0	0	1433	284	25	5	
FIT 50-80-3	7298	0	0	1529	300	28	6	
FIT 50-85-3	7580	0	0	1560	303	28	10	*
FIT 45-75-3	8038	0	0	1619	310	27	9	*
FIT 45-80-3	8434	0	0	1665	318	28	8	
FIT 45-85-3	9016	0	0	1728	325	29	9	
FIT 50-75-2	8839	0	0	1762	325	28	1935	*
FIT 40-80-3	9971	0	0	1802	332	29	12	*
FIT 40-85-3	10504	0	0	1858	338	30	11	*
FIT 50-80-2	9900	0	0	1870	341	31	9	
FIT 50-85-2	10394	0	0	1915	345	32	11	*
FIT 45-75-2	10973	0	0	1994	352	30	11	*
FIT 45-80-2	11672	0	0	2064	362	32	9	
FIT 45-85-2	12407	0	0	2129	368	33	11	
FIT 40-80-2	13843	0	0	2242	378	32	11	*
FIT 40-85-2	14331	0	0	2285	382	33	11	
FIT 45-75-1	17835	0	0	2698	403	34	19	*
FIT 45-80-1	19157	0	0	2797	413	36	16	
FIT 45-85-1	20074	0	0	2858	417	36	17	*
FIT 40-75-1	21262	0	0	2942	417	34	35	*
FIT 40-80-1	22578	0	0	3040	427	36	17	
FIT 40-85-1	23492	0	0	3101	431	37	18	
FIT-DNA 40-75-1	14326	0	0	4235	441	37	115	*
FIT-DNA 40-80-1	15086	0	0	4351	447	38	79	*
FIT-DNA 40-85-1	15609	0	0	4426	449	38	75	
SIG 50-75-10	0	2119	0	2986	352	32	8	

table continues

Modality, and age to start, age to stop, interval (years)	Stool tests	SIGs	CTCs	Colonos-copies [b]	LYG	CRC deaths averted	ER [c]	Near-efficient [d]
SIG 50-80-10	0	2388	0	3120	358	33	21	*
SIG 45-75-10	0	2691	0	3314	373	33	16	*
SIG 45-85-10	0	2866	0	3384	374	34	18	*
SIG 40-75-10	0	2992	0	3396	378	33	16	*
SIG 50-75-5	0	3181	0	3426	380	34	16	*
SIG 50-80-5	0	3388	0	3503	383	35	17	*
SIG 40-80-10	0	3260	0	3529	384	34	17	*
SIG 45-75-5	0	3865	0	3761	403	35	15	
SIG 45-80-5	0	4070	0	3837	405	36	27	*
SIG 45-85-5	0	4201	0	3871	406	36	33	*
SIG 40-75-5	0	4631	0	4012	413	36	23	
SIG 40-80-5	0	4837	0	4088	416	36	26	
SIG 40-85-5	0	4967	0	4122	417	36	67	
CTC 50-75-10	0	0	2374	1873	300	27	6	
CTC 50-80-10	0	0	2741	2006	315	30	8	*
CTC 45-75-10	0	0	3045	2106	322	29	10	*
CTC 50-75-5	0	0	3850	2430	368	33	8	
CTC 50-80-5	0	0	4137	2507	375	34	11	*
CTC 50-85-5	0	0	4325	2553	377	35	14	*
CTC 45-75-5	0	0	4630	2666	390	34	11	
CTC 45-80-5	0	0	4915	2742	397	35	11	
CTC 45-85-5	0	0	5102	2788	399	35	26	*
CTC 40-75-5	0	0	5458	2856	402	34	23	*
CTC 40-80-5	0	0	5742	2931	409	35	16	
CTC 40-85-5	0	0	5928	2977	411	36	25	

COL - Colonoscopy; FIT - Fecal immunochemical test; HSgFOBT - High-sensitivity guaiac-based fecal occult blood test; SIG - Flexible sigmoidoscopy; CTC - Computed tomographic colonography; LYG - Life-years gained; CRC - Colorectal cancer, ER - Efficiency ratio

[a] Strategies are ordered by class and by number of colonoscopies.

[b] Total number of colonoscopies performed per 1000 40-year-olds, including diagnostic colonoscopies and potential surveillance colonoscopies after adenoma removal.

[c] $ER = \frac{\textit{incremental colonoscopies w.r.t. previous efficient strategy}}{\textit{incremental LYG w.r.t. previous efficient strategy}}$. It is an incremental burden-to-benefits ratio.

[d] Strategies within 2% from the efficiency frontier within each class of screening modalities (colonoscopy, stool-based, flexible sigmoidoscopy, and CT colonography). All other listed strategies are on the efficiency frontier.

Supplementary Table A2.5: Outcomes per 1000 40-year-olds for screening strategies with similar age to start and age to stop screening as the selected benchmark colonoscopy strategy.

Modality, and age to start/ age to end/ interval, years	Outcomes per 1000 40-year-olds										
	No. of stool tests	No. of SIGs	No. of CTCs	No. of COLs	LYG	Complications	CRC deaths averted[a]	Efficiency ratio[b]	ER < benchmark[c]	LYG >= 90% of benchmark	Model-recommended strategy[d]
Colonoscopy											
COL 40/75/10[e]	0	0	0	6083	438	22	37	48	-	-	Yes
Stool tests											
FIT 40/75/3	9162	0	0	1704	314	11	26	5	Yes	No	
FIT 40/75/2	12,800	0	0	2139	363	13	30	9	Yes	No	
HSgFOBT 40/75/3	8410	0	0	2174	317	13	27	Dom.	-	No	
FIT-DNA 40/75/5	5793	0	0	2332	345	14	30	Dom.	-	No	
HSgFOBT 40/75/2	11,348	0	0	2749	366	15	31	Dom.	-	No	
FIT-DNA 40/75/3	7608	0	0	2818	383	15	32	Dom	-	No	
FIT 40/75/1	21,262	0	0	2942	417	16	34	15	Yes	Yes	Yes
HSgFOBT 40/75/1	17,001	0	0	3714	418	18	35	Dom.	-	Yes	
FIT-DNA 40/75/1	14,326	0	0	4235	441	19	37	56	No	Yes	
Flexible sigmoidoscopy											
SIG 40/75/10	0	2992	0	3396	378	18	33	9	Yes	No	
SIG 40/75/5	0	4631	0	4012	413	20	36	17	Yes	Yes	Yes
CT colonography											
CTC 40/75/10	0	0	3311	2134	322	13	27	6	Yes	No	
CTC 40/75/5	0	0	5458	2856	402	16	34	9	Yes	Yes	Yes

COL -Colonoscopy; Dom. - Dominated; FIT - Fecal immunochemical test; HSgFOBT - High-sensitivity guaiac-based fecal occult blood test; FIT-DNA - Multitarget stool DNA test; SIG - Flexible sigmoidoscopy; CTC - Computed tomographic colonography; LYG - Life-years gained; CRC - Colorectal cancer; ER - Efficiency ratio

[a] In the absence of screening, the model predicted 45 CRC Deaths.

[b] calculated as $\frac{\text{incremental colonoscopies w.r.t. previous efficient strategy}}{\text{incremental LYG w.r.t. previous efficient strategy}}$. It is an incremental burden-to-benefits ratio.

[c] A strategy can only be recommended by the model if it has an efficiency ratio lower than the efficiency ratio of the benchmark strategy (colonoscopy every 10 years from ages 40 to 75 years).

[d] A strategy is recommended by the model if it is an efficient or a near-efficient strategy with a lower burden-to-benefits ratio and at least 90% of the LYG compared to the benchmark strategy (colonoscopy screening every 10 years from ages 40 to 75 years).

[e] This strategy was selected by the model when an efficiency ratio threshold of 50 incremental colonoscopies per LYG was applied.

Chapter 3

Optimizing colorectal cancer screening by race and sex: Microsimulation analysis II to inform the American Cancer Society colorectal cancer screening guideline

Reinier G.S. Meester, Elisabeth F.P. Peterse, Amy B. Knudsen, Anne C. de Weerdt, Jennifer C. Chen, Anna P. Lietz, Andrea Dwyer, Dennis J. Ahnen, Rebecca L. Siegel, Robert A. Smith, Ann G. Zauber & Iris Lansdorp-Vogelaar

Cancer (2018), 124: 2974-2985

Abstract

Background

Colorectal cancer (CRC) risk varies by race and sex. This study, 1 of 2 microsimulation analyses to inform the 2018 American Cancer Society CRC screening guideline, explored the influence of race and sex on optimal CRC screening strategies.

Methods

Two Cancer Intervention and Surveillance Modeling Network microsimulation models, informed by US incidence data, were used to evaluate a variety of screening methods, ages to start and stop, and intervals for 4 demographic subgroups (black and white males and females) under 2 scenarios for the projected lifetime CRC risk for 40-year-olds: 1) assuming that risk had remained stable since the early screening era and 2) assuming that risk had increased proportionally to observed incidence trends under the age of 40 years. Model-based screening recommendations were based on the predicted level of benefit (life-years gained) and burden (required number of colonoscopies), the incremental burden-to-benefit ratio, and the relative efficiency in comparison with strategies with similar burdens.

Results

When lifetime CRC risk was assumed to be stable over time, the models differed in the recommended age to start screening for whites (45 vs 50 years) but consistently recommended screening from the age of 45 years for blacks. When CRC risk was assumed to be increased, the models recommended starting at the age of 45 years, regardless of race and sex. Strategies recommended under both scenarios included colonoscopy every 10 or 15 years, annual fecal immunochemical testing, and computed tomographic colonography every 5 years through the age of 75 years.

Conclusions

Microsimulation modeling suggests that CRC screening should be considered from the age of 45 years for blacks and for whites if the lifetime risk has increased proportionally to the incidence for younger adults.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States.[15] Screening can prevent death from CRC and has been promoted by multiple organizations since 1980.[115,116] Recommendations for screening have evolved over the years, with the emergence of new screening technologies, new evidence on the performance of various screening methods, and evidence of differential risk across population subgroups.

It has been well documented that individuals with African ancestry have higher rates of CRC incidence and mortality than individuals of other races or ethnicities in the United States and that men are at higher risk than women.[15] Similarly, longevity varies by race and sex.[117] These differences in cause-specific and other-cause mortality could influence the optimal start age, duration, and intensity of screening.[118] A higher risk of CRC may justify a more intensive screening approach, whereas a high risk of other-cause morbidity and mortality may reduce the benefit from screening at older ages.

There are differences in the current US guidelines for the age to start CRC screening in African Americans. Currently, the American College of Gastroenterology and the US Multi-Society Task Force recommend that African Americans begin screening at the age of 45 years, whereas those of other races should begin at the age of 50 years, regardless of sex. [119,120] The US Preventive Services Task Force (USPSTF) updated its screening recommendations for the US general population in 2016.[76] Although it acknowledged that black and Alaska Native individuals have higher CRC incidence and mortality rates than the general population and that microsimulation analyses indicated that there may be some merit to starting screening at the age of 45 years rather than 50 years even for the general population, it concluded that the current evidence best supports a starting age of 50 years for all individuals at average risk.

To inform the update of its 2008 CRC screening guideline,[101] the American Cancer Society requested a decision-analytic modeling analysis to further explore the question of optimal CRC screening strategies by race and sex. An accompanying article by Peterse et al [99] shows that based on increasing CRC rates in young birth cohorts, modeling supports earlier screening for the whole population. However, as explained in that article, there is controversy around the mechanism for that increase, with some arguing that it is a detection bias attributable to early uptake of screening rather than a true increase in risk.[111] In this article, we explore the potential benefit and burden from earlier screening for black men and women versus whites, and we consider 2 scenarios for current background CRC risk: one based on original models informed by data from a period before screening was widely adopted that assumed stable risk and another based on increasing risk as described by Peterse et al.[99]

Materials and methods

Four US demographic subgroups were distinguished: white females, black females, white males, and black males. There were insufficient data to include other races or to distinguish Hispanic ethnicity. Two independently developed microsimulation models for CRC were used to evaluate a large number of possible screening strategies with various screening modalities, ages to begin, ages to end, and screening intervals for each subgroup. Models were developed within the National Cancer Institute–funded Cancer Intervention and Surveillance Modeling Network. Apart from the distinction of race- and sex-specific population subgroups and scenarios considered for current CRC risk, the analyses were similar to those performed to inform USPSTF guideline recommendations (see **Supplementary Table A3.1** for a summary of all differences).[96,97]

Model description

The Microsimulation Screening Analysis–Colon (MISCAN-Colon) and the Simulation Model of Colorectal Cancer (SimCRC) have been described extensively in other studies [121] and in the Cancer Intervention and Surveillance Modeling Network model registry.[122] Each model consists of 3 components, which are used to simulate individual life histories from birth to death under alternative CRC screening strategies (**Model Appendix**). First, the demography component determines each simulated person's date of birth and death in the absence of CRC. Second, the natural history component is used to simulate the potential development of CRC and reductions in the overall years of life. The natural history of CRC is assumed to follow the adenoma-carcinoma sequence (**Supplementary Figure A3.1**). Simulated individuals may develop 1 or more adenomas. An adenoma may grow in size and develop into CRC, which then may transition through stages I to IV without symptoms or be clinically diagnosed at any stage. Depending on the varying rates of CRC progression and survival, simulated individuals may die of either other causes or clinically diagnosed CRC. The third component, the model's screening component, allows a simulated person's life trajectory to be altered because of the detection of preclinical CRC or the detection and removal of an adenoma.

The demography component was informed by all-cause mortality rates from the 2013 US life tables by race and sex.[117] For the natural history component, the age-specific adenoma onset was based on the prevalence and multiplicity of adenomas as observed in autopsy studies.[123-132] Race- and sex-specific CRC incidence by age, stage, and localization was calibrated to data from the Surveillance, Epidemiology, and End Results Program (SEER) from the period before screening was widely adopted [133]: SimCRC was calibrated to 1975-1979 data, a period devoid of screening, and MISCAN-Colon was calibrated to 1990-1994 data, a period with limited screening but more pronounced racial disparities in CRC risk (see **Supplementary Figure A3.2** for a comparison of incidence by period). Race- and sex-specific CRC survival in both models was based on recent SEER data.[134] The screening component was informed by data on the sensitivity and specificity of the test performed and, for endoscopic tests, the proportion visualizing the complete colon or rectum (**Table 3.1**).

The models have been validated against the mortality reductions of the UK Flexible Sigmoidoscopy Screening (UKFSS) trial of once-only sigmoidoscopy.[135] The MISCAN-Colon model has also been successfully validated to the Norwegian CRC Prevention (NORCCAP) Trial[136] and Screening for COlon and REctum (SCORE) Trial.[61]

Study population

For each of the 4 population subgroups described previously, the models simulated outcomes for 40-year-old individuals without a prior CRC diagnosis.

Scenarios for background risk

Two scenarios were considered for the projected lifetime risk of CRC in 40-year-olds in the absence of screening. In the first scenario, the conventional scenario in microsimulation models for CRC screening, [96,97] age-specific risks of CRC were assumed to have remained at the level observed before screening was widely adopted in the United States. In the second scenario, age-specific CRC risks for all ages older than 40 years were assumed to have increased proportionally to observed trends in incidence for individuals younger than 40 years old. [16] Hence, the assumed relative increase in lifetime risk across models was 1.80 to 1.90 for white females, 1.24 to 1.27 for black females, 2.07 to 2.13 for white males, and 1.41 to 1.56 for black males. The increase was assumed to have arisen from an increased rate of adenoma onset, primarily in the rectum and distal colon. More details on the background and methodology for these assumptions are in the article by Peterse et al.[99]

Screening strategies

Six screening modalities were evaluated: colonoscopy, fecal immunochemical testing (FIT) with a positivity cutoff at hemoglobin levels ≥ 20 μg/g of stool, high-sensitivity guaiac-based fecal occult blood testing (HSgFOBT), multitarget stool DNA testing (fecal immunochemical testing with a DNA stool test [FIT-DNA]), flexible sigmoidoscopy (SIG), and computed tomographic colonography (CTC). For each modality, multiple ages to begin and end screening and multiple screening intervals were evaluated for a total of 132 unique strategies for each population subgroup or 528 across all race and sex combinations (**Table 3.2**). In all evaluated strategies, individuals in whom adenomas were detected and removed received colonoscopy surveillance through the age of 85 years. It was assumed that there was 100% adherence to all procedures to avoid compensation of lower adherence rates by shorter recommended screening intervals. As a result, predicted outcomes from the model reflect the potential lifetime benefits and burden of screening with the assumption of full adherence to the entire screening process.

Table 3.1: Screening test characteristics used in the analysis [a]

Test characteristic	**Colonoscopy** [b] (per lesion, within reach)	**FIT** (per person)	**HSgFOBT** (per person)	**FIT-DNA** (per person)	**SIG** (per lesion, within reach)	**CTC** (per lesion)
Sensitivity for adenomas ≤5 mm, %	75 [70-79]	7.6 [6.7-8.6][f]	7.5 [7.5-7.5][h]	17.2 [15.9-18.6][f]	75 [70-79]	
Sensitivity for adenomas 6–9 mm, %	85 [80-92]		12.4 [10-26.2]		85 [80-92]	57 [48.9-71.6]
Sensitivity for adenomas ≥10 mm, %	95 [93.1-99.5]	23.8 [20.8-27][g]	23.9 [17.7-49.4]	42.4 [38.7-46.2][g]	95 [93.1-99.5]	84 [75.6-92.4]
Sensitivity for CRC, %	95 [93.1-99.5]	73.8 [62.3-83.3]	70 [61.5-79.4]	92.3 [84-97]	95 [93.1-99.5]	84 [75.6-92.4]
Specificity, %	86 [c]	96.4	92.5	89.8	87 [c]	88 [h]
Proportion completed, %	95 [d]	100	100	100	76 [d]	100
Risk of fatal complications, %	0.01 [e]	0	0	0	0 [e]	0

CTC - computed tomographic colonography; FIT - fecal immunochemical test with a positivity cutoff of ≥100 ng of hemoglobin (Hb) per mL of buffer (≥20 μg Hb/g of feces); FIT-DNA - multitarget stool DNA test (fecal immunochemical test with a DNA stool test); HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; SIG - flexible sigmoidoscopy.

[a] Ranges evaluated in sensitivity analysis are presented in brackets behind base-case characteristics.

[b] It was assumed that the same test characteristics for screening colonoscopies applied to colonoscopies for diagnostic follow-up or for surveillance.

[c] The lack of specificity with endoscopy reflects the detection of nonadenomatous polyps, which, in the case of sigmoidoscopy, may lead to unnecessary diagnostic colonoscopy, and in the case of colonoscopy, leads to unnecessary polypectomy, which is associated with an increased risk of colonoscopy complications.

[d] With colonoscopy 95% reached the end of the colorectum (cecum); for the remainder 5% the endpoint was distributed between the cecum and rectum. With SIG 76% reached the end the sigmoid colon; 14% had an endpoint between the beginning and the end of the sigmoid colon; 12% had an endpoint between the beginning and end of the descending colon.

[e] Case fatality was derived by combining the overall perforation rate from Warren and colleagues with mortality given perforation (0.0519) in Gatto and colleagues.[104,105] Sigmoidoscopy was modeled without biopsy or polypectomy of detected lesions, and was therefore assumed to have 0 mortality risk.

[f] For individuals with 1–5 mm adenomas, it was assumed that the sensitivity is equal to the positivity rate in individuals without adenomas. The sensitivity for individuals with 6–9 mm adenomas was such that the weighted average sensitivity for individuals with 1–9 mm

adenomas equals that for nonadvanced adenomas.
[g] Sensitivity for individuals with advanced adenomas (ie, adenomas ≥10 mm or adenomas with advanced histology). Sensitivity was not reported for the subset of individuals with ≥10 mm adenomas.
[h] It was assumed that 1–5 mm adenomas do not bleed and therefore cannot cause a positive stool test. It was also assumed that HSgFOBT can be positive because of bleeding from other causes, the probability of which is equal to positivity rate in individuals without adenomas.
[i] 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 3.2: Screening strategies evaluated by the model for each race and sex subgroup [a]

Screening modality	Age to begin screening, y	Age to end screening, y	Screening interval, y	No. of (unique) strategies [b]
No screening	45,50,55	75,80,85		1
Stool-based screening				
– FIT	45,50,55	75,80,85	1,2,3	27 (27)
– HSgFOBT	45,50,55	75,80,85	1,2,3	27 (27)
– FIT-DNA	45,50,55	75,80,85	1,3,5	27 (27)
SIG screening	45,50,55	75,80,85	5,10	18 (15)
CTC screening	45,50,55	75,80,85	5,10	18 (15)
Colonoscopy screening	45,50,55	75,80,85	5,10,15	27 (20)
Total number of (unique) screening strategies evaluated in the model				145 (132)

CTC - computed tomographic colonography; FIT - fecal immunochemical test; FIT-DNA - multitarget stool DNA test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; SIG - flexible sigmoidoscopy.
[a] Strategies were similar to those evaluated in an analysis for the US Preventive Services Task Force.[96] Combinations of SIG with stool-based screening were not considered here.
[b] The number of unique strategies excludes the strategies that result in the same screening regimen (eg, COL every 10 years from ages 50-80 years and from ages 50-85 years both include colonoscopies at age 50, 60, 70, and 80 years, and thus are not unique strategies).

Main outcomes

The benefit or effectiveness of screening was measured by the number of life-years gained (LYG) from the screening strategy; this accounted for life-years lost because of fatal screening complications. The primary fatal complication is perforation of the colon, which occurs at a rate less than 1 per 1000 colonoscopies; approximately 5% of these cases result in death.[137,138] The number of required colonoscopies was used as a measure of the aggregate burden of screening, and it included colonoscopies for screening,

follow-up, surveillance, and the diagnosis of symptomatic cancer. We controlled for the burden of tests other than colonoscopy by grouping and comparing tests with similar noncolonoscopy burdens. This resulted in 4 classes of screening modalities: colonoscopy, stool-based modalities, SIG, and CTC.

Efficient and near-efficient screening strategies

Efficient strategies were identified via the plotting of LYG with respect to the number of required colonoscopies. A strategy was considered efficient when it provided the largest incremental increase in LYG per additional colonoscopy performed in comparison with the next less colonoscopy-intensive screening strategy within the same class of screening modalities. The line connecting all efficient strategies is the efficient frontier. Near-efficient strategies were defined as strategies just below the efficient frontier that provided at least 98% of the maximum incremental benefit per additional colonoscopy performed in comparison with the next less effective strategy on the efficient frontier. For efficient and near-efficient screening strategies, the incremental number of colonoscopies (ΔCOL), the incremental number of life-years gained (ΔLYG), and the burden-to-benefit ratio (or efficiency ratio [ER]: ΔCOL/ΔLYG) in comparison with the next less effective strategy on the efficient frontier were calculated.

Model recommendations

Model-recommendable strategies fulfilled 3 main criteria: efficiency within their class of screening modality, comparable overall benefit as measured by LYG, and an acceptable balance of burden and benefit (see **Figure 3.1**).[96] First, an optimal colonoscopy screening strategy was selected. This was an efficient or near-efficient colonoscopy screening strategy required to provide at least as many LYG as the current general population recommendation of screening colonoscopy (every 10 years between 50 and 75 years) and to have a burden-to-benefit ratio of no more than 50 additional colonoscopies per LYG. This threshold was similar to the accepted balance in USPSTF model recommendations across models [96] and was judged to be an acceptable balance for this analysis by the American Cancer Society. The most effective colonoscopy strategy (defined by most LYG) meeting these requirements was recommended. Second, for each alternative class of screening modalities, all strategies with the same ages to begin and end screening as the optimal colonoscopy strategy (benchmark strategy) were identified, and within-class efficiency was re-assessed. Model-recommendable strategies were efficient or near-efficient strategies with at least 90% of the LYG of the benchmark colonoscopy strategy and with a burden-to-benefit ratio lower than the benchmark. Again, the most effective strategies within each class meeting the requirements were considered model-recommendable. It was possible to have no recommendable strategy within a class of screening modalities.

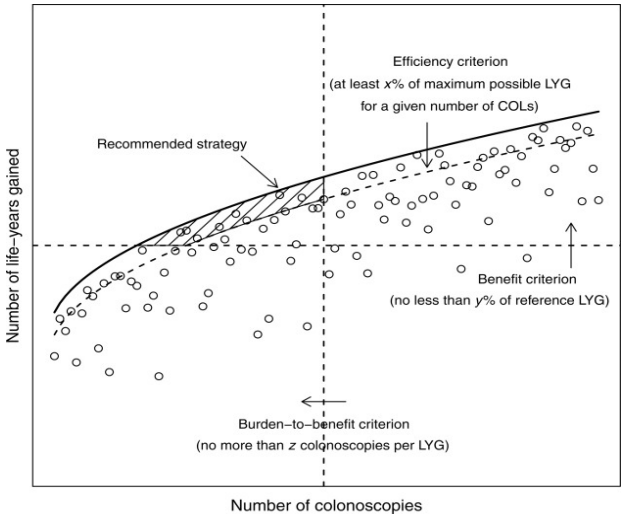


Figure 3.1: Illustration of the selection algorithm for model-recommendable strategies.Each dot represents the hypothetical outcomes for a single screening strategy. The bold line is the efficient frontier connecting efficient strategies (not plotted as separate dots). Dashed lines represent thresholds imposed by the decision algorithm: the efficiency criterion ensures that recommended strategies are efficient in terms of the yield in LYG for any level of colonoscopy requirement; the benefit criterion ensures that LYG do not lag far behind a selected reference strategy; the burden-to-benefit criterion ensures that the incremental number of required colonoscopies per LYG does not exceed a predefined number. The shaded area encompasses strategies fulfilling all three decision criteria. The model-recommended strategy is the strategy within this area with the highest predicted LYG.

Sensitivity analysis

In sensitivity analyses, 3 alternative scenarios were evaluated. First, we evaluated best-case and worst-case scenarios for the sensitivity of each evaluated screening modality, including potential follow-up or surveillance colonoscopy, to reflect uncertainty in the estimates of the diagnostic performance of each modality (Table 3.1). Second, we varied the minimum acceptance threshold for LYG to 75% instead of 90% for alternative screening strategies in comparison with colonoscopy screening. Third, we lowered the acceptance threshold for burden to benefit from 50 additional colonoscopies per LYG to 40. For each alternative scenario, model recommendations were re-assessed.

Results

In the absence of screening, the model-predicted life expectancy and CRC risk among 40-year-olds varied by race and sex. Life expectancy from the age of 40 years ranged from 35.3 to 42.3 years in the scenario of stable CRC risk and was lowest for black males and highest for white females (Supplementary Table A3.2). In the conservative scenario

of stable background CRC risk, the predicted lifetime CRC risk ranged from 59.3 to 70.7 per 1000 adults across population subgroups in MISCAN-Colon and from 58.7 to 78.6 per 1000 adults in SimCRC. In the scenario of increased CRC risk, predicted lifetime risk across population subgroups increased to 76.7 to 149.0 in MISCAN-Colon and to 79.9 to 162.5 in SimCRC. The predicted risk was highest for white males, but the rank order for other demographic subgroups differed across models and scenarios and in comparison with life-years lost to CRC; this reflected differences in incidence by age in the data used to inform each model (**Supplementary Figure A3.2**).

Screening benefit and burden

Screening was predicted to result in clinically significant LYG in comparison with no screening by both models, regardless of the population subgroup and scenario for CRC risk. In the scenario of stable age-specific CRC risk, predicted LYG across models, strategies, and population subgroups ranged from 117 to 348 per 1000 adults (**Supplementary Tables A3.3-A3.6**). The burden of screening, as measured by the lifetime number of required colonoscopies, varied from fewer than 800 per 1000 adults for triennial FIT during the ages of 55 to 75 years to almost 8000 per 1000 adults for colonoscopy every 5 years during the ages of 45 to 85 years. The predicted benefit of screening varied across population subgroups and was higher in SimCRC than MISCAN-Colon. In MISCAN-Colon, black females had the highest benefit from any of the screening strategies (range, 159-306 LYG per 1000 adults), white females had the lowest benefit (117-223 LYG), and white males and black males had similar intermediate benefits (141-258 and 149-284 LYG, respectively). In SimCRC, in contrast, black females and white males had the highest benefit from screening (175-348 and 194-334 LYG per 1000 40-year-olds, respectively), white females had somewhat fewer LYG (168-307 LYG), and black males had the lowest benefit from screening (142-272 LYG). In general, the lifetime number of colonoscopies required for screening was somewhat lower for black males and females because of their lower life expectancy in comparison with their white counterparts.

In the scenario with increased age-specific CRC risk, the predicted benefit from screening was substantially higher than that in the scenario of stable risk, with LYG ranging from 203 to 556 per 1000 adults in MISCAN-Colon and from 211 to 673 per 1000 adults in SimCRC; the maximum benefit from screening thus exceeded 0.5 LYG per individual in both models (**Supplementary Tables A3.3-A3.6**). The required number of colonoscopies was only moderately higher for most colonoscopy-based strategies in comparison with the scenario of stable risk and ranged from 684 to 8024 per 1000 adults across models, strategies, and population subgroups.

Efficient and near-efficient strategies

The set of strategies constituting the efficient frontier was similar across demographic subgroups and scenarios for CRC risk but differed between models (**Figure 3.2, Supplementary Figure A3.3** and **Supplementary Tables A3.3-A3.6**). In general, the predicted LYG range across evaluated strategies was smaller in MISCAN-Colon than SimCRC, and this resulted in a wider set of strategies considered near-efficient.

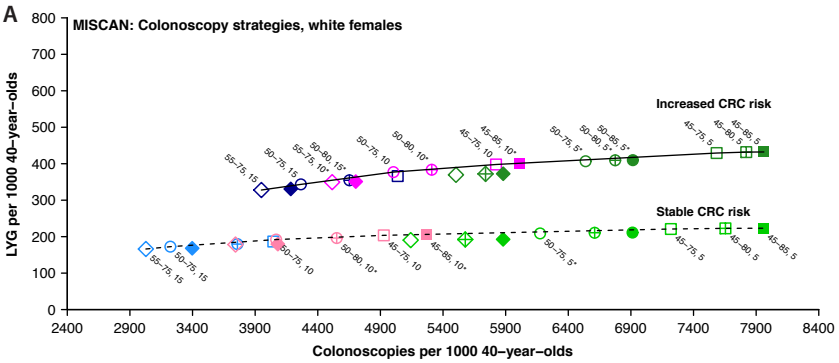
The incremental burden-to-benefit ratio across models and population subgroups ranged from 6.0 to 2032.9 from the least to most resource-intensive colonoscopy-based screening strategy in the scenario of stable CRC risk. The biggest increase in LYG per additional screening colonoscopy was derived from lowering the starting age for screening, with lower resulting ERs for blacks versus whites in MISCAN-Colon. The previously recommended strategy of colonoscopy every 10 years between the ages of 50 and 75 years was among the efficient strategies for all population subgroups in MISCAN-Colon (range of ERs, 37.7-43.2) but was less efficient in SimCRC than colonoscopy every 15 years between the ages of 45 and 75 years (range of ERs, 24.4-31.6). For strategies other than colonoscopy-based screening, the range of ERs across models, strategies, and population subgroups was smaller (2.0-149.8). Among the stool-based testing strategies, FIT screening was more efficient than most HSgFOBT and FIT-DNA strategies, regardless of race and sex.

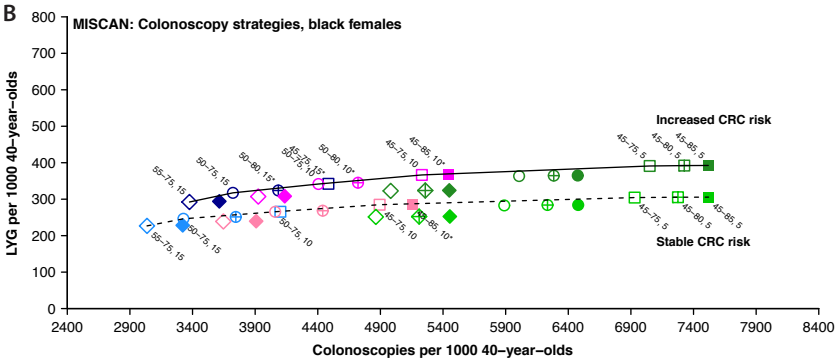
Compared with the scenario of stable CRC risk, the scenario of increased CRC risk was predicted to result in lower ERs because of increased LYG from screening; a smaller total ER range across models, evaluated strategies, and population subgroups (0.1-992.8); and a further expanded set of near-efficient strategies in MISCAN-Colon.

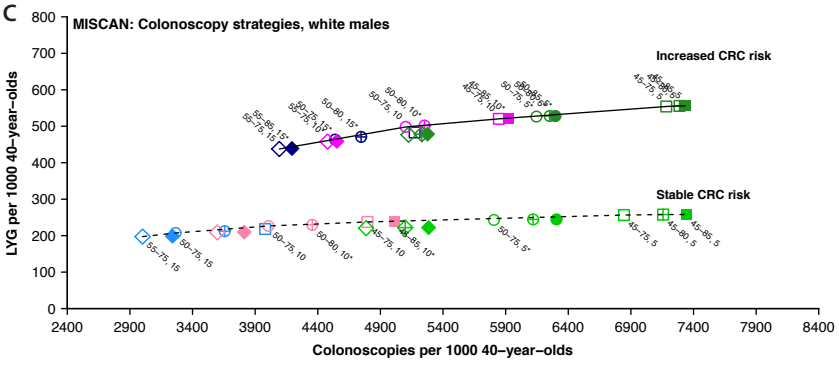
Model-recommendable strategies

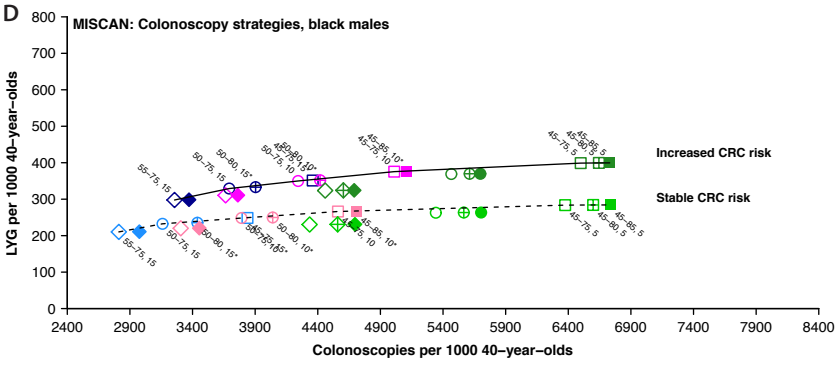
In the scenario of stable age-specific CRC risk, the 2 models differed in their recommended ages to start screening and their recommended colonoscopy screening intervals. Among all colonoscopy strategies deemed efficient or near-efficient in MISCAN-Colon, the optimal (most effective) strategy meeting both the imposed benefit and incremental burden-to-benefit criteria (ie, providing sufficient LYG and having an ER < 50) was colonoscopy every 10 years from the ages of 50 to 75 years for white males and females and colonoscopy every 10 years from the ages of 45 to 75 years for black males and females (**Table 3.3** and **Supplementary Table A3.7**). In SimCRC, colonoscopy screening every 15 years from the ages of 45 to 75 years was model-recommendable, regardless of race or sex. Among other screening strategies with the same start and stop ages, recommended strategies by both models included FIT every year and CTC every 5 years. From the stool-based screening modalities, HSgFOBT and FIT-DNA were not model-recommendable because of their inefficiency from higher false-positive rates and, in the case of FIT-DNA, also because of an unfavorable balance of burden and benefit (a minimum of 63.3 additional colonoscopies per LYG for annual FIT-DNA vs annual FIT). SIG was not model-recommendable because of a failure to provide at least 90% of the benefit of colonoscopy screening.

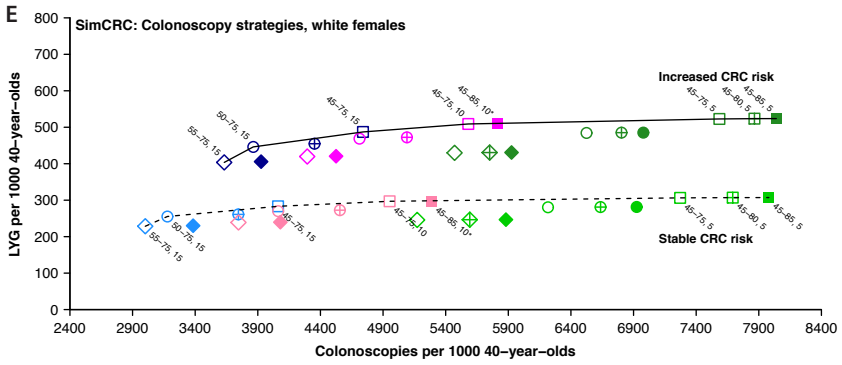
With assumed increased age-specific CRC risk, both models recommended screening between the ages of 45 and 75 years for all 4 demographic subgroups, with colonoscopy recommended every 10 years, FIT annually, SIG every 5 years, and CTC every 5 years, except for white males, for whom MISCAN-Colon recommended only colonoscopy every 5 years. SIG every 5 years was added to the list of model-recommendable strategies for other population subgroups because of its higher comparative effectiveness with more assumed distal tumors.

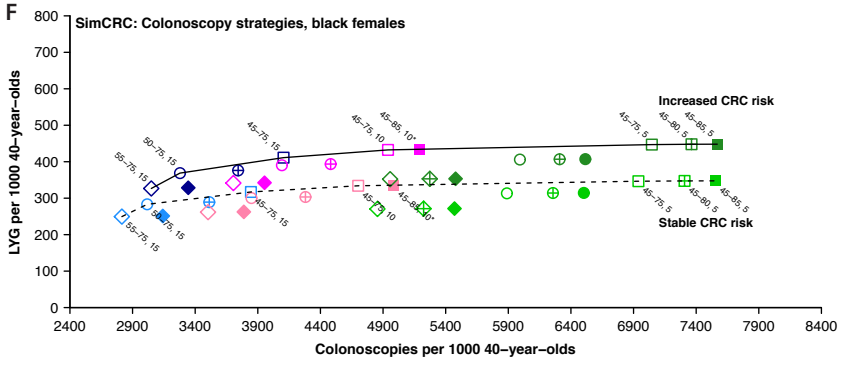

A
MISCAN: Colonoscopy strategies, white females
LYG per 1000 40–year–olds
Colonoscopies per 1000 40–year–olds
Increased CRC risk
Stable CRC risk

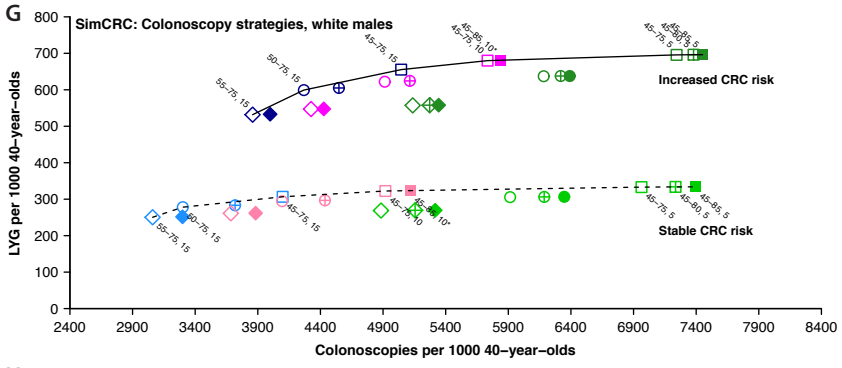

B
MISCAN: Colonoscopy strategies, black females
LYG per 1000 40–year–olds
Colonoscopies per 1000 40–year–olds
Increased CRC risk
Stable CRC risk


C
MISCAN: Colonoscopy strategies, white males
LYG per 1000 40–year–olds
Colonoscopies per 1000 40–year–olds
Increased CRC risk
Stable CRC risk


D
MISCAN: Colonoscopy strategies, black males
LYG per 1000 40–year–olds
Colonoscopies per 1000 40–year–olds
Increased CRC risk
Stable CRC risk


E
SimCRC: Colonoscopy strategies, white females
LYG per 1000 40–year–olds
Colonoscopies per 1000 40–year–olds
Increased CRC risk
Stable CRC risk


F
SimCRC: Colonoscopy strategies, black females
LYG per 1000 40–year–olds
Colonoscopies per 1000 40–year–olds
Increased CRC risk
Stable CRC risk


G
SimCRC: Colonoscopy strategies, white males
LYG per 1000 40–year–olds
Colonoscopies per 1000 40–year–olds
Increased CRC risk
Stable CRC risk

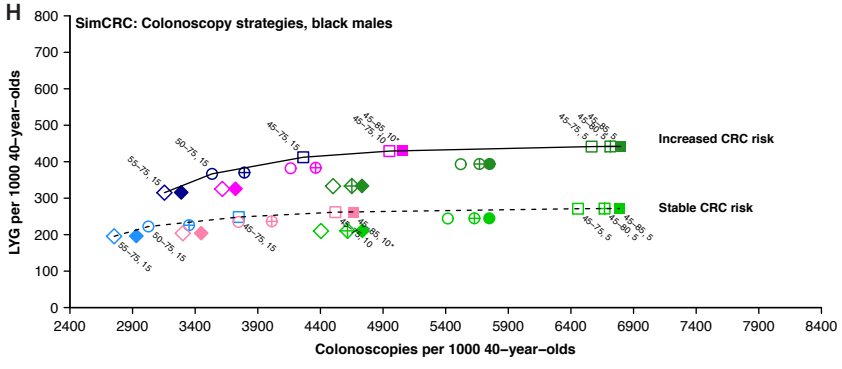

H
SimCRC: Colonoscopy strategies, black males
LYG per 1000 40–year–olds
Colonoscopies per 1000 40–year–olds
Increased CRC risk
Stable CRC risk

Figure 3.2: Lifetime number of colonoscopies and LYG for colonoscopy screening strategies under 2 scenarios for CRC risk by model and demographic subgroup. Colors reflect the screening interval (blue, 15 years; pink, 10 years; green, 5 years), symbols reflect the starting age (diamonds, 55 years; circles, 50 years; squares, 45 years), and the filling of the symbols reflects the end age (empty, 75 years; crossed, 80 years; and full, 85 years). Efficient and near-efficient strategies are labeled, with efficiency assessed among all evaluated colonoscopy-based screening strategies. In the stable-risk scenario, the risk within each age-, race-, and sex-specific demographic subgroup was assumed to have remained stable over time since the early screening phase in the United States (1975-1979 for SimCRC and 1990-1994 for MISCAN). In the increased-risk scenario, the CRC risk was increased proportionally to observed trends in CRC incidence among adults younger than 40 years. Estimated incidence rate ratios were 1.80 to 1.90 for white females (range across models), 1.24 to 1.27 for black females, 2.07 to 2.13 for white males, and 1.41 to 1.56 for black males.
CRC - colorectal cancer; LYG - life-years gained; MISCAN - Microsimulation Screening Analysis; SimCRC - Simulation Model of Colorectal Cancer.

Sensitivity analysis

Model recommendations were influenced by alternative assumptions for test performance, the minimum acceptable percentage of LYG for alternative strategies in comparison with colonoscopy screening, and a more stringent acceptance threshold for the burden-to-benefit ratio (**Supplementary Tables A3.8-A3.11**). Most notably, under worst-case performance assumptions, MISCAN-Colon no longer recommended CTC or SIG screening (**Supplementary Table A3.9**); with a 75% acceptance threshold for LYG rather than 90% in comparison with colonoscopy screening, both MISCAN-Colon and SimCRC included SIG in the set of model-recommendable strategies, regardless of the scenario for background risk (**Supplementary Table A3.10**); and with a burden-to-benefit threshold of a maximum of 40 additional colonoscopies per LYG rather than 50, MISCAN-Colon no longer recommended earlier screening for blacks in the stable CRC risk scenario (**Supplementary Table A3.11**).

Table 3.3: Model-recommendable strategies for two scenarios of CRC risk [a]

Model	Test class	White females	Black females	White males	Black Males
Scenario 1: Stable CRC risk [b]					
MISCAN	COL	50-75-10	45-75-10	50-75-10	45-75-10
	Stool	FIT 50-75-1	FIT 45-75-1	FIT 50-75-1	FIT 45-75-1
	SIG	-	-	-	-
	CTC	50-75-5	45-75-5	50-75-5	45-75-5
SimCRC	COL	45-75-15	45-75-15	45-75-15	45-75-15
	Stool	FIT 45-75-1	FIT 45-75-1	FIT 45-75-1	FIT 45-75-1
	SIG	-	-	-	-
	CTC	45-75-5	45-75-5	45-75-5	45-75-5
Scenario 2: Increased CRC risk [c]					
MISCAN	COL	45-75-10	45-75-10	45-75-5	45-75-10
	Stool	FIT 45-75-1	FIT 45-75-1	-	FIT 45-75-1
	SIG	45-75-5	45-75-5	-	45-75-5
	CTC	45-75-5	45-75-5	-	45-75-5
SimCRC	COL	45-75-10	45-75-10	45-75-10	45-75-10
	Stool	FIT 45-75-1	FIT 45-75-1	FIT 45-75-1	FIT 45-75-1
	SIG	45-75-5	45-75-5	45-75-5	45-75-5
	CTC	45-75-5	45-75-5	45-75-5	45-75-5

- = no model-recommendable strategy within this class; COL - colonoscopy; CTC - computed tomographic colonography; FIT - fecal immunochemical test; SIG - sigmoidoscopy.

[a] Numbers in each field of the table successively represent recommended age to start screening, age to stop, and interval, all in years. For the class of stool-based screening modalities, the model-recommendable modality is also included, i.e. FIT.

[b] Risk within each age-, race-, and sex-specific demographic subgroup was assumed to have remained stable over time since the early screening period in the U.S.

[c] CRC risk was increased proportional to observed trends in CRC incidence among adults under 40 years old. Estimated incidence rate ratios were 1.77-1.90 for white females (range across models), 1.27-1.30 for black females, 2.01-2.13 for white males, and 1.41-1.55 for black males.

Discussion

The results from this modeling study suggest that CRC screening should be considered from the age of 45 years in average-risk black Americans. The recommended age to begin screening among whites varied across models, with one model suggesting that screening should begin at the age of 50 years in a scenario of stable age-specific CRC risk and with the other suggesting that screening should begin at the age of 45 years. If lifetime risk increases proportionally to trends observed at younger ages, both models support recommending screening from the age of 45 years for all population subgroups. Within blacks and whites, recommendable strategies generally did not differ for men and women. Although men

are at higher risk for CRC than women, the higher potential benefit from screening is partly offset by their lower life expectancy. Model-recommendable strategies generally included colonoscopy screening every 10 or 15 years, FIT screening every year, and CTC every 5 years through the age of 75 years. SIG was not consistently model-recommendable because of its inability to meet the minimum benefit criterion, and HSgFOBT and FIT-DNA were not recommendable because of inefficiency.

Model-based recommendations were dependent on assumptions for CRC risk. The models used in this study were calibrated to data from a period in which guideline-adherent screening was uncommon to avoid serious contamination from either prevention of disease or an earlier diagnosis. By making this assumption, the models implicitly assumed that the current underlying age-specific risk of CRC in the absence of screening would be the same as that observed in the prescreening era. However, SEER data indicate that incidence has risen for every subsequent generation born since the 1950s,[16] and this suggests that the projected underlying lifetime risk for current 40- to 50-year-olds may be elevated in comparison with earlier birth cohorts. To reflect this uncertainty, we considered 2 scenarios for lifetime CRC risk: one in which age-, race-, and sex-specific risks were assumed to remain stable over time and another in which risks increased proportionally to trends observed in young-onset cases. As we showed, screening should be considered as early as the age of 45 years in both white and black men and women if the lifetime risk is increasing. This stems from converging risks in white and black adults younger than 40 years [139,140] and is consistent with the recommendation in an accompanying article by Peterse et al.[99] The article by Peterse et al. discusses the potential increase in disease risk in more detail, including possible causal mechanisms other than increased adenoma onset.

There were some discrepancies in screening recommendations across the 2 models. Under the first scenario of no increase in age-, race-, and sex-specific CRC risk over time, MISCAN-Colon recommended screening for black adults from the age of 45 years and for white adults from the age of 50 years, both at 10-year intervals for colonoscopy. In contrast, SimCRC recommended both white and black adults begin screening at the age of 45 years with longer recommended colonoscopy intervals of 15 years. These differences reflect the differences in the dwell time of adenomas (ie, the time from adenoma onset to symptom-detected cancer in the absence of screening among individuals with a CRC diagnosis)[40] and were observed in previous analyses for the USPSTF.[96] SimCRC has longer adenoma dwell times, and this suggests that screening can be deferred longer after a negative previous screening result. In addition, models were calibrated to different time periods from the early-screening era (1975-1979 for SimCRC and 1990-1994 for MISCAN-Colon). Although there may have been some screening during the more recent period used to inform MISCAN-Colon, this was to a large extent low-sensitivity guaiac-based fecal occult blood testing with limited presumed influence on CRC incidence.[141] CRC incidence was similar in blacks and whites until the mid-1980s, but it has since been higher among blacks than whites for screening-eligible ages[140]; this may partly explain why MISCAN-Colon recommended differential screening by race. Although colonoscopy every 15 years between the ages of 45 and 75 years was not considered efficient in MISCAN-Colon for white adults in the stable-risk scenario,

the colonoscopy requirement and the predicted number of LYG were close to those for colonoscopy every 10 years from the age of 50 to 75 years. This suggests that the former strategy might be considered an option if uniformity in starting ages across demographic population subgroups were desired. To date, younger recommended start ages for screening black individuals by some organizations [119,120] have not led to higher screening rates among blacks in comparison with whites aged 45 to 49 years according to National Health Interview Survey data.[142] Conversely, there is no evidence that race-specific recommendations negatively affect screening uptake among whites aged 50 to 54 years.

The cancer registry data used to inform the models in this study did not allow the simulation of races/ethnicities other than black and white. Although recommendations depend on patterns in risk across a person's lifetime and on other-cause mortality, we expect that model recommendations for other races/ethnicities except Alaskan Natives would be closer to those for whites than those for blacks because of the relatively similar observed CRC mortality risks.[15]

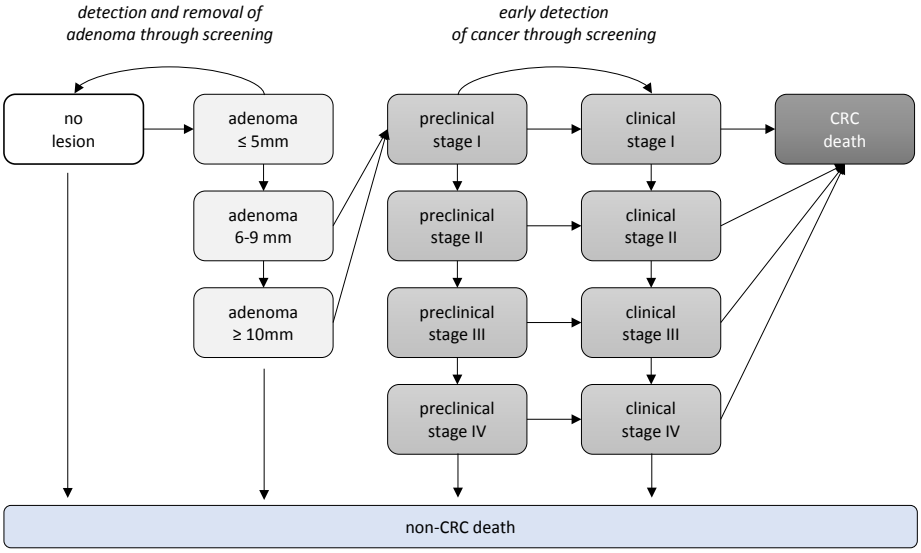
To our knowledge, this is the first time that race and sex differences have been formally considered for model-based screening recommendations. The approach and conclusions from the first stable age-specific risk scenario in this study were similar to a study performed by Lansdorp-Vogelaar et al.[143] Our model-recommended strategies differ from the 2016 USPSTF screening recommendations, which suggested offering screening from the ages of 50 to 75 years to all adults at average risk.[76] Consistent with 2009 American College of Gastroenterology [119] and 2017 US Multi-Society Task Force guidelines,[120] our models recommend 45 years as the preferred starting age for blacks. Previous modeling studies have suggested that personalizing the age to stop screening may result in more efficient use of resources and help to reduce potential harms from screening.[144] However, tailoring screening recommendations to different subgroups may complicate the promotion of screening in the primary care setting, and this may hamper guideline-consistent adherence. More research is needed to assess the performance of personalized screening programs before wide application in practice.

There are some general limitations to the approach of this study for selecting model-recommendable screening strategies. First, we predicted the potential benefit of screening under the assumption of 100% adherence to provide the best possible recommendation for patients who adhere to screening. In practice, some forms of screening may be less acceptable to people than others,[145] and preferences may vary by setting, race, and sex and over time.[146-148] These preferences are an important determinant of the success of any screening approach and should be considered in practice. A test that is predicted to have higher performance in the model in comparison with other tests under the assumption of full adherence may have lower population-based performance because of lower acceptance. Second, to measure the burden of screening, we used the required number of colonoscopies. This ruled out a direct comparison of all strategies because the burden from tests other than colonoscopy was not explicitly considered. In practice, the potential burden from the primary screening method, such as low-dose radiation exposure in CTC, should also be considered when one is recommending any of the

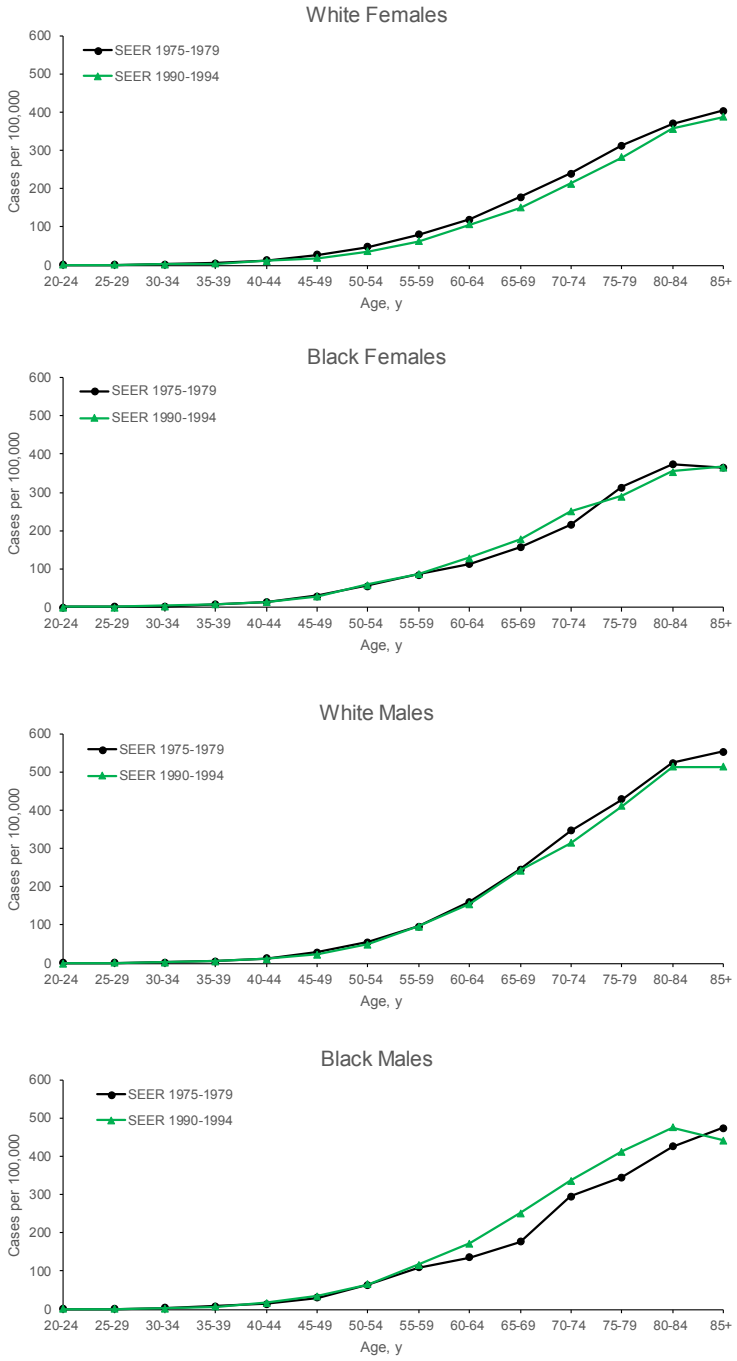
evaluated strategies. Finally, there are no objective or widely accepted standards for the decision criteria applied in this study to narrow down the set of potentially recommendable screening strategies. We used similar acceptance thresholds for the degree of efficiency (proximity to the efficient frontier), minimum number of LYG, and maximum number of colonoscopies per LYG as applied in analyses performed for the USPSTF.[96] As we showed in sensitivity analyses, sigmoidoscopy may be added to recommended screening modalities with a more relaxed benefit criterion of at least 75% of LYG in comparison with colonoscopy-based screening. Earlier ages to start screening may not be acceptable with more stringent burden-to-benefit thresholds.

In conclusion, using an established decision-analytic modeling approach, we suggest that screening for CRC should be considered between the ages 45 and 75 years for black adults in the United States and also for whites, particularly if lifetime risks have increased similarly to trends observed under the age of 40 years. Colonoscopy every 10 to 15 years, FIT every year, and CTC every 5 years were predicted to generate similar overall LYG with an acceptable colonoscopy burden. Our findings differ from previous model recommendations for the USPSTF, in which no distinction was made between blacks and whites, but are consistent with recent recommendations by the US Multi-Society Task Force.[120] In recommending any particular screening strategy, policymakers and physicians should consider patient preferences.

Appendix

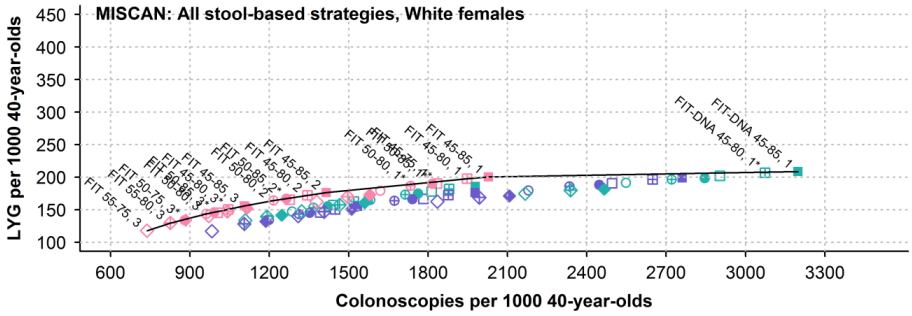


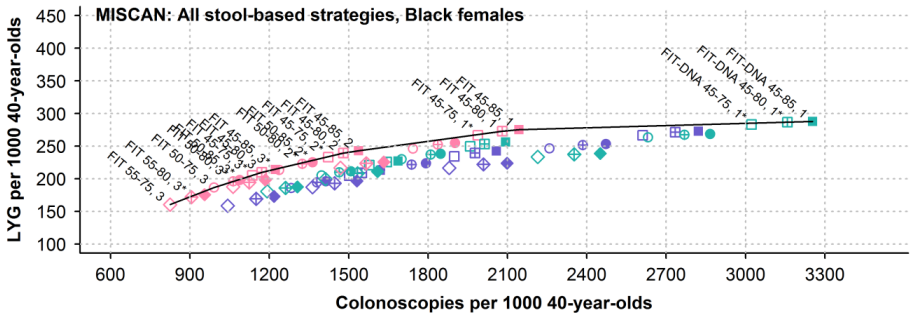
Supplementary Figure A3.1: Natural history of CRC and the effects of screening as simulated by MISCAN-Colon and SimCRC. The opportunity to intervene in the natural history through screening is noted in italic. Screening can either remove an adenoma, thus moving a person to the "no lesion" state, or diagnose a preclinical cancer, which, if detected at an earlier stage, may be more amenable to treatment.

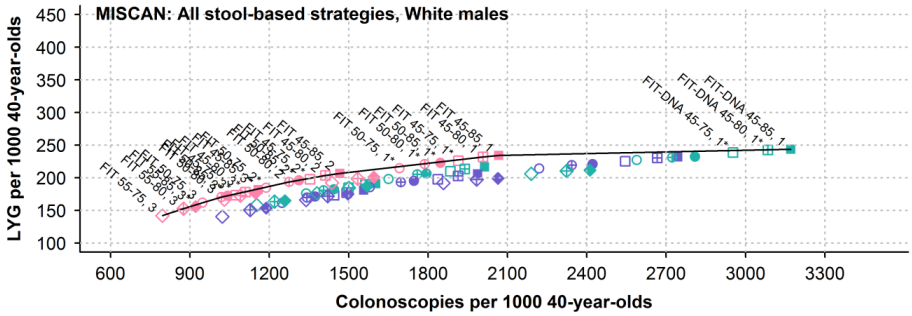


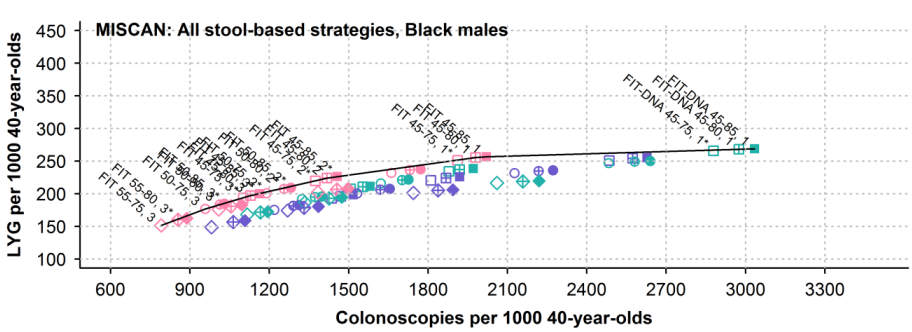
Supplementary Figure A3.2: CRC incidence by age, race and sex in the surveillance epidemiology end results program (SEER) for the period 1975-1979 *vs* 1990-1994.

A

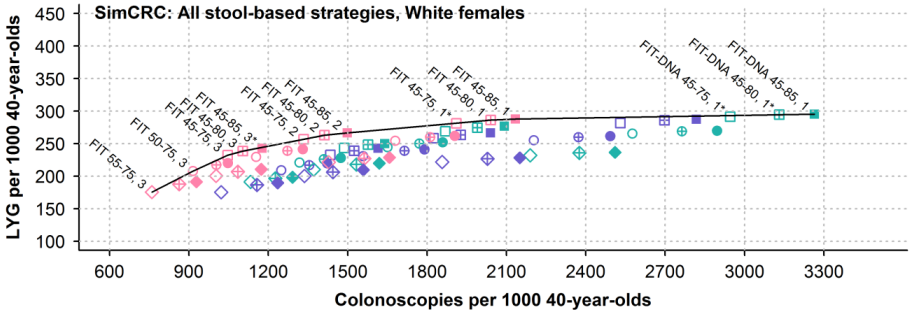

MISCAN: All stool-based strategies, White females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
100
150
200
250
300
350
400
450
600
900
1200
1500
1800
2100
2400
2700
3000
3300
FIT-DNA 45-85, 1
FIT-DNA 45-80, 1*
FIT 45-85, 1
FIT 45-80, 1
FIT 45-75, 1
FIT 50-80, 1*
FIT 50-75, 1*
FIT 45-85, 2
FIT 45-80, 2
FIT 45-75, 2
FIT 50-80, 2*
FIT 50-75, 2*
FIT 55-80, 2*
FIT 55-75, 2*
FIT 45-85, 3
FIT 45-80, 3
FIT 45-75, 3
FIT 50-80, 3*
FIT 50-75, 3*
FIT 55-80, 3*
FIT 55-75, 3

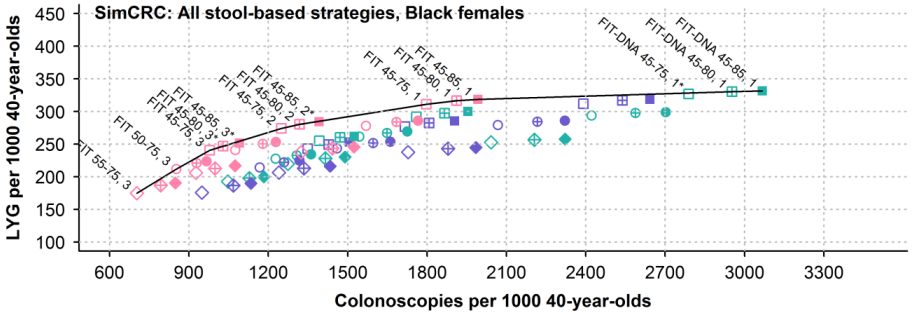

MISCAN: All stool-based strategies, Black females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
100
150
200
250
300
350
400
450
600
900
1200
1500
1800
2100
2400
2700
3000
3300
FIT-DNA 45-85, 1
FIT-DNA 45-80, 1*
FIT-DNA 45-75, 1*
FIT 45-85, 1
FIT 45-80, 1
FIT 45-75, 1*
FIT 50-80, 1*
FIT 50-75, 1*
FIT 45-85, 2
FIT 45-80, 2
FIT 45-75, 2*
FIT 50-80, 2*
FIT 50-75, 2*
FIT 55-80, 2*
FIT 55-75, 2*
FIT 45-85, 3
FIT 45-80, 3
FIT 45-75, 3
FIT 50-80, 3*
FIT 50-75, 3*
FIT 55-80, 3*
FIT 55-75, 3

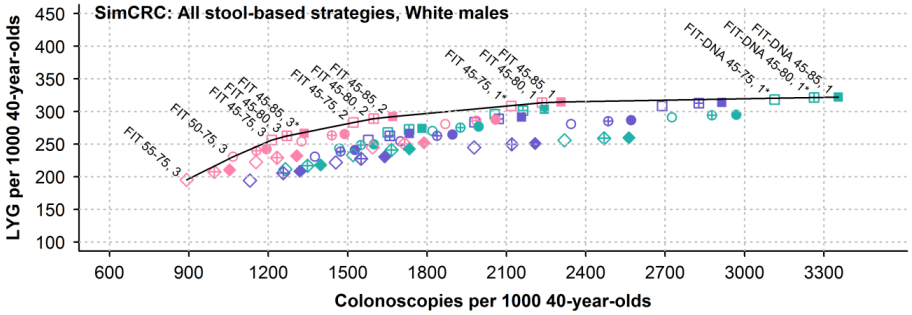

MISCAN: All stool-based strategies, White males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
100
150
200
250
300
350
400
450
600
900
1200
1500
1800
2100
2400
2700
3000
3300
FIT-DNA 45-85, 1
FIT-DNA 45-80, 1*
FIT-DNA 45-75, 1*
FIT 45-85, 1
FIT 45-80, 1
FIT 45-75, 1*
FIT 50-80, 1*
FIT 50-75, 1*
FIT 45-85, 2
FIT 45-80, 2
FIT 45-75, 2*
FIT 50-80, 2*
FIT 50-75, 2*
FIT 55-80, 2*
FIT 55-75, 2*
FIT 45-85, 3
FIT 45-80, 3
FIT 45-75, 3
FIT 50-80, 3*
FIT 50-75, 3*
FIT 55-80, 3*
FIT 55-75, 3

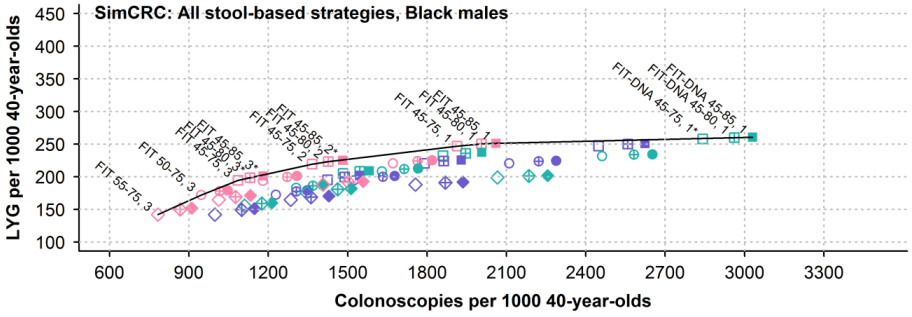

MISCAN: All stool-based strategies, Black males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
100
150
200
250
300
350
400
450
600
900
1200
1500
1800
2100
2400
2700
3000
3300
FIT-DNA 45-85, 1
FIT-DNA 45-80, 1*
FIT-DNA 45-75, 1*
FIT 45-85, 1
FIT 45-80, 1
FIT 45-75, 1*
FIT 50-80, 1*
FIT 50-75, 1*
FIT 45-85, 2
FIT 45-80, 2
FIT 45-75, 2*
FIT 50-80, 2*
FIT 50-75, 2*
FIT 55-80, 2*
FIT 55-75, 2*
FIT 45-85, 3
FIT 45-80, 3
FIT 45-75, 3
FIT 50-80, 3*
FIT 50-75, 3*
FIT 55-80, 3*
FIT 55-75, 3

A continued

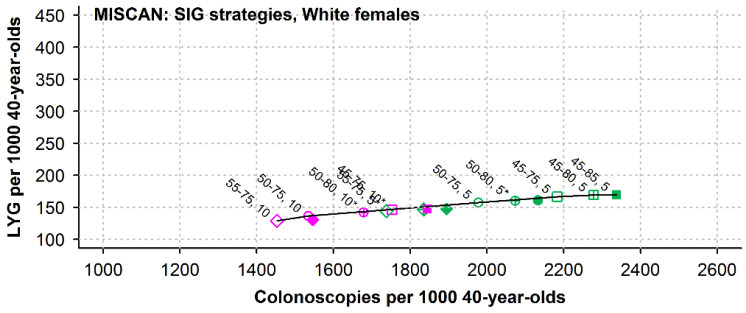

SimCRC: All stool-based strategies, White females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
FIT 55-75, 3
FIT 50-75, 3
FIT 45-85, 3*
FIT 45-80, 3
FIT 45-75, 3
FIT 45-85, 2*
FIT 45-80, 2
FIT 45-75, 2
FIT 45-85, 1
FIT 45-80, 1*
FIT 45-75, 1*
FIT-DNA 45-85, 1
FIT-DNA 45-80, 1*
FIT-DNA 45-75, 1*

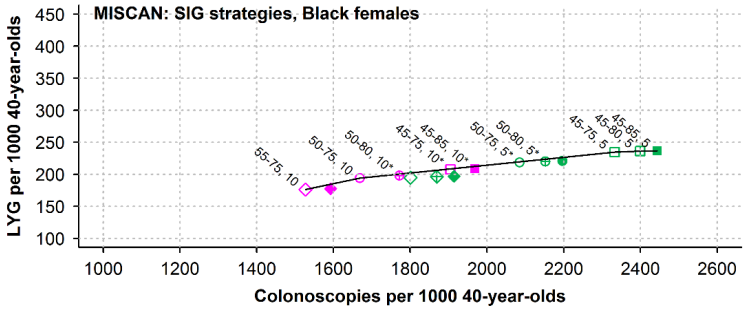

SimCRC: All stool-based strategies, Black females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
FIT 55-75, 3
FIT 50-75, 3
FIT 45-85, 3*
FIT 45-80, 3
FIT 45-75, 3
FIT 45-85, 2*
FIT 45-80, 2
FIT 45-75, 2
FIT 45-85, 1
FIT 45-80, 1*
FIT 45-75, 1*
FIT-DNA 45-85, 1
FIT-DNA 45-80, 1*
FIT-DNA 45-75, 1*

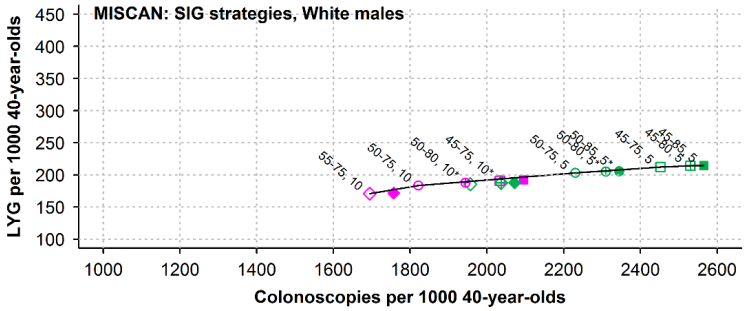

SimCRC: All stool-based strategies, White males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
FIT 55-75, 3
FIT 50-75, 3
FIT 45-85, 3*
FIT 45-80, 3
FIT 45-75, 3
FIT 45-85, 2*
FIT 45-80, 2
FIT 45-75, 2
FIT 45-85, 1
FIT 45-80, 1*
FIT 45-75, 1*
FIT-DNA 45-85, 1
FIT-DNA 45-80, 1*
FIT-DNA 45-75, 1*

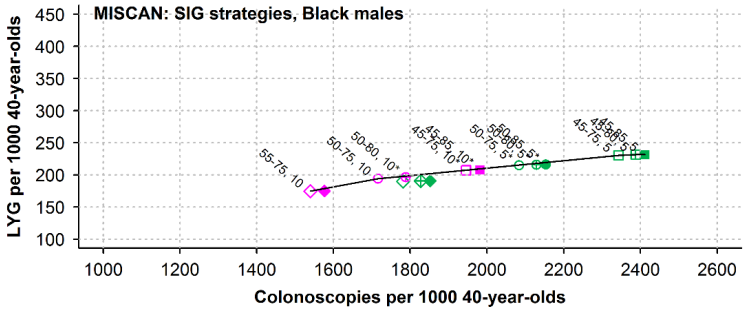

SimCRC: All stool-based strategies, Black males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
FIT 55-75, 3
FIT 50-75, 3
FIT 45-85, 3*
FIT 45-80, 3
FIT 45-75, 3
FIT 45-85, 2*
FIT 45-80, 2
FIT 45-75, 2
FIT 45-85, 1
FIT 45-80, 1*
FIT 45-75, 1*
FIT-DNA 45-85, 1
FIT-DNA 45-80, 1*
FIT-DNA 45-75, 1*

B

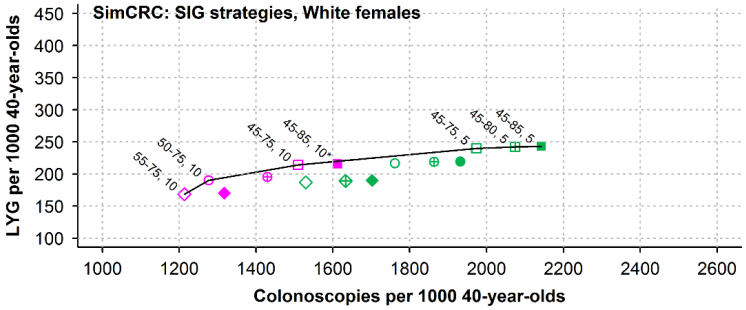

MISCAN: SIG strategies, White females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
55-75, 10
50-75, 10
50-80, 10*
45-75, 10*
50-75, 5*
50-80, 5*
45-75, 5*
45-80, 5*
45-85, 5*

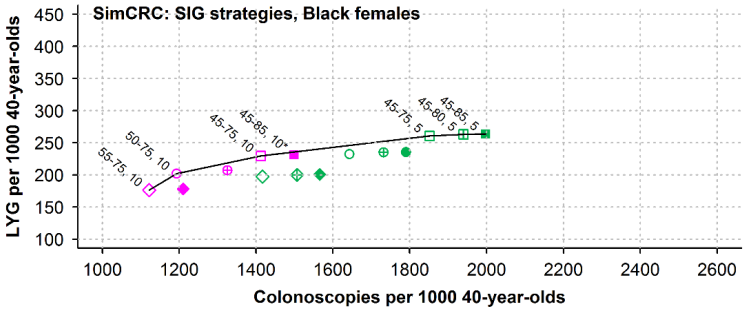

MISCAN: SIG strategies, Black females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
55-75, 10
50-75, 10
50-80, 10*
45-75, 10*
45-85, 10*
50-75, 5*
50-80, 5*
45-75, 5*
45-80, 5*
45-85, 5*

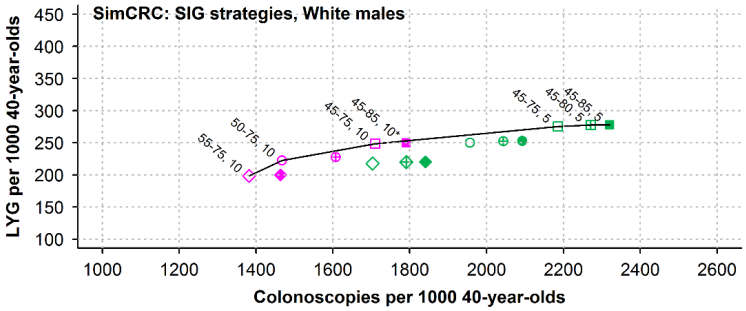

MISCAN: SIG strategies, White males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
55-75, 10
50-75, 10
50-80, 10*
45-75, 10*
50-75, 5*
50-80, 5*
45-75, 5*
45-80, 5*
45-85, 5*

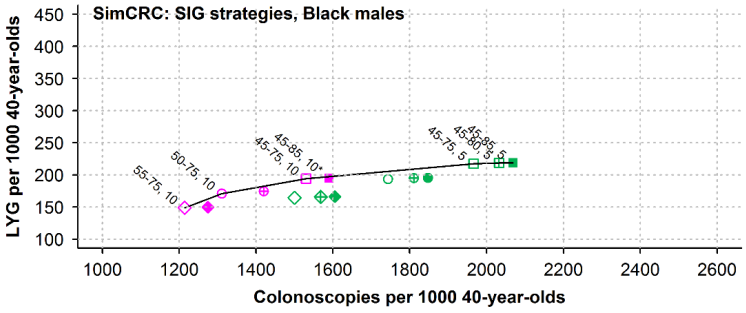

MISCAN: SIG strategies, Black males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
55-75, 10
50-75, 10
50-80, 10*
45-75, 10*
45-85, 10*
50-75, 5*
50-80, 5*
45-75, 5*
45-80, 5*
45-85, 5*

B continued

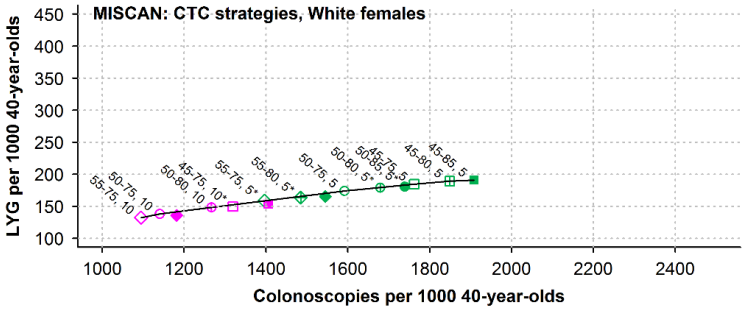

SimCRC: SIG strategies, White females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
50-75, 10
55-75, 10
45-75, 10
45-85, 10*
45-75, 5
45-80, 5
45-85, 5

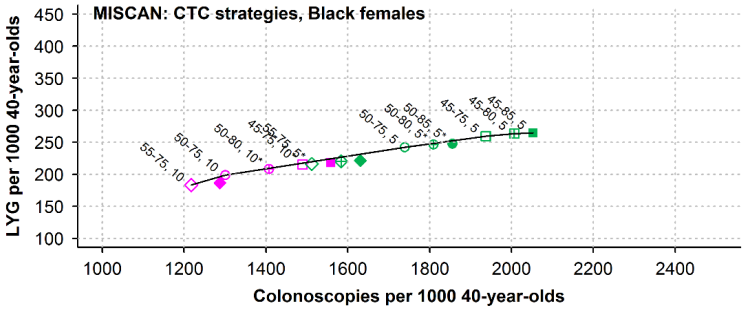

SimCRC: SIG strategies, Black females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
50-75, 10
55-75, 10
45-75, 10
45-85, 10*
45-75, 5
45-80, 5
45-85, 5

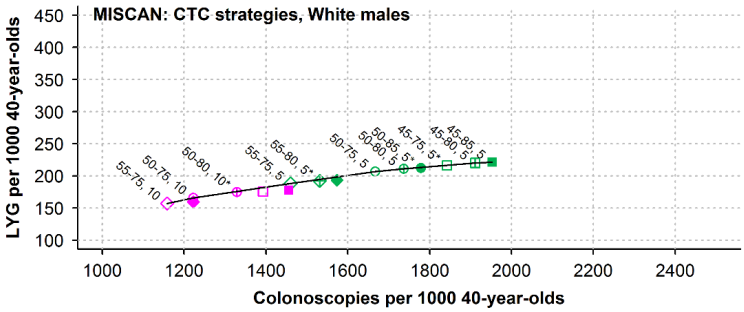

SimCRC: SIG strategies, White males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
50-75, 10
55-75, 10
45-75, 10
45-85, 10*
45-75, 5
45-80, 5
45-85, 5

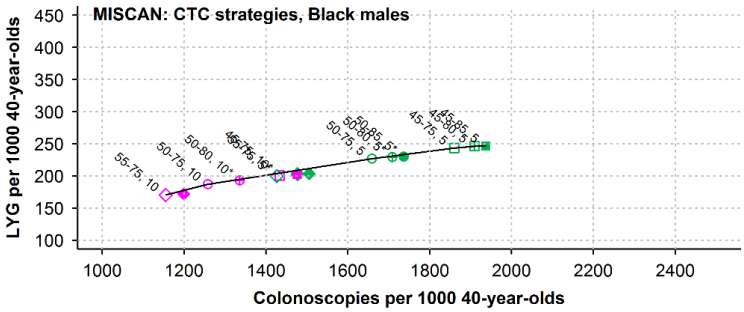

SimCRC: SIG strategies, Black males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
50-75, 10
55-75, 10
45-75, 10
45-85, 10*
45-75, 5
45-80, 5
45-85, 5

C

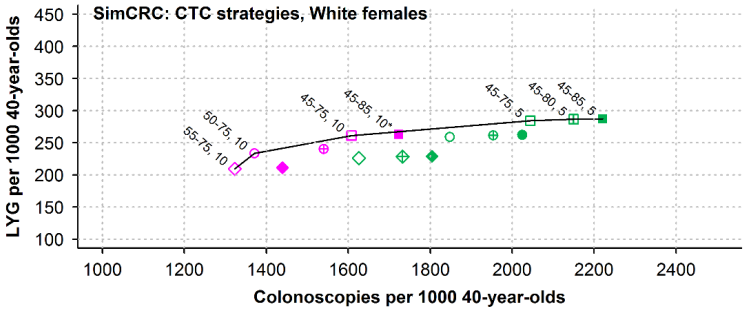

MISCAN: CTC strategies, White females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
450
400
350
300
250
200
150
100
1000
1200
1400
1600
1800
2000
2200
2400
50-75, 10
55-75, 10
50-80, 10*
45-75, 10*
55-75, 5*
55-80, 5*
50-75, 5
50-80, 5*
50-85, 5*
45-75, 5*
45-80, 5*
45-85, 5*

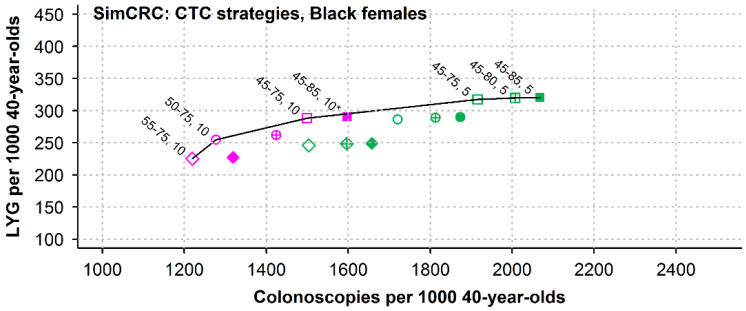

MISCAN: CTC strategies, Black females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
450
400
350
300
250
200
150
100
1000
1200
1400
1600
1800
2000
2200
2400
55-75, 10
50-75, 10
50-80, 10*
45-75, 10*
55-75, 5*
50-75, 5
50-80, 5*
50-85, 5*
45-75, 5*
45-80, 5*
45-85, 5*

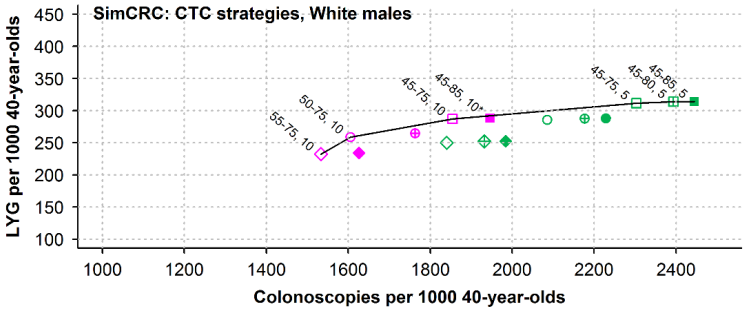

MISCAN: CTC strategies, White males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
450
400
350
300
250
200
150
100
1000
1200
1400
1600
1800
2000
2200
2400
55-75, 10
50-75, 10
50-80, 10*
55-75, 5*
55-80, 5*
50-75, 5
50-80, 5*
50-85, 5*
45-75, 5*
45-80, 5*
45-85, 5*

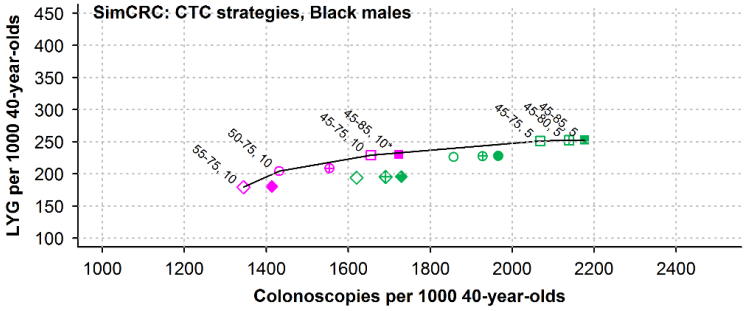

MISCAN: CTC strategies, Black males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
450
400
350
300
250
200
150
100
1000
1200
1400
1600
1800
2000
2200
2400
55-75, 10
50-75, 10
50-80, 10*
50-75, 5
50-80, 5*
50-85, 5*
45-75, 5*
45-80, 5*
45-85, 5*

C continued


SimCRC: CTC strategies, White females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
50-75, 10
55-75, 10
45-75, 10
45-85, 10*
45-75, 5
45-80, 5
45-85, 5


SimCRC: CTC strategies, Black females
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
50-75, 10
55-75, 10
45-75, 10
45-85, 10*
45-75, 5
45-80, 5
45-85, 5


SimCRC: CTC strategies, White males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
50-75, 10
55-75, 10
45-75, 10
45-85, 10*
45-75, 5
45-80, 5
45-85, 5


SimCRC: CTC strategies, Black males
LYG per 1000 40-year-olds
Colonoscopies per 1000 40-year-olds
50-75, 10
55-75, 10
45-75, 10
45-85, 10*
45-75, 5
45-80, 5
45-85, 5

Supplementary Figure A3.3: Lifetime number of colonoscopies and LYG for stool-based (A), sigmoidoscopy (B) and CTC (C) screening strategies under a scenario of stable CRC risk, by model and demographic subgroup [a]

A: Colors reflect the screening test (pink=FIT; purple=HSgFOBT; turquoise=FIT-DNA), symbols reflect the starting age (diamond=55; circle=50; square=45 years), fill reflects end age (empty=75; cross=80; full=85 years). Efficient and near-efficient* strategies are labelled, with efficiency assessed among all evaluated stool-based screening strategies.

B: Colors reflect the screening interval (pink=10; green=5 years), symbols reflect the starting age (diamond=55; circle=50; square=45 years), fill reflects end age (empty=75; cross=80; full=85 years). Efficient and near-efficient* strategies are labelled, with efficiency assessed among all evaluated SIG-based screening strategies.

C: Colors reflect the screening interval (pink=10; green=5 years), symbols reflect the starting age (diamond=55; circle=50; square=45 years), fill reflects end age (empty=75; cross=80; full=85 years). Efficient and near-efficient* strategies are labelled, with efficiency assessed among all evaluated CTC-based screening strategies.

[a] Risk within each age-, race-, and sex-specific demographic subgroup was assumed to have remained stable over time since the early screening phase in the U.S. (1975-1979 for SimCRC; 1990-1994 for MISCAN). Outcomes for a scenario with assumed increased risk are included in Supplementary Tables A3.3-A3.6.

Supplementary Table A3.1: Summary of differences of this analysis compared with a previous analysis for the US preventive services task force.

	ACS analysis	USPSTF analysis
Desion models	MISCAN-Colon and SimCRC	MISCAN-Colon, SimCRC, and CRC-Spin
Simulated population	Race- and sex-specific 40-year-old adults at average risk of CRC	All 40-year-old adults at average risk of CRC
Data source, life expectancy	2013 U.S. lifetables	2009 U.S. lifetables
Data source, CRC risk	SEER 1975-1979 (SimCRC) and SEER 1990-1994 (MISCAN-Colon)	SEER 1975-1979
Evaluated scenarios	Stable and increased age-specific risk based on trends in incidence under age 40, including a shift to more distal localization	Stable age-specific risk
Evaluated strategies	Single-test strategies only	Single- and hybrid test strategies
Decision criterion for selection of model-recommendable strategies, efficiency	Reassessed for classes of screening modality other than colonoscopy after selecting age to start and stop	Assessed among start ages 50 and 55 and stop ages 75, 80, and 85 for all screening modalities
Decision criterion for selection of model-recommendable strategies, incremental burden-to-benefit	For colonoscopy-based screening strategies, an acceptance threshold for the incremental number of colonoscopies per LYG of maximum 50 was applied	For colonoscopy-based screening strategies, an acceptance threshold of less than or equal to the incremental number of colonoscopies per LYG for the strategy recommended by the USPSTF in 2008, namely colonoscopy every 10 years from ages 50 to 75, was applied; this number ranged from 39-65 across the three models included in that study

ACS - American Cancer Society; LYG - life-year gained; SEER - Surveillance Epidemiology and End Results Program; USPSTF - US Preventive Services Task Force.

Supplementary Table A3.2: Simulated life expectancy and lifetime CRC risk in the absence of screening under two scenarios of CRC risk, by model and demographic subgroup

	White females	Black females	White males	Black males
Scenario 1: Stable CRC risk [a]				
MISCAN-Colon				
Life expectancy, years	42.3	40.0	38.5	35.3
Lifetime CRC incidence [b]	59.3	59.9	70.7	62.0
Lifetime CRC mortality [b]	21.9	28.4	27.2	29.6
LY lost to CRC [b]	278	387	322	365
SimCRC				
Life expectancy, years	42.3	40.0	38.4	35.3
Lifetime CRC incidence [b]	66.5	64.4	78.6	58.7
Lifetime CRC mortality [b]	25.7	30.0	31.0	27.0
LY lost to CRC [b]	335	387	366	307
Scenario 2: Increased CRC risk [c]				
MISCAN-Colon				
Life expectancy, years	42.1	39.9	38.1	35.1
Lifetime CRC incidence [b]	112.6	76.7	149.0	88.0
Lifetime CRC mortality [b]	42.9	36.8	59.0	42.5
LY lost to CRC [b]	539	497	696	518
SimCRC				
Life expectancy, years	42.1	39.9	38.1	35.1
Lifetime CRC incidence [b]	119.5	79.9	162.5	91.7
Lifetime CRC mortality [b]	45.4	37.6	64.6	43.2
LY lost to CRC [b]	541	490	739	510

LY - life-years.

[a] Risk within each age-, race-, and sex-specific demographic subgroup was assumed to have remained stable over time since the early screening period in the U.S. (1975-1979 for SimCRC; 1990-1994 for MISCAN).

[b] CRC outcomes, per 1000 40-year-olds.

[c] CRC risk was increased proportional to observed trends in CRC incidence among adults under 40 years old. Estimated incidence rate ratios were 1.80-1.90 for white females (range across models), 1.24-1.27 for black females, 2.07-2.13 for white males, and 1.41-1.56 for black males.

Supplementary Table A3.3: Lifetime number of colonoscopies and LYG for all evaluated screening strategies under two scenarios for CRC risk, by model, in white females [a]

		Outcomes per 1000 40-year-olds								
Subgroup	Modality, and age to begin- end screening, interval, y	Stool tests	SIGs	CTCs	COLs [b]	LYG	CRC cases averted	CRC deaths averted [c]	Relative distance from efficient frontier [d]	ER [e]
MISCAN - Scenario 1: Stable CRC risk										
WF	No screening	0	0	0	59	0	0	0	-	-
WF	COL 55-75, 15	0	0	0	3028	166	33	15	0%	17.9
WF	COL 55-80, 15	0	0	0	3028	166	33	15	0%	17.9
WF	COL 55-85, 15	0	0	0	3397	168	33	16	-4.7%	Dom.
WF	COL 50-75, 15	0	0	0	3223	172	32	15	0%	30.8
WF	COL 50-80, 15	0	0	0	3758	180	34	16	-2.9%	Dom.
WF	COL 50-85, 15	0	0	0	3758	180	34	16	-2.9%	Dom.
WF	COL 45-75, 15	0	0	0	4045	187	35	16	-2.5%	Dom.
WF	COL 45-80, 15	0	0	0	4045	187	35	16	-2.5%	Dom.
WF	COL 45-85, 15	0	0	0	4045	187	35	16	-2.5%	Dom.
WF	COL 55-75, 10	0	0	0	3743	178	36	17	-3.3%	Dom.
WF	COL 55-80, 10	0	0	0	3743	178	36	17	-3.3%	Dom.
WF	COL 55-85, 10	0	0	0	4081	180	36	17	-6.6%	Dom.
WF	COL 50-75, 10	0	0	0	4067	192	36	17	0%	43.2
WF	COL 50-80, 10	0	0	0	4551	196	38	18	-1.2%	116.5*
WF	COL 50-85, 10	0	0	0	4551	196	38	18	-1.2%	116.5*
WF	COL 45-75, 10	0	0	0	4927	204	38	18	0%	74.4
WF	COL 45-80, 10	0	0	0	4927	204	38	18	0%	74.4
WF	COL 45-85, 10	0	0	0	5265	205	38	18	-0.7%	297.2*
WF	COL 55-75, 5	0	0	0	5142	190	39	18	-7.2%	Dom.
WF	COL 55-80, 5	0	0	0	5578	192	39	18	-7.8%	Dom.
WF	COL 55-85, 5	0	0	0	5880	193	40	18	-8.7%	Dom.
WF	COL 50-75, 5	0	0	0	6175	209	40	18	-1.9%	231.7*
WF	COL 50-80, 5	0	0	0	6611	211	41	19	-2.6%	Dom.
WF	COL 50-85, 5	0	0	0	6913	211	41	19	-3.4%	Dom.
WF	COL 45-75, 5	0	0	0	7219	221	41	19	0%	131.9
WF	COL 45-80, 5	0	0	0	7655	223	42	19	0%	237.0
WF	COL 45-85, 5	0	0	0	7957	223	42	19	0%	908.9
WF	FIT 55-75, 3	5566	0	0	737	118	13	10	0%	5.8
WF	FIT 55-80, 3	6683	0	0	826	130	15	12	0%	7.5
WF	FIT 55-85, 3	7494	0	0	884	134	15	13	-1.3%	Dom.
WF	FIT 50-75, 3	7173	0	0	880	134	15	11	-1.0%	12.5*
WF	FIT 50-80, 3	8236	0	0	962	144	16	13	0%	9.5
WF	FIT 50-85, 3	8654	0	0	991	146	16	13	-0.1%	13.1*
WF	FIT 45-75, 3	8806	0	0	1004	145	16	12	-1.3%	Dom.
WF	FIT 45-80, 3	9347	0	0	1044	151	17	13	-0.1%	12.4*

table continues

MISCAN - Scenario 1: Stable CRC risk										
WF	FIT 45-85, 3	10206	0	0	1105	156	17	14	0%	12.0
WF	FIT 55-75, 2	8188	0	0	971	140	18	12	-3.1%	Dom.
WF	FIT 55-80, 2	9206	0	0	1041	147	19	14	-2.1%	Dom.
WF	FIT 55-85, 2	10371	0	0	1115	152	19	14	-3.0%	Dom.
WF	FIT 50-75, 2	9907	0	0	1115	154	19	13	-1.7%	Dom.
WF	FIT 50-80, 2	11420	0	0	1216	164	21	14	0%	13.5
WF	FIT 50-85, 2	12193	0	0	1265	167	21	15	-0.1%	16.7*
WF	FIT 45-75, 2	12244	0	0	1277	165	20	14	-1.5%	Dom.
WF	FIT 45-80, 2	13249	0	0	1344	172	21	15	0%	16.1
WF	FIT 45-85, 2	14402	0	0	1415	176	22	16	0%	16.3
WF	FIT 55-75, 1	13579	0	0	1379	162	24	14	-6.8%	Dom.
WF	FIT 55-80, 1	15655	0	0	1496	170	26	16	-5.4%	Dom.
WF	FIT 55-85, 1	17232	0	0	1580	173	27	16	-5.5%	Dom.
WF	FIT 50-75, 1	16959	0	0	1620	179	26	15	-2.8%	Dom.
WF	FIT 50-80, 1	19018	0	0	1734	187	28	16	-1.2%	30.8*
WF	FIT 50-85, 1	20587	0	0	1816	190	28	17	-1.4%	30.3*
WF	FIT 45-75, 1	20462	0	0	1834	190	27	16	-1.5%	30.5*
WF	FIT 45-80, 1	22513	0	0	1947	197	29	17	0%	25.1
WF	FIT 45-85, 1	24077	0	0	2028	200	29	17	0%	28.6
WF	FIT-DNA 55-75, 5	3821	0	0	1109	134	18	12	-14.3%	Dom.
WF	FIT-DNA 55-80, 5	4304	0	0	1191	140	19	13	-13.9%	Dom.
WF	FIT-DNA 55-85, 5	4652	0	0	1247	142	19	14	-14.6%	Dom.
WF	FIT-DNA 50-75, 5	4652	0	0	1286	147	20	13	-12.5%	Dom.
WF	FIT-DNA 50-80, 5	5131	0	0	1367	153	20	14	-11.7%	Dom.
WF	FIT-DNA 50-85, 5	5477	0	0	1421	155	20	14	-12.2%	Dom.
WF	FIT-DNA 45-75, 5	5508	0	0	1441	157	21	13	-11.5%	Dom.
WF	FIT-DNA 45-80, 5	5985	0	0	1520	162	21	14	-10.0%	Dom.
WF	FIT-DNA 45-85, 5	6330	0	0	1574	164	21	15	-10.0%	Dom.
WF	FIT-DNA 55-75, 3	4807	0	0	1322	148	22	13	-13.4%	Dom.
WF	FIT-DNA 55-80, 3	5701	0	0	1466	157	24	15	-11.7%	Dom.
WF	FIT-DNA 55-85, 3	6344	0	0	1561	161	24	15	-11.8%	Dom.
WF	FIT-DNA 50-75, 3	6138	0	0	1581	165	24	14	-9.8%	Dom.
WF	FIT-DNA 50-80, 3	6984	0	0	1714	173	26	15	-8.0%	Dom.
WF	FIT-DNA 50-85, 3	7315	0	0	1762	175	26	16	-8.1%	Dom.
WF	FIT-DNA 45-75, 3	7498	0	0	1813	178	25	15	-7.5%	Dom.
WF	FIT-DNA 45-80, 3	7929	0	0	1879	182	26	15	-6.6%	Dom.
WF	FIT-DNA 45-85, 3	8610	0	0	1979	186	27	16	-6.4%	Dom.
WF	FIT-DNA 55-75, 1	9625	0	0	2167	175	31	16	-13.2%	Dom.
WF	FIT-DNA 55-80, 1	10928	0	0	2339	180	33	17	-11.2%	Dom.
WF	FIT-DNA 55-85, 1	11936	0	0	2466	182	33	17	-10.7%	Dom.
WF	FIT-DNA 50-75, 1	11871	0	0	2548	191	33	16	-6.2%	Dom.
WF	FIT-DNA 50-80, 1	13195	0	0	2721	196	34	17	-4.3%	Dom.
WF	FIT-DNA 50-85, 1	14190	0	0	2846	198	35	18	-3.8%	Dom.
WF	FIT-DNA 45-75, 1	14257	0	0	2903	202	34	17	-2.2%	Dom.
WF	FIT-DNA 45-80, 1	15567	0	0	3074	207	35	18	-0.4%	159.6*
WF	FIT-DNA 45-85, 1	16561	0	0	3198	209	36	18	0%	140.2
WF	HSgFOBT 55-75, 3	5191	0	0	983	117	14	10	-19.5%	Dom.

table continues

MISCAN - Scenario 1: Stable CRC risk										
WF	HSgFOBT 55-80, 3	6198	0	0	1105	128	16	12	-17.7%	Dom.
WF	HSgFOBT 55-85, 3	6925	0	0	1187	132	16	13	-18.4%	Dom.
WF	HSgFOBT 50-75, 3	6637	0	0	1199	134	17	11	-17.5%	Dom.
WF	HSgFOBT 50-80, 3	7590	0	0	1312	143	17	13	-15.8%	Dom.
WF	HSgFOBT 50-85, 3	7964	0	0	1353	145	17	13	-15.8%	Dom.
WF	HSgFOBT 45-75, 3	8104	0	0	1393	146	18	12	-16.7%	Dom.
WF	HSgFOBT 45-80, 3	8589	0	0	1449	150	18	13	-15.4%	Dom.
WF	HSgFOBT 45-85, 3	9356	0	0	1533	155	18	14	-14.4%	Dom.
WF	HSgFOBT 55-75, 2	7408	0	0	1309	140	19	13	-17.4%	Dom.
WF	HSgFOBT 55-80, 2	8287	0	0	1407	147	20	14	-16.6%	Dom.
WF	HSgFOBT 55-85, 2	9284	0	0	1511	151	20	14	-16.4%	Dom.
WF	HSgFOBT 50-75, 2	8900	0	0	1530	155	21	13	-14.5%	Dom.
WF	HSgFOBT 50-80, 2	10199	0	0	1673	164	22	15	-12.2%	Dom.
WF	HSgFOBT 50-85, 2	10859	0	0	1741	166	22	15	-12.2%	Dom.
WF	HSgFOBT 45-75, 2	10924	0	0	1783	167	22	14	-12.7%	Dom.
WF	HSgFOBT 45-80, 2	11786	0	0	1877	172	23	15	-11.4%	Dom.
WF	HSgFOBT 45-85, 2	12768	0	0	1978	176	23	16	-11.3%	Dom.
WF	HSgFOBT 55-75, 1	11197	0	0	1835	162	26	15	-15.8%	Dom.
WF	HSgFOBT 55-80, 1	12775	0	0	1994	169	27	16	-15.2%	Dom.
WF	HSgFOBT 55-85, 1	13974	0	0	2108	171	28	16	-14.7%	Dom.
WF	HSgFOBT 50-75, 1	13803	0	0	2179	180	28	15	-10.8%	Dom.
WF	HSgFOBT 50-80, 1	15376	0	0	2335	186	29	16	-8.2%	Dom.
WF	HSgFOBT 50-85, 1	16565	0	0	2447	188	30	17	-7.5%	Dom.
WF	HSgFOBT 45-75, 1	16527	0	0	2496	190	29	16	-6.5%	Dom.
WF	HSgFOBT 45-80, 1	18091	0	0	2649	196	30	17	-4.1%	Dom.
WF	HSgFOBT 45-85, 1	19275	0	0	2760	199	31	17	-3.4%	Dom.
WF	SIG 55-75, 10	0	2367	0	1453	129	26	12	0%	10.8
WF	SIG 55-80, 10	0	2367	0	1453	129	26	12	0%	10.8
WF	SIG 55-85, 10	0	2724	0	1546	131	26	13	-4.9%	Dom.
WF	SIG 50-75, 10	0	2537	0	1534	137	26	12	0%	10.5
WF	SIG 50-80, 10	0	3031	0	1679	142	27	13	-1.0%	26.6*
WF	SIG 50-85, 10	0	3031	0	1679	142	27	13	-1.0%	26.6*
WF	SIG 45-75, 10	0	3284	0	1753	146	27	13	-0.5%	22.9*
WF	SIG 45-80, 10	0	3284	0	1753	146	27	13	-0.5%	22.9*
WF	SIG 45-85, 10	0	3640	0	1844	148	28	14	-2.4%	Dom.
WF	SIG 55-75, 5	0	3454	0	1738	144	29	14	-1.5%	27.3*
WF	SIG 55-80, 5	0	3867	0	1835	147	30	14	-2.8%	Dom.
WF	SIG 55-85, 5	0	4161	0	1895	147	30	14	-4.1%	Dom.
WF	SIG 50-75, 5	0	4220	0	1978	158	30	14	0%	21.1
WF	SIG 50-80, 5	0	4631	0	2074	160	31	15	-1.0%	37.1*
WF	SIG 50-85, 5	0	4924	0	2133	161	31	15	-2.1%	Dom.
WF	SIG 45-75, 5	0	5025	0	2183	167	31	15	0%	23.1
WF	SIG 45-80, 5	0	5435	0	2279	169	32	15	0%	36.5
WF	SIG 45-85, 5	0	5727	0	2338	170	32	15	0%	92.2
WF	CTC 55-75, 10	0	0	2448	1095	132	22	12	0%	7.8
WF	CTC 55-80, 10	0	0	2448	1095	132	22	12	0%	7.8
WF	CTC 55-85, 10	0	0	2837	1182	136	22	13	-4.0%	Dom.

table continues

MISCAN - Scenario 1: Stable CRC risk										
WF	CTC 50-75, 10	0	0	2614	1141	138	21	12	0%	7.9
WF	CTC 50-80, 10	0	0	3148	1267	149	24	14	0%	12.1
WF	CTC 50-85, 10	0	0	3148	1267	149	24	14	0%	12.1
WF	CTC 45-75, 10	0	0	3394	1320	150	23	13	-1.9%	45.6*
WF	CTC 45-80, 10	0	0	3394	1320	150	23	13	-1.9%	45.6*
WF	CTC 45-85, 10	0	0	3781	1406	153	24	14	-3.9%	Dom.
WF	CTC 55-75, 5	0	0	3657	1397	159	27	14	0.0%	12.8*
WF	CTC 55-80, 5	0	0	4110	1485	164	29	15	-1.1%	14.3*
WF	CTC 55-85, 5	0	0	4437	1545	165	30	16	-2.9%	Dom.
WF	CTC 50-75, 5	0	0	4466	1592	174	29	15	0%	12.8
WF	CTC 50-80, 5	0	0	4917	1679	179	30	16	-0.2%	17.4*
WF	CTC 50-85, 5	0	0	5242	1739	181	31	16	-1.4%	22.4*
WF	CTC 45-75, 5	0	0	5305	1762	184	30	15	0%	16.2
WF	CTC 45-80, 5	0	0	5754	1849	189	31	16	0%	18.0
WF	CTC 45-85, 5	0	0	6079	1908	191	32	17	0%	38.8
MISCAN - Scenario 2: Increased CRC risk										
WF	No screening	0	0	0	113	0	0	0	-	-
WF	COL 55-75, 15	0	0	0	3950	328	65	31	0%	11.7
WF	COL 55-80, 15	0	0	0	3950	328	65	31	0%	11.7
WF	COL 55-85, 15	0	0	0	4184	331	65	32	-2.5%	Dom.
WF	COL 50-75, 15	0	0	0	4266	343	64	30	0%	20.5
WF	COL 50-80, 15	0	0	0	4652	355	68	33	-1.8%	34.0*
WF	COL 50-85, 15	0	0	0	4652	355	68	33	-1.8%	34.0*
WF	COL 45-75, 15	0	0	0	5038	366	68	33	-3.1%	Dom.
WF	COL 45-80, 15	0	0	0	5038	366	68	33	-3.1%	Dom.
WF	COL 45-85, 15	0	0	0	5038	366	68	33	-3.1%	Dom.
WF	COL 55-75, 10	0	0	0	4515	349	70	33	-1.5%	40.5*
WF	COL 55-80, 10	0	0	0	4515	349	70	33	-1.5%	40.5*
WF	COL 55-85, 10	0	0	0	4703	351	70	33	-3.4%	Dom.
WF	COL 50-75, 10	0	0	0	5004	377	71	34	0%	21.9
WF	COL 50-80, 10	0	0	0	5310	383	73	35	-0.4%	48.4*
WF	COL 50-85, 10	0	0	0	5310	383	73	35	-0.4%	48.4*
WF	COL 45-75, 10	0	0	0	5823	398	74	35	0%	39.4
WF	COL 45-80, 10	0	0	0	5823	398	74	35	0%	39.4
WF	COL 45-85, 10	0	0	0	6011	399	75	35	-0.4%	119.7*
WF	COL 55-75, 5	0	0	0	5503	370	74	34	-5.2%	Dom.
WF	COL 55-80, 5	0	0	0	5740	372	76	35	-6.0%	Dom.
WF	COL 55-85, 5	0	0	0	5880	372	76	35	-6.6%	Dom.
WF	COL 50-75, 5	0	0	0	6539	407	78	36	-0.9%	79.7*
WF	COL 50-80, 5	0	0	0	6775	409	79	36	-1.3%	82.7*
WF	COL 50-85, 5	0	0	0	6916	410	79	37	-1.8%	91.5*
WF	COL 45-75, 5	0	0	0	7585	429	80	37	0%	56.1
WF	COL 45-80, 5	0	0	0	7821	432	81	37	0%	93.0
WF	COL 45-85, 5	0	0	0	7962	432	81	37	0%	328.0
WF	FIT 55-75, 3	5302	0	0	1195	227	27	20	0%	4.8
WF	FIT 55-80, 3	6248	0	0	1317	249	30	24	0%	5.6
WF	FIT 55-85, 3	6893	0	0	1390	257	29	25	-1.0%	9.1*

table continues

MISCAN - Scenario 2: Increased CRC risk										
WF	FIT 50-75, 3	6815	0	0	1407	259	30	22	-1.2%	9.2*
WF	FIT 50-80, 3	7700	0	0	1516	278	32	25	0%	6.9
WF	FIT 50-85, 3	8031	0	0	1553	282	32	26	0.0%	8.8*
WF	FIT 45-75, 3	8367	0	0	1583	281	32	24	-1.6%	Dom.
WF	FIT 45-80, 3	8818	0	0	1635	291	34	25	-0.2%	9.2*
WF	FIT 45-85, 3	9500	0	0	1711	300	34	27	0%	8.8
WF	FIT 55-75, 2	7623	0	0	1532	271	36	25	-3.1%	Dom.
WF	FIT 55-80, 2	8444	0	0	1620	284	38	27	-1.9%	16.3*
WF	FIT 55-85, 2	9328	0	0	1706	292	38	28	-2.3%	Dom.
WF	FIT 50-75, 2	9268	0	0	1742	298	38	25	-1.8%	Dom.
WF	FIT 50-80, 2	10477	0	0	1867	317	41	28	0%	9.0
WF	FIT 50-85, 2	11058	0	0	1922	323	41	30	0.0%	10.6*
WF	FIT 45-75, 2	11456	0	0	1964	322	41	27	-1.5%	Dom.
WF	FIT 45-80, 2	12254	0	0	2046	334	43	29	-0.1%	10.6*
WF	FIT 45-85, 2	13118	0	0	2127	342	43	30	0%	10.5
WF	FIT 55-75, 1	12302	0	0	2082	316	49	28	-6.6%	Dom.
WF	FIT 55-80, 1	13860	0	0	2209	330	52	31	-5.1%	Dom.
WF	FIT 55-85, 1	14960	0	0	2290	335	53	32	-5.0%	Dom.
WF	FIT 50-75, 1	15404	0	0	2411	350	52	30	-2.7%	Dom.
WF	FIT 50-80, 1	16931	0	0	2532	364	55	32	-1.1%	18.9*
WF	FIT 50-85, 1	18014	0	0	2611	369	56	33	-1.0%	18.2*
WF	FIT 45-75, 1	18692	0	0	2690	371	54	31	-1.6%	19.3*
WF	FIT 45-80, 1	20204	0	0	2808	385	57	33	-0.1%	16.1*
WF	FIT 45-85, 1	21280	0	0	2885	390	58	34	0%	16.0
WF	FIT-DNA 55-75, 5	3570	0	0	1690	259	36	24	-13.1%	Dom.
WF	FIT-DNA 55-80, 5	3951	0	0	1785	269	38	26	-12.6%	Dom.
WF	FIT-DNA 55-85, 5	4209	0	0	1844	273	38	27	-13.3%	Dom.
WF	FIT-DNA 50-75, 5	4347	0	0	1938	287	39	25	-11.6%	Dom.
WF	FIT-DNA 50-80, 5	4721	0	0	2029	297	41	27	-10.8%	Dom.
WF	FIT-DNA 50-85, 5	4976	0	0	2086	301	41	28	-11.2%	Dom.
WF	FIT-DNA 45-75, 5	5161	0	0	2145	303	41	26	-11.7%	Dom.
WF	FIT-DNA 45-80, 5	5532	0	0	2234	314	42	28	-10.1%	Dom.
WF	FIT-DNA 45-85, 5	5784	0	0	2290	317	42	29	-10.1%	Dom.
WF	FIT-DNA 55-75, 3	4475	0	0	1989	287	44	26	-12.8%	Dom.
WF	FIT-DNA 55-80, 3	5169	0	0	2148	305	47	29	-11.3%	Dom.
WF	FIT-DNA 55-85, 3	5628	0	0	2241	311	48	30	-11.1%	Dom.
WF	FIT-DNA 50-75, 3	5684	0	0	2337	322	48	28	-9.3%	Dom.
WF	FIT-DNA 50-80, 3	6325	0	0	2478	337	51	30	-7.4%	Dom.
WF	FIT-DNA 50-85, 3	6561	0	0	2525	340	51	31	-7.3%	Dom.
WF	FIT-DNA 45-75, 3	6941	0	0	2633	345	50	29	-7.8%	Dom.
WF	FIT-DNA 45-80, 3	7268	0	0	2703	353	52	30	-6.8%	Dom.
WF	FIT-DNA 45-85, 3	7754	0	0	2800	360	53	32	-6.4%	Dom.
WF	FIT-DNA 55-75, 1	8442	0	0	3003	341	61	31	-12.8%	Dom.
WF	FIT-DNA 55-80, 1	9319	0	0	3149	350	64	33	-11.1%	Dom.
WF	FIT-DNA 55-85, 1	9936	0	0	3244	353	65	33	-10.6%	Dom.
WF	FIT-DNA 50-75, 1	10441	0	0	3478	375	65	33	-5.7%	Dom.
WF	FIT-DNA 50-80, 1	11320	0	0	3622	383	67	34	-4.1%	Dom.

table continues

MISCAN - Scenario 2: Increased CRC risk										
WF	FIT-DNA 50-85, 1	11927	0	0	3715	386	68	35	-3.7%	Dom.
WF	FIT-DNA 45-75, 1	12627	0	0	3902	395	66	33	-2.0%	178.8*
WF	FIT-DNA 45-80, 1	13492	0	0	4043	404	69	35	-0.4%	82.8*
WF	FIT-DNA 45-85, 1	14096	0	0	4135	407	70	35	0%	74.0
WF	HSgFOBT 55-75, 3	4968	0	0	1466	227	29	20	-16.2%	Dom.
WF	HSgFOBT 55-80, 3	5814	0	0	1611	247	32	24	-14.5%	Dom.
WF	HSgFOBT 55-85, 3	6382	0	0	1698	254	31	25	-14.9%	Dom.
WF	HSgFOBT 50-75, 3	6317	0	0	1763	260	33	23	-14.9%	Dom.
WF	HSgFOBT 50-80, 3	7098	0	0	1892	277	35	25	-13.3%	Dom.
WF	HSgFOBT 50-85, 3	7387	0	0	1936	281	35	26	-13.3%	Dom.
WF	HSgFOBT 45-75, 3	7695	0	0	2019	283	36	24	-14.8%	Dom.
WF	HSgFOBT 45-80, 3	8091	0	0	2082	291	37	25	-13.8%	Dom.
WF	HSgFOBT 45-85, 3	8686	0	0	2171	300	37	27	-13.1%	Dom.
WF	HSgFOBT 55-75, 2	6922	0	0	1896	271	38	25	-15.2%	Dom.
WF	HSgFOBT 55-80, 2	7615	0	0	2002	283	40	27	-14.3%	Dom.
WF	HSgFOBT 55-85, 2	8347	0	0	2104	290	41	28	-14.6%	Dom.
WF	HSgFOBT 50-75, 2	8325	0	0	2203	301	42	26	-13.3%	Dom.
WF	HSgFOBT 50-80, 2	9334	0	0	2353	318	44	29	-10.9%	Dom.
WF	HSgFOBT 50-85, 2	9811	0	0	2417	322	45	30	-10.7%	Dom.
WF	HSgFOBT 45-75, 2	10188	0	0	2526	325	45	28	-11.4%	Dom.
WF	HSgFOBT 45-80, 2	10851	0	0	2623	336	46	29	-10.0%	Dom.
WF	HSgFOBT 45-85, 2	11557	0	0	2718	343	47	31	-9.6%	Dom.
WF	HSgFOBT 55-75, 1	10189	0	0	2569	317	52	29	-14.3%	Dom.
WF	HSgFOBT 55-80, 1	11322	0	0	2717	328	54	31	-13.4%	Dom.
WF	HSgFOBT 55-85, 1	12110	0	0	2810	332	55	32	-13.7%	Dom.
WF	HSgFOBT 50-75, 1	12523	0	0	3012	351	56	31	-10.3%	Dom.
WF	HSgFOBT 50-80, 1	13634	0	0	3153	362	58	32	-8.0%	Dom.
WF	HSgFOBT 50-85, 1	14407	0	0	3243	366	59	33	-7.3%	Dom.
WF	HSgFOBT 45-75, 1	15026	0	0	3402	372	58	31	-6.1%	Dom.
WF	HSgFOBT 45-80, 1	16121	0	0	3539	383	60	33	-4.0%	Dom.
WF	HSgFOBT 45-85, 1	16886	0	0	3628	387	61	34	-3.3%	Dom.
WF	SIG 55-75, 10	0	1985	0	2935	310	62	30	0%	9.1
WF	SIG 55-80, 10	0	1985	0	2935	310	62	30	0%	9.1
WF	SIG 55-85, 10	0	2181	0	3034	312	62	30	-2.6%	Dom.
WF	SIG 50-75, 10	0	2198	0	3132	331	62	30	0%	9.4
WF	SIG 50-80, 10	0	2492	0	3307	339	65	32	-0.7%	20.4*
WF	SIG 50-85, 10	0	2492	0	3307	339	65	32	-0.7%	20.4*
WF	SIG 45-75, 10	0	2795	0	3466	350	65	31	-0.5%	17.0*
WF	SIG 45-80, 10	0	2795	0	3466	350	65	31	-0.5%	17.0*
WF	SIG 45-85, 10	0	2989	0	3564	353	66	32	-1.5%	19.7*
WF	SIG 55-75, 5	0	2673	0	3229	331	66	31	-1.9%	Dom.
WF	SIG 55-80, 5	0	2894	0	3327	334	67	32	-2.6%	Dom.
WF	SIG 55-85, 5	0	3035	0	3376	335	67	32	-3.2%	Dom.
WF	SIG 50-75, 5	0	3300	0	3618	362	69	33	0%	15.7
WF	SIG 50-80, 5	0	3520	0	3715	366	70	33	-0.4%	25.0*
WF	SIG 50-85, 5	0	3661	0	3763	366	70	34	-0.9%	31.1*
WF	SIG 45-75, 5	0	4005	0	3930	379	70	33	0%	17.8

table continues

MISCAN - Scenario 2: Increased CRC risk										
WF	SIG 45-80, 5	0	4224	0	4026	383	72	34	0%	25.1
WF	SIG 45-85, 5	0	4365	0	4075	384	72	34	0%	60.2
WF	CTC 55-75, 10	0	0	2275	1761	258	43	24	0%	6.4
WF	CTC 55-80, 10	0	0	2275	1761	258	43	24	0%	6.4
WF	CTC 55-85, 10	0	0	2567	1863	264	45	26	-2.8%	Dom.
WF	CTC 50-75, 10	0	0	2471	1838	269	42	23	0%	7.2
WF	CTC 50-80, 10	0	0	2894	1996	288	46	27	-0.3%	8.2*
WF	CTC 50-85, 10	0	0	2894	1996	288	46	27	-0.3%	8.2*
WF	CTC 45-75, 10	0	0	3178	2074	291	46	26	-2.7%	Dom.
WF	CTC 45-80, 10	0	0	3178	2074	291	46	26	-2.7%	Dom.
WF	CTC 45-85, 10	0	0	3467	2174	297	47	27	-4.7%	Dom.
WF	CTC 55-75, 5	0	0	3309	2162	310	54	29	0%	7.8
WF	CTC 55-80, 5	0	0	3644	2259	319	57	30	-0.5%	10.4*
WF	CTC 55-85, 5	0	0	3870	2319	322	58	31	-1.7%	13.0*
WF	CTC 50-75, 5	0	0	4058	2431	340	57	30	0%	8.9
WF	CTC 50-80, 5	0	0	4389	2525	349	60	32	0%	10.5
WF	CTC 50-85, 5	0	0	4613	2584	352	61	32	-0.6%	22.1*
WF	CTC 45-75, 5	0	0	4853	2652	358	58	31	-0.4%	14.1*
WF	CTC 45-80, 5	0	0	5182	2745	367	61	32	0%	12.2
WF	CTC 45-85, 5	0	0	5405	2803	370	62	33	0%	22.3
SimCRC - Scenario 1: Stable CRC risk										
WF	No screening	0	0	0	66	0	0	0	-	-
WF	COL 55-75, 15	0	0	0	3001	229	48	21	0%	12.8
WF	COL 55-80, 15	0	0	0	3001	229	48	21	0%	12.8
WF	COL 55-85, 15	0	0	0	3384	230	48	21	-12.1%	Dom.
WF	COL 50-75, 15	0	0	0	3178	255	50	21	0%	6.6
WF	COL 50-80, 15	0	0	0	3745	261	52	22	-4.5%	Dom.
WF	COL 50-85, 15	0	0	0	3745	261	52	22	-4.5%	Dom.
WF	COL 45-75, 15	0	0	0	4062	283	55	23	0%	31.6
WF	COL 45-80, 15	0	0	0	4062	283	55	23	0%	31.6
WF	COL 45-85, 15	0	0	0	4062	283	55	23	0%	31.6
WF	COL 55-75, 10	0	0	0	3746	239	51	22	-12.6%	Dom.
WF	COL 55-80, 10	0	0	0	3746	239	51	22	-12.6%	Dom.
WF	COL 55-85, 10	0	0	0	4080	240	51	22	-15.5%	Dom.
WF	COL 50-75, 10	0	0	0	4062	270	54	23	-4.7%	Dom.
WF	COL 50-80, 10	0	0	0	4555	273	55	23	-6.3%	Dom.
WF	COL 50-85, 10	0	0	0	4555	273	55	23	-6.3%	Dom.
WF	COL 45-75, 10	0	0	0	4952	297	58	24	0%	64.8
WF	COL 45-80, 10	0	0	0	4952	297	58	24	0%	64.8
WF	COL 45-85, 10	0	0	0	5286	298	58	24	-0.2%	511.6*
WF	COL 55-75, 5	0	0	0	5172	246	53	22	-17.5%	Dom.
WF	COL 55-80, 5	0	0	0	5592	247	54	22	-17.7%	Dom.
WF	COL 55-85, 5	0	0	0	5881	247	54	22	-18.0%	Dom.
WF	COL 50-75, 5	0	0	0	6217	280	58	24	-7.2%	Dom.
WF	COL 50-80, 5	0	0	0	6637	281	58	24	-7.5%	Dom.
WF	COL 50-85, 5	0	0	0	6925	281	58	24	-7.8%	Dom.
WF	COL 45-75, 5	0	0	0	7272	306	61	24	0%	248.3

table continues

SimCRC - Scenario 1: Stable CRC risk										
WF	COL 45-80, 5	0	0	0	7692	307	61	25	0%	597.2
WF	COL 45-85, 5	0	0	0	7980	307	61	25	0%	1998.2
WF	FIT 55-75, 3	5618	0	0	760	176	24	15	0%	3.9
WF	FIT 55-80, 3	6735	0	0	863	188	26	17	-4.8%	Dom.
WF	FIT 55-85, 3	7460	0	0	928	191	26	18	-9.0%	Dom.
WF	FIT 50-75, 3	7252	0	0	915	208	28	17	0%	4.8
WF	FIT 50-80, 3	8207	0	0	1003	217	30	18	-3.1%	Dom.
WF	FIT 50-85, 3	8728	0	0	1048	220	30	19	-5.3%	Dom.
WF	FIT 45-75, 3	8777	0	0	1046	232	31	18	0%	5.4
WF	FIT 45-80, 3	9458	0	0	1104	239	32	19	0%	9.0
WF	FIT 45-85, 3	10289	0	0	1176	243	32	20	-0.5%	16.2*
WF	FIT 55-75, 2	8126	0	0	1003	200	30	17	-10.6%	Dom.
WF	FIT 55-80, 2	9124	0	0	1085	207	32	18	-12.5%	Dom.
WF	FIT 55-85, 2	10249	0	0	1173	211	32	19	-13.7%	Dom.
WF	FIT 50-75, 2	9840	0	0	1154	230	34	18	-5.3%	Dom.
WF	FIT 50-80, 2	11322	0	0	1272	239	36	20	-5.1%	Dom.
WF	FIT 50-85, 2	12069	0	0	1330	241	36	21	-5.9%	Dom.
WF	FIT 45-75, 2	12158	0	0	1333	257	38	20	0%	12.5
WF	FIT 45-80, 2	13143	0	0	1412	263	39	21	0%	12.9
WF	FIT 45-85, 2	14258	0	0	1498	266	39	22	0%	24.2
WF	FIT 55-75, 1	13408	0	0	1428	221	39	19	-16.0%	Dom.
WF	FIT 55-80, 1	15410	0	0	1563	227	41	20	-15.6%	Dom.
WF	FIT 55-85, 1	16903	0	0	1658	229	41	21	-15.9%	Dom.
WF	FIT 50-75, 1	16764	0	0	1680	254	44	21	-6.8%	Dom.
WF	FIT 50-80, 1	18753	0	0	1811	260	45	22	-6.5%	Dom.
WF	FIT 50-85, 1	20240	0	0	1905	262	46	22	-6.9%	Dom.
WF	FIT 45-75, 1	20234	0	0	1911	281	47	22	-0.2%	28.5*
WF	FIT 45-80, 1	22216	0	0	2041	286	48	23	0%	27.7
WF	FIT 45-85, 1	23698	0	0	2134	288	49	23	0%	53.5
WF	FIT-DNA 55-75, 5	3809	0	0	1133	191	30	17	-20.6%	Dom.
WF	FIT-DNA 55-80, 5	4285	0	0	1227	197	31	18	-20.8%	Dom.
WF	FIT-DNA 55-85, 5	4624	0	0	1291	198	31	18	-21.7%	Dom.
WF	FIT-DNA 50-75, 5	4638	0	0	1318	221	34	18	-13.6%	Dom.
WF	FIT-DNA 50-80, 5	5111	0	0	1410	226	35	19	-14.0%	Dom.
WF	FIT-DNA 50-85, 5	5449	0	0	1474	228	35	20	-14.2%	Dom.
WF	FIT-DNA 45-75, 5	5489	0	0	1486	243	37	19	-8.6%	Dom.
WF	FIT-DNA 45-80, 5	5960	0	0	1577	248	38	20	-7.8%	Dom.
WF	FIT-DNA 45-85, 5	6297	0	0	1640	250	38	20	-8.0%	Dom.
WF	FIT-DNA 55-75, 3	4965	0	0	1372	210	36	18	-19.1%	Dom.
WF	FIT-DNA 55-80, 3	5851	0	0	1533	218	38	20	-18.6%	Dom.
WF	FIT-DNA 55-85, 3	6349	0	0	1619	220	38	20	-18.8%	Dom.
WF	FIT-DNA 50-75, 3	6335	0	0	1651	245	41	20	-10.1%	Dom.
WF	FIT-DNA 50-80, 3	6999	0	0	1771	250	42	21	-9.5%	Dom.
WF	FIT-DNA 50-85, 3	7529	0	0	1859	252	42	21	-9.8%	Dom.
WF	FIT-DNA 45-75, 3	7510	0	0	1869	269	44	21	-3.9%	Dom.
WF	FIT-DNA 45-80, 3	8214	0	0	1990	274	45	22	-3.5%	Dom.
WF	FIT-DNA 45-85, 3	8812	0	0	2093	277	46	22	-3.6%	Dom.

table continues

SimCRC - Scenario 1: Stable CRC risk										
WF	FIT-DNA 55-75, 1	9509	0	0	2190	232	46	21	-19.4%	Dom.
WF	FIT-DNA 55-80, 1	10771	0	0	2376	236	47	21	-18.6%	Dom.
WF	FIT-DNA 55-85, 1	11726	0	0	2510	237	48	22	-18.5%	Dom.
WF	FIT-DNA 50-75, 1	11755	0	0	2576	265	50	22	-8.8%	Dom.
WF	FIT-DNA 50-80, 1	13042	0	0	2764	269	52	23	-8.0%	Dom.
WF	FIT-DNA 50-85, 1	13987	0	0	2897	270	52	23	-7.9%	Dom.
WF	FIT-DNA 45-75, 1	14124	0	0	2946	291	53	23	-0.7%	239.9*
WF	FIT-DNA 45-80, 1	15396	0	0	3132	294	55	24	0.0%	153.1*
WF	FIT-DNA 45-85, 1	16340	0	0	3264	295	55	24	0%	149.8
WF	HSgFOBT 55-75, 3	5303	0	0	1022	176	26	15	-22.9%	Dom.
WF	HSgFOBT 55-80, 3	6312	0	0	1157	187	27	17	-23.2%	Dom.
WF	HSgFOBT 55-85, 3	6912	0	0	1235	190	28	18	-23.8%	Dom.
WF	HSgFOBT 50-75, 3	6794	0	0	1249	209	30	17	-16.5%	Dom.
WF	HSgFOBT 50-80, 3	7584	0	0	1355	217	32	18	-16.1%	Dom.
WF	HSgFOBT 50-85, 3	8135	0	0	1423	219	32	19	-16.7%	Dom.
WF	HSgFOBT 45-75, 3	8097	0	0	1434	233	33	18	-11.8%	Dom.
WF	HSgFOBT 45-80, 3	8821	0	0	1525	239	34	19	-10.6%	Dom.
WF	HSgFOBT 45-85, 3	9533	0	0	1615	243	35	20	-10.3%	Dom.
WF	HSgFOBT 55-75, 2	7342	0	0	1337	200	32	18	-22.1%	Dom.
WF	HSgFOBT 55-80, 2	8205	0	0	1444	206	33	19	-21.9%	Dom.
WF	HSgFOBT 55-85, 2	9173	0	0	1559	210	34	19	-22.0%	Dom.
WF	HSgFOBT 50-75, 2	8835	0	0	1559	231	36	19	-14.1%	Dom.
WF	HSgFOBT 50-80, 2	10114	0	0	1715	239	38	20	-12.9%	Dom.
WF	HSgFOBT 50-85, 2	10756	0	0	1790	241	38	21	-13.0%	Dom.
WF	HSgFOBT 45-75, 2	10852	0	0	1824	258	40	20	-7.2%	Dom.
WF	HSgFOBT 45-80, 2	11701	0	0	1928	263	41	21	-6.6%	Dom.
WF	HSgFOBT 45-85, 2	12658	0	0	2039	266	41	22	-6.8%	Dom.
WF	HSgFOBT 55-75, 1	11066	0	0	1857	222	40	20	-20.6%	Dom.
WF	HSgFOBT 55-80, 1	12609	0	0	2029	227	42	20	-20.6%	Dom.
WF	HSgFOBT 55-85, 1	13763	0	0	2151	228	42	21	-20.7%	Dom.
WF	HSgFOBT 50-75, 1	13679	0	0	2204	255	45	21	-11.5%	Dom.
WF	HSgFOBT 50-80, 1	15223	0	0	2373	260	47	22	-10.2%	Dom.
WF	HSgFOBT 50-85, 1	16369	0	0	2493	261	47	22	-9.9%	Dom.
WF	HSgFOBT 45-75, 1	16396	0	0	2530	282	49	22	-3.1%	Dom.
WF	HSgFOBT 45-80, 1	17931	0	0	2698	286	50	23	-1.9%	Dom.
WF	HSgFOBT 45-85, 1	19074	0	0	2818	288	50	23	-1.7%	Dom.
WF	SIG 55-75, 10	0	2431	0	1214	168	35	15	0%	6.8
WF	SIG 55-80, 10	0	2431	0	1214	168	35	15	0%	6.8
WF	SIG 55-85, 10	0	2805	0	1317	170	35	16	-12.4%	Dom.
WF	SIG 50-75, 10	0	2595	0	1277	190	37	16	0%	2.9
WF	SIG 50-80, 10	0	3115	0	1429	195	39	17	-5.1%	Dom.
WF	SIG 50-85, 10	0	3115	0	1429	195	39	17	-5.1%	Dom.
WF	SIG 45-75, 10	0	3359	0	1510	214	41	17	0%	9.7
WF	SIG 45-80, 10	0	3359	0	1510	214	41	17	0%	9.7
WF	SIG 45-85, 10	0	3732	0	1612	216	41	18	-1.9%	64.1*
WF	SIG 55-75, 5	0	3583	0	1530	187	40	17	-13.1%	Dom.
WF	SIG 55-80, 5	0	4013	0	1633	189	40	18	-14.3%	Dom.

table continues

SimCRC - Scenario 1: Stable CRC risk										
WF	SIG 55-85, 5	0	4318	0	1702	190	41	18	-15.5%	Dom.
WF	SIG 50-75, 5	0	4369	0	1761	216	44	19	-5.1%	Dom.
WF	SIG 50-80, 5	0	4796	0	1864	219	44	19	-6.5%	Dom.
WF	SIG 50-85, 5	0	5099	0	1932	219	45	19	-7.7%	Dom.
WF	SIG 45-75, 5	0	5179	0	1973	240	46	20	0%	17.8
WF	SIG 45-80, 5	0	5604	0	2074	242	47	20	0%	45.7
WF	SIG 45-85, 5	0	5907	0	2142	243	47	20	0%	108.9
WF	CTC 55-75, 10	0	0	2407	1323	209	42	19	0%	6.0
WF	CTC 55-80, 10	0	0	2407	1323	209	42	19	0%	6.0
WF	CTC 55-85, 10	0	0	2769	1440	211	42	20	-12.6%	Dom.
WF	CTC 50-75, 10	0	0	2578	1371	234	44	19	0%	2.0
WF	CTC 50-80, 10	0	0	3085	1540	240	46	21	-5.2%	Dom.
WF	CTC 50-85, 10	0	0	3085	1540	240	46	21	-5.2%	Dom.
WF	CTC 45-75, 10	0	0	3336	1608	261	48	21	0%	8.6
WF	CTC 45-80, 10	0	0	3336	1608	261	48	21	0%	8.6
WF	CTC 45-85, 10	0	0	3696	1723	263	48	22	-1.6%	60.8*
WF	CTC 55-75, 5	0	0	3548	1626	226	47	20	-13.8%	Dom.
WF	CTC 55-80, 5	0	0	3966	1733	228	48	21	-14.7%	Dom.
WF	CTC 55-85, 5	0	0	4260	1804	229	48	21	-15.6%	Dom.
WF	CTC 50-75, 5	0	0	4341	1848	259	51	22	-5.4%	Dom.
WF	CTC 50-80, 5	0	0	4757	1954	261	52	22	-6.4%	Dom.
WF	CTC 50-85, 5	0	0	5051	2025	262	52	22	-7.4%	Dom.
WF	CTC 45-75, 5	0	0	5163	2045	284	53	23	0%	19.0
WF	CTC 45-80, 5	0	0	5579	2150	287	55	23	0%	44.3
WF	CTC 45-85, 5	0	0	5872	2221	287	55	23	0%	109.8
SimCRC - Scenario 2: Increased CRC risk										
WF	No screening	0	0	0	120	0	0	0	-	-
WF	COL 55-75, 15	0	0	0	3181	370	82	35	0%	8.3
WF	COL 55-80, 15	0	0	0	3181	370	82	35	0%	8.3
WF	COL 55-85, 15	0	0	0	3540	375	84	36	-8.1%	Dom.
WF	COL 50-75, 15	0	0	0	3300	396	80	34	0%	4.7
WF	COL 50-80, 15	0	0	0	3889	414	88	38	-2.6%	Dom.
WF	COL 50-85, 15	0	0	0	3889	414	88	38	-2.6%	Dom.
WF	COL 45-75, 15	0	0	0	4218	442	91	39	0%	19.9
WF	COL 45-80, 15	0	0	0	4218	442	91	39	0%	19.9
WF	COL 45-85, 15	0	0	0	4218	442	91	39	0%	19.9
WF	COL 55-75, 10	0	0	0	3943	397	90	38	-7.3%	Dom.
WF	COL 55-80, 10	0	0	0	3943	397	90	38	-7.3%	Dom.
WF	COL 55-85, 10	0	0	0	4228	399	91	39	-9.8%	Dom.
WF	COL 50-75, 10	0	0	0	4254	434	92	38	-2.2%	Dom.
WF	COL 50-80, 10	0	0	0	4723	442	97	40	-3.6%	Dom.
WF	COL 50-85, 10	0	0	0	4723	442	97	40	-3.6%	Dom.
WF	COL 45-75, 10	0	0	0	5138	473	99	41	0%	29.4
WF	COL 45-80, 10	0	0	0	5138	473	99	41	0%	29.4
WF	COL 45-85, 10	0	0	0	5424	475	100	41	-0.1%	142.9*
WF	COL 55-75, 5	0	0	0	5343	413	96	39	-13.0%	Dom.
WF	COL 55-80, 5	0	0	0	5695	416	97	40	-13.1%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk										
WF	COL 55-85, 5	0	0	0	5914	416	98	40	-13.4%	Dom.
WF	COL 50-75, 5	0	0	0	6393	461	101	41	-5.0%	Dom.
WF	COL 50-80, 5	0	0	0	6745	463	103	42	-5.2%	Dom.
WF	COL 50-85, 5	0	0	0	6964	463	104	42	-5.5%	Dom.
WF	COL 45-75, 5	0	0	0	7453	495	105	42	0%	106.6
WF	COL 45-80, 5	0	0	0	7805	497	107	43	0%	146.4
WF	COL 45-85, 5	0	0	0	8024	498	107	43	0%	472.9
WF	FIT 55-75, 3	5566	0	0	871	271	39	23	0%	2.8
WF	FIT 55-80, 3	6627	0	0	1002	299	43	28	-3.1%	Dom.
WF	FIT 55-85, 3	7289	0	0	1084	308	44	30	-6.7%	Dom.
WF	FIT 50-75, 3	7200	0	0	1027	316	45	26	0%	3.5
WF	FIT 50-80, 3	8106	0	0	1140	338	48	30	-1.9%	5.1*
WF	FIT 50-85, 3	8582	0	0	1196	345	49	31	-3.5%	Dom.
WF	FIT 45-75, 3	8732	0	0	1155	348	48	28	0%	3.9
WF	FIT 45-80, 3	9380	0	0	1229	364	51	30	0%	4.8
WF	FIT 45-85, 3	10143	0	0	1322	375	52	33	-0.4%	8.3*
WF	FIT 55-75, 2	8025	0	0	1140	318	50	28	-7.8%	Dom.
WF	FIT 55-80, 2	8961	0	0	1244	335	54	31	-8.5%	Dom.
WF	FIT 55-85, 2	9972	0	0	1353	345	55	33	-9.5%	Dom.
WF	FIT 50-75, 2	9766	0	0	1279	354	54	29	-4.5%	Dom.
WF	FIT 50-80, 2	11159	0	0	1430	379	59	33	-3.4%	Dom.
WF	FIT 50-85, 2	11831	0	0	1501	385	60	35	-4.2%	Dom.
WF	FIT 45-75, 2	12090	0	0	1459	393	59	32	-0.6%	7.9*
WF	FIT 45-80, 2	13017	0	0	1560	410	63	34	0%	7.3
WF	FIT 45-85, 2	14022	0	0	1666	419	64	36	0%	11.2
WF	FIT 55-75, 1	13210	0	0	1595	360	66	33	-12.8%	Dom.
WF	FIT 55-80, 1	15050	0	0	1759	376	71	35	-11.5%	Dom.
WF	FIT 55-85, 1	16349	0	0	1869	381	72	37	-11.7%	Dom.
WF	FIT 50-75, 1	16603	0	0	1840	405	72	35	-5.8%	Dom.
WF	FIT 50-80, 1	18435	0	0	2002	421	76	37	-4.4%	Dom.
WF	FIT 50-85, 1	19730	0	0	2111	426	78	39	-4.7%	Dom.
WF	FIT 45-75, 1	20115	0	0	2064	439	76	36	-1.3%	20.1*
WF	FIT 45-80, 1	21941	0	0	2225	455	81	39	0%	15.6
WF	FIT 45-85, 1	23235	0	0	2333	460	82	40	0%	20.2
WF	FIT-DNA 55-75, 5	3770	0	0	1267	300	50	27	-18.7%	Dom.
WF	FIT-DNA 55-80, 5	4216	0	0	1380	314	53	30	-18.4%	Dom.
WF	FIT-DNA 55-85, 5	4519	0	0	1456	319	53	31	-19.4%	Dom.
WF	FIT-DNA 50-75, 5	4607	0	0	1446	340	55	29	-13.8%	Dom.
WF	FIT-DNA 50-80, 5	5050	0	0	1557	353	58	32	-13.8%	Dom.
WF	FIT-DNA 50-85, 5	5353	0	0	1632	357	58	33	-14.1%	Dom.
WF	FIT-DNA 45-75, 5	5466	0	0	1607	368	59	30	-10.9%	Dom.
WF	FIT-DNA 45-80, 5	5908	0	0	1718	381	62	33	-9.7%	Dom.
WF	FIT-DNA 45-85, 5	6210	0	0	1792	386	62	34	-9.6%	Dom.
WF	FIT-DNA 55-75, 3	4916	0	0	1516	334	59	30	-17.1%	Dom.
WF	FIT-DNA 55-80, 3	5745	0	0	1710	356	65	34	-15.6%	Dom.
WF	FIT-DNA 55-85, 3	6187	0	0	1809	361	66	35	-15.6%	Dom.
WF	FIT-DNA 50-75, 3	6293	0	0	1796	383	66	33	-10.4%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk										
WF	FIT-DNA 50-80, 3	6913	0	0	1940	398	70	35	-8.8%	Dom.
WF	FIT-DNA 50-85, 3	7385	0	0	2041	404	72	37	-8.8%	Dom.
WF	FIT-DNA 45-75, 3	7484	0	0	2003	414	70	34	-6.1%	Dom.
WF	FIT-DNA 45-80, 3	8144	0	0	2150	430	74	36	-4.5%	Dom.
WF	FIT-DNA 45-85, 3	8679	0	0	2268	437	76	38	-4.4%	Dom.
WF	FIT-DNA 55-75, 1	9367	0	0	2380	381	79	35	-17.3%	Dom.
WF	FIT-DNA 55-80, 1	10505	0	0	2587	392	83	37	-15.4%	Dom.
WF	FIT-DNA 55-85, 1	11311	0	0	2724	395	84	38	-15.0%	Dom.
WF	FIT-DNA 50-75, 1	11653	0	0	2757	426	84	37	-8.4%	Dom.
WF	FIT-DNA 50-80, 1	12814	0	0	2968	438	89	39	-6.5%	Dom.
WF	FIT-DNA 50-85, 1	13612	0	0	3104	441	90	40	-6.2%	Dom.
WF	FIT-DNA 45-75, 1	14057	0	0	3120	460	88	38	-2.1%	Dom.
WF	FIT-DNA 45-80, 1	15206	0	0	3328	471	93	40	-0.3%	90.1*
WF	FIT-DNA 45-85, 1	16003	0	0	3464	474	94	41	0%	79.4
WF	HSgFOBT 55-75, 3	5256	0	0	1136	273	42	24	-20.6%	Dom.
WF	HSgFOBT 55-80, 3	6215	0	0	1295	299	47	28	-20.0%	Dom.
WF	HSgFOBT 55-85, 3	6764	0	0	1384	306	47	30	-20.5%	Dom.
WF	HSgFOBT 50-75, 3	6751	0	0	1361	319	48	27	-16.5%	Dom.
WF	HSgFOBT 50-80, 3	7502	0	0	1486	338	52	30	-15.3%	Dom.
WF	HSgFOBT 50-85, 3	8005	0	0	1564	345	53	31	-15.8%	Dom.
WF	HSgFOBT 45-75, 3	8066	0	0	1539	350	52	28	-13.9%	Dom.
WF	HSgFOBT 45-80, 3	8756	0	0	1646	367	55	31	-12.2%	Dom.
WF	HSgFOBT 45-85, 3	9411	0	0	1751	376	56	33	-11.4%	Dom.
WF	HSgFOBT 55-75, 2	7259	0	0	1475	319	54	29	-19.8%	Dom.
WF	HSgFOBT 55-80, 2	8070	0	0	1600	334	57	31	-19.1%	Dom.
WF	HSgFOBT 55-85, 2	8941	0	0	1728	343	58	33	-18.9%	Dom.
WF	HSgFOBT 50-75, 2	8779	0	0	1684	357	58	30	-15.0%	Dom.
WF	HSgFOBT 50-80, 2	9986	0	0	1866	379	63	34	-12.3%	Dom.
WF	HSgFOBT 50-85, 2	10564	0	0	1950	384	64	35	-12.1%	Dom.
WF	HSgFOBT 45-75, 2	10808	0	0	1945	396	63	32	-9.4%	Dom.
WF	HSgFOBT 45-80, 2	11610	0	0	2067	411	67	35	-7.7%	Dom.
WF	HSgFOBT 45-85, 2	12474	0	0	2192	419	68	37	-7.5%	Dom.
WF	HSgFOBT 55-75, 1	10925	0	0	2021	360	68	33	-18.4%	Dom.
WF	HSgFOBT 55-80, 1	12351	0	0	2214	375	73	36	-17.4%	Dom.
WF	HSgFOBT 55-85, 1	13357	0	0	2342	380	74	37	-17.5%	Dom.
WF	HSgFOBT 50-75, 1	13579	0	0	2358	406	75	35	-11.7%	Dom.
WF	HSgFOBT 50-80, 1	15008	0	0	2550	421	79	38	-9.1%	Dom.
WF	HSgFOBT 50-85, 1	16010	0	0	2677	425	80	39	-8.4%	Dom.
WF	HSgFOBT 45-75, 1	16337	0	0	2676	440	79	36	-5.2%	Dom.
WF	HSgFOBT 45-80, 1	17759	0	0	2866	454	83	39	-2.7%	Dom.
WF	HSgFOBT 45-85, 1	18759	0	0	2994	459	84	40	-2.0%	Dom.
WF	SIG 55-75, 10	0	2334	0	1783	347	77	33	0%	4.8
WF	SIG 55-80, 10	0	2334	0	1783	347	77	33	0%	4.8
WF	SIG 55-85, 10	0	2629	0	1924	351	78	34	-10.2%	Dom.
WF	SIG 50-75, 10	0	2530	0	1808	375	77	33	0%	0.9
WF	SIG 50-80, 10	0	2971	0	2040	389	83	36	-4.5%	Dom.
WF	SIG 50-85, 10	0	2971	0	2040	389	83	36	-4.5%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk										
WF	SIG 45-75, 10	0	3257	0	2103	416	85	36	0%	7.2
WF	SIG 45-80, 10	0	3257	0	2103	416	85	36	0%	7.2
WF	SIG 45-85, 10	0	3551	0	2243	420	86	37	-1.3%	37.4*
WF	SIG 55-75, 5	0	3352	0	2108	370	83	35	-11.1%	Dom.
WF	SIG 55-80, 5	0	3690	0	2240	375	86	36	-11.6%	Dom.
WF	SIG 55-85, 5	0	3913	0	2319	377	86	37	-12.4%	Dom.
WF	SIG 50-75, 5	0	4129	0	2352	413	88	37	-4.5%	Dom.
WF	SIG 50-80, 5	0	4465	0	2483	418	91	38	-5.1%	Dom.
WF	SIG 50-85, 5	0	4688	0	2562	419	92	39	-5.9%	Dom.
WF	SIG 45-75, 5	0	4937	0	2567	446	92	38	0%	15.5
WF	SIG 45-80, 5	0	5274	0	2698	451	95	39	0%	25.0
WF	SIG 45-85, 5	0	5496	0	2777	453	95	40	0%	59.7
WF	CTC 55-75, 10	0	0	2386	1507	338	71	32	0%	4.1
WF	CTC 55-80, 10	0	0	2386	1507	338	71	32	0%	4.1
WF	CTC 55-85, 10	0	0	2707	1656	343	73	34	-10.8%	Dom.
WF	CTC 50-75, 10	0	0	2574	1510	361	70	31	0%	0.1
WF	CTC 50-80, 10	0	0	3049	1738	379	77	35	-4.6%	Dom.
WF	CTC 50-85, 10	0	0	3049	1738	379	77	35	-4.6%	Dom.
WF	CTC 45-75, 10	0	0	3325	1780	405	79	35	0%	6.2
WF	CTC 45-80, 10	0	0	3325	1780	405	79	35	0%	6.2
WF	CTC 45-85, 10	0	0	3646	1927	410	81	36	-2.1%	Dom.
WF	CTC 55-75, 5	0	0	3500	1841	373	81	35	-9.2%	Dom.
WF	CTC 55-80, 5	0	0	3874	1976	380	84	37	-10.3%	Dom.
WF	CTC 55-85, 5	0	0	4121	2060	382	85	37	-11.5%	Dom.
WF	CTC 50-75, 5	0	0	4302	2057	416	86	37	-3.5%	Dom.
WF	CTC 50-80, 5	0	0	4675	2192	423	89	38	-4.6%	Dom.
WF	CTC 50-85, 5	0	0	4922	2275	425	90	39	-5.7%	Dom.
WF	CTC 45-75, 5	0	0	5134	2248	449	89	38	0%	10.4
WF	CTC 45-80, 5	0	0	5507	2382	457	93	40	0%	18.2
WF	CTC 45-85, 5	0	0	5754	2465	459	94	40	0%	45.7

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

[a] Both models evaluated two scenarios for CRC risk: one in which age-specific risks were assumed to have remained stable since the early screening period in the U.S. (1975-1979 for SimCRC; 1990-1994 for MISCAN), and one in which risks were assumed to have increased proportional to observed trends among adults under age 40 years. Strategies for each model and scenario are ordered successively by screening modality, interval (↓), end age (↑), and start age (↓).

[b] Total number of colonoscopies performed per 1000 40-year-olds, including diagnostic colonoscopies and potential surveillance colonoscopies after adenoma removal. The number of screening-related complications ranged from 3.5 to 27.6 per 1000 40-year-olds across models, scenarios, and strategies.

[c] Including deaths from complications of screening.

[d] The difference in LYG compared to (combinations of) adjacent strategies on the efficient frontier. Near-efficient strategies have a loss in LYG of less than 2% before rounding. For the least intensive screening strategy evaluated within each class of screening modality, the difference was zero by definition.
[e] Efficiency ratio = incremental number of colonoscopies/LYG with respect to the next less effective strategy on the efficient frontier, a burden-to-benefit ratio. Only calculated for efficient and near-efficient strategies (marked with an asterisk*), i.e. strategies within 2% from the efficient frontier among all evaluated strategies within a class of screening modalities (colonoscopy, stool-based, sigmoidoscopy, and CTC).

Supplementary Table A3.4: Lifetime number of colonoscopies and LYG for all evaluated screening strategies under two scenarios for CRC risk, by model, in black females [a]

		Outcomes per 1000 40-year-olds								
Subgroup	Modality, and age to begin- end screening, interval, y	Stool tests	SIGs	CTCs	COLs [b]	LYG	CRC cases averted	CRC deaths averted [c]	Relative distance from efficient frontier [d]	ER [e]
MISCAN - Scenario 1: Stable CRC risk										
BF	No screening	0	0	0	60	0	0	0	-	-
BF	COL 55-75, 15	0	0	0	3037	227	34	20	0%	13.1
BF	COL 55-80, 15	0	0	0	3037	227	34	20	0%	13.1
BF	COL 55-85, 15	0	0	0	3322	228	34	21	-7.1%	Dom.
BF	COL 50-75, 15	0	0	0	3327	246	35	21	0%	15.0
BF	COL 50-80, 15	0	0	0	3746	251	36	22	-2.3%	Dom.
BF	COL 50-85, 15	0	0	0	3746	251	36	22	-2.3%	Dom.
BF	COL 45-75, 15	0	0	0	4101	266	37	22	-0.4%	Dom.
BF	COL 45-80, 15	0	0	0	4101	266	37	22	-0.4%	Dom.
BF	COL 45-85, 15	0	0	0	4101	266	37	22	-0.4%	Dom.
BF	COL 55-75, 10	0	0	0	3646	239	36	21	-6.2%	Dom.
BF	COL 55-80, 10	0	0	0	3646	239	36	21	-6.2%	Dom.
BF	COL 55-85, 10	0	0	0	3908	240	37	22	-8.4%	Dom.
BF	COL 50-75, 10	0	0	0	4060	266	38	22	0%	37.7
BF	COL 50-80, 10	0	0	0	4439	268	39	23	-2.2%	Dom.
BF	COL 50-85, 10	0	0	0	4439	268	39	23	-2.2%	Dom.
BF	COL 45-75, 10	0	0	0	4894	285	40	23	0%	43.4
BF	COL 45-80, 10	0	0	0	4894	285	40	23	0%	43.4
BF	COL 45-85, 10	0	0	0	5155	286	40	23	-0.6%	348.0*
BF	COL 55-75, 5	0	0	0	4864	251	39	22	-11.5%	Dom.
BF	COL 55-80, 5	0	0	0	5209	252	39	22	-12.3%	Dom.
BF	COL 55-85, 5	0	0	0	5454	253	39	23	-13.0%	Dom.
BF	COL 50-75, 5	0	0	0	5888	283	41	24	-3.9%	Dom.
BF	COL 50-80, 5	0	0	0	6234	284	42	24	-4.6%	Dom.
BF	COL 50-85, 5	0	0	0	6479	284	42	24	-5.3%	Dom.
BF	COL 45-75, 5	0	0	0	6930	304	43	24	0%	104.0
BF	COL 45-80, 5	0	0	0	7276	305	44	25	0%	370.5
BF	COL 45-85, 5	0	0	0	7520	306	44	25	0%	950.9
BF	FIT 55-75, 3	5191	0	0	825	161	15	14	0%	4.8
BF	FIT 55-80, 3	6137	0	0	906	172	16	16	-0.8%	7.1*
BF	FIT 55-85, 3	6798	0	0	955	176	16	16	-3.0%	Dom.
BF	FIT 50-75, 3	6726	0	0	991	187	17	15	0%	6.3
BF	FIT 50-80, 3	7618	0	0	1063	196	18	17	0.0%	7.8*
BF	FIT 50-85, 3	7959	0	0	1088	198	18	17	-0.6%	8.7*
BF	FIT 45-75, 3	8297	0	0	1136	205	19	16	-0.2%	7.9*
BF	FIT 45-80, 3	8752	0	0	1171	210	19	17	0%	7.8
BF	FIT 45-85, 3	9454	0	0	1222	214	19	18	-0.3%	11.9*

table continues

MISCAN - Scenario 1: Stable CRC risk										
BF	FIT 55-75, 2	7554	0	0	1063	188	19	16	-4.2%	Dom.
BF	FIT 55-80, 2	8406	0	0	1124	194	20	18	-4.7%	Dom.
BF	FIT 55-85, 2	9351	0	0	1185	198	20	18	-6.2%	Dom.
BF	FIT 50-75, 2	9240	0	0	1237	213	22	18	-1.3%	Dom.
BF	FIT 50-80, 2	10503	0	0	1324	223	23	19	-0.7%	11.9*
BF	FIT 50-85, 2	11128	0	0	1364	225	23	19	-1.4%	12.7*
BF	FIT 45-75, 2	11477	0	0	1422	233	23	19	-0.3%	10.8*
BF	FIT 45-80, 2	12314	0	0	1480	239	24	19	0%	10.5
BF	FIT 45-85, 2	13246	0	0	1538	243	24	20	0%	16.7
BF	FIT 55-75, 1	12431	0	0	1469	217	26	19	-9.0%	Dom.
BF	FIT 55-80, 1	14150	0	0	1567	223	27	20	-8.5%	Dom.
BF	FIT 55-85, 1	15418	0	0	1633	226	28	20	-9.0%	Dom.
BF	FIT 50-75, 1	15658	0	0	1743	246	29	20	-3.1%	Dom.
BF	FIT 50-80, 1	17357	0	0	1837	252	30	21	-2.7%	Dom.
BF	FIT 50-85, 1	18615	0	0	1902	255	30	22	-3.1%	Dom.
BF	FIT 45-75, 1	19041	0	0	1988	267	30	21	-0.4%	18.8*
BF	FIT 45-80, 1	20731	0	0	2080	273	31	22	0%	18.0
BF	FIT 45-85, 1	21984	0	0	2144	275	32	22	0%	28.8
BF	FIT-DNA 55-75, 5	3535	0	0	1192	181	20	16	-14.6%	Dom.
BF	FIT-DNA 55-80, 5	3935	0	0	1261	186	20	17	-14.9%	Dom.
BF	FIT-DNA 55-85, 5	4214	0	0	1306	188	20	17	-15.8%	Dom.
BF	FIT-DNA 50-75, 5	4336	0	0	1397	205	22	17	-11.4%	Dom.
BF	FIT-DNA 50-80, 5	4731	0	0	1464	210	22	18	-11.7%	Dom.
BF	FIT-DNA 50-85, 5	5008	0	0	1508	212	22	19	-12.2%	Dom.
BF	FIT-DNA 45-75, 5	5168	0	0	1578	221	23	18	-9.8%	Dom.
BF	FIT-DNA 45-80, 5	5561	0	0	1644	226	24	19	-9.3%	Dom.
BF	FIT-DNA 45-85, 5	5836	0	0	1687	227	23	19	-9.5%	Dom.
BF	FIT-DNA 55-75, 3	4457	0	0	1412	200	24	17	-14.3%	Dom.
BF	FIT-DNA 55-80, 3	5203	0	0	1533	208	25	19	-14.0%	Dom.
BF	FIT-DNA 55-85, 3	5719	0	0	1609	211	25	19	-14.4%	Dom.
BF	FIT-DNA 50-75, 3	5716	0	0	1700	230	27	19	-8.7%	Dom.
BF	FIT-DNA 50-80, 3	6415	0	0	1810	237	28	20	-8.1%	Dom.
BF	FIT-DNA 50-85, 3	6681	0	0	1848	238	28	20	-8.3%	Dom.
BF	FIT-DNA 45-75, 3	7012	0	0	1960	250	28	20	-6.2%	Dom.
BF	FIT-DNA 45-80, 3	7369	0	0	2014	253	29	21	-5.9%	Dom.
BF	FIT-DNA 45-85, 3	7917	0	0	2093	256	29	21	-6.2%	Dom.
BF	FIT-DNA 55-75, 1	8771	0	0	2215	233	32	20	-15.4%	Dom.
BF	FIT-DNA 55-80, 1	9839	0	0	2352	237	33	21	-14.4%	Dom.
BF	FIT-DNA 55-85, 1	10642	0	0	2451	239	34	21	-14.3%	Dom.
BF	FIT-DNA 50-75, 1	10898	0	0	2632	263	35	22	-6.2%	Dom.
BF	FIT-DNA 50-80, 1	11980	0	0	2770	267	36	22	-5.3%	Dom.
BF	FIT-DNA 50-85, 1	12773	0	0	2866	269	36	23	-5.2%	Dom.
BF	FIT-DNA 45-75, 1	13174	0	0	3023	283	37	23	-0.8%	112.0*
BF	FIT-DNA 45-80, 1	14243	0	0	3158	287	38	23	0.0%	87.2*
BF	FIT-DNA 45-85, 1	15035	0	0	3254	288	38	23	0%	86.5
BF	HSgFOBT 55-75, 3	4861	0	0	1043	159	16	14	-17.9%	Dom.
BF	HSgFOBT 55-80, 3	5715	0	0	1150	169	16	16	-18.2%	Dom.

table continues

MISCAN - Scenario 1: Stable CRC risk										
BF	HSgFOBT 55-85, 3	6309	0	0	1218	173	16	16	-19.3%	Dom.
BF	HSgFOBT 50-75, 3	6243	0	0	1283	186	18	16	-15.8%	Dom.
BF	HSgFOBT 50-80, 3	7042	0	0	1380	194	19	17	-15.4%	Dom.
BF	HSgFOBT 50-85, 3	7347	0	0	1414	196	19	17	-15.8%	Dom.
BF	HSgFOBT 45-75, 3	7649	0	0	1502	205	20	17	-15.0%	Dom.
BF	HSgFOBT 45-80, 3	8056	0	0	1550	209	20	17	-14.1%	Dom.
BF	HSgFOBT 45-85, 3	8681	0	0	1619	213	20	18	-13.9%	Dom.
BF	HSgFOBT 55-75, 2	6865	0	0	1363	187	20	17	-18.0%	Dom.
BF	HSgFOBT 55-80, 2	7600	0	0	1447	193	21	18	-18.2%	Dom.
BF	HSgFOBT 55-85, 2	8409	0	0	1531	197	21	18	-18.9%	Dom.
BF	HSgFOBT 50-75, 2	8325	0	0	1619	213	23	18	-13.7%	Dom.
BF	HSgFOBT 50-80, 2	9408	0	0	1738	222	24	19	-12.7%	Dom.
BF	HSgFOBT 50-85, 2	9941	0	0	1793	224	24	20	-12.9%	Dom.
BF	HSgFOBT 45-75, 2	10252	0	0	1899	234	25	19	-10.9%	Dom.
BF	HSgFOBT 45-80, 2	10967	0	0	1977	239	25	20	-10.4%	Dom.
BF	HSgFOBT 45-85, 2	11759	0	0	2058	242	25	20	-10.7%	Dom.
BF	HSgFOBT 55-75, 1	10314	0	0	1880	217	27	19	-17.3%	Dom.
BF	HSgFOBT 55-80, 1	11617	0	0	2009	222	28	20	-17.4%	Dom.
BF	HSgFOBT 55-85, 1	12578	0	0	2099	224	28	20	-18.1%	Dom.
BF	HSgFOBT 50-75, 1	12793	0	0	2259	246	30	21	-10.9%	Dom.
BF	HSgFOBT 50-80, 1	14086	0	0	2385	251	31	21	-9.5%	Dom.
BF	HSgFOBT 50-85, 1	15037	0	0	2473	253	31	22	-9.2%	Dom.
BF	HSgFOBT 45-75, 1	15400	0	0	2611	266	32	21	-5.0%	Dom.
BF	HSgFOBT 45-80, 1	16681	0	0	2735	271	33	22	-3.8%	Dom.
BF	HSgFOBT 45-85, 1	17627	0	0	2822	273	33	22	-3.5%	Dom.
BF	SIG 55-75, 10	0	2181	0	1527	176	27	16	0%	8.3
BF	SIG 55-80, 10	0	2181	0	1527	176	27	16	0%	8.3
BF	SIG 55-85, 10	0	2471	0	1593	177	27	17	-3.9%	Dom.
BF	SIG 50-75, 10	0	2377	0	1669	194	28	17	0%	8.0
BF	SIG 50-80, 10	0	2786	0	1772	198	29	17	-1.2%	26.0*
BF	SIG 50-85, 10	0	2786	0	1772	198	29	17	-1.2%	26.0*
BF	SIG 45-75, 10	0	3060	0	1905	208	30	18	-0.4%	17.3*
BF	SIG 45-80, 10	0	3060	0	1905	208	30	18	-0.4%	17.3*
BF	SIG 45-85, 10	0	3348	0	1969	209	30	18	-1.7%	20.3*
BF	SIG 55-75, 5	0	3162	0	1801	195	30	18	-3.7%	Dom.
BF	SIG 55-80, 5	0	3504	0	1869	196	30	18	-4.8%	Dom.
BF	SIG 55-85, 5	0	3745	0	1914	197	30	18	-5.8%	Dom.
BF	SIG 50-75, 5	0	3884	0	2085	219	32	19	-0.4%	17.0*
BF	SIG 50-80, 5	0	4223	0	2152	220	32	19	-1.5%	18.4*
BF	SIG 50-85, 5	0	4463	0	2197	221	32	19	-2.4%	Dom.
BF	SIG 45-75, 5	0	4650	0	2333	235	33	20	0%	16.4
BF	SIG 45-80, 5	0	4988	0	2399	236	34	20	0%	40.0
BF	SIG 45-85, 5	0	5226	0	2443	237	34	20	0%	87.2
BF	CTC 55-75, 10	0	0	2259	1218	183	24	17	0%	6.3
BF	CTC 55-80, 10	0	0	2259	1218	183	24	17	0%	6.3
BF	CTC 55-85, 10	0	0	2570	1288	186	24	17	-5.3%	Dom.
BF	CTC 50-75, 10	0	0	2460	1301	199	24	17	0%	5.4

table continues

MISCAN - Scenario 1: Stable CRC risk										
BF	CTC 50-80, 10	0	0	2900	1407	208	26	18	-0.6%	11.5*
BF	CTC 50-85, 10	0	0	2900	1407	208	26	18	-0.6%	11.5*
BF	CTC 45-75, 10	0	0	3179	1490	215	26	18	-1.1%	11.5*
BF	CTC 45-80, 10	0	0	3179	1490	215	26	18	-1.1%	11.5*
BF	CTC 45-85, 10	0	0	3488	1559	218	27	19	-2.8%	Dom.
BF	CTC 55-75, 5	0	0	3347	1512	216	29	19	-1.7%	12.3*
BF	CTC 55-80, 5	0	0	3717	1584	220	30	20	-3.0%	Dom.
BF	CTC 55-85, 5	0	0	3977	1631	221	31	20	-4.4%	Dom.
BF	CTC 50-75, 5	0	0	4122	1739	242	31	20	0%	10.1
BF	CTC 50-80, 5	0	0	4490	1810	246	32	21	-0.9%	17.5*
BF	CTC 50-85, 5	0	0	4748	1856	248	33	21	-2.0%	22.4*
BF	CTC 45-75, 5	0	0	4935	1937	260	33	21	0%	11.4
BF	CTC 45-80, 5	0	0	5301	2007	264	34	22	0%	17.6
BF	CTC 45-85, 5	0	0	5559	2053	265	34	22	0%	39.7
MISCAN - Scenario 2: Increased CRC risk										
BF	No screening	0	0	0	77	0	0	0	-	-
BF	COL 55-75, 15	0	0	0	3375	292	44	26	0%	11.3
BF	COL 55-80, 15	0	0	0	3375	292	44	26	0%	11.3
BF	COL 55-85, 15	0	0	0	3614	294	45	27	-5.0%	Dom.
BF	COL 50-75, 15	0	0	0	3723	317	46	27	0%	13.8
BF	COL 50-80, 15	0	0	0	4085	324	47	28	-1.9%	56.4*
BF	COL 50-85, 15	0	0	0	4085	324	47	28	-1.9%	56.4*
BF	COL 45-75, 15	0	0	0	4485	342	48	29	-0.5%	136.4*
BF	COL 45-80, 15	0	0	0	4485	342	48	29	-0.5%	136.4*
BF	COL 45-85, 15	0	0	0	4485	342	48	29	-0.5%	136.4*
BF	COL 55-75, 10	0	0	0	3925	307	47	28	-5.4%	Dom.
BF	COL 55-80, 10	0	0	0	3925	307	47	28	-5.4%	Dom.
BF	COL 55-85, 10	0	0	0	4136	308	47	28	-7.2%	Dom.
BF	COL 50-75, 10	0	0	0	4405	342	50	29	0%	28.2
BF	COL 50-80, 10	0	0	0	4721	345	50	30	-1.7%	89.4*
BF	COL 50-85, 10	0	0	0	4721	345	50	30	-1.7%	89.4*
BF	COL 45-75, 10	0	0	0	5231	366	52	30	0%	33.2
BF	COL 45-80, 10	0	0	0	5231	366	52	30	0%	33.2
BF	COL 45-85, 10	0	0	0	5442	367	52	30	-0.5%	233.4*
BF	COL 55-75, 5	0	0	0	4982	323	50	29	-10.1%	Dom.
BF	COL 55-80, 5	0	0	0	5258	324	50	29	-11.7%	Dom.
BF	COL 55-85, 5	0	0	0	5450	324	50	29	-12.3%	Dom.
BF	COL 50-75, 5	0	0	0	6008	363	54	31	-3.6%	Dom.
BF	COL 50-80, 5	0	0	0	6284	365	54	31	-4.2%	Dom.
BF	COL 50-85, 5	0	0	0	6476	365	54	31	-4.8%	Dom.
BF	COL 45-75, 5	0	0	0	7050	391	56	32	0%	74.1
BF	COL 45-80, 5	0	0	0	7326	392	56	32	0%	249.5
BF	COL 45-85, 5	0	0	0	7518	392	56	32	0%	550.7
BF	FIT 55-75, 3	5082	0	0	1000	205	20	18	0%	4.5
BF	FIT 55-80, 3	5965	0	0	1091	219	21	20	-0.4%	6.4*
BF	FIT 55-85, 3	6569	0	0	1145	224	21	21	-2.2%	Dom.
BF	FIT 50-75, 3	6577	0	0	1195	238	22	20	0%	6.0

table continues

MISCAN - Scenario 1: Stable CRC risk										
BF	FIT 50-80, 3	7403	0	0	1276	250	23	22	0%	6.8
BF	FIT 50-85, 3	7714	0	0	1303	252	23	22	-0.5%	10.9*
BF	FIT 45-75, 3	8114	0	0	1363	261	24	21	-0.3%	7.4*
BF	FIT 45-80, 3	8535	0	0	1402	267	25	22	0%	7.0
BF	FIT 45-85, 3	9175	0	0	1458	273	25	23	-0.2%	10.1*
BF	FIT 55-75, 2	7324	0	0	1276	240	25	21	-3.8%	Dom.
BF	FIT 55-80, 2	8104	0	0	1343	248	26	23	-4.1%	Dom.
BF	FIT 55-85, 2	8952	0	0	1406	253	26	24	-5.5%	Dom.
BF	FIT 50-75, 2	8974	0	0	1480	272	28	23	-1.5%	Dom.
BF	FIT 50-80, 2	10125	0	0	1574	284	29	24	-0.7%	10.3*
BF	FIT 50-85, 2	10684	0	0	1615	287	29	25	-1.2%	10.9*
BF	FIT 45-75, 2	11148	0	0	1691	297	30	24	-0.4%	9.6*
BF	FIT 45-80, 2	11909	0	0	1752	305	31	25	0%	9.3
BF	FIT 45-85, 2	12741	0	0	1812	310	31	26	0%	13.6
BF	FIT 55-75, 1	11915	0	0	1732	278	34	24	-8.3%	Dom.
BF	FIT 55-80, 1	13448	0	0	1831	287	35	26	-7.8%	Dom.
BF	FIT 55-85, 1	14552	0	0	1895	289	36	26	-8.1%	Dom.
BF	FIT 50-75, 1	15021	0	0	2044	316	37	26	-2.7%	Dom.
BF	FIT 50-80, 1	16529	0	0	2138	324	39	28	-2.0%	Dom.
BF	FIT 50-85, 1	17621	0	0	2201	327	39	28	-2.4%	Dom.
BF	FIT 45-75, 1	18305	0	0	2319	341	39	27	-0.5%	16.1*
BF	FIT 45-80, 1	19800	0	0	2411	349	41	28	0%	15.2
BF	FIT 45-85, 1	20885	0	0	2472	352	41	29	0%	22.5
BF	FIT-DNA 55-75, 5	3435	0	0	1411	231	26	21	-14.0%	Dom.
BF	FIT-DNA 55-80, 5	3798	0	0	1484	238	26	22	-14.0%	Dom.
BF	FIT-DNA 55-85, 5	4046	0	0	1530	240	26	23	-14.7%	Dom.
BF	FIT-DNA 50-75, 5	4211	0	0	1648	261	28	22	-11.1%	Dom.
BF	FIT-DNA 50-80, 5	4569	0	0	1718	268	29	23	-11.2%	Dom.
BF	FIT-DNA 50-85, 5	4814	0	0	1762	270	29	24	-11.8%	Dom.
BF	FIT-DNA 45-75, 5	5024	0	0	1853	282	30	23	-9.8%	Dom.
BF	FIT-DNA 45-80, 5	5379	0	0	1921	288	31	24	-9.1%	Dom.
BF	FIT-DNA 45-85, 5	5623	0	0	1964	290	31	25	-9.3%	Dom.
BF	FIT-DNA 55-75, 3	4321	0	0	1663	256	31	23	-13.4%	Dom.
BF	FIT-DNA 55-80, 3	4994	0	0	1787	267	33	24	-13.2%	Dom.
BF	FIT-DNA 55-85, 3	5447	0	0	1861	270	33	25	-13.6%	Dom.
BF	FIT-DNA 50-75, 3	5529	0	0	1989	294	34	25	-8.5%	Dom.
BF	FIT-DNA 50-80, 3	6153	0	0	2099	303	36	26	-7.8%	Dom.
BF	FIT-DNA 50-85, 3	6386	0	0	2136	304	36	26	-8.0%	Dom.
BF	FIT-DNA 45-75, 3	6780	0	0	2278	319	37	26	-6.2%	Dom.
BF	FIT-DNA 45-80, 3	7098	0	0	2333	324	37	27	-5.7%	Dom.
BF	FIT-DNA 45-85, 3	7578	0	0	2409	328	38	27	-6.0%	Dom.
BF	FIT-DNA 55-75, 1	8299	0	0	2522	300	42	27	-14.9%	Dom.
BF	FIT-DNA 55-80, 1	9215	0	0	2649	305	43	27	-14.0%	Dom.
BF	FIT-DNA 55-85, 1	9886	0	0	2736	306	44	28	-13.9%	Dom.
BF	FIT-DNA 50-75, 1	10319	0	0	2980	338	46	28	-6.0%	Dom.
BF	FIT-DNA 50-80, 1	11242	0	0	3105	343	47	29	-5.2%	Dom.
BF	FIT-DNA 50-85, 1	11903	0	0	3190	344	47	29	-5.1%	Dom.

table continues

MISCAN - Scenario 1: Stable CRC risk										
BF	FIT-DNA 45-75, 1	12503	0	0	3403	363	48	29	-0.8%	81.6*
BF	FIT-DNA 45-80, 1	13413	0	0	3526	368	49	30	0.0%	65.0*
BF	FIT-DNA 45-85, 1	14072	0	0	3610	369	49	30	0%	64.4
BF	HSgFOBT 55-75, 3	4771	0	0	1222	203	20	18	-16.2%	Dom.
BF	HSgFOBT 55-80, 3	5566	0	0	1336	216	21	20	-16.3%	Dom.
BF	HSgFOBT 55-85, 3	6105	0	0	1405	220	21	21	-17.7%	Dom.
BF	HSgFOBT 50-75, 3	6111	0	0	1497	237	24	20	-14.8%	Dom.
BF	HSgFOBT 50-80, 3	6848	0	0	1598	248	25	22	-14.2%	Dom.
BF	HSgFOBT 50-85, 3	7123	0	0	1633	250	24	22	-14.5%	Dom.
BF	HSgFOBT 45-75, 3	7479	0	0	1745	261	26	21	-14.1%	Dom.
BF	HSgFOBT 45-80, 3	7853	0	0	1794	267	26	22	-13.4%	Dom.
BF	HSgFOBT 45-85, 3	8418	0	0	1864	272	26	23	-13.1%	Dom.
BF	HSgFOBT 55-75, 2	6672	0	0	1580	239	26	21	-16.6%	Dom.
BF	HSgFOBT 55-80, 2	7340	0	0	1665	247	27	23	-16.6%	Dom.
BF	HSgFOBT 55-85, 2	8058	0	0	1748	251	27	24	-17.7%	Dom.
BF	HSgFOBT 50-75, 2	8090	0	0	1873	272	30	23	-13.1%	Dom.
BF	HSgFOBT 50-80, 2	9067	0	0	1993	283	31	25	-11.9%	Dom.
BF	HSgFOBT 50-85, 2	9537	0	0	2046	286	31	25	-12.1%	Dom.
BF	HSgFOBT 45-75, 2	9948	0	0	2185	300	32	24	-10.3%	Dom.
BF	HSgFOBT 45-80, 2	10591	0	0	2263	306	33	25	-9.7%	Dom.
BF	HSgFOBT 45-85, 2	11287	0	0	2340	310	33	26	-9.9%	Dom.
BF	HSgFOBT 55-75, 1	9915	0	0	2149	278	35	25	-16.2%	Dom.
BF	HSgFOBT 55-80, 1	11058	0	0	2273	285	37	26	-16.1%	Dom.
BF	HSgFOBT 55-85, 1	11879	0	0	2354	287	37	26	-16.8%	Dom.
BF	HSgFOBT 50-75, 1	12277	0	0	2571	316	39	27	-10.6%	Dom.
BF	HSgFOBT 50-80, 1	13403	0	0	2689	323	40	28	-9.1%	Dom.
BF	HSgFOBT 50-85, 1	14211	0	0	2769	325	41	28	-8.9%	Dom.
BF	HSgFOBT 45-75, 1	14780	0	0	2957	342	41	28	-4.8%	Dom.
BF	HSgFOBT 45-80, 1	15894	0	0	3073	348	42	29	-3.6%	Dom.
BF	HSgFOBT 45-85, 1	16695	0	0	3151	350	43	29	-3.3%	Dom.
BF	SIG 55-75, 10	0	1998	0	2222	267	41	24	0%	8.0
BF	SIG 55-80, 10	0	1998	0	2222	267	41	24	0%	8.0
BF	SIG 55-85, 10	0	2223	0	2287	268	41	25	-2.6%	Dom.
BF	SIG 50-75, 10	0	2202	0	2441	294	42	25	0%	7.9
BF	SIG 50-80, 10	0	2527	0	2549	299	43	26	-0.8%	22.4*
BF	SIG 50-85, 10	0	2527	0	2549	299	43	26	-0.8%	22.4*
BF	SIG 45-75, 10	0	2812	0	2743	314	45	26	0%	15.1
BF	SIG 45-80, 10	0	2812	0	2743	314	45	26	0%	15.1
BF	SIG 45-85, 10	0	3035	0	2806	315	45	27	-0.8%	49.3*
BF	SIG 55-75, 5	0	2784	0	2483	285	44	26	-4.1%	Dom.
BF	SIG 55-80, 5	0	3047	0	2547	287	44	26	-4.9%	Dom.
BF	SIG 55-85, 5	0	3230	0	2588	287	44	26	-5.5%	Dom.
BF	SIG 50-75, 5	0	3429	0	2850	319	47	27	-0.6%	22.6*
BF	SIG 50-80, 5	0	3690	0	2913	321	47	28	-1.2%	25.6*
BF	SIG 50-85, 5	0	3872	0	2953	321	47	28	-1.8%	29.2*
BF	SIG 45-75, 5	0	4134	0	3161	340	48	28	0%	16.0
BF	SIG 45-80, 5	0	4394	0	3224	342	49	29	0%	33.8

table continues

MISCAN - Scenario 1: Stable CRC risk										
BF	SIG 45-85, 5	0	4576	0	3263	343	49	29	0%	73.3
BF	CTC 55-75, 10	0	0	2190	1473	235	31	21	0%	5.9
BF	CTC 55-80, 10	0	0	2190	1473	235	31	21	0%	5.9
BF	CTC 55-85, 10	0	0	2467	1547	239	32	22	-4.1%	Dom.
BF	CTC 50-75, 10	0	0	2400	1574	254	31	21	0%	5.5
BF	CTC 50-80, 10	0	0	2800	1689	266	33	23	-0.5%	9.5*
BF	CTC 50-85, 10	0	0	2800	1689	266	33	23	-0.5%	9.5*
BF	CTC 45-75, 10	0	0	3090	1786	274	34	23	-1.4%	10.3*
BF	CTC 45-80, 10	0	0	3090	1786	274	34	23	-1.4%	10.3*
BF	CTC 45-85, 10	0	0	3365	1858	278	34	24	-3.0%	Dom.
BF	CTC 55-75, 5	0	0	3207	1802	277	38	25	-1.2%	9.9*
BF	CTC 55-80, 5	0	0	3536	1875	282	39	26	-2.2%	Dom.
BF	CTC 55-85, 5	0	0	3762	1921	284	40	26	-3.5%	Dom.
BF	CTC 50-75, 5	0	0	3955	2062	310	41	26	0%	8.6
BF	CTC 50-80, 5	0	0	4281	2133	316	42	27	-0.6%	13.6*
BF	CTC 50-85, 5	0	0	4505	2178	317	43	27	-1.5%	17.4*
BF	CTC 45-75, 5	0	0	4748	2284	333	42	27	0%	10.0
BF	CTC 45-80, 5	0	0	5072	2354	338	44	28	0%	13.6
BF	CTC 45-85, 5	0	0	5295	2399	339	44	28	0%	30.6
SimCRC - Scenario 1: Stable CRC risk										
BF	No screening	0	0	0	64	0	0	0	-	-
BF	COL 55-75, 15	0	0	0	2815	250	46	23	0%	11.0
BF	COL 55-80, 15	0	0	0	2815	250	46	23	0%	11.0
BF	COL 55-85, 15	0	0	0	3141	251	47	23	-12.9%	Dom.
BF	COL 50-75, 15	0	0	0	3017	283	48	24	0%	6.0
BF	COL 50-80, 15	0	0	0	3512	289	51	25	-4.7%	Dom.
BF	COL 50-85, 15	0	0	0	3512	289	51	25	-4.7%	Dom.
BF	COL 45-75, 15	0	0	0	3845	317	53	26	0%	24.4
BF	COL 45-80, 15	0	0	0	3845	317	53	26	0%	24.4
BF	COL 45-85, 15	0	0	0	3845	317	53	26	0%	24.4
BF	COL 55-75, 10	0	0	0	3503	262	49	24	-13.7%	Dom.
BF	COL 55-80, 10	0	0	0	3503	262	49	24	-13.7%	Dom.
BF	COL 55-85, 10	0	0	0	3789	262	50	24	-16.6%	Dom.
BF	COL 50-75, 10	0	0	0	3849	300	52	26	-5.3%	Dom.
BF	COL 50-80, 10	0	0	0	4280	303	54	26	-6.9%	Dom.
BF	COL 50-85, 10	0	0	0	4280	303	54	26	-6.9%	Dom.
BF	COL 45-75, 10	0	0	0	4701	334	56	27	0%	50.4
BF	COL 45-80, 10	0	0	0	4701	334	56	27	0%	50.4
BF	COL 45-85, 10	0	0	0	4987	335	57	28	-0.3%	380.6*
BF	COL 55-75, 5	0	0	0	4855	270	51	25	-19.2%	Dom.
BF	COL 55-80, 5	0	0	0	5224	271	52	25	-19.5%	Dom.
BF	COL 55-85, 5	0	0	0	5470	271	52	25	-19.8%	Dom.
BF	COL 50-75, 5	0	0	0	5888	313	56	27	-8.0%	Dom.
BF	COL 50-80, 5	0	0	0	6257	314	56	27	-8.3%	Dom.
BF	COL 50-85, 5	0	0	0	6503	314	56	27	-8.6%	Dom.
BF	COL 45-75, 5	0	0	0	6939	347	59	28	0%	179.2
BF	COL 45-80, 5	0	0	0	7307	347	59	28	0%	433.8

table continues

SimCRC - Scenario 1: Stable CRC risk										
BF	COL 45-85, 5	0	0	0	7554	348	59	28	0%	1225.4
BF	FIT 55-75, 3	5347	0	0	703	175	23	15	0%	3.7
BF	FIT 55-80, 3	6340	0	0	793	187	25	17	-5.3%	Dom.
BF	FIT 55-85, 3	6964	0	0	849	191	25	18	-9.7%	Dom.
BF	FIT 50-75, 3	6947	0	0	852	212	27	18	0%	4.0
BF	FIT 50-80, 3	7794	0	0	929	221	28	19	-3.7%	Dom.
BF	FIT 50-85, 3	8243	0	0	966	223	29	20	-6.1%	Dom.
BF	FIT 45-75, 3	8461	0	0	978	241	30	19	0%	4.4
BF	FIT 45-80, 3	9066	0	0	1029	247	31	20	0.0%	8.2*
BF	FIT 45-85, 3	9784	0	0	1091	251	31	21	-1.3%	10.5*
BF	FIT 55-75, 2	7713	0	0	927	206	29	18	-10.0%	Dom.
BF	FIT 55-80, 2	8598	0	0	999	213	30	20	-12.5%	Dom.
BF	FIT 55-85, 2	9570	0	0	1074	217	31	20	-14.2%	Dom.
BF	FIT 50-75, 2	9438	0	0	1075	241	33	20	-4.7%	Dom.
BF	FIT 50-80, 2	10754	0	0	1179	251	35	22	-5.7%	Dom.
BF	FIT 50-85, 2	11398	0	0	1229	253	35	22	-6.9%	Dom.
BF	FIT 45-75, 2	11722	0	0	1249	274	36	22	0%	8.1
BF	FIT 45-80, 2	12597	0	0	1318	280	37	23	0%	11.1
BF	FIT 45-85, 2	13561	0	0	1392	284	38	24	-0.3%	19.7*
BF	FIT 55-75, 1	12744	0	0	1324	237	37	21	-15.5%	Dom.
BF	FIT 55-80, 1	14522	0	0	1442	243	39	22	-15.6%	Dom.
BF	FIT 55-85, 1	15812	0	0	1524	246	40	23	-16.3%	Dom.
BF	FIT 50-75, 1	16076	0	0	1569	278	42	23	-6.2%	Dom.
BF	FIT 50-80, 1	17843	0	0	1685	284	44	24	-6.6%	Dom.
BF	FIT 50-85, 1	19127	0	0	1766	286	44	25	-7.4%	Dom.
BF	FIT 45-75, 1	19536	0	0	1797	311	45	25	0%	15.7
BF	FIT 45-80, 1	21297	0	0	1912	317	47	26	0%	20.2
BF	FIT 45-85, 1	22578	0	0	1992	319	47	26	0%	40.3
BF	FIT-DNA 55-75, 5	3613	0	0	1047	193	29	18	-22.6%	Dom.
BF	FIT-DNA 55-80, 5	4031	0	0	1128	198	30	19	-23.6%	Dom.
BF	FIT-DNA 55-85, 5	4321	0	0	1183	200	30	19	-24.9%	Dom.
BF	FIT-DNA 50-75, 5	4438	0	0	1227	228	33	19	-16.2%	Dom.
BF	FIT-DNA 50-80, 5	4853	0	0	1307	233	34	20	-16.7%	Dom.
BF	FIT-DNA 50-85, 5	5141	0	0	1361	234	34	21	-17.2%	Dom.
BF	FIT-DNA 45-75, 5	5288	0	0	1392	255	36	21	-10.5%	Dom.
BF	FIT-DNA 45-80, 5	5702	0	0	1471	260	37	22	-10.4%	Dom.
BF	FIT-DNA 45-85, 5	5989	0	0	1525	262	37	22	-10.8%	Dom.
BF	FIT-DNA 55-75, 3	4730	0	0	1274	220	34	20	-20.5%	Dom.
BF	FIT-DNA 55-80, 3	5518	0	0	1416	228	36	21	-20.5%	Dom.
BF	FIT-DNA 55-85, 3	5947	0	0	1490	230	37	22	-21.0%	Dom.
BF	FIT-DNA 50-75, 3	6077	0	0	1544	261	39	22	-11.4%	Dom.
BF	FIT-DNA 50-80, 3	6665	0	0	1649	267	41	23	-11.4%	Dom.
BF	FIT-DNA 50-85, 3	7124	0	0	1725	269	41	24	-12.1%	Dom.
BF	FIT-DNA 45-75, 3	7257	0	0	1759	292	42	23	-5.5%	Dom.
BF	FIT-DNA 45-80, 3	7883	0	0	1866	297	44	24	-5.4%	Dom.
BF	FIT-DNA 45-85, 3	8399	0	0	1954	300	44	25	-5.5%	Dom.
BF	FIT-DNA 55-75, 1	9062	0	0	2042	253	44	23	-20.8%	Dom.

table continues

SimCRC - Scenario 1: Stable CRC risk										
BF	FIT-DNA 55-80, 1	10183	0	0	2206	257	45	24	-20.1%	Dom.
BF	FIT-DNA 55-85, 1	11008	0	0	2322	258	46	24	-20.1%	Dom.
BF	FIT-DNA 50-75, 1	11299	0	0	2422	294	48	25	-9.3%	Dom.
BF	FIT-DNA 50-80, 1	12442	0	0	2588	298	50	26	-8.7%	Dom.
BF	FIT-DNA 50-85, 1	13259	0	0	2703	299	50	26	-8.7%	Dom.
BF	FIT-DNA 45-75, 1	13664	0	0	2789	327	52	26	-0.5%	99.5*
BF	FIT-DNA 45-80, 1	14795	0	0	2953	330	53	27	0%	82.9
BF	FIT-DNA 45-85, 1	15610	0	0	3067	331	53	27	0%	94.9
BF	HSgFOBT 55-75, 3	5049	0	0	949	176	24	16	-24.8%	Dom.
BF	HSgFOBT 55-80, 3	5945	0	0	1068	187	26	17	-25.9%	Dom.
BF	HSgFOBT 55-85, 3	6462	0	0	1134	190	27	18	-27.0%	Dom.
BF	HSgFOBT 50-75, 3	6511	0	0	1167	214	29	18	-18.8%	Dom.
BF	HSgFOBT 50-80, 3	7211	0	0	1260	222	30	19	-19.3%	Dom.
BF	HSgFOBT 50-85, 3	7687	0	0	1318	225	31	20	-19.9%	Dom.
BF	HSgFOBT 45-75, 3	7815	0	0	1349	243	32	19	-13.9%	Dom.
BF	HSgFOBT 45-80, 3	8458	0	0	1428	249	33	20	-13.3%	Dom.
BF	HSgFOBT 45-85, 3	9073	0	0	1506	253	33	21	-13.4%	Dom.
BF	HSgFOBT 55-75, 2	6975	0	0	1240	207	31	19	-24.3%	Dom.
BF	HSgFOBT 55-80, 2	7741	0	0	1335	213	32	20	-24.4%	Dom.
BF	HSgFOBT 55-85, 2	8578	0	0	1433	216	32	21	-24.8%	Dom.
BF	HSgFOBT 50-75, 2	8481	0	0	1459	243	35	20	-16.0%	Dom.
BF	HSgFOBT 50-80, 2	9617	0	0	1597	252	37	22	-15.6%	Dom.
BF	HSgFOBT 50-85, 2	10171	0	0	1661	254	37	22	-16.1%	Dom.
BF	HSgFOBT 45-75, 2	10472	0	0	1717	277	38	22	-9.5%	Dom.
BF	HSgFOBT 45-80, 2	11226	0	0	1808	282	40	23	-9.4%	Dom.
BF	HSgFOBT 45-85, 2	12052	0	0	1904	285	40	24	-9.7%	Dom.
BF	HSgFOBT 55-75, 1	10533	0	0	1728	238	39	22	-22.5%	Dom.
BF	HSgFOBT 55-80, 1	11905	0	0	1879	243	40	23	-22.9%	Dom.
BF	HSgFOBT 55-85, 1	12901	0	0	1985	245	41	23	-23.1%	Dom.
BF	HSgFOBT 50-75, 1	13136	0	0	2068	279	44	24	-12.7%	Dom.
BF	HSgFOBT 50-80, 1	14507	0	0	2217	284	45	25	-11.6%	Dom.
BF	HSgFOBT 50-85, 1	15498	0	0	2321	286	45	25	-11.4%	Dom.
BF	HSgFOBT 45-75, 1	15850	0	0	2391	312	47	25	-3.6%	Dom.
BF	HSgFOBT 45-80, 1	17214	0	0	2539	317	48	26	-2.6%	Dom.
BF	HSgFOBT 45-85, 1	18201	0	0	2642	318	49	26	-2.4%	Dom.
BF	SIG 55-75, 10	0	2303	0	1122	177	33	17	0%	6.0
BF	SIG 55-80, 10	0	2303	0	1122	177	33	17	0%	6.0
BF	SIG 55-85, 10	0	2623	0	1210	178	33	17	-12.7%	Dom.
BF	SIG 50-75, 10	0	2500	0	1193	202	35	17	0%	2.8
BF	SIG 50-80, 10	0	2957	0	1326	207	37	18	-5.3%	Dom.
BF	SIG 50-85, 10	0	2957	0	1326	207	37	18	-5.3%	Dom.
BF	SIG 45-75, 10	0	3231	0	1412	230	38	19	0%	7.9
BF	SIG 45-80, 10	0	3231	0	1412	230	38	19	0%	7.9
BF	SIG 45-85, 10	0	3548	0	1499	231	39	20	-1.9%	53.4*
BF	SIG 55-75, 5	0	3401	0	1417	198	37	19	-14.1%	Dom.
BF	SIG 55-80, 5	0	3778	0	1507	200	38	19	-15.4%	Dom.
BF	SIG 55-85, 5	0	4038	0	1566	201	39	19	-16.5%	Dom.

table continues

SimCRC - Scenario 1: Stable CRC risk										
BF	SIG 50-75, 5	0	4182	0	1643	232	41	20	-5.5%	Dom.
BF	SIG 50-80, 5	0	4557	0	1732	235	42	21	-6.9%	Dom.
BF	SIG 50-85, 5	0	4815	0	1790	236	42	21	-8.1%	Dom.
BF	SIG 45-75, 5	0	4992	0	1852	261	44	22	0%	14.2
BF	SIG 45-80, 5	0	5365	0	1940	263	45	22	0%	37.9
BF	SIG 45-85, 5	0	5623	0	1998	264	45	22	0%	86.5
BF	CTC 55-75, 10	0	0	2283	1220	225	40	21	0%	5.1
BF	CTC 55-80, 10	0	0	2283	1220	225	40	21	0%	5.1
BF	CTC 55-85, 10	0	0	2592	1319	227	41	21	-12.9%	Dom.
BF	CTC 50-75, 10	0	0	2485	1278	255	42	22	0%	2.0
BF	CTC 50-80, 10	0	0	2930	1424	262	45	23	-5.5%	Dom.
BF	CTC 50-85, 10	0	0	2930	1424	262	45	23	-5.5%	Dom.
BF	CTC 45-75, 10	0	0	3211	1499	288	46	24	0%	6.7
BF	CTC 45-80, 10	0	0	3211	1499	288	46	24	0%	6.7
BF	CTC 45-85, 10	0	0	3518	1597	290	47	24	-1.6%	48.0*
BF	CTC 55-75, 5	0	0	3370	1504	246	45	23	-14.8%	Dom.
BF	CTC 55-80, 5	0	0	3738	1597	248	46	23	-15.7%	Dom.
BF	CTC 55-85, 5	0	0	3989	1658	249	46	23	-16.7%	Dom.
BF	CTC 50-75, 5	0	0	4159	1721	286	49	25	-5.7%	Dom.
BF	CTC 50-80, 5	0	0	4525	1813	289	50	25	-6.8%	Dom.
BF	CTC 50-85, 5	0	0	4776	1874	290	50	25	-7.8%	Dom.
BF	CTC 45-75, 5	0	0	4980	1916	317	52	26	0%	14.3
BF	CTC 45-80, 5	0	0	5345	2007	320	53	26	0%	35.4
BF	CTC 45-85, 5	0	0	5596	2068	320	53	27	0%	83.4
SimCRC - Scenario 2: Increased CRC risk										
BF	No screening	0	0	0	80	0	0	0	-	-
BF	COL 55-75, 15	0	0	0	2733	306	54	28	0%	8.7
BF	COL 55-80, 15	0	0	0	2733	306	54	28	0%	8.7
BF	COL 55-85, 15	0	0	0	3067	308	55	28	-12.9%	Dom.
BF	COL 50-75, 15	0	0	0	2923	346	56	28	0%	4.7
BF	COL 50-80, 15	0	0	0	3429	356	60	30	-4.7%	Dom.
BF	COL 50-85, 15	0	0	0	3429	356	60	30	-4.7%	Dom.
BF	COL 45-75, 15	0	0	0	3755	391	63	32	0%	18.7
BF	COL 45-80, 15	0	0	0	3755	391	63	32	0%	18.7
BF	COL 45-85, 15	0	0	0	3755	391	63	32	0%	18.7
BF	COL 55-75, 10	0	0	0	3434	325	59	30	-13.2%	Dom.
BF	COL 55-80, 10	0	0	0	3434	325	59	30	-13.2%	Dom.
BF	COL 55-85, 10	0	0	0	3727	326	60	30	-16.3%	Dom.
BF	COL 50-75, 10	0	0	0	3768	372	62	31	-4.9%	Dom.
BF	COL 50-80, 10	0	0	0	4212	377	65	32	-6.7%	Dom.
BF	COL 50-85, 10	0	0	0	4212	377	65	32	-6.7%	Dom.
BF	COL 45-75, 10	0	0	0	4623	416	67	33	0%	34.8
BF	COL 45-80, 10	0	0	0	4623	416	67	33	0%	34.8
BF	COL 45-85, 10	0	0	0	4917	417	68	34	-0.3%	223.5*
BF	COL 55-75, 5	0	0	0	4821	338	62	31	-19.1%	Dom.
BF	COL 55-80, 5	0	0	0	5202	339	63	31	-19.4%	Dom.
BF	COL 55-85, 5	0	0	0	5456	340	63	31	-19.7%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk										
BF	COL 50-75, 5	0	0	0	5859	392	68	33	-8.0%	Dom.
BF	COL 50-80, 5	0	0	0	6239	394	69	34	-8.3%	Dom.
BF	COL 50-85, 5	0	0	0	6493	394	69	34	-8.6%	Dom.
BF	COL 45-75, 5	0	0	0	6913	435	71	35	0%	121.6
BF	COL 45-80, 5	0	0	0	7293	436	72	35	0%	241.7
BF	COL 45-85, 5	0	0	0	7547	437	73	35	0%	687.9
BF	FIT 55-75, 3	5338	0	0	684	211	26	18	0%	2.9
BF	FIT 55-80, 3	6332	0	0	771	227	28	20	-5.4%	Dom.
BF	FIT 55-85, 3	6954	0	0	825	231	28	21	-9.9%	Dom.
BF	FIT 50-75, 3	6946	0	0	827	258	31	21	0%	3.1
BF	FIT 50-80, 3	7791	0	0	901	270	32	23	-3.6%	Dom.
BF	FIT 50-85, 3	8242	0	0	939	273	33	23	-6.1%	Dom.
BF	FIT 45-75, 3	8465	0	0	949	294	34	23	0%	3.4
BF	FIT 45-80, 3	9073	0	0	998	302	35	24	0%	6.0
BF	FIT 45-85, 3	9792	0	0	1059	308	36	25	-1.3%	10.2*
BF	FIT 55-75, 2	7711	0	0	896	251	33	22	-9.9%	Dom.
BF	FIT 55-80, 2	8599	0	0	967	260	35	23	-12.4%	Dom.
BF	FIT 55-85, 2	9576	0	0	1041	265	35	25	-14.1%	Dom.
BF	FIT 50-75, 2	9448	0	0	1038	294	38	24	-4.6%	Dom.
BF	FIT 50-80, 2	10772	0	0	1140	307	40	26	-5.5%	Dom.
BF	FIT 50-85, 2	11420	0	0	1189	311	40	27	-6.7%	Dom.
BF	FIT 45-75, 2	11747	0	0	1207	336	42	26	0%	6.1
BF	FIT 45-80, 2	12627	0	0	1276	345	43	27	0%	7.9
BF	FIT 45-85, 2	13597	0	0	1348	350	44	29	-0.3%	14.2*
BF	FIT 55-75, 1	12784	0	0	1275	291	43	26	-15.5%	Dom.
BF	FIT 55-80, 1	14585	0	0	1393	300	46	27	-15.4%	Dom.
BF	FIT 55-85, 1	15893	0	0	1474	303	46	28	-16.2%	Dom.
BF	FIT 50-75, 1	16149	0	0	1513	343	49	28	-6.1%	Dom.
BF	FIT 50-80, 1	17941	0	0	1629	352	51	30	-6.3%	Dom.
BF	FIT 50-85, 1	19244	0	0	1710	355	52	30	-7.2%	Dom.
BF	FIT 45-75, 1	19641	0	0	1735	384	53	30	0%	11.6
BF	FIT 45-80, 1	21428	0	0	1850	393	55	31	0%	13.4
BF	FIT 45-85, 1	22729	0	0	1930	396	56	32	0%	26.3
BF	FIT-DNA 55-75, 5	3614	0	0	1012	235	33	21	-22.9%	Dom.
BF	FIT-DNA 55-80, 5	4034	0	0	1092	242	34	22	-23.9%	Dom.
BF	FIT-DNA 55-85, 5	4325	0	0	1146	244	35	23	-25.2%	Dom.
BF	FIT-DNA 50-75, 5	4445	0	0	1185	277	38	23	-16.6%	Dom.
BF	FIT-DNA 50-80, 5	4863	0	0	1264	284	39	24	-17.2%	Dom.
BF	FIT-DNA 50-85, 5	5153	0	0	1317	286	39	25	-17.8%	Dom.
BF	FIT-DNA 45-75, 5	5301	0	0	1347	312	41	25	-11.1%	Dom.
BF	FIT-DNA 45-80, 5	5717	0	0	1424	319	42	26	-10.9%	Dom.
BF	FIT-DNA 45-85, 5	6006	0	0	1478	321	42	26	-11.4%	Dom.
BF	FIT-DNA 55-75, 3	4739	0	0	1229	268	39	24	-21.0%	Dom.
BF	FIT-DNA 55-80, 3	5535	0	0	1370	279	42	25	-20.8%	Dom.
BF	FIT-DNA 55-85, 3	5968	0	0	1444	282	43	26	-21.4%	Dom.
BF	FIT-DNA 50-75, 3	6098	0	0	1492	320	45	26	-11.9%	Dom.
BF	FIT-DNA 50-80, 3	6693	0	0	1596	328	47	28	-11.8%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk										
BF	FIT-DNA 50-85, 3	7158	0	0	1672	332	48	28	-12.5%	Dom.
BF	FIT-DNA 45-75, 3	7288	0	0	1700	359	49	28	-5.9%	Dom.
BF	FIT-DNA 45-80, 3	7923	0	0	1807	367	51	29	-5.7%	Dom.
BF	FIT-DNA 45-85, 3	8446	0	0	1896	371	52	30	-6.0%	Dom.
BF	FIT-DNA 55-75, 1	9131	0	0	1976	312	52	28	-21.4%	Dom.
BF	FIT-DNA 55-80, 1	10277	0	0	2142	318	54	29	-20.4%	Dom.
BF	FIT-DNA 55-85, 1	11120	0	0	2260	320	55	29	-20.3%	Dom.
BF	FIT-DNA 50-75, 1	11400	0	0	2348	364	57	30	-9.6%	Dom.
BF	FIT-DNA 50-80, 1	12569	0	0	2517	370	59	31	-8.7%	Dom.
BF	FIT-DNA 50-85, 1	13404	0	0	2634	372	60	32	-8.7%	Dom.
BF	FIT-DNA 45-75, 1	13792	0	0	2709	406	61	32	-0.8%	79.9*
BF	FIT-DNA 45-80, 1	14948	0	0	2876	412	63	33	0.0%	60.9*
BF	FIT-DNA 45-85, 1	15782	0	0	2993	414	64	33	0%	60.6
BF	HSgFOBT 55-75, 3	5041	0	0	924	213	28	19	-25.7%	Dom.
BF	HSgFOBT 55-80, 3	5939	0	0	1041	227	30	21	-26.5%	Dom.
BF	HSgFOBT 55-85, 3	6455	0	0	1106	231	30	22	-27.7%	Dom.
BF	HSgFOBT 50-75, 3	6512	0	0	1135	261	33	21	-19.7%	Dom.
BF	HSgFOBT 50-80, 3	7213	0	0	1226	271	35	23	-20.0%	Dom.
BF	HSgFOBT 50-85, 3	7692	0	0	1284	274	35	24	-20.6%	Dom.
BF	HSgFOBT 45-75, 3	7822	0	0	1311	297	37	23	-14.5%	Dom.
BF	HSgFOBT 45-80, 3	8471	0	0	1390	306	38	24	-13.8%	Dom.
BF	HSgFOBT 45-85, 3	9088	0	0	1466	311	39	26	-14.0%	Dom.
BF	HSgFOBT 55-75, 2	6972	0	0	1204	252	35	22	-24.9%	Dom.
BF	HSgFOBT 55-80, 2	7743	0	0	1298	261	37	24	-24.8%	Dom.
BF	HSgFOBT 55-85, 2	8585	0	0	1396	265	38	25	-25.3%	Dom.
BF	HSgFOBT 50-75, 2	8493	0	0	1415	297	40	24	-16.7%	Dom.
BF	HSgFOBT 50-80, 2	9639	0	0	1551	309	42	26	-16.2%	Dom.
BF	HSgFOBT 50-85, 2	10198	0	0	1616	312	43	27	-16.6%	Dom.
BF	HSgFOBT 45-75, 2	10500	0	0	1666	340	44	27	-10.2%	Dom.
BF	HSgFOBT 45-80, 2	11261	0	0	1757	348	46	28	-10.0%	Dom.
BF	HSgFOBT 45-85, 2	12096	0	0	1853	352	47	29	-10.4%	Dom.
BF	HSgFOBT 55-75, 1	10562	0	0	1675	292	45	26	-22.9%	Dom.
BF	HSgFOBT 55-80, 1	11954	0	0	1826	300	47	27	-23.3%	Dom.
BF	HSgFOBT 55-85, 1	12967	0	0	1933	303	48	28	-23.6%	Dom.
BF	HSgFOBT 50-75, 1	13198	0	0	2005	344	51	29	-13.4%	Dom.
BF	HSgFOBT 50-80, 1	14592	0	0	2156	352	53	30	-12.0%	Dom.
BF	HSgFOBT 50-85, 1	15600	0	0	2261	354	54	30	-11.7%	Dom.
BF	HSgFOBT 45-75, 1	15942	0	0	2322	386	55	30	-4.2%	Dom.
BF	HSgFOBT 45-80, 1	17331	0	0	2471	393	57	32	-2.9%	Dom.
BF	HSgFOBT 45-85, 1	18336	0	0	2576	396	58	32	-2.7%	Dom.
BF	SIG 55-75, 10	0	2256	0	1336	272	48	25	0%	4.6
BF	SIG 55-80, 10	0	2256	0	1336	272	48	25	0%	4.6
BF	SIG 55-85, 10	0	2554	0	1434	274	49	26	-12.4%	Dom.
BF	SIG 50-75, 10	0	2460	0	1415	310	51	26	0%	2.1
BF	SIG 50-80, 10	0	2891	0	1564	317	53	27	-5.4%	Dom.
BF	SIG 50-85, 10	0	2891	0	1564	317	53	27	-5.4%	Dom.
BF	SIG 45-75, 10	0	3174	0	1657	351	56	29	0%	5.9

table continues

SimCRC - Scenario 2: Increased CRC risk										
BF	SIG 45-80, 10	0	3174	0	1657	351	56	29	0%	5.9
BF	SIG 45-85, 10	0	3471	0	1754	353	57	29	-1.3%	45.8*
BF	SIG 55-75, 5	0	3288	0	1611	292	52	27	-15.0%	Dom.
BF	SIG 55-80, 5	0	3640	0	1706	295	54	27	-16.8%	Dom.
BF	SIG 55-85, 5	0	3881	0	1768	296	54	28	-17.6%	Dom.
BF	SIG 50-75, 5	0	4059	0	1851	340	58	29	-6.6%	Dom.
BF	SIG 50-80, 5	0	4410	0	1945	343	59	30	-7.4%	Dom.
BF	SIG 50-85, 5	0	4650	0	2006	344	59	30	-8.2%	Dom.
BF	SIG 45-75, 5	0	4862	0	2068	379	61	31	0%	14.6
BF	SIG 45-80, 5	0	5212	0	2162	382	62	31	0%	32.1
BF	SIG 45-85, 5	0	5452	0	2223	383	63	31	0%	78.9
BF	CTC 55-75, 10	0	0	2293	1153	275	47	25	0%	3.9
BF	CTC 55-80, 10	0	0	2293	1153	275	47	25	0%	3.9
BF	CTC 55-85, 10	0	0	2606	1251	278	48	26	-12.9%	Dom.
BF	CTC 50-75, 10	0	0	2495	1209	311	49	26	0%	1.6
BF	CTC 50-80, 10	0	0	2947	1353	320	52	28	-5.6%	Dom.
BF	CTC 50-85, 10	0	0	2947	1353	320	52	28	-5.6%	Dom.
BF	CTC 45-75, 10	0	0	3228	1425	354	54	28	0%	5.0
BF	CTC 45-80, 10	0	0	3228	1425	354	54	28	0%	5.0
BF	CTC 45-85, 10	0	0	3540	1522	357	55	29	-1.8%	32.7*
BF	CTC 55-75, 5	0	0	3399	1428	303	53	27	-14.3%	Dom.
BF	CTC 55-80, 5	0	0	3773	1521	308	55	28	-15.4%	Dom.
BF	CTC 55-85, 5	0	0	4030	1582	309	55	29	-16.5%	Dom.
BF	CTC 50-75, 5	0	0	4196	1639	354	58	30	-5.7%	Dom.
BF	CTC 50-80, 5	0	0	4570	1731	358	60	31	-6.9%	Dom.
BF	CTC 50-85, 5	0	0	4826	1793	359	60	31	-8.1%	Dom.
BF	CTC 45-75, 5	0	0	5024	1829	394	62	31	0%	10.0
BF	CTC 45-80, 5	0	0	5398	1921	398	63	32	0%	22.7
BF	CTC 45-85, 5	0	0	5654	1982	399	64	33	0%	54.7

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

[a] Both models evaluated two scenarios for CRC risk: one in which age-specific risks were assumed to have remained stable since the early screening period in the U.S. (1975-1979 for SimCRC; 1990-1994 for MISCAN), and one in which risks were assumed to have increased proportional to observed trends among adults under age 40 years. Strategies for each model and scenario are ordered successively by screening modality, interval (↓), end age (↑), and start age (↓).

[b] Total number of colonoscopies performed per 1000 40-year-olds, including diagnostic colonoscopies and potential surveillance colonoscopies after adenoma removal. The number of screening-related complications ranged from 1.6 to 18.9 per 1000 40-year-olds across models, scenarios, and strategies.

[c] Including deaths from complications of screening.

[d] The difference in LYG compared to (combinations of) adjacent strategies on the efficient frontier. Near-efficient strategies have a loss in LYG of less than 2% before rounding. For the least intensive screening strategy evaluated within each class of screening modality, the difference was zero by definition.
[e] Efficiency ratio = incremental number of colonoscopies/LYG with respect to the next less effective strategy on the efficient frontier, a burden-to-benefit ratio. Only calculated for efficient and near-efficient strategies (marked with an asterisk*), i.e. strategies within 2% from the efficient frontier among all evaluated strategies within a class of screening modalities (colonoscopy, stool-based, sigmoidoscopy, and CTC).

Supplementary Table A3.5: Lifetime number of colonoscopies and LYG for all evaluated screening strategies under two scenarios for CRC risk, by model, in white males [a]

		Outcomes per 1000 40-year-olds								
Subgroup	Modality, and age to begin- end screening, interval, y	Stool tests	SIGs	CTCs	COLs [b]	LYG	CRC cases averted	CRC deaths averted [c]	Relative distance from efficient frontier [d]	ER [e]
MISCAN - Scenario 1: Stable CRC risk										
WM	No screening	0	0	0	71	0	0	0	-	-
WM	COL 55-75, 15	0	0	0	3001	197	39	20	0%	14.8
WM	COL 55-80, 15	0	0	0	3001	197	39	20	0%	14.8
WM	COL 55-85, 15	0	0	0	3240	198	39	20	-3.8%	Dom.
WM	COL 50-75, 15	0	0	0	3264	207	39	20	0%	26.4
WM	COL 50-80, 15	0	0	0	3657	212	41	21	-2.3%	Dom.
WM	COL 50-85, 15	0	0	0	3657	212	41	21	-2.3%	Dom.
WM	COL 45-75, 15	0	0	0	3979	218	41	21	-3.4%	Dom.
WM	COL 45-80, 15	0	0	0	3979	218	41	21	-3.4%	Dom.
WM	COL 45-85, 15	0	0	0	3979	218	41	21	-3.4%	Dom.
WM	COL 55-75, 10	0	0	0	3598	209	42	21	-3.3%	Dom.
WM	COL 55-80, 10	0	0	0	3598	209	42	21	-3.3%	Dom.
WM	COL 55-85, 10	0	0	0	3813	210	42	21	-5.4%	Dom.
WM	COL 50-75, 10	0	0	0	4007	227	43	21	0%	38.6
WM	COL 50-80, 10	0	0	0	4357	230	44	22	-0.8%	116.6*
WM	COL 50-85, 10	0	0	0	4357	230	44	22	-0.8%	116.6*
WM	COL 45-75, 10	0	0	0	4797	238	45	22	0%	72.0
WM	COL 45-80, 10	0	0	0	4797	238	45	22	0%	72.0
WM	COL 45-85, 10	0	0	0	5012	238	45	22	-0.6%	351.8*
WM	COL 55-75, 5	0	0	0	4786	221	45	22	-7.1%	Dom.
WM	COL 55-80, 5	0	0	0	5098	222	45	22	-7.6%	Dom.
WM	COL 55-85, 5	0	0	0	5285	222	45	22	-8.3%	Dom.
WM	COL 50-75, 5	0	0	0	5807	243	47	23	-1.5%	181.2*
WM	COL 50-80, 5	0	0	0	6119	244	48	23	-2.1%	Dom.
WM	COL 50-85, 5	0	0	0	6305	245	48	23	-2.8%	Dom.
WM	COL 45-75, 5	0	0	0	6844	257	48	23	0%	108.1
WM	COL 45-80, 5	0	0	0	7157	258	49	24	0%	225.9
WM	COL 45-85, 5	0	0	0	7343	258	49	24	0%	1902.6
WM	FIT 55-75, 3	5146	0	0	796	142	16	14	0%	5.1
WM	FIT 55-80, 3	6037	0	0	876	153	17	15	0%	7.6
WM	FIT 55-85, 3	6615	0	0	922	156	17	16	-1.5%	13.3*
WM	FIT 50-75, 3	6689	0	0	947	162	18	15	0%	7.9
WM	FIT 50-80, 3	7524	0	0	1019	171	19	17	0%	8.0
WM	FIT 50-85, 3	7824	0	0	1042	172	19	17	-0.2%	12.9*
WM	FIT 45-75, 3	8274	0	0	1074	173	20	16	-1.4%	21.1*
WM	FIT 45-80, 3	8702	0	0	1109	178	20	16	-0.5%	12.5*
WM	FIT 45-85, 3	9327	0	0	1158	182	19	17	-0.6%	12.2*

table continues

MISCAN - Scenario 1: Stable CRC risk									
WM FIT 55-75, 2	7481	0	0	1030	167	21	16	-3.0%	Dom.
WM FIT 55-80, 2	8279	0	0	1091	173	22	17	-2.4%	Dom.
WM FIT 55-85, 2	9107	0	0	1148	176	22	18	-3.2%	Dom.
WM FIT 50-75, 2	9204	0	0	1188	185	23	17	-0.7%	12.0*
WM FIT 50-80, 2	10388	0	0	1275	194	24	19	0%	11.0
WM FIT 50-85, 2	10936	0	0	1312	196	24	19	-0.2%	16.5*
WM FIT 45-75, 2	11465	0	0	1354	197	25	18	-1.0%	22.1*
WM FIT 45-80, 2	12251	0	0	1412	203	25	19	0%	14.4
WM FIT 45-85, 2	13070	0	0	1466	207	25	20	0%	16.0
WM FIT 55-75, 1	12335	0	0	1437	192	29	19	-6.2%	Dom.
WM FIT 55-80, 1	13936	0	0	1534	199	31	20	-5.3%	Dom.
WM FIT 55-85, 1	15040	0	0	1595	201	31	20	-5.5%	Dom.
WM FIT 50-75, 1	15619	0	0	1693	214	32	20	-1.3%	29.7*
WM FIT 50-80, 1	17205	0	0	1787	221	33	21	-0.5%	23.0*
WM FIT 50-85, 1	18301	0	0	1847	223	33	21	-0.7%	23.6*
WM FIT 45-75, 1	19081	0	0	1915	226	33	20	-0.8%	23.5*
WM FIT 45-80, 1	20659	0	0	2008	232	34	21	0%	21.4
WM FIT 45-85, 1	21751	0	0	2067	234	34	22	0%	28.6
WM FIT-DNA 55-75, 5	3495	0	0	1152	158	22	16	-13.3%	Dom.
WM FIT-DNA 55-80, 5	3861	0	0	1220	164	22	17	-13.4%	Dom.
WM FIT-DNA 55-85, 5	4096	0	0	1259	165	22	17	-14.3%	Dom.
WM FIT-DNA 50-75, 5	4308	0	0	1340	176	24	17	-11.3%	Dom.
WM FIT-DNA 50-80, 5	4670	0	0	1405	181	24	18	-10.8%	Dom.
WM FIT-DNA 50-85, 5	4904	0	0	1444	182	24	18	-11.3%	Dom.
WM FIT-DNA 45-75, 5	5156	0	0	1499	185	25	17	-11.3%	Dom.
WM FIT-DNA 45-80, 5	5517	0	0	1563	190	25	18	-10.2%	Dom.
WM FIT-DNA 45-85, 5	5750	0	0	1602	191	25	18	-10.3%	Dom.
WM FIT-DNA 55-75, 3	4427	0	0	1380	176	26	17	-12.4%	Dom.
WM FIT-DNA 55-80, 3	5129	0	0	1501	185	28	19	-11.4%	Dom.
WM FIT-DNA 55-85, 3	5577	0	0	1570	187	28	19	-11.6%	Dom.
WM FIT-DNA 50-75, 3	5701	0	0	1650	198	29	18	-8.0%	Dom.
WM FIT-DNA 50-80, 3	6352	0	0	1759	205	30	20	-6.9%	Dom.
WM FIT-DNA 50-85, 3	6585	0	0	1794	206	30	20	-7.0%	Dom.
WM FIT-DNA 45-75, 3	7017	0	0	1885	210	31	19	-7.3%	Dom.
WM FIT-DNA 45-80, 3	7352	0	0	1939	213	31	20	-6.8%	Dom.
WM FIT-DNA 45-85, 3	7837	0	0	2014	216	31	20	-6.8%	Dom.
WM FIT-DNA 55-75, 1	8705	0	0	2190	206	37	20	-12.3%	Dom.
WM FIT-DNA 55-80, 1	9690	0	0	2324	210	38	21	-11.0%	Dom.
WM FIT-DNA 55-85, 1	10380	0	0	2412	211	39	21	-10.8%	Dom.
WM FIT-DNA 50-75, 1	10885	0	0	2589	227	40	21	-4.8%	Dom.
WM FIT-DNA 50-80, 1	11884	0	0	2723	231	41	22	-3.6%	Dom.
WM FIT-DNA 50-85, 1	12566	0	0	2809	232	41	22	-3.4%	Dom.
WM FIT-DNA 45-75, 1	13234	0	0	2953	239	41	21	-1.3%	194.0*
WM FIT-DNA 45-80, 1	14221	0	0	3085	243	42	22	-0.2%	120.7*
WM FIT-DNA 45-85, 1	14903	0	0	3171	244	42	22	0%	114.8
WM HSgFOBT 55-75, 3	4813	0	0	1022	141	17	14	-17.7%	Dom.
WM HSgFOBT 55-80, 3	5616	0	0	1128	151	18	15	-16.5%	Dom.

table continues

MISCAN - Scenario 1: Stable CRC risk										
WM	HSgFOBT 55-85, 3	6133	0	0	1188	154	18	16	-17.3%	Dom.
WM	HSgFOBT 50-75, 3	6201	0	0	1248	161	20	15	-15.8%	Dom.
WM	HSgFOBT 50-80, 3	6947	0	0	1342	169	20	17	-14.6%	Dom.
WM	HSgFOBT 50-85, 3	7215	0	0	1373	171	20	17	-14.7%	Dom.
WM	HSgFOBT 45-75, 3	7623	0	0	1445	173	21	16	-15.8%	Dom.
WM	HSgFOBT 45-80, 3	8005	0	0	1492	177	22	17	-14.8%	Dom.
WM	HSgFOBT 45-85, 3	8561	0	0	1557	181	21	17	-14.2%	Dom.
WM	HSgFOBT 55-75, 2	6788	0	0	1339	166	23	16	-16.3%	Dom.
WM	HSgFOBT 55-80, 2	7473	0	0	1420	172	23	17	-15.8%	Dom.
WM	HSgFOBT 55-85, 2	8179	0	0	1497	175	23	18	-16.0%	Dom.
WM	HSgFOBT 50-75, 2	8279	0	0	1580	185	25	17	-12.6%	Dom.
WM	HSgFOBT 50-80, 2	9290	0	0	1697	193	26	19	-11.1%	Dom.
WM	HSgFOBT 50-85, 2	9755	0	0	1747	195	26	19	-11.1%	Dom.
WM	HSgFOBT 45-75, 2	10234	0	0	1837	198	27	18	-11.7%	Dom.
WM	HSgFOBT 45-80, 2	10904	0	0	1914	203	27	19	-10.8%	Dom.
WM	HSgFOBT 45-85, 2	11597	0	0	1987	206	27	20	-10.9%	Dom.
WM	HSgFOBT 55-75, 1	10212	0	0	1858	192	31	19	-14.6%	Dom.
WM	HSgFOBT 55-80, 1	11419	0	0	1984	197	32	20	-14.5%	Dom.
WM	HSgFOBT 55-85, 1	12250	0	0	2064	199	32	20	-14.9%	Dom.
WM	HSgFOBT 50-75, 1	12737	0	0	2221	214	34	20	-9.0%	Dom.
WM	HSgFOBT 50-80, 1	13937	0	0	2343	219	35	21	-7.3%	Dom.
WM	HSgFOBT 50-85, 1	14760	0	0	2422	221	35	21	-6.9%	Dom.
WM	HSgFOBT 45-75, 1	15423	0	0	2545	225	35	20	-5.4%	Dom.
WM	HSgFOBT 45-80, 1	16615	0	0	2666	230	36	21	-3.7%	Dom.
WM	HSgFOBT 45-85, 1	17436	0	0	2744	232	36	22	-3.3%	Dom.
WM	SIG 55-75, 10	0	2103	0	1695	171	34	17	0%	9.5
WM	SIG 55-80, 10	0	2103	0	1695	171	34	17	0%	9.5
WM	SIG 55-85, 10	0	2331	0	1757	172	34	18	-3.0%	Dom.
WM	SIG 50-75, 10	0	2328	0	1822	183	35	18	0%	10.0
WM	SIG 50-80, 10	0	2681	0	1944	188	36	19	-0.9%	29.2*
WM	SIG 50-85, 10	0	2681	0	1944	188	36	19	-0.9%	29.2*
WM	SIG 45-75, 10	0	2997	0	2034	191	36	18	-1.4%	27.9*
WM	SIG 45-80, 10	0	2997	0	2034	191	36	18	-1.4%	27.9*
WM	SIG 45-85, 10	0	3225	0	2096	192	36	19	-2.4%	Dom.
WM	SIG 55-75, 5	0	3012	0	1957	185	37	19	-2.4%	Dom.
WM	SIG 55-80, 5	0	3303	0	2037	187	38	19	-3.3%	Dom.
WM	SIG 55-85, 5	0	3486	0	2072	188	38	19	-4.0%	Dom.
WM	SIG 50-75, 5	0	3737	0	2231	203	39	20	0%	20.6
WM	SIG 50-80, 5	0	4026	0	2310	205	40	20	-0.6%	39.6*
WM	SIG 50-85, 5	0	4209	0	2345	206	40	20	-1.1%	50.2*
WM	SIG 45-75, 5	0	4522	0	2452	212	40	20	0%	24.8
WM	SIG 45-80, 5	0	4810	0	2530	214	41	20	0%	39.7
WM	SIG 45-85, 5	0	4993	0	2565	214	41	20	0%	131.0
WM	CTC 55-75, 10	0	0	2234	1159	157	26	16	0%	6.9
WM	CTC 55-80, 10	0	0	2234	1159	157	26	16	0%	6.9
WM	CTC 55-85, 10	0	0	2498	1223	159	26	17	-3.8%	Dom.
WM	CTC 50-75, 10	0	0	2456	1223	166	26	15	0%	7.2

table continues

MISCAN - Scenario 1: Stable CRC risk									
WM CTC 50-80, 10	0	0	2862	1329	175	28	17	-0.6%	12.0*
WM CTC 50-85, 10	0	0	2862	1329	175	28	17	-0.6%	12.0*
WM CTC 45-75, 10	0	0	3171	1393	176	28	17	-3.4%	Dom.
WM CTC 45-80, 10	0	0	3171	1393	176	28	17	-3.4%	Dom.
WM CTC 45-85, 10	0	0	3433	1456	178	28	17	-5.1%	Dom.
WM CTC 55-75, 5	0	0	3320	1460	188	33	18	0%	10.7
WM CTC 55-80, 5	0	0	3659	1531	192	34	19	-1.1%	16.7*
WM CTC 55-85, 5	0	0	3877	1574	193	34	20	-2.5%	Dom.
WM CTC 50-75, 5	0	0	4110	1667	207	35	19	0%	11.0
WM CTC 50-80, 5	0	0	4447	1737	211	36	20	0%	16.6
WM CTC 50-85, 5	0	0	4664	1779	212	36	20	-0.5%	41.7*
WM CTC 45-75, 5	0	0	4940	1842	216	36	20	-0.3%	21.6*
WM CTC 45-80, 5	0	0	5276	1911	220	37	21	0%	19.3
WM CTC 45-85, 5	0	0	5492	1953	221	37	21	0%	41.2
MISCAN - Scenario 2: Increased CRC risk									
WM No screening	0	0	0	149	0	0	0	-	-
WM COL 55-75, 15	0	0	0	4093	438	85	44	0%	9.0
WM COL 55-80, 15	0	0	0	4093	438	85	44	0%	9.0
WM COL 55-85, 15	0	0	0	4194	439	85	44	-1.0%	70.6*
WM COL 50-75, 15	0	0	0	4540	463	87	44	-0.2%	17.3*
WM COL 50-80, 15	0	0	0	4746	471	89	46	-1.3%	19.8*
WM COL 50-85, 15	0	0	0	4746	471	89	46	-1.3%	19.8*
WM COL 45-75, 15	0	0	0	5173	483	90	46	-3.4%	Dom.
WM COL 45-80, 15	0	0	0	5173	483	90	46	-3.4%	Dom.
WM COL 45-85, 15	0	0	0	5173	483	90	46	-3.4%	Dom.
WM COL 55-75, 10	0	0	0	4478	458	90	46	-0.6%	18.9*
WM COL 55-80, 10	0	0	0	4478	458	90	46	-0.6%	18.9*
WM COL 55-85, 10	0	0	0	4553	459	90	46	-1.4%	Dom.
WM COL 50-75, 10	0	0	0	5102	498	93	47	0%	16.7
WM COL 50-80, 10	0	0	0	5252	502	95	48	-0.1%	38.9*
WM COL 50-85, 10	0	0	0	5252	502	95	48	-0.1%	38.9*
WM COL 45-75, 10	0	0	0	5846	520	96	48	0%	33.5
WM COL 45-80, 10	0	0	0	5846	520	96	48	0%	33.5
WM COL 45-85, 10	0	0	0	5920	521	96	49	-0.2%	108.8*
WM COL 55-75, 5	0	0	0	5125	477	94	47	-4.4%	Dom.
WM COL 55-80, 5	0	0	0	5231	478	95	48	-4.7%	Dom.
WM COL 55-85, 5	0	0	0	5276	478	95	48	-4.9%	Dom.
WM COL 50-75, 5	0	0	0	6146	526	100	50	-0.3%	48.5*
WM COL 50-80, 5	0	0	0	6251	528	100	50	-0.5%	52.3*
WM COL 50-85, 5	0	0	0	6297	528	100	50	-0.7%	57.5*
WM COL 45-75, 5	0	0	0	7182	554	102	51	0%	39.5
WM COL 45-80, 5	0	0	0	7288	556	103	51	0%	67.2
WM COL 45-85, 5	0	0	0	7334	556	103	51	0%	555.4
WM FIT 55-75, 3	4750	0	0	1416	311	37	30	0%	4.1
WM FIT 55-80, 3	5418	0	0	1531	333	39	34	0%	5.2
WM FIT 55-85, 3	5804	0	0	1589	339	38	36	-0.9%	8.8*
WM FIT 50-75, 3	6165	0	0	1661	353	42	33	-0.5%	6.4*

table continues

MISCAN - Scenario 2: Increased CRC risk										
WM	FIT 50-80, 3	6771	0	0	1760	372	43	36	0%	5.9
WM	FIT 50-85, 3	6970	0	0	1790	375	43	37	-0.1%	8.5*
WM	FIT 45-75, 3	7643	0	0	1853	378	45	35	-1.6%	15.0*
WM	FIT 45-80, 3	7953	0	0	1902	387	45	36	-0.7%	9.0*
WM	FIT 45-85, 3	8371	0	0	1964	395	45	38	-0.7%	8.6*
WM	FIT 55-75, 2	6661	0	0	1774	364	48	36	-2.5%	Dom.
WM	FIT 55-80, 2	7209	0	0	1852	377	50	38	-1.8%	17.8*
WM	FIT 55-85, 2	7721	0	0	1916	383	50	40	-2.2%	Dom.
WM	FIT 50-75, 2	8277	0	0	2027	402	53	37	-1.0%	8.6*
WM	FIT 50-80, 2	9079	0	0	2137	421	55	41	0%	7.6
WM	FIT 50-85, 2	9412	0	0	2177	425	55	42	-0.1%	9.8*
WM	FIT 45-75, 2	10343	0	0	2270	431	56	39	-0.9%	12.8*
WM	FIT 45-80, 2	10870	0	0	2341	443	57	41	0%	9.3
WM	FIT 45-85, 2	11365	0	0	2401	449	57	43	0%	9.5
WM	FIT 55-75, 1	10514	0	0	2348	420	65	41	-5.2%	Dom.
WM	FIT 55-80, 1	11486	0	0	2448	433	68	43	-4.5%	Dom.
WM	FIT 55-85, 1	12073	0	0	2501	436	68	44	-4.5%	Dom.
WM	FIT 50-75, 1	13419	0	0	2724	468	71	43	-1.4%	17.1*
WM	FIT 50-80, 1	14362	0	0	2818	480	73	46	-0.5%	13.7*
WM	FIT 50-85, 1	14937	0	0	2869	483	74	46	-0.6%	13.8*
WM	FIT 45-75, 1	16592	0	0	3033	495	74	45	-0.8%	13.8*
WM	FIT 45-80, 1	17522	0	0	3125	506	76	47	0%	12.7
WM	FIT 45-85, 1	18090	0	0	3174	510	77	47	0%	13.8
WM	FIT-DNA 55-75, 5	3141	0	0	1904	347	49	35	-11.0%	Dom.
WM	FIT-DNA 55-80, 5	3385	0	0	1980	357	50	37	-10.7%	Dom.
WM	FIT-DNA 55-85, 5	3524	0	0	2019	360	49	38	-11.2%	Dom.
WM	FIT-DNA 50-75, 5	3880	0	0	2187	384	53	37	-10.0%	Dom.
WM	FIT-DNA 50-80, 5	4117	0	0	2260	393	54	39	-9.4%	Dom.
WM	FIT-DNA 50-85, 5	4254	0	0	2297	396	53	39	-9.7%	Dom.
WM	FIT-DNA 45-75, 5	4674	0	0	2413	405	56	38	-10.1%	Dom.
WM	FIT-DNA 45-80, 5	4908	0	0	2484	414	56	40	-9.1%	Dom.
WM	FIT-DNA 45-85, 5	5044	0	0	2521	416	56	40	-9.2%	Dom.
WM	FIT-DNA 55-75, 3	3948	0	0	2246	387	59	38	-10.6%	Dom.
WM	FIT-DNA 55-80, 3	4400	0	0	2375	403	62	41	-9.7%	Dom.
WM	FIT-DNA 55-85, 3	4648	0	0	2435	407	63	42	-9.9%	Dom.
WM	FIT-DNA 50-75, 3	5056	0	0	2635	434	65	41	-7.2%	Dom.
WM	FIT-DNA 50-80, 3	5459	0	0	2744	447	68	43	-6.1%	Dom.
WM	FIT-DNA 50-85, 3	5587	0	0	2775	449	68	44	-6.1%	Dom.
WM	FIT-DNA 45-75, 3	6240	0	0	2951	460	68	42	-6.6%	Dom.
WM	FIT-DNA 45-80, 3	6446	0	0	3005	466	70	43	-6.1%	Dom.
WM	FIT-DNA 45-85, 3	6716	0	0	3070	472	70	45	-6.0%	Dom.
WM	FIT-DNA 55-75, 1	7075	0	0	3227	451	81	44	-11.6%	Dom.
WM	FIT-DNA 55-80, 1	7565	0	0	3321	458	83	46	-10.6%	Dom.
WM	FIT-DNA 55-85, 1	7858	0	0	3371	459	84	46	-10.4%	Dom.
WM	FIT-DNA 50-75, 1	8916	0	0	3756	497	87	47	-4.3%	Dom.
WM	FIT-DNA 50-80, 1	9402	0	0	3848	503	88	48	-3.4%	Dom.
WM	FIT-DNA 50-85, 1	9687	0	0	3896	505	89	48	-3.3%	Dom.

table continues

MISCAN - Scenario 2: Increased CRC risk										
WM	FIT-DNA 45-75, 1	11006	0	0	4210	522	89	47	-1.0%	85.7*
WM	FIT-DNA 45-80, 1	11484	0	0	4299	528	91	49	-0.2%	61.9*
WM	FIT-DNA 45-85, 1	11768	0	0	4347	529	91	49	0%	58.9
WM	HSgFOBT 55-75, 3	4485	0	0	1647	308	39	30	-12.6%	Dom.
WM	HSgFOBT 55-80, 3	5082	0	0	1773	328	41	34	-12.0%	Dom.
WM	HSgFOBT 55-85, 3	5419	0	0	1835	334	40	35	-12.3%	Dom.
WM	HSgFOBT 50-75, 3	5740	0	0	1983	353	45	33	-12.0%	Dom.
WM	HSgFOBT 50-80, 3	6271	0	0	2090	369	46	36	-10.9%	Dom.
WM	HSgFOBT 50-85, 3	6443	0	0	2121	372	46	37	-11.1%	Dom.
WM	HSgFOBT 45-75, 3	7045	0	0	2260	379	48	35	-12.8%	Dom.
WM	HSgFOBT 45-80, 3	7316	0	0	2312	387	49	37	-12.0%	Dom.
WM	HSgFOBT 45-85, 3	7676	0	0	2377	394	48	38	-11.7%	Dom.
WM	HSgFOBT 55-75, 2	6098	0	0	2085	363	51	36	-12.3%	Dom.
WM	HSgFOBT 55-80, 2	6555	0	0	2170	374	52	38	-11.8%	Dom.
WM	HSgFOBT 55-85, 2	6971	0	0	2238	380	52	40	-12.0%	Dom.
WM	HSgFOBT 50-75, 2	7465	0	0	2444	405	57	38	-10.6%	Dom.
WM	HSgFOBT 50-80, 2	8122	0	0	2562	420	58	41	-9.0%	Dom.
WM	HSgFOBT 50-85, 2	8389	0	0	2604	424	58	42	-8.9%	Dom.
WM	HSgFOBT 45-75, 2	9211	0	0	2792	434	60	40	-9.6%	Dom.
WM	HSgFOBT 45-80, 2	9639	0	0	2868	444	62	42	-8.7%	Dom.
WM	HSgFOBT 45-85, 2	10033	0	0	2930	449	61	43	-8.5%	Dom.
WM	HSgFOBT 55-75, 1	8811	0	0	2770	421	68	42	-12.0%	Dom.
WM	HSgFOBT 55-80, 1	9493	0	0	2873	430	70	43	-11.5%	Dom.
WM	HSgFOBT 55-85, 1	9895	0	0	2927	433	71	44	-11.7%	Dom.
WM	HSgFOBT 50-75, 1	10968	0	0	3269	468	75	44	-8.4%	Dom.
WM	HSgFOBT 50-80, 1	11624	0	0	3365	477	77	46	-6.9%	Dom.
WM	HSgFOBT 50-85, 1	12014	0	0	3416	480	77	46	-6.6%	Dom.
WM	HSgFOBT 45-75, 1	13359	0	0	3692	495	78	45	-4.5%	Dom.
WM	HSgFOBT 45-80, 1	14003	0	0	3786	504	80	47	-3.1%	Dom.
WM	HSgFOBT 45-85, 1	14387	0	0	3836	506	80	47	-2.8%	Dom.
WM	SIG 55-75, 10	0	1676	0	3228	408	80	42	0%	7.6
WM	SIG 55-80, 10	0	1676	0	3228	408	80	42	0%	7.6
WM	SIG 55-85, 10	0	1767	0	3280	409	80	42	-1.1%	41.4*
WM	SIG 50-75, 10	0	1934	0	3513	439	82	42	0%	9.1
WM	SIG 50-80, 10	0	2095	0	3637	446	84	44	-0.7%	19.0*
WM	SIG 50-85, 10	0	2095	0	3637	446	84	44	-0.7%	19.0*
WM	SIG 45-75, 10	0	2451	0	3825	457	85	44	-1.4%	17.4*
WM	SIG 45-80, 10	0	2451	0	3825	457	85	44	-1.4%	17.4*
WM	SIG 45-85, 10	0	2541	0	3876	458	85	44	-1.9%	18.9*
WM	SIG 55-75, 5	0	2157	0	3504	432	85	44	-1.3%	11.2*
WM	SIG 55-80, 5	0	2270	0	3571	435	86	44	-1.9%	Dom.
WM	SIG 55-85, 5	0	2328	0	3590	436	86	44	-2.1%	Dom.
WM	SIG 50-75, 5	0	2718	0	3959	474	89	46	0%	12.8
WM	SIG 50-80, 5	0	2829	0	4024	477	90	46	-0.2%	22.6*
WM	SIG 50-85, 5	0	2887	0	4043	477	90	46	-0.4%	26.2*
WM	SIG 45-75, 5	0	3389	0	4302	494	91	46	0%	16.9
WM	SIG 45-80, 5	0	3500	0	4367	497	92	47	0%	23.0

table continues

MISCAN - Scenario 2: Increased CRC risk										
WM	SIG 45-85, 5	0	3558	0	4385	497	92	47	0%	66.2
WM	CTC 55-75, 10	0	0	1995	2033	345	58	35	0%	5.5
WM	CTC 55-80, 10	0	0	1995	2033	345	58	35	0%	5.5
WM	CTC 55-85, 10	0	0	2156	2105	350	58	36	-2.0%	Dom.
WM	CTC 50-75, 10	0	0	2255	2149	364	58	35	0%	6.2
WM	CTC 50-80, 10	0	0	2526	2282	381	61	38	-1.0%	7.7*
WM	CTC 50-85, 10	0	0	2526	2282	381	61	38	-1.0%	7.7*
WM	CTC 45-75, 10	0	0	2875	2385	386	62	37	-3.9%	Dom.
WM	CTC 45-80, 10	0	0	2875	2385	386	62	37	-3.9%	Dom.
WM	CTC 45-85, 10	0	0	3033	2455	390	62	38	-5.4%	Dom.
WM	CTC 55-75, 5	0	0	2836	2449	412	72	41	0%	6.3
WM	CTC 55-80, 5	0	0	3036	2522	420	74	43	-0.4%	9.5*
WM	CTC 55-85, 5	0	0	3151	2560	421	75	43	-1.1%	11.7*
WM	CTC 50-75, 5	0	0	3542	2757	452	76	43	0%	7.7
WM	CTC 50-80, 5	0	0	3740	2828	459	78	44	0%	9.5
WM	CTC 50-85, 5	0	0	3852	2864	461	79	45	-0.4%	22.3*
WM	CTC 45-75, 5	0	0	4315	2999	474	78	44	-0.2%	11.8*
WM	CTC 45-80, 5	0	0	4510	3069	481	80	45	0%	11.0
WM	CTC 45-85, 5	0	0	4622	3105	483	81	46	0%	21.9
SimCRC - Scenario 1: Stable CRC risk										
WM	No screening	0	0	0	79	0	0	0	-	-
WM	COL 55-75, 15	0	0	0	3060	250	57	25	0%	11.9
WM	COL 55-80, 15	0	0	0	3060	250	57	25	0%	11.9
WM	COL 55-85, 15	0	0	0	3299	252	57	25	-9.5%	Dom.
WM	COL 50-75, 15	0	0	0	3301	278	59	25	0%	8.7
WM	COL 50-80, 15	0	0	0	3719	283	61	27	-3.3%	Dom.
WM	COL 50-85, 15	0	0	0	3719	283	61	27	-3.3%	Dom.
WM	COL 45-75, 15	0	0	0	4098	307	64	27	0%	28.0
WM	COL 45-80, 15	0	0	0	4098	307	64	27	0%	28.0
WM	COL 45-85, 15	0	0	0	4098	307	64	27	0%	28.0
WM	COL 55-75, 10	0	0	0	3685	261	60	26	-10.5%	Dom.
WM	COL 55-80, 10	0	0	0	3685	261	60	26	-10.5%	Dom.
WM	COL 55-85, 10	0	0	0	3883	262	60	26	-12.4%	Dom.
WM	COL 50-75, 10	0	0	0	4094	294	64	27	-4.0%	Dom.
WM	COL 50-80, 10	0	0	0	4436	297	65	28	-5.2%	Dom.
WM	COL 50-85, 10	0	0	0	4436	297	65	28	-5.2%	Dom.
WM	COL 45-75, 10	0	0	0	4918	322	68	29	0%	51.8
WM	COL 45-80, 10	0	0	0	4918	322	68	29	0%	51.8
WM	COL 45-85, 10	0	0	0	5116	323	68	29	-0.2%	385.3*
WM	COL 55-75, 5	0	0	0	4884	269	63	27	-16.4%	Dom.
WM	COL 55-80, 5	0	0	0	5156	270	63	27	-16.7%	Dom.
WM	COL 55-85, 5	0	0	0	5316	270	63	27	-16.9%	Dom.
WM	COL 50-75, 5	0	0	0	5915	306	68	28	-6.7%	Dom.
WM	COL 50-80, 5	0	0	0	6187	306	68	28	-6.9%	Dom.
WM	COL 50-85, 5	0	0	0	6347	306	68	29	-7.1%	Dom.
WM	COL 45-75, 5	0	0	0	6963	333	71	29	0%	191.3
WM	COL 45-80, 5	0	0	0	7235	334	71	30	0%	423.8

table continues

SimCRC - Scenario 1: Stable CRC risk									
WM COL 45-85, 5	0	0	0	7396	334	71	30	0%	1396.2
WM FIT 55-75, 3	5158	0	0	891	195	31	18	0%	4.2
WM FIT 55-80, 3	6025	0	0	996	207	34	21	-4.1%	Dom.
WM FIT 55-85, 3	6522	0	0	1053	211	34	21	-7.5%	Dom.
WM FIT 50-75, 3	6708	0	0	1067	231	36	21	0%	4.9
WM FIT 50-80, 3	7441	0	0	1155	240	38	22	-2.6%	Dom.
WM FIT 50-85, 3	7799	0	0	1194	242	38	23	-4.3%	Dom.
WM FIT 45-75, 3	8194	0	0	1213	256	40	22	0%	5.7
WM FIT 45-80, 3	8716	0	0	1270	262	41	23	0%	9.1
WM FIT 45-85, 3	9293	0	0	1335	267	41	24	-0.5%	15.9*
WM FIT 55-75, 2	7358	0	0	1153	223	39	21	-9.4%	Dom.
WM FIT 55-80, 2	8113	0	0	1233	229	40	23	-11.4%	Dom.
WM FIT 55-85, 2	8874	0	0	1307	232	41	23	-12.5%	Dom.
WM FIT 50-75, 2	9061	0	0	1325	254	43	23	-4.8%	Dom.
WM FIT 50-80, 2	10180	0	0	1440	263	45	24	-4.7%	Dom.
WM FIT 50-85, 2	10684	0	0	1489	265	45	25	-5.4%	Dom.
WM FIT 45-75, 2	11274	0	0	1522	283	47	24	0%	12.2
WM FIT 45-80, 2	12017	0	0	1598	289	48	25	0%	12.7
WM FIT 45-85, 2	12769	0	0	1670	292	48	26	0%	23.6
WM FIT 55-75, 1	12001	0	0	1594	245	48	24	-15.1%	Dom.
WM FIT 55-80, 1	13468	0	0	1715	251	50	25	-14.7%	Dom.
WM FIT 55-85, 1	14439	0	0	1789	252	50	25	-15.0%	Dom.
WM FIT 50-75, 1	15221	0	0	1869	281	54	26	-6.2%	Dom.
WM FIT 50-80, 1	16675	0	0	1987	286	55	27	-5.9%	Dom.
WM FIT 50-85, 1	17640	0	0	2059	287	56	27	-6.2%	Dom.
WM FIT 45-75, 1	18598	0	0	2119	308	57	27	-0.2%	28.1*
WM FIT 45-80, 1	20047	0	0	2235	313	59	28	0%	26.8
WM FIT 45-85, 1	21009	0	0	2307	315	59	28	0%	49.3
WM FIT-DNA 55-75, 5	3463	0	0	1264	212	39	21	-19.1%	Dom.
WM FIT-DNA 55-80, 5	3813	0	0	1348	217	40	22	-19.4%	Dom.
WM FIT-DNA 55-85, 5	4031	0	0	1398	218	39	22	-20.0%	Dom.
WM FIT-DNA 50-75, 5	4267	0	0	1468	243	43	22	-12.6%	Dom.
WM FIT-DNA 50-80, 5	4614	0	0	1550	248	44	23	-13.0%	Dom.
WM FIT-DNA 50-85, 5	4830	0	0	1599	250	44	24	-13.6%	Dom.
WM FIT-DNA 45-75, 5	5102	0	0	1652	268	46	23	-8.1%	Dom.
WM FIT-DNA 45-80, 5	5446	0	0	1733	272	47	24	-7.5%	Dom.
WM FIT-DNA 45-85, 5	5662	0	0	1781	274	47	25	-7.6%	Dom.
WM FIT-DNA 55-75, 3	4513	0	0	1520	233	45	22	-17.6%	Dom.
WM FIT-DNA 55-80, 3	5176	0	0	1666	241	47	24	-17.4%	Dom.
WM FIT-DNA 55-85, 3	5505	0	0	1733	243	47	24	-17.6%	Dom.
WM FIT-DNA 50-75, 3	5805	0	0	1820	270	50	25	-9.3%	Dom.
WM FIT-DNA 50-80, 3	6297	0	0	1927	275	52	26	-8.8%	Dom.
WM FIT-DNA 50-85, 3	6648	0	0	1995	277	52	26	-9.0%	Dom.
WM FIT-DNA 45-75, 3	6966	0	0	2056	296	53	26	-3.6%	Dom.
WM FIT-DNA 45-80, 3	7489	0	0	2163	301	55	27	-3.0%	Dom.
WM FIT-DNA 45-85, 3	7885	0	0	2243	303	55	27	-3.3%	Dom.
WM FIT-DNA 55-75, 1	8456	0	0	2320	256	55	25	-18.7%	Dom.

table continues

SimCRC - Scenario 1: Stable CRC risk										
WM	FIT-DNA 55-80, 1	9354	0	0	2469	259	57	26	-18.0%	Dom.
WM	FIT-DNA 55-85, 1	9954	0	0	2563	260	57	26	-17.9%	Dom.
WM	FIT-DNA 50-75, 1	10613	0	0	2726	291	60	27	-8.4%	Dom.
WM	FIT-DNA 50-80, 1	11528	0	0	2877	294	62	27	-7.7%	Dom.
WM	FIT-DNA 50-85, 1	12121	0	0	2970	295	62	28	-7.6%	Dom.
WM	FIT-DNA 45-75, 1	12911	0	0	3114	318	64	28	-0.7%	233.9*
WM	FIT-DNA 45-80, 1	13816	0	0	3263	321	65	28	0.0%	144.7*
WM	FIT-DNA 45-85, 1	14409	0	0	3355	322	65	29	0%	141.4
WM	HSgFOBT 55-75, 3	4876	0	0	1130	194	33	19	-19.6%	Dom.
WM	HSgFOBT 55-80, 3	5658	0	0	1256	206	35	21	-21.2%	Dom.
WM	HSgFOBT 55-85, 3	6070	0	0	1320	208	35	21	-21.8%	Dom.
WM	HSgFOBT 50-75, 3	6291	0	0	1376	231	38	21	-14.9%	Dom.
WM	HSgFOBT 50-80, 3	6898	0	0	1474	239	40	22	-14.5%	Dom.
WM	HSgFOBT 50-85, 3	7275	0	0	1527	241	40	23	-15.0%	Dom.
WM	HSgFOBT 45-75, 3	7576	0	0	1578	256	42	22	-10.9%	Dom.
WM	HSgFOBT 45-80, 3	8129	0	0	1660	263	43	23	-9.9%	Dom.
WM	HSgFOBT 45-85, 3	8621	0	0	1733	266	43	24	-9.6%	Dom.
WM	HSgFOBT 55-75, 2	6673	0	0	1455	222	40	22	-20.0%	Dom.
WM	HSgFOBT 55-80, 2	7325	0	0	1551	228	42	23	-20.2%	Dom.
WM	HSgFOBT 55-85, 2	7977	0	0	1640	231	42	23	-20.7%	Dom.
WM	HSgFOBT 50-75, 2	8158	0	0	1700	255	45	23	-13.2%	Dom.
WM	HSgFOBT 50-80, 2	9122	0	0	1838	263	47	25	-11.9%	Dom.
WM	HSgFOBT 50-85, 2	9552	0	0	1896	265	47	25	-12.0%	Dom.
WM	HSgFOBT 45-75, 2	10082	0	0	1979	283	49	25	-6.7%	Dom.
WM	HSgFOBT 45-80, 2	10721	0	0	2071	289	50	26	-6.0%	Dom.
WM	HSgFOBT 45-85, 2	11363	0	0	2157	291	51	26	-6.1%	Dom.
WM	HSgFOBT 55-75, 1	9971	0	0	1978	245	50	24	-19.3%	Dom.
WM	HSgFOBT 55-80, 1	11100	0	0	2120	250	51	25	-19.2%	Dom.
WM	HSgFOBT 55-85, 1	11847	0	0	2208	251	51	25	-19.6%	Dom.
WM	HSgFOBT 50-75, 1	12485	0	0	2345	281	55	26	-10.8%	Dom.
WM	HSgFOBT 50-80, 1	13612	0	0	2485	285	56	27	-9.7%	Dom.
WM	HSgFOBT 50-85, 1	14354	0	0	2571	286	57	27	-9.5%	Dom.
WM	HSgFOBT 45-75, 1	15127	0	0	2689	308	58	27	-2.9%	Dom.
WM	HSgFOBT 45-80, 1	16247	0	0	2828	313	60	28	-1.8%	Dom.
WM	HSgFOBT 45-85, 1	16986	0	0	2914	314	60	28	-1.6%	Dom.
WM	SIG 55-75, 10	0	2202	0	1382	198	45	20	0%	6.6
WM	SIG 55-80, 10	0	2202	0	1382	198	45	20	0%	6.6
WM	SIG 55-85, 10	0	2444	0	1464	200	45	20	-9.9%	Dom.
WM	SIG 50-75, 10	0	2423	0	1468	222	47	21	0%	3.6
WM	SIG 50-80, 10	0	2805	0	1608	228	49	22	-4.1%	Dom.
WM	SIG 50-85, 10	0	2805	0	1608	228	49	22	-4.1%	Dom.
WM	SIG 45-75, 10	0	3112	0	1711	248	51	22	0%	9.3
WM	SIG 45-80, 10	0	3112	0	1711	248	51	22	0%	9.3
WM	SIG 45-85, 10	0	3352	0	1791	250	52	23	-1.3%	58.5*
WM	SIG 55-75, 5	0	3211	0	1703	218	50	22	-12.1%	Dom.
WM	SIG 55-80, 5	0	3516	0	1791	220	51	22	-13.1%	Dom.
WM	SIG 55-85, 5	0	3705	0	1841	220	51	23	-13.9%	Dom.

table continues

SimCRC - Scenario 1: Stable CRC risk									
WM SIG 50-75, 5	0	3968	0	1957	250	55	24	-4.7%	Dom.
WM SIG 50-80, 5	0	4270	0	2044	252	56	24	-5.7%	Dom.
WM SIG 50-85, 5	0	4458	0	2093	253	56	24	-6.4%	Dom.
WM SIG 45-75, 5	0	4760	0	2185	275	58	25	0%	17.7
WM SIG 45-80, 5	0	5061	0	2271	277	59	25	0%	42.4
WM SIG 45-85, 5	0	5248	0	2320	278	59	25	0%	99.2
WM CTC 55-75, 10	0	0	2170	1533	232	51	23	0%	6.3
WM CTC 55-80, 10	0	0	2170	1533	232	51	23	0%	6.3
WM CTC 55-85, 10	0	0	2397	1626	234	52	24	-10.4%	Dom.
WM CTC 50-75, 10	0	0	2397	1605	259	53	24	0%	2.7
WM CTC 50-80, 10	0	0	2762	1763	265	56	25	-4.3%	Dom.
WM CTC 50-85, 10	0	0	2762	1763	265	56	25	-4.3%	Dom.
WM CTC 45-75, 10	0	0	3077	1854	287	58	26	0%	8.8
WM CTC 45-80, 10	0	0	3077	1854	287	58	26	0%	8.8
WM CTC 45-85, 10	0	0	3303	1946	288	58	26	-1.2%	61.6*
WM CTC 55-75, 5	0	0	3152	1840	250	56	25	-12.4%	Dom.
WM CTC 55-80, 5	0	0	3441	1932	252	57	25	-13.4%	Dom.
WM CTC 55-85, 5	0	0	3618	1984	253	57	25	-14.1%	Dom.
WM CTC 50-75, 5	0	0	3913	2086	285	61	26	-4.8%	Dom.
WM CTC 50-80, 5	0	0	4201	2177	287	62	27	-5.7%	Dom.
WM CTC 50-85, 5	0	0	4377	2229	288	62	27	-6.4%	Dom.
WM CTC 45-75, 5	0	0	4713	2303	312	64	27	0%	18.2
WM CTC 45-80, 5	0	0	5001	2393	314	65	28	0%	43.9
WM CTC 45-85, 5	0	0	5177	2444	314	65	28	0%	103.5
SimCRC - Scenario 2: Increased CRC risk									
WM No screening	0	0	0	162	0	0	0	-	-
WM COL 55-75, 15	0	0	0	3659	517	117	52	0%	6.8
WM COL 55-80, 15	0	0	0	3659	517	117	52	0%	6.8
WM COL 55-85, 15	0	0	0	3820	519	118	53	-4.7%	Dom.
WM COL 50-75, 15	0	0	0	3964	566	120	53	0%	6.2
WM COL 50-80, 15	0	0	0	4301	577	124	55	-2.0%	31.9*
WM COL 50-85, 15	0	0	0	4301	577	124	55	-2.0%	31.9*
WM COL 45-75, 15	0	0	0	4744	617	129	57	0%	15.2
WM COL 45-80, 15	0	0	0	4744	617	129	57	0%	15.2
WM COL 45-85, 15	0	0	0	4744	617	129	57	0%	15.2
WM COL 55-75, 10	0	0	0	4197	539	124	55	-7.2%	Dom.
WM COL 55-80, 10	0	0	0	4197	539	124	55	-7.2%	Dom.
WM COL 55-85, 10	0	0	0	4310	540	124	55	-8.2%	Dom.
WM COL 50-75, 10	0	0	0	4712	600	130	57	-2.4%	Dom.
WM COL 50-80, 10	0	0	0	4946	605	132	58	-3.4%	Dom.
WM COL 50-85, 10	0	0	0	4946	605	132	58	-3.4%	Dom.
WM COL 45-75, 10	0	0	0	5513	650	137	59	0%	23.5
WM COL 45-80, 10	0	0	0	5513	650	137	59	0%	23.5
WM COL 45-85, 10	0	0	0	5627	651	137	59	-0.1%	148.3*
WM COL 55-75, 5	0	0	0	5143	554	128	56	-12.6%	Dom.
WM COL 55-80, 5	0	0	0	5294	555	129	56	-13.3%	Dom.
WM COL 55-85, 5	0	0	0	5371	556	129	56	-13.7%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk										
WM	COL 50-75, 5	0	0	0	6186	623	137	59	-5.5%	Dom.
WM	COL 50-80, 5	0	0	0	6337	624	138	59	-5.6%	Dom.
WM	COL 50-85, 5	0	0	0	6414	624	138	59	-5.7%	Dom.
WM	COL 45-75, 5	0	0	0	7244	672	143	61	0%	79.1
WM	COL 45-80, 5	0	0	0	7395	673	144	61	0%	152.6
WM	COL 45-85, 5	0	0	0	7472	673	144	61	0%	427.6
WM	FIT 55-75, 3	4854	0	0	1363	409	69	39	0%	2.9
WM	FIT 55-80, 3	5553	0	0	1508	435	74	44	-3.4%	Dom.
WM	FIT 55-85, 3	5920	0	0	1579	442	74	46	-6.1%	Dom.
WM	FIT 50-75, 3	6326	0	0	1597	475	78	44	0%	3.5
WM	FIT 50-80, 3	6911	0	0	1717	495	82	47	-2.1%	Dom.
WM	FIT 50-85, 3	7171	0	0	1764	499	82	48	-3.5%	Dom.
WM	FIT 45-75, 3	7768	0	0	1784	522	84	46	0%	4.0
WM	FIT 45-80, 3	8180	0	0	1862	536	86	49	0%	5.7
WM	FIT 45-85, 3	8607	0	0	1942	544	87	50	-0.4%	10.2*
WM	FIT 55-75, 2	6779	0	0	1708	465	84	46	-7.7%	Dom.
WM	FIT 55-80, 2	7355	0	0	1810	478	87	48	-9.3%	Dom.
WM	FIT 55-85, 2	7886	0	0	1895	484	88	50	-10.4%	Dom.
WM	FIT 50-75, 2	8440	0	0	1928	523	92	48	-4.0%	Dom.
WM	FIT 50-80, 2	9295	0	0	2075	542	96	52	-3.7%	Dom.
WM	FIT 50-85, 2	9644	0	0	2130	545	97	52	-4.3%	Dom.
WM	FIT 45-75, 2	10548	0	0	2172	575	99	51	0.0%	7.9*
WM	FIT 45-80, 2	11113	0	0	2270	588	101	53	0%	7.8
WM	FIT 45-85, 2	11637	0	0	2352	593	102	55	0%	14.6
WM	FIT 55-75, 1	10764	0	0	2237	510	102	50	-12.6%	Dom.
WM	FIT 55-80, 1	11803	0	0	2372	521	106	53	-12.4%	Dom.
WM	FIT 55-85, 1	12420	0	0	2443	524	107	53	-12.6%	Dom.
WM	FIT 50-75, 1	13806	0	0	2573	576	112	54	-5.2%	Dom.
WM	FIT 50-80, 1	14834	0	0	2704	586	115	56	-4.8%	Dom.
WM	FIT 50-85, 1	15447	0	0	2775	589	116	56	-5.1%	Dom.
WM	FIT 45-75, 1	17055	0	0	2867	625	118	56	-0.3%	16.3*
WM	FIT 45-80, 1	18077	0	0	2997	635	121	58	0%	15.4
WM	FIT 45-85, 1	18687	0	0	3067	638	122	58	0%	26.9
WM	FIT-DNA 55-75, 5	3232	0	0	1799	443	83	44	-15.6%	Dom.
WM	FIT-DNA 55-80, 5	3498	0	0	1898	453	85	46	-16.2%	Dom.
WM	FIT-DNA 55-85, 5	3650	0	0	1950	455	85	47	-16.8%	Dom.
WM	FIT-DNA 50-75, 5	4004	0	0	2053	502	91	47	-10.4%	Dom.
WM	FIT-DNA 50-80, 5	4267	0	0	2149	511	93	49	-10.7%	Dom.
WM	FIT-DNA 50-85, 5	4417	0	0	2201	514	93	50	-11.3%	Dom.
WM	FIT-DNA 45-75, 5	4814	0	0	2272	544	96	49	-7.4%	Dom.
WM	FIT-DNA 45-80, 5	5076	0	0	2368	554	99	51	-6.9%	Dom.
WM	FIT-DNA 45-85, 5	5225	0	0	2419	556	99	52	-7.0%	Dom.
WM	FIT-DNA 55-75, 3	4161	0	0	2112	486	95	48	-14.4%	Dom.
WM	FIT-DNA 55-80, 3	4655	0	0	2278	502	100	51	-14.7%	Dom.
WM	FIT-DNA 55-85, 3	4876	0	0	2345	505	100	51	-14.9%	Dom.
WM	FIT-DNA 50-75, 3	5367	0	0	2475	554	105	52	-7.9%	Dom.
WM	FIT-DNA 50-80, 3	5732	0	0	2595	565	108	54	-7.3%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk									
WM FIT-DNA 50-85, 3	5965	0	0	2662	568	109	54	-7.4%	Dom.
WM FIT-DNA 45-75, 3	6500	0	0	2753	599	111	53	-3.3%	Dom.
WM FIT-DNA 45-80, 3	6884	0	0	2873	611	114	55	-2.7%	Dom.
WM FIT-DNA 45-85, 3	7150	0	0	2953	614	115	56	-2.9%	Dom.
WM FIT-DNA 55-75, 1	7459	0	0	2977	530	115	53	-16.3%	Dom.
WM FIT-DNA 55-80, 1	8054	0	0	3115	537	118	54	-15.9%	Dom.
WM FIT-DNA 55-85, 1	8405	0	0	3188	538	118	55	-15.8%	Dom.
WM FIT-DNA 50-75, 1	9487	0	0	3443	596	124	56	-7.3%	Dom.
WM FIT-DNA 50-80, 1	10092	0	0	3582	602	126	57	-6.6%	Dom.
WM FIT-DNA 50-85, 1	10440	0	0	3654	604	127	57	-6.5%	Dom.
WM FIT-DNA 45-75, 1	11686	0	0	3874	644	129	58	-0.8%	141.4*
WM FIT-DNA 45-80, 1	12284	0	0	4011	650	132	59	-0.1%	78.7*
WM FIT-DNA 45-85, 1	12631	0	0	4082	651	133	59	0%	75.8
WM HSgFOBT 55-75, 3	4602	0	0	1590	408	71	40	-13.9%	Dom.
WM HSgFOBT 55-80, 3	5231	0	0	1743	431	76	44	-15.7%	Dom.
WM HSgFOBT 55-85, 3	5537	0	0	1812	437	76	45	-17.1%	Dom.
WM HSgFOBT 50-75, 3	5943	0	0	1894	475	81	44	-12.0%	Dom.
WM HSgFOBT 50-80, 3	6430	0	0	2012	492	84	47	-11.4%	Dom.
WM HSgFOBT 50-85, 3	6700	0	0	2068	496	85	48	-11.7%	Dom.
WM HSgFOBT 45-75, 3	7199	0	0	2136	521	87	46	-8.8%	Dom.
WM HSgFOBT 45-80, 3	7632	0	0	2232	534	90	49	-8.3%	Dom.
WM HSgFOBT 45-85, 3	7995	0	0	2312	541	91	50	-8.4%	Dom.
WM HSgFOBT 55-75, 2	6185	0	0	1986	463	86	46	-16.0%	Dom.
WM HSgFOBT 55-80, 2	6683	0	0	2093	475	89	48	-15.9%	Dom.
WM HSgFOBT 55-85, 2	7136	0	0	2182	481	90	49	-16.6%	Dom.
WM HSgFOBT 50-75, 2	7629	0	0	2283	523	95	48	-11.2%	Dom.
WM HSgFOBT 50-80, 2	8363	0	0	2438	540	99	52	-9.9%	Dom.
WM HSgFOBT 50-85, 2	8660	0	0	2495	543	99	52	-9.9%	Dom.
WM HSgFOBT 45-75, 2	9457	0	0	2609	575	102	51	-5.7%	Dom.
WM HSgFOBT 45-80, 2	9942	0	0	2711	587	105	53	-4.9%	Dom.
WM HSgFOBT 45-85, 2	10387	0	0	2797	592	105	55	-4.9%	Dom.
WM HSgFOBT 55-75, 1	9034	0	0	2581	509	104	51	-16.3%	Dom.
WM HSgFOBT 55-80, 1	9834	0	0	2722	519	107	53	-16.0%	Dom.
WM HSgFOBT 55-85, 1	10306	0	0	2796	521	108	53	-16.3%	Dom.
WM HSgFOBT 50-75, 1	11408	0	0	3008	575	114	54	-9.5%	Dom.
WM HSgFOBT 50-80, 1	12203	0	0	3146	584	117	56	-8.5%	Dom.
WM HSgFOBT 50-85, 1	12672	0	0	3219	587	117	56	-8.3%	Dom.
WM HSgFOBT 45-75, 1	13946	0	0	3397	624	120	56	-2.8%	Dom.
WM HSgFOBT 45-80, 1	14735	0	0	3533	633	123	58	-1.7%	Dom.
WM HSgFOBT 45-85, 1	15201	0	0	3606	636	123	58	-1.5%	Dom.
WM SIG 55-75, 10	0	2028	0	2134	459	102	47	0%	4.3
WM SIG 55-80, 10	0	2028	0	2134	459	102	47	0%	4.3
WM SIG 55-85, 10	0	2189	0	2222	462	103	48	-7.1%	Dom.
WM SIG 50-75, 10	0	2281	0	2250	504	106	47	0%	2.6
WM SIG 50-80, 10	0	2562	0	2424	516	110	50	-3.1%	Dom.
WM SIG 50-85, 10	0	2562	0	2424	516	110	50	-3.1%	Dom.
WM SIG 45-75, 10	0	2903	0	2557	554	114	51	0%	6.2

table continues

SimCRC - Scenario 2: Increased CRC risk										
WM	SIG 45-80, 10	0	2903	0	2557	554	114	51	0%	6.2
WM	SIG 45-85, 10	0	3063	0	2644	557	115	52	-0.8%	33.7*
WM	SIG 55-75, 5	0	2850	0	2500	493	112	50	-9.5%	Dom.
WM	SIG 55-80, 5	0	3052	0	2592	497	114	51	-10.8%	Dom.
WM	SIG 55-85, 5	0	3165	0	2637	498	114	51	-11.3%	Dom.
WM	SIG 50-75, 5	0	3561	0	2817	555	120	53	-3.7%	Dom.
WM	SIG 50-80, 5	0	3761	0	2908	558	122	54	-4.3%	Dom.
WM	SIG 50-85, 5	0	3873	0	2952	559	122	54	-4.8%	Dom.
WM	SIG 45-75, 5	0	4319	0	3091	599	125	55	0%	11.9
WM	SIG 45-80, 5	0	4518	0	3181	603	127	56	0%	23.3
WM	SIG 45-85, 5	0	4630	0	3225	604	128	56	0%	55.9
WM	CTC 55-75, 10	0	0	2006	2239	485	107	49	0%	4.3
WM	CTC 55-80, 10	0	0	2006	2239	485	107	49	0%	4.3
WM	CTC 55-85, 10	0	0	2158	2338	488	108	50	-8.3%	Dom.
WM	CTC 50-75, 10	0	0	2264	2335	532	110	50	0%	2.1
WM	CTC 50-80, 10	0	0	2535	2528	544	115	53	-3.5%	Dom.
WM	CTC 50-85, 10	0	0	2535	2528	544	115	53	-3.5%	Dom.
WM	CTC 45-75, 10	0	0	2882	2648	583	118	54	0%	6.1
WM	CTC 45-80, 10	0	0	2882	2648	583	118	54	0%	6.1
WM	CTC 45-85, 10	0	0	3033	2746	586	119	54	-1.1%	37.0*
WM	CTC 55-75, 5	0	0	2813	2596	521	117	52	-9.3%	Dom.
WM	CTC 55-80, 5	0	0	3005	2694	525	119	53	-10.6%	Dom.
WM	CTC 55-85, 5	0	0	3109	2740	526	119	54	-11.2%	Dom.
WM	CTC 50-75, 5	0	0	3530	2905	585	125	55	-3.7%	Dom.
WM	CTC 50-80, 5	0	0	3720	3001	589	127	56	-4.4%	Dom.
WM	CTC 50-85, 5	0	0	3824	3048	590	127	57	-5.0%	Dom.
WM	CTC 45-75, 5	0	0	4299	3164	632	130	57	0%	10.6
WM	CTC 45-80, 5	0	0	4490	3260	636	132	58	0%	24.4
WM	CTC 45-85, 5	0	0	4593	3307	637	132	58	0%	60.8

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

[a] Both models evaluated two scenarios for CRC risk: one in which age-specific risks were assumed to have remained stable since the early screening period in the U.S. (1975-1979 for SimCRC; 1990-1994 for MISCAN), and one in which risks were assumed to have increased proportional to observed trends among adults under age 40 years. Strategies for each model and scenario are ordered successively by screening modality, interval (↓), end age (↑), and start age (↓).

[b] Total number of colonoscopies performed per 1000 40-year-olds, including diagnostic colonoscopies and potential surveillance colonoscopies after adenoma removal. The number of screening-related complications ranged from 4.9 to 33.5 per 1000 40-year-olds across models, scenarios, and strategies.

[c] Including deaths from complications of screening.

[d] The difference in LYG compared to (combinations of) adjacent strategies on the efficient frontier. Near-efficient strategies have a loss in LYG of less than 2% before rounding. For the least intensive screening strategy evaluated within each class of screening modality, the difference was zero by definition.
[e] Efficiency ratio = incremental number of colonoscopies/LYG with respect to the next less effective strategy on the efficient frontier, a burden-to-benefit ratio. Only calculated for efficient and near-efficient strategies (marked with an asterisk*), i.e. strategies within 2% from the efficient frontier among all evaluated strategies within a class of screening modalities (colonoscopy, stool-based, sigmoidoscopy, and CTC).

Supplementary Table A3.6: Lifetime number of colonoscopies and LYG for all evaluated screening strategies under two scenarios for CRC risk, by model, in black males [a]

		Outcomes per 1000 40-year-olds								
Subgroup	Modality, and age to begin-end screening, interval, y	Stool tests	SIGs	CTCs	COLs [b]	LYG	CRC cases averted	CRC deaths averted [c]	Relative distance from efficient frontier [d]	ER [e]
MISCAN - Scenario 1: Stable CRC risk										
BM	No screening	0	0	0	62	0	0	0	-	-
BM	COL 55-75, 15	0	0	0	2812	210	33	21	0%	13.1
BM	COL 55-80, 15	0	0	0	2812	210	33	21	0%	13.1
BM	COL 55-85, 15	0	0	0	2975	211	33	21	-4.4%	Dom.
BM	COL 50-75, 15	0	0	0	3160	233	35	22	0%	15.7
BM	COL 50-80, 15	0	0	0	3438	235	36	22	-1.7%	93.1*
BM	COL 50-85, 15	0	0	0	3438	235	36	22	-1.7%	93.1*
BM	COL 45-75, 15	0	0	0	3839	249	37	23	-0.3%	190.8*
BM	COL 45-80, 15	0	0	0	3839	249	37	23	-0.3%	190.8*
BM	COL 45-85, 15	0	0	0	3839	249	37	23	-0.3%	190.8*
BM	COL 55-75, 10	0	0	0	3306	220	35	22	-6.7%	Dom.
BM	COL 55-80, 10	0	0	0	3306	220	35	22	-6.7%	Dom.
BM	COL 55-85, 10	0	0	0	3454	221	35	22	-8.1%	Dom.
BM	COL 50-75, 10	0	0	0	3791	248	38	23	0%	40.0
BM	COL 50-80, 10	0	0	0	4040	250	38	23	-1.7%	157.8*
BM	COL 50-85, 10	0	0	0	4040	250	38	23	-1.7%	157.8*
BM	COL 45-75, 10	0	0	0	4561	266	40	24	0%	42.9
BM	COL 45-80, 10	0	0	0	4561	266	40	24	0%	42.9
BM	COL 45-85, 10	0	0	0	4710	267	40	24	-0.4%	526.0*
BM	COL 55-75, 5	0	0	0	4335	231	37	23	-11.7%	Dom.
BM	COL 55-80, 5	0	0	0	4559	231	38	23	-13.2%	Dom.
BM	COL 55-85, 5	0	0	0	4697	231	38	23	-13.6%	Dom.
BM	COL 50-75, 5	0	0	0	5342	263	41	24	-4.0%	Dom.
BM	COL 50-80, 5	0	0	0	5566	263	41	24	-4.5%	Dom.
BM	COL 50-85, 5	0	0	0	5704	263	41	24	-5.0%	Dom.
BM	COL 45-75, 5	0	0	0	6375	284	43	25	0%	104.0
BM	COL 45-80, 5	0	0	0	6599	284	43	25	0%	476.0
BM	COL 45-85, 5	0	0	0	6737	284	43	25	0%	2032.9
BM	FIT 55-75, 3	4690	0	0	792	152	14	15	0%	4.8
BM	FIT 55-80, 3	5382	0	0	855	160	14	16	-0.7%	7.5*
BM	FIT 55-85, 3	5801	0	0	888	162	14	17	-2.3%	Dom.
BM	FIT 50-75, 3	6157	0	0	958	177	16	16	0%	6.6
BM	FIT 50-80, 3	6795	0	0	1014	183	17	18	0%	8.2
BM	FIT 50-85, 3	7013	0	0	1030	185	16	18	-0.5%	14.8*
BM	FIT 45-75, 3	7675	0	0	1102	194	18	18	-0.1%	8.5*
BM	FIT 45-80, 3	8003	0	0	1129	197	18	18	0%	8.3
BM	FIT 45-85, 3	8459	0	0	1164	200	18	19	-0.3%	13.1*

table continues

MISCAN - Scenario 1: Stable CRC risk										
BM	FIT 55-75, 2	6739	0	0	1009	176	18	17	-3.7%	Dom.
BM	FIT 55-80, 2	7350	0	0	1055	181	19	18	-4.1%	Dom.
BM	FIT 55-85, 2	7951	0	0	1096	183	19	19	-5.3%	Dom.
BM	FIT 50-75, 2	8439	0	0	1190	201	21	19	-1.0%	17.2*
BM	FIT 50-80, 2	9346	0	0	1256	208	21	20	-0.7%	12.3*
BM	FIT 50-85, 2	9742	0	0	1282	209	21	20	-1.2%	13.1*
BM	FIT 45-75, 2	10595	0	0	1375	220	23	20	-0.1%	10.9*
BM	FIT 45-80, 2	11194	0	0	1418	224	23	20	0%	10.8
BM	FIT 45-85, 2	11786	0	0	1457	226	23	21	0.0%	18.7*
BM	FIT 55-75, 1	11061	0	0	1384	202	25	20	-8.5%	Dom.
BM	FIT 55-80, 1	12282	0	0	1456	207	26	21	-8.7%	Dom.
BM	FIT 55-85, 1	13078	0	0	1498	208	26	21	-9.1%	Dom.
BM	FIT 50-75, 1	14208	0	0	1662	232	28	21	-2.5%	Dom.
BM	FIT 50-80, 1	15415	0	0	1731	236	29	22	-2.3%	Dom.
BM	FIT 50-85, 1	16204	0	0	1772	237	29	22	-2.7%	Dom.
BM	FIT 45-75, 1	17548	0	0	1912	251	30	22	-0.2%	18.1*
BM	FIT 45-80, 1	18746	0	0	1980	256	31	23	0%	17.8
BM	FIT 45-85, 1	19532	0	0	2021	257	31	23	0%	34.8
BM	FIT-DNA 55-75, 5	3159	0	0	1117	168	19	17	-14.1%	Dom.
BM	FIT-DNA 55-80, 5	3432	0	0	1166	172	19	17	-14.5%	Dom.
BM	FIT-DNA 55-85, 5	3599	0	0	1194	172	18	18	-15.2%	Dom.
BM	FIT-DNA 50-75, 5	3944	0	0	1324	192	21	18	-11.1%	Dom.
BM	FIT-DNA 50-80, 5	4214	0	0	1372	195	21	19	-11.4%	Dom.
BM	FIT-DNA 50-85, 5	4380	0	0	1399	196	21	19	-12.0%	Dom.
BM	FIT-DNA 45-75, 5	4769	0	0	1507	207	22	19	-9.5%	Dom.
BM	FIT-DNA 45-80, 5	5037	0	0	1554	211	22	20	-9.1%	Dom.
BM	FIT-DNA 45-85, 5	5202	0	0	1580	211	22	20	-9.4%	Dom.
BM	FIT-DNA 55-75, 3	4027	0	0	1334	187	23	18	-13.7%	Dom.
BM	FIT-DNA 55-80, 3	4567	0	0	1426	193	24	19	-14.1%	Dom.
BM	FIT-DNA 55-85, 3	4890	0	0	1474	195	24	20	-14.4%	Dom.
BM	FIT-DNA 50-75, 3	5231	0	0	1622	216	26	20	-8.4%	Dom.
BM	FIT-DNA 50-80, 3	5725	0	0	1702	221	26	21	-8.0%	Dom.
BM	FIT-DNA 50-85, 3	5893	0	0	1726	222	26	21	-8.2%	Dom.
BM	FIT-DNA 45-75, 3	6482	0	0	1879	234	28	21	-6.2%	Dom.
BM	FIT-DNA 45-80, 3	6736	0	0	1919	237	28	21	-6.1%	Dom.
BM	FIT-DNA 45-85, 3	7088	0	0	1971	239	28	22	-6.4%	Dom.
BM	FIT-DNA 55-75, 1	7811	0	0	2060	216	32	21	-15.9%	Dom.
BM	FIT-DNA 55-80, 1	8558	0	0	2158	219	32	22	-15.2%	Dom.
BM	FIT-DNA 55-85, 1	9055	0	0	2219	220	32	22	-15.2%	Dom.
BM	FIT-DNA 50-75, 1	9890	0	0	2483	247	35	23	-6.0%	Dom.
BM	FIT-DNA 50-80, 1	10646	0	0	2581	249	35	23	-5.4%	Dom.
BM	FIT-DNA 50-85, 1	11137	0	0	2641	250	35	23	-5.4%	Dom.
BM	FIT-DNA 45-75, 1	12136	0	0	2879	266	36	23	-0.5%	96.4*
BM	FIT-DNA 45-80, 1	12883	0	0	2975	268	37	24	0%	83.5
BM	FIT-DNA 45-85, 1	13372	0	0	3034	269	37	24	0%	96.8
BM	HSgFOBT 55-75, 3	4408	0	0	982	149	15	15	-17.0%	Dom.
BM	HSgFOBT 55-80, 3	5034	0	0	1064	157	15	16	-17.2%	Dom.

table continues

MISCAN - Scenario 1: Stable CRC risk										
BM	HSgFOBT 55-85, 3	5409	0	0	1108	159	14	17	-18.4%	Dom.
BM	HSgFOBT 50-75, 3	5731	0	0	1219	175	17	16	-14.8%	Dom.
BM	HSgFOBT 50-80, 3	6303	0	0	1291	181	17	18	-14.5%	Dom.
BM	HSgFOBT 50-85, 3	6498	0	0	1313	183	17	18	-14.9%	Dom.
BM	HSgFOBT 45-75, 3	7092	0	0	1435	193	19	18	-14.3%	Dom.
BM	HSgFOBT 45-80, 3	7385	0	0	1471	196	19	18	-13.7%	Dom.
BM	HSgFOBT 45-85, 3	7790	0	0	1517	198	19	19	-13.6%	Dom.
BM	HSgFOBT 55-75, 2	6149	0	0	1269	174	19	17	-17.1%	Dom.
BM	HSgFOBT 55-80, 2	6675	0	0	1331	179	19	18	-17.3%	Dom.
BM	HSgFOBT 55-85, 2	7188	0	0	1386	181	19	19	-18.3%	Dom.
BM	HSgFOBT 50-75, 2	7625	0	0	1532	200	22	19	-13.2%	Dom.
BM	HSgFOBT 50-80, 2	8400	0	0	1620	206	22	20	-12.5%	Dom.
BM	HSgFOBT 50-85, 2	8736	0	0	1655	207	22	20	-12.7%	Dom.
BM	HSgFOBT 45-75, 2	9484	0	0	1811	220	24	20	-10.5%	Dom.
BM	HSgFOBT 45-80, 2	9994	0	0	1868	224	24	21	-10.1%	Dom.
BM	HSgFOBT 45-85, 2	10494	0	0	1920	226	24	21	-10.5%	Dom.
BM	HSgFOBT 55-75, 1	9232	0	0	1745	201	26	20	-16.9%	Dom.
BM	HSgFOBT 55-80, 1	10152	0	0	1838	205	27	21	-17.2%	Dom.
BM	HSgFOBT 55-85, 1	10751	0	0	1894	206	27	21	-17.8%	Dom.
BM	HSgFOBT 50-75, 1	11660	0	0	2128	231	29	21	-10.4%	Dom.
BM	HSgFOBT 50-80, 1	12572	0	0	2218	235	30	22	-9.4%	Dom.
BM	HSgFOBT 50-85, 1	13164	0	0	2273	236	30	22	-9.3%	Dom.
BM	HSgFOBT 45-75, 1	14234	0	0	2485	251	31	22	-4.4%	Dom.
BM	HSgFOBT 45-80, 1	15137	0	0	2574	254	32	23	-3.5%	Dom.
BM	HSgFOBT 45-85, 1	15726	0	0	2628	255	32	23	-3.4%	Dom.
BM	SIG 55-75, 10	0	1917	0	1540	175	28	18	0%	8.5
BM	SIG 55-80, 10	0	1917	0	1540	175	28	18	0%	8.5
BM	SIG 55-85, 10	0	2084	0	1577	175	28	18	-2.0%	Dom.
BM	SIG 50-75, 10	0	2171	0	1716	194	29	18	0%	9.0
BM	SIG 50-80, 10	0	2441	0	1789	197	30	19	-0.9%	29.9*
BM	SIG 50-85, 10	0	2441	0	1789	197	30	19	-0.9%	29.9*
BM	SIG 45-75, 10	0	2778	0	1946	207	31	19	-0.1%	17.7*
BM	SIG 45-80, 10	0	2778	0	1946	207	31	19	-0.1%	17.7*
BM	SIG 45-85, 10	0	2943	0	1982	208	31	19	-0.9%	19.7*
BM	SIG 55-75, 5	0	2748	0	1782	190	30	19	-4.2%	Dom.
BM	SIG 55-80, 5	0	2971	0	1828	191	31	19	-5.0%	Dom.
BM	SIG 55-85, 5	0	3108	0	1852	191	31	19	-5.5%	Dom.
BM	SIG 50-75, 5	0	3439	0	2084	215	33	20	-0.3%	17.8*
BM	SIG 50-80, 5	0	3660	0	2129	216	33	21	-1.0%	19.1*
BM	SIG 50-85, 5	0	3797	0	2153	216	33	21	-1.6%	20.0*
BM	SIG 45-75, 5	0	4188	0	2343	230	34	21	0%	17.3
BM	SIG 45-80, 5	0	4409	0	2388	231	35	21	0%	47.3
BM	SIG 45-85, 5	0	4545	0	2412	231	35	21	0%	132.3
BM	CTC 55-75, 10	0	0	2014	1155	170	23	17	-0.3%	6.4
BM	CTC 55-80, 10	0	0	2014	1155	170	23	17	-0.3%	6.4
BM	CTC 55-85, 10	0	0	2200	1199	172	23	18	-3.2%	Dom.
BM	CTC 50-75, 10	0	0	2277	1258	187	24	17	0%	6.2

table continues

MISCAN - Scenario 1: Stable CRC risk										
BM	CTC 50-80, 10	0	0	2579	1336	193	25	19	-0.8%	12.7*
BM	CTC 50-85, 10	0	0	2579	1336	193	25	19	-0.8%	12.7*
BM	CTC 45-75, 10	0	0	2925	1434	201	26	19	-1.8%	12.9*
BM	CTC 45-80, 10	0	0	2925	1434	201	26	19	-1.8%	12.9*
BM	CTC 45-85, 10	0	0	3110	1477	202	26	19	-3.1%	Dom.
BM	CTC 55-75, 5	0	0	2976	1426	200	29	20	-1.8%	12.9*
BM	CTC 55-80, 5	0	0	3227	1477	203	29	20	-2.9%	Dom.
BM	CTC 55-85, 5	0	0	3381	1506	203	29	20	-3.9%	Dom.
BM	CTC 50-75, 5	0	0	3733	1659	227	31	21	0%	10.1
BM	CTC 50-80, 5	0	0	3983	1709	229	32	22	-0.7%	19.9*
BM	CTC 50-85, 5	0	0	4135	1737	230	32	22	-1.4%	25.1*
BM	CTC 45-75, 5	0	0	4538	1860	243	32	22	0%	12.0
BM	CTC 45-80, 5	0	0	4786	1910	246	33	22	0%	19.6
BM	CTC 45-85, 5	0	0	4938	1937	246	33	22	0%	48.3
MISCAN - Scenario 2: Increased CRC risk										
BM	No screening	0	0	0	88	0	0	0	-	-
BM	COL 55-75, 15	0	0	0	3256	298	48	30	0%	10.6
BM	COL 55-80, 15	0	0	0	3256	298	48	30	0%	10.6
BM	COL 55-85, 15	0	0	0	3372	299	48	30	-2.5%	Dom.
BM	COL 50-75, 15	0	0	0	3693	329	51	31	0%	13.9
BM	COL 50-80, 15	0	0	0	3904	333	52	32	-1.2%	55.6*
BM	COL 50-85, 15	0	0	0	3904	333	52	32	-1.2%	55.6*
BM	COL 45-75, 15	0	0	0	4359	351	53	32	-0.7%	95.4*
BM	COL 45-80, 15	0	0	0	4359	351	53	32	-0.7%	95.4*
BM	COL 45-85, 15	0	0	0	4359	351	53	32	-0.7%	95.4*
BM	COL 55-75, 10	0	0	0	3664	311	51	31	-5.0%	Dom.
BM	COL 55-80, 10	0	0	0	3664	311	51	31	-5.0%	Dom.
BM	COL 55-85, 10	0	0	0	3762	311	51	31	-6.3%	Dom.
BM	COL 50-75, 10	0	0	0	4243	350	55	33	0%	26.4
BM	COL 50-80, 10	0	0	0	4419	352	55	33	-1.1%	92.8*
BM	COL 50-85, 10	0	0	0	4419	352	55	33	-1.1%	92.8*
BM	COL 45-75, 10	0	0	0	5010	375	57	34	0%	30.1
BM	COL 45-80, 10	0	0	0	5010	375	57	34	0%	30.1
BM	COL 45-85, 10	0	0	0	5108	376	57	34	-0.3%	297.7*
BM	COL 55-75, 5	0	0	0	4459	324	54	32	-9.4%	Dom.
BM	COL 55-80, 5	0	0	0	4604	324	54	32	-10.4%	Dom.
BM	COL 55-85, 5	0	0	0	4691	324	54	32	-11.1%	Dom.
BM	COL 50-75, 5	0	0	0	5467	369	58	35	-3.5%	Dom.
BM	COL 50-80, 5	0	0	0	5612	370	59	35	-4.0%	Dom.
BM	COL 50-85, 5	0	0	0	5698	370	59	35	-4.3%	Dom.
BM	COL 45-75, 5	0	0	0	6499	399	61	36	0%	63.6
BM	COL 45-80, 5	0	0	0	6645	399	61	36	0%	273.3
BM	COL 45-85, 5	0	0	0	6731	400	61	36	0%	992.8
BM	FIT 55-75, 3	4520	0	0	1040	209	21	21	0%	4.6
BM	FIT 55-80, 3	5130	0	0	1115	220	21	23	-0.3%	6.5*
BM	FIT 55-85, 3	5482	0	0	1152	223	21	24	-1.6%	7.7*
BM	FIT 50-75, 3	5928	0	0	1250	242	24	23	0%	6.2

table continues

MISCAN - Scenario 2: Increased CRC risk										
BM	FIT 50-80, 3	6482	0	0	1314	252	24	25	0%	6.9
BM	FIT 50-85, 3	6665	0	0	1333	253	24	25	-0.4%	11.9*
BM	FIT 45-75, 3	7395	0	0	1428	267	26	25	-0.2%	7.6*
BM	FIT 45-80, 3	7679	0	0	1459	272	26	25	0%	7.3
BM	FIT 45-85, 3	8062	0	0	1498	275	26	26	-0.3%	10.7*
BM	FIT 55-75, 2	6392	0	0	1307	243	27	24	-3.1%	Dom.
BM	FIT 55-80, 2	6910	0	0	1359	249	27	26	-3.3%	Dom.
BM	FIT 55-85, 2	7400	0	0	1401	252	27	26	-4.4%	Dom.
BM	FIT 50-75, 2	8032	0	0	1534	278	30	26	-0.7%	11.5*
BM	FIT 50-80, 2	8796	0	0	1607	287	31	28	-0.4%	9.4*
BM	FIT 50-85, 2	9117	0	0	1634	289	31	28	-0.8%	10.0*
BM	FIT 45-75, 2	10094	0	0	1758	305	33	28	-0.2%	8.9*
BM	FIT 45-80, 2	10597	0	0	1806	311	33	29	0%	8.8
BM	FIT 45-85, 2	11076	0	0	1846	314	33	29	0.0%	14.5*
BM	FIT 55-75, 1	10282	0	0	1748	281	37	28	-7.6%	Dom.
BM	FIT 55-80, 1	11268	0	0	1820	287	38	29	-7.9%	Dom.
BM	FIT 55-85, 1	11884	0	0	1860	289	38	30	-8.2%	Dom.
BM	FIT 50-75, 1	13244	0	0	2085	323	41	30	-2.3%	Dom.
BM	FIT 50-80, 1	14210	0	0	2153	329	42	31	-2.0%	Dom.
BM	FIT 50-85, 1	14816	0	0	2191	331	42	32	-2.3%	Dom.
BM	FIT 45-75, 1	16433	0	0	2380	351	44	31	-0.3%	14.4*
BM	FIT 45-80, 1	17388	0	0	2446	357	45	32	0%	14.1
BM	FIT 45-85, 1	17990	0	0	2483	358	45	33	0%	23.7
BM	FIT-DNA 55-75, 5	3010	0	0	1420	233	27	24	-12.6%	Dom.
BM	FIT-DNA 55-80, 5	3239	0	0	1472	237	27	25	-13.0%	Dom.
BM	FIT-DNA 55-85, 5	3374	0	0	1499	239	27	25	-13.6%	Dom.
BM	FIT-DNA 50-75, 5	3759	0	0	1674	266	31	26	-10.2%	Dom.
BM	FIT-DNA 50-80, 5	3984	0	0	1724	270	31	27	-10.4%	Dom.
BM	FIT-DNA 50-85, 5	4116	0	0	1750	271	30	27	-10.9%	Dom.
BM	FIT-DNA 45-75, 5	4555	0	0	1892	287	33	27	-9.4%	Dom.
BM	FIT-DNA 45-80, 5	4777	0	0	1941	292	33	28	-9.0%	Dom.
BM	FIT-DNA 45-85, 5	4908	0	0	1967	293	33	28	-9.2%	Dom.
BM	FIT-DNA 55-75, 3	3819	0	0	1682	260	33	26	-12.3%	Dom.
BM	FIT-DNA 55-80, 3	4266	0	0	1775	269	35	27	-12.6%	Dom.
BM	FIT-DNA 55-85, 3	4519	0	0	1819	271	35	28	-13.3%	Dom.
BM	FIT-DNA 50-75, 3	4947	0	0	2026	300	38	28	-8.2%	Dom.
BM	FIT-DNA 50-80, 3	5348	0	0	2105	307	39	30	-7.8%	Dom.
BM	FIT-DNA 50-85, 3	5479	0	0	2128	308	39	30	-7.9%	Dom.
BM	FIT-DNA 45-75, 3	6134	0	0	2327	327	40	30	-6.1%	Dom.
BM	FIT-DNA 45-80, 3	6340	0	0	2366	330	41	30	-5.9%	Dom.
BM	FIT-DNA 45-85, 3	6615	0	0	2414	333	41	31	-6.1%	Dom.
BM	FIT-DNA 55-75, 1	7113	0	0	2475	304	46	30	-15.0%	Dom.
BM	FIT-DNA 55-80, 1	7674	0	0	2558	307	47	31	-14.5%	Dom.
BM	FIT-DNA 55-85, 1	8029	0	0	2605	308	47	31	-14.5%	Dom.
BM	FIT-DNA 50-75, 1	9026	0	0	2962	346	50	32	-5.6%	Dom.
BM	FIT-DNA 50-80, 1	9589	0	0	3043	350	51	33	-5.1%	Dom.
BM	FIT-DNA 50-85, 1	9937	0	0	3089	351	51	33	-5.1%	Dom.

table continues

MISCAN - Scenario 2: Increased CRC risk										
BM	FIT-DNA 45-75, 1	11132	0	0	3406	374	53	34	-0.4%	59.4*
BM	FIT-DNA 45-80, 1	11687	0	0	3486	377	54	34	0%	53.7
BM	FIT-DNA 45-85, 1	12034	0	0	3532	378	54	34	0%	61.3
BM	HSgFOBT 55-75, 3	4269	0	0	1229	206	21	21	-14.0%	Dom.
BM	HSgFOBT 55-80, 3	4817	0	0	1318	216	22	23	-14.2%	Dom.
BM	HSgFOBT 55-85, 3	5131	0	0	1362	219	21	23	-15.2%	Dom.
BM	HSgFOBT 50-75, 3	5532	0	0	1517	241	25	23	-13.4%	Dom.
BM	HSgFOBT 50-80, 3	6024	0	0	1593	249	25	25	-13.1%	Dom.
BM	HSgFOBT 50-85, 3	6185	0	0	1615	251	25	25	-13.3%	Dom.
BM	HSgFOBT 45-75, 3	6836	0	0	1775	267	28	25	-13.2%	Dom.
BM	HSgFOBT 45-80, 3	7087	0	0	1812	271	28	26	-13.0%	Dom.
BM	HSgFOBT 45-85, 3	7424	0	0	1858	274	28	26	-12.8%	Dom.
BM	HSgFOBT 55-75, 2	5861	0	0	1565	241	28	24	-14.9%	Dom.
BM	HSgFOBT 55-80, 2	6302	0	0	1627	247	28	26	-15.1%	Dom.
BM	HSgFOBT 55-85, 2	6712	0	0	1678	250	28	26	-15.9%	Dom.
BM	HSgFOBT 50-75, 2	7271	0	0	1884	278	32	26	-12.2%	Dom.
BM	HSgFOBT 50-80, 2	7913	0	0	1971	286	33	28	-11.4%	Dom.
BM	HSgFOBT 50-85, 2	8179	0	0	2003	288	33	28	-11.5%	Dom.
BM	HSgFOBT 45-75, 2	9028	0	0	2209	307	35	28	-9.8%	Dom.
BM	HSgFOBT 45-80, 2	9447	0	0	2266	312	36	29	-9.4%	Dom.
BM	HSgFOBT 45-85, 2	9842	0	0	2313	314	35	30	-9.6%	Dom.
BM	HSgFOBT 55-75, 1	8639	0	0	2107	281	38	28	-15.5%	Dom.
BM	HSgFOBT 55-80, 1	9362	0	0	2191	286	39	29	-15.5%	Dom.
BM	HSgFOBT 55-85, 1	9809	0	0	2238	287	39	29	-15.9%	Dom.
BM	HSgFOBT 50-75, 1	10890	0	0	2555	323	43	30	-10.2%	Dom.
BM	HSgFOBT 50-80, 1	11597	0	0	2635	328	43	31	-9.3%	Dom.
BM	HSgFOBT 50-85, 1	12034	0	0	2680	329	44	32	-9.1%	Dom.
BM	HSgFOBT 45-75, 1	13309	0	0	2965	351	46	32	-4.4%	Dom.
BM	HSgFOBT 45-80, 1	14005	0	0	3042	355	47	33	-3.6%	Dom.
BM	HSgFOBT 45-85, 1	14438	0	0	3086	357	47	33	-3.5%	Dom.
BM	SIG 55-75, 10	0	1701	0	2327	276	45	28	0%	8.1
BM	SIG 55-80, 10	0	1701	0	2327	276	45	28	0%	8.1
BM	SIG 55-85, 10	0	1812	0	2359	276	45	28	-1.1%	61.5*
BM	SIG 50-75, 10	0	1954	0	2607	308	48	29	0%	8.8
BM	SIG 50-80, 10	0	2142	0	2679	311	48	30	-0.7%	26.2*
BM	SIG 50-85, 10	0	2142	0	2679	311	48	30	-0.7%	26.2*
BM	SIG 45-75, 10	0	2479	0	2915	328	50	31	0%	15.0
BM	SIG 45-80, 10	0	2479	0	2915	328	50	31	0%	15.0
BM	SIG 45-85, 10	0	2588	0	2947	329	50	31	-0.5%	62.2*
BM	SIG 55-75, 5	0	2304	0	2554	292	48	30	-3.3%	Dom.
BM	SIG 55-80, 5	0	2451	0	2593	293	48	30	-4.4%	Dom.
BM	SIG 55-85, 5	0	2538	0	2612	293	48	30	-4.9%	Dom.
BM	SIG 50-75, 5	0	2895	0	2966	330	52	31	-0.6%	39.3*
BM	SIG 50-80, 5	0	3040	0	3005	331	52	32	-1.0%	38.3*
BM	SIG 50-85, 5	0	3127	0	3024	331	52	32	-1.3%	43.0*
BM	SIG 45-75, 5	0	3565	0	3309	354	54	32	0%	15.4
BM	SIG 45-80, 5	0	3710	0	3348	355	54	33	0%	38.4

table continues

MISCAN - Scenario 2: Increased CRC risk										
BM	SIG 45-85, 5	0	3797	0	3366	355	54	33	0%	97.7
BM	CTC 55-75, 10	0	0	1914	1513	238	33	24	0%	6.0
BM	CTC 55-80, 10	0	0	1914	1513	238	33	24	0%	6.0
BM	CTC 55-85, 10	0	0	2064	1560	241	33	25	-2.2%	Dom.
BM	CTC 50-75, 10	0	0	2186	1649	261	35	25	0%	6.1
BM	CTC 50-80, 10	0	0	2439	1734	269	36	26	-0.7%	10.0*
BM	CTC 50-85, 10	0	0	2439	1734	269	36	26	-0.7%	10.0*
BM	CTC 45-75, 10	0	0	2794	1856	281	37	26	-1.9%	Dom.
BM	CTC 45-80, 10	0	0	2794	1856	281	37	26	-1.9%	Dom.
BM	CTC 45-85, 10	0	0	2943	1901	283	37	27	-3.0%	Dom.
BM	CTC 55-75, 5	0	0	2770	1830	281	41	28	-0.7%	9.0*
BM	CTC 55-80, 5	0	0	2971	1881	284	42	29	-1.6%	9.8*
BM	CTC 55-85, 5	0	0	3089	1907	285	42	29	-2.5%	Dom.
BM	CTC 50-75, 5	0	0	3485	2113	318	45	30	0%	8.2
BM	CTC 50-80, 5	0	0	3684	2163	321	46	31	-0.4%	14.1*
BM	CTC 50-85, 5	0	0	3801	2189	322	46	31	-1.0%	17.7*
BM	CTC 45-75, 5	0	0	4258	2351	341	47	31	0%	10.1
BM	CTC 45-80, 5	0	0	4455	2400	345	48	32	0%	13.8
BM	CTC 45-85, 5	0	0	4572	2426	345	48	32	0%	36.6
SimCRC - Scenario 1: Stable CRC risk										
BM	No screening	0	0	0	59	0	0	0	-	-
BM	COL 55-75, 15	0	0	0	2753	195	42	21	0%	13.8
BM	COL 55-80, 15	0	0	0	2753	195	42	21	0%	13.8
BM	COL 55-85, 15	0	0	0	2930	196	42	21	-8.8%	Dom.
BM	COL 50-75, 15	0	0	0	3027	222	44	22	0%	10.2
BM	COL 50-80, 15	0	0	0	3351	226	46	22	-3.5%	Dom.
BM	COL 50-85, 15	0	0	0	3351	226	46	22	-3.5%	Dom.
BM	COL 45-75, 15	0	0	0	3748	248	48	23	0%	27.7
BM	COL 45-80, 15	0	0	0	3748	248	48	23	0%	27.7
BM	COL 45-85, 15	0	0	0	3748	248	48	23	0%	27.7
BM	COL 55-75, 10	0	0	0	3302	204	44	22	-12.3%	Dom.
BM	COL 55-80, 10	0	0	0	3302	204	44	22	-12.3%	Dom.
BM	COL 55-85, 10	0	0	0	3448	204	44	22	-14.1%	Dom.
BM	COL 50-75, 10	0	0	0	3745	235	48	23	-5.4%	Dom.
BM	COL 50-80, 10	0	0	0	4011	236	48	23	-6.5%	Dom.
BM	COL 50-85, 10	0	0	0	4011	236	48	23	-6.5%	Dom.
BM	COL 45-75, 10	0	0	0	4519	262	51	24	0%	57.9
BM	COL 45-80, 10	0	0	0	4519	262	51	24	0%	57.9
BM	COL 45-85, 10	0	0	0	4665	262	51	25	-0.1%	434.1*
BM	COL 55-75, 5	0	0	0	4404	210	46	22	-19.1%	Dom.
BM	COL 55-80, 5	0	0	0	4616	210	46	22	-19.7%	Dom.
BM	COL 55-85, 5	0	0	0	4735	211	46	22	-19.9%	Dom.
BM	COL 50-75, 5	0	0	0	5417	244	50	24	-8.2%	Dom.
BM	COL 50-80, 5	0	0	0	5629	245	51	24	-8.4%	Dom.
BM	COL 50-85, 5	0	0	0	5748	245	51	24	-8.5%	Dom.
BM	COL 45-75, 5	0	0	0	6456	271	53	25	0%	205.1
BM	COL 45-80, 5	0	0	0	6668	272	53	25	0%	484.2

table continues

SimCRC - Scenario 1: Stable CRC risk										
BM	COL 45-85, 5	0	0	0	6787	272	53	25	0%	1369.7
BM	FIT 55-75, 3	4788	0	0	782	142	23	15	0%	5.1
BM	FIT 55-80, 3	5489	0	0	867	150	24	16	-4.7%	Dom.
BM	FIT 55-85, 3	5865	0	0	910	152	24	17	-8.0%	Dom.
BM	FIT 50-75, 3	6294	0	0	946	172	27	17	0%	5.5
BM	FIT 50-80, 3	6881	0	0	1017	178	27	18	-3.1%	Dom.
BM	FIT 50-85, 3	7152	0	0	1046	179	27	18	-4.8%	Dom.
BM	FIT 45-75, 3	7763	0	0	1085	195	29	18	0%	6.1
BM	FIT 45-80, 3	8183	0	0	1131	199	30	19	0.0%	11.5*
BM	FIT 45-85, 3	8623	0	0	1181	201	30	19	-0.9%	14.5*
BM	FIT 55-75, 2	6797	0	0	1012	165	28	17	-9.8%	Dom.
BM	FIT 55-80, 2	7403	0	0	1076	169	29	18	-12.4%	Dom.
BM	FIT 55-85, 2	7981	0	0	1133	171	29	19	-13.7%	Dom.
BM	FIT 50-75, 2	8516	0	0	1180	194	32	19	-4.6%	Dom.
BM	FIT 50-80, 2	9417	0	0	1271	200	33	20	-5.3%	Dom.
BM	FIT 50-85, 2	9799	0	0	1308	201	33	20	-6.1%	Dom.
BM	FIT 45-75, 2	10684	0	0	1366	219	35	20	0%	11.4
BM	FIT 45-80, 2	11281	0	0	1426	223	36	21	0%	15.3
BM	FIT 45-85, 2	11852	0	0	1481	225	36	21	-0.3%	26.9*
BM	FIT 55-75, 1	11113	0	0	1407	188	35	20	-15.4%	Dom.
BM	FIT 55-80, 1	12291	0	0	1502	192	36	20	-15.6%	Dom.
BM	FIT 55-85, 1	13027	0	0	1558	193	37	21	-16.1%	Dom.
BM	FIT 50-75, 1	14301	0	0	1671	221	40	21	-6.2%	Dom.
BM	FIT 50-80, 1	15470	0	0	1764	224	41	22	-6.4%	Dom.
BM	FIT 50-85, 1	16201	0	0	1819	225	41	22	-7.0%	Dom.
BM	FIT 45-75, 1	17665	0	0	1914	247	43	23	0%	20.8
BM	FIT 45-80, 1	18830	0	0	2006	250	44	23	0%	26.2
BM	FIT 45-85, 1	19559	0	0	2060	251	44	24	0%	52.0
BM	FIT-DNA 55-75, 5	3198	0	0	1110	156	28	16	-20.8%	Dom.
BM	FIT-DNA 55-80, 5	3471	0	0	1176	159	28	17	-21.5%	Dom.
BM	FIT-DNA 55-85, 5	3633	0	0	1213	160	28	17	-22.3%	Dom.
BM	FIT-DNA 50-75, 5	3996	0	0	1305	183	32	18	-14.3%	Dom.
BM	FIT-DNA 50-80, 5	4267	0	0	1369	186	32	19	-15.1%	Dom.
BM	FIT-DNA 50-85, 5	4427	0	0	1405	187	32	19	-15.6%	Dom.
BM	FIT-DNA 45-75, 5	4828	0	0	1483	205	34	19	-9.2%	Dom.
BM	FIT-DNA 45-80, 5	5098	0	0	1546	208	35	20	-9.1%	Dom.
BM	FIT-DNA 45-85, 5	5258	0	0	1582	209	35	20	-9.4%	Dom.
BM	FIT-DNA 55-75, 3	4197	0	0	1346	176	33	18	-19.3%	Dom.
BM	FIT-DNA 55-80, 3	4731	0	0	1462	181	34	19	-19.6%	Dom.
BM	FIT-DNA 55-85, 3	4979	0	0	1513	182	34	20	-20.0%	Dom.
BM	FIT-DNA 50-75, 3	5457	0	0	1630	208	37	20	-10.7%	Dom.
BM	FIT-DNA 50-80, 3	5851	0	0	1714	212	38	21	-10.7%	Dom.
BM	FIT-DNA 50-85, 3	6117	0	0	1766	213	38	21	-11.2%	Dom.
BM	FIT-DNA 45-75, 3	6624	0	0	1860	232	40	21	-4.8%	Dom.
BM	FIT-DNA 45-80, 3	7045	0	0	1946	236	41	22	-4.8%	Dom.
BM	FIT-DNA 45-85, 3	7345	0	0	2007	237	41	23	-5.2%	Dom.
BM	FIT-DNA 55-75, 1	7867	0	0	2066	199	41	21	-20.8%	Dom.

table continues

SimCRC - Scenario 1: Stable CRC risk										
BM	FIT-DNA 55-80, 1	8588	0	0	2185	201	41	21	-20.3%	Dom.
BM	FIT-DNA 55-85, 1	9043	0	0	2256	202	42	21	-20.3%	Dom.
BM	FIT-DNA 50-75, 1	10012	0	0	2462	231	45	23	-9.3%	Dom.
BM	FIT-DNA 50-80, 1	10746	0	0	2582	234	46	23	-8.8%	Dom.
BM	FIT-DNA 50-85, 1	11196	0	0	2652	234	46	23	-8.8%	Dom.
BM	FIT-DNA 45-75, 1	12303	0	0	2843	258	48	24	-0.4%	121.1*
BM	FIT-DNA 45-80, 1	13030	0	0	2961	260	48	24	0%	104.5
BM	FIT-DNA 45-85, 1	13480	0	0	3031	260	49	24	0%	123.0
BM	HSgFOBT 55-75, 3	4530	0	0	998	142	24	15	-21.2%	Dom.
BM	HSgFOBT 55-80, 3	5161	0	0	1099	149	25	16	-23.7%	Dom.
BM	HSgFOBT 55-85, 3	5473	0	0	1147	151	25	17	-24.4%	Dom.
BM	HSgFOBT 50-75, 3	5907	0	0	1229	173	28	17	-16.7%	Dom.
BM	HSgFOBT 50-80, 3	6394	0	0	1307	178	29	18	-17.0%	Dom.
BM	HSgFOBT 50-85, 3	6680	0	0	1347	179	29	18	-17.7%	Dom.
BM	HSgFOBT 45-75, 3	7191	0	0	1423	195	31	18	-12.4%	Dom.
BM	HSgFOBT 45-80, 3	7636	0	0	1489	199	31	19	-11.8%	Dom.
BM	HSgFOBT 45-85, 3	8010	0	0	1545	202	32	19	-11.9%	Dom.
BM	HSgFOBT 55-75, 2	6176	0	0	1285	165	29	17	-22.3%	Dom.
BM	HSgFOBT 55-80, 2	6699	0	0	1361	169	30	18	-22.9%	Dom.
BM	HSgFOBT 55-85, 2	7195	0	0	1429	171	30	19	-23.6%	Dom.
BM	HSgFOBT 50-75, 2	7679	0	0	1523	195	33	19	-14.6%	Dom.
BM	HSgFOBT 50-80, 2	8455	0	0	1634	200	34	20	-14.3%	Dom.
BM	HSgFOBT 50-85, 2	8781	0	0	1678	201	34	20	-14.5%	Dom.
BM	HSgFOBT 45-75, 2	9567	0	0	1791	220	36	21	-8.5%	Dom.
BM	HSgFOBT 45-80, 2	10080	0	0	1863	224	37	21	-8.4%	Dom.
BM	HSgFOBT 45-85, 2	10568	0	0	1929	226	37	22	-8.8%	Dom.
BM	HSgFOBT 55-75, 1	9260	0	0	1756	188	36	20	-21.4%	Dom.
BM	HSgFOBT 55-80, 1	10168	0	0	1869	191	37	20	-21.9%	Dom.
BM	HSgFOBT 55-85, 1	10734	0	0	1936	192	37	21	-22.4%	Dom.
BM	HSgFOBT 50-75, 1	11759	0	0	2111	220	41	22	-12.4%	Dom.
BM	HSgFOBT 50-80, 1	12665	0	0	2222	224	42	22	-11.6%	Dom.
BM	HSgFOBT 50-85, 1	13228	0	0	2288	224	42	22	-11.4%	Dom.
BM	HSgFOBT 45-75, 1	14396	0	0	2448	247	44	23	-3.2%	Dom.
BM	HSgFOBT 45-80, 1	15296	0	0	2559	250	45	23	-2.4%	Dom.
BM	HSgFOBT 45-85, 1	15856	0	0	2624	251	45	24	-2.3%	Dom.
BM	SIG 55-75, 10	0	2031	0	1214	149	32	16	0%	7.8
BM	SIG 55-80, 10	0	2031	0	1214	149	32	16	0%	7.8
BM	SIG 55-85, 10	0	2210	0	1275	150	32	16	-9.7%	Dom.
BM	SIG 50-75, 10	0	2295	0	1311	171	34	17	0%	4.4
BM	SIG 50-80, 10	0	2593	0	1420	174	35	18	-4.4%	Dom.
BM	SIG 50-85, 10	0	2593	0	1420	174	35	18	-4.4%	Dom.
BM	SIG 45-75, 10	0	2938	0	1530	194	37	19	0%	9.4
BM	SIG 45-80, 10	0	2938	0	1530	194	37	19	0%	9.4
BM	SIG 45-85, 10	0	3116	0	1590	195	38	19	-1.2%	65.7*
BM	SIG 55-75, 5	0	2969	0	1500	164	36	18	-13.9%	Dom.
BM	SIG 55-80, 5	0	3208	0	1568	166	36	18	-15.5%	Dom.
BM	SIG 55-85, 5	0	3348	0	1605	166	37	18	-16.1%	Dom.

table continues

SimCRC - Scenario 1: Stable CRC risk										
BM	SIG 50-75, 5	0	3721	0	1744	193	40	19	-5.8%	Dom.
BM	SIG 50-80, 5	0	3957	0	1811	195	40	20	-6.7%	Dom.
BM	SIG 50-85, 5	0	4096	0	1848	195	40	20	-7.4%	Dom.
BM	SIG 45-75, 5	0	4511	0	1966	217	42	21	0%	18.8
BM	SIG 45-80, 5	0	4746	0	2032	219	43	21	0%	48.4
BM	SIG 45-85, 5	0	4885	0	2069	219	43	21	0%	104.6
BM	CTC 55-75, 10	0	0	2003	1345	179	38	19	0%	7.2
BM	CTC 55-80, 10	0	0	2003	1345	179	38	19	0%	7.2
BM	CTC 55-85, 10	0	0	2171	1414	180	38	19	-10.6%	Dom.
BM	CTC 50-75, 10	0	0	2271	1431	205	40	20	0%	3.5
BM	CTC 50-80, 10	0	0	2557	1554	208	41	21	-4.4%	Dom.
BM	CTC 50-85, 10	0	0	2557	1554	208	41	21	-4.4%	Dom.
BM	CTC 45-75, 10	0	0	2907	1655	229	43	22	0%	9.0
BM	CTC 45-80, 10	0	0	2907	1655	229	43	22	0%	9.0
BM	CTC 45-85, 10	0	0	3075	1723	230	43	22	-1.1%	68.2*
BM	CTC 55-75, 5	0	0	2917	1620	194	41	21	-14.0%	Dom.
BM	CTC 55-80, 5	0	0	3143	1691	195	42	21	-15.5%	Dom.
BM	CTC 55-85, 5	0	0	3274	1730	196	42	21	-16.1%	Dom.
BM	CTC 50-75, 5	0	0	3671	1857	226	45	22	-5.7%	Dom.
BM	CTC 50-80, 5	0	0	3896	1928	228	46	23	-6.6%	Dom.
BM	CTC 50-85, 5	0	0	4027	1966	228	46	23	-7.2%	Dom.
BM	CTC 45-75, 5	0	0	4469	2069	251	48	23	0%	19.0
BM	CTC 45-80, 5	0	0	4694	2139	252	48	24	0%	49.4
BM	CTC 45-85, 5	0	0	4824	2177	253	49	24	0%	119.8
SimCRC - Scenario 2: Increased CRC risk										
BM	No screening	0	0	0	92	0	0	0	-	-
BM	COL 55-75, 15	0	0	0	2870	314	63	32	0%	8.8
BM	COL 55-80, 15	0	0	0	2870	314	63	32	0%	8.8
BM	COL 55-85, 15	0	0	0	3033	316	63	32	-7.8%	Dom.
BM	COL 50-75, 15	0	0	0	3177	359	66	34	0%	6.8
BM	COL 50-80, 15	0	0	0	3479	365	69	35	-3.2%	Dom.
BM	COL 50-85, 15	0	0	0	3479	365	69	35	-3.2%	Dom.
BM	COL 45-75, 15	0	0	0	3898	402	72	36	0%	17.0
BM	COL 45-80, 15	0	0	0	3898	402	72	36	0%	17.0
BM	COL 45-85, 15	0	0	0	3898	402	72	36	0%	17.0
BM	COL 55-75, 10	0	0	0	3393	329	67	34	-11.5%	Dom.
BM	COL 55-80, 10	0	0	0	3393	329	67	34	-11.5%	Dom.
BM	COL 55-85, 10	0	0	0	3526	330	67	34	-13.2%	Dom.
BM	COL 50-75, 10	0	0	0	3869	381	72	36	-4.9%	Dom.
BM	COL 50-80, 10	0	0	0	4114	383	73	37	-6.2%	Dom.
BM	COL 50-85, 10	0	0	0	4114	383	73	37	-6.2%	Dom.
BM	COL 45-75, 10	0	0	0	4648	426	77	38	0%	31.0
BM	COL 45-80, 10	0	0	0	4648	426	77	38	0%	31.0
BM	COL 45-85, 10	0	0	0	4781	426	77	39	-0.1%	206.8*
BM	COL 55-75, 5	0	0	0	4430	340	70	35	-18.8%	Dom.
BM	COL 55-80, 5	0	0	0	4623	341	70	35	-19.8%	Dom.
BM	COL 55-85, 5	0	0	0	4730	341	70	35	-20.0%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk										
BM	COL 50-75, 5	0	0	0	5450	398	76	38	-8.2%	Dom.
BM	COL 50-80, 5	0	0	0	5643	399	77	38	-8.4%	Dom.
BM	COL 50-85, 5	0	0	0	5749	399	77	38	-8.6%	Dom.
BM	COL 45-75, 5	0	0	0	6496	443	81	40	0%	106.4
BM	COL 45-80, 5	0	0	0	6689	444	81	40	0%	226.0
BM	COL 45-85, 5	0	0	0	6795	444	81	40	0%	618.3
BM	FIT 55-75, 3	4642	0	0	947	234	36	23	0%	3.7
BM	FIT 55-80, 3	5288	0	0	1035	245	38	25	-4.3%	Dom.
BM	FIT 55-85, 3	5627	0	0	1078	248	38	26	-7.3%	Dom.
BM	FIT 50-75, 3	6107	0	0	1139	283	42	27	0%	3.9
BM	FIT 50-80, 3	6645	0	0	1211	292	44	28	-2.9%	Dom.
BM	FIT 50-85, 3	6891	0	0	1241	294	44	29	-4.4%	Dom.
BM	FIT 45-75, 3	7548	0	0	1301	321	47	29	0%	4.2
BM	FIT 45-80, 3	7934	0	0	1349	327	48	30	-0.1%	8.0*
BM	FIT 45-85, 3	8331	0	0	1398	331	48	31	-1.0%	10.3*
BM	FIT 55-75, 2	6534	0	0	1195	269	44	27	-9.2%	Dom.
BM	FIT 55-80, 2	7086	0	0	1260	275	45	28	-11.6%	Dom.
BM	FIT 55-85, 2	7604	0	0	1315	278	46	29	-13.9%	Dom.
BM	FIT 50-75, 2	8220	0	0	1390	317	50	30	-4.9%	Dom.
BM	FIT 50-80, 2	9040	0	0	1483	326	52	31	-5.7%	Dom.
BM	FIT 50-85, 2	9381	0	0	1519	328	52	32	-6.5%	Dom.
BM	FIT 45-75, 2	10333	0	0	1602	361	55	32	0%	7.6
BM	FIT 45-80, 2	10876	0	0	1663	367	56	33	0%	10.5
BM	FIT 45-85, 2	11388	0	0	1717	370	56	34	-0.3%	19.6*
BM	FIT 55-75, 1	10581	0	0	1601	305	54	31	-15.6%	Dom.
BM	FIT 55-80, 1	11643	0	0	1694	310	56	32	-16.0%	Dom.
BM	FIT 55-85, 1	12296	0	0	1747	312	56	32	-16.5%	Dom.
BM	FIT 50-75, 1	13674	0	0	1895	359	61	34	-6.5%	Dom.
BM	FIT 50-80, 1	14728	0	0	1986	365	63	35	-6.8%	Dom.
BM	FIT 50-85, 1	15379	0	0	2038	366	63	35	-7.3%	Dom.
BM	FIT 45-75, 1	16963	0	0	2163	404	66	36	0%	13.5
BM	FIT 45-80, 1	18013	0	0	2253	409	67	37	0%	17.3
BM	FIT 45-85, 1	18661	0	0	2305	411	68	37	0%	35.2
BM	FIT-DNA 55-75, 5	3096	0	0	1280	255	44	26	-19.3%	Dom.
BM	FIT-DNA 55-80, 5	3347	0	0	1345	260	45	27	-20.6%	Dom.
BM	FIT-DNA 55-85, 5	3492	0	0	1380	261	45	27	-21.3%	Dom.
BM	FIT-DNA 50-75, 5	3877	0	0	1501	301	50	29	-13.4%	Dom.
BM	FIT-DNA 50-80, 5	4125	0	0	1564	306	50	30	-14.2%	Dom.
BM	FIT-DNA 50-85, 5	4269	0	0	1599	307	50	30	-14.9%	Dom.
BM	FIT-DNA 45-75, 5	4695	0	0	1700	338	54	31	-8.5%	Dom.
BM	FIT-DNA 45-80, 5	4942	0	0	1762	343	54	32	-8.5%	Dom.
BM	FIT-DNA 45-85, 5	5085	0	0	1797	344	54	32	-8.8%	Dom.
BM	FIT-DNA 55-75, 3	4043	0	0	1526	286	51	29	-18.6%	Dom.
BM	FIT-DNA 55-80, 3	4529	0	0	1640	294	52	30	-19.5%	Dom.
BM	FIT-DNA 55-85, 3	4751	0	0	1688	295	53	31	-20.0%	Dom.
BM	FIT-DNA 50-75, 3	5263	0	0	1837	340	57	32	-10.6%	Dom.
BM	FIT-DNA 50-80, 3	5621	0	0	1920	345	59	33	-10.7%	Dom.

table continues

SimCRC - Scenario 2: Increased CRC risk										
BM	FIT-DNA 50-85, 3	5861	0	0	1969	346	59	33	-11.1%	Dom.
BM	FIT-DNA 45-75, 3	6410	0	0	2092	381	62	34	-4.4%	Dom.
BM	FIT-DNA 45-80, 3	6794	0	0	2176	387	63	35	-4.5%	Dom.
BM	FIT-DNA 45-85, 3	7063	0	0	2233	389	64	36	-4.8%	Dom.
BM	FIT-DNA 55-75, 1	7476	0	0	2233	322	62	33	-21.2%	Dom.
BM	FIT-DNA 55-80, 1	8126	0	0	2346	325	63	33	-20.9%	Dom.
BM	FIT-DNA 55-85, 1	8531	0	0	2411	326	63	34	-20.9%	Dom.
BM	FIT-DNA 50-75, 1	9559	0	0	2656	376	68	35	-9.6%	Dom.
BM	FIT-DNA 50-80, 1	10221	0	0	2770	380	69	36	-9.1%	Dom.
BM	FIT-DNA 50-85, 1	10622	0	0	2835	381	70	36	-9.1%	Dom.
BM	FIT-DNA 45-75, 1	11800	0	0	3059	420	73	37	-0.4%	77.9*
BM	FIT-DNA 45-80, 1	12456	0	0	3172	424	74	38	0%	65.7
BM	FIT-DNA 45-85, 1	12857	0	0	3236	425	74	38	0%	71.5
BM	HSgFOBT 55-75, 3	4401	0	0	1146	233	38	24	-18.1%	Dom.
BM	HSgFOBT 55-80, 3	4984	0	0	1248	244	39	25	-21.0%	Dom.
BM	HSgFOBT 55-85, 3	5267	0	0	1295	247	40	26	-23.0%	Dom.
BM	HSgFOBT 50-75, 3	5743	0	0	1402	284	44	27	-15.3%	Dom.
BM	HSgFOBT 50-80, 3	6191	0	0	1480	291	45	28	-15.7%	Dom.
BM	HSgFOBT 50-85, 3	6450	0	0	1520	293	45	29	-16.4%	Dom.
BM	HSgFOBT 45-75, 3	7007	0	0	1618	321	48	29	-11.4%	Dom.
BM	HSgFOBT 45-80, 3	7417	0	0	1683	328	50	30	-11.1%	Dom.
BM	HSgFOBT 45-85, 3	7756	0	0	1738	331	50	31	-11.2%	Dom.
BM	HSgFOBT 55-75, 2	5958	0	0	1445	268	45	27	-21.1%	Dom.
BM	HSgFOBT 55-80, 2	6436	0	0	1519	274	47	28	-21.7%	Dom.
BM	HSgFOBT 55-85, 2	6882	0	0	1584	277	47	29	-22.9%	Dom.
BM	HSgFOBT 50-75, 2	7434	0	0	1709	317	52	30	-14.3%	Dom.
BM	HSgFOBT 50-80, 2	8143	0	0	1817	325	53	31	-14.1%	Dom.
BM	HSgFOBT 50-85, 2	8437	0	0	1859	327	53	32	-14.3%	Dom.
BM	HSgFOBT 45-75, 2	9278	0	0	1999	362	57	32	-7.7%	Dom.
BM	HSgFOBT 45-80, 2	9747	0	0	2070	367	58	33	-7.6%	Dom.
BM	HSgFOBT 45-85, 2	10187	0	0	2133	369	58	34	-8.1%	Dom.
BM	HSgFOBT 55-75, 1	8863	0	0	1919	304	55	31	-21.2%	Dom.
BM	HSgFOBT 55-80, 1	9686	0	0	2027	309	57	32	-21.6%	Dom.
BM	HSgFOBT 55-85, 1	10192	0	0	2089	310	57	32	-22.1%	Dom.
BM	HSgFOBT 50-75, 1	11295	0	0	2301	359	62	34	-12.7%	Dom.
BM	HSgFOBT 50-80, 1	12116	0	0	2408	363	63	35	-11.9%	Dom.
BM	HSgFOBT 50-85, 1	12619	0	0	2469	365	64	35	-11.8%	Dom.
BM	HSgFOBT 45-75, 1	13879	0	0	2660	403	67	36	-3.2%	Dom.
BM	HSgFOBT 45-80, 1	14695	0	0	2766	407	68	37	-2.5%	Dom.
BM	HSgFOBT 45-85, 1	15197	0	0	2826	409	69	37	-2.4%	Dom.
BM	SIG 55-75, 10	0	1955	0	1478	276	55	28	0%	5.0
BM	SIG 55-80, 10	0	1955	0	1478	276	55	28	0%	5.0
BM	SIG 55-85, 10	0	2113	0	1538	277	55	29	-8.1%	Dom.
BM	SIG 50-75, 10	0	2224	0	1608	317	58	30	0%	3.2
BM	SIG 50-80, 10	0	2493	0	1718	322	60	31	-4.0%	Dom.
BM	SIG 50-85, 10	0	2493	0	1718	322	60	31	-4.0%	Dom.
BM	SIG 45-75, 10	0	2842	0	1855	358	63	33	0%	5.9

table continues

SimCRC - Scenario 2: Increased CRC risk										
BM	SIG 45-80, 10	0	2842	0	1855	358	63	33	0%	5.9
BM	SIG 45-85, 10	0	2999	0	1914	360	64	33	-0.7%	42.5*
BM	SIG 55-75, 5	0	2822	0	1751	295	59	30	-13.3%	Dom.
BM	SIG 55-80, 5	0	3035	0	1817	298	60	31	-15.5%	Dom.
BM	SIG 55-85, 5	0	3158	0	1852	298	61	31	-16.7%	Dom.
BM	SIG 50-75, 5	0	3550	0	2028	346	65	33	-6.6%	Dom.
BM	SIG 50-80, 5	0	3761	0	2092	348	66	34	-7.2%	Dom.
BM	SIG 50-85, 5	0	3883	0	2127	349	67	34	-7.6%	Dom.
BM	SIG 45-75, 5	0	4321	0	2277	388	70	35	0%	14.4
BM	SIG 45-80, 5	0	4531	0	2341	390	71	35	0%	30.7
BM	SIG 45-85, 5	0	4653	0	2376	390	71	36	0%	73.0
BM	CTC 55-75, 10	0	0	1937	1563	294	58	30	0%	5.0
BM	CTC 55-80, 10	0	0	1937	1563	294	58	30	0%	5.0
BM	CTC 55-85, 10	0	0	2088	1629	295	58	31	-9.2%	Dom.
BM	CTC 50-75, 10	0	0	2209	1682	336	62	32	0%	2.8
BM	CTC 50-80, 10	0	0	2469	1803	342	64	33	-4.0%	Dom.
BM	CTC 50-85, 10	0	0	2469	1803	342	64	33	-4.0%	Dom.
BM	CTC 45-75, 10	0	0	2823	1930	378	67	34	0%	6.0
BM	CTC 45-80, 10	0	0	2823	1930	378	67	34	0%	6.0
BM	CTC 45-85, 10	0	0	2973	1995	379	67	35	-1.0%	45.6*
BM	CTC 55-75, 5	0	0	2787	1839	316	63	32	-12.8%	Dom.
BM	CTC 55-80, 5	0	0	2990	1907	319	64	33	-14.8%	Dom.
BM	CTC 55-85, 5	0	0	3106	1943	319	64	33	-15.8%	Dom.
BM	CTC 50-75, 5	0	0	3518	2110	370	69	35	-5.9%	Dom.
BM	CTC 50-80, 5	0	0	3720	2177	372	70	36	-6.7%	Dom.
BM	CTC 50-85, 5	0	0	3836	2213	372	70	36	-7.2%	Dom.
BM	CTC 45-75, 5	0	0	4298	2348	412	73	37	0%	12.1
BM	CTC 45-80, 5	0	0	4500	2415	415	74	38	0%	31.0
BM	CTC 45-85, 5	0	0	4615	2451	415	75	38	0%	70.7

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

[a] Both models evaluated two scenarios for CRC risk: one in which age-specific risks were assumed to have remained stable since the early screening period in the U.S. (1975-1979 for SimCRC; 1990-1994 for MISCAN), and one in which risks were assumed to have increased proportional to observed trends among adults under age 40 years. Strategies for each model and scenario are ordered successively by screening modality, interval (↓), end age (↑), and start age (↓).

[b] Total number of colonoscopies performed per 1000 40-year-olds, including diagnostic colonoscopies and potential surveillance colonoscopies after adenoma removal. The number of screening-related complications ranged from 4.2 to 18.6 per 1000 40-year-olds across models, scenarios, and strategies.

[c] Including deaths from complications of screening.

[d] The difference in LYG compared to (combinations of) adjacent strategies on the efficient frontier. Near-efficient strategies have a loss in LYG of less than 2% before rounding. For the least intensive screening strategy evaluated within each class of screening modality, the difference was zero by definition.
[e] Efficiency ratio = incremental number of colonoscopies/LYG with respect to the next less effective strategy on the efficient frontier, a burden-to-benefit ratio. Only calculated for efficient and near-efficient strategies (marked with an asterisk*), i.e. strategies within 2% from the efficient frontier among all evaluated strategies within a class of screening modalities (colonoscopy, stool-based, sigmoidoscopy, and CTC).

Supplementary Table A3.7: Outcomes for CRC screening strategies with screening between similar ages as the selected benchmark colonoscopy strategy, under two scenarios for CRC risk, by model and demographic subgroup [a]

		Outcomes per 1000 40-year olds											
Subgroup	Modality, and age to begin- end screening, interval, y	Stool tests	SIGs	CTCs	COLs	LYG	CRC cases averted	CRC deaths averted [b]	Relative distance from efficient frontier [c]	ER [d]	ER < bench-mark [e]	LYG > 90% of bench-mark	Model recommen-dable strategy [f]
MISCAN - Scenario 1: Stable CRC risk													
WF	**Colonoscopy**												
	COL 50-75, 10	0	0	0.0	4067	192	36	17	0%	43.2	-	-	Yes
	Stool tests												
	FIT 50-75, 3	7173	0	0	880	134	15	11	0%	6.1	Yes	No	
	FIT 50-75, 2	9907	0	0	1115	154	19	13	0%	11.9	Yes	No	
	HSgFOBT 50-75, 3	6637	0	0	1199	134	17	11	-15.1%	Dom.	-	No	
	FIT-DNA 50-75, 5	4652	0	0	1286	147	20	13	-9.3%	Dom.	-	No	
	HSgFOBT 50-75, 2	8900	0	0	1530	155	21	13	-11.5%	Dom.	-	No	
	FIT-DNA 50-75, 3	6138	0	0	1581	165	24	14	-6.9%	Dom.	-	No	
	FIT 50-75, 1	16959	0	0	1620	179	26	15	0%	19.8	Yes	Yes	Yes
	HSgFOBT 50-75, 1	13803	0	0	2179	180	28	15	-3.7%	Dom.	-	Yes	
	FIT-DNA 50-75, 1	11871	0	0	2548	191	33	16	0%	76.4	No	Yes	
	Sigmoidoscopy												
	SIG 50-75, 10	0	2537	0	1534	137	26	12	0%	10.8	Yes	No	
	SIG 50-75, 5	0	4220	0	1978	158	30	14	0%	21.1	Yes	No	
	CT colonography												
	CTC 50-75, 10	0	0	2614	1141	138	21	12	0%	7.8	Yes	No	
	CTC 50-75, 5	0	0	4466	1592	174	29	15	0%	12.6	Yes	Yes	Yes
BF	**Colonoscopy**												
	COL 45-75, 10	0	0	0	4894	285	40	23	0%	43.4	-	-	Yes
	Stool tests												
	FIT 45-75, 3	8297	0	0	1136	205	19	16	0%	5.2	Yes	No	
	FIT 45-75, 2	11477	0	0	1422	233	23	19	0%	10.2	Yes	No	
	HSgFOBT 45-75, 3	7649	0	0	1502	205	20	17	-14.0%	Dom.	-	No	
	FIT-DNA 45-75, 5	5168	0	0	1578	221	23	18	-8.8%	Dom.	-	No	
	HSgFOBT 45-75, 2	10252	0	0	1899	234	25	19	-10.4%	Dom.	-	No	
	FIT-DNA 45-75, 3	7012	0	0	1960	250	28	20	-5.8%	Dom.	-	No	
	FIT 45-75, 1	19041	0	0	1988	267	30	21	0%	16.9	Yes	Yes	Yes
	HSgFOBT 45-75, 1	15400	0	0	2611	266	32	21	-3.6%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	13174	0	0	3023	283	37	23	0%	63.7	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	3060	0	1905	208	30	18	0%	8.9	Yes	No	
	SIG 45-75, 5	0	4650	0	2333	235	33	20	0%	15.9	Yes	No	
	CT colonography												
	CTC 45-75, 10	0	0	3179	1490	215	26	18	0%	6.6	Yes	No	
	CTC 45-75, 5	0	0	4935	1937	260	33	21	0%	10.1	Yes	Yes	Yes
WM	**Colonoscopy**												
	COL 50-75, 10	0	0	0.0	4007	227	43	21	0%	38.6	-	-	Yes
	Stool tests												
	FIT 50-75, 3	6689	0	0	947	162	18	15	0%	5.4	Yes	No	
	FIT 50-75, 2	9204	0	0	1188	185	23	17	0%	10.5	Yes	No	
	HSgFOBT 50-75, 3	6201	0	0	1248	161	20	15	-14.3%	Dom.	-	No	
	FIT-DNA 50-75, 5	4308	0	0	1340	176	24	17	-9.1%	Dom.	-	No	
	HSgFOBT 50-75, 2	8279	0	0	1580	185	25	17	-10.8%	Dom.	-	No	
	FIT-DNA 50-75, 3	5701	0	0	1650	198	29	18	-6.5%	Dom.	-	No	

table continues

MISCAN - Scenario 1: Stable CRC risk													
	FIT 50-75, 1	15619	0	0	1693	214	32	20	0%	17.0	Yes	Yes	Yes
	HSgFOBT 50-75, 1	12737	0	0	2221	214	34	20	-3.5%	Dom.	-	Yes	
	FIT-DNA 50-75, 1	10885	0	0	2589	227	40	21	0%	69.7	No	Yes	
	Sigmoidoscopy												
	SIG 50-75, 10	0	2328	0	1822	183	35	18	0%	9.5	Yes	No	
	SIG 50-75, 5	0	3737	0	2231	203	39	20	0%	20.6	Yes	No	
	CT colonography												
	CTC 50-75, 10	0	0	2456	1223	166	26	15	0%	6.9	Yes	No	
	CTC 50-75, 5	0	0	4110	1667	207	35	19	0%	10.8	Yes	Yes	Yes
BM	**Colonoscopy**												
	COL 45-75, 10	0	0	0.0	4561	266	40	24	0%	42.9	-	-	Yes
	Stool tests												
	FIT 45-75, 3	7675	0	0	1102	194	18	18	0%	5.4	Yes	No	
	FIT 45-75, 2	10595	0	0	1375	220	23	20	0%	10.5	Yes	No	
	HSgFOBT 45-75, 3	7092	0	0	1435	193	19	18	-13.6%	Dom.	-	No	
	FIT-DNA 45-75, 5	4769	0	0	1507	207	22	19	-8.9%	Dom.	-	No	
	HSgFOBT 45-75, 2	9484	0	0	1811	220	24	20	-10.2%	Dom.	-	No	
	FIT-DNA 45-75, 3	6482	0	0	1879	234	28	21	-6.0%	Dom.	-	No	
	FIT 45-75, 1	17548	0	0	1912	251	30	22	0%	17.0	Yes	Yes	Yes
	HSgFOBT 45-75, 1	14234	0	0	2485	251	31	22	-3.5%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	12136	0	0	2879	266	36	23	0%	67.4	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	2778	0	1946	207	31	19	0%	9.1	Yes	No	
	SIG 45-75, 5	0	4188	0	2343	230	34	21	0%	17.1	Yes	No	
	CT colonography												
	CTC 45-75, 10	0	0	2925	1434	201	26	19	0%	6.8	Yes	No	
	CTC 45-75, 5	0	0	4538	1860	243	32	22	0%	10.0	Yes	Yes	Yes
MISCAN - Scenario 2: Increased CRC risk													
WF	**Colonoscopy**												
	COL 45-75, 10	0	0	0.0	5823	398	74	35	0%	39.4	-	-	Yes
	Stool tests												
	FIT 45-75, 3	8367	0	0	1583	281	32	24	0%	5.2	Yes	No	
	FIT 45-75, 2	11456	0	0	1964	322	41	27	0%	9.3	Yes	No	
	HSgFOBT 45-75, 3	7695	0	0	2019	283	36	24	-13.2%	Dom.	-	No	
	FIT-DNA 45-75, 5	5161	0	0	2145	303	41	26	-9.3%	Dom.	-	No	
	HSgFOBT 45-75, 2	10188	0	0	2526	325	45	28	-9.7%	Dom.	-	No	
	FIT-DNA 45-75, 3	6941	0	0	2633	345	50	29	-6.2%	Dom.	-	No	
	FIT 45-75, 1	18692	0	0	2690	371	54	31	0%	14.7	Yes	Yes	Yes
	HSgFOBT 45-75, 1	15026	0	0	3402	372	58	31	-3.4%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	12627	0	0	3902	395	66	33	0%	50.6	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	2795	0	3466	350	65	31	0%	9.6	Yes	No	
	SIG 45-75, 5	0	4005	0	3930	379	70	33	0%	16.1	Yes	Yes	Yes
	CT colonography												
	CTC 45-75, 10	0	0	3178	2074	291	46	26	0%	6.7	Yes	No	
	CTC 45-75, 5	0	0	4853	2652	358	58	31	0%	8.6	Yes	Yes	Yes
BF	**Colonoscopy**												
	COL 45-75, 10	0	0	0	5231	366	52	30	0%	33.2	-	-	Yes
	Stool tests												
	FIT 45-75, 3	8114	0	0	1363	261	24	21	0%	4.9	Yes	No	
	FIT 45-75, 2	11148	0	0	1691	297	30	24	0%	9.1	Yes	No	
	HSgFOBT 45-75, 3	7479	0	0	1745	261	26	21	-13.2%	Dom.	-	No	
	FIT-DNA 45-75, 5	5024	0	0	1853	282	30	23	-8.8%	Dom.	-	No	
	HSgFOBT 45-75, 2	9948	0	0	2185	300	32	24	-9.7%	Dom.	-	No	
	FIT-DNA 45-75, 3	6780	0	0	2278	319	37	26	-5.6%	Dom.	-	No	
	FIT 45-75, 1	18305	0	0	2319	341	39	27	0%	14.4	Yes	Yes	Yes
	HSgFOBT 45-75, 1	14780	0	0	2957	342	41	28	-3.5%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	12503	0	0	3403	363	48	29	0%	49.4	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	2812	0	2743	314	45	26	0%	8.5	Yes	No	

table continues

MISCAN - Scenario 2: Increased CRC risk													
	SIG 45-75, 5	0	4134	0	3161	340	48	28	0%	16.0	Yes	Yes	Yes
	CT colonography												
	CTC 45-75, 10	0	0	3090	1786	274	34	23	0%	6.2	Yes	No	
	CTC 45-75, 5	0	0	4748	2284	333	42	27	0%	8.5	Yes	Yes	Yes
WM	**Colonoscopy**												
	COL 45-75, 5	0	0	0.0	7182	554	102	51	0%	39.5	-	-	Yes
	Stool tests												
	FIT 45-75, 3	7643	0	0	1853	378	45	35	0%	4.5	Yes	No	
	FIT 45-75, 2	10343	0	0	2270	431	48	35	0%	7.8	Yes	No	
	HSgFOBT 45-75, 3	7045	0	0	2260	379	56	39	-11.9%	Dom.	-	No	
	FIT-DNA 45-75, 5	4674	0	0	2413	405	56	38	-8.7%	Dom.	-	No	
	HSgFOBT 45-75, 2	9211	0	0	2792	434	60	40	-8.6%	Dom.	-	No	
	FIT-DNA 45-75, 3	6240	0	0	2951	460	68	42	-5.8%	Dom.	-	No	
	FIT 45-75, 1	16592	0	0	3033	495	74	45	0%	12.0	Yes	No	
	HSgFOBT 45-75, 1	13359	0	0	3692	495	78	45	-2.9%	Dom.	-	No	
	FIT-DNA 45-75, 1	11006	0	0	4210	522	89	47	0%	43.8	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	2451	0	3825	457	85	44	0%	8.0	Yes	No	
	SIG 45-75, 5	0	3389	0	4302	494	91	46	0%	12.8	Yes	No	
	CT colonography												
	CTC 45-75, 10	0	0	2875	2385	386	62	37	0%	5.8	Yes	No	
	CTC 45-75, 5	0	0	4315	2999	474	78	44	0%	7.0	Yes	No	
BM	**Colonoscopy**												
	COL 45-75, 10	0	0	0.0	5010	375	57	34	0%	30.1	-	-	Yes
	Stool tests												
	FIT 45-75, 3	7395	0	0	1428	267	26	25	0%	5.0	Yes	No	
	FIT 45-75, 2	10094	0	0	1758	305	33	28	0%	8.6	Yes	No	
	HSgFOBT 45-75, 3	6836	0	0	1775	267	28	25	-12.9%	Dom.	-	No	
	FIT-DNA 45-75, 5	4555	0	0	1892	287	33	27	-8.8%	Dom.	-	No	
	HSgFOBT 45-75, 2	9028	0	0	2209	307	35	28	-9.4%	Dom.	-	No	
	FIT-DNA 45-75, 3	6134	0	0	2327	327	40	30	-5.9%	Dom.	-	No	
	FIT 45-75, 1	16433	0	0	2380	351	44	31	0%	13.6	Yes	Yes	Yes
	HSgFOBT 45-75, 1	13309	0	0	2965	351	46	32	-3.5%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	11132	0	0	3406	374	53	34	0%	45.2	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	2479	0	2915	328	50	31	0%	8.6	Yes	No	
	SIG 45-75, 5	0	3565	0	3309	354	54	32	0%	15.4	Yes	Yes	Yes
	CT colonography												
	CTC 45-75, 10	0	0	2794	1856	281	37	26	0%	6.3	Yes	No	
	CTC 45-75, 5	0	0	4258	2351	341	47	31	0%	8.2	Yes	Yes	Yes
SimCRC - Scenario 1: Stable CRC risk													
WF	**Colonoscopy**												
	COL 45-75, 15	0	0	0.0	4062	283	55	23	0%	31.6	-	-	Yes
	Stool tests												
	FIT 45-75, 3	8777	0	0	1046	232	31	18	0%	4.2	Yes	No	
	FIT 45-75, 2	12158	0	0	1333	257	38	20	0%	11.6	Yes	Yes	
	HSgFOBT 45-75, 3	8097	0	0	1434	233	33	18	-10.8%	Dom.	-	No	
	FIT-DNA 45-75, 5	5489	0	0	1486	243	37	19	-7.6%	Dom.	-	No	
	HSgFOBT 45-75, 2	10852	0	0	1824	258	40	20	-6.9%	Dom.	-	Yes	
	FIT-DNA 45-75, 3	7510	0	0	1869	269	44	21	-3.7%	Dom.	-	Yes	
	FIT 45-75, 1	20234	0	0	1911	281	47	22	0%	23.9	Yes	Yes	Yes
	HSgFOBT 45-75, 1	16396	0	0	2530	282	49	22	-1.9%	1034.5*	No	Yes	
	FIT-DNA 45-75, 1	14124	0	0	2946	291	53	23	0%	100.7	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	3359	0	1510	214	41	17	0%	6.7	Yes	No	
	SIG 45-75, 5	0	5179	0	1973	240	46	20	0%	17.8	Yes	No	
	CT colonography												
	CTC 45-75, 10	0	0	3336	1608	261	48	21	0%	5.9	Yes	Yes	
	CTC 45-75, 5	0	0	5163	2045	284	53	23	0%	19.0	Yes	Yes	Yes

table continues

SimCRC - Scenario 1: Stable CRC risk													
BF	**Colonoscopy**												
	COL 45-75, 15	0	0	0	3845	317	53	26	0%	24.4	-	-	Yes
	Stool tests												
	FIT 45-75, 3	8461	0	0	978	241	30	19	0%	3.8	Yes	No	
	FIT 45-75, 2	11722	0	0	1249	274	36	22	0%	8.1	Yes	No	
	HSgFOBT 45-75, 3	7815	0	0	1349	243	32	19	-13.5%	Dom.	-	No	
	FIT-DNA 45-75, 5	5288	0	0	1392	255	36	21	-10.1%	Dom.	-	No	
	HSgFOBT 45-75, 2	10472	0	0	1717	277	38	22	-9.4%	Dom.	-	No	
	FIT-DNA 45-75, 3	7257	0	0	1759	292	42	23	-5.4%	Dom.	-	Yes	
	FIT 45-75, 1	19536	0	0	1797	311	45	25	0%	14.9	Yes	Yes	Yes
	HSgFOBT 45-75, 1	15850	0	0	2391	312	47	25	-2.7%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	13664	0	0	2789	327	52	26	0%	63.3	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	3231	0	1412	230	38	19	0%	5.9	Yes	No	
	SIG 45-75, 5	0	4992	0	1852	261	44	22	0%	14.2	Yes	No	
	CT colonography												
	CTC 45-75, 10	0	0	3211	1499	288	46	24	0%	5.0	Yes	Yes	
	CTC 45-75, 5	0	0	4980	1916	317	52	26	0%	14.3	Yes	Yes	Yes
WM	**Colonoscopy**												
	COL 45-75, 15	0	0	0.0	4098	307	64	27	0%	28.0	-	-	Yes
	Stool tests												
	FIT 45-75, 3	8194	0	0	1213	256	40	22	0%	4.4	Yes	No	
	FIT 45-75, 2	11274	0	0	1522	283	47	24	0%	11.5	Yes	Yes	
	HSgFOBT 45-75, 3	7576	0	0	1578	256	42	22	-10.2%	Dom.	-	No	
	FIT-DNA 45-75, 5	5102	0	0	1652	268	46	23	-7.2%	Dom.	-	No	
	HSgFOBT 45-75, 2	10082	0	0	1979	283	49	25	-6.2%	Dom.	-	Yes	
	FIT-DNA 45-75, 3	6966	0	0	2056	296	53	26	-3.2%	Dom.	-	Yes	
	FIT 45-75, 1	18598	0	0	2119	308	57	27	0%	23.8	Yes	Yes	Yes
	HSgFOBT 45-75, 1	15127	0	0	2689	308	58	27	-1.8%	8070.7*	No	Yes	
	FIT-DNA 45-75, 1	12911	0	0	3114	318	64	28	0%	99.4	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	3112	0	1711	248	51	22	0%	6.6	Yes	No	
	SIG 45-75, 5	0	4760	0	2185	275	58	25	0%	17.7	Yes	No	
	CT colonography												
	CTC 45-75, 10	0	0	3077	1854	287	58	26	0%	6.2	Yes	Yes	
	CTC 45-75, 5	0	0	4713	2303	312	64	27	0%	18.2	Yes	Yes	Yes
BM	**Colonoscopy**												
	COL 45-75, 15	0	0	0.0	3748	248	48	23	0%	27.7	-	-	Yes
	Stool tests												
	FIT 45-75, 3	7763	0	0	1085	195	29	18	0%	5.3	Yes	No	
	FIT 45-75, 2	10684	0	0	1366	219	35	20	0%	11.4	Yes	No	
	HSgFOBT 45-75, 3	7191	0	0	1423	195	31	18	-12.1%	Dom.	-	No	
	FIT-DNA 45-75, 5	4828	0	0	1483	205	34	19	-8.9%	Dom.	-	No	
	HSgFOBT 45-75, 2	9567	0	0	1791	220	36	21	-8.4%	Dom.	-	No	
	FIT-DNA 45-75, 3	6624	0	0	1860	232	40	21	-4.8%	Dom.	-	Yes	
	FIT 45-75, 1	17665	0	0	1914	247	43	23	0%	20.0	Yes	Yes	Yes
	HSgFOBT 45-75, 1	14396	0	0	2448	247	44	23	-2.4%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	12303	0	0	2843	258	48	24	0%	84.2	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	2938	0	1530	194	37	19	0%	7.6	Yes	No	
	SIG 45-75, 5	0	4511	0	1966	217	42	21	0%	18.8	Yes	No	
	CT colonography												
	CTC 45-75, 10	0	0	2907	1655	229	43	22	0%	7.0	Yes	Yes	
	CTC 45-75, 5	0	0	4469	2069	251	48	23	0%	19.0	Yes	Yes	Yes
SimCRC - Scenario 2: Increased CRC risk													
WF	**Colonoscopy**												
	COL 45-75, 10	0	0	0.0	5138	473	99	41	0%	29.4	-	-	Yes
	Stool tests												
	FIT 45-75, 3	8732	0	0	1155	348	48	28	0%	3.0	Yes	No	
	FIT 45-75, 2	12090	0	0	1459	393	59	32	0%	6.8	Yes	No	

table continues

SimCRC - Scenario 2: Increased CRC risk													
	HSgFOBT 45-75, 3	8066	0	0	1539	350	52	28	-12.3%	Dom.	-	No	
	FIT-DNA 45-75, 5	5466	0	0	1607	368	59	30	-8.9%	Dom.	-	No	
	HSgFOBT 45-75, 2	10808	0	0	1945	396	63	32	-7.9%	Dom.	-	No	
	FIT-DNA 45-75, 3	7484	0	0	2003	414	70	34	-4.7%	Dom.	-	No	
	FIT 45-75, 1	20115	0	0	2064	439	76	36	0%	13.3	Yes	Yes	Yes
	HSgFOBT 45-75, 1	16337	0	0	2676	440	79	36	-2.4%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	14057	0	0	3120	460	88	38	0%	49.4	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	3257	0	2103	416	85	36	0%	4.8	Yes	No	
	SIG 45-75, 5	0	4937	0	2567	446	92	38	0%	15.5	Yes	Yes	Yes
	CT colonography												
	CTC 45-75, 10	0	0	3325	1780	405	79	35	0%	4.1	Yes	No	
	CTC 45-75, 5	0	0	5134	2248	449	89	38	0%	10.4	Yes	Yes	Yes
BF	**Colonoscopy**												
	COL 45-75, 10	0	0	0	4623	416	67	33	0%	34.8	-	-	Yes
	Stool tests												
	FIT 45-75, 3	8465	0	0	949	294	34	23	0%	3.0	Yes	No	
	FIT 45-75, 2	11747	0	0	1207	336	42	26	0%	6.1	Yes	No	
	HSgFOBT 45-75, 3	7822	0	0	1311	297	37	23	-14.0%	Dom.	-	No	
	FIT-DNA 45-75, 5	5301	0	0	1347	312	41	25	-10.6%	Dom.	-	No	
	HSgFOBT 45-75, 2	10500	0	0	1666	340	44	27	-10.1%	Dom.	-	No	
	FIT-DNA 45-75, 3	7288	0	0	1700	359	49	28	-5.8%	Dom.	-	No	
	FIT 45-75, 1	19641	0	0	1735	384	53	30	0%	10.9	Yes	Yes	Yes
	HSgFOBT 45-75, 1	15942	0	0	2322	386	55	30	-2.9%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	13792	0	0	2709	406	61	32	0%	45.6	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	3174	0	1657	351	56	29	0%	4.5	Yes	No	
	SIG 45-75, 5	0	4862	0	2068	379	61	31	0%	14.6	Yes	Yes	Yes
	CT colonography												
	CTC 45-75, 10	0	0	3228	1425	354	54	28	0%	3.8	Yes	No	
	CTC 45-75, 5	0	0	5024	1829	394	62	31	0%	10.0	Yes	Yes	Yes
WM	**Colonoscopy**												
	COL 45-75, 10	0	0	0.0	5513	650	137	59	0%	23.5	-	-	Yes
	Stool tests												
	FIT 45-75, 3	7768	0	0	1784	522	84	46	0%	3.1	Yes	No	
	HSgFOBT 45-75, 3	7199	0	0	2136	521	87	46	-8.7%	Dom.	-	No	
	FIT 45-75, 2	10548	0	0	2172	575	99	51	0%	7.3	Yes	No	
	FIT-DNA 45-75, 5	4814	0	0	2272	544	96	49	-6.5%	Dom.	-	No	
	HSgFOBT 45-75, 2	9457	0	0	2609	575	102	51	-5.1%	Dom.	-	No	
	FIT-DNA 45-75, 3	6500	0	0	2753	599	111	53	-2.9%	Dom.	-	Yes	
	FIT 45-75, 1	17055	0	0	2867	625	118	56	0%	13.9	Yes	Yes	Yes
	HSgFOBT 45-75, 1	13946	0	0	3397	624	120	56	-1.6%	Dom.	-	Yes	
	FIT-DNA 45-75, 1	11686	0	0	3874	644	129	58	0%	54.2	No	Yes	
	Sigmoidoscopy												
	SIG 45-75, 10	0	2903	0	2557	554	114	51	0%	4.3	Yes	No	
	SIG 45-75, 5	0	4319	0	3091	599	125	55	0%	11.9	Yes	Yes	Yes
	CT colonography												
	CTC 45-75, 10	0	0	2882	2648	583	118	54	0%	4.3	Yes	No	
	CTC 45-75, 5	0	0	4299	3164	632	130	57	0%	10.6	Yes	Yes	Yes
BM	**Colonoscopy**												
	COL 45-75, 10	0	0	0.0	4648	426	77	38	0%	31.0	-	-	Yes
	Stool tests												
	FIT 45-75, 3	7548	0	0	1301	321	47	29	0%	3.8	Yes	No	
	FIT 45-75, 2	10333	0	0	1602	361	55	32	0%	7.6	Yes	No	
	HSgFOBT 45-75, 3	7007	0	0	1618	321	48	29	-11.3%	Dom.	-	No	
	FIT-DNA 45-75, 5	4695	0	0	1700	338	54	31	-8.2%	Dom.	-	No	
	HSgFOBT 45-75, 2	9278	0	0	1999	362	57	32	-7.6%	Dom.	-	No	
	FIT-DNA 45-75, 3	6410	0	0	2092	381	62	34	-4.4%	Dom.	-	No	
	FIT 45-75, 1	16963	0	0	2163	404	66	36	0%	13.1	Yes	Yes	Yes
	HSgFOBT 45-75, 1	13879	0	0	2660	403	67	36	-2.5%	Dom.	-	Yes	

table continues

SimCRC - Scenario 2: Increased CRC risk												
FIT-DNA 45-75, 1	11800	0	0	3059	420	73	37	0%	54.9	No	Yes	
Sigmoidoscopy												
SIG 45-75, 10	0	2842	0	1855	358	63	33	0%	4.9	Yes	No	
SIG 45-75, 5	0	4321	0	2277	388	70	35	0%	14.4	Yes	Yes	Yes
CT colonography												
CTC 45-75, 10	0	0	2823	1930	378	67	34	0%	4.9	Yes	No	
CTC 45-75, 5	0	0	4298	2348	412	73	37	0%	12.1	Yes	Yes	Yes

BF - black female; BM - black male; COL - colonoscopy; CRC - colorectal cancer; CTC - computed tomographic colonography; Dom. - dominated strategy; ER - efficiency ratio (incremental burden-to-benefit ratio); FIT - fecal immunochemical test; FIT-DNA - multitarget stool DNA test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; LYG - life-years gained; SIG - flexible sigmoidoscopy; WF - white female; WM - white male.

[a] Both models evaluated two scenarios for CRC risk: one in which age-specific risks were assumed to have remained stable since the early screening period in the U.S. (1975-1979 for SimCRC; 1990-1994 for MISCAN), and one in which age-specific risks were assumed to have increased proportional to observed trends among adults under age 40 years.
[b] Including deaths from complications of screening.
[c] The difference in LYG compared to a combination of efficient strategies with similar number of required colonoscopies; measure of inefficiency. Values for strategies other than colonoscopy screening differ from those in Supplementary Tables A3.3-A3.6, as efficiency was reassessed including only strategies with similar start and stop ages as the benchmark (model-recommendable) colonoscopy strategy.
[d] Efficiency ratio = incremental number of colononoscopies/LYG compared to the next less effective strategy on the efficient frontier; an incremental burden-to-benefit ratio. Values for strategies other than colonoscopy screening differ from those in Supplementary Tables A3.3-A3.6, as efficiency was reassessed including only efficient and near-efficient* options among the strategies with similar start and stop ages as the benchmark (model-recommendable) colonoscopy strategy.
[e] Efficient or near-efficient strategy with an efficiency ratio lower than the benchmark (model-recommendable) colonoscopy strategy.
[f] Efficient or near-efficient strategy with a lower burden-to-benefit ratio and at least 90% of the LYG compared to the benchmark (model-recommendable) colonoscopy strategy.

Supplementary Table A3.8: Model-recommendable strategies under two scenarios of CRC risk, with best-case test performance assumptions [a]

Model	Test class	White females	Black females	White males	Black Males
Scenario 1: Stable CRC risk [b]					
MISCAN	COL	50-75, 10	45-75, 10	50-75, 10	45-75, 10
	Stool	FIT 50-75, 1	FIT 45-75, 1	FIT 50-75, 1	FIT 45-75, 1
	SIG	-	-	**50-75, 5**	-
	CTC	50-75, 5	45-75, 5	50-75, 5	45-75, 5
SimCRC	COL	45-75, 15	45-75, 15	45-75, 15	45-75, 15
	Stool	FIT 45-75, 1	FIT 45-75, 1	**FIT 45-75, 2**	FIT 45-75, 1
	SIG	-	-	**45-75, 5**	-
	CTC	45-75, 5	45-75, 5	45-75, 5	45-75, 5
Scenario 2: Increased CRC risk [c]					
MISCAN		45-75, 10	45-75, 10	45-75, 5	45-75, 10
		FIT 45-75, 1	FIT 45-75, 1	**FIT 45-75, 1**	FIT 45-75, 1
		X	**X**	-	**X**
		45-75, 5	45-75, 5	**-**	45-75, 5
SimCRC		45-75, 10	45-75, 10	45-75, 10	45-75, 10
		FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1
		45-75, 5	45-75, 5	45-75, 5	45-75, 5
		45-75, 5	45-75, 5	45-75, 5	45-75, 5

- = no model-recommendable strategy within this class; COL - colonoscopy; CRC - colorectal cancer; CTC - computed tomographic colonography; FIT - fecal immunochemical test; SIG - flexible sigmoidoscopy; X - class of screening modality was no longer recommended in the sensitivity analysis.

[a] Numbers in each field of the table successively represent recommended age to start screening, age to stop, and interval, all in years. For the class of stool-based screening modalities, the model-recommendable modality is also included, i.e. FIT. Changes from the base-case are designated in bold-faced letters. Best-case test performance assumptions are provided in Table 3.1.

[b] Risk within each age-, race-, and sex-specific demographic subgroup was assumed to have remained stable over time since the early screening period in the U.S (1975-1979 for SimCRC; 1990-1994 for MISCAN).

[c] CRC risk was increased proportional to observed trends in CRC incidence among adults under 40 years old. Estimated incidence rate ratios were 1.80-1.90 for white females (range across models), 1.24-1.27 for black females, 2.07-2.13 for white males, and 1.41-1.56 for black males.

Supplementary Table A3.9: Model-recommendable strategies under two scenarios of CRC risk, with worst-case test performance assumptions [a]

Model	Test class	White females	Black females	White males	Black Males
Scenario 1: Stable CRC risk [b]					
MISCAN	COL	50-75, 10	45-75, 10	50-75, 10	45-75, 10
	Stool	**X**	FIT 45-75, 1	FIT 50-75, 1	FIT 45-75, 1
	SIG	-	-	-	-
	CTC	**X**	**X**	**X**	**X**
SimCRC	COL	45-75, 15	**45-75, 10**	**45-75, 10**	45-75, 15
	Stool	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1
	SIG	-	-	-	-
	CTC	45-75, 5	45-75, 5	45-75, 5	45-75, 5
Scenario 2: Increased CRC risk [c]					
MISCAN	COL	45-75, 10	45-75, 10	45-75, 5	45-75, 10
	Stool	FIT 45-75, 1	FIT 45-75, 1	**FIT-DNA 45-75, 1**	FIT 45-75, 1
	SIG	**X**	**X**	-	**X**
	CTC	**X**	**X**	-	**X**
SimCRC	COL	45-75, 10	45-75, 10	45-75, 10	45-75, 10
	Stool	**X**	**FIT-DNA 45-75, 1**	FIT 45-75, 1	FIT 45-75, 1
	SIG	45-75, 5	45-75, 5	45-75, 5	45-75, 5
	CTC	45-75, 5	45-75, 5	45-75, 5	45-75, 5

- = no model-recommendable strategy within this class; COL - colonoscopy; CRC - colorectal cancer; CTC - computed tomographic colonography; FIT - fecal immunochemical test; FIT-DNA - multitarget stool DNA test; SIG - flexible sigmoidoscopy; X - class of screening modality was no longer recommended in the sensitivity analysis.

[a] Numbers in each field of the table successively represent recommended age to start screening, age to stop, and interval, all in years. For the class of stool-based screening modalities, the model-recommendable modality is also included, i.e. FIT or FIT-DNA. Changes from the base-case are designated in bold-faced letters. Worst-case test performance assumptions are provided in Table 3.1.

[b] Risk within each age-, race-, and sex-specific demographic subgroup was assumed to have remained stable over time since the early screening period in the U.S (1975-1979 for SimCRC; 1990-1994 for MISCAN).

[c] CRC risk was increased proportional to observed trends in CRC incidence among adults under 40 years old. Estimated incidence rate ratios were 1.80-1.90 for white females (range across models), 1.24-1.27 for black females, 2.07-2.13 for white males, and 1.41-1.56 for black males.

Supplementary Table A3.10: Model-recommendable strategies under two scenarios of CRC risk, applying a lower acceptance threshold for LYG relative to the benchmark colonoscopy strategy [a]

Model	Test class	White females	Black females	White males	Black Males
Scenario 1: Stable CRC risk [b]					
MISCAN	COL	50-75, 10	45-75, 10	50-75, 10	45-75, 10
	Stool	FIT 50-75, 1	FIT 45-75, 1	FIT 50-75, 1	FIT 45-75, 1
	SIG	**50-75, 5**	**45-75, 5**	**50-75, 5**	**45-75, 5**
	CTC	50-75, 5	45-75, 5	50-75, 5	45-75, 5
SimCRC	COL	45-75, 15	45-75, 15	45-75, 15	45-75, 15
	Stool	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1
	SIG	**45-75, 5**	**45-75, 5**	**45-75, 5**	**45-75, 5**
	CTC	45-75, 5	45-75, 5	45-75, 5	45-75, 5
Scenario 2: Increased CRC risk [c]					
MISCAN	COL	45-75, 10	45-75, 10	45-75, 5	45-75, 10
	Stool	FIT 45-75, 1	FIT 45-75, 1	**FIT 45-75, 1**	FIT 45-75, 1
	SIG	45-75, 5	45-75, 5	**45-75, 5**	45-75, 5
	CTC	45-75, 5	45-75, 5	**45-75, 5**	45-75, 5
SimCRC	COL	45-75, 10	45-75, 10	45-75, 10	45-75, 10
	Stool	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1
	SIG	45-75, 5	45-75, 5	45-75, 5	45-75, 5
	CTC	45-75, 5	45-75, 5	45-75, 5	45-75, 5

COL - colonoscopy; CRC - colorectal cancer; CTC - computed tomographic colonography; FIT - fecal immunochemical test; SIG - flexible sigmoidoscopy.

[a] Model-recommendable strategies were required to provide at least 75% (rather than 90% in the base-case) of the predicted LYG for the model-recommendable colonoscopy screening strategy. Numbers in each field of the table successively represent recommended age to start screening, age to stop, and interval, all in years. For the class of stool-based screening modalities, the model-recommendable modality is also included, i.e. FIT. Changes from the base-case are designated in bold-faced letters.

[b] Risk within each age-, race-, and sex-specific demographic subgroup was assumed to have remained stable over time since the early screening period in the U.S (1975-1979 for SimCRC; 1990-1994 for MISCAN).

[c] CRC risk was increased proportional to observed trends in CRC incidence among adults under 40 years old. Estimated incidence rate ratios were 1.80-1.90 for white females (range across models), 1.24-1.27 for black females, 2.07-2.13 for white males, and 1.41-1.56 for black males.

Supplementary Table A3.11: Model-recommendable strategies under two scenarios of CRC risk, applying a more stringent acceptance threshold for required number of colonoscopies per LYG [a]

Model	Test class	White females	Black females	White males	Black Males
Scenario 1: Stable CRC risk [b]					
MISCAN	COL	50-75, 10 [d]	**50-75, 10**	50-75, 10	**50-75, 10**
	Stool	FIT 50-75, 1	**FIT 50-75, 1**	FIT 50-75, 1	**FIT 50-75, 1**
	SIG	-	-	-	-
	CTC	50-75, 5	**50-75, 5**	50-75, 5	**50-75, 5**
SimCRC	COL	45-75, 15	45-75, 15	45-75, 15	45-75, 15
	Stool	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1
	SIG	-	-	-	-
	CTC	45-75, 5	45-75, 5	45-75, 5	45-75, 5
Scenario 2: Increased CRC risk [c]					
MISCAN	COL	45-75, 10	45-75, 10	45-75, 5	45-75, 10
	Stool	FIT 45-75, 1	FIT 45-75, 1	-	FIT 45-75, 1
	SIG	45-75, 5	45-75, 5	-	45-75, 5
	CTC	45-75, 5	45-75, 5	-	45-75, 5
SimCRC	COL	45-75, 10	45-75, 10	45-75, 10	45-75, 10
	Stool	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1
	SIG	45-75, 5	45-75, 5	45-75, 5	45-75, 5
	CTC	45-75, 5	45-75, 5	45-75, 5	45-75, 5

- = no model-recommendable strategy within this class; COL - colonoscopy; CRC - colorectal cancer; CTC - computed tomographic colonography; FIT - fecal immunochemical test; SIG - flexible sigmoidoscopy.

[a] Model-recommendable strategies could require no more than 40 additional colonoscopies per LYG (rather than 50 in the base-case) compared to the next less effective strategy on the efficient frontier. Numbers in each field of the table successively represent recommended age to start screening, age to stop, and interval, all in years. For the class of stool-based screening modalities, the model-recommendable modality is also included, i.e. FIT. Changes from the base-case are designated in bold-faced letters.

[b] Risk within each age-, race-, and sex-specific demographic subgroup was assumed to have remained stable over time since the early screening period in the U.S (1975-1979 for SimCRC; 1990-1994 for MISCAN).

[c] CRC risk was increased proportional to observed trends in CRC incidence among adults under 40 years old. Estimated incidence rate ratios were 1.80-1.90 for white females (range across models), 1.24-1.27 for black females, 2.07-2.13 for white males, and 1.41-1.56 for black males.

[d] For white females, MISCAN-Colon recommended colonoscopy every 10 years between age 50 and 75 years despite failure to meet the applied burden-to-benefit ratio criterion. Less intensive strategies did not meet the prioritized benefit criterion.

Chapter 4

The impact of the increased colorectal cancer treatment costs and incidence in young adults on the cost-effectiveness of colorectal cancer screening

Elisabeth F.P. Peterse, Amy B. Knudsen, Anna Lietz, Jennifer M. Kolb, Frank I. Scott, Ann G. Zauber & Iris Lansdorp-Vogelaar

Submitted

Abstract

Objectives

This study evaluates the impact of the rising colorectal cancer (CRC) incidence observed in young adults and increasing costs of CRC care on the cost-effectiveness of CRC screening in the US.

Methods

MISCAN-Colon was used to compare the cost-effectiveness of CRC screening across four scenarios, differing in incidence (with or without incorporating an incidence multiplier reflecting recent trends) and cancer care costs (1998-2003 vs 2007-2013 estimates). For each scenario, 132 screening strategies were evaluated, including six different screening tests. To select optimal screening strategies, incremental cost-effectiveness ratios (ICERs) were calculated.

Results

The benefits of screening increased with recent incidence trends, whereas the net costs of screening fell with increased costs of cancer care. For colonoscopy screening every 10 years from ages 45 to 75 years, the benefits increased from 35 to 56 quality-adjusted life-years (QALYs) gained per 1000 40-year-olds, whereas the net per person costs decreased from $541 to $30, accounting for realistic adherence. As a result, the ICER of colonoscopy screening at age 45 compared to 50 years improved from $82,300 to $38,700 per QALY gained, assuming perfect adherence. From a cost-effectiveness perspective, annual FIT from ages 40 to 85 years would be the optimal screening strategy at a willingness-to-pay threshold of $50,000 or $100,000 per QALY gained.

Conclusions

As a result of the increasing incidence and costs of cancer care, the cost-effectiveness of CRC screening greatly improved, which further supports screening initiation at age 45 years rather than age 50 years.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States.[149] CRC screening can prevent mortality related to CRC through both removal of premalignant adenomas and by early CRC diagnosis.[51] As a result of increased uptake of screening, overall CRC incidence and mortality have been declining.[150,151] However, CRC incidence in the prescreening ages (i.e., before age 50) has been increasing for the last two decades.[16] Age-period-cohort modeling suggested that the increase in CRC incidence is primarily the result of a strong birth cohort effect that began in those born in the 1950s.[16] Consequently, it is expected that these and subsequent generations will carry forward elevated disease risk as they age, although screening will likely somewhat counteract the trend.

Based on the increased incidence of CRC in individuals below age 50 years, the reasonable expectation that screening will perform similarly in individuals aged 45-49 as in those age 50 and above, and the results from our modeling analyses,[98,99] the 2018 American Cancer Society (ACS) CRC screening guidelines included a qualified recommendation to start screening at age 45 years in average risk individuals.[78] Our prior analyses demonstrated that screening initiation at age 45 years has a favorable balance between additional life-years gained and colonoscopies required.[98,99] However, in these analyses, costs were not taken into account. Furthermore, previous cost-effectiveness analyses used CRC care costs based on 1998–2003 data from Medicare claims,[102,152-155] which are not representative of current cancer care costs as, for example, therapy with monoclonal antibodies was introduced after that period. Therefore, we aimed to evaluate the impact of the rising CRC incidence in young adults and the increasing CRC care costs on the optimal screening modality, age to start screening, age to end screening and screening interval from a cost-effectiveness perspective.

Methods

MISCAN-Colon

This study used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model, developed by the Department of Public Health within Erasmus MC University Medical Center, Rotterdam, the Netherlands. It is a part of the US National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) and has been used to inform screening recommendations world-wide,[98,99,156-158] including those of the US Preventive Services Task Force (USPSTF)[96] and the ACS.[98,99] Details of the model can be found elsewhere (**Model Appendix**).[102,103] In short, the model generates, with random variation, 10 million individual life histories to simulate the US population in terms of life expectancy and cancer risk.[159] As each simulated person ages, one or more adenomas may develop, which can progress in size and can develop into preclinical cancer (stages I to IV). At each stage, CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the person's age, and the location of the cancer.[134] Screening can alter individual life

trajectories because screening can result in the removal of adenomas, or in the detection of preclinical cancer. Screening may also result in complications, over-diagnosis, and over-treatment, which are also taken into account by the model.[104,105,160]

Scenarios

To evaluate the impact of the increased CRC incidence observed in young adults and the increased CRC care costs on the cost-effectiveness of CRC screening, four scenarios were evaluated, reflecting two assumptions about CRC incidence and two assumptions about the costs of cancer care. In scenarios 1 and 2, CRC incidence was that predicted by the original MISCAN-Colon model, which was calibrated to 1975-1979 data from the Surveillance, Epidemiology and End Results Program (SEER).[96] This period was chosen because it reflects CRC incidence prior to the dissemination of screening. In scenarios 3 and 4, adenoma onset was increased 1.591 fold across all ages based on age-period-cohort modeling from Siegel et al.[16], in order to reflect incidence among a recent birth cohort (i.e., those born in 1975).[99] Furthermore, in scenarios 1 and 3, 1998-2003 net costs of CRC-related care by stage at diagnosis and phase of care were used.[161] In scenarios 2 and 4, recent cost estimates were used, which were obtained from an analysis of 2007-2013 SEER-Medicare linked data (personal communication, Angela Mariotto, PhD[162]).

Screening strategies

In line with our analyses for the ACS, a total of 132 unique screening strategies were evaluated, including six different screening modalities: colonoscopy, fecal immunochemical testing (FIT), high-sensitivity guaiac-based fecal occult blood testing (HSgFOBT), multi-target stool DNA testing (mtSDNA), flexible sigmoidoscopy (SIG), and computed tomographic colonography (CTC).[99] For each modality, multiple start ages (40, 45, or 50 years), and stop ages (75, 80, or 85 years) were evaluated, as well as multiple screening intervals (**Table 4.1**). Test characteristics used were in accordance with previous analyses [96,99] and can be found in **Appendix 4.1**.

Costs

Costs of screening, screening-related complications, and cancer treatment were computed from a Health Care perspective and included allowed payments as well as out-of-pocket costs (**Table 4.2, Appendix 4.2**).[15,161-165] For individuals younger than age 65 years, commercial costs were used, whereas for individuals aged 65 years and older, Centers for Medicare and Medicaid Services (CMS) costs were used. As no data are available to inform commercial cost estimates for colonoscopy complications and CRC treatment, CMS estimates were multiplied by 1.35 for individuals younger than age 65 years based on the observed mean ratio of commercial to Medicare payment rates for colorectal tests.[166]

Disutilities

We incorporated disutilities for undergoing a CRC screening test, for having a colonoscopy complication and for having CRC. Estimates of the test disutilities 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 (Appendix 4.2).[167-170] Complication and CRC care disutilities (Appendix 4.2) were in line with previous analyses.[154,171,172]

Table 4.1: Screening strategies evaluated by the microsimulation model

Screening Modality	Age to start screening (years)	Age to stop screening (years)	Screening interval (years)	No. of (unique) strategies [a]
No screening				1 (1)
Colonoscopy	40,45,50	75,80,85	5,10,15	27 (20)
Stool-based tests				
– Fecal immunochemical test	40,45,50	75,80,85	1,2,3	27 (27)
– High-sensitivity guaiac-based fecal occult blood test	40,45,50	75,80,85	1,2,3	27 (27)
– Multitarget stool DNA test	40,45,50	75,80,85	1,3,5	27 (27)
Flexible sigmoidoscopy	40,45,50	75,80,85	5,10	18 (15)
Computed tomographic colonography	40,45,50	75,80,85	5,10	18 (15)
Total				**145 (132)**

[a] The number of unique strategies excluded the strategies that overlap (eg, colonoscopy every 10 years from ages 50-80 years and from ages 50-85 years both include colonoscopies at age 50, 60, 70, and 80 years, and thus are not unique strategies).

Outcomes

Primary outcomes of this study were: the number of CRC cases, CRC deaths, screening tests, diagnostic follow-up procedures, quality-adjusted life-years (QALY) gained compared to no screening, and associated costs. We applied the recommended 3% annual discount rate for the number of QALYs gained and the costs.[109]

Analysis

We performed an incremental cost-effectiveness analysis under the assumption of perfect adherence to screening, diagnostic follow-up and surveillance.[107]. Analyses with lower adherence levels are not suitable to select recommended strategies, as using suboptimal adherence can lead to selecting screening strategies that recommend too many screenings for individuals that perfectly adhere to the recommendations. Strategies that were more costly and less effective (i.e. fewer QALY gained) than (a combination of) other strategies were considered dominated; remaining strategies maximized the number of QALYs gained for a given cost (i.e., were efficient). In addition to a cost-effectiveness analysis for all screening strategies combined, a separate cost-effectiveness analysis was performed that only included colonoscopy strategies, as colonoscopy is the most-frequently used CRC screening test in the US.[173] Incremental cost-effectiveness ratios (ICERs) were calculated to determine the optimal strategy.

Table 4.2: Overview of costs and disutilities used in this study.

SCREENING TESTS				
Test / procedure	*Commercial costs ($)*	*CMS costs ($)*	*Disutility when positive*	*Disutility when negative*
Colonoscopy				
Screening w/o lesion removal	1,330.13	898.11	NA	0.000496
Diagnostic w/o lesion removal [a]	1,330.13	847.07	NA	0.000496
Surveillance w/o lesion removal	1,330.13	845.53	NA	0.000496
Any colonoscopy with lesion removal	1,760.67	1,223.71	0.001401	NA
FIT	23.79	21.82	0.001330	0.000063
HSgFOBT	5.67	4.46	0.001330	0.000063
mtSDNA	512.43	512.43	0.001394	0.000126
SIG	397.44	379.75	0.001415	0.000147
CTC	742.22	287.24	0.001559	0.000292

COLORECTAL CANCER CARE								
	Initial care		*Continuing care*		*Terminal care death CRC*		*Terminal care death other cause*	
2007-2013 | 1998-2003 Commercial costs per LY CRC care ($)								
Stage I CRC	51,774	46,169	5,328	3,911	104,483	83,638	27,440	20,457
Stage II CRC	73,418	63,935	6,196	3,645	117,777	83,279	29,528	17,772
Stage III CRC	106,670	78,832	9,586	5,268	123,305	88,213	40,367	23,686
Stage IV CRC	158,511	104,358	45,444	16,846	155,054	118,402	97,101	63,901
2007-2013 | 1998-2003 CMS costs per LY CRC care ($)								
Stage I CRC	38,351	34,199	3,946	2,897	77,395	61,954	20,326	15,153
Stage II CRC	54,384	47,360	4,590	2,700	87,242	61,688	21,872	13,164
Stage III CRC	79,015	58,394	7,101	3,902	91,337	65,343	29,901	17,545
Stage IV CRC	117,416	77,302	33,662	12,479	114,855	87,706	71,926	47,334
Utility losses per LY with CRC care								
Stage I CRC	0.12		0.05		0.70		0.05	
Stage II CRC	0.18		0.05		0.70		0.05	
Stage III CRC	0.24		0.24		0.70		0.24	
Stage IV CRC	0.70		0.70		0.70		0.70	

COLONOSCOPY COMPLICATIONS			
	Commercial costs ($)	*CMS costs ($)*	*Utility losses*
Serious gastrointestinal event	$10,914	$8,085	0.0055
Other gastrointestinal event	$8,256	$6,116	0.0027
Cardiovascular event	$8,889	$6,584	0.0048

CMS - Centers for Medicare and Medicaid Services; FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multi-target stool DNA test; SIG - flexible sigmoidoscopy; CTC - computed tomographic colonography; LY - life-year

[a] Used for colonoscopies performed as a diagnostic follow-up after a positive non-colonoscopy test and for colonoscopies performed for diagnosis of symptom-detected CRC cases.

Willingness-to-pay thresholds of $50,000, $100,000 and $200,000 per QALY gained were evaluated,[109] although the $50,000 per QALY gained might be too low to represent society's willingness to pay for QALYs gained.[174]

Evaluation of benefits and costs under realistic adherence

For all four scenarios, the benefits of the efficient strategies were evaluated assuming that 60% (realistic adherence [173,175,176]) and 80% (adherence level targeted by the National Colorectal Cancer Roundtable [177]) of the population is up to date with screening (**Appendix 4.3**). We assumed an 80% [55,114] and 90% adherence to potential diagnostic follow-up and surveillance colonoscopy for the realistic and targeted adherence scenarios, respectively (**Appendix 4.3**).

Sensitivity analyses

In sensitivity analyses, we evaluated the robustness of the current (i.e., accounting for recent incidence trends and costs of cancer care) cost-effectiveness of all CRC screening strategies to six alternative model assumptions. First, we evaluated a scenario in which the increased risk of the 1975 cohort will not be carried forward when the cohort ages, only increasing CRC incidence below age 50 years. Second, we evaluated a scenario in which adenoma onset was increased 1.25 fold instead of 1.591 fold, based on age-adjusted rates of CRC among 20-44-year-olds by period of diagnosis (1975-1979 and 2012-2016) in SEER. Third, we evaluated a scenario in which the increased CRC incidence was caused by faster adenoma progression to malignancy rather than an increased onset of adenomas. Fourth, we applied hazard ratios for median survival from clinical trials [178] to our stage III and stage IV survival estimates [134] in line with a previous study,[103] to take into account that the increased treatment costs might be accompanied by an improved survival. Lastly, commercial costs estimates and CMS cost estimates were applied to all individuals irrespectively of age in our fifth and six sensitivity analysis, respectively.

Results

Without incorporating recent incidence trends and using 1998-2003 CRC care costs, the model predicted, in the absence of screening, 68 CRC cases and 28 CRC deaths with a total CRC-related costs of $2.57 million over the lifetimes of 1000 40-year-olds (**Table 4.3**). When incidence trends were incorporated and 2007-2013 care costs were used, this increased to 108 cases (+59%) and 45 deaths (+62%). The total CRC-related costs were estimated at 5.87 million (+128%) per 1000 40-year-olds (**Appendix 4.4**). Comparing scenarios 1 and 3, which both used 1998-2003 care costs but differ in assumed incidence, demonstrates that the increase in incidence alone is responsible for a 64% increase (+$1.60 million per 1000 40-year-olds) in total CRC-related costs. The impact of the increased costs of cancer care is revealed by comparing scenarios 1 and 2, which both not incorporated in increased incidence but differ in assumed cancer care costs. The difference in total CRC-related costs between these scenarios was $1.11 million per 1000 40-year-olds, an increase of 43% (**Appendix 4.4**).

As a consequence of the increased CRC incidence, the QALYs gained by screening increased. When assuming perfect adherence, the benefits of screening ranged from 99 to 187 QALY gained per 1000 40-year-olds when recent incidence trends were incorporated, and from 62 to 101 QALY gained when these incidence trends were not incorporated (**Appendix 4.4**). Furthermore, due to the increased CRC care costs, the net costs of screening decreased. When incidence trends were not incorporated and 1998-2003 cost estimates were used (scenario 1), no screening strategies were cost-saving compared to no screening. However, when incidence trends were incorporated and 2007-2013 CRC care costs were used (scenario 4), all FIT strategies were cost-saving, as well as the large majority of HSgFOBT strategies, 3 sigmoidoscopy screening strategies with an interval of 10 years, and colonoscopy screening from ages 50 to 75 years every 15 years (**Appendix 4.4**).

Efficient strategies

In all four scenarios, efficient strategies were those with annual FIT screening or with colonoscopy screening every 5 years (**Figure 4.1, Table 4.3**). In contrast to the other scenarios, in scenario 4 (increased incidence and cancer care costs), none of the efficient strategies involved stopping screening at age 75 years, the currently-recommended age to end screening (**Figure 4.1, Table 4.3**). The increased incidence and cancer care costs improved the cost-effectiveness of colonoscopy screening compared to FIT screening, as the ICER for colonoscopy screening every 5 years from ages 40 to 80 years decreased from $287,900 to $138,600 (**Table 4.3**). Whether colonoscopy screening every 5 years from ages 40 to 80 years or annual FIT screening from ages 40 to 85 was optimal depended on the willingness-to-pay threshold, as the ICERs for these strategies were $138,600 and $26,800, respectively (scenario 4, **Table 4.3**).

As colonoscopy is the most common screening modality in the US, efficient frontiers were also created only including colonoscopy-based screening strategies (**Table 4.4, Appendix 4.5**). As a consequence of the increased incidence and cancer care costs, the ICERs of colonoscopy screening every 10 years from ages 45 to 75 and ages 50 to 75 years decreased from $82,300 to $38,700 and from $61,700 to $20,700, respectively (**Table 4.4**). Therefore, the current balance between benefits and costs of colonoscopy screening every 10 years from ages 45 to 75 years is better than the previous balance of colonoscopy screening every 10 years from ages 50 to 75 years. With a willingness-to-pay threshold of $50,000, colonoscopy screening every 10 years from ages 45 to 75 years was optimal, whereas with higher willingness-to-pay thresholds colonoscopy screening every 5 years provided an acceptable balance between additional benefits and costs.

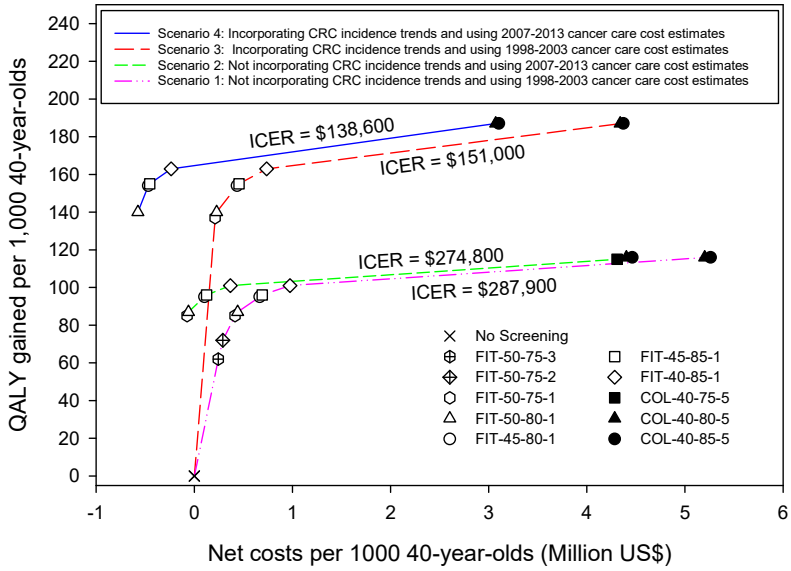


Figure 4.1: Efficient frontiers for the four different scenarios when all screening modalities are considered. Net costs (compared to no screening) and QALY gained per 1000 40-year-olds for efficient screening strategies (i.e. . strategies that maximized the number of QALYs gained for a given cost). Strategies are abbreviated as modality – start age- stop age – interval (years). QALY - quality-adjusted life-years; FIT - fecal immunochemical test; COL - colonoscopy

Evaluation of benefits and costs under realistic adherence

When incorporating realistic and targeted adherence, the benefits of CRC screening and needed colonoscopy capacity decreased compared to assuming perfect adherence (**Table 4.5, Appendix 4.6**). For example, colonoscopy screening from ages 45 to 75 every 10 years resulted in 165, 97, and 56 QALY gained per 1000 40-year-olds compared to no screening with perfect, targeted, and realistic adherence, respectively, in the scenarios that incorporated increased incidence (**Appendix 4.6**). In scenario 4, which incorporated increased incidence and cancer care costs, realistic CRC screening participation with FIT resulted in higher total CRC-related costs than with perfect adherence, whereas the reverse was observed for colonoscopy screening strategies. Comparing scenario 1 to scenario 4 reveals that as a consequence of the increasing CRC incidence and cancer care costs, the total CRC related costs for colonoscopy screening every 10 years from ages 45 to 75 years with realistic adherence increased from $3.11 million to $5.90 million per 1000 40-year-olds, an increase of 90% (**Appendix 4.6**).

Table 4.3: The impact of the increased CRC incidence in young adults and the increased CRC care costs on screening strategies in the efficient frontier when all screening modalities are considered. Outcomes are per 1000 40-year-olds.

Modality - start age - stop age - interval	CRC cases	CRC deaths	No. of colonos-copies	LY gained	QALY gained	Total costs (million $)	Cost-saving vs no screening	ICER
	-------Undiscounted-------			*----------3% discounted ----------*				
Scenario 1: Not incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates								
No screening	67.5	28.2	70	0	0	2.57	-	-
FIT-50-75-3	48.6	12.7	1,010	56	62	2.81	No	3,900
FIT-50-75-2	44.0	10.7	1,260	64	72	2.86	No	4,800
FIT-50-75-1	35.9	7.9	1,770	74	85	2.99	No	9,600
FIT-50-80-1	34.6	6.8	1,870	75	87	3.01	No	14,900
FIT-45-80-1	33.1	6.2	2,110	82	95	3.24	No	26,900
FIT-45-85-1	32.7	5.6	2,180	83	96	3.26	No	45,400
FIT-40-85-1	32.1	5.3	2,380	87	101	3.54	No	55,100
COL-40-80-5	18.8	3.4	8,440	97	116	7.77	No	287,900
COL-40-85-5	18.7	3.3	8,680	97	116	7.83	No	13,023,200
Scenario 2: Not incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates								
FIT-50-75-1	35.9	7.9	1,770	74	85	3.61	Yes	-
FIT-50-80-1	34.6	6.8	1,870	75	87	3.62	Yes	8,000
FIT-45-80-1	33.1	6.2	2,110	82	95	3.79	No	19,600
FIT-45-85-1	32.7	5.6	2,180	83	96	3.81	No	38,700
FIT-40-85-1	32.1	5.3	2,380	87	101	4.05	No	47,300
COL-40-75-5	19.4	3.7	8,090	96	115	7.99	No	274,800
COL-40-80-5	18.8	3.4	8,440	97	116	8.09	No	276,900
COL-40-85-5	18.7	3.3	8,680	97	116	8.15	No	12,933,300
Scenario 3: Incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates								
No screening	108.1	45.4	110	0	0	4.11	-	-
FIT-50-75-1	56.1	12.5	2,400	118	137	4.32	No	800
FIT-50-80-1	54.1	10.7	2,500	120	140	4.34	No	5,500
FIT-45-80-1	51.7	9.7	2,800	132	154	4.54	No	15,200
FIT-45-85-1	51.2	9.0	2,860	132	155	4.56	No	23,500
FIT-40-85-1	49.9	8.5	3,100	139	163	4.85	No	34,600
COL-40-80-5	29.6	5.4	8,540	154	187	8.45	No	151,000
COL-40-85-5	29.5	5.3	8,670	154	187	8.48	No	956,900

table continues

Scenario 4: Incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates								
FIT-50-80-1	54.1	10.7	2,500	120	140	5.30	Yes	-
FIT-45-80-1	51.7	9.7	2,800	132	154	5.40	Yes	7,200
FIT-45-85-1	51.2	9.0	2,860	132	155	5.42	Yes	16,800
FIT-40-85-1	49.9	8.5	3,100	139	163	5.64	Yes	26,800
COL-40-80-5	29.6	5.4	8,540	154	187	8.94	No	138,600
COL-40-85-5	29.5	5.3	8,670	154	187	8.98	No	941,800

CRC - colorectal cancer; LY - life-years; QALY - quality-adjusted life-years; ICER - incremental cost-effectiveness ratio (compared to previous efficient strategy); FIT - fecal immunochemical test; COL - colonoscopy

Table 4.4: The impact of the increased CRC incidence in young adults and the increased CRC care costs on screening strategies in the efficient frontier when only colonoscopy is considered. Outcomes are per 1000 40-year-olds.

Modality - start age - stop age - interval	CRC cases	CRC deaths	No. of colonos-copies	LY gained	QALY gained	Total costs (million $)	Cost-saving vs no screening	ICER
	-------Undiscounted-------			*----------3% discounted ----------*				
Scenario 1: Not incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates								
No screening	67.5	28.2	70	0	0	2.57	-	-
COL-50-75-15	28.9	7.7	3,380	73	87	3.72	No	13,200
COL-50-75-10	25.3	6.0	4,130	79	94	4.17	No	61,700
COL-45-75-10	23.4	5.1	4,960	85	102	4.81	No	82,300
COL-40-80-10	22.6	4.6	5,700	89	107	5.73	No	184,100
COL-45-75-5	20.1	4.0	7,030	92	110	6.29	No	193,800
COL-40-75-5	19.4	3.7	8,090	96	115	7.67	No	245,000
COL-40-80-5	18.8	3.4	8,440	97	116	7.77	No	287,600
COL-40-85-5	18.7	3.3	8,680	97	116	7.83	No	13,023,200
Scenario 2: Not incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates								
No screening	67.5	28.2	70	0	0	3.68	-	-
COL-50-75-15	28.9	7.7	3,380	73	87	4.27	No	6,800
COL-50-75-10	25.3	6.0	4,130	79	94	4.67	No	54,900
COL-45-75-10	23.4	5.1	4,960	85	102	5.25	No	73,600
COL-40-80-10	22.6	4.6	5,700	89	107	6.13	No	177,700
COL-45-75-5	20.1	4.0	7,030	92	110	6.65	No	180,700
COL-40-75-5	19.4	3.7	8,090	96	115	7.99	No	236,700
COL-40-80-5	18.8	3.4	8,440	97	116	8.09	No	276,900
COL-40-85-5	18.7	3.3	8,680	97	116	8.15	No	12,933,300

table continues

Scenario 3: Incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates								
No screening	108.1	45.4	110	0	0	4.11	-	-
COL-50-75-15	44.7	11.8	4,180	117	140	5.01	No	6,400
COL-50-75-10	39.4	9.2	4,840	126	151	5.33	No	30,000
COL-45-75-10	36.4	7.9	5,650	137	165	5.95	No	46,900
COL-45-75-5	31.6	6.3	7,280	146	177	7.06	No	89,800
COL-45-80-5	30.9	5.9	7,490	147	177	7.11	No	114,200
COL-40-80-5	29.6	5.4	8,540	154	187	8.45	No	145,300
COL-40-85-5	29.5	5.3	8,670	154	187	8.48	No	956,800
Scenario 4: Incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates								
COL-50-75-15	44.7	11.8	4,180	117	140	5.87	Yes	-
COL-50-75-10	39.4	9.2	4,840	126	151	6.12	No	20,700
COL-45-75-10	36.4	7.9	5,650	137	165	6.63	No	38,700
COL-45-75-5	31.6	6.3	7,280	146	177	7.63	No	81,300
COL-45-80-5	30.9	5.9	7,490	147	177	7.68	No	104,700
COL-40-80-5	29.6	5.4	8,540	154	187	8.94	No	137,000
COL-40-85-5	29.5	5.3	8,670	154	187	8.98	No	941,800

CRC - colorectal cancer; LY - life-years; QALY - quality-adjusted life-years; ICER - incremental cost-effectiveness ratio (compared to previous efficient strategy); COL - colonoscopy

Table 4.5: The benefits and costs of efficient screening strategies incorporating 60% or 80% screening adherence. Outcomes are per 1000 40-year-olds.

Modality - start age - stop age - interval	CRC cases	CRC deaths	No. of colonos-copies	LY gained	QALY gained	Total costs (million $)
	Undiscounted			*3% discounted*		
	60% adherence					
Scenario 1: Not incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates						
No screening	67.5	28.2	70	0	0	2.57
FIT-50-75-3	59.6	20.5	420	25	27	2.68
FIT-50-75-2	56.0	18.2	580	34	37	2.72
FIT-50-75-1	48.5	14.1	950	48	54	2.79
FIT-50-80-1	47.6	12.9	1,020	50	56	2.81
FIT-45-80-1	46.0	12.2	1,160	57	64	2.92
FIT-45-85-1	45.9	11.6	1,200	57	64	2.94
FIT-40-85-1	44.8	11.0	1,380	63	72	3.15
COL-40-80-5	34.1	10.5	5,090	66	79	5.61
COL-40-85-5	34.1	10.4	5,240	66	79	5.64
Scenario 2: Not incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates						
FIT-50-75-1	48.5	14.1	950	48	54	3.62
FIT-50-80-1	47.6	12.9	1,020	50	56	3.64

table continues

FIT-45-80-1	46.0	12.2	1,160	57	64	3.69
FIT-45-85-1	45.9	11.6	1,200	57	64	3.71
FIT-40-85-1	44.8	11.0	1,380	63	72	3.88
COL-40-75-5	34.7	10.8	4,870	66	78	6.13
COL-40-80-5	34.1	10.5	5,090	66	79	6.19
COL-40-85-5	34.1	10.4	5,240	66	79	6.23
Scenario 3: Incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates						
No screening	108.1	45.4	110	0	0	4.11
FIT-50-75-1	76.6	22.4	1,310	77	88	4.22
FIT-50-80-1	75.1	20.5	1,390	80	91	4.24
FIT-45-80-1	72.6	19.3	1,570	90	103	4.33
FIT-45-85-1	72.5	18.5	1,610	91	104	4.35
FIT-40-85-1	70.6	17.6	1,830	101	115	4.56
COL-40-80-5	54.3	16.7	5,180	106	127	6.58
COL-40-85-5	54.2	16.6	5,260	106	127	6.60
Scenario 4: Incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates						
FIT-50-80-1	75.1	20.5	1,390	80	91	5.54
FIT-45-80-1	72.6	19.3	1,570	90	103	5.56
FIT-45-85-1	72.5	18.5	1,610	91	104	5.57
FIT-40-85-1	70.6	17.6	1,830	101	115	5.70
COL-40-80-5	54.3	16.7	5,180	106	127	7.50
COL-40-85-5	54.2	16.6	5,260	106	127	7.53
----------80% adherence----------						
Scenario 1: Not incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates						
No screening	67.5	28.2	70	0	0	2.57
FIT-50-75-3	54.7	16.8	660	39	43	2.73
FIT-50-75-2	50.4	14.5	870	47	53	2.77
FIT-50-75-1	42.6	11.3	1,310	60	68	2.86
FIT-50-80-1	41.5	10.2	1,390	61	70	2.88
FIT-45-80-1	40.1	9.6	1,580	68	78	3.04
FIT-45-85-1	39.9	9.1	1,630	69	79	3.06
FIT-40-85-1	38.9	8.6	1,830	74	85	3.33
COL-40-80-5	26.7	7.0	6,730	81	97	6.67
COL-40-85-5	26.6	7.0	6,920	81	97	6.72
Scenario 2: Not incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates						
FIT-50-75-1	42.6	11.3	1,310	60	68	3.60
FIT-50-80-1	41.5	10.2	1,390	61	70	3.61
FIT-45-80-1	40.1	9.6	1,580	68	78	3.71
FIT-45-85-1	39.9	9.1	1,630	69	79	3.73
FIT-40-85-1	38.9	8.6	1,830	74	85	3.95
COL-40-75-5	27.2	7.3	6,450	81	97	7.05
COL-40-80-5	26.7	7.0	6,730	81	97	7.13
COL-40-85-5	26.6	7.0	6,920	81	97	7.18

table continues

Scenario 3: Incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates						
No screening	108.1	45.4	110	0	0	4.11
FIT-50-75-1	67.2	18.0	1,780	95	110	4.25
FIT-50-80-1	65.5	16.3	1,870	98	113	4.26
FIT-45-80-1	63.0	15.2	2,100	109	126	4.40
FIT-45-85-1	62.6	14.4	2,150	110	127	4.42
FIT-40-85-1	61.2	13.9	2,390	118	136	4.67
COL-40-80-5	42.3	11.3	6,810	130	156	7.49
COL-40-85-5	42.2	11.2	6,910	130	156	7.52
Scenario 4: Incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates						
FIT-50-80-1	65.5	16.3	1,870	98	113	5.40
FIT-45-80-1	63.0	15.2	2,100	109	126	5.45
FIT-45-85-1	62.6	14.4	2,150	110	127	5.47
FIT-40-85-1	61.2	13.9	2,390	118	136	5.65
COL-40-80-5	42.3	11.3	6,810	130	156	8.20
COL-40-85-5	42.2	11.2	6,910	130	156	8.23

CRC - colorectal cancer; LY - life-years; QALY - quality-adjusted life-years; FIT - fecal immunochemical test; COL - colonoscopy

Table 4.6: Optimal screening strategies evaluated in sensitivity analyses, applying a willingness-to-pay threshold of $50,000, $100,000 or $200,000 per quality-adjusted life-year gained. 2007-2013 cancer care cost estimates were used for all sensitivity analyses. Changes compared to the base case are displayed in grey.

	----------Including all screening tests ----------		
	$50,000	*$100,000*	*$200,000*
Base case (scenario 4)	FIT-40-85-1	FIT-40-85-1	COL-40-80-5
Age effect	FIT-40-85-1	FIT-40-85-1	FIT-40-85-1
Incidence rate ratio of 1.25	FIT-40-85-1	FIT-40-85-1	COL-40-80-5
Fast adenoma progression	FIT-40-85-1	FIT-40-85-1	COL-40-80-5
Improved survival	FIT-40-85-1	FIT-40-85-1	COL-40-80-5
Commercial costs all ages	FIT-40-85-1	FIT-40-85-1	COL-40-80-5
CMS costs all ages	FIT-40-85-1	COL-40-75-5	COL-40-80-5
	----------Only including colonoscopy screening----------		
	$50,000	*$100,000*	*$200,000*
Base case (scenario 4)	COL-45-75-10	COL-45-75-5	COL-40-80-5
Age effect	COL-50-75-15	COL-45-75-10	COL-40-80-10
Incidence rate ratio of 1.25	COL-50-75-10	COL-45-75-10	COL-40-80-5
Fast adenoma progression	COL-45-75-10	COL-45-75-5	COL-40-80-5
Improved survival	COL-45-75-10	COL-45-75-5	COL-40-80-5
Commercial costs all ages	COL-45-75-10	COL-45-75-5	COL-40-80-5
CMS costs all ages	COL-45-75-10	COL-40-75-5	COL-40-80-5

CMS - Centers for Medicare and Medicaid Services; FIT - fecal immunochemical test; COL - colonoscopy

Sensitivity analyses

Current optimal screening strategies did not vary when the increased CRC incidence was simulated as faster adenoma progression rather than an increased adenoma onset, or when an improved survival was assumed (**Table 4.6**). However, when the incidence was only increased in individuals below age 50 years, colonoscopy screening was not cost-effective compared to FIT screening (ICER: $262,900, **Appendix 4.7**), and when only colonoscopy strategies were considered, starting screening at age 45 years was not cost-effective at the most stringent willingness-to-pay threshold of $50,000 (ICER: $58,600, **Appendix 4.8**). When we used an incidence rate ratio of 1.25 rather than 1.591, colonoscopy at age 45 years was not cost-effective either at a willingness-to-pay threshold of $50,000 (ICER: $53,900, **Appendix 4.8**). Results were robust for alternative cost assumptions, although colonoscopy screening was cost-effective compared to FIT screening at a willingness-to-pay threshold of $100,000 when CMS costs were assumed for all ages (**Table 4.6**). When assuming realistic adherence, the benefits and costs of colonoscopy screening every 10 years from ages 45 to 75 years varied between 36 and 57 QALY gained, and between $4.15 million and $7.15 million per 1000 40-year-olds, respectively, across all sensitivity analyses (**Appendices 4.9 & 4.10**).

Discussion

Our results indicate that the balance between the benefits and costs of CRC screening has greatly improved as a consequence of the increasing CRC incidence and care costs, as the QALYs gained by screening increased, whereas the net costs of screening decreased. For colonoscopy screening from ages 45 to 75 years every 10 years (current ACS recommendation), the benefits increased from 35 to 56 quality-adjusted life-year (QALY) gained per 1000 40-year-olds, whereas the net per person costs decreased from $541 to $30, accounting for realistic adherence. When assuming perfect adherence, the ICER of colonoscopy screening every 10 years from ages 45 to 75 years (current ACS recommendation) compared to ages 50 to 75 years (current USPSTF recommendation) improved from $82,300 to $38,700 per QALY gained. Several screening strategies became cost-saving compared to no screening, such as all FIT screening strategies and colonoscopy screening from ages 50 to 75 years every 15 years.

Currently, screening is recommended from ages 45/50 years to 75 years with any of the tests evaluated in this study.[76,78,81] In line with previous analyses,[172,179] we found that only FIT and colonoscopy were efficient screening modalities. Furthermore, our results support the earlier start age of 45 years. From a cost-effectiveness perspective, screening initiation at age 40 years seems worth exploring. However, other considerations need to be taken into account besides cost-effectiveness. There is little empirical evidence on screening efficacy in average risk individuals below age 50 years, as only a few studies evaluated screening initiation at age 40 years.[180-182] Observational data on screening initiation at age 45 years will become available as a results of the updated ACS guideline.[78] Based on these data inferences can be made on the effectiveness of screening at this age. Only when these data have confirmed screening effectiveness and the increase in

CRC incidence in younger adults persists, starting screening before age 45 could be considered.

The current analyses are an extension of our analyses that were used to inform the 2018 ACS CRC screening guidelines.[99] We did not incorporate costs in our previous analysis,[99] as the ACS chose not to apply cost as a decision-making criterion. Furthermore, life-years gained were used rather than QALY gained, and perfect adherence was assumed. This study addresses these previous limitations and further supports screening initiation at age 45 years. Our estimate of the current cost-effectiveness of screening initiation at age 45 years rather than age 50 years is in line with the estimate from Ladabaum *et al.*, who estimated an ICER of $33,900 per QALY gained.[152]

Our study has three noteworthy limitations. First, the current age-specific CRC risk in the absence of screening is uncertain. We compared a scenario with 1975-1979 incidence, which was before screening implementation, to a scenario in which we used an incidence rate multiplier based on the increased CRC incidence observed in the prescreening ages.[16] In a sensitivity analyses, we evaluated a scenario with a lower incidence rate multiplier and a scenario in which we assumed that the increased incidence was not carried forward by the 1975 birth cohort when they age. The assumed background incidence impacts the balance between the benefits, harms, and costs of screening. Future research is needed to better understand secular trends both in time of birth as well as differential effects across the lifespan.

Second, we did not have commercial treatment cost estimates. In line with previous analyses, we multiplied CMS cost estimates by 1.35.[166] CRC care costs are an important component of the cost-effectiveness of screening, as screening can prevent CRC or can diagnose the disease in an earlier stage, thereby resulting in cost-savings. We performed sensitivity analyses in which we applied CMS rates or commercial rates to all ages, and observed that this minimally impacted our conclusions.

Third, it is likely that the increase in CRC care costs are accompanied by an improvement in CRC survival. Survival in our model is based on an analyses by Rutter et al.[134], who estimated stage-specific survival based on SEER data of CRC cases diagnosed until 2003, with a follow-up until 2010. In a sensitivity analysis, we explored the impact of assuming an improved stage III and stage IV survival based on hazard ratios from clinical trials,[178] and observed that his minimally impacted our results. Future studies are needed to determine the impact of these new drugs on CRC stage-specific survival on a national level.

Despite these limitations, our study may be of great value to policy makers and fellow researchers, as it demonstrates how the increasing incidence and cancer care costs impact the cost-effectiveness of CRC screening. Our results indicate that CRC screening initiation at age 45 years is now cost-effective. So far, the ACS is the only organization that recommends CRC screening initiation at age 45 years.[78] According to data from the National Health Interview Survey, utilization rates among 45 to 49 year olds increased

from 4.8% in the first quarter to 11.7% in the last quarter of 2018, coinciding with the release of the ACS guidelines.[183] The USPSTF is currently updating their CRC screening guidelines (www.uspreventiveservicestaskforce.org).

In conclusion, as a result of the increasing incidence and cancer care costs, the cost-effectiveness of CRC screening greatly improved, which further supports screening initiation at age 45 years rather than age 50 years.

Appendix 4.1

Table 1: Per lesion screening test sensitivities and specificities used in the analysis.

Test characteristic	Colonoscopy [a] (within reach)	FIT	HSgFOBT	mtSDNA	SIG (within reach)	CTC
Sensitivity for adenomas ≤5 mm, %	75	0 [e]	0 [e]	0 [e]	75	
Sensitivity for adenomas 6–9 mm, %	85	11.4	4.29	22	85	57
Sensitivity for adenomas ≥10 mm, %	95	15.9	14.7	28.4	95	84
Sensitivity for CRC, %	95	88.6/62.6 [f]	85.9/56.8 [f]	96.7/86.4 [f]	95	84
Specificity, %	86 [b]	96.4	92.5	89.8	87 [b]	88 [g]
Reach, %	95 [c]	100	100	100	76 [c]	100
Risk of fatal complications, %	0.01 [d]	0	0	0	0 [d]	0

FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multi-target stool DNA test; SIG - flexible sigmoidoscopy; CTC - computed tomographic colonography; CRC - colorectal cancer

[a] It was assumed that the same test characteristics for screening colonoscopies applied to colonoscopies for diagnostic follow-up or for surveillance.

[b] The lack of specificity with endoscopy reflects the detection of nonadenomatous polyps, which, in the case of flexible sigmoidoscopy, may lead to unnecessary diagnostic colonoscopy, and in the case of colonoscopy, leads to unnecessary polypectomy, which is associated with an increased risk of colonoscopy complications.

[c] 95% of the colonoscopies reached the end of the colorectum (cecum); for the remainder 5% the endpoint was distributed between the cecum and rectum. With flexible sigmoidoscopy, 76% reached the end the sigmoid colon; 14% had an endpoint between the beginning and the end of the sigmoid colon; 12% had an endpoint between the beginning and end of the descending colon.

[d] Case fatality was derived by combining the overall perforation rate from Warren et al.[104] with mortality given perforation (0.0519) in Gatto et al.[105] Flexible sigmoidoscopy was modeled without biopsy or polypectomy of detected lesions, and was therefore assumed to have 0 mortality risk.

[e] It was assumed that 1–5 mm adenomas do not bleed and therefore cannot cause a positive stool test.

[f] "Short" before clinical diagnosis / "Long" before clinical diagnosis.[184g] 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.

Appendix 4.2: Detailed description of costs and disutilities used.

Costs

Overview

This study was performed from a heath care sector perspective. All costs are expressed in 2017 US dollars, from the year they have been derived, using the Personal Health Care Deflator price index. In line with the 2016 recommendations of the second panel of cost-effectiveness analyses,[109] the following elements are included:

Sector	Type of Impact (list category within each sector with unit of measure if relevant)[a]	Included in This Reference Case Analysis From…Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
Formal Health Care Sector				
Health	Health outcomes (effects)			
	Longevity effects	☑	☐	
	Health-related quality-of-life effects	☑	☐	
	Other health effects (eg, adverse events and secondary transmissions of infections)	☑	☐	
	Medical costs			
	Paid for by third-party payers	☑	☐	
	Paid for by patients out-of-pocket	☑	☐	
	Future related medical costs (payers and patients)	☑	☐	
	Future unrelated medical costs (payers and patients)	☒	☐	
Informal Health Care Sector				
Health	Patient-time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non–Health Care Sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	☐	
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production[b]	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal or Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of intervention on home improvements (eg, removing lead paint)	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other (specify)	Other impacts	NA	☐	

Figure 1: Inventory of costs included in the analyses, based on the inventory template from Sanders et al. JAMA 2016

Cost of screening, follow-up, and surveillance procedures

Costs of screening, follow-up, and surveillance tests are based on Medicare payments for individuals ≥ age 65. Commercial costs will be used for individuals ≤ age 65 years.

Table 1: Medicare test cost assumptions.

HCPCS Code*	Use in model	Avg. Medicare allowed amount for procedure	Avg. Medicare allowed pathology payment	Avg. Medicare allowed anesthesia services payment [a]	Total payment	Bowel preparation kit [b]	Total health care perspective costs	Source
82270	HSgFOBT	$4.46	0	0	$4.46	0	$4.46	2017 Clinical Laboratory Fee Schedule (CLFS) National Limit
82274	FIT	$21.82	0	0	$21.82	0	$21.82	2017 Clinical Laboratory Fee Schedule (CLFS) National Limit
81528	mtSDNA	$512.43	0	0	$512.43	0	$512.43	2017 Clinical Laboratory Fee Schedule (CLFS) National Limit
G0104	SIG	$318.53	0	$47.37	$365.90	$13.85	$379.75	2014 allowed payments, inflated to 2017 dollars
74261	CTC [c]	$236.15	0	0	$236.15	$51.09	$287.24	2017 Physician Fee Schedule
G0105	Surveillance COL w/o lesion removal	$705.89	0	$88.55	$794.44	$51.09	$845.53	2014 allowed payments, inflated to 2017 dollars.
G0121	Screening COL w/o lesion removal	$750.25	0	$96.76	$847.02	$51.09	$898.11	2014 allowed payments, inflated to 2017 dollars.
45378	Follow-up COL w/o lesion removal	$701.76	0	$94.22	$795.98	$51.09	$847.07	2014 allowed payments, inflated to 2017 dollars.
45380-45381, 45383-45385	Any COL w/ lesion removal	$936.55	$132.25	$102.82	$1,171.62	$51.09	$1,222.71	2014 allowed payments, inflated to 2017 dollars.

FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multi-target stool DNA test; SIG - flexible sigmoidoscopy; CTC - computed tomographic colonography.

[a] Includes propofol and facility payments, when appropriate.

[b] Costs for bowel preparation agents for colonoscopy, sigmoidoscopy and CTC were based on the section "Colon Cleansing Medications" on GoodRX.com.

[c] There is no national average payment for CTC because it is not a covered procedure. We based our estimate on the payment for a diagnostic CTC w/o IV contrast.

Table 2: Commercial test cost assumptions.

Use in model	Avg. Commercial allowed amount for procedure	Avg. Commercial allowed pathology payment	Avg. Commercial allowed anesthesia services payment	Total payment	Bowel preparation kit [a]	Total health care perspective costs	Source
gFOBT	$5.67	0	0	$5.67	0	$5.67	Ladabaum et al. Am J Gastroenterology 2014, inflated to 2017 dollars
FIT	$23.79	0	0	$23.79	0	$23.79	Ladabaum et al. Am J Gastroenterology 2014, inflated to 2017 dollars
mtSDNA	$512.43	0	0	$512.43	0	$512.43	2017 Clinical Laboratory Fee Schedule (CLFS) National Limit [b]
SIG	$334.24	0	$49.35	$383.59	$13.85	$397.44	Ladabaum et al. Am J Gastroenterology 2014, inflated to 2017 dollars
CTC	$691.13	0	0	$691.13	$51.09	$742.22	Ladabaum et al. Am J Gastroenterology 2014, inflated to 2017 dollars
Any COL w/o lesion removal [c]	$1,083.15	0	$195.90	$1279.04	$51.09	$1330.13	Ladabaum et al. Am J Gastroenterology 2014, inflated to 2017 dollars
Any COL w/ lesion removal	$1,205.51	$308.18	$195.90	$1709.58	$51.09	$1760.67	Ladabaum et al. Am J Gastroenterology 2014, inflated to 2017 dollars

FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multi-target stool DNA test; SIG - flexible sigmoidoscopy; CTC - computed tomographic colonography.

[a] Costs for bowel preparation agents for colonoscopy, sigmoidoscopy and CTC were based on the section "Colon Cleansing Medications" on GoodRX.com.
[b] mtSDNA was not included in the estimate from Ladabaum et al. As costs of the other stool-based tests are not that different between commercial and medicare settings, we used the estimate of the 2017 CLFS for the commercial mtSDNA estimate as well.
[c] Ladabaum et al. did not distinguish costs between negative screening, diagnostic follow-up and surveillance colonoscopies. Therefore, the same estimate is used for all three types of colonoscopy.

The commercial costs are based on allowed payments – the contractually agreed amount the plan pays the provider for the service, after application of contractual discount provisions and other plan rules. The provider may receive this payment from the insurance plan or from the patient through co-payments or deductibles.

Colonoscopy complications costs

As no estimates have been published about commercial costs of colonoscopy complications, we decided to use a ratio of 1.35 in line with Ladabaum et al. [166]

Table 3: Medicare and commercial costs for colonoscopy complications used in the analysis

Colonoscopy complication	Cost ($), CMS perspective	Patient cost-sharing ($)	Total Medicare cost ($), health care perspective	Total commercial cost ($), health care perspective
Serious gastrointestinal complication	$6,847	$1,238	$8,085	$10,914
Other gastrointestinal complication	$4,878	$1,238	$6,116	$8,256
Cardiovascular complication	$5,347	$1,238	$6,584	$8,889

CMS - Centers for Medicare and Medicaid Services

Costs of cancer care

Net costs of CRC-related care by stage at diagnosis and phase of care were obtained from an analysis of 2007-2013 SEER-Medicare linked data (personal communication, Angela Mariotto, PhD[162]). The terminal phase takes precedence over the initial and continuing phase. The terminal phase reflects the last 12 months of life. The initial phase reflects the 12 months following diagnosis for persons who survive for more than 12 months (if survive for ≤12 months, person only experiences the terminal phase). The continuing phase is the time between the initial phase and the terminal phase for persons who survive for more than 24 months.

Table 4: 2007-2013 medicare annual costs of cancer care by stage at diagnosis and phase of care.

	Annual cost ($)			
Phase of cancer care	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial phase	$38,351	$54,384	$79,015	$117,416
Continuing phase	$3,946	$4,590	$7,101	$33,662
Terminal phase, death colorectal cancer	$77,395	$87,242	$91,337	$114,855
Terminal phase, death other causes	$20,326	$21,872	$29,901	$71,926

Table 5: 2007-2013 commercial annual costs of cancer care by stage at diagnosis and phase of care.

	Annual cost ($)			
Phase of cancer care	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial phase	$51,774	$73,418	$106,670	$158,511
Continuing phase	$5,328	$6,196	$9,586	$45,444
Terminal phase, death colorectal cancer	$104,483	$117,777	$123,305	$155,054
Terminal phase, death other causes	$27,440	$29,528	$40,367	$97,101

To evaluate the impact of the increased colorectal cancer care cost on the cost-effectiveness of colorectal cancer screening, the cost estimates from the period 1998-2003 were used as a comparison.[161] As no estimates have been published about commercial costs of colorectal cancer care, we decided to use a ratio of 1.35 in line with Ladabaum et al. [166]

Table 6: 1998-2003 Medicare annual costs of cancer care by stage at diagnosis and phase of care.

	Annual cost ($)			
Phase of cancer care	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial phase	$34,199	$47,360	$58,394	$77,302
Continuing phase	$2,897	$2,700	$3,902	$12,479
Terminal phase, death colorectal cancer	$61,954	$61,688	$65,343	$87,706
Terminal phase, death other causes	$15,153	$13,164	$17,545	$47,334

Table 7: 1998-2003 commercial annual costs of cancer care by stage at diagnosis and phase of care.

	Annual cost ($)			
Phase of cancer care	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial phase	$46,169	$63,935	$78,832	$104,358
Continuing phase	$3,911	$3,645	$5,268	$16,846
Terminal phase, death colorectal cancer	$83,638	$83,279	$88,213	$118,402
Terminal phase, death other causes	$20,457	$17,772	$23,686	$63,901

Disutilities
Time estimates of procedures

Table 8: Time spent on procedure, based on Jonas et al. [167]**.**

Colonoscopy component	**Patient time**
	Hours
Bowel preparation	16.70
Travel to	0.42
Waiting/preparing	1.40
Sedation (assume always used)	0.20
Procedure	0.33
Onsite recovery	0.78
Travel home	0.58
Recovery to routine	15.80
Colonoscopy – total	**36.22**

Table 9: Time spent on flexible sigmoidoscopy. [a]

SIG component	**Patient time**	**Assumptions**
	Hours	
Bowel preparation	1.5	Expert opinion
Travel to	0.42	Same as colonoscopy
Waiting/ preparing	0.85	For individuals without sedation, the waiting/ preparing time was 50% of that of colonoscopy; for individuals with sedation it is the same as for colonoscopy.
Sedation	0.04	For individuals without sedation, it is 0; for individuals with sedation, it is the same as colonoscopy.
Procedure	0.33	Generally 20 minutes, expert opinion
Onsite recovery	0.48	No on-site recovery for individuals without sedation; same as colonoscopy for individuals with sedation
Travel home	0.58	Same as colonoscopy
Recovery to routine	6.56	For individuals without sedation, we assume the recovery time is 25% of that of colonoscopy; for individuals with sedation we assume the same time as for colonoscopy
SIG - total	**10.77**	

SIG - flexible sigmoidoscopy

[a] We assumed sedation was used for 22% of flexible sigmoidoscopies based on CMS claims data.

Table 10: Time spent on CTC.

CTC component	Patient time	Assumptions
	Hours	
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	Approximately 15 minutes
Onsite recovery	0.00	No on-site recovery
Travel home	0.58	Same as colonoscopy
Recovery to routine	0.00	Immediately back to routine
CTC - total	**19.35**	

CTC - computed tomographic colonography

We assume that the stool-based test take 1 hour.

Test disutilities

Table 11: Assumptions for utility losses associated with the screening tests itself.

Screening modality	Disutility	Source	Time the disutility applies in hours [a]	Utility loss per event
Colonoscopy (regardless of type)	0.12	Swan et al. [168]	36.22	0.000496
SIG	0.12	Same as colonoscopy	10.77	0.000147
CTC	0.12	Same as colonoscopy	19.35	0.000265
FIT	0	Expert opinion	1	0
HSgFOBT	0	Expert opinion	1	0
mtSDNA	0	Expert opinion	1	0

FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multi-target stool DNA test; SIG - flexible sigmoidoscopy; CTC - computed tomographic colonography.

[a] See Tables 8-10 to see how these were derived.

Waiting for test result

Table 12: Assumptions for utility losses associated with waiting for the test result.

Screening modality	Disutility	Source	Time the disutility applies in days [a]	Utility loss per event
Colonoscopy without polypectomy	0	Immediate results	0	0
Colonoscopy with polypectomy	0.033036	Expert opinion, same as waiting for a diagnostic follow-up after a positive FIT	10	0.000905
SIG	0	Immediate results	0	0
CTC	0.003304	Expert opinion, 10% of waiting for a diagnostic follow-up after a positive FIT	3	0.000027
FIT			7	0.000063
HSgFOBT			7	0.000063
mtSDNA			14	0.000127

FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multi-target stool DNA test; SIG - flexible sigmoidoscopy; CTC - computed tomographic colonography.

[a] These time estimates are based on expert opinion.

Waiting for diagnostic follow-up colonoscopy

Table 13: Assumptions for utility losses associated with waiting for a diagnostic follow-up colonoscopy.

Screening modality	Disutility	Source	Time the disutility applies in days [a]	Utility loss per event
SIG CTC FIT HSgFOBT mtSDNA	0.033036	12.5% are very worried [169]. Assuming they experience half of the utility decrement as for a positive mammography as reported by Mandelblatt [170]	14	0.001267

FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multi-target stool DNA test; SIG - flexible sigmoidoscopy; CTC - computed tomographic colonography.

[a] These time estimates are based on expert opinion.

Summary of test disutilities

Table 14: Summary of test disutilities.

Test	Disutility when positive	Disutility when negative
Colonoscopy	0.001401	0.000496
SIG	0.001415	0.000147
CTC	0.001559	0.000292
FIT	0.001330	0.000063
HSgFOBT	0.001330	0.000063
mtSDNA	0.001394	0.000127

FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multi-target stool DNA test; SIG - flexible sigmoidoscopy; CTC - computed tomographic colonography.

Colonoscopy complication disutility assumptions

Table 15: Complication disutilities.

Colonoscopy complication	Utility loss	Notes
Serious gastrointestinal event	0.0055	4 days at 0.5 utility
Other gastrointestinal event	0.0027	2 days at 0.5 utility
Cardiovascular event	0.0048	3.5 days at 0.5 utility

Colorectal cancer care disutility assumptions

Table 16: Utility losses associated with cancer care by stage at diagnosis and phase of care. Source: Adapted from Ness et al.[171].

Phase of cancer care	Stage I	Stage II	Stage III	Stage IV
Initial phase	0.12	0.18	0.24	0.7
Continuing phase	0.05	0.05	0.24	0.7
Terminal phase, death CRC	0.7	0.7	0.7	0.7
Terminal phase, death other causes	0.05	0.05	0.24	0.7

CRC - colorectal cancer

Appendix 4.3

Table 1: Adherence simulated to determine benefits of different screening strategies.

Parameter	Scenario 60% up to date	Scenario 80% up to date
Stratum 1: Potential participants		
Size	90.00%	90.00%
Adherence to screening [a]	66.67%	88.89%
Adherence to screening if previously adherent [b]	90.00%	95.00%
Adherence to screening if previously not adherent [c]	20.00%	40.00%
Adherence to diagnostic follow-up [d] and surveillance	80.00%	90.00%
Stratum 2: Population that never participate		
Size	10.00%	10.00%
Adherence to screening	0.00%	0.00%

[a] As the 60% or 80% of the population that is up to date with screening is derived from stratum 1, these are calculated by 60/90 and 80/90, respectively.

[b] We assumed that respectively 90% [185,186] and 95% of the population that participated previously will participate again at the recommended interval.

[c] Calculated such that overall adherence in next screening round remains the same (i.e., 60%, 80%).

[d] Represents the adherence to a diagnostic colonoscopy after any positive non-colonoscopy test.[55,114]

Appendix 4.4. Results from all evaluated screening strategies in the four different scenarios, under the assumption of perfect adherence. Results are presented per 1,000 40-year-olds.

Table 1: Scenario 1: Not incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
No screening	-	-	-	68	28	70	0	0	2.57	-
Colonoscopy	40	75	5	19	4	8,090	96	115	7.67	No
Colonoscopy	40	75	10	24	5	5,310	89	106	5.62	No
Colonoscopy	40	75	15	27	6	4,390	81	96	4.92	No
Colonoscopy	40	80	5	19	3	8,440	97	116	7.77	No
Colonoscopy	40	80	10	23	5	5,700	89	107	5.73	No
Colonoscopy	40	80	15	27	6	4,390	81	96	4.92	No
Colonoscopy	40	85	5	19	3	8,680	97	116	7.83	No
Colonoscopy	40	85	10	23	5	5,700	89	107	5.73	No
Colonoscopy	40	85	15	27	6	4,680	81	97	5.00	No
Colonoscopy	45	75	5	20	4	7,030	92	110	6.29	No
Colonoscopy	45	75	10	23	5	4,960	85	102	4.81	No
Colonoscopy	45	75	15	27	6	4,150	79	94	4.43	No
Colonoscopy	45	80	5	19	4	7,390	92	110	6.39	No
Colonoscopy	45	80	10	23	5	4,960	85	102	4.81	No
Colonoscopy	45	80	15	27	6	4,150	79	94	4.43	No
Colonoscopy	45	85	5	19	4	7,620	92	110	6.45	No
Colonoscopy	45	85	10	23	5	5,230	85	102	4.88	No
Colonoscopy	45	85	15	27	6	4,150	79	94	4.43	No
Colonoscopy	50	75	5	22	5	5,990	84	101	5.17	No
Colonoscopy	50	75	10	25	6	4,130	79	94	4.17	No
Colonoscopy	50	75	15	29	8	3,380	73	87	3.72	No
Colonoscopy	50	80	5	21	4	6,350	84	101	5.27	No
Colonoscopy	50	80	10	24	5	4,520	79	95	4.28	No
Colonoscopy	50	80	15	27	7	3,810	74	88	3.84	No
Colonoscopy	50	85	5	21	4	6,580	84	101	5.33	No
Colonoscopy	50	85	10	24	5	4,520	79	95	4.28	No
Colonoscopy	50	85	15	27	7	3,810	74	88	3.84	No
FIT	40	75	1	34	7	2,220	85	99	3.49	No
FIT	40	75	2	42	10	1,550	74	84	3.16	No
FIT	40	75	3	47	12	1,210	64	72	3.04	No
FIT	40	80	1	32	6	2,320	87	100	3.52	No
FIT	40	80	2	41	8	1,640	76	87	3.18	No
FIT	40	80	3	46	10	1,290	67	75	3.07	No
FIT	40	85	1	32	5	2,380	87	101	3.54	No
FIT	40	85	2	41	8	1,680	77	87	3.20	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
FIT	40	85	3	47	10	1,340	68	76	3.10	No
FIT	45	75	1	34	7	2,010	81	94	3.21	No
FIT	45	75	2	42	10	1,440	70	80	2.98	No
FIT	45	75	3	47	12	1,150	62	69	2.92	No
FIT	45	80	1	33	6	2,110	82	95	3.24	No
FIT	45	80	2	42	9	1,500	72	82	3.00	No
FIT	45	80	3	47	11	1,180	63	71	2.93	No
FIT	45	85	1	33	6	2,180	83	96	3.26	No
FIT	45	85	2	42	8	1,560	73	82	3.03	No
FIT	45	85	3	47	10	1,240	64	72	2.97	No
FIT	50	75	1	36	8	1,770	74	85	2.99	No
FIT	50	75	2	44	11	1,260	64	72	2.86	No
FIT	50	75	3	49	13	1,010	56	62	2.81	No
FIT	50	80	1	35	7	1,870	75	87	3.01	No
FIT	50	80	2	43	9	1,350	66	75	2.89	No
FIT	50	80	3	48	11	1,080	58	65	2.85	No
FIT	50	85	1	34	6	1,940	76	88	3.04	No
FIT	50	85	2	43	8	1,390	67	75	2.91	No
FIT	50	85	3	48	11	1,110	59	65	2.86	No
HSgFOBT	40	75	1	32	7	2,960	85	98	3.79	No
HSgFOBT	40	75	2	40	9	2,120	74	85	3.39	No
HSgFOBT	40	75	3	45	12	1,640	64	72	3.22	No
HSgFOBT	40	80	1	31	6	3,090	86	99	3.82	No
HSgFOBT	40	80	2	39	8	2,240	76	87	3.43	No
HSgFOBT	40	80	3	44	10	1,750	67	75	3.26	No
HSgFOBT	40	85	1	31	5	3,180	87	100	3.85	No
HSgFOBT	40	85	2	39	7	2,300	77	87	3.45	No
HSgFOBT	40	85	3	45	10	1,810	67	75	3.29	No
HSgFOBT	45	75	1	32	7	2,650	80	93	3.43	No
HSgFOBT	45	75	2	40	9	1,930	70	80	3.16	No
HSgFOBT	45	75	3	46	12	1,520	61	69	3.06	No
HSgFOBT	45	80	1	32	6	2,780	82	94	3.47	No
HSgFOBT	45	80	2	40	8	2,010	72	81	3.19	No
HSgFOBT	45	80	3	45	11	1,570	63	70	3.08	No
HSgFOBT	45	85	1	31	6	2,870	82	95	3.49	No
HSgFOBT	45	85	2	40	8	2,090	72	82	3.22	No
HSgFOBT	45	85	3	46	10	1,640	64	71	3.11	No
HSgFOBT	50	75	1	34	8	2,310	74	85	3.15	No
HSgFOBT	50	75	2	42	10	1,650	63	72	2.99	No
HSgFOBT	50	75	3	47	13	1,310	55	62	2.91	No
HSgFOBT	50	80	1	33	7	2,440	75	86	3.18	No
HSgFOBT	50	80	2	41	9	1,780	66	74	3.02	No
HSgFOBT	50	80	3	47	11	1,410	58	64	2.95	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
HSgFOBT	50	85	1	33	6	2,530	75	87	3.21	No
HSgFOBT	50	85	2	41	8	1,830	66	75	3.04	No
HSgFOBT	50	85	3	47	11	1,450	58	64	2.96	No
mtSDNA	40	75	1	27	6	3,410	90	105	9.46	No
mtSDNA	40	75	3	37	9	2,130	78	90	6.08	No
mtSDNA	40	75	5	42	10	1,740	70	79	5.17	No
mtSDNA	40	80	1	26	5	3,550	91	106	9.67	No
mtSDNA	40	80	3	35	7	2,250	80	92	6.22	No
mtSDNA	40	80	5	41	9	1,810	71	80	5.25	No
mtSDNA	40	85	1	25	5	3,650	91	106	9.81	No
mtSDNA	40	85	3	35	7	2,330	81	93	6.32	No
mtSDNA	40	85	5	41	9	1,850	71	81	5.31	No
mtSDNA	45	75	1	27	6	3,070	85	100	7.78	No
mtSDNA	45	75	3	37	8	1,980	75	87	5.28	No
mtSDNA	45	75	5	42	10	1,590	66	75	4.56	No
mtSDNA	45	80	1	26	5	3,210	86	101	7.99	No
mtSDNA	45	80	3	36	8	2,040	76	88	5.35	No
mtSDNA	45	80	5	42	9	1,660	68	77	4.65	No
mtSDNA	45	85	1	26	5	3,310	87	101	8.13	No
mtSDNA	45	85	3	36	7	2,120	77	88	5.46	No
mtSDNA	45	85	5	42	9	1,710	68	77	4.70	No
mtSDNA	50	75	1	29	6	2,690	79	92	6.39	No
mtSDNA	50	75	3	38	9	1,730	68	79	4.54	No
mtSDNA	50	75	5	44	11	1,420	61	69	4.06	No
mtSDNA	50	80	1	28	6	2,830	80	93	6.61	No
mtSDNA	50	80	3	37	8	1,850	70	81	4.68	No
mtSDNA	50	80	5	43	10	1,490	62	70	4.15	No
mtSDNA	50	85	1	27	5	2,930	80	93	6.75	No
mtSDNA	50	85	3	37	8	1,890	71	81	4.73	No
mtSDNA	50	85	5	43	9	1,530	62	70	4.21	No
Sigmoidoscopy	40	75	5	28	7	2,750	79	93	4.74	No
Sigmoidoscopy	40	75	10	32	9	2,190	70	83	3.97	No
Sigmoidoscopy	40	80	5	27	7	2,830	79	94	4.80	No
Sigmoidoscopy	40	80	10	31	8	2,310	71	84	4.04	No
Sigmoidoscopy	40	85	5	27	7	2,880	79	94	4.84	No
Sigmoidoscopy	40	85	10	31	8	2,310	71	84	4.04	No
Sigmoidoscopy	45	75	5	28	7	2,560	75	89	4.19	No
Sigmoidoscopy	45	75	10	32	9	2,140	68	81	3.64	No
Sigmoidoscopy	45	80	5	28	7	2,630	76	90	4.25	No
Sigmoidoscopy	45	80	10	32	9	2,140	68	81	3.64	No
Sigmoidoscopy	45	85	5	28	7	2,680	76	90	4.28	No
Sigmoidoscopy	45	85	10	32	9	2,210	68	81	3.68	No
Sigmoidoscopy	50	75	5	29	8	2,310	70	83	3.72	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
Sigmoidoscopy	50	75	10	33	10	1,900	63	75	3.32	No
Sigmoidoscopy	50	80	5	29	7	2,390	70	83	3.78	No
Sigmoidoscopy	50	80	10	32	9	2,020	64	76	3.39	No
Sigmoidoscopy	50	85	5	29	7	2,430	70	83	3.81	No
Sigmoidoscopy	50	85	10	32	9	2,020	64	76	3.39	No
CTC	40	75	5	31	7	2,110	81	95	5.53	No
CTC	40	75	10	40	11	1,520	65	75	4.52	No
CTC	40	80	5	30	6	2,190	82	96	5.57	No
CTC	40	80	10	38	9	1,630	67	77	4.57	No
CTC	40	85	5	30	6	2,230	83	96	5.60	No
CTC	40	85	10	38	9	1,630	67	77	4.57	No
CTC	45	75	5	32	7	1,950	78	91	4.72	No
CTC	45	75	10	39	11	1,490	63	73	3.93	No
CTC	45	80	5	31	7	2,030	79	92	4.76	No
CTC	45	80	10	39	11	1,490	63	73	3.93	No
CTC	45	85	5	30	6	2,070	79	92	4.79	No
CTC	45	85	10	39	10	1,570	64	74	3.98	No
CTC	50	75	5	33	8	1,760	72	84	4.04	No
CTC	50	75	10	41	12	1,310	58	67	3.61	No
CTC	50	80	5	32	7	1,840	73	85	4.08	No
CTC	50	80	10	39	10	1,420	61	70	3.66	No
CTC	50	85	5	32	7	1,880	73	85	4.12	No
CTC	50	85	10	39	10	1,420	61	70	3.66	No

CRC - colorectal cancer; CTC - computed tomographic colonography; FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multitarget stool DNA; LYG - life-years gained; QALYG - quality-adjusted life-years gained; ACER - average cost-effectiveness ratio (compared to no screening).

Table 2: Scenario 2: Not incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
No screening	-	-	-	68	28	70	0	0	3.68	-
Colonoscopy	40	75	5	19	4	8,090	96	115	7.99	No
Colonoscopy	40	75	10	24	5	5,310	89	106	6.03	No
Colonoscopy	40	75	15	27	6	4,390	81	96	5.40	No
Colonoscopy	40	80	5	19	3	8,440	97	116	8.09	No
Colonoscopy	40	80	10	23	5	5,700	89	107	6.13	No
Colonoscopy	40	80	15	27	6	4,390	81	96	5.40	No
Colonoscopy	40	85	5	19	3	8,680	97	116	8.15	No
Colonoscopy	40	85	10	23	5	5,700	89	107	6.13	No
Colonoscopy	40	85	15	27	6	4,680	81	97	5.48	No
Colonoscopy	45	75	5	20	4	7,030	92	110	6.65	No
Colonoscopy	45	75	10	23	5	4,960	85	102	5.25	No
Colonoscopy	45	75	15	27	6	4,150	79	94	4.94	No
Colonoscopy	45	80	5	19	4	7,390	92	110	6.75	No
Colonoscopy	45	80	10	23	5	4,960	85	102	5.25	No
Colonoscopy	45	80	15	27	6	4,150	79	94	4.94	No
Colonoscopy	45	85	5	19	4	7,620	92	110	6.81	No
Colonoscopy	45	85	10	23	5	5,230	85	102	5.31	No
Colonoscopy	45	85	15	27	6	4,150	79	94	4.94	No
Colonoscopy	50	75	5	22	5	5,990	84	101	5.61	No
Colonoscopy	50	75	10	25	6	4,130	79	94	4.67	No
Colonoscopy	50	75	15	29	8	3,380	73	87	4.27	No
Colonoscopy	50	80	5	21	4	6,350	84	101	5.71	No
Colonoscopy	50	80	10	24	5	4,520	79	95	4.77	No
Colonoscopy	50	80	15	27	7	3,810	74	88	4.38	No
Colonoscopy	50	85	5	21	4	6,580	84	101	5.77	No
Colonoscopy	50	85	10	24	5	4,520	79	95	4.77	No
Colonoscopy	50	85	15	27	7	3,810	74	88	4.38	No
FIT	40	75	1	34	7	2,220	85	99	4.01	No
FIT	40	75	2	42	10	1,550	74	84	3.82	No
FIT	40	75	3	47	12	1,210	64	72	3.80	No
FIT	40	80	1	32	6	2,320	87	100	4.03	No
FIT	40	80	2	41	8	1,640	76	87	3.84	No
FIT	40	80	3	46	10	1,290	67	75	3.82	No
FIT	40	85	1	32	5	2,380	87	101	4.05	No
FIT	40	85	2	41	8	1,680	77	87	3.85	No
FIT	40	85	3	47	10	1,340	68	76	3.85	No
FIT	45	75	1	34	7	2,010	81	94	3.77	No
FIT	45	75	2	42	10	1,440	70	80	3.68	Yes
FIT	45	75	3	47	12	1,150	62	69	3.70	No
FIT	45	80	1	33	6	2,110	82	95	3.79	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
FIT	45	80	2	42	9	1,500	72	82	3.69	No
FIT	45	80	3	47	11	1,180	63	71	3.71	No
FIT	45	85	1	33	6	2,180	83	96	3.81	No
FIT	45	85	2	42	8	1,560	73	82	3.71	No
FIT	45	85	3	47	10	1,240	64	72	3.74	No
FIT	50	75	1	36	8	1,770	74	85	3.61	Yes
FIT	50	75	2	44	11	1,260	64	72	3.61	Yes
FIT	50	75	3	49	13	1,010	56	62	3.64	Yes
FIT	50	80	1	35	7	1,870	75	87	3.62	Yes
FIT	50	80	2	43	9	1,350	66	75	3.63	Yes
FIT	50	80	3	48	11	1,080	58	65	3.66	Yes
FIT	50	85	1	34	6	1,940	76	88	3.64	Yes
FIT	50	85	2	43	8	1,390	67	75	3.64	Yes
FIT	50	85	3	48	11	1,110	59	65	3.68	Yes
HSgFOBT	40	75	1	32	7	2,960	85	98	4.30	No
HSgFOBT	40	75	2	40	9	2,120	74	85	4.04	No
HSgFOBT	40	75	3	45	12	1,640	64	72	3.97	No
HSgFOBT	40	80	1	31	6	3,090	86	99	4.32	No
HSgFOBT	40	80	2	39	8	2,240	76	87	4.06	No
HSgFOBT	40	80	3	44	10	1,750	67	75	3.99	No
HSgFOBT	40	85	1	31	5	3,180	87	100	4.35	No
HSgFOBT	40	85	2	39	7	2,300	77	87	4.08	No
HSgFOBT	40	85	3	45	10	1,810	67	75	4.02	No
HSgFOBT	45	75	1	32	7	2,650	80	93	3.99	No
HSgFOBT	45	75	2	40	9	1,930	70	80	3.84	No
HSgFOBT	45	75	3	46	12	1,520	61	69	3.83	No
HSgFOBT	45	80	1	32	6	2,780	82	94	4.01	No
HSgFOBT	45	80	2	40	8	2,010	72	81	3.86	No
HSgFOBT	45	80	3	45	11	1,570	63	70	3.84	No
HSgFOBT	45	85	1	31	6	2,870	82	95	4.03	No
HSgFOBT	45	85	2	40	8	2,090	72	82	3.89	No
HSgFOBT	45	85	3	46	10	1,640	64	71	3.88	No
HSgFOBT	50	75	1	34	8	2,310	74	85	3.76	No
HSgFOBT	50	75	2	42	10	1,650	63	72	3.73	No
HSgFOBT	50	75	3	47	13	1,310	55	62	3.73	No
HSgFOBT	50	80	1	33	7	2,440	75	86	3.79	No
HSgFOBT	50	80	2	41	9	1,780	66	74	3.75	No
HSgFOBT	50	80	3	47	11	1,410	58	64	3.76	No
HSgFOBT	50	85	1	33	6	2,530	75	87	3.81	No
HSgFOBT	50	85	2	41	8	1,830	66	75	3.77	No
HSgFOBT	50	85	3	47	11	1,450	58	64	3.78	No
mtSDNA	40	75	1	27	6	3,410	90	105	9.89	No
mtSDNA	40	75	3	37	9	2,130	78	90	6.66	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
mtSDNA	40	75	5	42	10	1,740	70	79	5.85	No
mtSDNA	40	80	1	26	5	3,550	91	106	10.09	No
mtSDNA	40	80	3	35	7	2,250	80	92	6.80	No
mtSDNA	40	80	5	41	9	1,810	71	80	5.93	No
mtSDNA	40	85	1	25	5	3,650	91	106	10.23	No
mtSDNA	40	85	3	35	7	2,330	81	93	6.90	No
mtSDNA	40	85	5	41	9	1,850	71	81	5.99	No
mtSDNA	45	75	1	27	6	3,070	85	100	8.25	No
mtSDNA	45	75	3	37	8	1,980	75	87	5.89	No
mtSDNA	45	75	5	42	10	1,590	66	75	5.28	No
mtSDNA	45	80	1	26	5	3,210	86	101	8.45	No
mtSDNA	45	80	3	36	8	2,040	76	88	5.96	No
mtSDNA	45	80	5	42	9	1,660	68	77	5.36	No
mtSDNA	45	85	1	26	5	3,310	87	101	8.59	No
mtSDNA	45	85	3	36	7	2,120	77	88	6.06	No
mtSDNA	45	85	5	42	9	1,710	68	77	5.41	No
mtSDNA	50	75	1	29	6	2,690	79	92	6.92	No
mtSDNA	50	75	3	38	9	1,730	68	79	5.21	No
mtSDNA	50	75	5	44	11	1,420	61	69	4.82	No
mtSDNA	50	80	1	28	6	2,830	80	93	7.13	No
mtSDNA	50	80	3	37	8	1,850	70	81	5.34	No
mtSDNA	50	80	5	43	10	1,490	62	70	4.90	No
mtSDNA	50	85	1	27	5	2,930	80	93	7.27	No
mtSDNA	50	85	3	37	8	1,890	71	81	5.39	No
mtSDNA	50	85	5	43	9	1,530	62	70	4.96	No
Sigmoidoscopy	40	75	5	28	7	2,750	79	93	5.24	No
Sigmoidoscopy	40	75	10	32	9	2,190	70	83	4.54	No
Sigmoidoscopy	40	80	5	27	7	2,830	79	94	5.29	No
Sigmoidoscopy	40	80	10	31	8	2,310	71	84	4.61	No
Sigmoidoscopy	40	85	5	27	7	2,880	79	94	5.32	No
Sigmoidoscopy	40	85	10	31	8	2,310	71	84	4.61	No
Sigmoidoscopy	45	75	5	28	7	2,560	75	89	4.71	No
Sigmoidoscopy	45	75	10	32	9	2,140	68	81	4.22	No
Sigmoidoscopy	45	80	5	28	7	2,630	76	90	4.76	No
Sigmoidoscopy	45	80	10	32	9	2,140	68	81	4.22	No
Sigmoidoscopy	45	85	5	28	7	2,680	76	90	4.80	No
Sigmoidoscopy	45	85	10	32	9	2,210	68	81	4.27	No
Sigmoidoscopy	50	75	5	29	8	2,310	70	83	4.30	No
Sigmoidoscopy	50	75	10	33	10	1,900	63	75	3.95	No
Sigmoidoscopy	50	80	5	29	7	2,390	70	83	4.35	No
Sigmoidoscopy	50	80	10	32	9	2,020	64	76	4.02	No
Sigmoidoscopy	50	85	5	29	7	2,430	70	83	4.38	No
Sigmoidoscopy	50	85	10	32	9	2,020	64	76	4.02	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
CTC	40	75	5	31	7	2,110	81	95	6.05	No
CTC	40	75	10	40	11	1,520	65	75	5.20	No
CTC	40	80	5	30	6	2,190	82	96	6.08	No
CTC	40	80	10	38	9	1,630	67	77	5.24	No
CTC	40	85	5	30	6	2,230	83	96	6.11	No
CTC	40	85	10	38	9	1,630	67	77	5.24	No
CTC	45	75	5	32	7	1,950	78	91	5.26	No
CTC	45	75	10	39	11	1,490	63	73	4.61	No
CTC	45	80	5	31	7	2,030	79	92	5.30	No
CTC	45	80	10	39	11	1,490	63	73	4.61	No
CTC	45	85	5	30	6	2,070	79	92	5.32	No
CTC	45	85	10	39	10	1,570	64	74	4.66	No
CTC	50	75	5	33	8	1,760	72	84	4.65	No
CTC	50	75	10	41	12	1,310	58	67	4.34	No
CTC	50	80	5	32	7	1,840	73	85	4.68	No
CTC	50	80	10	39	10	1,420	61	70	4.38	No
CTC	50	85	5	32	7	1,880	73	85	4.71	No
CTC	50	85	10	39	10	1,420	61	70	4.38	No

CRC - colorectal cancer; CTC - computed tomographic colonography; FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multitarget stool DNA; LYG - life-years gained; QALYG - quality-adjusted life-years gained; ACER - average cost-effectiveness ratio (compared to no screening).

Table 3: Scenario 3: Incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
No screening	-	-	-	108	45	110	0	0	4.11	-
Colonoscopy	40	75	5	30	6	8,330	154	186	8.39	No
Colonoscopy	40	75	10	37	8	6,080	142	171	6.77	No
Colonoscopy	40	75	15	41	10	5,230	130	156	6.21	No
Colonoscopy	40	80	5	30	5	8,540	154	187	8.45	No
Colonoscopy	40	80	10	35	7	6,350	143	172	6.84	No
Colonoscopy	40	80	15	41	10	5,230	130	156	6.21	No
Colonoscopy	40	85	5	30	5	8,670	154	187	8.48	No
Colonoscopy	40	85	10	35	7	6,350	143	172	6.84	No
Colonoscopy	40	85	15	41	9	5,420	130	156	6.27	No
Colonoscopy	45	75	5	32	6	7,280	146	177	7.06	No
Colonoscopy	45	75	10	36	8	5,650	137	165	5.95	No
Colonoscopy	45	75	15	41	10	4,920	127	152	5.69	No
Colonoscopy	45	80	5	31	6	7,490	147	177	7.11	No
Colonoscopy	45	80	10	36	8	5,650	137	165	5.95	No
Colonoscopy	45	80	15	41	10	4,920	127	152	5.69	No
Colonoscopy	45	85	5	31	6	7,620	147	177	7.15	No
Colonoscopy	45	85	10	36	8	5,810	137	165	6.00	No
Colonoscopy	45	85	15	41	10	4,920	127	152	5.69	No
Colonoscopy	50	75	5	34	7	6,230	134	162	6.02	No
Colonoscopy	50	75	10	39	9	4,840	126	151	5.33	No
Colonoscopy	50	75	15	45	12	4,180	117	140	5.01	No
Colonoscopy	50	80	5	33	7	6,450	134	162	6.08	No
Colonoscopy	50	80	10	38	8	5,100	127	152	5.40	No
Colonoscopy	50	80	15	43	10	4,500	119	142	5.09	No
Colonoscopy	50	85	5	33	7	6,580	134	162	6.11	No
Colonoscopy	50	85	10	38	8	5,100	127	152	5.40	No
Colonoscopy	50	85	15	43	10	4,500	119	142	5.09	No
FIT	40	75	1	52	11	2,940	136	159	4.81	No
FIT	40	75	2	66	15	2,140	118	135	4.59	No
FIT	40	75	3	74	19	1,700	102	115	4.53	No
FIT	40	80	1	50	9	3,040	138	162	4.83	No
FIT	40	80	2	64	13	2,240	122	139	4.61	No
FIT	40	80	3	73	17	1,800	106	120	4.57	No
FIT	40	85	1	50	8	3,100	139	163	4.85	No
FIT	40	85	2	64	12	2,290	122	140	4.63	No
FIT	40	85	3	73	15	1,860	107	121	4.60	No
FIT	45	75	1	54	11	2,700	129	151	4.53	No
FIT	45	75	2	67	16	1,990	112	129	4.42	No
FIT	45	75	3	75	19	1,620	98	111	4.41	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
FIT	45	80	1	52	10	2,800	132	154	4.54	No
FIT	45	80	2	65	14	2,060	115	131	4.44	No
FIT	45	80	3	74	17	1,670	100	113	4.43	No
FIT	45	85	1	51	9	2,860	132	155	4.56	No
FIT	45	85	2	65	13	2,130	116	132	4.47	No
FIT	45	85	3	74	16	1,730	102	115	4.47	No
FIT	50	75	1	56	12	2,400	118	137	4.32	No
FIT	50	75	2	69	17	1,760	102	116	4.30	No
FIT	50	75	3	77	20	1,430	89	99	4.31	No
FIT	50	80	1	54	11	2,500	120	140	4.34	No
FIT	50	80	2	67	14	1,870	105	120	4.33	No
FIT	50	80	3	76	18	1,530	92	103	4.35	No
FIT	50	85	1	54	10	2,570	121	141	4.36	No
FIT	50	85	2	67	13	1,920	106	121	4.35	No
FIT	50	85	3	76	17	1,560	93	104	4.37	No
HSgFOBT	40	75	1	49	10	3,710	136	159	5.11	No
HSgFOBT	40	75	2	62	15	2,750	118	136	4.82	No
HSgFOBT	40	75	3	71	19	2,170	102	116	4.71	No
HSgFOBT	40	80	1	48	9	3,830	138	161	5.13	No
HSgFOBT	40	80	2	61	13	2,870	122	140	4.85	No
HSgFOBT	40	80	3	70	16	2,290	106	120	4.74	No
HSgFOBT	40	85	1	47	8	3,900	138	161	5.15	No
HSgFOBT	40	85	2	61	12	2,920	122	140	4.87	No
HSgFOBT	40	85	3	70	15	2,350	107	121	4.78	No
HSgFOBT	45	75	1	51	11	3,360	129	151	4.76	No
HSgFOBT	45	75	2	63	15	2,520	112	129	4.59	No
HSgFOBT	45	75	3	72	18	2,020	98	111	4.54	No
HSgFOBT	45	80	1	49	10	3,480	131	153	4.78	No
HSgFOBT	45	80	2	62	13	2,600	114	131	4.61	No
HSgFOBT	45	80	3	72	17	2,080	100	113	4.56	No
HSgFOBT	45	85	1	49	9	3,550	131	153	4.80	No
HSgFOBT	45	85	2	62	12	2,680	116	132	4.64	No
HSgFOBT	45	85	3	72	16	2,150	101	114	4.60	No
HSgFOBT	50	75	1	53	12	2,960	117	137	4.48	No
HSgFOBT	50	75	2	67	16	2,180	101	116	4.42	No
HSgFOBT	50	75	3	75	20	1,760	88	99	4.40	No
HSgFOBT	50	80	1	52	11	3,070	119	139	4.50	No
HSgFOBT	50	80	2	65	14	2,310	105	119	4.45	No
HSgFOBT	50	80	3	74	18	1,870	91	102	4.44	No
HSgFOBT	50	85	1	52	10	3,150	120	140	4.52	No
HSgFOBT	50	85	2	65	13	2,360	105	120	4.47	No
HSgFOBT	50	85	3	74	17	1,900	92	103	4.46	No
mtSDNA	40	75	1	41	9	4,240	143	170	10.32	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
mtSDNA	40	75	3	57	14	2,820	125	145	7.34	No
mtSDNA	40	75	5	66	16	2,330	111	127	6.53	No
mtSDNA	40	80	1	40	8	4,350	145	171	10.46	No
mtSDNA	40	80	3	55	11	2,940	128	148	7.46	No
mtSDNA	40	80	5	65	14	2,410	113	129	6.61	No
mtSDNA	40	85	1	39	7	4,430	145	172	10.55	No
mtSDNA	40	85	3	55	10	3,010	129	149	7.54	No
mtSDNA	40	85	5	65	14	2,450	113	130	6.66	No
mtSDNA	45	75	1	42	9	3,850	137	162	8.68	No
mtSDNA	45	75	3	57	13	2,640	120	139	6.54	No
mtSDNA	45	75	5	67	16	2,160	106	121	5.94	No
mtSDNA	45	80	1	41	8	3,970	138	163	8.82	No
mtSDNA	45	80	3	56	12	2,700	121	141	6.59	No
mtSDNA	45	80	5	66	15	2,230	107	123	6.01	No
mtSDNA	45	85	1	40	8	4,040	138	164	8.91	No
mtSDNA	45	85	3	56	11	2,780	122	142	6.68	No
mtSDNA	45	85	5	66	14	2,280	108	123	6.06	No
mtSDNA	50	75	1	45	10	3,410	125	148	7.35	No
mtSDNA	50	75	3	60	15	2,330	109	126	5.84	No
mtSDNA	50	75	5	69	17	1,940	97	110	5.45	No
mtSDNA	50	80	1	43	9	3,530	127	150	7.50	No
mtSDNA	50	80	3	58	13	2,450	112	129	5.95	No
mtSDNA	50	80	5	68	16	2,010	99	112	5.52	No
mtSDNA	50	85	1	43	9	3,600	127	150	7.59	No
mtSDNA	50	85	3	58	12	2,490	112	130	5.99	No
mtSDNA	50	85	5	68	15	2,060	99	113	5.58	No
Sigmoidoscopy	40	75	5	40	10	4,010	133	159	6.10	No
Sigmoidoscopy	40	75	10	46	12	3,400	120	144	5.45	No
Sigmoidoscopy	40	80	5	39	9	4,090	133	160	6.14	No
Sigmoidoscopy	40	80	10	45	11	3,530	122	146	5.50	No
Sigmoidoscopy	40	85	5	39	9	4,120	133	160	6.16	No
Sigmoidoscopy	40	85	10	45	11	3,530	122	146	5.50	No
Sigmoidoscopy	45	75	5	41	10	3,760	127	153	5.52	No
Sigmoidoscopy	45	75	10	46	12	3,310	117	140	5.08	No
Sigmoidoscopy	45	80	5	40	10	3,840	128	153	5.56	No
Sigmoidoscopy	45	80	10	46	12	3,310	117	140	5.08	No
Sigmoidoscopy	45	85	5	40	9	3,870	128	154	5.58	No
Sigmoidoscopy	45	85	10	46	12	3,380	117	140	5.12	No
Sigmoidoscopy	50	75	5	43	11	3,430	118	141	5.05	No
Sigmoidoscopy	50	75	10	49	13	2,990	109	130	4.75	No
Sigmoidoscopy	50	80	5	42	10	3,500	118	142	5.08	No
Sigmoidoscopy	50	80	10	47	12	3,120	110	131	4.81	No
Sigmoidoscopy	50	85	5	42	10	3,540	118	142	5.11	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
Sigmoidoscopy	50	85	10	47	12	3,120	110	131	4.81	No
CTC	40	75	5	49	11	2,860	130	153	6.72	No
CTC	40	75	10	63	18	2,130	103	120	5.89	No
CTC	40	80	5	47	10	2,930	131	155	6.75	No
CTC	40	80	10	60	15	2,270	107	124	5.93	No
CTC	40	85	5	47	10	2,980	132	156	6.77	No
CTC	40	85	10	60	15	2,270	107	124	5.93	No
CTC	45	75	5	50	12	2,670	124	147	5.92	No
CTC	45	75	10	62	17	2,110	101	118	5.29	No
CTC	45	80	5	48	10	2,740	126	148	5.95	No
CTC	45	80	10	62	17	2,110	101	118	5.29	No
CTC	45	85	5	48	10	2,790	126	149	5.97	No
CTC	45	85	10	61	15	2,190	102	119	5.33	No
CTC	50	75	5	52	13	2,430	114	135	5.27	No
CTC	50	75	10	65	19	1,870	93	108	4.99	No
CTC	50	80	5	50	11	2,510	116	137	5.30	No
CTC	50	80	10	62	16	2,010	97	112	5.03	No
CTC	50	85	5	49	11	2,550	116	137	5.32	No
CTC	50	85	10	62	16	2,010	97	112	5.03	No

CRC - colorectal cancer; CTC - computed tomographic colonography; FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multitarget stool DNA; LYG - life-years gained; QALYG - quality-adjusted life-years gained; ACER - average cost-effectiveness ratio (compared to no screening).

Table 4: Scenario 4: Incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
No screening	-	-	-	108	45	110	0	0	5.87	-
Colonoscopy	40	75	5	30	6	8,330	154	186	8.89	No
Colonoscopy	40	75	10	37	8	6,080	142	171	7.41	No
Colonoscopy	40	75	15	41	10	5,230	130	156	6.96	No
Colonoscopy	40	80	5	30	5	8,540	154	187	8.94	No
Colonoscopy	40	80	10	35	7	6,350	143	172	7.47	No
Colonoscopy	40	80	15	41	10	5,230	130	156	6.96	No
Colonoscopy	40	85	5	30	5	8,670	154	187	8.98	No
Colonoscopy	40	85	10	35	7	6,350	143	172	7.47	No
Colonoscopy	40	85	15	41	9	5,420	130	156	7.01	No
Colonoscopy	45	75	5	32	6	7,280	146	177	7.63	No
Colonoscopy	45	75	10	36	8	5,650	137	165	6.63	No
Colonoscopy	45	75	15	41	10	4,920	127	152	6.47	No
Colonoscopy	45	80	5	31	6	7,490	147	177	7.68	No
Colonoscopy	45	80	10	36	8	5,650	137	165	6.63	No
Colonoscopy	45	80	15	41	10	4,920	127	152	6.47	No
Colonoscopy	45	85	5	31	6	7,620	147	177	7.72	No
Colonoscopy	45	85	10	36	8	5,810	137	165	6.68	No
Colonoscopy	45	85	15	41	10	4,920	127	152	6.47	No
Colonoscopy	50	75	5	34	7	6,230	134	162	6.72	No
Colonoscopy	50	75	10	39	9	4,840	126	151	6.12	No
Colonoscopy	50	75	15	45	12	4,180	117	140	5.87	Yes
Colonoscopy	50	80	5	33	7	6,450	134	162	6.77	No
Colonoscopy	50	80	10	38	8	5,100	127	152	6.18	No
Colonoscopy	50	80	15	43	10	4,500	119	142	5.94	No
Colonoscopy	50	85	5	33	7	6,580	134	162	6.80	No
Colonoscopy	50	85	10	38	8	5,100	127	152	6.18	No
Colonoscopy	50	85	15	43	10	4,500	119	142	5.94	No
FIT	40	75	1	52	11	2,940	136	159	5.62	Yes
FIT	40	75	2	66	15	2,140	118	135	5.63	Yes
FIT	40	75	3	74	19	1,700	102	115	5.73	Yes
FIT	40	80	1	50	9	3,040	138	162	5.62	Yes
FIT	40	80	2	64	13	2,240	122	139	5.63	Yes
FIT	40	80	3	73	17	1,800	106	120	5.75	Yes
FIT	40	85	1	50	8	3,100	139	163	5.64	Yes
FIT	40	85	2	64	12	2,290	122	140	5.65	Yes
FIT	40	85	3	73	15	1,860	107	121	5.78	Yes
FIT	45	75	1	54	11	2,700	129	151	5.41	Yes
FIT	45	75	2	67	16	1,990	112	129	5.51	Yes
FIT	45	75	3	75	19	1,620	98	111	5.64	Yes

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
FIT	45	80	1	52	10	2,800	132	154	5.40	Yes
FIT	45	80	2	65	14	2,060	115	131	5.51	Yes
FIT	45	80	3	74	17	1,670	100	113	5.65	Yes
FIT	45	85	1	51	9	2,860	132	155	5.42	Yes
FIT	45	85	2	65	13	2,130	116	132	5.54	Yes
FIT	45	85	3	74	16	1,730	102	115	5.68	Yes
FIT	50	75	1	56	12	2,400	118	137	5.30	Yes
FIT	50	75	2	69	17	1,760	102	116	5.48	Yes
FIT	50	75	3	77	20	1,430	89	99	5.61	Yes
FIT	50	80	1	54	11	2,500	120	140	5.30	Yes
FIT	50	80	2	67	14	1,870	105	120	5.48	Yes
FIT	50	80	3	76	18	1,530	92	103	5.63	Yes
FIT	50	85	1	54	10	2,570	121	141	5.31	Yes
FIT	50	85	2	67	13	1,920	106	121	5.50	Yes
FIT	50	85	3	76	17	1,560	93	104	5.65	Yes
HSgFOBT	40	75	1	49	10	3,710	136	159	5.91	No
HSgFOBT	40	75	2	62	15	2,750	118	136	5.83	Yes
HSgFOBT	40	75	3	71	19	2,170	102	116	5.88	No
HSgFOBT	40	80	1	48	9	3,830	138	161	5.91	No
HSgFOBT	40	80	2	61	13	2,870	122	140	5.84	Yes
HSgFOBT	40	80	3	70	16	2,290	106	120	5.90	No
HSgFOBT	40	85	1	47	8	3,900	138	161	5.93	No
HSgFOBT	40	85	2	61	12	2,920	122	140	5.86	Yes
HSgFOBT	40	85	3	70	15	2,350	107	121	5.94	No
HSgFOBT	45	75	1	51	11	3,360	129	151	5.62	Yes
HSgFOBT	45	75	2	63	15	2,520	112	129	5.66	Yes
HSgFOBT	45	75	3	72	18	2,020	98	111	5.76	Yes
HSgFOBT	45	80	1	49	10	3,480	131	153	5.63	Yes
HSgFOBT	45	80	2	62	13	2,600	114	131	5.67	Yes
HSgFOBT	45	80	3	72	17	2,080	100	113	5.77	Yes
HSgFOBT	45	85	1	49	9	3,550	131	153	5.64	Yes
HSgFOBT	45	85	2	62	12	2,680	116	132	5.70	Yes
HSgFOBT	45	85	3	72	16	2,150	101	114	5.80	Yes
HSgFOBT	50	75	1	53	12	2,960	117	137	5.45	Yes
HSgFOBT	50	75	2	67	16	2,180	101	116	5.58	Yes
HSgFOBT	50	75	3	75	20	1,760	88	99	5.69	Yes
HSgFOBT	50	80	1	52	11	3,070	119	139	5.45	Yes
HSgFOBT	50	80	2	65	14	2,310	105	119	5.60	Yes
HSgFOBT	50	80	3	74	18	1,870	91	102	5.72	Yes
HSgFOBT	50	85	1	52	10	3,150	120	140	5.47	Yes
HSgFOBT	50	85	2	65	13	2,360	105	120	5.61	Yes
HSgFOBT	50	85	3	74	17	1,900	92	103	5.74	Yes
mtSDNA	40	75	1	41	9	4,240	143	170	10.98	No

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
mtSDNA	40	75	3	57	14	2,820	125	145	8.27	No
mtSDNA	40	75	5	66	16	2,330	111	127	7.61	No
mtSDNA	40	80	1	40	8	4,350	145	171	11.11	No
mtSDNA	40	80	3	55	11	2,940	128	148	8.36	No
mtSDNA	40	80	5	65	14	2,410	113	129	7.68	No
mtSDNA	40	85	1	39	7	4,430	145	172	11.19	No
mtSDNA	40	85	3	55	10	3,010	129	149	8.43	No
mtSDNA	40	85	5	65	14	2,450	113	130	7.73	No
mtSDNA	45	75	1	42	9	3,850	137	162	9.41	No
mtSDNA	45	75	3	57	13	2,640	120	139	7.50	No
mtSDNA	45	75	5	67	16	2,160	106	121	7.06	No
mtSDNA	45	80	1	41	8	3,970	138	163	9.54	No
mtSDNA	45	80	3	56	12	2,700	121	141	7.55	No
mtSDNA	45	80	5	66	15	2,230	107	123	7.13	No
mtSDNA	45	85	1	40	8	4,040	138	164	9.63	No
mtSDNA	45	85	3	56	11	2,780	122	142	7.63	No
mtSDNA	45	85	5	66	14	2,280	108	123	7.18	No
mtSDNA	50	75	1	45	10	3,410	125	148	8.19	No
mtSDNA	50	75	3	60	15	2,330	109	126	6.90	No
mtSDNA	50	75	5	69	17	1,940	97	110	6.65	No
mtSDNA	50	80	1	43	9	3,530	127	150	8.32	No
mtSDNA	50	80	3	58	13	2,450	112	129	6.99	No
mtSDNA	50	80	5	68	16	2,010	99	112	6.71	No
mtSDNA	50	85	1	43	9	3,600	127	150	8.41	No
mtSDNA	50	85	3	58	12	2,490	112	130	7.03	No
mtSDNA	50	85	5	68	15	2,060	99	113	6.77	No
Sigmoidoscopy	40	75	5	40	10	4,010	133	159	6.81	No
Sigmoidoscopy	40	75	10	46	12	3,400	120	144	6.28	No
Sigmoidoscopy	40	80	5	39	9	4,090	133	160	6.84	No
Sigmoidoscopy	40	80	10	45	11	3,530	122	146	6.33	No
Sigmoidoscopy	40	85	5	39	9	4,120	133	160	6.86	No
Sigmoidoscopy	40	85	10	45	11	3,530	122	146	6.33	No
Sigmoidoscopy	45	75	5	41	10	3,760	127	153	6.28	No
Sigmoidoscopy	45	75	10	46	12	3,310	117	140	5.93	No
Sigmoidoscopy	45	80	5	40	10	3,840	128	153	6.32	No
Sigmoidoscopy	45	80	10	46	12	3,310	117	140	5.93	No
Sigmoidoscopy	45	85	5	40	9	3,870	128	154	6.34	No
Sigmoidoscopy	45	85	10	46	12	3,380	117	140	5.97	No
Sigmoidoscopy	50	75	5	43	11	3,430	118	141	5.90	No
Sigmoidoscopy	50	75	10	49	13	2,990	109	130	5.70	Yes
Sigmoidoscopy	50	80	5	42	10	3,500	118	142	5.93	No
Sigmoidoscopy	50	80	10	47	12	3,120	110	131	5.75	Yes

table continues

Modality	Start age	End age	Interval	CRC cases	CRC deaths	Colonos-copies[a]	LYG	QALYG	Costs (million$)	Cost-saving vs no screening
Sigmoidoscopy	50	85	5	42	10	3,540	118	142	5.96	No
Sigmoidoscopy	50	85	10	47	12	3,120	110	131	5.75	Yes
CTC	40	75	5	49	11	2,860	130	153	7.53	No
CTC	40	75	10	63	18	2,130	103	120	6.96	No
CTC	40	80	5	47	10	2,930	131	155	7.55	No
CTC	40	80	10	60	15	2,270	107	124	6.98	No
CTC	40	85	5	47	10	2,980	132	156	7.57	No
CTC	40	85	10	60	15	2,270	107	124	6.98	No
CTC	45	75	5	50	12	2,670	124	147	6.78	No
CTC	45	75	10	62	17	2,110	101	118	6.36	No
CTC	45	80	5	48	10	2,740	126	148	6.79	No
CTC	45	80	10	62	17	2,110	101	118	6.36	No
CTC	45	85	5	48	10	2,790	126	149	6.81	No
CTC	45	85	10	61	15	2,190	102	119	6.41	No
CTC	50	75	5	52	13	2,430	114	135	6.22	No
CTC	50	75	10	65	19	1,870	93	108	6.14	No
CTC	50	80	5	50	11	2,510	116	137	6.24	No
CTC	50	80	10	62	16	2,010	97	112	6.16	No
CTC	50	85	5	49	11	2,550	116	137	6.26	No
CTC	50	85	10	62	16	2,010	97	112	6.16	No

CRC - colorectal cancer; CTC - computed tomographic colonography; FIT - fecal immunochemical test; HSgFOBT - high-sensitivity guaiac-based fecal occult blood test; mtSDNA - multitarget stool DNA; LYG - life-years gained; QALYG - quality-adjusted life-years gained; ACER - average cost-effectiveness ratio (compared to no screening).

Appendix 4.5

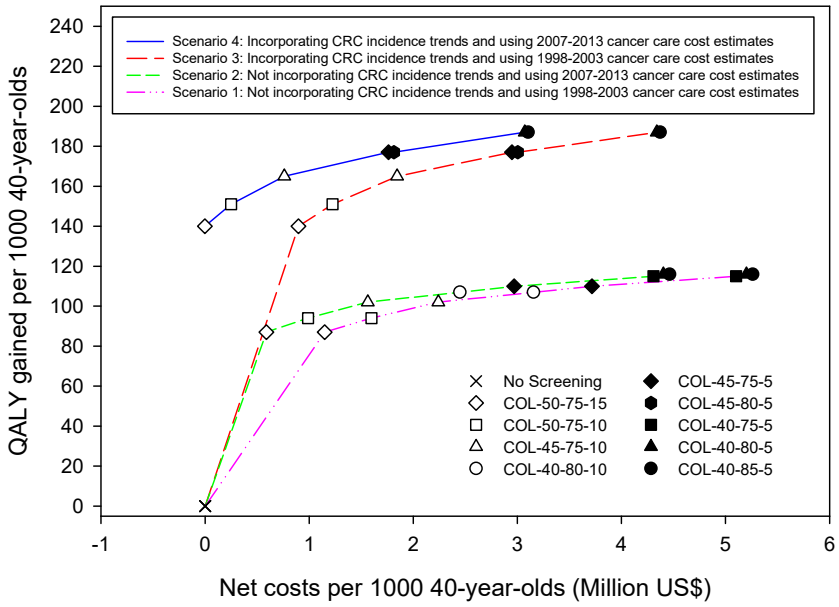


Figure 1: Efficient frontiers for the four different scenarios when only colonoscopy is considered. Net costs (compared to no screening) and QALY gained for 1,000 40-year-olds for efficient screening strategies. Strategies are abbreviated as modality – start age-stop age – interval (years). QALY - quality-adjusted life-years; COL - colonoscopy

Appendix 4.6

Table 1. The benefits and costs of efficient colonoscopy screening strategies, incorporating 60% or 80% screening adherence. Outcomes are per 1000 40-year-olds.

Modality - start age - stop age - interval	CRC cases	CRC deaths	No. of colonos-copies	LY gained	QALY gained	Total costs (million $)
	Undiscounted			*3% discounted*		
	60% adherence					
Scenario 1: Not incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates						
No screening	67.5	28.2	70	0	0	2.57
COL-50-75-15	57.4	22.6	820	18	21	2.78
COL-50-75-10	53.5	20.3	1,200	24	29	2.94
COL-45-75-10	50.6	18.8	1,610	30	35	3.11
COL-40-80-10	39.5	12.9	3,330	56	67	4.39
COL-45-75-5	42.2	14.5	2,920	45	53	3.77
COL-40-75-5	34.7	10.8	4,870	66	78	5.54
COL-40-80-5	34.1	10.5	5,090	66	79	5.61
Scenario 2: Not incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates						
No screening	67.5	28.2	70	0	0	3.68
COL-50-75-15	57.4	22.6	820	18	21	3.76
COL-50-75-10	53.5	20.3	1,200	24	29	3.87
COL-45-75-10	50.6	18.8	1,610	30	35	4.00
COL-40-80-10	39.5	12.9	3,330	56	67	5.07
COL-45-75-5	42.2	14.5	2,920	45	53	4.54
COL-40-75-5	34.7	10.8	4,870	66	78	6.13
COL-40-80-5	34.1	10.5	5,090	66	79	6.19
COL-40-85-5	34.1	10.4	5,240	66	79	6.23
Scenario 3: Incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates						
No screening	108.1	45.4	110	0	0	4.11
COL-50-75-15	91.6	36.2	1,020	29	34	4.24
COL-50-75-10	85.3	32.6	1,420	39	46	4.35
COL-45-75-10	80.7	30.1	1,830	47	56	4.49
COL-45-75-5	67.3	23.3	3,060	71	85	4.95
COL-45-80-5	66.5	22.6	3,210	72	86	4.99
COL-40-80-5	54.3	16.7	5,180	106	127	6.58
COL-40-85-5	54.2	16.6	5,260	106	127	6.60
Scenario 4: Incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates						
COL-50-75-15	91.6	36.2	1,020	29	34	5.79
COL-50-75-10	85.3	32.6	1,420	39	46	5.83
COL-45-75-10	80.7	30.1	1,830	47	56	5.90

table continues

COL-45-75-5	67.3	23.3	3,060	71	85	6.17
COL-45-80-5	66.5	22.6	3,210	72	86	6.21
COL-40-80-5	54.3	16.7	5,180	106	127	7.50
COL-40-85-5	54.2	16.6	5,260	106	127	7.53
	---------- 80% adherence ----------					
Scenario 1: Not incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates						
No screening	67.5	28.2	70	0	0	2.57
COL-50-75-15	48.4	17.7	1,550	34	40	3.00
COL-50-75-10	42.8	14.6	2,180	43	51	3.28
COL-45-75-10	39.1	12.8	2,810	51	60	3.60
COL-40-80-10	31	8.6	4,490	73	87	5.04
COL-45-75-5	31.3	9.2	4,620	66	79	4.66
COL-40-75-5	27.2	7.3	6,450	81	97	6.59
COL-40-80-5	26.7	7.0	6,730	81	97	6.67
Scenario 2: Not incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates						
No screening	67.5	28.2	70	0	0	3.68
COL-50-75-15	48.4	17.7	1,550	34	40	3.85
COL-50-75-10	42.8	14.6	2,180	43	51	4.07
COL-45-75-10	39.1	12.8	2,810	51	60	4.32
COL-40-80-10	31	8.6	4,490	73	87	5.59
COL-45-75-5	31.3	9.2	4,620	66	79	5.25
COL-40-75-5	27.2	7.3	6,450	81	97	7.05
COL-40-80-5	26.7	7.0	6,730	81	97	7.13
COL-40-85-5	26.6	7.0	6,920	81	97	7.17
Scenario 3: Incorporating CRC incidence trends and using 1998-2003 cancer care cost estimates						
No screening	108.1	45.4	110	0	0	4.11
COL-50-75-15	76.6	28.2	1,920	55	65	4.40
COL-50-75-10	67.7	23.3	2,560	69	82	4.60
COL-45-75-10	62	20.4	3,200	81	97	4.88
COL-45-75-5	49.6	14.6	4,800	105	127	5.65
COL-45-80-5	48.9	14.1	4,980	106	127	5.70
COL-40-80-5	42.3	11.3	6,810	130	156	7.49
COL-40-85-5	42.2	11.2	6,910	130	156	7.52
Scenario 4: Incorporating CRC incidence trends and using 2007-2013 cancer care cost estimates						
COL-50-75-15	76.6	28.2	1,920	55	65	5.75
COL-50-75-10	67.7	23.3	2,560	69	82	5.85
COL-45-75-10	62	20.4	3,200	81	97	6.02
COL-45-75-5	49.6	14.6	4,800	105	127	6.59
COL-45-80-5	48.9	14.1	4,980	106	127	6.63
COL-40-80-5	42.3	11.3	6,810	130	156	8.20
COL-40-85-5	42.2	11.2	6,910	130	156	8.23

CRC - colorectal cancer; LY - life-years; QALY - quality-adjusted life-years; FIT - fecal immunochemical test; COL - colonoscopy

Appendix 4.7: The impact of alternative assumptions on strategies in the efficient frontier when all screening tests are considered, under the assumption of perfect adherence. 2007-2013 cancer care cost estimates were used for all sensitivity analyses. Outcomes are per 1000 40-year-olds.

Modality - start age - stop age - interval	CRC cases	CRC deaths	No. of colonoscopies	LY gained	QALY gained	Total costs (million $)	Cost-saving vs no screening	ICER
	------ Undiscounted ------			*---------- 3% discounted ----------*				
Base case (scenario 4)								
FIT-50-80-1	54.1	10.7	2,500	120	140	5.30	Yes	-
FIT-45-80-1	51.7	9.7	2,800	132	154	5.40	Yes	7,200
FIT-45-85-1	51.2	9.0	2,860	132	155	5.42	Yes	16,800
FIT-40-85-1	49.9	8.5	3,100	139	163	5.64	Yes	26,800
COL-40-80-5	29.6	5.4	8,540	154	187	8.94	No	138,600
COL-40-85-5	29.5	5.3	8,670	154	187	8.98	No	941,800
Age effect								
FIT-50-75-2	43.9	10.9	1,330	66	75	3.74	Yes	-
FIT-50-75-1	35.8	8.2	1,850	76	88	3.75	Yes	500
FIT-50-80-1	34.6	7.1	1,950	78	90	3.77	Yes	8,600
FIT-45-80-1	32.9	6.3	2,200	86	100	3.92	No	15,500
FIT-40-80-1	31.9	5.9	2,420	92	106	4.15	No	35,100
FIT-40-85-1	31.6	5.4	2,490	92	107	4.17	No	39,100
COL-40-75-5	19.5	3.7	8,090	102	122	8.05	No	262,900
COL-40-80-5	18.9	3.5	8,440	102	122	8.15	No	286,500
COL-40-85-5	18.8	3.4	8,680	102	122	8.20	No	796,837,200
Incidence rate ratio of 1.25								
FIT-50-75-1	44.6	10.1	2,060	92	107	4.33	Yes	-
FIT-50-80-1	43.0	8.6	2,160	94	109	4.34	Yes	2,500
FIT-45-80-1	41.2	7.8	2,420	103	120	4.48	Yes	13,400
FIT-45-85-1	40.7	7.1	2,480	104	121	4.50	Yes	23,400
FIT-40-85-1	39.9	6.8	2,700	109	127	4.74	No	37,500
COL-40-80-5	23.3	4.3	8,490	121	146	8.44	No	194,900
COL-40-85-5	23.2	4.2	8,670	122	146	8.49	No	2,180,700
Fast adenoma progression								
FIT-50-80-1	58.9	11.8	1,880	125	144	5.30	Yes	-
FIT-45-80-1	56.5	10.8	2,110	137	159	5.34	Yes	1,700
FIT-40-80-1	55.2	10.2	2,320	145	169	5.51	Yes	17,800
FIT-40-85-1	54.7	9.4	2,390	146	170	5.52	Yes	18,400
COL-40-80-5	33.2	6.1	8,400	163	195	9.01	No	135,000
COL-40-85-5	33.1	6	8,630	163	195	9.07	No	1,365,400

table continues

Improved survival								
FIT-50-80-1	54.1	10.3	2,500	114	136	5.36	Yes	-
FIT-45-80-1	51.7	9.3	2,800	125	150	5.45	Yes	6,100
FIT-45-85-1	51.2	8.6	2,860	125	151	5.46	Yes	16,300
FIT-40-85-1	49.9	8.1	3,100	132	159	5.67	Yes	26,000
COL-40-80-5	29.6	5.1	8,540	146	182	8.96	No	140,900
COL-40-85-5	29.5	5.1	8,670	146	182	9.00	No	980,000
Commercial costs all ages								
FIT-50-80-1	54.1	10.7	2,500	120	140	6.22	Yes	-
FIT-45-80-1	51.7	9.7	2,800	132	154	6.31	Yes	5,100
FIT-45-85-1	51.2	9.0	2,860	132	155	6.33	Yes	24,000
FIT-40-80-1	50.4	9.3	3,040	138	162	6.52	Yes	25,500
FIT-40-85-1	49.9	8.5	3,100	139	163	6.54	Yes	26,200
COL-40-75-5	30.3	5.8	8,330	154	186	9.88	No	142,700
COL-40-80-5	29.6	5.4	8,540	154	187	9.95	No	161,600
COL-40-85-5	29.5	5.3	8,670	154	187	10.00	No	1,387,600
CMS costs all ages								
FIT-50-80-1	54.1	10.7	2,500	120	140	4.52	Yes	-
FIT-45-80-1	51.7	9.7	2,800	132	154	4.57	Yes	2,700
FIT-45-85-1	51.2	9.0	2,860	132	155	4.58	Yes	16,800
FIT-40-80-1	50.4	9.3	3,040	138	162	4.71	Yes	17,300
FIT-40-85-1	49.9	8.5	3,100	139	163	4.73	Yes	18,500
COL-45-75-5	31.6	6.3	7,280	146	177	5.99	No	88,800
COL-40-75-5	30.3	5.8	8,330	154	186	6.82	No	90,200
COL-40-80-5	29.6	5.4	8,540	154	187	6.87	No	107,400
COL-40-85-5	29.5	5.3	8,670	154	187	6.90	No	941,800

CRC - colorectal cancer; LY - life-years; QALY - quality-adjusted life-years; ICER – incremental cost-effectiveness ratio; FIT - fecal immunochemical test; COL - colonoscopy; CMS – centers for medicare and medicaid services

Appendix 4.8: The impact of alternative assumptions on strategies in the efficient frontier when only colonoscopy strategies are considered, under the assumption of perfect adherence. 2007-2013 cancer care cost estimates were used for all sensitivity analyses. Outcomes are per 1000 40-year-olds.

Modality - start age - stop age - interval	CRC cases	CRC deaths	No. of colonoscopies	LY gained	QALY gained	Total costs (million $)	Cost-saving vs no screening	ICER
	------ *Undiscounted* ------			---------- *3% discounted* ----------				
Base case (scenario 4)								
COL-50-75-15	44.7	11.8	4,180	117	140	5.87	Yes	-
COL-50-75-10	39.4	9.2	4,840	126	151	6.12	No	20,700
COL-45-75-10	36.4	7.9	5,650	137	165	6.63	No	38,700
COL-45-75-5	31.6	6.3	7,280	146	177	7.63	No	81,300
COL-45-80-5	30.9	5.9	7,490	147	177	7.68	No	104,700
COL-40-80-5	29.6	5.4	8,540	154	187	8.94	No	137,000
COL-40-85-5	29.5	5.3	8,670	154	187	8.98	No	941,800
Age effect								
No Screening	68.9	29.1	70	0	0	3.83	-	-
COL-50-75-15	29	7.8	3,450	76	91	4.41	No	6,400
COL-45-75-10	23.5	5.3	5,020	89	107	5.37	No	58,600
COL-40-80-10	22.5	4.6	5,770	95	113	6.23	No	132,500
COL-40-75-5	19.5	3.7	8,090	102	122	8.05	No	222,800
COL-40-80-5	18.9	3.5	8,440	102	122	8.15	No	286,500
COL-40-85-5	18.8	3.4	8,680	102	122	8.20	No	796,837,200
Incidence rate ratio of 1.25								
COL-50-75-15	35.8	9.6	3,750	91	109	4.97	No	-
COL-50-75-10	31.4	7.5	4,460	99	118	5.30	No	37,300
COL-45-75-10	29	6.4	5,280	107	128	5.85	No	53,900
COL-45-75-5	24.9	5	7,150	115	138	7.07	No	122,800
COL-45-80-5	24.2	4.7	7,440	115	139	7.14	No	166,100
COL-40-80-5	23.3	4.3	8,490	121	146	8.44	No	179,400
COL-40-85-5	23.2	4.2	8,670	122	146	8.49	No	2,180,700
Fast adenoma progression								
COL-50-75-15	50.3	13.6	3,340	120	143	5.72	Yes	-
COL-50-75-10	44.4	10.7	4,090	130	155	6.01	Yes	20,200
COL-45-75-10	41.2	9.2	4,920	142	170	6.44	No	29,400
COL-45-75-5	35.5	7.2	6,990	153	184	7.69	No	86,100
COL-40-75-5	34.2	6.6	8,050	162	195	8.92	No	119,700
COL-40-80-5	33.2	6.1	8,400	163	195	9.01	No	123,500
COL-40-85-5	33.1	6	8,630	163	195	9.07	No	1,365,400

table continues

Improved survival								
COL-50-75-15	44.7	11.2	4,180	111	137	5.94	Yes	-
COL-50-75-10	39.4	8.8	4,840	119	148	6.18	No	20,500
COL-45-75-10	36.4	7.6	5,650	129	161	6.68	No	38,700
COL-45-75-5	31.6	6	7,280	139	173	7.67	No	82,800
COL-45-80-5	30.9	5.6	7,490	139	173	7.72	No	105,900
COL-40-80-5	29.6	5.1	8,540	146	182	8.96	No	139,800
COL-40-85-5	29.5	5.1	8,670	146	182	9.00	No	980,000
Commercial costs all ages								
COL-50-75-15	44.7	11.8	4,180	117	140	6.90	Yes	-
COL-50-75-10	39.4	9.2	4,840	126	151	7.05	Yes	13,700
COL-45-75-10	36.4	7.9	5,650	137	165	7.63	No	43,900
COL-45-75-5	31.6	6.3	7,280	146	177	8.62	No	81,000
COL-40-75-5	30.3	5.8	8,330	154	186	9.88	No	136,000
COL-40-80-5	29.6	5.4	8,540	154	187	9.95	No	161,600
COL-40-85-5	29.5	5.3	8,670	154	187	10.0	No	1,387,600
CMS costs all ages								
COL-50-75-15	44.7	11.8	4,180	117	140	4.89	Yes	-
COL-50-75-10	39.4	9.2	4,840	126	151	4.97	Yes	1,400
COL-45-75-10	36.4	7.9	5,650	137	165	5.34	Yes	27,900
COL-45-75-5	31.6	6.3	7,280	146	177	5.99	No	52,600
COL-40-75-5	30.3	5.8	8,330	154	186	6.82	No	90,200
COL-40-80-5	29.6	5.4	8,540	154	187	6.87	No	107,400
COL-40-85-5	29.5	5.3	8,670	154	187	6.90	No	941,800

CRC - colorectal cancer; LY - life-years; QALY - quality-adjusted life-years; ICER - incremental cost-effectiveness ratio; COL – colonoscopy; CMS - centers for medicare and medicaid services

Appendix 4.9: The benefits and costs of efficient screening strategies in sensitivity analysis, incorporating 60% or 80% screening adherence. 2007-2013 cancer care cost estimates were used for all sensitivity analyses. Outcomes are per 1000 40-year-olds.

Modality - start age - stop age - interval	CRC cases	CRC deaths	No. of colonos-copies	LY gained	QALY gained	Total costs (million $)
	Undiscounted			*3% discounted*		
	60% adherence					
Base case (scenario 4)						
FIT-50-80-1	75.1	20.5	1,390	80	91	5.54
FIT-45-80-1	72.6	19.3	1,570	90	103	5.56
FIT-45-85-1	72.5	18.5	1,610	91	104	5.57
FIT-40-85-1	70.6	17.6	1,830	101	115	5.70
COL-40-80-5	54.3	16.7	5,180	106	127	7.50
COL-40-85-5	54.2	16.6	5,260	106	127	7.53
Age effect						
FIT-50-75-2	56.5	18.4	610	35	38	3.82
FIT-50-75-1	48.7	14.2	990	50	57	3.77
FIT-50-80-1	47.8	13.1	1,060	52	58	3.78
FIT-45-80-1	46.1	12.3	1,210	59	67	3.83
FIT-40-80-1	44.7	11.6	1,410	67	76	4.00
FIT-40-85-1	44.7	11.1	1,450	67	76	4.01
COL-40-75-5	35.0	10.9	4,880	70	83	6.23
COL-40-80-5	34.5	10.6	5,100	70	83	6.29
Incidence rate ratio of 1.25						
FIT-50-75-1	60.7	17.8	1,110	60	69	4.44
FIT-50-80-1	59.5	16.4	1,180	63	71	4.45
FIT-45-80-1	57.6	15.4	1,340	71	80	4.50
FIT-45-85-1	57.5	14.7	1,390	72	81	4.51
FIT-40-85-1	55.9	14.0	1,580	79	90	4.67
COL-40-80-5	42.7	13.2	5,130	83	99	6.75
COL-40-85-5	42.6	13.1	5,250	83	99	6.78
Fast adenoma progression						
FIT-50-80-1	78.7	21.4	1,030	83	93	5.71
FIT-45-80-1	76.3	20.2	1,170	94	106	5.69
FIT-40-80-1	74.5	19.2	1,350	105	119	5.77
FIT-40-85-1	74.5	18.3	1,400	106	120	5.79
COL-40-80-5	57.6	17.6	5,070	110	131	7.69
COL-40-85-5	57.5	17.5	5,220	110	131	7.72
Improved survival						
FIT-50-80-1	75.1	19.6	1,390	76	89	5.65
FIT-45-80-1	72.6	18.5	1,570	86	100	5.65
FIT-45-85-1	72.5	17.6	1,610	86	101	5.67
FIT-40-85-1	70.6	16.8	1,830	95	112	5.78
COL-40-80-5	54.2	16.0	5,180	100	124	7.58
COL-40-85-5	54.2	15.8	5,260	100	124	7.60

table continues

Commercial costs all ages						
FIT-50-80-1	75.1	20.5	1,390	80	91	6.63
FIT-45-80-1	72.6	19.3	1,570	90	103	6.62
FIT-45-85-1	72.5	18.5	1,610	91	104	6.64
FIT-40-80-1	70.7	18.5	1,790	100	114	6.73
FIT-40-85-1	70.6	17.6	1,830	101	115	6.75
COL-40-75-5	54.9	17.2	5,030	105	126	8.53
COL-40-80-5	54.3	16.7	5,180	106	127	8.58
COL-40-85-5	54.2	16.6	5,260	106	127	8.62
CMS costs all ages						
FIT-50-80-1	75.1	20.5	1,390	80	91	4.87
FIT-45-80-1	72.6	19.3	1,570	90	103	4.85
FIT-45-85-1	72.5	18.5	1,610	91	104	4.87
FIT-40-80-1	70.7	18.5	1,790	100	114	4.93
FIT-40-85-1	70.6	17.6	1,830	101	115	4.94
COL-45-75-5	67.3	23.3	3,060	71	85	5.29
COL-40-75-5	54.9	17.2	5,030	105	126	6.03
COL-40-80-5	54.3	16.7	5,180	106	127	6.06
COL-40-85-5	54.2	16.6	5,260	106	127	6.08
	---------- 80% adherence ----------					
Base case (scenario 4)						
FIT-50-80-1	65.5	16.3	1,870	98	113	5.40
FIT-45-80-1	63.0	15.2	2,100	109	126	5.45
FIT-45-85-1	62.6	14.4	2,150	110	127	5.47
FIT-40-85-1	61.2	13.9	2,390	118	136	5.65
COL-40-80-5	42.3	11.3	6,810	130	156	8.20
COL-40-85-5	42.2	11.2	6,910	130	156	8.23
Age effect						
FIT-50-75-2	50.6	14.7	920	49	55	3.78
FIT-50-75-1	42.8	11.5	1,370	62	71	3.75
FIT-50-80-1	41.8	10.4	1,450	63	73	3.76
FIT-45-80-1	40.2	9.7	1,640	71	82	3.86
FIT-40-80-1	39.0	9.2	1,860	78	89	4.06
FIT-40-85-1	38.9	8.7	1,910	78	90	4.08
COL-40-75-5	27.5	7.4	6,450	86	102	7.13
COL-40-80-5	27	7.1	6,740	86	102	7.21
Incidence rate ratio of 1.25						
FIT-50-75-1	53.3	14.4	1,520	75	86	4.37
FIT-50-80-1	51.9	13.0	1,600	77	88	4.38
FIT-45-80-1	50.1	12.2	1,810	85	98	4.47
FIT-45-85-1	49.8	11.5	1,860	86	99	4.48
FIT-40-85-1	48.7	11.0	2,080	93	107	4.69
COL-40-80-5	33.2	8.9	6,770	102	123	7.58
COL-40-85-5	33.2	8.8	6,920	102	123	7.62

table continues

Fast adenoma progression						
FIT-50-80-1	69.6	17.1	1,400	102	116	5.51
FIT-45-80-1	67.3	16.0	1,580	114	131	5.51
FIT-40-80-1	65.8	15.3	1,780	123	141	5.64
FIT-40-85-1	65.6	14.5	1,840	124	142	5.66
COL-40-80-5	45.7	11.9	6,700	136	163	8.34
COL-40-85-5	45.6	11.8	6,890	136	163	8.39
Improved survival						
FIT-50-80-1	65.5	15.6	1,870	93	110	5.49
FIT-45-80-1	63.0	14.5	2,100	103	123	5.52
FIT-45-85-1	62.6	13.8	2,150	104	124	5.54
FIT-40-85-1	61.2	13.3	2,390	111	133	5.71
COL-40-80-5	42.3	10.8	6,810	123	152	8.25
COL-40-85-5	42.2	10.7	6,910	123	152	8.28
Commercial costs all ages						
FIT-50-80-1	65.5	16.3	1,870	98	113	6.41
FIT-45-80-1	63.0	15.2	2,100	109	126	6.44
FIT-45-85-1	62.6	14.4	2,150	110	127	6.46
FIT-40-80-1	61.5	14.6	2,340	117	136	6.61
FIT-40-85-1	61.2	13.9	2,390	118	136	6.63
COL-40-75-5	42.9	11.6	6,630	129	156	9.18
COL-40-80-5	42.3	11.3	6,810	130	156	9.24
COL-40-85-5	42.2	11.2	6,910	130	156	9.28
CMS costs all ages						
FIT-50-80-1	65.5	16.3	1,870	98	113	4.69
FIT-45-80-1	63.0	15.2	2,100	109	126	4.70
FIT-45-85-1	62.6	14.4	2,150	110	127	4.71
FIT-40-80-1	61.5	14.6	2,340	117	136	4.81
FIT-40-85-1	61.2	13.9	2,390	118	136	4.83
COL-45-75-5	49.6	14.6	4,800	105	127	5.43
COL-40-75-5	42.9	11.6	6,630	129	156	6.41
COL-40-80-5	42.3	11.3	6,810	130	156	6.45
COL-40-85-5	42.2	11.2	6,910	130	156	6.47

CRC - colorectal cancer; LY - life-years; QALY - quality-adjusted life-years; FIT - fecal immunochemical test; COL – colonoscopy

Appendix 4.10: The benefits and costs of efficient colonoscopy screening strategies in sensitivity analysis, incorporating 60% or 80% screening adherence. 2007-2013 cancer care cost estimates were used for all sensitivity analyses. Outcomes are per 1000 40-year-olds.

Modality - start age - stop age - interval	CRC cases	CRC deaths	No. of colonos-copies	LY gained	QALY gained	Total costs (million $)
	Undiscounted			*3% discounted*		
	60% adherence					
Base case (scenario 4)						
COL-50-75-15	91.6	36.2	1,020	29	34	5.79
COL-50-75-10	85.3	32.6	1,420	39	46	5.83
COL-45-75-10	80.7	30.1	1,830	47	56	5.90
COL-45-75-5	67.3	23.3	3,060	71	85	6.17
COL-45-80-5	66.5	22.6	3,210	72	86	6.21
COL-40-80-5	54.3	16.7	5,180	106	127	7.50
COL-40-85-5	54.2	16.6	5,260	106	127	7.53
Age effect						
No screening	68.7	28.8	70	0	0	3.84
COL-50-75-15	58.3	23.1	830	18	22	3.91
COL-45-75-10	51.5	19.2	1,620	31	36	4.15
COL-40-80-10	39.9	13.0	3,360	60	71	5.19
COL-40-75-5	35.0	10.9	4,880	70	83	6.23
COL-40-80-5	34.5	10.6	5,100	70	83	6.29
COL-40-85-5	34.5	10.5	5,250	70	83	6.33
Incidence rate ratio 1.25						
COL-50-75-15	72.1	28.5	910	22	26	4.62
COL-50-75-10	67.2	25.7	1,300	30	36	4.71
COL-45-75-10	63.6	23.8	1,710	37	44	4.81
COL-45-75-5	53.0	18.4	2,990	56	67	5.23
COL-45-80-5	52.3	17.8	3,170	57	67	5.28
COL-40-80-5	42.7	13.2	5,130	83	99	6.75
COL-40-85-5	42.6	13.1	5,250	83	99	6.78
Fast adenoma progression						
COL-50-75-15	92.5	37.0	830	29	34	5.98
COL-50-75-10	86.8	33.5	1,210	39	46	6.02
COL-45-75-10	82.6	31.0	1,610	48	57	6.07
COL-45-75-5	70.1	24.2	2,910	73	87	6.38
COL-40-75-5	58.4	18.2	4,850	109	131	7.63
COL-40-80-5	57.6	17.6	5,070	110	131	7.69
COL-40-85-5	57.5	17.5	5,220	110	131	7.72

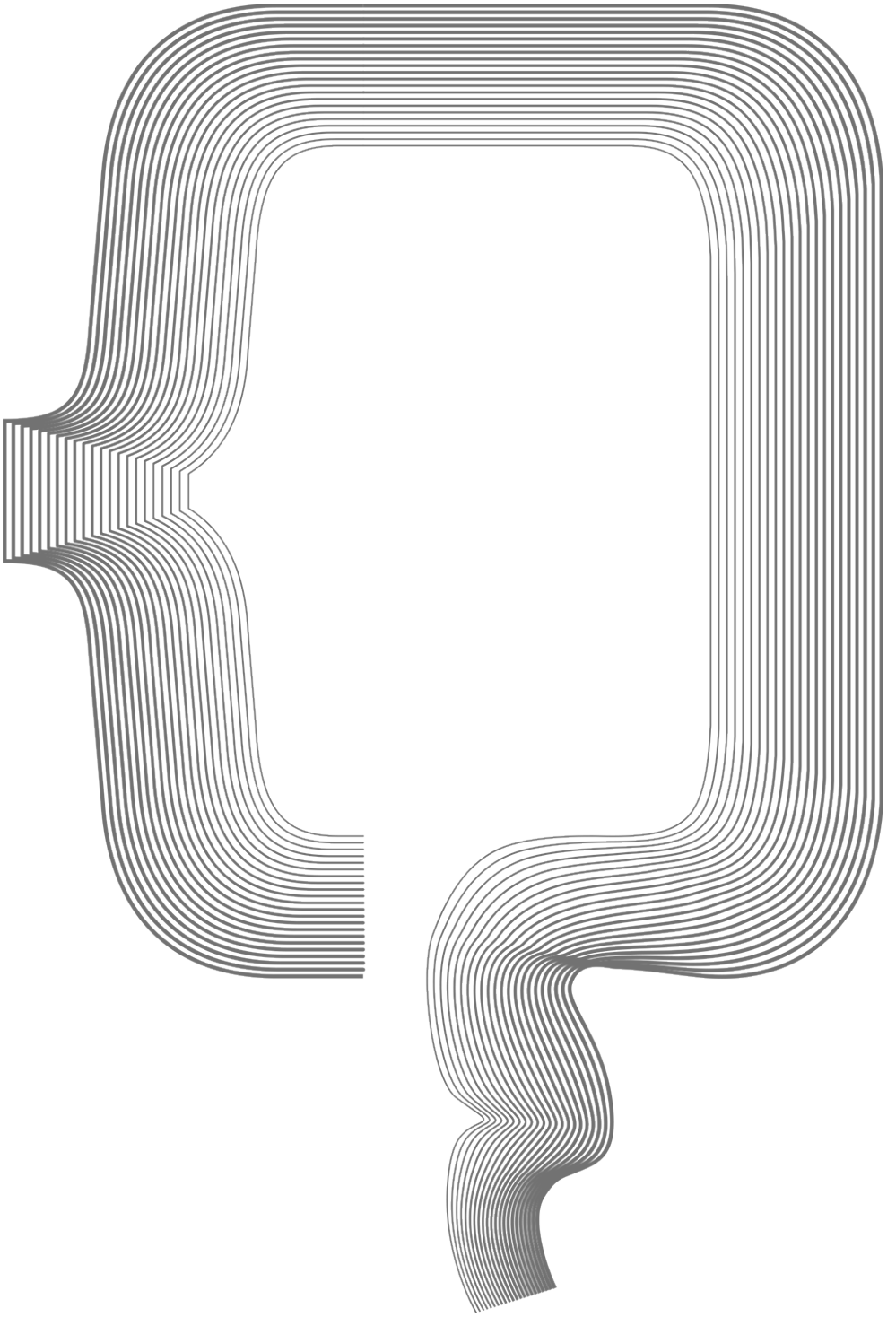
table continues

Improved survival						
COL-50-75-15	91.6	34.5	1,020	27	33	5.95
COL-50-75-10	85.3	31.1	1,420	37	45	5.98
COL-45-75-10	80.7	28.6	1,830	45	55	6.05
COL-45-75-5	67.3	22.1	3,060	67	83	6.29
COL-45-80-5	66.5	21.5	3,210	68	84	6.32
COL-40-80-5	54.2	16.0	5,180	100	124	7.58
COL-40-85-5	54.2	15.8	5,260	100	124	7.60
Commercial costs all ages						
COL-50-75-15	91.6	36.2	1,020	29	34	7.08
COL-50-75-10	85.3	32.6	1,420	39	46	7.06
COL-45-75-10	80.7	30.1	1,830	47	56	7.15
COL-45-75-5	67.3	23.3	3,060	71	85	7.34
COL-40-75-5	54.9	17.2	5,030	105	126	8.53
COL-40-80-5	54.3	16.7	5,180	106	127	8.58
COL-40-85-5	54.2	16.6	5,260	106	127	8.62
CMS costs all ages						
COL-50-75-15	91.6	36.2	1,020	29	34	5.20
COL-50-75-10	85.3	32.6	1,420	39	46	5.16
COL-45-75-10	80.7	30.1	1,830	47	56	5.21
COL-45-75-5	67.3	23.3	3,060	71	85	5.29
COL-40-75-5	54.9	17.2	5,030	105	126	6.03
COL-40-80-5	54.3	16.7	5,180	106	127	6.06
COL-40-85-5	54.2	16.6	5,260	106	127	6.08
	---------- 80% adherence ----------					
Base case (scenario 4)						
COL-50-75-15	76.6	28.2	1,920	55	65	5.75
COL-50-75-10	67.7	23.3	2,560	69	82	5.85
COL-45-75-10	62.0	20.4	3,200	81	97	6.02
COL-45-75-5	49.6	14.6	4,800	105	127	6.59
COL-45-80-5	48.9	14.1	4,980	106	127	6.63
COL-40-80-5	42.3	11.3	6,810	130	156	8.20
COL-40-85-5	42.2	11.2	6,910	130	156	8.23
Age effect						
No screening	68.7	28.8	70	0	0	3.84
COL-50-75-15	49.1	18.1	1,580	35	42	4.00
COL-45-75-10	39.8	13.1	2,840	53	62	4.47
COL-40-80-10	31.2	8.7	4,540	77	92	5.70
COL-40-75-5	27.5	7.4	6,450	86	102	7.13
COL-40-80-5	27.0	7.1	6,740	86	102	7.21
COL-40-85-5	26.9	7.1	6,920	86	102	7.26

table continues

Incidence rate ratio 1.25						
COL-50-75-15	60.6	22.3	1,720	43	51	4.67
COL-50-75-10	53.5	18.5	2,360	54	64	4.83
COL-45-75-10	48.9	16.1	2,990	64	76	5.05
COL-45-75-5	39.1	11.6	4,710	83	99	5.82
COL-45-80-5	38.4	11.2	4,950	83	100	5.88
COL-40-80-5	33.2	8.9	6,770	102	123	7.58
COL-40-85-5	33.2	8.8	6,920	102	123	7.62
Fast adenoma progression						
COL-50-75-15	79.4	29.4	1,540	55	65	5.86
COL-50-75-10	71.0	24.5	2,160	70	83	5.96
COL-45-75-10	65.6	21.5	2,790	83	99	6.09
COL-45-75-5	53.2	15.5	4,590	110	131	6.75
COL-40-75-5	46.6	12.4	6,420	136	163	8.27
COL-40-80-5	45.7	11.9	6,700	136	163	8.34
COL-40-85-5	45.6	11.8	6,890	136	163	8.39
Improved survival						
COL-50-75-15	76.6	26.8	1,920	52	64	5.88
COL-50-75-10	67.7	22.2	2,560	65	80	5.97
COL-45-75-10	62.0	19.4	3,200	77	95	6.13
COL-45-75-5	49.6	13.9	4,800	100	124	6.67
COL-45-80-5	48.9	13.5	4,980	100	124	6.71
COL-40-80-5	42.3	10.8	6,810	123	152	8.25
COL-40-85-5	42.2	10.7	6,910	123	152	8.28
Commercial costs all ages						
COL-50-75-15	76.6	28.2	1,920	55	65	6.98
COL-50-75-10	67.7	23.3	2,560	69	82	6.97
COL-45-75-10	62.0	20.4	3,200	81	97	7.18
COL-45-75-5	49.6	14.6	4,800	105	127	7.67
COL-40-75-5	42.9	11.6	6,630	129	156	9.18
COL-40-80-5	42.3	11.3	6,810	130	156	9.24
COL-40-85-5	42.2	11.2	6,910	130	156	9.28
CMS costs all ages						
COL-50-75-15	76.6	28.2	1,920	55	65	5.07
COL-50-75-10	67.7	23.3	2,560	69	82	5.04
COL-45-75-10	62.0	20.4	3,200	81	97	5.16
COL-45-75-5	49.6	14.6	4,800	105	127	5.43
COL-40-75-5	42.9	11.6	6,630	129	156	6.41
COL-40-80-5	42.3	11.3	6,810	130	156	6.45
COL-40-85-5	42.2	11.2	6,910	130	156	6.47

CRC - colorectal cancer; LY - life-years; QALY - quality-adjusted life-years; FIT - fecal immunochemical test; COL - colonoscopy



Part II

Interventions to improve adherence

Chapter 5

Value of waiving coinsurance for colorectal cancer screening in Medicare beneficiaries

Elisabeth F. P. Peterse, Reinier G. S. Meester, Andrea Gini, Chyke A. Doubeni, Daniel S. Anderson, Franklin G. Berger, Ann G. Zauber & Iris Lansdorp-Vogelaar

Health Affairs (Millwood) (2017), 36:2151-2159

Abstract

Financial barriers to colorectal cancer screening persist despite the Affordable Care Act (ACA). Medicare beneficiaries may face 20 percent coinsurance for a screening colonoscopy when the procedure includes the removal of polyps or follows a positive fecal screening test. Using an established microsimulation model, we estimated that waiving this coinsurance would result in 1.7 fewer colorectal cancer deaths (a decrease of 13 percent) and $17,000 higher colorectal cancer–related costs (an increase of 0.6 percent) for the Centers for Medicare and Medicaid Services per 1,000 sixty-five-year-olds, assuming a 10-percentage-point increase in the rates of first colonoscopy screening, follow-up, and surveillance. If the rates did not change, waiving coinsurance would increase total costs by $51,000 (1.9 percent) per 1,000 sixty-five-year-olds. Estimated screening benefits were comparable when fecal testing was assumed to be the primary screening method. Moreover, waiving coinsurance would be cost-effective if the screening rate increased by 0.6 percentage points, assuming a willingness-to-pay threshold of $50,000 per quality-adjusted life-year gained. Thus, the waiver is likely to have a favorable balance of health and cost impact.

Introduction

Colorectal cancer is the second leading cause of cancer death in the United States (US). It is estimated that in 2017, over 135,000 new cases will be diagnosed, and more than 50,000 deaths due to the disease will occur.[187] Screening may prevent such deaths and is therefore recommended for people ages 50-75 years by the US Preventive Services Task Force.[76] Despite the overwhelming evidence for the effectiveness of screening,[51] in 2015 only 61.1 percent of eligible people reported having received colorectal cancer testing consistent with current guidelines (Stacey Fedewa, director of screening and risk factor surveillance, American Cancer Society, personal communication, February 1, 2017). Removing financial barriers is an effective way to increase participation in colorectal cancer screening.[188,189] Provisions of the Affordable Care Act (ACA) aimed to improve health care access and affordability of preventive services for all Americans[190] and eliminated cost sharing for services such as colorectal cancer screening that are recommended with by the task force a grade A or B.[191-195] Financial barriers for receipt of colorectal cancer screening persist despite the ACA. For Medicare beneficiaries, the group with the highest age-related disease risk, negative screening colonoscopy and fecal test such as fecal immunochemical test (FIT) are full covered–that is, the beneficiary has no deductible or coinsurance. However, beneficiaries without supplemental insurance face out-of-pocket spending when a polyp is detected and removed during the course of a screening colonoscopy, as the service is then classified by Medicare as diagnostic rather than preventive and is subject to a 20 percent coinsurance.[196] Beneficiaries are also responsible for both the part B deductible and the 20 percent coinsurance payment for colonoscopy when it is performed after a positive fecal test, regardless of the outcome. Since the 2011-2012 session of Congress, bills have been introduced to amend title XVIII of the Social Security Act to waive colonoscopy screening coinsurance for Medicare beneficiaries, regardless of the findings of the procedure. On the basis of Medicare claims, it has been estimated that the amendment increase Medicare spending on colonoscopies by US $48 million annually.[196] Because of the lack of studies on the potential impact of waiving the coinsurance on screening rates and the corresponding savings in colorectal cancer treatment, none of the introduced legislation has become law. To help inform future Medicare reimbursement policy, we estimated the potential impact of waiving Medicare coinsurance for screening colonoscopies with polyp removal and for diagnostic colonoscopies performed after a positive FIT. Using a well-established microsimulation model, we evaluated several scenarios for the effect of such a waiver on take-up of screening to determine whether, and under what circumstances, it could prove cost-effective.

Study data and methods

The Microsimulation Screening Analysis-Colon model

We used the Microsimulation Screening Analysis-Colon model to estimate the cost-effectiveness of waiving coinsurance for every component of colorectal cancer screening from the prospective of the Centers for Medicare and Medicaid Services (CMS). The model was developed by the Department of Public Health in the Erasmus University Medical

Center, and it has been described extensively elsewhere (**Model Appendix**).[102,103] It is part of the National Cancer Institute's Cancer intervention and Surveillance Modeling Network [197] and has been used to inform screening recommendations of the US Preventive Services Task Force.[96,97] In brief, the model generates, with random variation, the life histories of people in a large cohort to simulate the US population in terms of life expectancy and cancer risk. Each simulated person ages over time and may develop one or more adenomas that can progress from small (no more than 5 mm), to medium (6-9 mm) to large size (10 mm or more). Some adenomas develop into preclinical cancer, which may progress through stages I to IV. At each disease transition point, colorectal cancer may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the location of the cancer, and the person's age. Some simulated life histories are altered by the effect of detecting and removing adenomas or diagnosing colorectal cancer at an earlier stage, which results in a better prognosis. Screening also results in overdiagnosis and overtreatment and may have several complications, which are considered in the modelling. The Microsimulation Screening Analysis-Colon model quantifies the effectiveness and associated costs of the screening by comparing outcomes with and without a specific screening intervention. Further details about the model and its natural history assumptions are presented in the **Model Appendix**.

Analysis

We simulated an average-risk Medicare-eligible US population cohort of sixty-five-year-olds, 60 percent of whom were then up-to-date with screening according to guidelines of the US Preventive Services Task Force (which recommend colonoscopy screening at ages fifty and sixty or annual FIT screening from age fifty to age sixty-four). We then simulated potential increases in screening rates and benefits and costs due to waiving the Medicare coinsurance from age sixty-five over the patient's lifetime. We simulated screening until age seventy-five, following the task force's guidelines.

Patients with a positive FIT result were referred to diagnostic colonoscopy. Detected adenomas were removed and followed by colonoscopy surveillance every three to five years, depending on the number and the size of adenomas detected, as recommended by current guidelines.[107] Test characteristics were based on a study by Amy Knudsen and coauthors.[96] We assumed a Medicare reimbursement of $21.65 per FIT.[198] Estimates of the costs of colonoscopy screening, follow-up, and surveillance without polyp removal and of colonoscopies with polyp removal were obtained from an analysis of 2014 Medicare claims data from the Chronic Conditions Data Warehouse and updated to 2015 US dollars using the Consumer Price Index (CPI). Costs of colorectal cancer care were obtained from an analysis of data for the period 1998–2003 that linked information from the Surveillance, Epidemiology, and End Results (SEER) database with data from Medicare claims,[199] updated to 2015 US dollars using the CPI. Detailed model assumptions regarding test characteristics, utility losses in terms of quality-adjusted life-years (QALYs), and costs are in **Supplementary Table A5.1.**

Five scenarios were simulated that differed with regard to coinsurance and screening rate— which were evaluated separately for FIT- and colonoscopy-based screening

strategies. The first scenario was the current state, in which 70 percent of the total population ages 50–75 had received at least one screening, 60 percent adhered to screening recommendations,[113,176,200] 80 percent adhered to potential diagnostic and surveillance colonoscopy recommendations,[55,87] and there was a 20 percent coinsurance for screening colonoscopy with polypectomy and colonoscopy after a positive FIT result (no supplemental insurance was taken into account) (for more details on adherence assumptions as applicable to each round, see **Supplementary Table A5.1**).

In the second scenario, coinsurance for all participants was waived, with no assumed effect on screening rates. In the third scenario, waiving coinsurance was assumed to lead to a 5-percentage-point increase in the rate of completion of a diagnostic colonoscopy and surveillance after a positive FIT result.

In the fourth scenario, waiving coinsurance produced a 5-percentage-point increase in the initial screening rate and in diagnostic follow-up and surveillance rates. In this scenario, the percentage of people up-to-date with screening and ever having been screened increased to 65 percent and 73.75 percent, respectively (for similar relative reductions in the number not current with screening and never screened). In the fifth scenario, we simulated a 10-percentage-point increase in the initial screening rate and diagnostic follow-up and surveillance rates, which resulted in 70 percent and 77.5 percent of people being up-to-date with screening and ever having been screened, respectively (see **Supplementary Table A5.1**). The levels of increased screening participation simulated in the fourth and the fifth scenarios match the effect seen with the elimination of coinsurance for screening colonoscopies.[191,192,201]

For all coinsurance and screening-rate scenarios, and for both the FIT- and colonoscopy-based screening regimens, our main outcomes were numbers of colorectal cancer cases and deaths, number of colonoscopies potentially subject to coinsurance, life-years and QALYs gained compared to no screening, and associated costs. We applied the conventional 3 percent annual discount rate to all outcomes except for the numbers of colorectal cancer cases and deaths and of colonoscopies with coinsurance requirements. In addition, because the true effect on screening participation of waiving coinsurance is unknown, we determined the threshold increase in screening rate at which full coverage of colonoscopy by CMS is cost-effective compared to the current state based on willingness-to-pay thresholds of $100,000 and $50,000 per QALY gained.[202]

Sensitivity analyses

In sensitivity analyses, we used the following seven alternative assumptions to evaluate the robustness of our results: 60 percent of the cohort of sixty-five-year-olds had been screened once at age fifty-five using colonoscopy and received colonoscopy screening at ages sixty-five and seventy-five; none of the cohort of sixty-five-year-olds received screening before that age; the costs for colonoscopy were 10–75 percent higher (see **Supplementary Table A5.1**); treatment costs for the initial phases of stage III and IV and the terminal phase of colorectal cancer care (at all stages) were 10–75 percent higher (see **Supplementary Table A5.1**); the population that participated in screening

only if coinsurance was waived (socioeconomically disadvantaged people without supplemental insurance) and the population that never participated had a 1.2-fold higher incidence of colorectal cancer than the population that participated in screening regardless of the cost (based on a study by Raymond Oliphant and coauthors);[203] test sensitivities of FIT and colonoscopy were lower (worst case) or higher (best case) than our base-case analyses (see **Supplementary Table A5.1**); and potential increases in screening rates, benefits, and costs were simulated from age fifty on.

Limitations

Our study had a few limitations. First, the effect of waiving coinsurance on participation is not well known because of the paucity of published studies. We therefore evaluated several scenarios based on estimates of the effect of the coinsurance waiver for screening colonoscopies, and we determined a threshold of increased screening at which waiving the coinsurance was cost-effective. Second, the costs of colorectal cancer treatment derived from SEER-Medicare linked data for 1998–2003 might be underestimates, as therapy with monoclonal antibodies received approval by the Food and Drug Administration after that period. Therefore, we underestimated cost savings due to averted treatment expenses for cancer cases in our base-case analyses, and we explored the impact of higher treatment costs in our sensitivity analyses. Third, no up-to-date information was available on the proportion of Medicare beneficiaries with supplemental insurance. Supplemental coverage may vary across packages and states. We assumed a 20 percent increase in costs for CMS for all colonoscopies with polypectomy and those performed after a positive FIT after waiving the coinsurance. Since for people with Medicare Advantage, the private plans that receive premiums from CMS may already cover expenses, this likely overestimated the increase in cost from CMS's perspective and therefore the cost-effectiveness threshold of waiving coinsurance. Likewise, the health impact of waiving coinsurance might mainly occur among people without supplemental coverage (an estimated 14 percent of Medicare beneficiaries in 2010),[204] given that those with additional insurance might not benefit financially from the coinsurance change.

Study results

Potential benefits and costs of waiving coinsurance

We estimated that in the current state, using the colonoscopy regimen with coinsurance, 12.8 colorectal cancer deaths occurred and 124.1 QALYs were gained per 1,000 sixty-five-year-olds (**Table 5.1**). The total number of procedures per 1,000 Medicare beneficiaries was 1,132, of which 410 (36 percent) were potentially subject to coinsurance requirements. We estimated the total lifetime costs for CMS, which included colorectal cancer screening, surveillance, and treatment, with coinsurance, to be $2.675 million per 1,000 sixty-five-year-olds (**Table 5.1** and **Supplementary Table A5.2**).

The benefits of waiving coinsurance for a screening colonoscopy in which a polyp is removed varied with the assumed increase in participation. For the colonoscopy strategy, if there was no change in screening rate as a result of waiving the coinsurance,

the benefits of screening would not change, but the total costs of screening and treatment would increase to $2.726 million (an increase of $51,000, or 1.9 percent) per 1,000 sixty-five-year-olds (**Table 5.1**). In contrast, an assumed 5-percentagepoint increase in the rates of first colonoscopy screening and surveillance decreased the number of colorectal cancer deaths by 0.9 (6.4 percent), accompanied by an increase of $33,000 (1.2 percent) in total costs, with a cost per QALY gained (or cost-effectiveness ratio) of $4,086. A 10-percentage-point increase instead decreased deaths by 1.7 (13 percent) and increased costs by only $17,000 (0.6 percent), resulting in a cost- effectiveness ratio of $1,035.

The potential benefits and costs of waiving all coinsurance for colorectal cancer screening were comparable using a FIT-based strategy (**Table 5.1**). Of special interest is the scenario in which a 5-percentage-point increase in adherence to diagnostic follow-up and surveillance was assumed to be a consequence of waiving coinsurance. This resulted in a cost-effectiveness ratio of $48,606 compared to the current state, which suggests that even if only adherence to diagnostic follow-up and surveillance increased by this amount—with no increase in adherence to primary FIT screening—waiving the coinsurance would be cost-effective.

In the colonoscopy strategy, costs were higher at ages seventy, seventy-five, and eighty because of the increased costs for screening and surveillance colonoscopies, but costs were lower at the other ages if the waiver increased the screening rate (see **Supplementary Figure A5.1**). In the FIT strategy, waiving coinsurance was estimated to initially increase costs but to lead to cost savings after a decade because of averted cases of colorectal cancer. The estimated increase in per person costs was slightly higher for the colonoscopy strategy compared to the FIT strategy (see **Supplementary Figure A5.1**).

Cost-effectiveness threshold determination

Assuming a willingness-to-pay threshold of $100,000 per QALY gained, we estimated that waiving all coinsurance would be cost-effective if it increased screening participation by 0.4 percentage points (from 60.0 percent to 60.4 percent) in a colonoscopy-based screening protocol and by 0.3 percentage points (from 60.0 percent to 60.3 percent) in a FIT-based screening protocol (**Figure 5.1**). When a willingness-to-pay threshold of $50,000 was applied, we estimated that in both protocols the screening rate would need to increase 0.6 percentage points, to 60.6 percent, for waiving coinsurance to be cost-effective.

Table 5.1: Colorectal cancer (CRC) outcomes per 1,000 sixty-five-year-old Medicare beneficiaries, by screening category, coinsurance requirement, and change in adherence.

Category Scenario[a]	**CRC cases**[a]	**CRC deaths**[a]	**Colonoscopies with coinsurance requirements**[a]	**Life-years gained**[b]	**QALYs gained**[b]	**Costs (millions)**[b]	**Costs per QALY gained**[b]
No screening	60.1	26.6	60.1	0.0	0.0	3.276	-[c]
Colonoscopy							
With coinsurance							
Current state	34.2	12.8	410[d]	104.1	124.1	2.675	-[c]
Without coinsurance, assuming:							
No impact on adherence	34.2	12.8	410	104.1	124.1	2.726	-[c]
5 percentage point increase in diagnostic follow-up and surveillance.	34.1	12.7	411	104.1	124.1	2.728	$1,142,885
5 percentage point increase in first screening, diagnostic follow-up, and surveillance.	32.9	11.9	439	111.0	132.2	2.708	4,086
10 percentage point increase in first screening, diagnostic follow-up, and surveillance.	31.6	11.1	470	117.9	140.4	2.692	1,035
Fecal immunochemical test							
With coinsurance							
Current state	39.5	14.0	357	99.4	115.9	2.743	-[c]
Without coinsurance, assuming:							
No impact on adherence	39.5	14.0	357	99.4	115.9	2.785	-[c]
5 percentage point increase in diagnostic follow-up and surveillance.	39.2	13.9	368	100.1	116.7	2.783	48,606
5 percentage point increase in first screening, diagnostic follow-up and surveillance.	38.5	13.2	391	106.2	123.7	2.772	3,747
10 percentage point increase in first screening, diagnostic follow-up and surveillance.	37.3	12.4	427	112.9	131.6	2.758	974

Increases are compared to the current state (a 60 percent screening rate and 80 percent adherence rates to diagnostic follow-up and surveillance after a positive FIT). QALYs are quality-adjusted life-years.

[a] Not discounted.

[b] Discounted at the conventional 3 percent annual rate.

[c] Not applicable.

[d] Out of a total 1,132 colonoscopies.

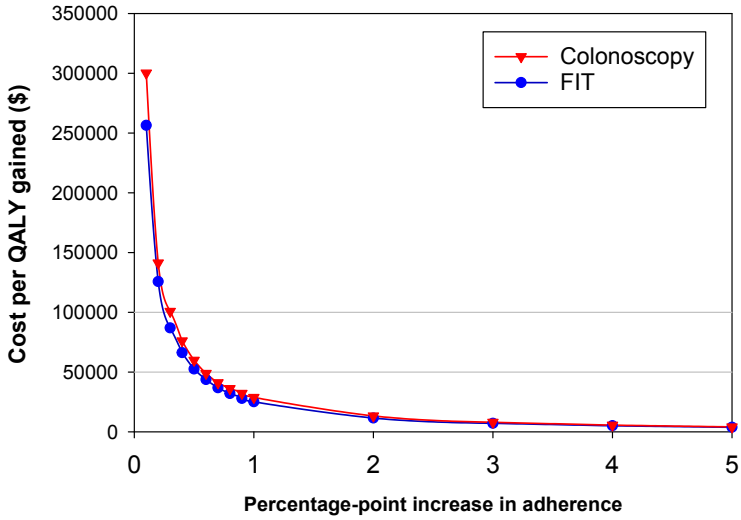


Figure 5.1: Predicted increases in costs per quality-adjusted life-year (QALY) gained if coinsurance for colorectal cancer screening were waived, by percentage-point increase in adherence to screening, diagnostic follow-up, and surveillance. Increases in costs and adherence are compared to the current state for sixty-five-year-old Medicare beneficiaries (who have a screening rate of 60 percent and an 80 percent adherence rate to diagnostic follow-up and surveillance), and are 3 percent discounted to the age of 65. With a willingness-to-pay threshold of $50,000 or even $100,000 per QALY gained, waiving coinsurance is cost-effective with even small increases in adherence. FIT is fecal immunochemical test.

Sensitivity analyses

Several sensitivity analyses affected the percentage-point increase in screening rate required for waiving coinsurance to be cost-effective. First, in the sensitivity analysis that assumed one previous colonoscopy screening at age fifty-five or no screening before age sixty-five increased the thresholds at which waiving coinsurance was cost-effective from 0.6 to 0.9 and 1.8 percentage points, respectively, using a willingness-to-pay threshold of $50,000 per QALY gained (Table 5.2). Second, in the sensitivity analysis that assumed higher colonoscopy costs, the threshold increased up to 1.3 percentage points. Third, if we simulated potential increases in screening rates, benefits, and costs starting at age fifty rather than age sixty-five, the threshold more than doubled (increasing to 1.8 percentage points). Sensitivity analyses that evaluated the effect of alternative assumptions for treatment costs, higher colorectal cancer risk in additional participants, and test sensitivities demonstrated that these assumptions minimally affected the percentage-point increase in screening rate needed to make waiving coinsurance cost-effective. The needed increase in screening rate did not exceeded 1.8 percentage points in any of the sensitivity analyses.

Table 5.2: Percentage-point increases in screening rate for colorectal cancer (CRC), diagnostic follow-up, and surveillance needed for waiving coinsurance for Medicare beneficiaries to be cost-effective, by selected assumptions.

Assumption	Colonoscopy, by willingness to pay per QALY gained		FIT, by willingness to pay per QALY gained	
	$100,000	*$50,000*	*$100,000*	*$50,000*
Base-Case	0.4	0.6	0.3	0.6
One previous screening at age 55[a]	0.5	0.9	-[b]	-[b]
With no screening before age 65[a]	0.8	1.8	0.4	0.8
Higher Colonoscopy costs of:				
10%	0.4	0.7	0.3	0.6
25%	0.4	0.8	0.4	0.7
50%	0.5	1.0	0.5	0.9
75%	0.6	1.3	0.5	1.0
Higher Treatment costs[c] of:				
10%	0.4	0.6	0.3	0.6
25%	0.3	0.6	0.3	0.6
50%	0.3	0.6	0.3	0.5
75%	0.3	0.6	0.3	0.5
Higher CRC risk in additional participants	0.3	0.5	0.3	0.5
Worst-case test sensitivity	0.4	0.6	0.3	0.6
Best-case test sensitivity	0.3	0.6	0.3	0.6
50-year-olds	0.8	1.8	0.5	1.0

Increases are compared to the current state among sixty-five-year-old beneficiaries (a 60 percent screening rate and 80 percent adherence rates to diagnostic follow-up and surveillance after a positive fecal immunochemical test [FIT]). All costs were discounted at the conventional 3 percent annual rate. QALYs - quality-adjusted life-years.
[a] Screenings at ages sixty-five and seventy-five.
[b] Not applicable.
[c] For initial phase stages III and IV and for terminal phase (all stages) CRC care.

Costs per QALY gained compared to the current state remained below $25,000 in every scenario if waiving coinsurance resulted in an increase in the screening rate (see Supplementary Figure A5.2). Strikingly, in the sensitivity analysis that assumed at least 25 percent higher costs of colorectal cancer care, the increase in costs of waiving coinsurance was totally offset by savings in the colorectal cancer care costs if the waiver resulted in a 10-percentage-point increase in the screening rate, which means that in this scenario, waiving coinsurance would be cost-saving (see Supplementary Figure A5.2 and Supplementary Table A5.3).

Discussion

Colorectal cancer screening is an effective prevention method, and removing financial barriers has been identified as a promising intervention for enhancing participation in the screening.[188,189] While we did not estimate the effect on participation of waiving coinsurance for screening colonoscopies with polyp removal or for colonoscopies performed after a positive FIT, we showed that the policy would be cost-effective if it increased the screening rate from 60.0 percent to 60.6 percent in Medicare beneficiaries, using a willingness-to-pay threshold of $50,000 per QALY gained. Even if waiving all coinsurance for colorectal cancer screening did not result in an increase in the screening rate, total costs for Medicare would increase by only 1.9 percent for the colonoscopy strategy and 1.5 percent for the FIT strategy (assuming that costs were discounted at the conventional 3 percent annual rate). Our sensitivity analyses demonstrated that if the actual costs were at least 25 percent higher than the current state for initial phases of care for stages III and IV colorectal cancer, and for terminal phases of care for all stages, waiving coinsurance would be cost-saving if it increased screening rates from 60 percent to 70 percent.

Literature on cost and health impacts of waiving coinsurance

We are aware of one previous study that examined the potential budget impact of waiving coinsurance for all screening related colonoscopies. David Howard and co-authors reported a 10 percent increase in total colonoscopy costs after coinsurance was waived for a diagnostic colonoscopy after a positive FIT and for a positive screening colonoscopy.[196] The increases in total colonoscopy costs in our analyses were 7.3 percent (the costs of screening, diagnostic follow-up, surveillance, and associated complications) in the colonoscopy strategy and 11.8 percent (the costs of diagnostic follow-up, surveillance, and associated complications) for the FIT strategy, if waiving coinsurance did not increase screening rate. However, the study by Howard and coauthors focused only on colonoscopy costs and did not consider cost savings from averted cases of colorectal cancer.[196] The strength of our study is that we also considered the potential impact of waiving coinsurance on screening behavior and estimated costs of the entire colorectal cancer screening process—including screening, diagnosis, surveillance, complications, and care—thereby placing the increase in costs from waiving coinsurance in a more complete context. To our knowledge, ours is the first study to explore the potential benefits of waiving coinsurance for a colonoscopy with polypectomy and for a follow-up colonoscopy after a positive FIT. The predicted health benefits of the waiver depend on its assumed impact on the screening rate. As a potential source of information for the expected impact, several studies have looked at the effect of similar legislation changes in which coinsurance was removed for screening colonoscopies. Shabnam Khatami and colleagues reported that waiving coinsurance for a negative screening colonoscopy resulted in an annual increase in colonoscopy use of 8.0–9.5 percent among employees of the University of Texas System,[201] an increase of 18 percent. Mary Hamman and Kandice Kapinos found a 4-percentage-point increase in annual colonoscopy rates in men ages 66–75 within one year of the ACA's enactment. They found even larger increases among socioeconomically disadvantaged men.[192]

Stacey Fedewa and coauthors compared data from the National Health Interview Survey for 2013 and 2008 and found a 9.8-percentage-point increase in colorectal cancer screening prevalence among Medicare beneficiaries after mandates on coverage of preventive care from the ACA took effect.[191] However, it is important to note that the ACA affected more factors than cost sharing that could have influenced screening participation, such as providing a free annual wellness visit and a temporary primary care bonus for physicians. In contrast, some studies found no effect of the elimination of cost sharing for screening colonoscopies on rates of colorectal cancer screening,[205-207] despite the fact that financial concerns constitute one of the most reported barriers to the screening. Substantial financial barriers may persist despite ACA provisions (for example, coinsurance requirements remain for an estimated 36 percent of the procedures), which reflects the complexity of the current reimbursement policy for both patients and providers. Other factors such as the need to take time off from work, family responsibilities, transportation, and fear of or other perceptions about the screening test also affect screening participation.[208,209]

Policy implications

We showed that waiving coinsurance would be cost-effective even with a modest increase of 0.6 percentage points in the screening rate, assuming a current rate of 60 percent. If all colonoscopies used in screening were fully reimbursed regardless of their findings or indications, a clear and consistent message could be communicated—which in itself might be a stimulus for screening participation in addition to reducing financial barriers. In general, FIT screening was associated with a lower number of procedures subject to coinsurance. If FIT screening becomes more popular in the United States, following trends observed in several settings,[158,210] the costs of waiving the coinsurance would be even lower. It is likely that waiving coinsurance would primarily affect the out-of-pocket spending of Medicare beneficiaries of low socioeconomic status, who more often than other beneficiaries lack Medigap and supplemental insurance.[204] Beneficiaries of very low socioeconomic status are eligible for Medicaid and may be protected from coinsurance in the thirty-one states that, along with the District of Columbia, expanded eligibility for Medicaid under the ACA.[204] However, in the remaining nineteen states, people of low socioeconomic status neither are eligible for Medicaid as well as Medicare nor can afford supplemental insurance. This means that waiving coinsurance might also contribute to reducing disparities in colorectal cancer in the United States.[74] Health disparities are larger in the United States than in many other Western countries,[211] and reducing them is an important objective of Healthy People 2020.[212]

Conclusion

The results of our study can inform the public debate and policy related to the balance of costs and benefits of waiving Medicare beneficiaries' coinsurance for colonoscopy screening in instances where a polyp is removed or the procedure is a follow-up to a positive FIT result. We estimated that waiving coinsurance would be cost-effective if screening rates increased from 60.0 percent to 60.6 percent, assuming a willingness- to-pay threshold of $50,000 per QALY gained—which suggests that the waiver would likely have a very favorable balance of health and cost impact.

Appendix

Supplementary Table A5.1.

TEST CHARACTERISTICS		
	Colonoscopy	*FIT*
Specificity	86%[a]	96.4%
Sensitivity[b]		
[Worst-case –Best-case][c]		
Adenoma 1-5 mm	75% [70.0-79.0%]	0.00% [0.00-0.00%][d]
Adenoma 6-9 mm	85% [80.0-92.0%]	11.4% [8.30-15.2%]
Adenoma 10+ mm	95% [93.1-99.5%]	15.9% [13.7-18.3%]
Colorectal cancer	95% [93.1-99.5%]	62.565/88.6% [48/81.1-75.3/93.4%][e]
Reach	95% reaches the cecum	
Costs (2015 US$) [+10-75%]		21.65
without polypectomy screening	699.41 [769.35-1049.12]	
without polypectomy diagnostic	591.42 [650.56-887.13] / 722.68 [794.95-1084.02][f]	
without polypectomy surveillance	682.06 [750.27-1023.09]	
with polypectomy	814.12 [895.53-1221.18]/ 982.40 [1080.64-1473.60][f]	
diagnosis of CRC by symptoms	814.12 [895.53-1221.18]	
Utility loss (QALYs)	0.002 (1.5 day at 0.5 utility)	0

COLORECTAL CANCER CARE				
Costs per LY CRC care[g] **(2015 US$)** [+10-75%]	*Initial care*	*Continuing care*	*Terminal care death CRC*	*Terminal care death other cause*
Stage I CRC	29,135	2,319	52,228 [57,451-91,399]	12,868
Stage II CRC	40,207	2,161	52,081 [57,289-91,141]	11,255
Stage III CRC	49,023 [53,925 – 85,790]	3,089	54,877 [60,365-96,035]	14,891
Stage IV CRC	64,015 [70,416 – 112,026]	9,573	73,649 [81,014-128,886]	39,980
Utility losses per LY with CRC care[h]				
Stage I CRC	0.12	0.05	0.70	0.05
Stage II CRC	0.18	0.05	0.70	0.05
Stage III CRC	0.24	0.24	0.70	0.24
Stage IV CRC	0.70	0.70	0.70	0.70

table continues

COMPLICATIONS COLONOSCOPY								
				Costs (2015 US$)			*Utility losses*	
Serious gastrointestinal event[i]				6,665			0.0055 (4 days at 0.5 utility)	
Other Gastrointestinal event[j]				4,749			0.0027 (2 days at 0.5 utility)	
Cardiovascular event[k]				5,205			0.0048 (3.5 days at 0.5 utility)	
ADHERENCES SIMULATED[l]								
Scenario	*Size stratum 1*	*Size stratum 2* [mn]	*Size stratum 3* [mn]	*Adh. scr.*	*Adh. next scr. if prev. adh.*[o]	*Adh. next scr. if prev. unadh.*[p]	*Adh. Diagnostic FU* [q] *& surv.*	*Adh.*
				----------*Stratum 1 and Stratum 2* ----------				*Stratum3*
Current adherence	70%	0%	30%	85.71%[r]	90.00%	60.00%	80.00%	0
+5 %point FU and Surv.	70%	0%	30%	85.71%	90.00%	60.00%	85.00%	0
+5%point 1st Scr. FU and Surv.	70%	3.75%	26.25%	88.14%	91.25%	65.00%	85.00%	0
+10%point 1st Scr. FU and Surv	70%	7.5%	22.5%	90.32%	92.50%	70.00%	90.00%	0

CRC - colorectal cancer; Str. – Stratum; Adh =-Adherence; Scr. – Screening; prev. – previously; FU - diagnostic follow-up; Surv. - Surveillance.

[a] The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, where the non-adenomatous lesions are removed and therefore induce polypectomy and biopsy.

[b] The sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies [213] .We assumed the same test characteristics for diagnostic colonoscopy as for screening colonoscopy.

[c] In the worst- and best-case test sensitivity FIT scenarios, the corresponding worst- and best-case values for colonoscopy were used.

[d] We assumed that small adenomas do not bleed, and therefore cannot cause a positive stool test.

[e] "Long" before clinical diagnosis / "Short" before clinical diagnosis.

[f] CMS costs in the current state with coinsurance/ CMS costs if coinsurance is waived

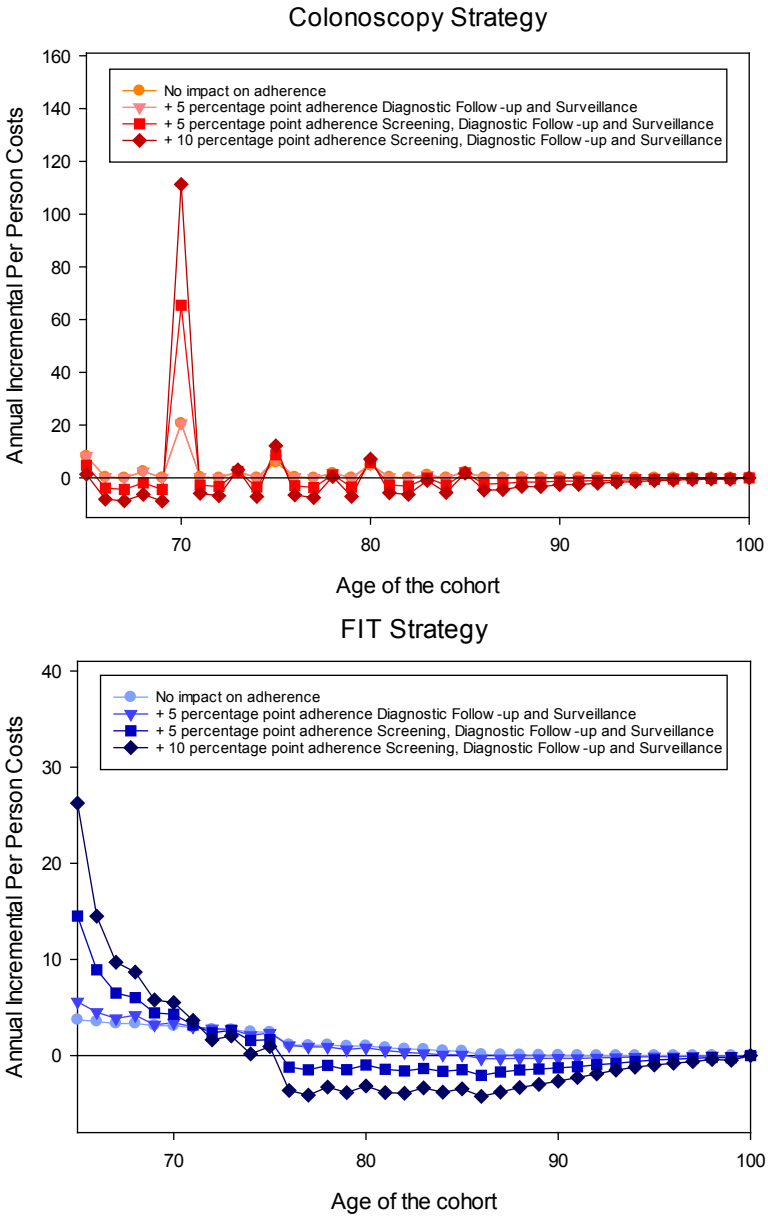
[g] CRC care costs were obtained from an analysis of 1998-2003 SEER-Medicare linked data [199] and updated to 2015 US dollars using the Consumer Price Index. CRC care was divided in three clinically relevant phases. The initial care phase was defined as the first 12 months after diagnosis, the terminal care phase as the final 12 months of life, and the continuing care phase as all months in between. For patients surviving less than 24 months, the last 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase. As these costs are derived from 2003 data, these costs exclude the potential use of expensive monoclonal antibodies cetuximab and bevacizumab as these received FDA approval for treatment of colorectal cancer in 2004. Therefore, we assumed 10%, 25%, 50% and 75%

higher treatment costs for initial phase stage III and IV, and terminal care CRC death all stages.
[h] Utility losses for LYs with initial care were derived from a study by Ness et al. [171]. For LYs with continuing care for stage I and II CRC, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV CRC, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.
[i] Serious gastrointestinal events are perforations, gastrointestinal bleeding, or transfusions. The rate depends on age, formula 1/[exp(9.27953 – 0.06105 x Age) + 1] – 1/[exp(10.78719 – 0.06105 x Age) + 1].
[j] Other gastrointestinal events are paralytic ileus, nausea and vomiting, dehydration, or abdominal pain. The rate depends on age, formula 1/[exp(8.81404 – 0.05903 x Age) + 1] – 1/[exp(9.61197 – 0.05903 x Age) + 1].
[k] Cardiovascular events are myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock. The rate depends on age, formula 1/[exp(9.09053 – 0.07056 x Age) + 1] – 1/[exp(9.38297 – 0.07056 x Age) + 1].
[l] To reflect observed screening rates in the United States, the population of 10 million men and women was divided in three strata: stratum 1 (70%) contained current participants [175,176,185], stratum 2 (0-7.5%) contained additional participants, stratum 3 (30-22.5%) never attended screening.
[m] In sensitivity analyses 5, we assumed that stratum 2 and stratum 3 have a relative risk of getting CRC of 1.2 compared to the population that attends irrespectively of costs, based on the study of Oliphant et al. [203].
[n] We decreased the population that is never screened with the same proportion as the population that is currently not up to date with CRC screening by increasing the proportion of the population in stratum 2.
[o] We assumed 90% adherence next screening if previously adherent [185,186]. We decreased the population that not adheres to the next screening round if previously adherent by the same proportion as the population that is currently not up to date with CRC screening.
[p] Calculated that overall adherence in next screening round remains the same.
[q] Represents the adherence to a diagnostic colonoscopy after a positive FIT test.
[r] Calculated as 60/70, which reflects the ratio up to date with screening compared to the people ever screened.

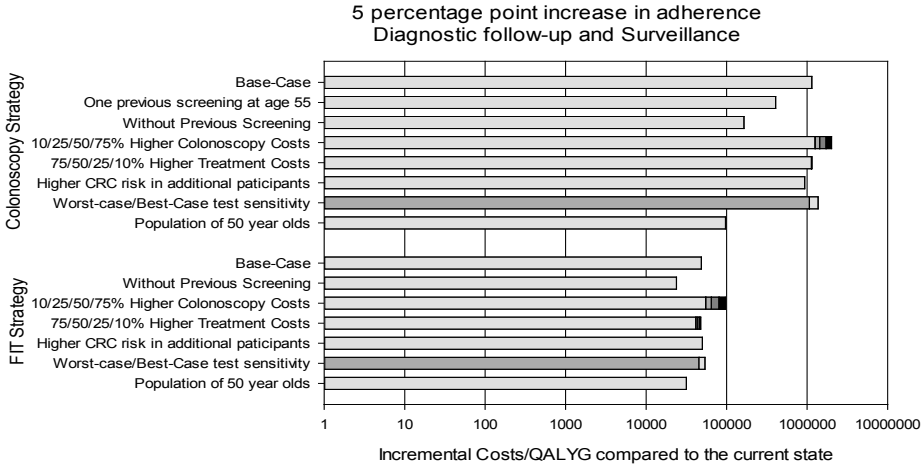
Supplementary Table A5.2: Costs in million US dollars per 1,000 65-year-olds (3% discounted).

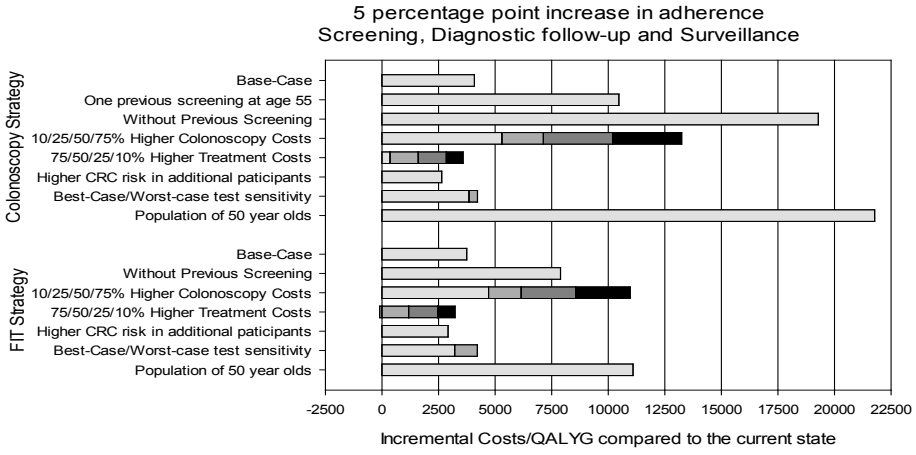
Category *Scenario*[a]	**Screening costs**	**Diagnostic costs**	**Surveillance costs**	**Complications costs**	**CRC care costs**	**Total costs**
No screening	0.000	0.034	0.000	0.005	3.236	3.276
Colonoscopy						
With coinsurance						
Current state	0.238	0.016	0.412	0.032	1.978	2.675
Without coinsurance						
No impact on adherence	0.252	0.016	0.449	0.032	1.978	2.726
With 5 percentage point increase in adherence diagnostic follow-up and surveillance.	0.252	0.016	0.452	0.032	1.977	2.728
With 5 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	0.283	0.014	0.468	0.034	1.910	2.708
With 10 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	0.314	0.013	0.488	0.036	1.840	2.692
FIT						
With coinsurance						
Current state	0.077	0.111	0.224	0.022	2.309	2.743
Without coinsurance						
No impact on adherence	0.077	0.131	0.246	0.022	2.309	2.785
With 5 percentage point increase in adherence diagnostic follow-up and surveillance.	0.076	0.136	0.253	0.023	2.296	2.783
With 5 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	0.083	0.148	0.263	0.024	2.255	2.772
With 10 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	0.089	0.166	0.281	0.025	2.196	2.758

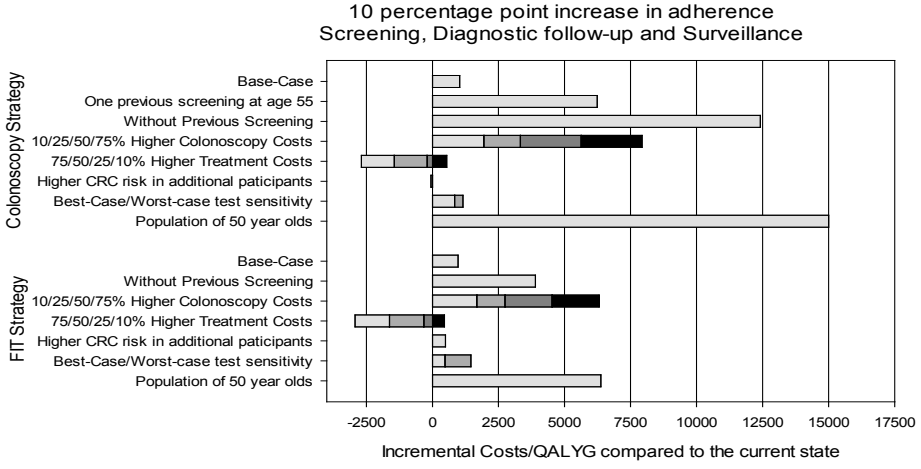
[a] In the current state, we assumed a 60% adherence in first screening, an 80% adherence to diagnostic follow-up after a positive FIT, and an 80% adherence to surveillance. In the second scenario, coinsurance is waived without an effect on adherence. In the third scenario, waiving coinsurance is assumed to lead to a 5 percentage point increase in adherence to diagnostic follow-up and surveillance. In the fourth and the fifth scenario, we simulated a 5 percentage point and 10 percentage point increase in adherence to screening, diagnostic follow-up and surveillance as a consequence of coinsurance removal, respectively.



Supplementary Figure A5.1: Annual incremental costs of waiving coinsurance from a CMS perspective (including costs of screening, diagnostic follow-up, and surveillance and savings of treatment, 3% discounted) compared to a situation without coinsurance removal by screening strategy and screening rate scenario. Most of the increase in costs would occur immediately upon waiving all coinsurance, while after a decade costs start to stabilize and decline due to costs savings in CRC treatment costs. In the graph of the colonoscopy strategy, the peaks reflect the screening and surveillance years.


5 percentage point increase in adherence
Diagnostic follow-up and Surveillance
Colonoscopy Strategy
Base-Case
One previous screening at age 55
Without Previous Screening
10/25/50/75% Higher Colonoscopy Costs
75/50/25/10% Higher Treatment Costs
Higher CRC risk in additional paticipants
Worst-case/Best-Case test sensitivity
Population of 50 year olds
FIT Strategy
Base-Case
Without Previous Screening
10/25/50/75% Higher Colonoscopy Costs
75/50/25/10% Higher Treatment Costs
Higher CRC risk in additional paticipants
Worst-case/Best-Case test sensitivity
Population of 50 year olds
1
10
100
1000
10000
100000
1000000
10000000
Incremental Costs/QALYG compared to the current state


5 percentage point increase in adherence
Screening, Diagnostic follow-up and Surveillance
Colonoscopy Strategy
Base-Case
One previous screening at age 55
Without Previous Screening
10/25/50/75% Higher Colonoscopy Costs
75/50/25/10% Higher Treatment Costs
Higher CRC risk in additional paticipants
Best-Case/Worst-case test sensitivity
Population of 50 year olds
FIT Strategy
Base-Case
Without Previous Screening
10/25/50/75% Higher Colonoscopy Costs
75/50/25/10% Higher Treatment Costs
Higher CRC risk in additional paticipants
Best-Case/Worst-case test sensitivity
Population of 50 year olds
-2500
0
2500
5000
7500
10000
12500
15000
17500
20000
22500
Incremental Costs/QALYG compared to the current state


10 percentage point increase in adherence
Screening, Diagnostic follow-up and Surveillance
Colonoscopy Strategy
Base-Case
One previous screening at age 55
Without Previous Screening
10/25/50/75% Higher Colonoscopy Costs
75/50/25/10% Higher Treatment Costs
Higher CRC risk in additional paticipants
Best-Case/Worst-case test sensitivity
Population of 50 year olds
FIT Strategy
Base-Case
Without Previous Screening
10/25/50/75% Higher Colonoscopy Costs
75/50/25/10% Higher Treatment Costs
Higher CRC risk in additional paticipants
Best-Case/Worst-case test sensitivity
Population of 50 year olds
-2500
0
2500
5000
7500
10000
12500
15000
17500
Incremental Costs/QALYG compared to the current state

Supplementary Figure A5.2: Cost-effectiveness of waiving coinsurance for every component of CRC screening with alternative model assumptions if this coinsurance waiver would lead to a 5 percentage point increase in adherence diagnostic follow-up and Surveillance (top) or a 5 percentage point (middle) or a 10 percentage point (bottom) increase in adherence to screening, diagnostic follow-up and surveillance. The costs and QALY gained were compared to the current state, in which we assumed a 60% adherence in screening, an 80% adherence to diagnostic follow-up after a positive FIT, and an 80% adherence to surveillance. In the first sensitivity analysis, 60% of the cohort had one previous colonoscopy screening at the age of 55. We then simulated potential increases in screening uptake, benefits and costs due to waiving the Medicare coinsurance from age 65 years onward, implementing screening rounds at age 65 and 75. In the second sensitivity analyses, no screening before the age of 65 was assumed. In the third sensitivity analyses, we assumed 10-75% higher colonoscopy costs. The different shades of grey represent the cost-effectiveness of a 10%, 25%, 50% and 75% higher colonoscopy costs, respectively, where the results of assuming a 10% higher colonoscopy costs are shown in the lightest color, and the results of assuming a 75% higher colonoscopy costs are shown in black. In the fourth sensitivity analyses, 10-75% higher treatment cost for initial phase stage III and IV and for Terminal phase CRC care (all stages) were simulated. The different shades of grey represent the cost-effectiveness of a 75%, 50%, 25% and 10% higher treatment costs, respectively, where the results of assuming a 75% higher treatment costs is shown in the lightest color, and the results of assuming a 10% higher treatment costs are shown in black. In the fifth sensitivity analysis, we assumed that the population that only attends if coinsurance of every CRC screening component are fully waived and the population that never attends have a relative risk of getting CRC of 1.2 compared to the population that attends irrespectively of costs. In the sixth sensitivity analyses, we assumed Best-Case (light grey) and Worst-Case (dark grey) test sensitivities. In the seventh sensitivity analysis, we simulated potential increases in screening rate, benefits and costs from age 50 onward.

Supplementary Table A5.3: Results sensitivity analyses: Quality-adjusted life-years gained and Total costs from a CMS perspective per 1,000 65-year-old Medicare Beneficiaries, by screening category, coinsurance requirement and screening rate scenario (3% discounted).

Category *Scenario*[a]	*Base-case*		*One previous screening at age 55*		*Previously unscreened*	
	QALY gained	**Total costs (million $)**	**QALY gained**	**Total costs (million $)**	**QALY gained**	**Total costs (million $)**
No screening	0.0	3.276	0	3.211	0	2.832
Colonoscopy						
With coinsurance						
Current state	124.1	2.675	112.7	2.929	69.1	3.020
Without coinsurance						
No impact on adherence	124.1	2.726	112.7	2.996	69.1	3.105
With 5 percentage point increase in adherence diagnostic follow-up and surveillance.	124.1	2.728	112.9	3.000	69.7	3.114
With 5 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	132.2	2.708	120.6	3.012	75.2	3.138
With 10 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	140.4	2.692	128.6	3.028	81.4	3.172
FIT						
With coinsurance						
Current state	115.9	2.743	-	-	57.5	2.867
Without coinsurance						
No impact on adherence	115.9	2.785	-	-	57.5	2.913
With 5 percentage point increase in adherence diagnostic follow-up and surveillance.	116.7	2.783	-	-	59.2	2.909
With 5 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	123.7	2.772	-	-	63.2	2.912
With 10 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	131.6	2.758	-	-	68.9	2.912

table continues

Category *Scenario*[a]	*Higher treatment costs (10-75%)*[b]		*Higher treatment costs (10-75%)*[b]		*Higher CRC risk additional participants*[c]	
	QALY gained	**Total costs (million $)**	**QALY gained**	**Total costs (million $)**	**QALY gained**	**Total costs (million $)**
No screening	0.0	3.420 – 4.358	0.0	3.420 – 4.358	0	3.276
Colonoscopy						
With coinsurance						
Current state	124.1	2.745 – 3.201	124.1	2.745 – 3.201	116.8	2.731
Without coinsurance						
No impact on adherence	124.1	2.796 – 3.252	124.1	2.796 – 3.252	116.8	2.780
With 5 percentage point increase in adherence diagnostic follow-up and surveillance.	124.1	2.798 – 3.254	124.1	2.798 – 3.254	116.9	2.782
With 5 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	132.2	2.774 – 3.202	132.2	2.774 – 3.202	125.9	2.755
With 10 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	140.4	2.754 – 3.157	140.4	2.754 – 3.157	135.0	2.730
FIT						
With coinsurance						
Current state	115.9	2.817 – 3.301	115.9	2.817 – 3.301	109.5	2.779
Without coinsurance						
No impact on adherence	115.9	2.859 – 3.344	115.9	2.859 – 3.344	109.5	2.819
With 5 percentage point increase in adherence diagnostic follow-up and surveillance.	116.7	2.857 – 3.336	116.7	2.857 – 3.336	110.3	2.818
With 5 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	123.7	2.842 – 3.301	123.7	2.842 – 3.301	118.2	2.804
With 10 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	131.6	2.824 – 3.255	131.6	2.824 – 3.255	126.9	2.787

table continues

Category *Scenario*[a]	*Test sensitivity (Worst-case ; Best-case)*[d]		*50-year-olds*	
	QALY gained	**Total costs (million $)**	**QALY gained**	**Total costs (million $)**
No screening	0	3.276	0	2.433
Colonoscopy				
With coinsurance				
Current state	120.8 ; 128.3	2.719 ; 2.628	75.4	2.835
Without coinsurance				
No impact on adherence	120.8 ; 128.3	2.770 ; 2.679	75.4	2.927
With 5 percentage point increase in adherence diagnostic follow-up and surveillance.	120.8 ; 128.3	2.772 ; 2.681	76.4	2.935
With 5 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	128.8 ; 136.5	2.753 ; 2.660	82.1	2.980
With 10 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	136.9 ; 144.8	2.737 ; 2.642	88.7	3.035
FIT				
With coinsurance				
Current state	106.5 ; 125.4	2.830 ; 2.644	70.8	2.491
Without coinsurance				
No impact on adherence	106.5 ; 125.4	2.871 ; 2.687	70.8	2.554
With 5 percentage point increase in adherence diagnostic follow-up and surveillance.	107.3 ; 126.1	2.871 ; 2.685	72.8	2.554
With 5 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	114.1 ; 133.5	2.862 ; 2.670	77.3	2.563
With 10 percentage point increase in adherence first screening, diagnostic follow-up and surveillance.	121.7 ; 141.7	2.852 ; 2.651	83.8	2.574

QALY - quality-adjusted life-years gained compared to no screening; CRC - colorectal cancer

[a] In the current state, we assumed a 60% adherence in first screening, an 80% adherence to diagnostic follow-up after a positive FIT, and an 80% adherence to surveillance. In the second scenario, coinsurance is waived without an effect on adherence. In the third scenario, waiving coinsurance is assumed to lead to a 5 percentage point increase in adherence to diagnostic follow-up and surveillance. In the fourth and the fifth scenario, we simulated a 5 percentage point and 10 percentage point increase in adherence, diagnostic follow-up and surveillance as a consequence of coinsurance removal, respectively.

[b] In the fourth sensitivity analysis, we assumed a 10%, 25%, 50% and 75% higher treatment cost for initial phase stage III and IV and for Terminal phase CRC care (all stages) as the costs of CRC care were obtained from an analysis of 1998-2003 SEER-Medicare linked data which excludes costs for potential use of expensive monoclonal antibodies cetuximab and bevacizumab as these received FDA approval for treatment of colorectal cancer in 2004.
[c] In the fifth sensitivity analysis, we assumed that the population that only attends if coinsurance of every CRC screening component is fully waived and the population that never attends have a relative risk of getting CRC of 1.2 compared to the population that attends irrespectively of costs.
[d] We tested worst-case and best-case test sensitivity of FIT and colonoscopy. In the worst- and best-case test sensitivity FIT scenarios, the corresponding worst- and best-case values for colonoscopy were used.

Chapter 6

Comparing the cost-effectiveness of innovative colorectal cancer screening tests

Elisabeth F.P. Peterse, Reinier G.S. Meester, Lucie de Jonge,
Amir-Houshang Omidvari, Fernando Alarid-Escudero, Amy B. Knudsen,
Ann G. Zauber & Iris Lansdorp-Vogelaar

Journal of the National Cancer Institute (2020), Epub

Abstract

Background

Colorectal cancer (CRC) screening with colonoscopy and the fecal immunochemical test (FIT) is underutilized. Innovative tests could increase screening acceptance. This study determined which of the available alternatives is most promising from a cost-effectiveness perspective.

Methods

The previously-validated MISCAN-Colon model was used to evaluate the cost-effectiveness of screening with capsule endoscopy every 5 or 10 years, computed tomographic colonography (CTC) every 5 years, the multi-target stool DNA (mtSDNA) test every 1 or 3 years, and the methylated *SEPT9* DNA plasma assay (m*SEPT9*) every 1 or 2 years. We also compared these strategies to annual FIT screening and colonoscopy screening every 10 years. Quality-adjusted life-years gained (QALYG), number of colonoscopies, and incremental cost-effectiveness ratios (ICERs) were projected. We assumed a willingness-to-pay threshold of $100,000 per QALYG.

Results

Among the alternative tests, CTC every 5 years, annual m*SEPT9* and annual mtSDNA screening had ICERs of $1,092, $63,253 and $214,974 per QALYG, respectively. Other screening strategies were more costly and less effective than (a combination of) these three. Under the assumption of perfect adherence, annual m*SEPT9* screening resulted in more QALYG, CRC cases averted and CRC deaths averted than annual FIT screening, but led to a high rate of colonoscopy referral (51% after 3 years, 69% after 5 years). The alternative tests were not cost-effective compared to FIT and colonoscopy.

Conclusion

This study suggests that for individuals not willing to participate in FIT or colonoscopy screening, m*SEPT9* is the test of choice if the high colonoscopy referral rate is acceptable to them.

Introduction

Colorectal cancer (CRC) is a leading cause of cancer death in the United States (US), with an estimated 53,000 associated deaths in 2020.[214] CRC screening can prevent CRC death through earlier detection or through removal of premalignant polyps,[51,64] and is recommended from age 50 to 75 years by the US Preventive Services Task Force (USPSTF)[76] and from age 45 to 75 years by the American Cancer Society (ACS).[78] Despite the effectiveness of screening, almost 40% of 50 to 75-year-olds reported not having received guideline-consistent CRC screening. Important barriers for screening include fear and disgust of the screening test.[208,209] Therefore, new tests that circumvent these barriers are needed to increase screening participation.

Fecal occult blood testing and colonoscopy were already proposed as CRC screening tests in the late 1960s.[215,216] More recently developed FDA-approved tests are capsule endoscopy, specifically the PillCam COLON 2 (PillCam), the computed tomographic colonography (CTC), the multitarget stool DNA test (mtSDNA), also known as Cologuard® (Exact Sciences Corporation), and the methylated *SEPT9* DNA plasma assay (m*SEPT9*), also known as the Epi proColon® (Epigenomics AG). All these tests require colonoscopy follow-up of individuals with a positive test result. Several studies have suggested that these alternative tests are not cost-effective compared to colonoscopy or fecal immunochemical test (FIT) screening.[172,217-222] However, these tests have potential to attract the population not currently participating in screening. The m*SEPT9* requires a blood sample, which may be preferred for some patients over collecting a stool sample or a more invasive test. The CTC, PillCam and mtSDNA all have better test sensitivities than FIT while being less invasive than colonoscopy. Therefore it is important to evaluate which of these alternative tests should be offered to individuals who are not willing to participate in FIT or colonoscopy screening. No study has compared all of these alternative screening tests in terms of cost-effectiveness. Therefore, in this study, the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model was used to evaluate the comparative cost-effectiveness of the PillCam, the CTC, the mtSDNA and the m*SEPT9*.

Methods

MISCAN-Colon

The MISCAN-Colon model was developed by the Department of Public Health within Erasmus University Medical Center, Rotterdam, the Netherlands, and has been described in detail elsewhere (**Model Appendix**).[102,103] It is part of the US National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) [144] and has been used to inform screening recommendations.[96,98,99] In brief, the model generates, with random variation, a large population similar to the US population in terms of life expectancy and CRC risk. As each simulated person ages, one or more adenomas may develop, which can progress in size and can develop into preclinical cancer (stages I to IV). During each stage CRC may be diagnosed because of symptoms.

Screening can alter some simulated life histories, as CRC can be prevented or diagnosed at an earlier stage. Screening may also result in complications, over-diagnosis and over-treatment, which are also taken into account by the model.

Screening strategies

We simulated screening from age 50 through 75 years in an-average risk population, with perfect adherence to screening, diagnostic follow-up and surveillance recommendations [76,107]. We used the same model assumptions as for the 2018 ACS guidelines, which accounts for recent trends in CRC incidence.[16,99] The screening strategies evaluated were CTC every 5 years, mtSDNA testing every 1 or 3 years,[76] PillCam every 5 or 10 years, and annual or biennial m*SEPT9* testing. These alternative screening strategies were compared to colonoscopy every 10 years and annual FIT. Positive non-colonoscopy tests were followed by a diagnostic colonoscopy, and individuals in whom adenomas were detected and removed received colonoscopy surveillance through age 85 years.[107]
To compare the different screening strategies, an incremental cost-effectiveness analysis was performed, ranking strategies based on costs. Strategies that were more costly and less effective than a (combination of) other strategies were considered dominated. Remaining strategies provided good value for money (i.e. were efficient). For the efficient strategies, the incremental cost-effectiveness ratios (ICERs) were obtained by dividing the additional costs by the additional quality-adjusted life-years gained (QALYG) compared with the next less costly alternative strategy. In this analysis, we assumed a willingness-to-pay threshold of $100,000 per QALYG.[109,174]

Test characteristics

m*SEPT9* performance characteristics were based on Potter et al. [223](**Table 6.1** and **Supplementary Table A6.1**), which was used for the FDA approval of m*SEPT9*. [224] In this study, 1544 samples were retrospectively selected from the PRESEPT trial.[225] A CRC sensitivity and specificity of 68.2% and 78.8%, were reported, respectively, with a sensitivity for advanced adenoma of 21.6%. PillCam characteristics were based on the study of Rex et al., in which 695 asymptomatic individuals were successfully screened using the PillCam, followed by colonoscopy several weeks later.[226] This study reported a sensitivity of 92% and 91% for adenomas larger than 10mm and 6mm, respectively, with a specificity of 83%.[226] Colonoscopy, FIT, CTC and mtSDNA characteristics were similar to previous analyses from our group (**Table 6.1**).[96,99] All test characteristics were varied in probabilistic sensitivity analyses (see below).

Table 6.1: Test characteristics

Screening test	Sensitivity (%)[a]				Specificity (%) [b]	Source[c]
	Adenomas ≤ 5 mm	Adenomas 6-9 mm	Adenomas ≥ 10 mm	CRC		
Direct Visualization						
Colonoscopy[d]	75	85	95	95	100[e]	van Rijn et al. 2006 [213]
CTC	12[f]	57	84	84[g]	88[h]	Johnson et al. 2008 [227]
PillCam	17[f]	91[i]	92	92[g]	83	Rex et al. 2015 [226]
Stool-based						
FIT	7.6[j]		23.8[k]	73.8	96.4	Imperiale et al. 2014 [72]
mtSDNA	17.2[j]		42.4[k]	92.3	89.8	Imperiale et al. 2014 [72]
Blood-based						
m*SEPT9*	21.2[f]	21.2[f]	21.6[k]	68.2	78.8	Potter et al. 2014 [223]

CTC - computed tomographic colonography; PillCam - PillCam COLON 2; FIT - fecal immunochemical test; mtSDNA - multitarget stool DNA; m*SEPT9* - methylated *SEPT9* DNA plasma assay

[a] The sensitivities of CTC and colonoscopy are presented per lesion; the sensitivities of the other tests are presented per person which were calibrated to per lesion test sensitivities that were used as MISCAN-Colon model input.

[b] Specificity is defined as the probability of having a negative test result for individuals without lesions (including adenomas and CRC), unless otherwise noted.

[c] Additional details about these studies (designs, sample sizes, periods and regions) can be found in Supplementary Table A6.1.

[d] We assumed that 95% of colonoscopies reach the cecum.

[e] We accounted for the detection of nonadenomatous polyps, which is 14% based on Schroy et al. 2013 [228].

[f] Sensitivity equals the false-positivity rate. It is 1 – specificity.

[g] The same sensitivity for CRC as for adenomas ≥ 10 mm was assumed.

[h] The lack of specificity of a CTC reflects the detection of > 5 mm nonadenomatous lesions, artifacts, stool and adenomas smaller than the 6-mm threshold for referral to colonoscopy that are measured as > 5 mm.

[i] Value of all adenomas ≥ 6 mm

[j] Sensitivity for persons with nonadvanced adenomas. For persons with 1-5 mm, it was assumed that the sensitivity is equal to the positivity in persons without adenomas. The sensitivity for adenomas 6-9 mm was chosen such that the weighted average sensitivity is equal to that for nonadvanced adenomas.

[k] Sensitivity for persons with advanced adenomas. In MISCAN-Colon, advanced adenomas are equated to large adenomas.

Costs and disutilities

Costs of screening, screening-related complications, and cancer care were computed from a societal perspective, obtained from various sources, and included (as relevant), payments, co-insurance, cathartic bowel preparation agents, and patient- and escort time costs (**Table 6.2; Supplementary Tables A6.2-A6.6**). Costs were updated to 2017 US dollars using the Personal Health Care Deflator Price Index. Estimated test disutilities included those associated with the test itself, and those related to fear or anxiety while waiting for the test result or a follow-up colonoscopy after a positive result (**Supplementary Table A6.4**). Complication and CRC care disutilities were in line with previous analyses.[154,172]

Table 6.2: Assumptions regarding disutilities and costs of screening tests (2017 $).

Screening test	Disutility	Total CMS payment	Cost of bowel preparation kit	Patient / escort time costs	Total cost
Colonoscopy screening w/o polypectomy	0.000496	$794	$51	$434	$1,279
Colonoscopy follow-up w/o polypectomy	0.000496	$847	$51	$434	$1,332
Colonoscopy surveillance w/o polypectomy	0.000496	$796	$51	$434	$1,281
Colonoscopy with polypectomy	0.001401	$1,172	$51	$434	$1,656
CTC	0.001559 / 0.000292[a]	$236	$51	$206	$493
PillCam	0.001692 / 0.000425[a]	$939	$104	$310	$1,352
FIT	0.001330 / 0.000063[a]	$22	-	$18	$40
mtSDNA	0.001394 / 0.000127[a]	$512	-	$18	$531
m*SEPT9*	0.001330 / 0.000063[a]	$192	-	$18	$210

CMS - Centers for Medicare and Medicaid Services; CTC - computed tomographic colonography; PillCam - PillCam COLON 2; FIT - fecal immunochemical test; mtSDNA - multitarget stool DNA; m*SEPT9* - methylated *SEPT9* DNA plasma assay

[a] Assumed disutility per event if test is positive / assumed disutility per event if test is negative.

Scenario analyses

We repeated analyses under several alternative scenarios. In the first scenario, we evaluated CRC screening from age 45 years instead of 50 years, in line with the most recent ACS screening guideline.[78] In the second scenario, we used the version of the MISCAN-model which informed the 2016 USPSTF CRC screening recommendations, with CRC incidence based on 1975-1979 data [96] instead of more recent data. In the third scenario, we accounted for suboptimal adherence to diagnostic and surveillance colonoscopy and for decreasing adherence over multiple screening rounds.[229] For this scenario, we assumed a 100% adherence at the first screening and that 90% of the people

screened at a given age would participate again at the next recommended age.[185,230] In line with current CRC participation rates,[231] we assumed screening adherence would not drop below 60% at any age by assuming that 15% of the people who previously did not participate would participate at the next recommended age. We further assumed 80% adherence to diagnostic and surveillance colonoscopy.[55,114] Finally, we evaluated a scenario in which 12% of the advanced adenomas and 18% of CRCs were systematically missed by the m*SEPT9,* due to no methylation of the *SEPT9* gene promoter.[232]

Probabilistic sensitivity analyses

To evaluate the model parameter uncertainty, a probabilistic sensitivity analysis was performed, varying the characteristics, costs and disutilities of all screening tests as well as the costs and disutilities of CRC treatment and colonoscopy complications (**Supplementary Tables A6.7-A6.8**). For every evaluated screening strategy, we performed 1000 simulation runs of 10 million persons, in which we sampled parameters values from distributions that reflect the parameter's current level of evidence (**Supplementary Tables A6.7-A6.8**). The results of the probabilistic sensitivity analysis were displayed with cost-effectiveness acceptability curves and a frontier representing the proportion that each strategy is cost-effective, and the strategy with the highest expected net monetary benefit at each cost-effectiveness threshold, respectively.[233] Results were analyzed using R with the package BCEA.[234,235]

Results

Projected outcomes

Without screening, the model predicted 108 CRC cases and 45 CRC deaths per 1000 50-year-olds (**Figure 6.1**). The number of CRC cases and deaths ranged from 37 to 59 and from 8 to 15, respectively, for the different screening strategies. The strategy that prevented most CRC deaths was colonoscopy screening every 10 years, while screening with the PillCam every 10 years prevented the fewest.

In the absence of screening, the model predicted life-time CRC-related costs of $7.286 million per 1000 50-year-olds (**Table 6.3**). None of the alternative screening strategies were cost-saving compared with no screening. Of the alternative strategies, CTC screening every 5 years had the lowest costs ($7.479 million), whereas annual mtSDNA screening was the most expensive ($10.798 million). The number of QALYG compared to no screening ranged from 165 for PillCam screening every 10 years to 205 for annual mtSDNA screening; the number of total colonoscopies required ranged from 1,824 per 1000 50-year-olds for CTC every 5 years to 3,827 for annual mSEPT9 screening (**Table 6.3**).

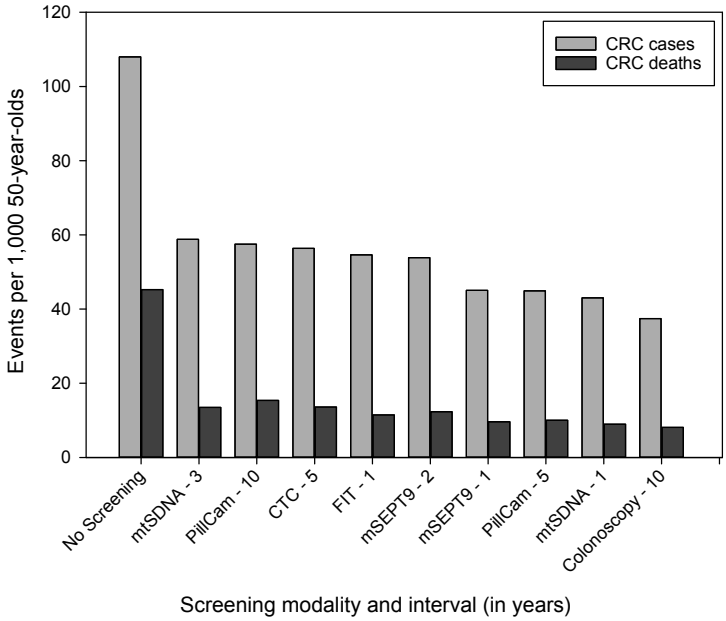


Figure 6.1: Colorectal cancer cases and deaths with the different screening strategies. CRC - colorectal cancer; m*SEPT9* - methylated *SEPT9* DNA plasma assay; PillCam - PillCam COLON 2; mtSDNA - multitarget stool DNA; CTC - computed tomographic colonography; FIT - fecal immunochemical test

Cost-effectiveness analysis

For individuals who are not willing to undergo FIT or colonoscopy screening (i.e. those for whom FIT and colonoscopy are not considered acceptable alternatives), CTC every 5 years and annual mSEPT9 were efficient strategies, with ICERs of $1,092 and $63,253 per QALYG, respectively (**Figure 6.2, Table 6.3**). Annual screening with the mSEPT9 resulted in a high number of individuals referred to colonoscopy: 51% after 3 years and 69% after 5 years. PillCam strategies were dominated by other strategies, while annual mtSDNA screening had an ICER of $214,974 per QALYG which is above the willingness-to-pay threshold.

When considering all screening strategies including FIT and colonoscopy, colonoscopy every 10 years resulted in an ICER of $48,155 per QALYG compared to annual FIT screening and was therefore the cost-effective strategy in this analysis (**Table 6.3, Figure 6.2**). Annual FIT screening was cost saving compared to no screening. All alternative strategies were dominated by FIT and colonoscopy screening. The number of QALYG, CRC cases prevented and CRC deaths prevented for annual m*SEPT9* were higher than for annual FIT screening (**Figure 6.1, Table 6.3**). However, the test burden in terms of number of diagnostic colonoscopies was 63% higher, and the total costs were 26% higher compared to annual screening with FIT (**Table 6.3**).

Table 6.3: Outcomes per 1000 50-year-olds for different screening strategies.

		Undiscounted			
Screening test	**Interval (years)**	**No. of screening tests**	**No. of diagnostic colonoscopies[a]**	**No. of surveillance colonoscopies**	**Total no. of colonoscopies**
No screening	-	0	108	0	108
FIT	1	15,044	791	1,558	2,349
CTC	5	4,292	628	1,196	1,824
Colonoscopy	10	1,995	15	2,725	4,735
m*SEPT9*	2	5,802	1,269	1,932	3,201
m*SEPT9*	1	7,159	1,548	2,279	3,827
mtSDNA	3	5,583	785	1,494	2,279
PillCam	10	2,383	671	1,502	2,173
PillCam	5	3,710	899	1,837	2,736
mtSDNA	1	10,185	1,233	2,101	3,334

		3% Discounted				
Screening test	**Interval (years)**	**LYG**	**QALYG**	**Total costs (Million $)**	**ICER ($ per QALYG)**	**ICER ($ per QALYG) without FIT and colonoscopy**
No screening	-	0	0	7.286	-	-
FIT	1	162	189	6.793	Cost Saving	-
CTC	5	151	177	7.479	D	1,092
Colonoscopy	10	174	209	7.751	48,155	-
m*SEPT9*	2	151	175	8.298	D	D
m*SEPT9*	1	165	194	8.574	D	63,253
mtSDNA	3	151	175	8.887	D	D
PillCam	10	141	165	8.951	D	D
PillCam	5	166	196	9.940	D	D
mtSDNA	1	173	205	10.798	D	214,974

ICER - incremental cost-effectiveness ratio; m*SEPT9* - methylated *SEPT9* DNA plasma assay; CTC - computed tomographic colonography; mtSDNA - multitarget stool DNA; PillCam - PillCam COLON 2; D - dominated

[a] Includes both diagnostic follow-up colonoscopies and colonoscopies for clinical detection of colorectal cancer. LYG = life-years gained, QALYG = quality-adjusted life-years gained,

Scenario analyses

In all our scenario analyses, the same three strategies were efficient for individuals not willing to undergo FIT or colonoscopy screening - CTC screening every 5 years, annual m*SEPT9* and annual mtSDNA. Our results were robust for alternative assumptions regarding start age of screening, screening adherence and systematically missing adenomas or cancers, which resulted in ICERs for annual m*SEPT9* of $66,372, $41,041 and $68,682 per QALYG compared with the next-best alternative, respectively (**Table 6.4** and **Supplementary Table A6.9**). However, when we simulated a lower CRC incidence, annual m*SEPT9* resulted in an ICER of $119,336 per QALYG. Hence, CTC

screening every 5 years was the cost-effective strategy for these individuals with an ICER of $9,397 per QALYG (**Supplementary Table A6.9**). Although efficient, annual mtSDNA screening was never cost-effective using a willingness-to-pay threshold of $100,000 per QALYG. When FIT and colonoscopy were also considered, colonoscopy screening every 10 years was the cost-effective strategy in all our scenario analyses (**Supplementary Table A6.9**).

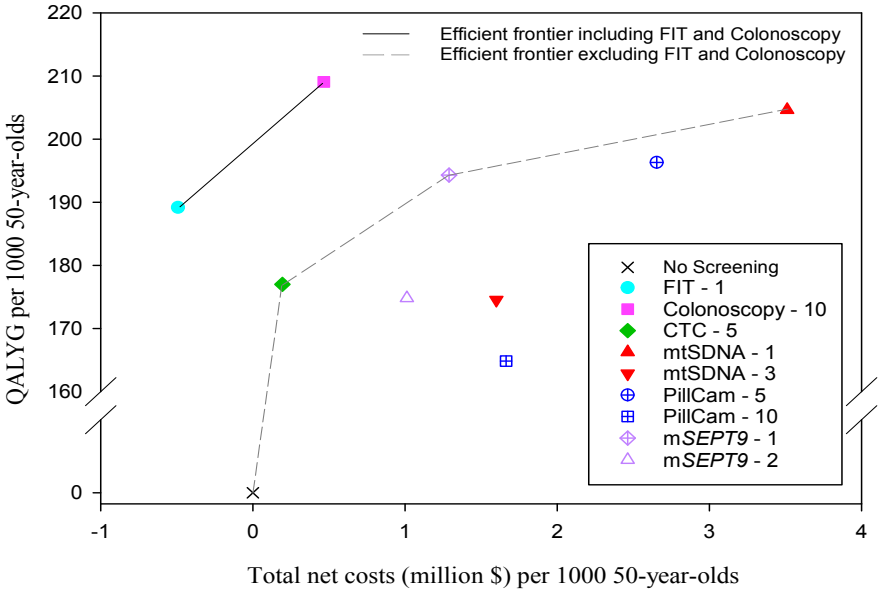


Figure 6.2: Efficient Frontier. Lifetime costs and quality-adjusted life-years of the evaluated screening strategies.
QALYG - quality-adjusted life-years gained; FIT - fecal immunochemical test; mSEPT9 - methylated SEPT9 DNA plasma assay; CTC - computed tomographic colonography; mtSDNA - multitarget stool DNA; PillCam - PillCam COLON 2.

Probabilistic sensitivity analyses

For individuals who are not willing to undergo FIT or colonoscopy screening, annual screening with m*SEPT9* was the cost-effective strategy in 54% of the 1,000 simulations evaluated in the probabilistic sensitivity analyses at a willingness-to-pay threshold of $100,000 per QALYG (**Figure 6.3**). In 20% and 17% of the simulations, annual mtSDNA screening and CTC screening every 5 years were cost-effective strategies, respectively. At higher willingness-to-pay thresholds, the probability that annual mtSDNA screening was the cost-effective strategy increased, while the probability that CTC screening every 5 years was cost-effective decreased. At a willingness-to-pay threshold of $200,000 per QALYG, the probabilities were 48%, 47% and 1% for mtSDNA, m*SEPT9* and CTC, respectively (**Figure 6.3**).

Table 6.4: Most effective strategy with an ICER below $100,000 per quality-adjusted life-year gained, by scenario analysis and inclusion of FIT and colonoscopy.

Analysis	Most effective strategy excluding FIT and colonoscopy	Most effective strategy including FIT and colonoscopy
Base case	Annual m*SEPT9*	Colonoscopy every 10 years
Screening from age 45	Annual m*SEPT9*	Colonoscopy every 10 years
USPSTF model; lower CRC incidence	CTC every 5 years[a]	Colonoscopy every 10 years
Adjusted adherence	Annual m*SEPT9*	Colonoscopy every 10 years
Systematic false-negativity m*SEPT9*	Annual m*SEPT9*	Colonoscopy every 10 years

ICER - incremental cost-effectiveness ratio; FIT - fecal immunochemical test; USPSTF - United States Preventative Services Task Force; m*SEPT9* - methylated *SEPT9* DNA plasma assay; CRC - colorectal cancer; CTC - computed tomographic colonography; QALYG - quality-adjusted life-years gained

[a] In this scenario, the ICER for annual m*SEPT9* was $119,336 per QALYG, just above the willingness-to-pay threshold.

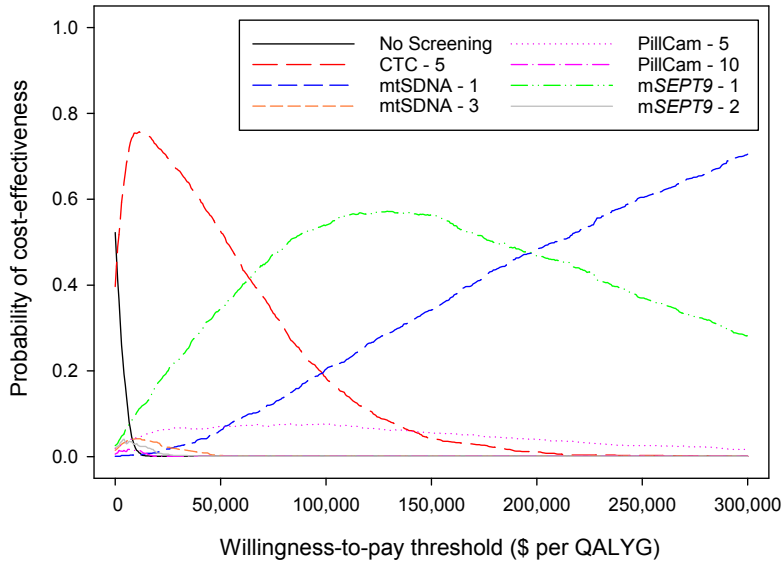


Figure 6.3: Cost-Effectiveness Acceptability Curve and Frontier.
m*SEPT9* - methylated SEPT9 DNA plasma assay; PillCam - PillCam COLON 2; mtSDNA - multitarget stool DNA; CTC - computed tomographic colonography; QALYG - quality-adjusted life-years gained;-
* The cost-effectiveness acceptability frontier (CEAF) plots the probability that the optimal screening strategy is cost-effective over a range of cost-effectiveness thresholds.

Discussion

New strategies are needed to increase CRC screening participation in the US, given rates reached a plateau of approximately 60%.[231] By comparing the incremental cost-effectiveness of CTC, PillCam, mtSDNA and m*SEPT9* from a societal perspective, this study revealed that of these alternatives annual screening with m*SEPT9* is cost-effective. Annual screening with the m*SEPT9* had an ICER of $63,253 per QALYG. Other efficient strategies were CTC screening every 5 years (ICER: $1,092 per QALYG) and annual mtSDNA screening (ICER: $214,974 per QALYG), which were not optimal given the willingness-to-pay threshold ($100,000 per QALYG).

The uncertainty of our conclusion is reflected in our probabilistic sensitivity analyses, in which the m*SEPT9* was the cost-effective strategy in 54% of our analyses. Test accuracy of the m*SEPT9* is not as well established as for some of the other test evaluated in this study. In line with requirements of the FDA, a prospective trail including 4,500 participants is currently being performed which will provide essential additional information about test characteristics of the m*SEPT9*, and adherence to multiple rounds of testing and follow-up.[236]

Among the tests evaluated in this analysis, the m*SEPT9* has the lowest sensitivity for both adenomas and CRC. Therefore, an important driver of its cost-effectiveness compared to CTC, PillCam and mtSDNA is the substantially lower cost of the test. Similar as for FIT screening, the effectiveness of the m*SEPT9* depends on annual repetition of the test, and similar to any other non-colonoscopy-based screening strategy, receipt of diagnostic follow-up colonoscopy. Due to the relatively low specificity of the m*SEPT9* (79%) compared with the other tests, a high number of individuals are referred to a diagnostic follow-up colonoscopy regardless of disease status (51% after 3 years and 69% after 5 years with annual repetition of the test). Consequently, 21% of simulated individuals with a non-advanced adenoma received a colonoscopy when screened with m*SEPT9*, in contrast to 7.6% when screened with FIT. Although non-advanced adenomas generally confer low risk, they are more common than advanced adenomas and some may have aggressive biology. The detection of non-advanced adenomas in these colonoscopies contributed to the slightly higher QALYG, CRC cases averted and CRC deaths averted for m*SEPT9* screening *vs*. FIT screening despite its lower test sensitivity for advanced adenomas and cancers.

To our knowledge, this is the first study that simultaneously evaluated the PillCam, CTC, m*SEPT9* and mtSDNA in a single cost-effectiveness analysis. In addition, it is the first cost-effectiveness analysis of these tests that uses updated test characteristics, CRC treatment costs and CRC incidence. As expected, updated test characteristics, costs, and incidence levels have a substantial impact on cost-effectiveness outcomes. One cost-effectiveness analysis reported that m*SEPT9* is less effective and more costly than FIT screening,[221] with costs of $8,400 to $11,500 per QALYG compared to no screening. This study based the test characteristics of the m*SEPT9* on the study by Church et al.,[225] which used an earlier version of the test. Changes that were made to the m*SEPT9* as

part of the development process for its premarket approval by the FDA resulted in the version used for the Potter et al. study, [223] which has an increased sensitivity but a decreased specificity compared with the version used by Church et al.[237] Our analyses suggest that with the current version of the m*SEPT9*, annual m*SEPT9* screening is not less effective than annual FIT screening, but is still more costly and requires considerably more colonoscopies. One previous study found a cost-effectiveness ratio of $29,244 per QALYG of 10-yearly PillCam screening *vs*. no screening,[222] compared to approximately $10,000 in our study with updated assumptions. Previous analyses that evaluated the cost-effectiveness of mtSDNA described that the mtSDNA is too expensive to be cost-effective compared to FIT and colonoscopy screening.[172,217,218] This study suggests that even when FIT and colonoscopy screening are not considered, the costs of mtSDNA screening are still too high compared to other alternative tests. Finally, our group's previous analyses on CTC suggested that CTC is not an efficient strategy when compared to FIT and colonoscopy.[219,220] This study suggest that for individuals that are not willing to do FIT and colonoscopy, CTC is an efficient strategy. However, annual screening with the m*SEPT9* had an ICER of $63,253 per QALYG compared to 5-yearly CTC, and is therefore preferred from a cost-effectiveness perspective.

Several limitations of our study are noteworthy. First, we assumed that no adenomas and cancers were systematically missed over time by a particular screening test. This assumption may not hold for the stool-based tests, because bleeding of a lesion is not necessarily a random event.[238] Furthermore, it may not hold for the m*SEPT9* because approximately 18% of the tumors do not have methylation of the *SEPT9* gene promoter [232] and will remain undetected at every subsequent m*SEPT9* screening until their *SEPT9* gene promoter is methylated. The systematic miss rates for the different screening tests are unknown. We performed a scenario analysis in which we assumed that 12% of advanced adenomas and 18% of CRCs are systematically missed by the m*SEPT9*, which minimally impacted our results. This is in line with a previous study, which suggested that incorporating systematically missing adenomas with stool-based test has minimal impact on effectiveness of FIT screening.[238]

Second, we assumed perfect adherence to screening, diagnostic follow-up and surveillance in our base case analysis. This implies that the model predicted the maximum achievable benefit for all screening tests. Unfortunately, there is limited data on test-specific adherence to every step in the screening process (getting screening, diagnostic follow-up, treatment and/or surveillance) over multiple rounds of screening (e.g. from ages 50 to 75 years), making it impossible to inform our analyses with empirical evidence. We performed a scenario analysis that accounted for suboptimal adherence to follow-up and surveillance colonoscopies and for decreasing adherence over multiple screening rounds. Although the effectiveness of all screening modalities decreased with a lower adherence, the impact on ICERs was limited.

Third, the current lifetime risk of developing CRC in the absence of screening is uncertain. Our assumed CRC incidence is in line with previous analyses for the ACS and the observation that the increased CRC incidence in young adults is a cohort

effect.[16,99] We explored the effect of a lower CRC incidence in a scenario analysis, which suggested that when CRC incidence resembles 1975-1979 data, CTC screening every 5 years is the cost-effective strategy as the ICER of annual screening with the m*SEPT9* is approximately $120,000, just above the willingness-to-pay threshold.

Our study can be used to inform clinicians, as it ranks the different CRC screening tests from a cost-effectiveness perspective. Individuals who are not willing to be screened with FIT or colonoscopy should be advised to undergo m*SEPT9* screening if the high colonoscopy referral rate is acceptable to them. CTC should be the next test of choice. Ultimately, the best test is the "one that gets done". Although lack of participation may have various reasons, such as lack of resources in rural areas or more general reluctance against screening, previous studies suggest that the m*SEPT9* has the potential to attract the population that currently does not participate in screening.[239,240] A recent study found substantially higher uptake of a blood-based test compared to a FIT in individuals who were overdue for screening,[239] and another study found that among people who declined stool-based tests, there was a 25% uptake of a blood-based test.[240] This suggests that the m*SEPT9* might be a suitable test to increase current CRC screening participation.

In conclusion, a well-established microsimulation model demonstrates that for people who are unwilling to be screened with FIT or colonoscopy, annual screening with the m*SEPT9* is the test of choice given its cost-effectiveness profile compared to CTC, PillCam and mtSDNA. The number of CRC cases and deaths averted, and the number QALYG from annual m*SEPT9* screening are even higher than from annual FIT screening. However, the number of colonoscopies required for the m*SEPT9* is 63% higher, and the total costs are 26% higher compared to annual FIT screening. Therefore, physicians should first offer individuals to participate in CRC screening using FIT or colonoscopy.

Appendix

Supplementary Table A6.1: Study designs, sample sizes, periods and regions of the studies that were used to inform the test characteristics of the evaluated colorectal cancer screening tests.

Screening test	Source	Design	Sample size	Period	Region
Colonoscopy	van Rijn et al. 2006 [213]	Systematic review	465	1991-2004	Multiple
CTC	Johnson et al. 2008 [227]	Prospective trial	2600	2005-2006	US
PillCam	Rex et al. 2015 [226]	Prospective trial	695	2011-2012	US & Israel
FIT	Imperiale et al. 2014 [72]	Prospective trial	9989	2011-2012	US & Canada
mtSDNA	Imperiale et al. 2014 [72]	Prospective trial	9989	2011-2012	US & Canada
m*SEPT9*	Potter et al. 2014 [223]	Retrospective trial[a]	1544	2008-2010	US & Germany

CTC - computed tomographic colonography; PillCam - PillCam COLON 2; FIT - fecal immunochemical test, mtSDNA - multitarget stool DNA; m*SEPT9* - methylated *SEPT9* DNA plasma assay

[a] Subjects for this study were selected retrospectively from the Prospective Evaluation of Septin 9 Performance in CRC Screening (PRESEPT) trial.[225]

Supplementary Table A6.2: Time spent on colonoscopy, CTC and PillCam, based on Jonas et al. [167]

Procedure component	Patient time Hours			Escort time Hours [b]	Total time Hours	Assumptions
	COL	CTC	PillCam [a]	COL	COL	
Bowel preparation	16.7	16.7	16.7	0	16.7	Same for all procedures
Travel to	0.42	0.42	0.42	0.42	0.83	Same for all procedures
Waiting/ preparing	1.4	1.4	1.4	1.4	2.8	Same for all procedures
Sedation	0.2	0	0	0.2	0.4	Sedation is only used for COL
Procedure	0.33	0.25	6	0.33	0.67	CTC: 15 minutes, according to this: https://radiology.uchicago.edu/page/virtual-colonoscopy-patients PillCam: 76% of the patients excreted the capsule within 6 hours [226]
Onsite recovery	0.78	0	0	0.78	1.57	CTC & PillCam: no on-site recovery
Travel home	0.58	0.58	0.58	0.58	1.17	Same for all procedures
Recovery to routine	15.8	0	0	0	15.8	CTC & PillCam: immediately back to routine
Sleep	-16	-8	-8	0	-16	
Total	20.22	**11.35**	**17.1**	3.72	**23.93**	

COL – colonoscopy; CTC - computed tomographic colonography; PillCam - PillCam COLON 2

[a] We assume that the methylated *SEPT9* DNA plasma assay and the stool-based tests take 1 hour.

[b] We assume that no escort was needed for screening with the CTC and the PillCam as these procedures do not require sedation.

Supplementary Table A6.3: Societal costs of screening, follow-up, and surveillance procedures (2017 $).

HCPCS Code	Use in model	Avg. Medicare-allowed procedure/ test payment	Avg. Medicare-allowed pathology payment	Avg. Medicare-allowed anesthesia services payment[a]	Total payment	Bowel preparation kit[b]	Time costs[c]	Total cost (societal, 2017 $)[d]	Source
G0121	Screening COL w/o lesion removal	$705.89	NA	$88.55	$794.44	$51.09	$433.67	**$1,279.20**	2014 allowed payments, inflated to 2017 dollars.[e]
45378	Follow-up COL w/o lesion removal	$750.25	NA	$96.76	$847.02	$51.09	$433.67	**$1,331.78**	2014 allowed payments, inflated to 2017 dollars.[e]
G0105	Surveillance COL w/o lesion removal	$701.76	NA	$94.22	$795.98	$51.09	$433.67	**$1,280.74**	2014 allowed payments, inflated to 2017 dollars.[e]
45380-45381, 45383-45385	Any COL w/ lesion removal	$936.55	$132.25	$102.82	$1,171.62	$51.09	$433.67	**$1,656.38**	2014 allowed payments, inflated to 2017 dollars.[e]
74261	CTC[f]	$236.15	NA	NA	$236.15	$51.09	$205.66	**$492.90**	2017 Physician Fee Schedule
91110	PillCam[g]	$938.50	NA	NA	$938.50	$104.09[h]	$309.85	**$1,352.44**	2017 Physician Fee Schedule
G0328 or 82274	FIT	$21.82	NA	NA	$21.82	NA	$18.12	**$39.94**	2017 CLFS
81528	mtSDNA	$512.43	NA	NA	$512.43	NA	$18.12	**$530.55**	2017 CLFS
81327	m*SEPT9*	$192	NA	NA	$192	NA	$18.12	**$210.12**	2019 CLFS[i]

COL – colonoscopy; CTC - computed tomographic colonography; PillCam - PillCam COLON 2; FIT - fecal immunochemical test; mtSDNA - multitarget stool DNA; m*SEPT9* - methylated *SEPT9* DNA plasma assay; CLFS - clinical laboratory fee schedule

[a] Includes propofol and facility payments, when appropriate.

[b] Costs for bowel preparation agents for colonoscopy, CTC and PillCam were based on the section "Colon Cleansing Medications" on GoodRX.com.
[c] We assume that the value of an hour of patient/escort time is equal to the median wage rate in the US in 2017. The 2017 median hourly wage rate ($18.12) comes from the U.S. Bureau of Labor Statistics (BLS) May 2017 National Occupational Employment and Wage Estimates.
[d] All costs are expressed in 2017 US dollars. Costs from other years are inflated to 2017 dollars using the Personal Health Care Deflator price index (https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/Tables.zip).
[e] Colonoscopy costs were based on an analysis of 2014 Medicare claims data from the Chronic Conditions Data Warehouse performed by the Centers for Medicare and Medicaid Services (CMS).[15] There is no national average payment for CTC because it is not a covered procedure. We based our estimate on the payment for a diagnostic CTC w/o IV contrast.
[f] As there is no estimate of the PillCam COLON 2 (0355T), we used the price of the PillCam™ SB 3 system (91110) that is used for visualization of the small bowel.
[g] As explained in the study by Rex et al. [226], the PillCam requires an additional 6 oz of an oral sulfate solution (e.g., SUPREP) to boost the PillCam through the small intestine and to add fluid to the colon, which is why additional costs for SUPREP were included in the estimate for PillCam. The price for 2 bottles SUPREP on GoodRX.com is $106 dollars. Therefore, we assumed an additional $53 dollars for the bowel preparation of PillCam.
[h] The 2019 Clinical Laboratory Fee Schedule was used for the m*SEPT9* as previous years are not representative of current reimbursement rates (reimbursement went from $84 in 2017 to $192 in 2019, https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched).

Supplementary Table A6.4: Assumptions for utility losses associated with the screening tests.

Utility loss of the test itself				
Screening modality	*Disutility*	*Source*	*Time the disutility applies in hours*[a]	*Utility loss per event*
Colonoscopy	0.12	Swan et al. [168]	36.22	0.000496
CTC	0.12	Same as colonoscopy	19.35	0.000265
PillCam	0.12	Same as colonoscopy	25.1	0.000344
FIT	0	Expert opinion	1	0
mtSDNA	0	Expert opinion	1	0
m*SEPT9*	0	Expert opinion	1	0
Utility loss of waiting for the test result				
Screening modality	*Disutility*	*Source*	*Time the disutility applies in days*[b]	*Utility loss per event*
Colonoscopy without polypectomy	0	Immediate results	0	0
Colonoscopy with polypectomy	0.033036	Expert opinion, same as waiting for a diagnostic follow-up after a positive FIT	10	0.000905
CTC	0.003304	Expert opinion, 10% of waiting for a diagnostic follow-up after a positive FIT	3	0.000027
PillCam			9	0.000081
FIT			7	0.000063
mtSDNA			14	0.000127
m*SEPT9*			7	0.000063
Utility loss of waiting for a diagnostic follow-up colonoscopy				
Screening modality	*Disutility*	*Source*	*Time the disutility applies in days*[b]	*Utility loss per event*
CTC PillCam FIT mtSDNA m*SEPT9*	0.033036	12.5% are very worried [169]. Assuming they experience half of the utility decrement as for a positive mammography as reported by Mandelblatt [170]	14	0.001267
Total utility loss				
Screening modality	*Disutility when positive*		*Disutility when negative*	
Colonoscopy	0.001401		0.000496	
CTC	0.001559		0.000292	
PillCam	0.001692		0.000425	
FIT	0.001330		0.000063	
mtSDNA	0.001394		0.000127	
m*SEPT9*	0.001330		0.000063	

CTC - computed tomographic colonography; PillCam - PillCam COLON 2; FIT - fecal immunochemical test; mtSDNA - multitarget stool DNA; m*SEPT9* - methylated *SEPT9* DNA plasma assay

[a] See Supplementary Table A6.2 on how these were derived, without subtracting time for sleeping.

[b] These time estimates are based on expert opinion.

Supplementary Table A6.5: Assumptions for colorectal cancer care.

Phase of cancer care[a]	**Time costs**			
	Hours	*Annual costs (2017 $)*		*Source*
Initial phase	243.5	$4,412		Yabroff et al. [241]
Continuing phase	19.56	$354		Yabroff et al. [242]
Terminal phase, death CRC	282.8	$5,124		Yabroff et al. [241]
Terminal phase, death other causes	282.8	$5,124		Yabroff et al. [241]
Phase of cancer care[a]	**Annual societal costs (2017 $)**[b]			
	Stage I	*Stage II*	*Stage III*	*Stage IV*
Initial phase	$42,763	$58,796	$83,427	$121,828
Continuing phase	$4,301	$4,944	$7,456	$34,017
Terminal phase, death CRC	$82,519	$92,366	$96,461	$119,979
Terminal phase, death other causes	$25,450	$26,997	$35,026	$77,051
Phase of cancer care[a]	**Utility losses**[c]			
	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

[a] The terminal phase takes precedence over the initial and continuing phase. The terminal phase reflects the last 12 months of life. The initial phase reflects the 12 months following diagnosis for persons who survival for more than 12 months (if survive for ≤12 months, person only experiences the terminal phase). The continuing phase is the time between the initial phase and the terminal phase for persons who survive for more than 24 months.

[b] Source: Patient time costs + 2007-2013 SEER-Medicare linked data (update prior analysis [161], personal communication, Angela Mariotto, PhD)

[c] Source: Adapted from Ness et al.[171]

Supplementary Table A6.6: Assumptions for complications.

Complications	**Rate per colonoscopy**
Positive colonoscopy (with adenoma polypectomy)	
Serious gastrointestinal event[a]	1/[exp(9.27953 – 0.06105 × Age) + 1] – 1/[exp(10.78719 – 0.06105 × Age) + 1]
Other gastrointestinal event[b]	1/[exp(8.81404 – 0.05903 × Age) + 1] – 1/[exp(9.61197 – 0.05903 × Age) + 1]
Cardiovascular event[c]	1/[exp(9.09053 – 0.07056 × Age) + 1] – 1/[exp(9.38297 – 0.07056 × Age) +1]
Negative colonoscopy (without adenoma polypectomy)	
	0

Complications	**Time spent with complications from colonoscopy**			
	Days	*Days homecare*	*Total hours of awake time*	*Source*
Serious gastointestinal event[a]	8	7	240	Expert opinion
Other gastrointestinal event[b]	4	2	96	Expert opinion
Cardiovascular event[c]	5	7	192	Expert opinion

Complications	**Costs**[d]				
	Cost ($), CMS perspective	*Patient cost-sharing ($)*	*Time costs ($)*	*Total cost ($), societal perspective*	*Source*
Serious gastointestinal event[a]	6,847	1,238	4,349	12,434	2013 CMS costs
Other gastrointestinal event[b]	4,878	1,238	1,740	7,855	2013 CMS costs
Cardiovascular event[c]	5,347	1,238	3,479	10,063	2013 CMS costs

Complications	**Utility losses**	
	Utility loss	*Rationale [expert opinion]*
Serious gastointestinal event[a]	0.0055	4 days at 0.5 utility
Other gastrointestinal event[b]	0.0027	2 days at 0.5 utility
Cardiovascular event[c]	0.0048	3.5 days at 0.5 utility

CMS - Centers for Medicare and Medicaid Services

[a] Serious gastrointestinal events are fatal complications, perforations, gastrointestinal bleeding or transfusions.

[b] Other gastrointestinal events are paralytic ileus, nausea and vomiting, dehydration, abdominal pain.

[c] Cardiovascular events are myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock.

[d] All costs are expressed in 2017 US dollars. Costs from other years are inflated to 2017 dollars using the Personal Health Care Deflator price index (https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/Tables.zip).

Supplementary Table A6.7. Test characteristics varied in the probabilistic sensitivity analysis.

Test characteristic[ab]	Mean	Source	95% CI[c]	Source
Colonoscopy				
Sensitivity for adenomas ≤5 mm, %	75	van Rijn et al. 2006 [213]	[70, 79]	Zauber et al. 2008 [97]
Sensitivity for adenomas 6-9 mm, %	85	van Rijn et al. 2006 [213]	[80, 92]	Zauber et al. 2008 [97]
Sensitivity for adenomas ≥10 mm, %	95	van Rijn et al. 2006 [213]	[93.1, 99.5]	Johnson et al. 2008 [227]
Sensitivity for colorectal cancer, %[d]	95	by assumption	[93.1, 99.5]	by assumption
Specificity, %	100	*Not varied*		
CTC				
Sensitivity for adenomas ≤5 mm, %	0[f]	*Not varied*		
Sensitivity for adenomas 6-9 mm, %	57	Johnson et al. 2008 [227]	[48.9, 71.6]	Johnson et al. 2008 [227]
Sensitivity for adenomas ≥10 mm, %	84	Johnson et al. 2008 [227]	[75.6, 92.4]	Johnson et al. 2008 [227]
Sensitivity for colorectal cancer, %[d]	84	Johnson et al. 2008 [227]	[75.6, 92.4]	Johnson et al. 2008 [227]
Specificity, %	88	Johnson et al. 2008 [227]	[84, 92]	Johnson et al. 2008 [227]
PillCam				
Sensitivity for adenomas ≤5 mm, %	0[f]	*Not varied*		
Sensitivity for adenomas 6-9 mm, %	86.5	Rex et al. 2015 [226]	[78.4, 92.1]	Rex et al. 2015 [226]
Sensitivity for adenomas ≥10 mm, %	87.5	Rex et al. 2015 [226]	[75.4, 96.0]	Rex et al. 2015 [226]
Sensitivity for colorectal cancer, %[d]	87.5	Rex et al. 2015 [226]	[75.4, 96.0]	Rex et al. 2015 [226]
Specificity, %	83	Rex et al. 2015 [226]	[80, 86]	Rex et al. 2015 [226]
FIT				
Sensitivity for adenomas ≤5 mm, %	0[f]	*Not varied*		
Sensitivity for adenomas 6-9 mm, %	11.4	Imperiale et al. 2014 [72]	[8.2, 15.2]	Imperiale et al. 2014 [72]
Sensitivity for adenomas ≥10 mm, %	15.9	Imperiale et al. 2014 [72]	[13.7, 18.3]	Imperiale et al. 2014 [72]
Sensitivity for colorectal cancer, % Long/short before clinical diagnosis[e]	62.6/ 88.6	Imperiale et al. 2014 [72]	[48, 75.3]/ [81, 93.4]	Imperiale et al. 2014 [72]
Specificity, %	96.4	Imperiale et al. 2014 [72]	[95.8, 96.9]	Imperiale et al. 2014 [72]
mtSDNA				
Sensitivity for adenomas ≤5 mm, %	0[f]	*Not varied*		
Sensitivity for adenomas 6-9 mm, %	22	Imperiale et al. 2014 [72]	[17, 27.9]	Imperiale et al. 2014 [72]

table continues

Test characteristic[ab]	Mean	Source	95% CI[c]	Source
Sensitivity for adenomas ≥10 mm, %	28.4	Imperiale et al. 2014 [72]	[25.2, 31.6]	Imperiale et al. 2014 [72]
Sensitivity for colorectal cancer, % Long/short before clinical diagnosis[e]	86.4 96.7	Imperiale et al. 2014 [72]	[73.5, 94.7]/ [92.8, 98.8]	Imperiale et al. 2014 [72]
Specificity, %	89.8	Imperiale et al. 2014 [72]	[88.9, 90.7]	Imperiale et al. 2014 [72]
mSEPT9				
Sensitivity for adenomas ≤5 mm, %	0[f]	*Not varied*		
Sensitivity for adenomas 6-9 mm, %	0[f]	*Not varied*		
Sensitivity for adenomas ≥10 mm, %	0.28	Potter et al. 2014 [223]	[0, 3]	Potter et al. 2014 [223]
Sensitivity for colorectal cancer, %	59.4	Potter et al. 2014 [223]	[40, 74.3]	Potter et al. 2014 [223]
Specificity, %	78.8	Potter et al. 2014 [223]	[77, 81]	Potter et al. 2014 [223]

CI - confidence interval; CTC - computed tomographic colonography; PillCam - PillCam COLON 2; FIT = fecal immunochemical test; mtSDNA= multitarget stool DNA; m*SEPT9* = methylated *SEPT9* DNA plasma assay

[a] All test sensitivities in this table are per lesion. For the PillCam, FIT, mtSDNA, and m*SEPT9* the per lesion sensitivities that are used as inputs for MISCAN-Colon were calibrated to per person estimates derived from literature.

[b] For all test, we assumed that test sensitivities for smaller lesions could not exceed test sensitivities for bigger lesions. To do this, we used the preference order algorithm developed by Goldhaber-Fiebert and Jalal. [243], with epsilon = 0.05, delta = 0.01.

[c] We assumed beta distributions for the test characteristics and derived their parameters using method of moments.

Standard deviations were generated from 95% confindence intervals using $s = \frac{UB-LB}{2\phi^{-1}(0.975)}$

With s= standard deviation, UB=upperbound, LB= lowerbound, $\phi^{-1}(0.976) \approx 1.96$.

The means and standard deviations were used to generate shape parameters for the beta distributions using $\alpha = m\left(\frac{m(1-m)}{s^2} - 1\right)$ and $\beta = (1-m)\left(\frac{m(1-m)}{s^2} - 1\right)$.

[d] We assumed the same sensitivity for colorectal cancer and for advanced adenomas. Therefore, the same value that was drawn from the distibution was used for for both.

[e] For stool-based tests, we used different sensitivities for colorectal cancers that are either long or short before clinical diagnosis based on Lansdorp-Vogelaar et al. [184] .

[f] The probability that these lesions are detected equals the false-positivity rate, which is 1 – specificity.

Supplementary Table A6.8: Costs and disutilities varied in the probabilistic sensitivity analysis.

Test costs and disutilities						
Test	*Mean costs ($)*	*95% CI costs ($)*[b]	*Mean disutility when positive*	*95% CI disutiliy when positive*[b]	*Mean disutility when negative*	*95% CI disutiliy when negative*[b]
Colonoscopy						
Screening[a]	1,279	[640, 2,558]	-	-	0.0005[c]	[0.00025, 0.00099][c]
Diagnostic[a]	1,332	[666, 2,664]	-	-	0.0005[c]	[0.00025, 0.00099][c]
Surveillance[a]	1,281	[640, 2,561]	-	-	0.0005[c]	[0.00025, 0.00099][c]
With polypectomy	1,656	[828, 3,313]	0.001401	[0.0007, 0.0028]	-	-
CTC	493	[246, 986]	0.00156	[0.00078, 0.00321]	0.00029	[0.00015, 0.00058]
PillCam	1,352	[676, 2,705]	0.00169	[0.00085, 0.00338]	0.00043	[0.00021, 0.00085]
FIT	40	[20, 80]	0.00133	[0.00067, 0.00266]	0.00006	[0.0003, 0.000013]
mtSDNA	531	[265, 1,061]	0.00139	[0.0007, 0.00279]	0.00013	[0.00006, 0.00025]

Treatment costs ($)					
Phase of cancer care[d]	*Value*	*Stage I*	*Stage II*	*Stage III*	*Stage IV*
Initial phase	Mean	42,763	58,796	83,427	121,828
	CI[e]	[21,381, 85,526]	[29,398, 117,592]	[41,716, 166,854]	[60,914, 243,656]
Continuing phase	Mean	4,301	4,944	7,456	34,017
	CI[e]	[2,151, 8,602]	[2,472, 9;888]	[3,728, 14,912]	[17,006, 68,034]
Terminal phase, death CRC	Mean	82,519	92,366	96,461	119,979
	CI[e]	[41,260, 165,038]	[46,183, 184,732]	[48,231, 192,922]	[59,990, 239,958]
Terminal phase, death other causes	Mean	25,450	26,997	35,026	77,051
	CI[e]	[12,725, 50,900]	[13,499, 53,994]	[17,513, 70,052]	[38,526, 154,102]

Treatment disutilities					
Phase of cancer care[d,f,g]	*Value*	*Stage I*	*Stage II*	*Stage III*	*Stage IV*
Initial phase	Mean	0.12	0.18	0.24	0.70
	CI[h]	[0.0605, 0.1795]	[0.1205, 0.2395]	[0.1805, 0.2995]	[0.6405, 0.7595]
Continuing phase	Mean	0.05[i]	0.05[i]	0.24	0.70
	CI[h]	[0, 0.1095]	[0, 0.1095]	[0.1805, 0.2995]	[0.6405, 0.7595]
Terminal phase, death CRC	Mean	0.70[j]	0.70[j]	0.70[j]	0.70[e]
	CI[h]	[0.6405, 0.7595]	[0.6405, 0.7595]	[0.6405, 0.7595]	[0.6405, 0.7595]
Terminal phase, death other causes	Mean	0.05[k]	0.05[k]	0.24	0.70
	CI[h]	[0, 0.1095]	[0, 0.1095]	[0.1805, 0.2995]	[0.6405, 0.7595]

table continues

Complication costs and disutilities				
Complications	*Mean costs ($)*	*95% CI costs ($)*[b]	*Mean disutility*	*95% CI disutiliy*[b]
Serious gastrointestinal event	12,434	[6,271, 24,868]	0.0055	[0.00274, 0.010959]
Other gastrointestinal event	7,855	[3,928, 15,710]	0.0027	[0.001378, 0.005479]
Cardiovascular event	10,063	[5,032, 20,126]	0.0048	[0.00240, 0.009589]

CI - confidence interval; CRC - colorectal cancer; CTC - computed tomographic colonography; PillCam - PillCam COLON 2; FIT - fecal immunochemical test; mtSDNA - multitarget stool DNA; m*SEPT9* - methylated *SEPT9* DNA plasma assay

[a] These are costs for procedures without polypectomy.

[b] We used gamma distributions for all cost and disutility values. CIs were derived by halving and doubling the mean value. The CIs were used to derive the mean and standard deviation, μ and σ, respectively, that were used to obtain shape parameter k and scale parameter θ using method of moments by $k = \frac{\mu^2}{\sigma^2}$ and $\theta = \frac{\sigma^2}{\mu}$.

[c] We assumed disutility for any type of colonoscopy without polypectomy, so the same value that was drawn from the distibution was used for all three different types.

[d] The terminal phase takes precedence over the initial and continuing phase. The terminal phase reflects the last 12 months of life. The initial phase reflects the 12 months following diagnosis for persons who survival for more than 12 months (if survive for ≤ 12 months, person only experiences the terminal phase). The continuing phase is the time between the initial phase and the terminal phase for persons who survive for more than 24 months.

[e] We used gamma distributions for all treatment costs. CIs were derived by halving and doubling the mean value. The CIs were used to derive the mean and standard deviation, μ and σ, respectively, that were used to obtain shape parameter k and scale parameter θ using method of moments by $k = \frac{\mu^2}{\sigma^2}$ and $\theta = \frac{\sigma^2}{\mu}$.

[f] We used gamma distributions for all disutility values.

[g] For all, we assumed that disutilities for lower stages could not exceed disutilities for higher stages. To do this, we used the preference order algorithm developed by Goldhaber-Fiebert and Jalal. [243], with epsilon = 0.05, delta = 0.01.

[h] CIs were based on Ness et al. [171], using ±0.05/0.84 as bounds. The CIs were used to derive the mean and standard deviation, μ and σ, respectively, that were used to obtain shape parameter k and scale parameter θ using method of moments by $k = \frac{\mu^2}{\sigma^2}$ and $\theta = \frac{\sigma^2}{\mu}$.

[l] For the continuing phase of care, the value drawn from the distribution was used for both Stage I and Stage II CRC.

[j] For the terminal phase of care, the value drawn from the distrubtion was used for for all stages.

[k] For the terminal phase of care with death from other causes, the value drawn from the distrubtion was used for both Stage I and Stage II CRC.

Supplementary Table A6.9: Results of the scenario analysis. Outcomes are per 1000 50-year-olds, unless otherwise specified.

Scenario analysis 1, assuming screening from age 45 to age 75. Outcomes are per 1000 45-year-olds.

Screening test	*Interval (years)*	*No. of screening tests*	*No. of diagnostic colonoscopies*[a]	*No. of surveillance colonoscopies*	*Total no. of colonoscopies*
		Undiscounted			
No screening	-	0	110	0	110
FIT	1	18,278	898	1,735	2,633
CTC	5	5,144	705	1,261	1,966
Colonoscopy	10	2,497	13	2,992	5,002
mSEPT9	2	6,946	1,510	2,190	3,700
mSEPT9	1	8,467	1,824	2,534	4,358
mtSDNA	3	6,804	904	1,672	2,576
PillCam	10	3,026	790	1,649	2,439
PillCam	5	4,439	1,012	1,998	3,010
mtSDNA	1	12,307	1,432	2,326	3,758

Screening test	*Interval (years)*	*LYG*	*QALYG*	*Total costs (Million $)*	*ICER ($ per QALYG)*	*ICER ($ per QALYG) without FIT and Colonoscopy*
		3% Discounted				
No screening	-	0	0	6.630	-	-
FIT	1	153	179	6.404	Cost Saving	-
CTC	5	140	165	7.241	D	3,705
Colonoscopy	10	162	195	7.697	78,669	-
mSEPT9	2	143	167	8.049	D	D
mSEPT9	1	156	183	8.469	D	66,372
mtSDNA	3	142	166	8.754	D	D
PillCam	10	131	154	8.899	D	D
PillCam	5	154	183	10.085	D	D
mtSDNA	1	162	192	11.125	D	303,378

table continues

Scenario analysis 2, using the model version that was used to inform the 2016 USPSTF screening guidelines, which does not account for the increasing incidence.

Screening test	*Interval (years)*	*No. of screening tests*	*No. of diagnostic colonoscopies*[a]	*No. of surveillance colonoscopies*	*Total no. of colonoscopies*
		Undiscounted			
No screening	-	0	67	0	67
FIT	1	16,378	748	985	1,733
CTC	5	4,526	608	746	1,354
Colonoscopy	10	2,278	10	1,753	4,041
mSEPT9	2	6,244	1,349	1,233	2,582
mSEPT9	1	7,902	1,695	1,458	3,153
mtSDNA	3	5,973	746	945	1,691
PillCam	10	2,528	598	948	1,546
PillCam	5	4,085	866	1,166	2,032
mtSDNA	1	11,394	1,286	1,339	2,625

Screening test	*Interval (years)*	*LYG*	*QALYG*	*Total costs (Million $)*	*ICER ($ per QALYG)*	*ICER ($ per QALYG) without FIT and Colonoscopy*
		3% Discounted				
No screening	-	0	0	4.560	-	-
FIT	1	101	117	4.757	1,683	-
CTC	5	94	110	5.593	D	9,397
Colonoscopy	10	108	130	6.004	99,296	-
mSEPT9	2	94	108	6.251	D	D
mSEPT9	1	103	120	6.744	D	119,336
mtSDNA	3	94	108	6.849	D	D
PillCam	10	88	102	6.922	D	D
PillCam	5	103	121	8.337	D	D
mtSDNA	1	108	126	9.329	D	379,789

table continues

Scenario analysis 3, assuming that 90% of the people that participated in a previous round would participate in a subsequent round, and 15% of the people that did not participate in the previous round would participate in the subsequent round. An 80% adherence to diagnostic follow-up and surveillance was assumed.

Screening test	*Interval (years)*	*No. of screening tests*	*No. of diagnostic colonoscopies[a]*	*No. of surveillance colonoscopies*	*Total no. of colonoscopies*
		Undiscounted			
No screening	-	0	108	0	108
FIT	1	11,612	658	1,311	1,969
CTC	5	3,767	574	1,103	1,677
Colonoscopy	10	1,869	18	2,634	4,521
mSEPT9	2	5,203	1,148	1,757	2,905
mSEPT9	1	6,625	1,439	2,143	3,582
mtSDNA	3	4,809	696	1,331	2,027
PillCam	10	2,246	639	1,439	2,078
PillCam	5	3,346	829	1,726	2,555
mtSDNA	1	8,723	1,090	1,915	3,005

Screening test	*Interval (years)*	*LYG*	*QALYG*	*Total costs (Million $)*	*ICER ($ per QALYG)*	*ICER ($ per QALYG) without FIT and Colonoscopy*
		3% Discounted				
No screening	-	0	0	7.286	-	-
FIT	1	143	165	6.919	Cost Saving	-
CTC	5	138	161	7.503	D	1,346
Colonoscopy	10	169	203	7.707	20,495	-
mSEPT9	2	139	161	8.229	D	D
mSEPT9	1	158	185	8.482	D	41,041
mtSDNA	3	136	157	8.723	D	D
PillCam	10	134	158	8.892	D	D
PillCam	5	156	185	9.731	D	D
mtSDNA	1	164	192	10.238	D	239,907

table continues

Scenario analysis 4, assuming 12% of advanced adenomas and 18% of colorectal cancers are systematically missed by the m*SEPT9*.

Screening test	*Interval (years)*	*No. of screening tests*	*No. of diagnostic colonoscopies*[a]	*No. of surveillance colonoscopies*	*Total no. of colonoscopies*
		Undiscounted			
No screening	-	0	108	0	108
FIT	1	15,044	791	1,558	2,349
CTC	5	4,292	628	1,196	1,824
Colonoscopy	10	1,995	15	2,725	4,735
mSEPT9	2	5,804	1,269	1,932	3,201
mSEPT9	1	7,162	1,548	2,279	3,827
mtSDNA	3	5,583	785	1,494	2,279
PillCam	10	2,383	671	1,502	2,173
PillCam	5	3,710	899	1,837	2,736
mtSDNA	1	10,185	1,233	2,101	3,334

Screening test	*Interval (years)*	*LYG*	*QALYG*	*Total costs (Million $)*	*ICER ($ per QALYG)*	*ICER ($ per QALYG) without FIT and Colonoscopy*
		3% Discounted				
No screening	-	0	0	7.286	-	-
FIT	1	162	189	6.793	Cost Saving	-
CTC	5	151	177	7.479	D	1,092
Colonoscopy	10	174	209	7.751	48,155	-
mSEPT9	2	149	173	8.281	D	D
mSEPT9	1	164	193	8.567	D	68,682
mtSDNA	3	151	175	8.887	D	D
PillCam	10	141	165	8.951	D	D
PillCam	5	166	196	9.940	D	D
mtSDNA	1	173	205	10.798	D	188,729

LYG - life-years gained; QALYG - quality-adjusted life-years gained; ICER - incremental cost-effectiveness ratio; FIT - fecal immunochemical test; m*SEPT9* - methylated *SEPT9* DNA plasma assay; CTC - computed tomographic colonography; mtSDNA - multitarget stool DNA; PillCam - PillCam COLON 2; D – dominated

[a] Includes both diagnostic follow-up colonoscopies and colonoscopies for clinical detection of colorectal cancer.

Chapter 7

Prioritizing cancer screenings in women with restrictive preferences

Glen B. Taksler, Elisabeth F.P. Peterse, Isarah Willems, Kevin ten Haaf, Erik E.L. Jansen, Inge M.C.M. de Kok, Nicolien T. van Ravesteyn, Harry J. de Koning & Iris Lansdorp-Vogelaar

Submitted

Abstract

Background
Only half of women obtain all evidence-based cancer screenings.

Methods
We evaluated optimal screening strategies in women willing to obtain some, but not all, US Preventive Services Task Force (USPSTF)-recommended screenings. Utilizing a microsimulation model of females born in 1965, we considered 45 hypothetical screening strategies. Strategies comprised breast, cervical, colorectal and/or lung cancer screenings, restricted to 1, 2, 3 or 4 screenings/year, or all eligible screenings once every 5 years. We measured life-years gained from restricted cancer screenings relative to full compliance with USPSTF recommendations ("maximum benefits"), stratified by lung cancer screening eligibility ("LC-eligible/ineligible"). We repeated the analysis with 2018 adherence rates.

Results
It was possible to reduce screening intensity to just 1 carefully chosen test/year in women ineligible for lung cancer screening and 2 tests/year in eligible women, while maintaining ≥94% of maximum benefits. Highly-ranked strategies screened for a variety of cancers but less often than USPSTF-recommended. For example, among LC-ineligible women willing to obtain 1 screening/year, the optimal strategy frequently delayed breast and cervical cancer screenings by 1 year and skipped occasional mammograms (94% of maximum benefits). Among LC-eligible women, lung cancer screening was essential; strategies omitting it provided ≤25% of maximum benefits. If adherence in a population of LC-eligible women obtaining 2 screenings/year were to increase by 1%-2%, it would achieve the same benefit as USPSTF recommendations at 2018 adherence rates.

Conclusion
Women unable or unwilling to obtain all guideline-recommended cancer screenings may be able to reduce screening intensity with minimal impact on overall benefits.

Introduction

In 2020, 1.8 million new cancer cases and 606,520 cancer deaths are expected in the US;[149] more years of life are lost to cancer than any other cause-of-death.[244] One important path to reducing cancer-related mortality is screening, which in women is guideline-recommended for breast, cervical, colorectal and, for those with heavy smoking histories, lung cancer. Each screening varies in its ability to improve longevity and quality of life,[96,170,245,246] and adherence varies widely.[247-249]

Reasons for noncompliance with guidelines include concern about test preparation,[250] adverse events from screening such as false-positives and overdiagnosis,[251-254] and misunderstanding about risks and benefits.[255-258] Patients also may be time-limited or overwhelmed. The United States Preventive Services Task Force and Advisory Committee on Immunization Practices recommend 41 clinical services for nonpregnant adults, just 4 of which are cancer-related.[25,259] Individuals are asked to juggle these in the context of competing needs for non-preventive medical care.[260-262] Moreover, amidst COVID-19, social distancing, high-risk factors (e.g., age) and fear may prevent women from obtaining evidence-based screenings. In prior work, patients who were eligible for more preventive services were less likely to utilize cancer screenings.[263]

Ultimately, the goal of early detection is to prevent death from any cancer, regardless of type. Yet, in this holistic setting, the benefits and harms of a woman choosing to receive some, but not all, guideline-recommended cancer screenings are unknown. For example, for some individuals, it may be most valuable to screen for some cancers but skip others entirely, or alternately, to obtain a variety of cancer screenings even if less-often than guideline-recommended. A provider also might prioritize screenings that offer the greatest increase in life expectancy[264,265] or quality of life.[266-268]

In this study, we sought to quantify optimal cancer screening strategies for women who were unwilling or unable to obtain all guideline-recommended screenings.

Methods

Figure 7.1 summarizes our methods. We utilized the validated state-transition MIcrosimulation SCreening ANalysis (MISCAN) models for breast cancer (MISCAN-Fadia), cervical cancer, colorectal cancer, and lung cancer to estimate benefits and harms of different screening strategies. The models are part of the National Cancer Institute's (NCI) Cancer Intervention and Surveillance Modeling Network (CISNET), developed by the Department of Public Health at Erasmus University Medical Center.[269] Each model simulates the natural history of disease, major risk factors, screening behavior and diffusion of new technology to assess benefits and risks of screening interventions. Details are published elsewhere.[102,170,197,270-273] Previously, the models have helped inform recommendations by the US Preventive Services Task Force (USPSTF) and American Cancer Society.[96,99,170,245,246]

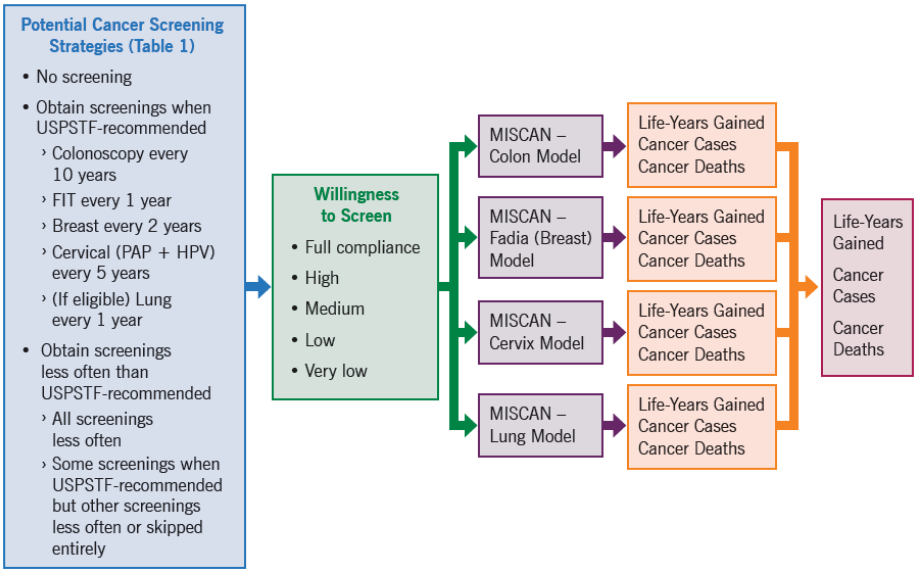


Figure 7.1: Description of Modeling Framework

Population

We modeled the population of US females born in 1965 (aged 55 y in 2020). For these women, the USPSTF recommended ≥3 cancer screenings: annual FIT or decennial colonoscopy until age 75 y, biennial mammography until age 74 y, and either triennial PAP, HPV testing every 5 y or PAP/HPV co-testing every 5 y until age 65 y.[25] Additionally, for some women, the USPSTF recommended annual low-dose lung CT until age 80 y.[25] Therefore, we stratified the population by lung cancer screening eligibility ("LC-eligible/ineligible"), defined as aged 55-80 years, current smoker or former smoker who quit ≤15 years ago, and ≥30-pack-year smoking history at age 55 years.

For each strata, we simulated 10 million women born in 1965. We utilized NCI's Smoking History Generator, which assesses individual smoking histories based on historical smoking patterns in the US,[274,275] to estimate single-year all-cause survival probabilities. This process allowed us to generate background risk of death stratified by LC-eligibility. Additionally, for LC-eligible women, we accounted for higher incidence of lung cancer (directly modeled in the microsimulation), colorectal cancer (1.56 relative risk) and cervical cancer (1.60 relative risk).[272,273,276-278]

Scenarios

Using these models, we considered lifetime cancer screening trajectories for US females aged ≥50 y. Specifically, we examined 45 strategies where women obtained some, but not all, USPSTF-recommended screenings (**Table 7.1**). Eleven strategies were "simple," defined as obtaining screenings for some cancers when USPSTF-recommended but omitting other screenings entirely, and 34 strategies were "complex,"

defined as obtaining screenings for most or all cancer sites but less-often than USPSTF-recommended (for example, biennially instead of annually). We categorized a woman's willingness to screen as full compliance (willing to obtain all USPSTF-recommended screenings); high, medium or low (willing to obtain up to 3, 2 or 1 screenings per year); or very low (willing to obtain all guideline-recommended cancer screenings once every 5 years). For LC-ineligible women, the full and high compliance categories were the same because guidelines never recommended >3 screenings per year; we refer to this category as full compliance. These conditions were not intended to suggest that women limit themselves to a strict number of screenings but rather, to proxy for overall interest in cancer screening. In the extremes, a woman was always or rarely willing to follow guideline recommendations.

Table 7.1: Cancer screening strategies. We considered various cancer screening strategies for a cohort of hypothetical 50-year-old women who were willing (or able) to obtain some, but not all, USPSTF-recommended cancer screenings.

		Type of strategy (simple or complex)[a]	Cancer screenings (total number of screenings at ages ≥50 y in parentheses)			
Strategy			**Breast**	**Cervical**	**Colorectal**	**Lung**
Females eligible for lung cancer screening						
Full compliance with USPSTF recommendations (≤4 cancer acreenings per year)						
1	All USPSTF-recommended screenings (COL)	Simple	Biennial 50-74 y (13)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	Annual 55-80 y (26)
2	All USPSTF-recommended screenings (FIT)	Simple	Biennial 50-74 y (13)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	Annual 55-80 y (26)
3[b]	All USPSTF-recommended screenings (COL) plus annual breast	Simple	Annual 50-75 y (26)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	Annual 55-80 y (26)
4[b]	All USPSTF-recommended screenings (FIT) plus annual breast	Simple	Annual 50-75 y (26)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	Annual 55-80 y (26)
High willingness to screen for cancer (≤3 cancer screenings per year)						
5	Biennial breast, annual lung, add COL or cervical as appropriate.	Complex	Biennial 50-74 y (13)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	Annual 55-80 y but skip 60 y (25)

table continues

Strategy		Type of strategy (simple or complex)[a]	Cancer screenings (total number of screenings at ages ≥50 y in parentheses)			
			Breast	**Cervical**	**Colorectal**	**Lung**
6	Biennial breast, annual FIT and lung. Obtain cervical in non-breast.	Complex	Biennial 50-74 y (13)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	Annual 55-80 y but skip 60 y (25)
7[b]	Annual breast and lung, add COL or cervical as appropriate.	Complex	Annual 50-75 y (26)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	Annual 55-80 y but skip 60 y (25)
8[b]	Annual breast, FIT and lung; skip lung for cervical.	Complex	Annual 50-75 y (26)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	Annual 55-80 y but skip 60 y (25)
Medium willingness to screen for cancer (≤2 cancer screenings per year)						
9[c]	Biennial breast, add cervical as appropriate.	Simple	Biennial 51-73 y (12)	50, 55, 60, 65 y (4)	-	-
10[c]	Annual FIT, biennial breast.	Simple	Biennial 51-73 y (12)	-	Annual 50-75 y (FIT) (26)	-
11	Annual lung and FIT.	Simple	-	-	Annual 50-75 y (FIT) (26)	Annual 55-80 y (26)
12	Annual lung, biennial breast.	Simple	Biennial 51-73 y (12)	-	-	Annual 55-80 y (26)
13	Biennial breast, annual lung, skip lung for COL and cervical.	Complex	Biennial 51-73 y (12)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	Annual 56-59, 61-64, 66-80 y (23)
14	Annual FIT, alternate breast and lung, skip for cervical.	Complex	51, 53, 56, 58, 61, 63, Biennial 66-74 y (11)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	57, 59, 62, 64, Biennial 67-73, Annual 75-80 y (14)
15	Annual lung, alternate breast and FIT, skip for cervical.	Complex	51, 53, 56, 58, 61, 63, Biennial 66-74 y (11)	50, 55, 60, 65 y (4)	50, 52, 54, 57, 59, 62, 64, Biennial 67-75 y (12)	Annual 55-80 y (26)
16[b]	Annual breast and lung, skip for COL and cervical.	Complex	Annual 51-59, Annual 61-75 y (24)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	Annual 56-59, Annual 61-64, Annual 66-69, Annual 71-80 y (22)
17[b]	Annual breast, alternate FIT and lung, skip for cervical.	Complex	Annual 50-75 y (26)	50, 55, 60, 65 y (4)	50, 53, 56, 58, 61, 63, Biennial 66-74, 75 y (12)	57, 59, 62, 64, Biennial 67-73, Annual 75-80 y (14)

table continues

		Type of strategy (simple or complex)[a]	Cancer screenings (total number of screenings at ages ≥50 y in parentheses)			
Strategy			**Breast**	**Cervical**	**Colorectal**	**Lung**
Low willingness to screen for cancer (≤1 cancer screenings per year)						
18[c]	Biennial breast only	Simple	Biennial 50-74 y (13)	-	-	-
19	Cervical only	Simple	-	50, 55, 60, 65 y (4)	-	
20[c]	COL only	Simple	-	-	50, 60, 70 y (COL) (3)	-
21[c]	FIT only	Simple	-	-	Annual 50-75 y (FIT) (26)	-
22	Annual lung only	Simple	-	-	-	Annual 55-80 y (26)
23[c]	Alternate FIT and breast, skip for cervical.	Complex	52, 54, 56, 59, 61, Biennial 64-74 y (11)	51, 57, 63 y (3)	50, 53, 55, 58, 60, 62, Biennial 65-75 y (12)	-
24[c]	Alternate FIT and breast. Omit cervical, lung.	Complex	Biennial 51-73 y (12)	-	Biennial 50-74 y (FIT) (13)	-
25	Alternate FIT and lung, skip for cervical. Omit breast.	Complex	-	50, 55, 60, 65 y (4)	51, 53, 56, 58, 61, 63, Biennial 66-74 y (FIT) (12)	52, 54, 57, 59, 62, 64, Biennial 67-73 y, Annual 75-80 y (16)
26	Alternate FIT and lung. Omit cervical, breast.	Complex	-	-	Annual 50-54, Biennial 56-74 y (FIT) (15)	Biennial 55-73 y, Annual 75-80 y (16)
27	Alternate breast and lung, skip for COL and cervical.	Complex	52, 54, 57, 59, 63, 66, 68, 71, 73 y (9)	51, 56, 61, 65 y (4)	50, 60, 70 y (3)	55, 58, 62, 64, 67, 69, 72, 74, Annual 76-80 y (13)
28	Alternate breast and lung, skip for COL. Omit cervical.	Complex	Biennial 50-60, Biennial 63-69, 72, 74 y (12)	-	51, 61, 71 y (3)	55, 57, 59, Biennial 62-70, 73, Annual 75-80 y (15)
29	Alternate FIT, breast, and lung. Omit cervical.	Complex	51, 53, 55, Triennial 58-73 y (9)	-	50, 52, 54, Triennial 3 years 57-75 y (10)	Triennial 56-74 y (7)
30[b,c]	Annual breast only	Simple	Annual 50-75 y (26)	-	-	-

table continues

Strategy		Type of strategy (simple or complex)[a]	Cancer screenings (total number of screenings at ages ≥50 y in parentheses)			
			Breast	**Cervical**	**Colorectal**	**Lung**
31[b,c]	Annual breast, skip for COL and cervical. Omit lung.	Complex	Annual 52-55, Annual 57-59, 61, Annual 63-69, Annual 71-75 y (20)	51, 56, 62 y (3)	50, 60, 70 y (COL) (3)	-
Very low willingness to screen for cancer (all screenings once every 5 years)						
32	All recommended screenings once every 5 years (COL)	Complex	50, 55, 60, 65, 70 y (5)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	Annual 55-80 y (26)
33	All recommended screenings once every 5 years (FIT)	Complex	50, 55, 60, 65, 70 y (5)	50, 55, 60, 65 y (4)	50, 55, 60, 65, 70, 75 y (FIT) (6)	50, 55, 60, 65, 70, 75, 80 y (7)
Females ineligible for lung cancer screening						
Full compliance with USPSTF recommendations (≤3 cancer screenings per year)						
34	All USPSTF-recommended screenings (COL)	Simple	Biennial 50-74 y (13)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	-
35	All USPSTF-recommended screenings (FIT)	Simple	Biennial 50-74 y (13)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	-
36[b]	All USPSTF-recommended screenings (COL) plus annual breast	Simple	Annual 50-75 y (26)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	-
37[b]	All USPSTF-recommended screenings (FIT) plus annual breast	Simple	Annual 50-75 y (26)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	-
Medium Willingness to Screen for Cancer (≤2 Cancer Screenings Per Year)						
9[c]	Biennial breast, add cervical as appropriate.	Simple	Biennial 50-74 y (13)	50, 55, 60, 65 y (4)	-	-
10[c]	Biennial breast, annual FIT.	Simple	Biennial 50-74 y (13)	-	Annual 50-75 y (FIT) (26)	-
38	Biennial breast, add COL and cervical within 1 year of recommendation.	Complex	Biennial 51-73 y (12)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	-
39	Biennial breast, annual FIT, skip breast for cervical.	Complex	51, 53, 56, 58, 61, 63, Biennial 66-74 y (11)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	-

table continues

		Type of strategy (simple or complex)[a]	Cancer screenings (total number of screenings at ages ≥50 y in parentheses)			
Strategy			**Breast**	**Cervical**	**Colorectal**	**Lung**
40[b]	Annual breast, add COL and cervical as appropriate, skip an occasional mammogram.	Complex	Annual 51-59, Annual 61-75 y (24)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	-
41[b]	Annual breast and FIT, skip breast for cervical.	Complex	Annual 51-54, Annual 56-59, Annual 61-64, Annual 66-75 y (22)	50, 55, 60, 65 y (4)	Annual 50-75 y (FIT) (26)	-
Low willingness to screen for cancer (≤1 cancer screening per year)						
18[c]	Biennial breast only	Simple	Biennial 50-74 y	-	-	-
19[c]	Cervical only	Simple	-	50, 55, 60, 65 y (4)	-	
20[c]	COL only	Simple	-	-	50, 60, 70 y (COL) (3)	-
21[c]	FIT only	Simple	-	-	Annual 50-75 y (FIT) (26)	-
23[c]	Alternate FIT and breast, skip for cervical.	Complex	51, 54, 56, 59, 61, Biennial 64-74 y (11)	52, 57, 62 y (3)	50, 53, 55, 58, 60, Biennial 63-75 y (FIT) (12)	-
24[c]	Alternate FIT and breast. Omit cervical.	Complex	Biennial 51-73 y (12)	-	Biennial 50-75 y (FIT) (26)	-
42	Biennial breast, add COL and cervical within 1 year of recommendation but skip an occasional mammogram.	Complex	52, 54, 57, 59, Biennial 62-68, 71, 73 y (10)	51, 56, 61, 65 y (4)	50, 60, 70 y (COL) (3)	-
30[b,c]	Annual breast only	Simple	Annual 50-75 y (26)	-	-	-
31[b,c]	Annual breast, skip for COL and cervical.	Complex	Annual 52-55, Annual 57-59, 61, Annual 63-69, Annual 71-75 y (20)	51, 56, 62 y (3)	50, 60, 70 y (COL) (3)	-
43[b]	Annual breast, skip for COL. Omit cervical.	Complex	Annual 51-59, Annual 61-69, Annual 71-75 y (23)	-	50, 60, 70 y (COL) (3)	-

table continues

	Strategy	Type of strategy (simple or complex)[a]	Cancer screenings (total number of screenings at ages ≥50 y in parentheses)			
			Breast	Cervical	Colorectal	Lung
Very low willingness to screen for cancer (all screenings once every 5 years)						
44	All recommended screenings once every 5 years (COL)	Complex	50, 55, 60, 65, 70 y (5)	50, 55, 60, 65 y (4)	50, 60, 70 y (COL) (3)	-
45	All recommended screenings once every 5 years (FIT)	Complex	50, 55, 60, 65, 70 y (5)	50, 55, 60, 65 y (4)	50, 55, 60, 65, 70, 75 y (FIT) (6)	-

COL – Colonoscopy; FIT - Fecal immunochemical testing.

[a] Simple strategies were defined as obtaining some screenings when recommended by the USPSTF but omitting other screenings entirely. Complex strategies were defined as obtaining some screenings less-often than USPSTF-recommended.

[b] Strategy for sensitivity analysis, to facilitate comparison with American Cancer Society guidelines.

[c] Same strategy estimated for women eligible and ineligible for lung cancer screening.

Test characteristics

Assumptions regarding test characteristics and follow-up of positive results have been published previously.[96,246,272,279,280] Additionally, for colorectal cancer, we considered colonoscopy as the benchmark because prior works suggests slightly more life-years gained from colonoscopy than FIT.[96] For lung and breast cancer screenings, we assumed low-dose computed tomography (CT) and digital mammography, respectively. For cervical cancer screening, we assumed HPV with cytology triage of positive results.

Similar to decision analyses accompanying USPSTF recommendations,[96,170,245,281] we assumed full adherence to each screening scenario. We relaxed this assumption in a threshold analysis (below). To assess cervical cancer screening benefits, we assumed full adherence before age 50 y. For comparison, the 2018 National Health Interview Survey (NHIS) suggests that 86.0% of women aged 40-49 y were up-to-date with cervical cancer screening.[282]

Outcomes

The primary outcome was life-years gained ("LYG") from all cancer screenings relative to full compliance with USPSTF recommendations ("maximum benefits"), using colonoscopy for colorectal cancer screening. We did not consider harms because by design, their frequency would be lower for less-intensive screening strategies than for full compliance. Results were stratified by lung cancer screening eligibility. All results were expressed per 1,000 50-year-old women and rounded to the nearest integer to avoid overprecision.

Analysis

For each level of willingness to screen, we rank-ordered strategies by maximum benefits. Additionally, we recognized that in practice, simple screening strategies (obtaining full screening for some diseases and none for others) would likely be easier to implement than complex strategies (obtaining screenings for most diseases, but less-often than USPSTF-recommended). Therefore, among women with low or medium willingness to screen, we compared the highest-ranked simple and complex strategies.

Threshold analysis

We also considered the possibility that patients may be more likely to adhere to less-intensive screening plans than to guideline recommendations. This possibility was consistent with recent work finding that cancer screening utilization was higher when the number of recommended services was lower.[263] To assess this possibility, we estimated the proportion of women up-to-date with each screening in the recommended age group (e.g., 50-65 y for cervical cancer screening) from the 2018 National Health Interview Survey[282] (for breast, cervical and colorectal cancers) and the 2018 Behavioral Risk Factor Surveillance System (BRFSS)[283] (for lung cancer, which was not available in the 2018 NHIS), stratified by LC-eligibility (Supplemenatry Table A7.1).

To stratify NHIS data by LC-eligibility, we calculated pack-years and (if applicable) years since quitting. However, for former smokers, NHIS last asked about pack-years in 2015.[282] Therefore, we calculated the proportion of former smokers who were LC-eligible in 2015 (stratified by 5-year age group) and randomly assigned LC-eligibility to former smokers in 2018 accordingly, employing 100 bootstrap iterations to estimate up-to-date status with lung cancer screening.

For each cancer screening strategy, we estimated LYG at the 2018 adherence rates, assuming that for subsequent screening rounds, 90% of those who previously obtained screening would do so again and the remainder would be women overdue for screening.[185,284] Then, we solved for the change in adherence rates needed for LYG from each strategy to equal that for the benchmark USPSTF-recommended strategy. To do so, we counterfactually decreased the proportion of non-adherence for colonoscopy in 1 percentage point increments (e.g., from 42% to 41%) to a minimum of zero. We scaled other screenings proportionately (e.g., for breast cancer from 27% to 27%*41%/42%=26.36%), resulting in the same relative reduction for the number not currently up-to-date with screening. We compared resulting LYG from each less-intensive strategy with those available from USPSTF recommendations, to assess whether any increase in adherence could approximate the historic net benefits of USPSTF recommendations.

Sensitivity analysis

We conducted 4 sensitivity analyses. First, we considered alternate outcomes of number of deaths and number of cancer cases. Second, we considered annual mammography, recommended as an option by the American Cancer Society, between ages 50-75 years.[285] Third, we considered a higher risk of developing colorectal cancer, reflective of recent

higher incidence in young adults,[16] using previously-published methods.[99] Fourth, we modeled a cohort of women who did not receive any cervical cancer screening before age 50 y.

This study did not meet the definition of human subjects research at the Institutional Review Boards of Cleveland Clinic and Erasmus University Medical Center.

Results

Figure 7.2 illustrates life-years gained ("LYG") from cancer screening based on willingness to screen. Supplementary Table A7.2 presents full results. Results are shown as a percentage of the LYG from full attainment of USPSTF recommendations.

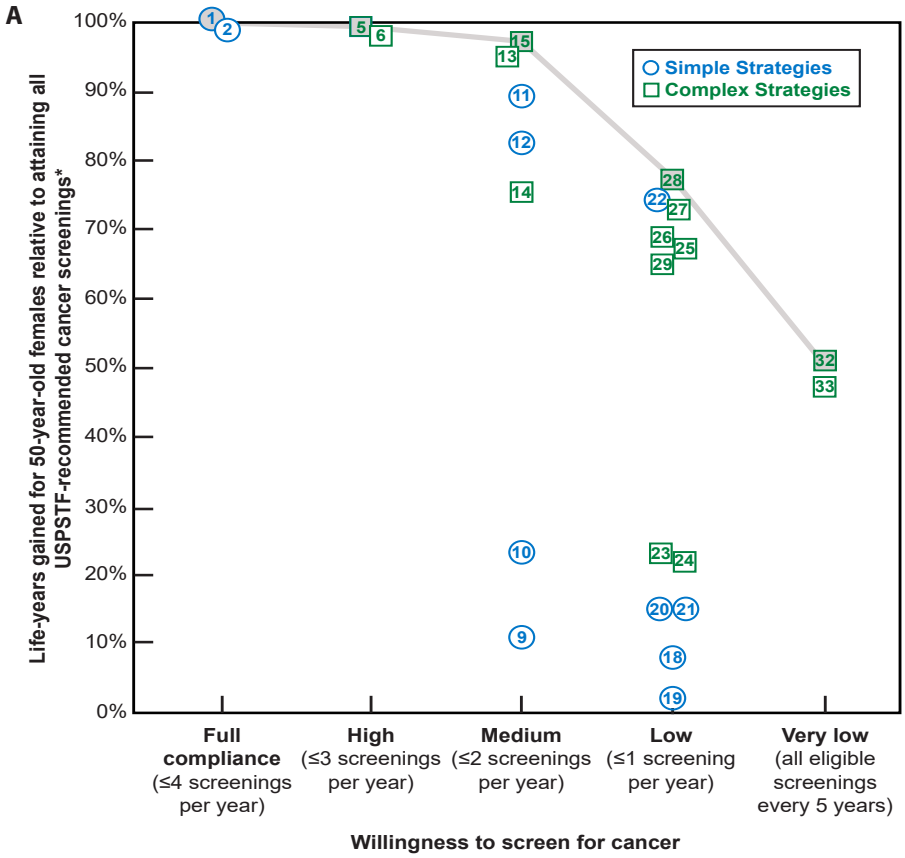
Women eligible for lung cancer screening

Among eligible women (Figure 7.2A), lung cancer screening was essential; strategies omitting it provided ≤25% of maximum benefits. The USPSTF-recommended strategy conferred 1,103 LYG from screening per 1,000 50-year-old women with colonoscopy (strategy #1, "maximum benefits") or 1,097 per 1,000 with FIT (#2). As expected, women willing to obtain fewer screenings could obtain lower net benefits. *High compliance (≤3 screenings/year).* Women who occasionally delayed screenings by 1 year to receive ≤3 cancer screenings/year could do so with minimal loss in benefits (#5, 99% of maximum benefits). *Medium compliance (≤2 screenings/year).* The top-ranked simple strategy (#11) was annual lung and FIT testing, affording 88% of maximum benefits. The top-ranked complex strategy (#15) conferred 97% of maximum benefits: annual lung, alternate FIT and mammography, and skip every 3rd mammogram (i.e., every 6th year) for cervical cancer screening until age 65 y. For comparison, breast and cervical cancer screenings (#9) provided only 11% of maximum benefits. *Low compliance (≤1 screening/year).* The top-ranked simple strategy (#22) was annual lung only (omitting all other screenings), providing 74% of maximum benefits. These benefits were about 5 times the next highest-ranked simple strategies (#20/21), colonoscopy or FIT, each conferring 15% of maximum benefits. Annual lung ranked similar to the top-ranked complex strategy (#28, alternate breast and lung, skip when due for colonoscopy, 76%). *Very low compliance.* For women willing to obtain all eligible screenings once every 5 years, the share of maximum benefits declined to 51% with decennial colonoscopy (#32) or 48% with FIT (#33). Therefore, for eligible women who currently obtain only breast and cervical cancer screenings (#9 in ≤2 screenings/year; 11% of maximum benefits), reducing screening frequency to once every 5 years but adding lung and FIT screenings at that interval would quadruple overall benefits to 48%.

Women ineligible for lung cancer screening

Figure 7.2B shows results. *Full compliance.* The USPSTF-recommended strategy conferred 339 LYG from screening per 1,000 50-year-old women with colonoscopy (#34, "maximum benefits") or 332 per 1,000 with FIT (#35). These benefits were about 70% lower than for LC-eligible women. As with those results, women willing

to obtain fewer screenings could expect lower net benefits. *Medium compliance (≤2 screenings/year).* The top-ranked simple strategy (#10) was biennial breast and annual FIT, conferring 89% of maximum benefits. This was lower than the top-ranked complex strategy with FIT (#39, biennial breast and annual FIT but skipping mammography when due for cervical cancer screening, 93%) or colonoscopy (#38, biennial breast, add colonoscopy and cervical screenings within 1 year of USPSTF recommendation, 99%). For comparison, obtaining only guideline-recommended breast and cervical cancer screenings (#9) offered just 47% of maximum benefits. *Low compliance (≤1 screening/year).* The top-ranked simple strategy was colorectal cancer screening (annual FIT [#21], 51% of maximum benefits, or colonoscopy [#20], 53%). By contrast, the top-ranked complex strategy conferred 85% of maximum benefits with FIT (#24, alternating FIT and mammography, and omitting cervical cancer screening for ages ≥50 y) or 94% of maximum benefits with colonoscopy (#42, biennial breast, add colonoscopy and cervical within 1 year of USPSTF recommendation but skip an occasional mammogram). *Very low compliance.* For women willing to obtain all eligible screenings once every 5 years, the share of maximum benefits declined to 81% with decennial colonoscopy (#44) or 68% with FIT (#45).



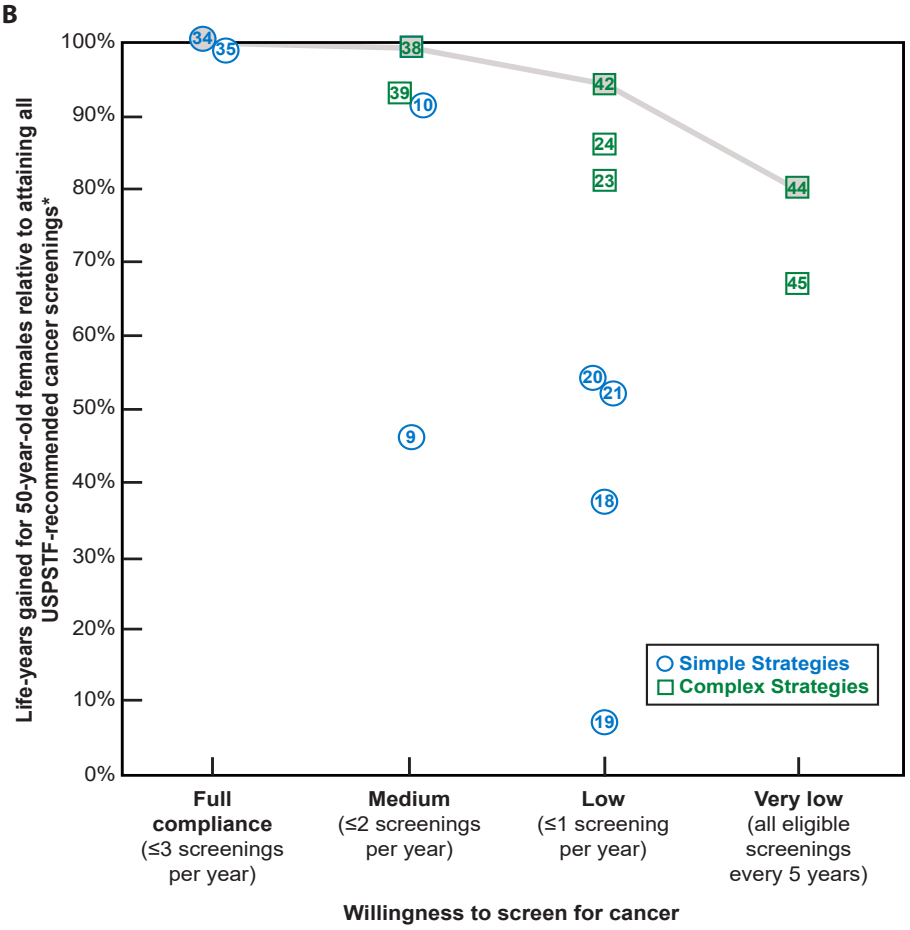


Figure 7.2: Life-years gained for females with restrictive cancer screenings preferences, as compared with USPSTF recommendations. **A**: Females eligible for lung cancer screening. **B** : Females ineligible for lung cancer screening. For each cancer screening strategy in Table 7.1, we estimated life-years gained relative to USPSTF recommendations (with colonoscopy-based colorectal cancer screenings) and rank-ordered them. Gray shading denotes top-ranked strategies, which are connected by a gray line. Strategy numbers are shown in Table 7.1. Supplementary Table A7.2 provides more detailed results.

USPSTF - United States Preventive Services Task Force; COL – Colonoscopy; FIT - Fecal immunochemical test.

*Life-years gained from attaining all USPSTF-recommended cancer screenings, with colonoscopy: 1,103 per 1,000 50-year-old females eligible for lung cancer screening and 339 per 1,000 50-year old females ineligible for lung cancer screening.

Threshold analysis

Just 51.6% of women were up-to-date with breast, cervical and colorectal cancer screenings in 2018, and 16.9% of eligible women were up-to-date with lung cancer screening (Supplementary Table A7.1). If women were more likely to adhere to less-intensive screening plans than to guideline recommendations, then LYG would improve (Table 7.2). For LC-eligible women, if those obtaining ≤2 screenings/year (strategy #13) were to increase adherence by 1%-2% (depending on screening test), they would achieve the same population benefit as USPSTF recommendations. Additionally, an annual lung only strategy (#22) had a 41.0% threshold adherence rate. Therefore, if prioritizing lung cancer screening could result in one-quarter more LC-eligible women obtaining consistent screening (41.0% minus 16.9% historical adherence), then an annual lung only strategy should produce the same population benefit as all USPSTF cancer screening recommendations combined.

For LC-ineligible women, 1 screening/year (#42) would provide similar LYG to USPSTF recommendations if adherence rates were to increase by 4%-6% (depending on screening test). Very low screening would require a much higher increase (e.g., 23 percentage points for colonoscopy).

Table 7.2: Threshold adherence rates at which restricted cancer screening strategies result in equal population benefits as USPSTF recommended strategy at current adherence rates. We repeated the primary analysis at historical adherence rates. We then simulated the increase in adherence rates needed for life-years gained from each less-intensive screening strategy to equal USPSTF recommendations.

Willingness to screen	Strategy		Life-years gained per 1,000 50-year-old females (full adherence)	Threshold adherence rates (%)			
				Breast	Cervical	Colorectal	Lung
Females eligible for lung cancer screening							
Full compliance	1	All USPSTF-recommended screenings (COL)	1,103	57.8	60.2	62.2	16.9
	2	All USPSTF recommended screenings (FIT)	1,097	57.8	60.2	62.2	16.9
High	5	Biennial breast, annual lung, add COL or cervical as appropriate.	1,090	59.1	61.1	63.0	19.2
	6	Biennial breast, annual FIT and lung. Obtain cervical in non-breast.	1,085	59.1	61.1	63.0	19.2
Medium	15	Annual lung, alternate breast and FIT, skip for cervical.	1,065	60.2	62.1	64.0	21.4

table continues

Willingness to screen		Strategy	Life-years gained per 1,000 50-year-old females (full adherence)	Threshold adherence rates (%)			
				Breast	Cervical	Colorectal	Lung
	13	Biennial breast, annual lung, skip lung for COL and cervical.	1,050	59.1	61.1	63.0	19.2
	11	Annual lung and FIT.	975	-	-	66.0	25.7
Low	28	Alternate breast and lung, skip for COL. Omit cervical.	842	64.6	-	68.0	30.1
	22	Annual lung only	811	-	-	-	41.0
Very low	32	All recommended screenings once every 5 years (COL)	564	74.6	75.8	77.0	49.8
	33	All recommended screenings once every 5 years (FIT)	526	82.3	83.2	84.0	65.1
Females ineligible for lung cancer screening							
Full compliance	34	All USPSTF recommended screenings (COL)	339	70.7	77.3	63.7	-
	35	All USPSTF recommended screenings (FIT)	332	70.7	77.3	63.7	-
Medium	38	Biennial breast, add COL and cervical within 1 year of recommendation.	335	71.8	77.6	65.0	-
	39	Biennial breast, annual FIT, skip breast for cervical.	315	78.3	82.3	73.0	-
Low	42	Biennial breast, add COL and cervical within 1 year of recommendation but skip an occasional mammogram.	319	75.8	80.8	70.0	-
	24	Alternate FIT and breast. Omit cervical.	287	95.2	-	94.0	-
	21	FIT only	173	-	-	N/A*	-
Very low	44	All recommended screenings once every 5 years (COL)	274	89.5	91.7	87.0	-
	45	All recommended screenings once every 5 years (FIT)	229	N/A*	N/A*	N/A*	-

*Suboptimal strategy even with a 100% adherence rate.

Sensitivity analyses

In sensitivity analysis, results were similar for number of cancer deaths and cases as outcomes (**Supplementary Figures A7.1-A7.2**). For annual mammography, results were more sensitive for LC-ineligible than LC-eligible women (**Supplementary Figure A7.3**). As compared with the top-ranked annual mammography strategy, the top-ranked biennial breast strategy reduced the share of maximum benefits by 9-14 percentage points among LC-ineligible women, depending on screening intensity, but ≤4 percentage points among eligible women. For higher risk of developing colorectal cancer, optimal strategies remained identical to the baseline analysis (**Supplementary Figure A7.4**). For women without cervical cancer screening before age 50 y, top-ranked strategies were unchanged, though the magnitude of maximum benefits from attaining all USPSTF recommendations slightly increased (by 17.0 and 20.7 LYG per 1,000 50-year-old LC-ineligible and LC-eligible women, respectively) (**Supplementary Figure A7.5**).

Discussion

In this study, we considered a holistic framework of cancer screening, seeking to prevent death from any cancer, regardless of type. We found that women who were unwilling or unable to receive all guideline-recommended cancer screenings may be able to reduce screening intensity with minimal impact on overall benefits. In particular, it was possible to reduce cancer screening intensity to just 1 (typically different screening) test/year in women ineligible for lung cancer screening and 2 tests/year in women eligible for lung cancer screening, while maintaining 94% and 97% of benefits, respectively. This result suggests that women who prefer to reduce cancer screening intensity may be able to do so with small loss in benefits, provided they choose an optimal less-intensive strategy.

To our knowledge, this is the first study to develop next-best alternatives for women with reduced cancer screening compliance. With nationally-representative data suggesting that in 2018, only half of women were up-to-date with breast, colorectal and cervical cancer screening recommendations[282] (other recent work found 35% in England[286]), and one in 6 eligible women up-to-date with lung cancer screening,[283] studies are greatly needed. For women who choose to reduce cancer screening intensity, typically it was more valuable to combine all types of screenings, even if less-often than recommended, than to screen only for specific cancers. This result reflected diminishing returns to cancer screening, with each additional screening for the same type of cancer generally providing less benefit than earlier screenings. We also found minimal impact from skipping an occasional screening or delaying it by 1 year.

However, among LC-eligible women with low willingness to screen, it was optimal to screen for lung cancer but skip all other screenings entirely. Annual lung cancer screening contributed 74% of maximum benefits, nearly 5 times the benefit as colorectal cancer screening and 9 times that of biennial mammography. At first, this result may seem surprising because prior work suggests that lung cancer screening offers much lower

benefits than other types of screening (life-years gained per 1,000 at-risk population: 55 [lung][245] vs. 275 [colorectal][96] and 122 [breast][170]). Yet, our denominator was LC-eligible women whereas that in prior work was the general population, approximately 80% of whom were LC-ineligible.[245] Additionally, results from the population-based NELSON randomized trial suggest greater cancer-specific mortality reduction from lung cancer screening in women than men.[287] These findings must be viewed in context of substantial criticism based on mixed clinical trial results[288-291] and findings of high false-positive rates in Veterans' Health Administration data (54.8 false-positives per 100 subjects screened),[292] resulting in unnecessary biopsies and lack of effective shared decision-making.[253,254] However, the NELSON trial used a volume-based nodule management protocol, reducing false-positives to just 12 per 100 subjects screened.[287] Therefore, our findings emphasize the importance of shared decision-making.

In an era of patient-centered care, it is important to respect patient wishes. Patients may be eligible for up to 41 preventive services, just 4 of which are cancer screenings,[25,259] and may be time-limited,[293-297] particularly after managing chronic conditions.[260-262] We suggest that a caring approach would engage these patients in conversation to understand their needs and interest in cancer screening, and help them decide on an appropriate strategy. Montori et al. employ this approach for diabetes management.[298] For example, while a woman may not limit herself to a prespecified number of screenings, she may be much more willing to obtain breast and cervical cancer screenings than colorectal and lung.[247,248] Cervical cancer screening, which begins in young adulthood, and breast cancer, the leading cause of cancer-related death in women aged <50 y, are likely more relatable than colorectal and lung cancers. The latter cancer types increase in prevalence at older ages and therefore may be less interesting, less dramatic or invisible[299] to a 50-year-old.

Yet, we found that a breast and cervical cancer-only screening strategy reduced the share of maximum benefits to 47% in LC-ineligible women and 11% in LC-eligible women, similar to benefits offered by FIT only (51% and 15%, respectively) or colonoscopy (53% and 15%, respectively). Therefore, a provider might counsel a 50-year-old woman who is hesitant to begin colorectal cancer screening that she could double her overall value of cancer screening with an easy-to-use home stool test. Similarly, while one would not imagine discussing "skip every 3rd mammogram" in practice, our results suggest that if skipping an occasional mammogram helps make a patient more willing to obtain colorectal or lung cancer screenings, then she likely would benefit from doing so.

An important strength of this study is employing screening to reduce all-cancer mortality, rather than that due to specific cancers. However, our work also has four noteworthy limitations. First, we employed a separate model for each cancer type, instead of an integrated model. Therefore, women who died in a microsimulation for one cancer may have remained alive in a microsimulation for another cancer. However, each cancer-specific mortality was included in background mortality risk, reducing the population-level impact of this limitation. Second, we may have overestimated LYG from preventing one cancer case because some women had risk factors placing them

at higher risk of both cancer and other major disease (e.g., advanced heart disease). Similarly, we may have underestimated cancer risk for some women because of non-tobacco risk factors, such as obesity, alcohol misuse or history of childhood cancer.[300-302] Third, we did not consider women's likely preference for tests that are easier and cheaper to obtain. Fourth, in July 2020, the USPSTF proposed to expand lung cancer screening, which we did not consider.[303]

Future studies should expand our work beyond cancer screenings. An ongoing pilot trial seeks to help prioritize all major preventive services, cancer- and non-cancer related, at a clinical level through individualized estimates of life expectancy gains (NCT03023813). Expansion to population health will require more advanced understanding of heterogeneity across patients of different race, family history, comorbidity and genetic factors. We suggest that, just like patients, health systems cannot fully emphasize all evidence-based preventive services and therefore must choose how to allocate limited resources. This theme is highly relevant during COVID-19 when social distancing limits the availability of preventive care and more broadly, may be applicable to low- and middle-income countries unable to administer all preventive services. Future work may focus attention where it is most likely to help patient populations live longer, healthier lifespans. Post-COVID-19, our results suggest that if prioritization could lead to even modest increases in patient adherence, life-years could be gained in a population.

In conclusion, **w**omen who are unwilling or unable to obtain all guideline-recommended cancer screenings may be able to reduce screening intensity with minimal impact on overall benefits. For eligible women, lung cancer screening was essential. Providers might consider these results as part of a holistic cancer screening discussion.

Appendix

Supplementary Table A7.1: Proportion of Women Up-To-Date with Each Screening Recommendation. For scenarios based on historical compliance with USPSTF cancer screening recommendations, we estimated the proportion of women up-to-date using the 2018 National Health Interview Survey (NHIS) (for breast, cervical and colorectal cancers) and the 2018 Behavioral Risk Factor Surveillance System (BRFSS) (for lung cancer, which was not available in the 2018 NHIS).[282,283] For colorectal cancer screening, we considered screening by any method.

	Cancer screening type[a]				
	Breast	**Cervical**	**Colorectal**	**Total (breast, cervical, colorectal)[b]**	**Lung**
Eligible for lung cancer screening	57.8%	60.2%	62.2%	45.0%	16.9%[b]
Ineligible for lung cancer screening	70.7%	77.3%	63.7%	52.4%	-
Total	69.5%	76.0%	63.5%	51.6%	8.7%[c]

[a] Excluding individuals with known diagnostic testing and known history of cancer at the same site. For colorectal cancer, we also excluded individuals with known history of polyp(s).
[b] Up-to-date status with lung cancer screening not included in the total because it was derived from the 2018 BRFSS.
[c] 7.6% of women not eligible for lung cancer screening reported obtaining a CT to check for lung cancer in the past 12 m. Ignoring these tests, the total share of women aged 55-80 who obtained lung cancer screening the past 12 m would be 0.2%.

Supplementary Table A7.2: More Details on Life-Years Gained from Cancer Screening with Restrictive Screening Preferences. For each cancer screening strategy shown in Table 7.1, we estimated life-years gained relative to USPSTF recommendations (with colonoscopy-based colorectal cancer screenings) and rank-ordered them. For each cancer screening strategy shown in Table 7.1, we estimated life-years gained relative to USPSTF recommendations (with colonoscopy-based colorectal cancer screenings) and rank-ordered them.

				Life-years gained from cancer screenings		
					As compared with USPSTF screening recommendations (colonoscopy-based colorectal cancer screening)	
Strategy		**Number of cancer cases**	**Number of cancer deaths**	**Life-years gained**	**Difference**	**%**
Results per 100,000 50-year-old females, unless otherwise noted						
	Full compliance with USPSTF recommendations					
	Females eligible for lung cancer screening (≤4 cancer screenings per year)					
1	**All USPSTF-recommended screenings (COL)**	**376.1**	**131.1**	**1,102.8**	**0.0**	**100%[a]**
2	All USPSTF-recommended screenings (FIT)	380.6	131.5	1,097.4	-5.4	99.5%
	Females ineligible for lung cancer screening (≤3 cancer screenings per year)					
34	**All USPSTF-recommended screenings (COL)**	**204.1**	**52.3**	**338.7**	**0.0**	**100%[a]**
35	All USPSTF-recommended screenings (FIT)	209.0	52.8	332.4	-6.3	98%
	High willingness to screen for cancer (≤3 cancer screenings per year)					
	Females eligible for lung cancer screening					
5	**Biennial breast, annual lung, add COL or cervical as appropriate.**	**376.1**	**131.8**	**1,090.1**	**-12.6**	**99%[b]**
6	Biennial breast, annual FIT and lung. Obtain cervical in non-breast.	380.6	132.4	1,084.7	-18.0	98%
	Medium willingness to screen for cancer (≤2 cancer screenings per year)					
	Females eligible for lung cancer screening					
15	**Annual lung, alternate breast and FIT, skip for cervical.**	**388.0**	**133.5**	**1,064.7**	**-38.0**	**97%[b]**
13	Biennial breast, annual lung, skip lung for COL and cervical.	376.3	133.4	1,050.3	-52.5	95%
11	**Annual lung and FIT.**	**385.9**	**140.5**	**974.5**	**-128.2**	**88%[a]**
12	Annual lung, biennial breast.	429.4	148.6	901.0	-201.8	82%
14	Annual FIT, alternate breast and lung, skip for cervical.	379.9	147.4	831.6	-271.1	75%
10	Annual FIT, biennial breast.	374.1	194.5	254.2	-848.6	23%

table continues

				Life-years gained from cancer screenings		
					As compared with USPSTF screening recommendations (colonoscopy-based colorectal cancer screening)	
Strategy		**Number of cancer cases**	**Number of cancer deaths**	**Life-years gained**	**Difference**	**%**
9	Biennial breast, add cervical as appropriate.	414.9	206.3	122.8	-979.9	11%
	Females ineligible for lung cancer screening					
38	**Biennial breast, add COL and cervical within 1 year of recommendation.**	**204.4**	**52.2**	**335.1**	**-3.5**	**99%[b]**
39	Biennial breast, annual FIT, skip breast for cervical.	209.7	53.6	315.1	-23.6	93%
10[a]	**Biennial breast, annual FIT.**	**212.0**	**54.9**	**302.2**	**-36.5**	**89%[a]**
9	Biennial breast, add cervical as appropriate.	252.7	66.9	159.8	-178.9	47%
	Low willingness to screen for cancer (≤1 cancer screening per year)					
	Females eligible for lung cancer screening					
28	**Alternate breast and lung, skip for COL. Omit cervical.**	**379.4**	**148.4**	**841.7**	**-261.0**	**76%[b]**
22	**Annual lung only**	**430.7**	**154.9**	**810.7**	**-292.1**	**74%[a]**
27	Alternate breast and lung, skip for COL and cervical.	375.4	149.7	803.8	-298.9	73%
26	Alternate FIT and lung. Omit cervical, breast.	388.2	155.4	759.6	-343.2	69%
25	Alternate FIT and lung, skip for cervical. Omit breast.	386.4	154.1	750.3	-352.5	68%
29	Alternate FIT, breast, and lung. Omit cervical.	390.0	157.8	715.7	-387.0	65%
23	Alternate FIT and breast, skip for cervical.	376.8	193.7	256.1	-846.6	23%
24	Alternate FIT and breast. Omit cervical, lung.	379.1	195.3	240.9	-861.8	22%
20	COL only	370.9	200.3	169.2	-933.5	15%
21	FIT only	375.4	200.8	163.9	-938.9	15%
18	Biennial breast only	418.9	208.9	90.3	-1,012.5	8%
19	Cervical only	416.2	212.5	32.5	-1,070.2	3%
	Females ineligible for lung cancer screening					
42	**Biennial breast, add COL and cervical within 1 year of recommendation but skip an occasional mammogram.**	**205.0**	**53.0**	**318.7**	**-19.9**	**94%[b]**
24	Alternate FIT and breast. Omit cervical.	217.0	55.8	286.5	-52.5	85%

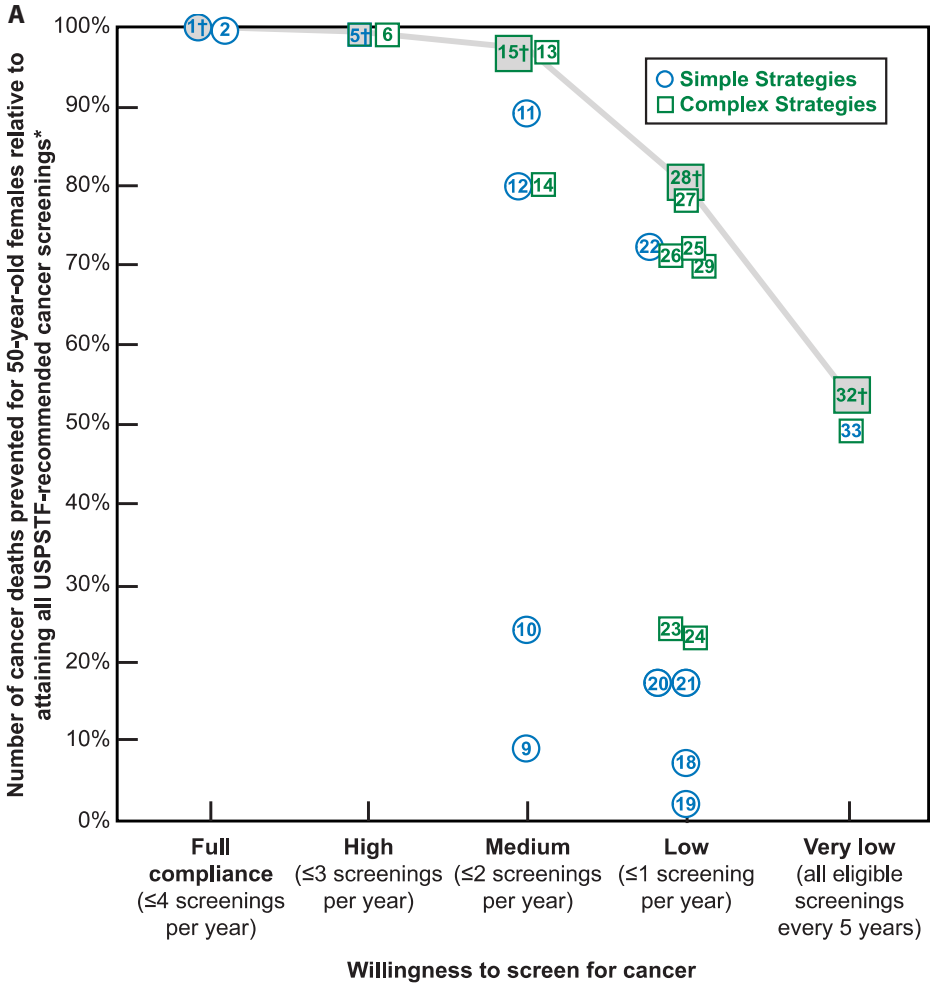
table continues

				Life-years gained from cancer screenings		
					As compared with USPSTF screening recommendations (colonoscopy-based colorectal cancer screening)	
Strategy		**Number of cancer cases**	**Number of cancer deaths**	**Life-years gained**	**Difference**	**%**
23	Alternate FIT and breast, skip for cervical.	219.5	57.4	268.6	-70.1	79%
20	**COL only.**	**210.8**	**62.0**	**178.9**	**-159.8**	**53%[a]**
21	FIT only.	215.6	62.5	172.6	-166.1	51%
18	Biennial breast only.	256.1	69.4	123.4	-215.3	36%
	Very low willingness to screen for cancer (all screenings once every 5 years)					
	Females eligible for lung cancer screening					
32	**All recommended screenings once every 5 years (COL)**	**371.3**	**170.2**	**564.1**	**-538.6**	**51%[b]**
33	All recommended screenings once every 5 years (FIT)	388.7	173.2	525.7	-577.1	48%
	Females ineligible for lung cancer screening					
44	**All recommended screenings once every 5 years (COL)**	**206.1**	**56.2**	**273.5**	**-65.1**	**81%[b]**
45	All recommended screenings once every 5 years (FIT)	223.8	59.5	228.6	-110.1	68%
	No screening					
	Females eligible for lung cancer screening					
	No screening	420.2	215.2	0.0	-1,102.8	0%
	Females ineligible for lung cancer screening					
	No screening	259.4	76.6	0.0	-338.7	0%

USPSTF - United States Preventive Services Task Force; COL – Colonoscopy; FIT - Fecal immunochemical test.

[a] Top-ranked simple strategy, stratified by willingness to screen for cancer and eligibility for lung cancer screening.

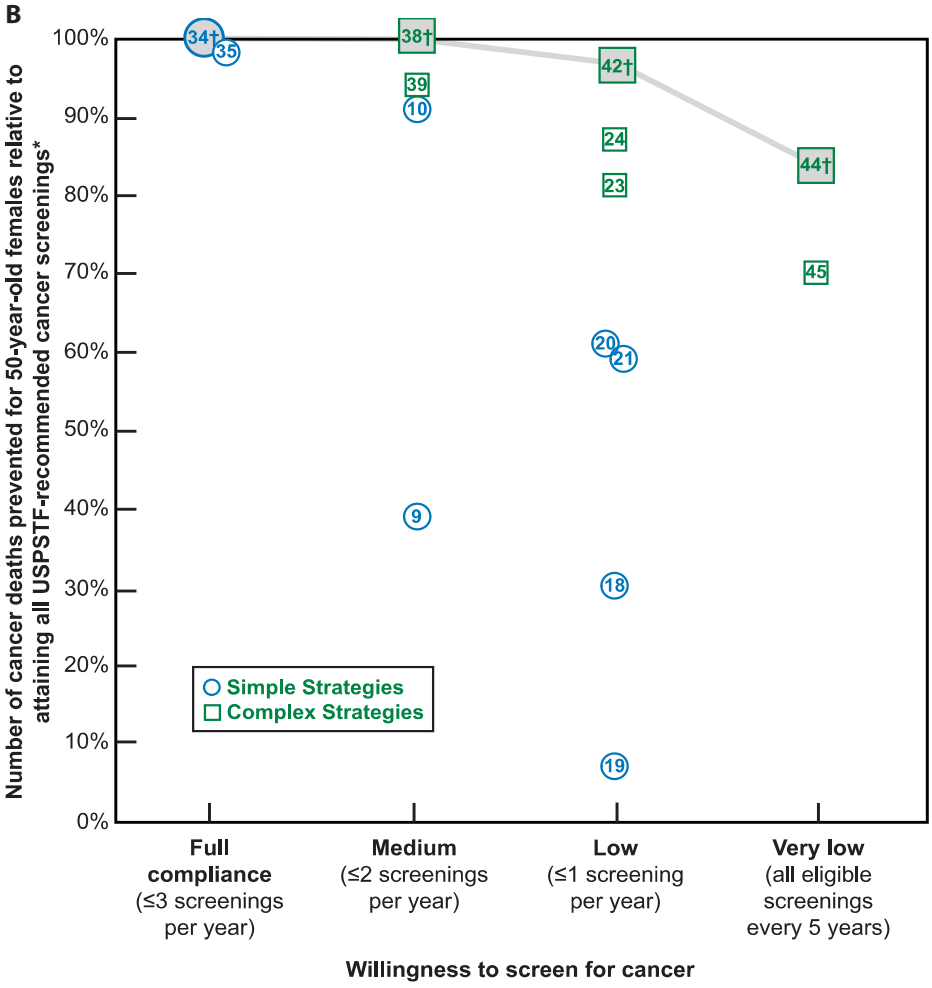
[b] Top-ranked complex strategy, stratified by willingness to screen for cancer and eligibility for lung cancer screening.

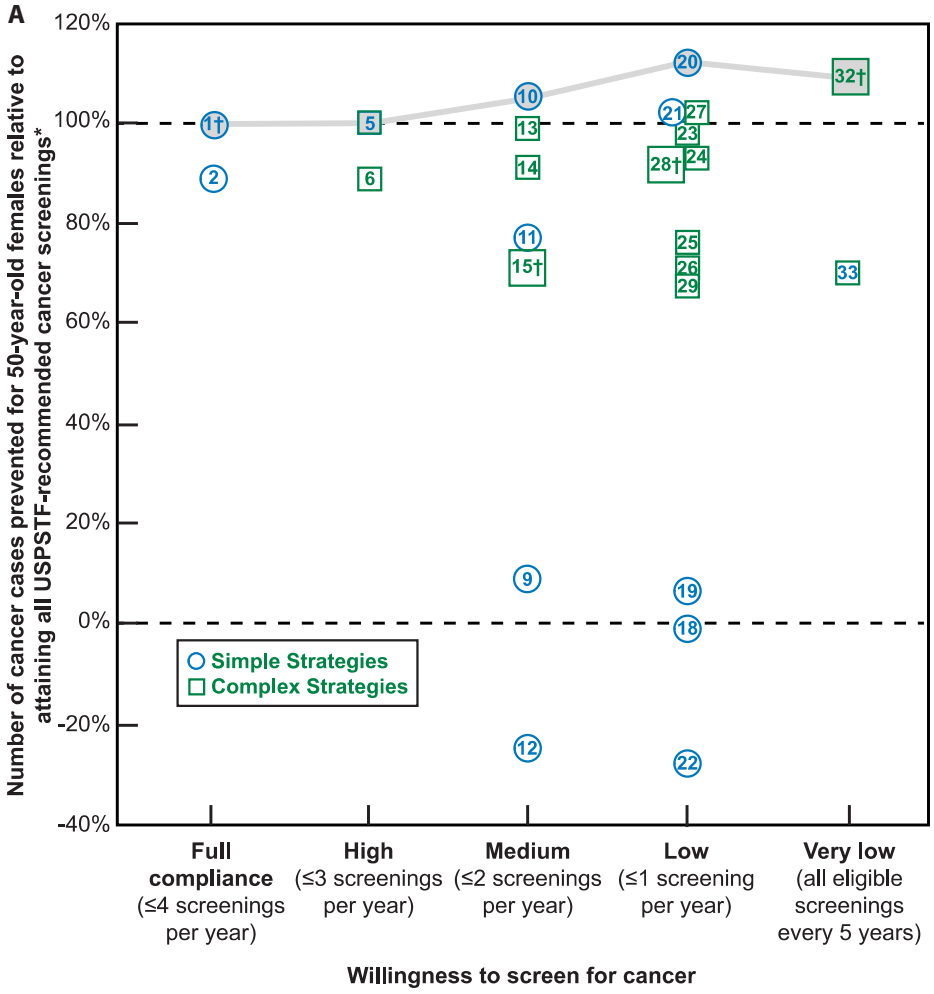


Supplementary Figure A7.1: Alternate outcome: Number of cancer deaths prevented for restrictive cancer screening strategies, as compared with USPSTF recommendations. **A**: Females eligible for lung cancer screening. **B**: Females ineligible for lung cancer screening. We repeated the analysis in Figure 7.2 with an alternate outcome of number of breast, cervical, colorectal and lung cancer deaths prevented. Gray shading denotes top-ranked strategies, which are connected by a gray line. Strategy numbers are shown in Table 7.1.

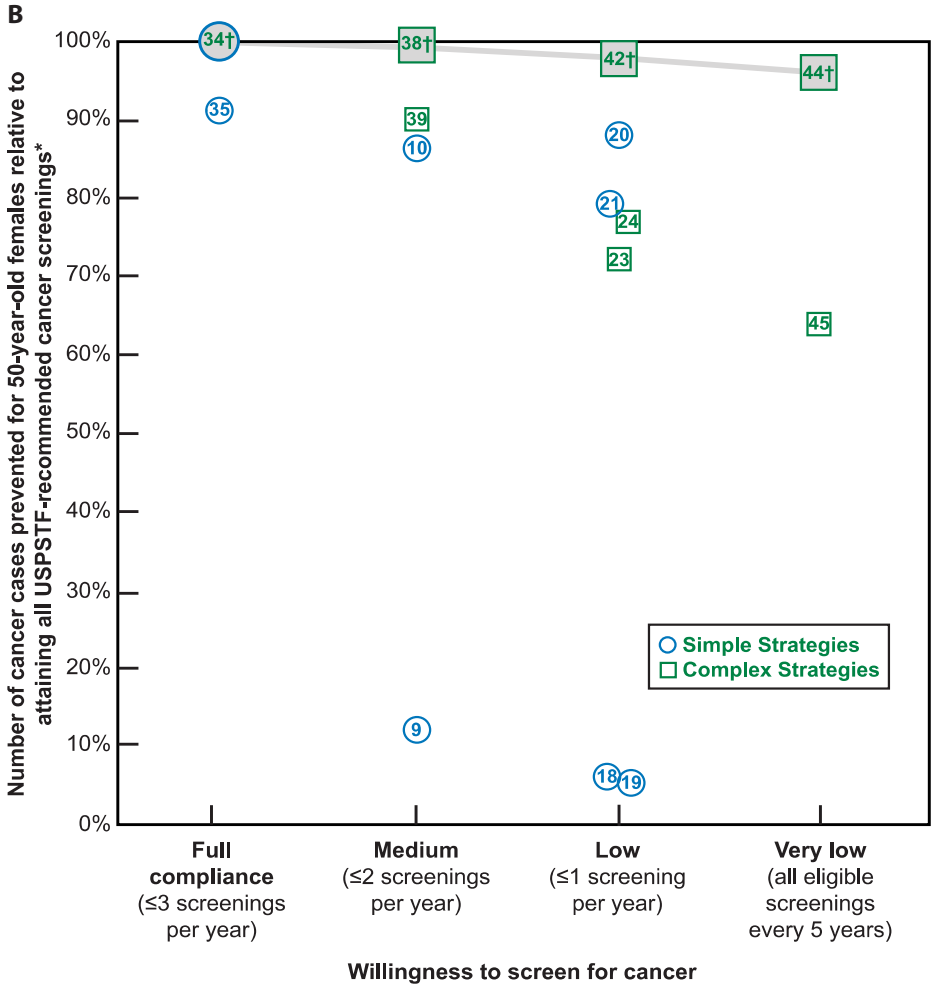
*Number of cancer deaths from attaining all USPSTF-recommended cancer screenings, with colonoscopy: 131.1 per 1,000 50-year-old females eligible for lung cancer screening and 52.3 per 1,000 50-year old females ineligible for lung cancer screening.

†Denotes a top-ranked cancer screening strategy in the base case analysis of Figure 7.2.


B
Number of cancer deaths prevented for 50-year-old females relative to attaining all USPSTF-recommended cancer screenings*
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
34†
35
38†
39
10
42†
24
23
44†
45
20
21
9
18
19
Simple Strategies
Complex Strategies
Full compliance (≤3 screenings per year)
Medium (≤2 screenings per year)
Low (≤1 screening per year)
Very low (all eligible screenings every 5 years)
Willingness to screen for cancer



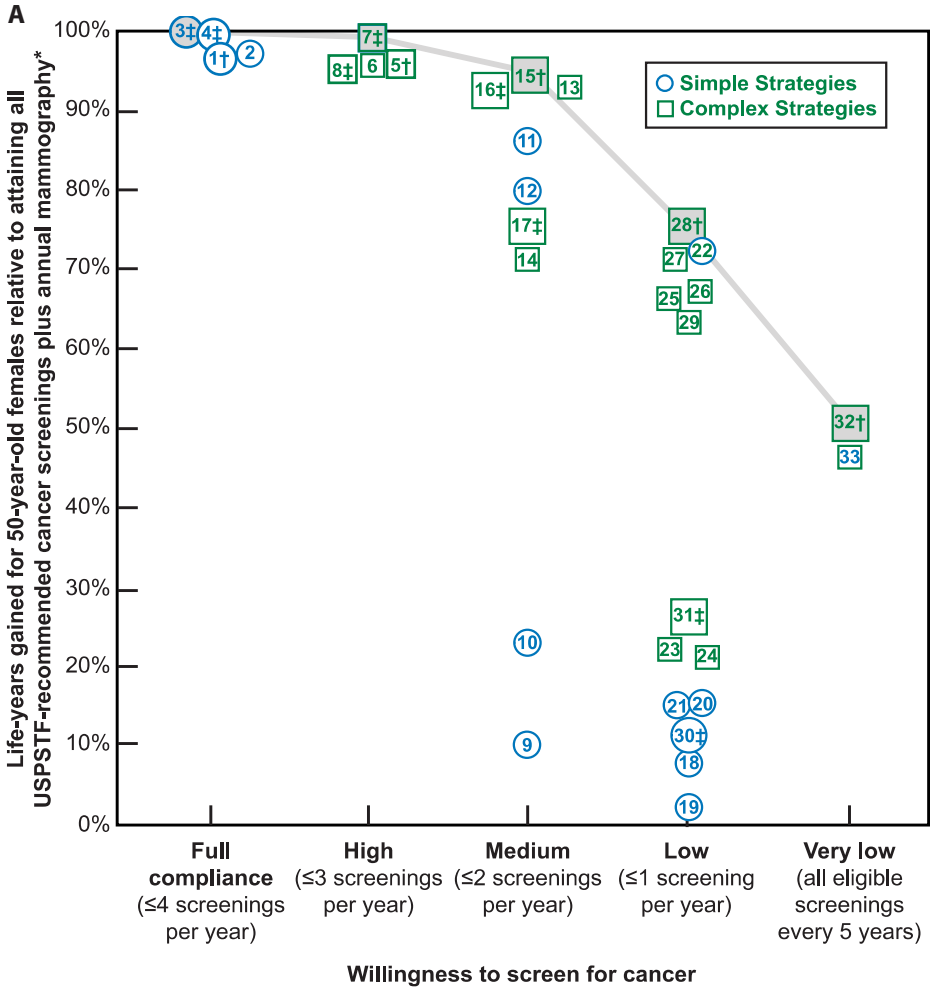
Supplementary Figure A7.2: Alternate outcome: Number of cancer cases prevented for restrictive cancer screening strategies, as compared with USPSTF recommendations. **A**: Females eligible for lung cancer screening. **B**: Females ineligible for lung cancer screening. We repeated the analysis in Figure 7.2 with an alternate outcome of number of breast, cervical, colorectal and lung cancer cases prevented. Gray shading denotes top-ranked strategies, which are connected by a gray line. Strategy numbers are shown in Table 7.1. Numbers exceeding 100% suggest that a restricted cancer screening strategy detected fewer cancer cases than the USPSTF-recommended strategy because of reduced overdiagnosis. However, because some life-threatening cancers were not detected, these strategies may have been associated with increased mortality as compared with USPSTF recommendations (Supplementary Figure A7.1).



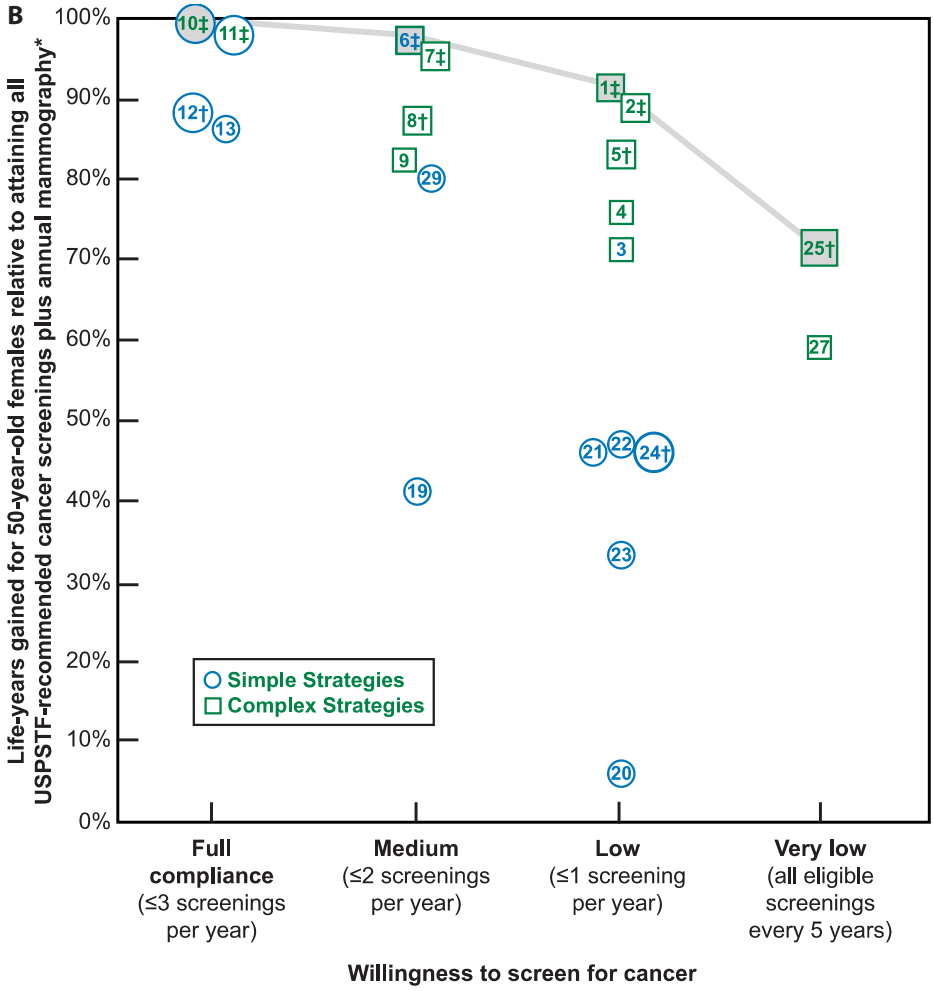
Negative numbers were possible for lung and breast cancer screenings, which detected but did not prevent cancers. In these cases, a restricted cancer screening strategy detected more cancer cases than a no screening scenario (overdiagnosis) without offsetting prevention of unscreened cancers.

* Number of cancer cases from attaining all USPSTF-recommended cancer screenings, with colonoscopy: 376.1 per 1,000 50-year-old females eligible for lung cancer screening and 204.1 per 1,000 50-year old females ineligible for lung cancer screening.

†Denotes a top-ranked cancer screening strategy in the base case analysis of Figure 7.2.



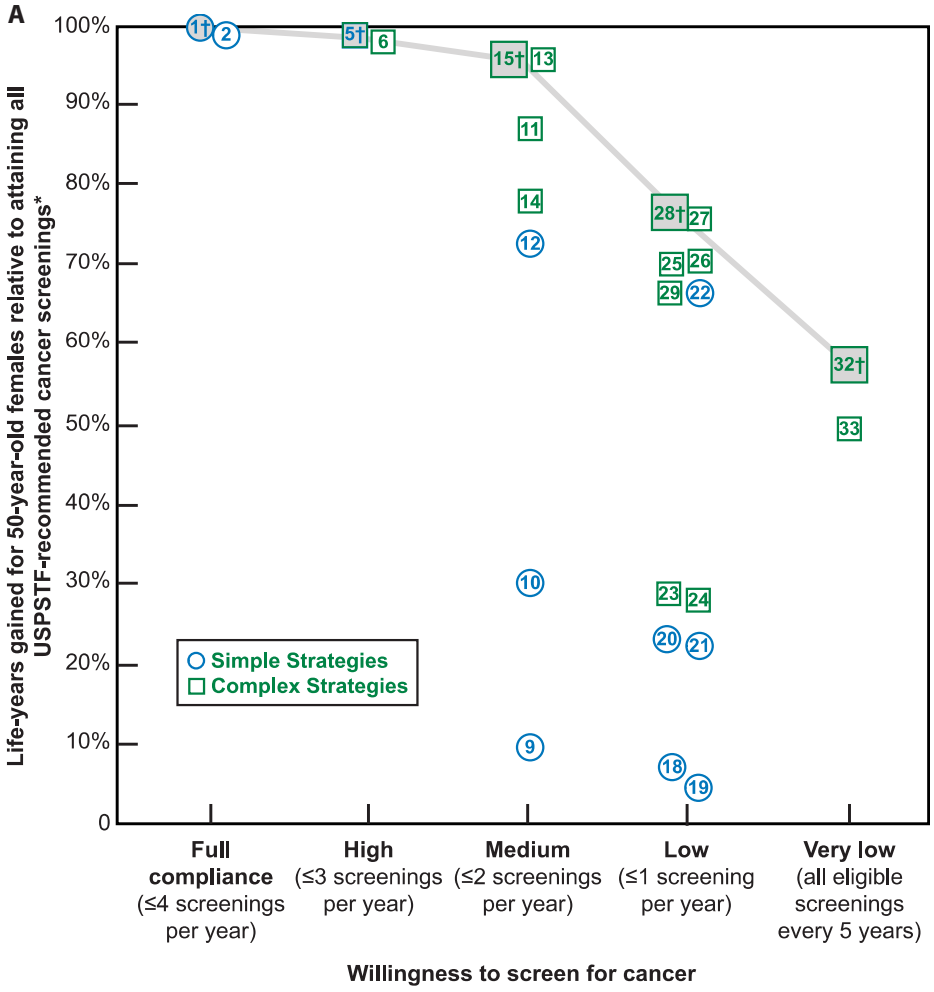
Supplementary Figure A7.3: Alternate outcome: Number of life-years gained for restrictive cancer screening strategies, as compared with attaining all USPSTF-recommended cancer screenings plus annual mammography**. A**: Females eligible for lung cancer screening.
B: Females ineligible for lung cancer screening. The American Cancer Society (ACS) recommends that women be offered the option of starting annual mammograms between ages 40-44 y, then annual mammography between ages 45-54 y and a choice of annual or biennial mammography as long as a woman is in good health and expected to live 10 y or longer. Therefore, we repeated the analysis in Figure 7.2 with an alternate comparison to life-years gained from attaining all USPSTF-recommended cancer screenings plus annual mammography. Gray shading denotes top-ranked strategies, which are connected by a gray line. Strategy numbers are shown in Table 7.1.
* Number of life-years gained from attaining all USPSTF-recommended cancer screenings, with colonoscopy, plus annual mammography:



1,134.6 per 1,000 50-year-old females eligible for lung cancer screening and 383.6 per 1,000 50-year old females ineligible for lung cancer screening.

†Denotes a top-ranked cancer screening strategy in the base case analysis of Figure 7.2.

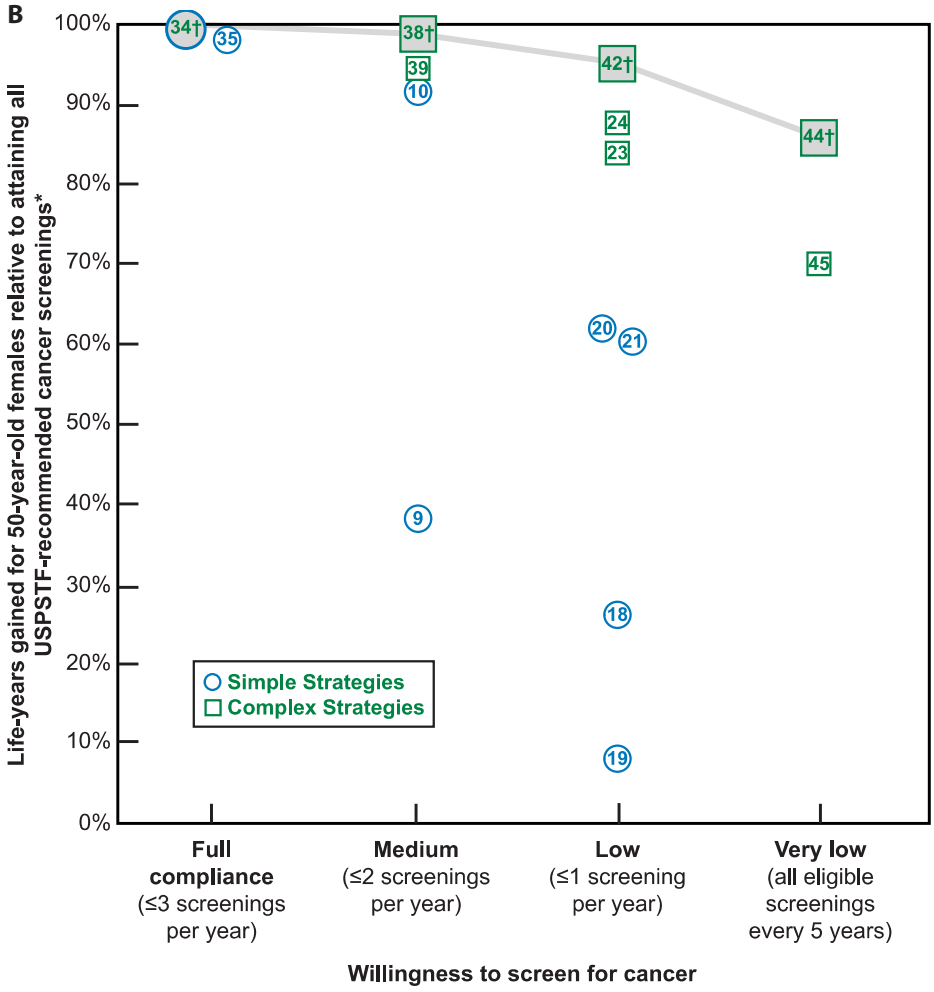
‡Denotes a cancer screening strategy with annual mammography.

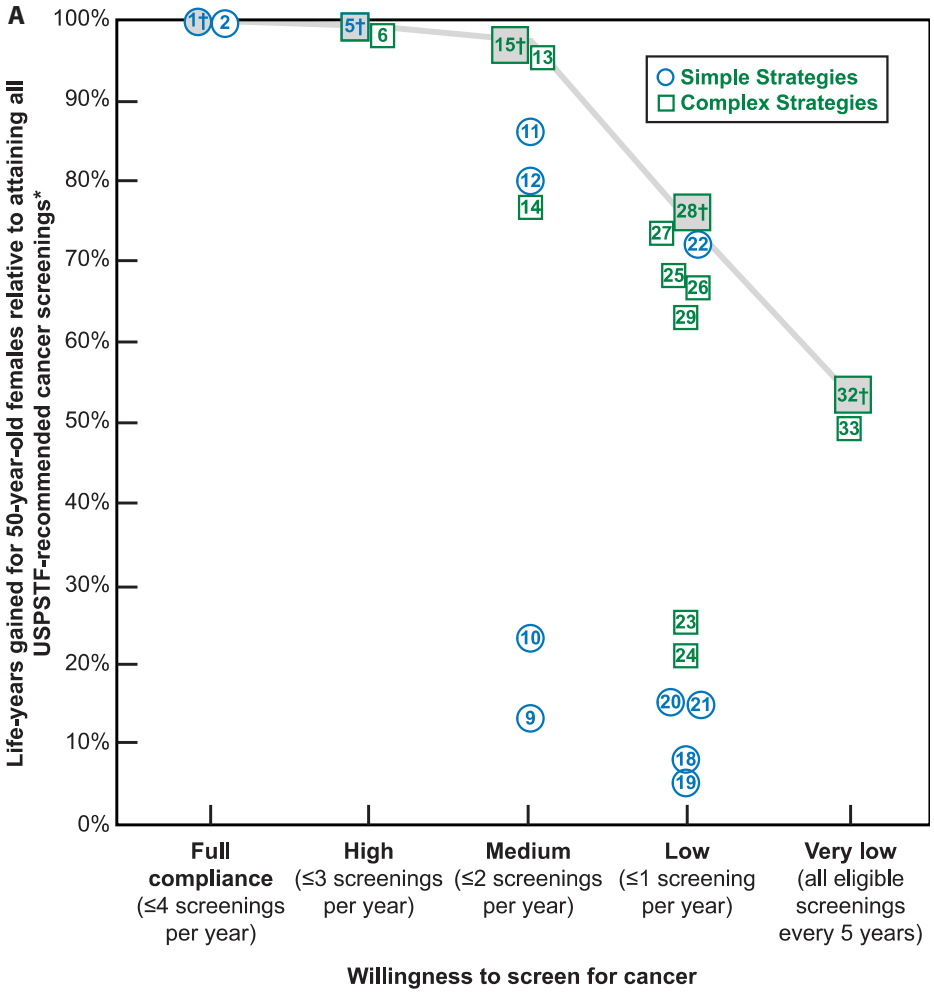


Supplementary Figure A7.4: Sensitivity Analysis: Higher background risk of developing colorectal cancer. **A**: Females eligible for lung cancer screening. **B**: Females ineligible for lung cancer screening. We repeated the analysis in Figure 7.2 for a cohort of women with a higher risk of developing colorectal cancer, reflective of recent higher incidence in young adults. Gray shading denotes top-ranked strategies, which are connected by a gray line. Strategy numbers are shown in Table 7.1.

*Number of LYG from attaining all USPSTF-recommended cancer screenings, with colonoscopy: 1,213.6 per 1,000 50-year-old females eligible for lung cancer screening and 453.6 per 1,000 50-year old females ineligible for lung cancer screening.

†Denotes a top-ranked cancer screening strategy in the base case analysis of Figure 7.2.

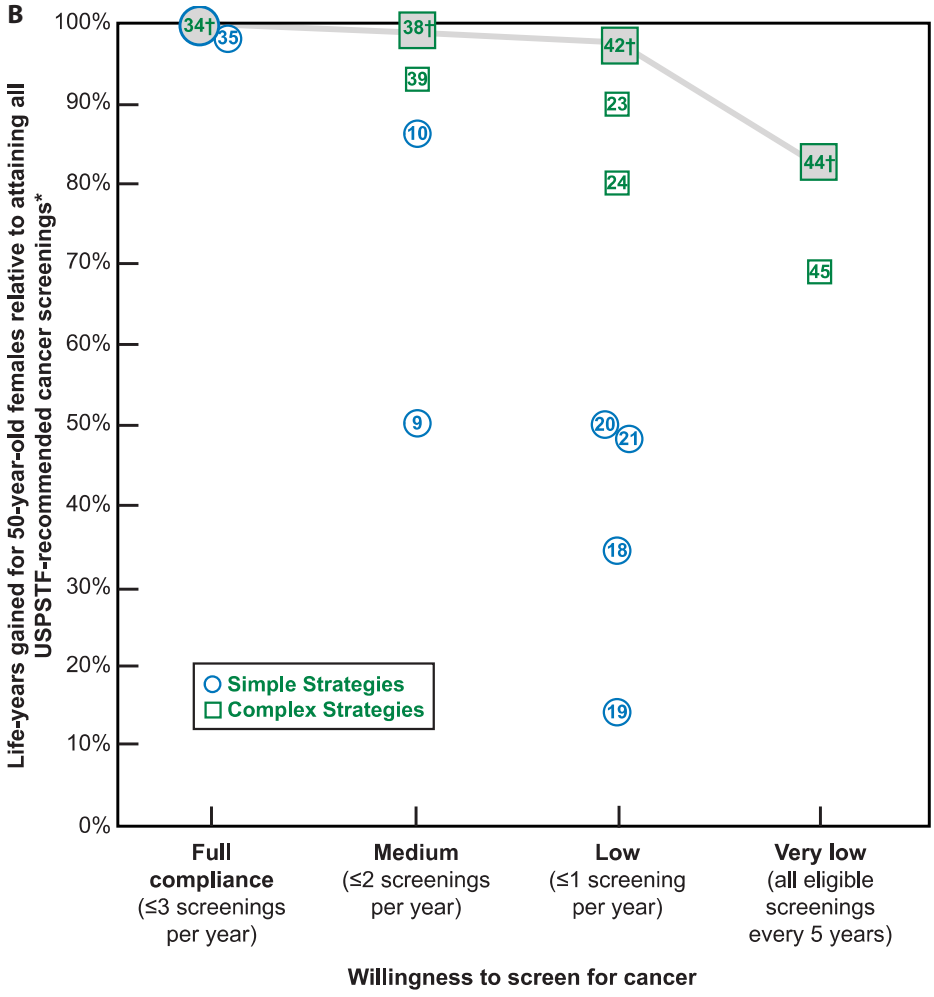

B
Life-years gained for 50-year-old females relative to attaining all USPSTF-recommended cancer screenings*
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
34†
35
38†
39
10
42†
24
23
44†
45
20
21
9
18
19
Simple Strategies
Complex Strategies
Full compliance (≤3 screenings per year)
Medium (≤2 screenings per year)
Low (≤1 screening per year)
Very low (all eligible screenings every 5 years)
Willingness to screen for cancer



Supplementary Figure A7.5: Sensitivity Analysis: Women with no cervical cancer screening before age 50 y. **A**: Females eligible for lung cancer screening. **B**: Females ineligible for lung cancer screening. We repeated the analysis in Figure 7.2 for a cohort of women with no cervical cancer screening before age 50 y. Gray shading denotes top-ranked strategies, which are connected by a gray line. Strategy numbers are shown in Table 7.1.

*Number of life-years gained from attaining all USPSTF-recommended cancer screenings, with colonoscopy: 1,112.8 per 1,000 50-year-old females eligible for lung cancer screening and 348.9 per 1,000 50-year old females ineligible for lung cancer screening.

†Denotes a top-ranked cancer screening strategy in the base case analysis of Figure 7.2.


B
Life-years gained for 50-year-old females relative to attaining all USPSTF-recommended cancer screenings*
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
34†
35
38†
39
10
9
42†
23
24
20
21
18
19
44†
45
Simple Strategies
Complex Strategies
Full compliance (≤3 screenings per year)
Medium (≤2 screenings per year)
Low (≤1 screening per year)
Very low (all eligible screenings every 5 years)
Willingness to screen for cancer

Chapter 8

Comparative effectiveness and cost-effectiveness of mailed-out fecal immunochemical tests versus collection at general practitioner

Elisabeth F.P. Peterse, Caroline B. Osoro, Marc Bardou & Iris Lansdorp-Vogelaar

Submitted

Abstract

Introduction

Participation in colorectal cancer (CRC) screening in France has been well below the 45% considered acceptable by European guidelines, potentially attributable to the need to collect the Faecal Immunochemical Test (FIT) at the general practitioner. The aim of this study was to estimate the potential benefits and costs of including the FIT in the invitation letter.

Methods

A well-established microsimulation model was used to simulate the French population 35 years and older in 2018 and estimate quality-adjusted life-years gained (QALYG) and costs of the current screening program, as well as a variation of the program where the FIT was mailed to participants and adherence was assumed to increase to 45%. We also estimated the threshold increase in participation needed to make this intervention cost-effective.

Results

Under the current program, 53.8 CRC cases and 25.2 CRC deaths per 1,000 individuals are expected to occur over a lifetime. If sending out the FIT increases screening participation from the current 32.2% to 45%, this intervention would result in 6% fewer CRC deaths and 3% fewer cases, resulting in an estimated cost-effectiveness ratio of €2,149 per QALYG. Sending out the FIT would only need to increase participation by 0.7% point for this intervention to be considered cost-effective.

Conclusion

Including the FIT in the invitation letter is likely a very cost-effective intervention to increase participation in CRC screening. These results for France are also informative for many other countries around the world where FIT needs to be collected at pharmacies or general practitioners.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide with 1.8 million new cases and 881,000 deaths estimated to have occurred in 2018.[1] It is a growing public health concern due to both ageing of the population and change in dietary as well as physical activity patterns in economically transitioning countries.[304] The disease has a slow progression from adenoma to carcinoma and good patient outcomes following early detection. As such, with diagnosis and treatment of (pre-) cancerous lesions, screening offers significant health and economic benefits.[305,306] The European Union recommends population-based screening for colorectal cancer with regular monitoring at adequate intervals. It considers a participation rate of 45% as acceptable which would result in at least 15% reduction in CRC mortality.[307]

Population-based biennial screening using guaiac faecal occult blood test (gFOBT) was implemented in France in 2009 for ages 50-74 years, shifting to the Fecal immunochemical test (FIT) in 2015.[308] From the start, participation and adherence to screening has been low (~34%),[309] and even dropped significantly to 23.1% in 2014-2015 at the switch from gFOBT to FIT.[310] This participation rate is much lower (32.3% in 2017-2018), than that in neighbouring European countries.[311] The low level of participation in screening can potentially be explained by the requirement for participants to visit their General Practitioner (GP) to collect the test.

Compared to encouraging participants to visit their GP, mailed-out FIT with the invitation letter has been found to result in significantly higher participation rates.[312] In a campaign with the rollout of FIT in France in 2015, compliance to screening increased when the test kit was mailed to non-participants (45%) as compared to only a reminder letter (28%).[313] A case could be made that should France or any other country mail the FIT to individuals eligible for screening, screening participation rates may increase. However, the costs incurred in mailing the FIT might present an economic barrier. Currently, it is not known whether the additional benefits of mailing the FIT outweigh the extra costs.

The aim of this study was to estimate the potential impact of including the FIT in the invitation letter on the benefits, costs and cost-effectiveness of the French colorectal cancer screening program.

Materials and methods

MISCAN-Colon

The microsimulation screening analysis model for CRC (MISCAN-Colon) used for this study was developed at the Department of Public Health of Erasmus MC, University Medical Centre Rotterdam (the Netherlands). The model has been essential in informing CRC screening policies in the Netherlands,[156] the U.S.,[99] Australia,[157] and other European countries.[314] It simulates the individual life histories of a large population

from birth to death. Each simulated individual ages over time and may develop one or more adenomas. Adenomas may progress in size from small (≤5 mm) to medium (6–9 mm) to large (≥10 mm), and some adenomas will become malignant. Cancer can progress from a localized stage I cancer to a metastasized stage IV cancer. By comparing life histories in the presence and absence of screening, the model evaluates the effect of screening. The MISCAN model structure and underlying assumptions have been extensively described in a previous publication[315] and in the **Model Appendix**. For this project, MISCAN-colon was adjusted to replicate the French population. To do so, we used national data on colorectal cancer incidence [316] and stage distribution,[317] as well as 5-year CRC survival.[318] We assumed that the adenoma onset was different but not the progression of the disease.

Population simulated according to the French screening programme

We simulated an average-risk 35 to 75-year-old French population in 2018 following the French national colorectal cancer screening program and followed them for a lifetime. Eligible 50 to 74-year-old adults were offered biennial screening using guaiac faecal occult blood test between 2009 and 2014 and faecal immunochemical test after April 2015. We used data from the Santé Publique France to inform screening participation in 2017 and 2018 (32.3%).[319] Screening participation in 2016 was assumed at 28.6%.[311] Screening participation from 2009 to 2015 was based on four rounds of a population-based open cohort study from Alsace, eastern France.[320] Furthermore, we assumed a 91% participation rate for diagnostic colonoscopy after a positive FIT.[320] Participants with negative colonoscopy findings returned to the screening program after 5 years. For those with adenomas detected, surveillance colonoscopy was offered, every three to five years depending on the number and size of adenomas, in line with the French guidelines, assuming an adherence of 80%.[321]

Test characteristics for gFOBT, FIT, and colonoscopy were based on previous studies (**Supplementary Table A8.1**).[322] FIT characteristics were selected that reproduced the adenoma and CRC detection rate observed in the French population.[310]

Future screening scenarios

For screening after 2019, four scenarios were simulated that differed with respect to the method of invitation and the assumed FIT participation:

1. Current program: we assumed no changes in the program and the participation rate in 2018 would remain constant in subsequent years.
2. Mailed FIT, no increase in participation: we assumed that the FIT would be mailed with the invitation letter without an increase in participation.
3. Mailed FIT with direct increase in participation: we assumed that sending the FIT kit with the invitation letter would result in an immediate increase in participation rate to 45%.[313]
4. Mailed FIT with gradual increase in participation: rather than an immediate increase in participation, a gradual increase was evaluated, assuming 45% screening participation from 2028 onwards.

In all mailed FIT scenarios, we assumed that 10% of participants would still consult their General practitioner after receiving the FIT in the mail.

Analysis

For all four scenarios, we estimated the number of colorectal cancer cases and deaths, the number of eligible participants invited to screening, the QALYs gained as well as the costs incurred when compared to the current screening program. We applied a 3 percent annual discount rate on quality-adjusted life years gained and costs.

The QALYs gained and the total cost were used to calculate the incremental cost-effectiveness ratio (ICER) of mailed out FIT compared to the current situation to determine the cost effectiveness of mailing the FIT kit with the invitation letter. Costs were evaluated from the perspective of the French Health Care Insurance system[323,324] and were inflation-adjusted to 2017 euros (**Supplementary Table A8.2**).[325] We assumed the price of the FIT kit to be €6.79[323] and the cost of mailing the FIT to a participant as €1.41.[326] Disutility associated with colonoscopy and CRC treatment, to estimate quality-adjusted life-years (QALYs), have been published previously and are reported in **Supplementary Table A8.3.**[171,327]

Threshold analysis

Because the true effect on screening participation of sending the FIT with the invitation letter is unknown, we determined the threshold increase in participation rate needed for mailed out FIT to be cost-effective compared to the current programme. As there is no threshold defined by the French Health Authorities, we used €30,000 per QALY gained as the threshold for cost-effectiveness, which is similar to the GDP per capita as put forward by the WHO commission on Macroeconomics and Health.[328]

Sensitivity analyses

We evaluated the robustness of our results to the following assumptions: We assumed a ten percent higher or ten percent lower CRC incidence, a higher and lower FIT cut-off, 25% higher and lower treatment costs, 25% higher and lower FIT costs as well as 30% of participants consulting their GP after receiving the mailed FIT with the invitation letter.

Results

In a scenario without screening, we estimated 61.6 colorectal cancer cases and 31.5 deaths per 1,000 individuals over a lifetime. With the current invitation method, we estimated 53.8 colorectal cancer cases and 25.2 deaths per 1,000 individuals. The QALYs gained were 38.9 per 1,000 individuals, and total costs were €1.088 million per 1,000 people resulting in an ICER of €248 per QALY gained compared to no screening (**Table 8.1**). When the new invitation method was implemented without an increase in participation, the benefits of screening would not change, but the total cost increased by 1.2% to €1.101 million per 1,000 people. If mailing the FIT kit would result in an immediate increase in participation to 45%, there were 6% fewer colorectal cancer

deaths (1.5 per 1,000), 3% fewer cases (1.6 per 1,000) and 21% more QALYs gained compared to the existing invitation method. The total cost would be 1.6% higher at €1.105 million per 1,000 individuals, resulting in an ICER of €2,149 per QALY gained compared to the current invitation method. If participation increased gradually to 45%, there were 5% fewer colorectal cancer deaths (1.2 per 1,000), 2% fewer cases (1.3 per 1,000) and 16% more QALYs gained compared to the current situation. The total cost would be 1.5% higher (€1.104 million per 1,000 people), with an ICER of €2.604 per QALY gained compared to the current situation (Table 8.1).

Table 8.1: Outcomes per 1,000 individuals for the evaluated scenarios

Scenario	CRC cases	CRC deaths	QALYs gained	Screening costs[a] (€)	Diagnostic colonoscopy costs (€)	Surveillance colonoscopy cost (€)
No screening	61.6	31.5	0	0	39,138	0
Current invitation	53.8	25.2	38.9	59,061	87,503	55,296
New invitation (no increase)	53.8	25.2	38.9	72,349	87,503	55,296
New invitation (immediate increase)	52.2	23.7	47.1	77,527	103,631	67,512
New invitation (gradual increase)	52.5	24.0	45.1	76,346	99,761	64,265

Scenario	Care costs (€)	Total costs (millions) (€)	Net costs (€)	Cost (€) /QALY gained compared to no screening	ICER compared to current situation
No screening	1,039,213	1.078	NA	NA	NA
Current invitation	886,138	1.088	9,648	248	NA
New invitation (no increase)	886,138	1.101	22,935	589	NA
New invitation (immediate increase)	856,807	1.105	27,126	576	2,149
New invitation (gradual increase)	863,701	1.104	25,721	570	2,604

CRC - colorectal cancer; QALY - Quality-adjusted life-years; ICER - Incremental cost-effectiveness ratio

[a] Screening costs include : organization, information, FIT kit, postage, lab analysis and General practitioner consultation costs.

Cost-effectiveness threshold analyses

Even with considerably lower increases in participation, mailing out the FIT still remained a highly cost-effective intervention. For example, at a 5% point immediate increase in participation, the ICER of mailed FIT versus current programme is €4,584 per QALY gained. With an immediate increase in participation, the increase need only be 0.7% point for the mailed FIT to be cost-effective at a willingness-to-pay threshold

of €30,000 per QALY gained (**Figure 8.1**). If the increase in participation was gradual rather than immediate, an increase in participation of 1.0% point was needed to make mailed out FIT cost-effective.

Sensitivity analyses

Alternative assumptions regarding CRC incidence, FIT cut-off, treatment costs, FIT costs and consultation of general practitioner did not change our findings. ICERs for the new invitation method varied between €1,248 and €3,051 per QALY gained when an immediate increase in participation to 45% was assumed and between €1,609 and €3,628 per QALY gained with a gradual increase in participation (**Supplementary Table A8.4**). Variation in treatment cost had the most impact on the ICER with €3,051 per QALY gained in a scenario with 25% lower treatment costs and €1,248 for 25% higher treatment costs (**Figure 8.2**). In all sensitivity analyses, participation would not need to increase by more than 1.1% point in case of immediate increase in participation and not more than 1.4% point in case of gradual increase for the mailing of the FIT to be cost-effective at a willingness-to-pay threshold of €30,000/QALY gained (**Table 8.2**).

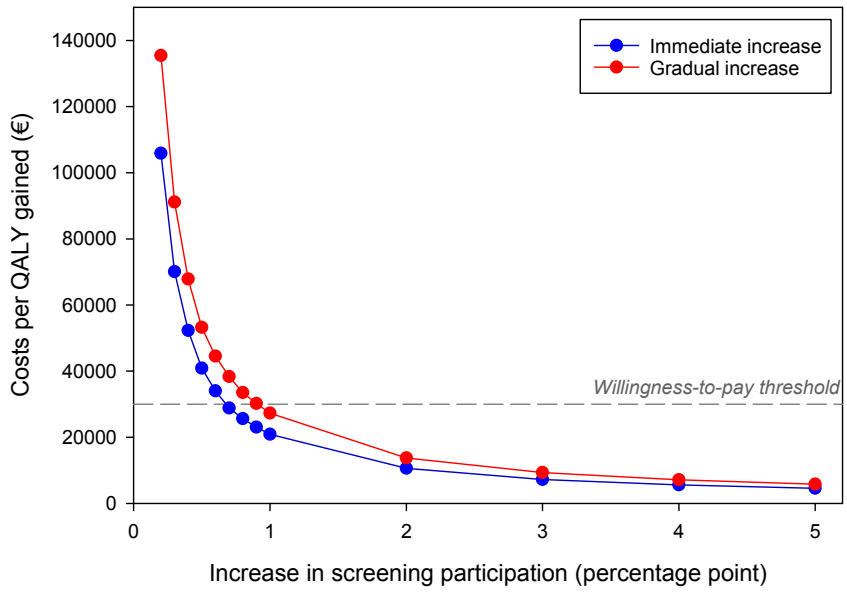


Figure 8.1: Predicted cost per QALY gained for mailed FIT by percentage-point increase in adherence compared to the current situation.

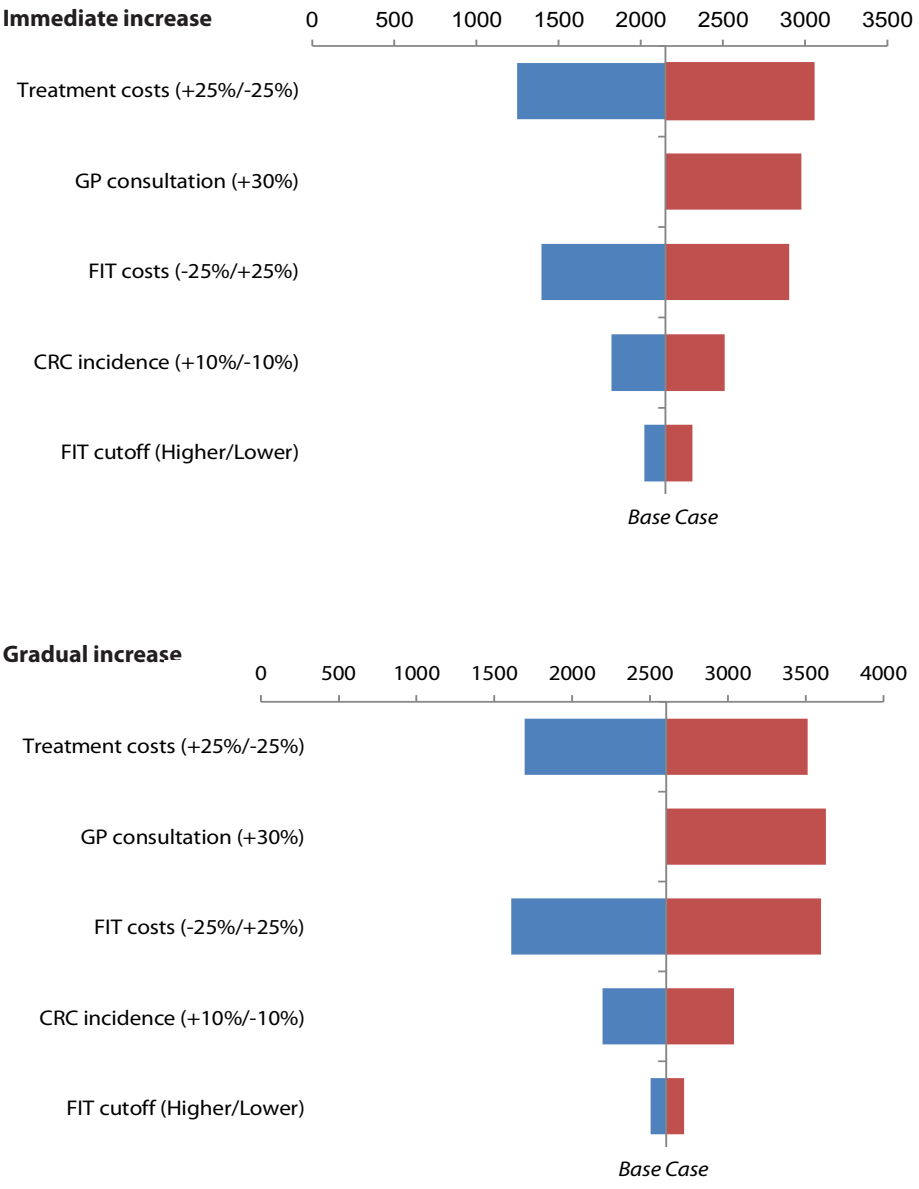


Figure 8.2: Incremental cost-effectiveness ratios (ICERs) for the sensitivity analyses scenarios assuming an immediate or a gradual increase in participation to 45%.

Table 8.2: Predicted percentage point increase in adherence compared to the current situation for the sensitivity scenarios.

Sensitivity scenario	% point increase needed (WTP €30,000/QALY) for immediate increase in participation	% point increase needed (WTP €30,000/QALY) for gradual increase in participation
10% higher CRC incidence	0.7	0.8
10% lower CRC incidence	0.8	1.1
Higher FIT cut off	0.8	1.0
Lower FIT cut off	0.7	0.9
25% higher treatment costs	0.7	0.9
25% lower treatment costs	0.7	1.0
25% higher FIT costs	1.1	1.4
25% lower FIT costs	0.4	0.5
30% more people consulting GP	1.0	1.3

WTP - Willingness to pay threshold; QALY - Quality adjusted life year; FIT - Fecal immunochemical test; CRC - Colorectal cancer; GP - General Practitioner

Discussion

This study shows that mailing the FIT with the invitation letter, and assuming an immediate increase to 45% in participation, will result in 6% fewer colorectal cancer deaths and 3% fewer cases compared to the current situation. Assuming a gradual increase in participation compared to the current situation, our study shows that 5% fewer deaths and 2% fewer cases are expected to occur. An immediate increase in participation to 45% would result in an estimated cost-effectiveness ratio of €2,149 per QALY gained compared to €2,604 with a gradual increase. Mailing out the FIT needs to increase participation by only 0.7% point in case of an immediate increase and 1.0% point with gradual increase for it to be cost-effective at willingness-to-pay threshold of €30,000 per QALY gained.

The very low threshold participation needed may seem surprising given the substantial amount of FIT kits sent out in vain. Indeed, sending out the FIT kits increases the screening costs by 22%. However, two factors explain the modest impact required for cost effectiveness. First, if screening participation increases, more cancer cases are prevented by the removal of pre-cancerous lesions and more cancers are diagnosed at an earlier stage. This leads to substantial cost savings in CRC treatment. Second, mailing the FIT kits allows individuals to participate without consulting their GP, which leads to cost savings in GP consultation costs.

The expected impact of mailing the FIT on participation is likely to be considerably higher than the required thresholds. Several studies have demonstrated the effectiveness of mailed FIT-based screening programs.[329] A Flemish study demonstrated a 25% point

increase in participation with mailing of test kits (52.3%) versus GP collection (27.7%),[330] which is in line with results from a US study, in which a nearly double increase in colorectal cancer screening participation was reported with mailed FIT compared with a screening promotion and awareness campaign.[331] It has been argued that the French culture and not the screening program is the reason for low participation. However, looking at the countries surrounding France, this argument is unlikely with participation rates in the Netherlands at 71%[332] and 55% in Flanders.[311] Strikingly, the Basque region of Spain, bordering the Basque Region of France, has a participation rate of 72.4% in their population based screening program compared to 22.5% in the French Basque counterpart.[311] These differences point to the organization of the screening program.

A key strength of our analysis is that we made use of a well-established microsimulation model, replicating the French population and screening programme in a very detailed way. We determined the costs and benefits associated with screening using two different methods of invitation over a lifetime. Therefore, we not only included direct costs associated with the screening program but also the cost savings in treatment. However, our study also has its limitations. First, we cannot accurately predict the increase in participation with the introduction of the new invitation to screening method. Our assumption of a 45% screening participation might be conservative, as this was observed in individuals that did not participate in screening after it was proposed during a medical consultation.[313] We conducted a threshold analysis to ascertain the point at which it would be cost effective to mail the FIT kits. Second, we did not assume a difference in CRC risk between individuals that currently participate and individuals that currently do not participate in CRC screening. As we did not take the "Healthy screenee bias" [333] into account, our estimate of the cost-effectiveness of mailing the FIT kits is likely conservative. Third, we did not know if participants would consult their GP even after receiving the FIT at home. We evaluated a different GP consultation rate in a sensitivity analysis and demonstrated that this assumption minimally impacts our results. Fourth, we relied on costs from a previous study which we adjusted to 2017 rates. These costs may be outdated. As a sensitivity analysis, we assumed different scenarios with higher and lower FIT and treatment costs and found our results robust to these assumptions.

Notwithstanding these limitations, this study has important implications for the CRC screening programme in France. A shift to sending the screening test by mail with the invitation letter would likely increase participation in the screening program. We demonstrate that if it immediately increases participation by 0.7% point, mailing the FIT is already cost-effective. Low participation in a population-based colorectal cancer screening program is not a problem unique to France. Several other countries do not mail out the FIT kit, but require participants to collect it at general practitioners, pharmacies or other local health centres. Generally, participation in these countries is below 50%.[308] Since our analyses considers different rates of background CRC incidence, treatment costs, FIT cut-off and costs, as well as GP consultation, these countries could benefit from the results we present. Results may also be insightful for the many countries around Europe without organized screening programmes,[308] when planning their population-based programmes.

In conclusion, our analysis suggests that including the FIT in the invitation letter is likely a very cost-effective intervention to increase participation in CRC screening in France. These results are also informative for many other countries around the world where FIT needs to be collected at pharmacies or General practitioners.

Appendix

Supplementary Table A8.1: Per lesions sensitivity and specificity (percentage point) for Guaiac fecal occult blood test, Fecal immunochemical test and colonoscopy used in the analysis

Test	Adenoma ≤ 5mm	Adenoma 6-9mm	Adenoma = 10mm	CRC shortly before clinical diagnosis	CRC long before clinical diagnosis	Specificity
gFOBT	0	1.3	6.5	50.8	18.16	98.0
FIT	0	19.3	35.5	76.6	41.4	98.97
Colonoscopy	75	85	95	95	95	100
Alternative FIT for sensitivity analyses						
Higher cut off FIT	0	24.3	39.4	80.3	46.7	98.2
Lower cut off FIT	0	12.5	32.4	75.9	40.4	99.5

gFOBT- guaiac fecal occult blood test; FIT- Fecal immunochemical test; CRC- Colorectal cancer

Supplementary Table A8.2: Costs used in the analysis

Variable	Value (€)[a]	Sensitivity analyses	Source
Organizing cost per target individual	1.43		[323]
Information cost per target individual	0.74		[323]
GP consultation cost per target individual[b]	13.57		[323]
Cost of FIT test kit	6.79	75%/125%	[323]
Cost of laboratory analysis per FIT test kit	5.66		[323]
Cost of mailing a single FIT test kit (one way)	1.41		[326]
Diagnostic colonoscopy without polypectomy cost	937.12		[324]
Diagnostic colonoscopy with polypectomy cost	1152.08		[324]
Treatment cost			
Stage I	19902.84	75%/125%	[323]
Stage II	23155.88	75%/125%	[323]
Stage III	32816.60	75%/125%	[323]
Stage IV	39655.23	75%/125%	[323]

GP - General practitioner; FIT - Fecal immunochemical test;

[a] Costs are reported in 2017 Euros

[b] In the current scenario all participants need to consult their GP to collect the FIT. For the mailed-FIT scenarios, we assumed that 10% of participants still consult their GP. This was increased to 30% of participants in a sensitivity analysis.

Supplementary Table A8.3: Losses in utility associated with colonoscopy and colorectal cancer treatment

Colonoscopy	1 day lost per colonoscopy			
CRC from diagnosis onwards[a] (1-utility)				
	Initial treatment	*Continuous care*	*Terminal care death by CRC*	*Terminal care death by other causes*
Stage I	0.26 during first year	0.15[b]	0.75[c]	0.35[d]
Stage II	0.3 during first year	0.15[b]	0.75[c]	0.35[d]
Stage III	0.4 during first year	0.15[b]	0.75[c]	0.35[d]
Stage IV	0.75 during first year	0.15[b]	0.75[c]	0.35[d]
Sources	171	283	283	283

CRC - colorectal cancer

[a] CRC treatments were divided into three clinically relevant phases-initial, continuous and terminal care. The initial phase was defined as the first 12 months following diagnosis, the terminal phase was defined as the final 12 months of life, and the continuous phase was defined as all months between the initial and terminal phase. For patients surviving less than 24 months, the final 12 months were allocated to the terminal phase. The remaining months of observation were allocated to the initial phase.

[b] in years between initial and terminal phase.

[c] in last year before dying of CRC.

[d] in last year before dying of other causes

Supplementary Table A8.4: Outcomes per 1,000 individuals for the sensitivity analysis scenarios assuming a gradual and immediate increase in participation

Scenario	CRC cases	CRC deaths	QALYs gained	Screening costs (€)[a]	Diagnostic colonoscopy costs (€)
Higher CRC incidence					
No screening	68.3	34.9	0	0	43,382
Current invitation	59.8	28.0	42.8	58,828	94,009
New invitation (no increase)	59.8	28.0	42.8	72,051	94,009
New invitation (immediate increase)	58	26.3	51.8	77,153	110,825
New invitation (gradual increase)	58.3	26.6	49.6	75,991	106,784
Lower CRC incidence					
No screening	54.9	28.2	0	0	34,950
Current invitation	47.9	22.5	35.2	59,290	81,041
New invitation (no increase)	47.9	22.5	35.2	72,646	81,041
New invitation (immediate increase)	46.5	21.1	42.6	77,901	96,451
New invitation (gradual increase)	46.8	21.4	40.8	76,703	92,763
Higher FIT cut-off					
No screening	61.6	31.5	0	0	39,138
Current invitation	54.7	25.7	36.3	59,184	76,561
New invitation (no increase)	54.7	25.7	36.3	72,716	76,561
New invitation (immediate increase)	53.3	24.3	44	78,061	88,958
New invitation (gradual increase)	53.6	24.5	42.1	76,839	85,974
Lower FIT cut-off					
No screening	61.6	31.5	0	0	39,138
Current invitation	52.9	24.6	42.2	58,945	101,000
New invitation (no increase)	52.9	24.6	42.2	71,926	101,000
New invitation (immediate increase)	51.1	23.1	50.9	76,909	121,605
New invitation (gradual increase)	51.5	23.3	48.9	75,777	116,683
25% higher treatment costs					
No screening	61.6	31.5	0	0	39,138
Current invitation	53.8	25.2	38.9	59,061	87,503
New invitation (no increase)	53.8	25.2	38.9	72,349	87,503
New invitation (immediate increase)	52.2	23.7	47.1	77,527	103,631

Surveillance colonoscopy cost (€)	Care costs (€)	Total costs (millions) (€)	Net costs (€)	Cost (€) /QALY gained compared to no screening	ICER compared to current situation
0	1,151,694	1.195			
61,300	983,246	1.197	2,306	54	
61,300	983,246	1.211	15,530	363	
74,828	950,926	1.214	18,657	360	1,819
71,234	958,430	1.212	17,362	350	2,196
0	928,042	0.963			
49,197	789,887	0.979	16,423	467	
49,197	789,887	0.993	29,779	846	
60,080	763,532	0.998	34,972	821	2,509
57,191	769,785	0.996	33,449	820	3,039
0	1,039,213	1.078			
48,230	900,659	1.085	6,283	173	
48,230	900,659	1.098	19,815	546	
58,820	874,294	1.100	21,782	495	2,020
56,023	880,414	1.099	20,899	496	2,504
0	1,039,213	1.078			
62,784	87,0129	1.093	14,507	343	
62,784	87,0129	1.106	27,488	651	
76,644	83,7835	1.113	34,642	680	2,313
72,946	84,5419	1.111	32,474	665	2,718
0	1,299,017	1.338			
55,296	1,107,672	1.310	-28,621	-735	
55,296	1,107,672	1.323	-15,334	-394	
67,512	1,071,009	1.320	-18,475	-393	1,248

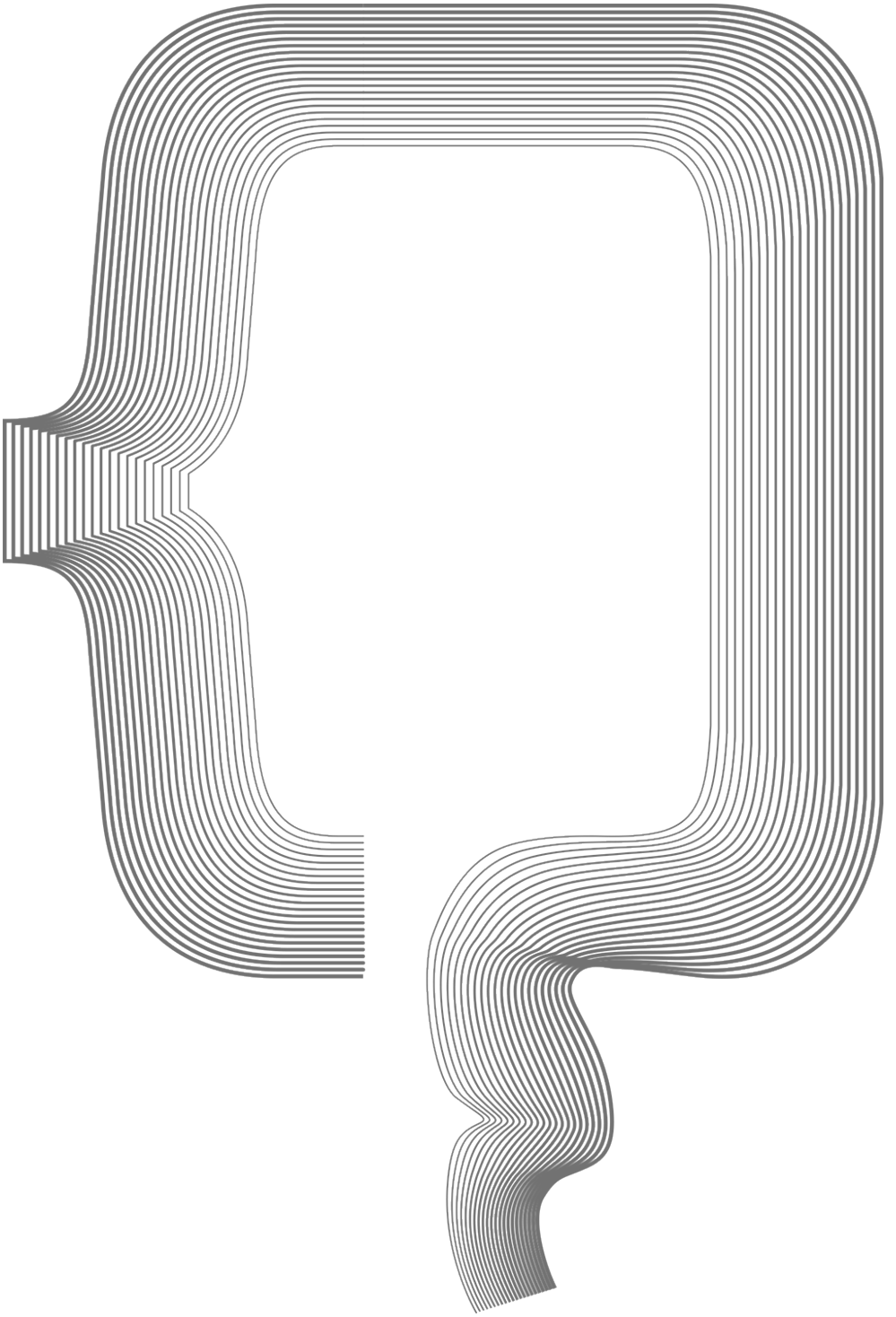
table continues

Scenario	CRC cases	CRC deaths	QALYs gained	Screening costs (€)[a]	Diagnostic colonoscopy costs (€)
New invitation (gradual increase)	52.5	24	45.1	76,346	99,761
25% lower treatment costs					
No screening	61.6	31.5	0	0	39,138
Current invitation	53.8	25.2	38.9	59,061	87,503
New invitation (no increase)	53.8	25.2	38.9	72,349	87,503
New invitation (immediate increase)	52.2	23.7	47.1	77,527	103,631
New invitation (gradual increase)	52.5	24	45.1	76,346	99,761
25% higher FIT cost					
No screening	61.6	31.5	0	0	39,138
Current invitation	53.8	25.2	38.9	62,140	87,503
New invitation (no increase)	53.8	25.2	38.9	81,630	87,503
New invitation (immediate increase)	52.2	23.7	47.1	86,730	103,631
New invitation (gradual increase)	52.5	24	45.1	85,569	99,761
25% lower FIT cost					
No screening	61.6	31.5	0	0	39,138
Current invitation	53.8	25.2	38.9	55,982	87,503
New invitation (no increase)	53.8	25.2	38.9	63,067	87,503
New invitation (immediate increase)	52.2	23.7	47.1	68,323	103,631
New invitation (gradual increase)	52.5	24	45.1	67,122	99,761
30% GP participation					
No screening	61.6	31.5	0	0	39,138
Current invitation	53.8	25.2	38.9	59,061	87,503
New invitation (no increase)	53.8	25.2	38.9	77,271	87,503
New invitation (immediate increase)	52.2	23.7	47.1	84,260	103,631
New invitation (gradual increase)	52.5	24	45.1	82,661	99,761

CRC - colorectal cancer; QALY - Quality adjusted life years; GP - General practitioner; FIT - Fecal immunochemical test; ICER - Incremental cost effectiveness ratio

[a] Screening costs include : Organization, Information, FIT kit, postage, lab analysis and General practitioner consultation costs

Surveillance colonoscopy cost (€)	Care costs (€)	Total costs (millions) (€)	Net costs (€)	Cost (€) /QALY gained compared to no screening	ICER compared to current situation
64,265	1,079,626	1.320	-18,157	-403	1,696
0	779,410	0.819			
55,296	664,603	0.866	47,916	1,231	
55,296	664,603	0.880	61,204	1,572	
67,512	642,605	0.891	72,728	1,545	3,051
64,265	647,776	0.888	69,599	1,543	3,513
0	1,039,213	1.078			
55,296	886,138	1.091	12,726	327	
55,296	886,138	1.111	32,217	828	
67,512	856,807	1.115	36,329	772	2,903
64,265	863,701	1.113	34,945	775	3,600
0	1,039,213	1.078			
55,296	886,138	1.085	6,569	169	
55,296	886,138	1.092	13,654	351	
67,512	856,807	1.096	17,923	381	1,396
64,265	863,701	1.095	16,497	366	1,609
0	1,039,213	1.078			
55,296	886,138	1.088	9,648	248	
55,296	886,138	1.106	27,858	716	
67,512	856,807	1.112	33,860	719	2,977
64,265	863,701	1.11	32,037	710	3,628



Part III

Screening and subsequent steps for Lynch syndrome patients

Chapter 9

Cost-effectiveness of active identification and subsequent colonoscopy surveillance of Lynch syndrome cases

Elisabeth F.P. Peterse, Steffie K. Naber, Corinne Daly, Aaron Pollett, Lawrence F. Paszat, Manon C.W. Spaander, Melyssa Aronson, Robert Gryfe, Linda Rabeneck, Iris Lansdorp-Vogelaar* & Nancy N. Baxter*

Clinical Gastroenterology and Hepatology (2020), 18: 2760-2767

*These authors contributed equally

Abstract

Background & aims

The province of Ontario, Canada is considering immunohistochemical followed by cascade analyses of all patients who received a diagnosis of colorectal cancer (CRC) at an age younger than 70 years to identify individuals with Lynch syndrome. We evaluated the costs and benefits of testing for Lynch syndrome and determined the optimal surveillance interval for first-degree relatives (FDRs) found to have Lynch syndrome.

Methods

We developed a patient flow diagram to determine costs and yield of immunohistochemical testing for Lynch syndrome in CRC cases and, for those found to have Lynch syndrome, their FDRs, accounting for realistic uptake. Subsequently, we used the MISCAN-colon model to compare costs and benefits of annual, biennial, and triennial surveillance in FDRs identified with Lynch syndrome vs colonoscopy screening every 10 years (usual care for individuals without a diagnosis of Lynch syndrome).

Results

Testing 1000 CRC cases was estimated to identify 20 CRC index cases and 29 FDRs with Lynch syndrome at a cost of $310,274. Despite the high cost of Lynch syndrome tests, offering the FDRs with Lynch syndrome biennial colonoscopy surveillance was cost-effective at $8785 per life-year gained compared with usual care because of a substantial increase in life-years gained (+122%) and cost savings in CRC care. Triennial surveillance was more costly and less effective, and annual surveillance showed limited additional benefit compared with biennial surveillance.

Conclusions

Immunohistochemical testing for Lynch syndrome in persons younger than 70 years who received a diagnosis of CRC and then testing FDRs of those found to have Lynch syndrome provide a good balance between costs and long-term benefits. Colonoscopy surveillance every 2 years is the optimal surveillance interval for patients with Lynch syndrome.

Introduction

Lynch syndrome (LS) is an autosomal dominant genetic disorder caused by a germline mutation in one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, or PMS2) or by last exomes deletions of EPCAM. LS is the most common cause of hereditary colorectal cancer (CRC) and accounts for approximately 3% of all CRC cases.[36] Individuals with LS have a 15%–66% probability of developing CRC before the age of 70 years, depending on sex and type of mutation.[37,334-338]The average age of CRC diagnosis in LS cases is 45 years,[37] which is substantially younger than the general population in which the majority of CRC cases are diagnosed in individuals aged 65 or older.[15] Intensive colonoscopy surveillance in LS cases that have not developed CRC yet has been shown to lead to a substantial reduction in CRC incidence and mortality.[339] However, to qualify for such intensive surveillance, individuals first need to be identified with LS. Historically, identification of individuals with LS has been based on the Amsterdam or revised Bethesda criteria.[340] However, sensitivity and specificity of these criteria are limited, and because both sets of criteria rely on accurate family history, their implementation in routine clinical practice has been poor.[340]

More recently, laboratory-based testing of CRC cases through immunohistochemistry (IHC) has been suggested as a more effective pathway for identifying individuals with LS.[340] First-degree relatives (FDRs) of LS-positive cases can undergo cascade testing: genetic counseling and testing for a known germline mutation in a mismatch repair gene. Those with LS can then be offered intensified colonoscopy surveillance to enable timely detection of CRC. Compared with currently used criteria, programmatic IHC testing is likely to increase the number of LS identifications. Therefore, the province of Ontario, Canada is currently considering introducing reflex testing of all CRC cases younger than age 70 years.[341] In this study, we (1) evaluated the costs and life-years gained (LYG) of IHC testing for LS followed by cascade testing in CRC cases younger than age 70 and (2) determined the optimal colonoscopy surveillance interval in LS-identified first-degree relatives (FDRs).

Methods

A pathway from CRC diagnosis to the identification of FDRs with LS, including the associated probabilities and costs, was developed on the basis of experience at the Familial Gastrointestinal Cancer Registry, Mount Sinai Hospital, Toronto, Ontario, supplemented with literature. Subsequently, we used the Microsimulation Screening Analysis (MISCAN)–Colon decision model to estimate costs and LYG of triennial, biennial, and annual colonoscopy in identified FDRs with LS. We compared results with those of colonoscopy screening every 10 years, the recommended strategy for individuals without an increased risk of CRC. Costs and LYG in both steps were combined to determine overall cost-effectiveness of universal LS testing and subsequent intensive colonoscopy surveillance.

Development of patient flow diagram

Figure 9.1 and Supplementary Table A9.1 describe the flow of CRC patients and their FDRs through IHC testing for LS. The patient flow diagram does not reflect cases that are missed because of a lack of test sensitivity. First, all CRC patients diagnosed younger than age 70 years are tested for expression deficiencies of MLH1, MSH2/6, and PMS2. Patients with MSH2/6 or PMS2 deficiencies are directly referred to a patient navigator, who informs them about the possibility of undergoing germline testing. The genomic DNA of tumors that lack MLH1 expression is first tested for the BRAF V600E mutation. If the tumor is BRAF wild-type, methylation of the MLH1 promoter is determined. Patients with MLH1-negative tumors are only referred to a patient navigator if they are BRAF wild-type and do not have hypermethylation of the MLH1 promoter (Figure 9.1). CRC patients who have a germline mutation receive post-test genetic counseling in which FDRs are traced. We assumed an average of 5.96 FDRs per CRC patient diagnosed with LS.[342] These FDRs are offered genetic counseling, subsequent germline testing, and, if positive for LS, post-test genetic counseling (Figure 9.1).

Microsimulation Screening Analysis–Colon model

MISCAN-Colon is a well-established microsimulation model for CRC that was developed at the Department of Public Health of the Erasmus MC, University Medical Center (Rotterdam, the Netherlands). The model's structure, underlying assumptions, and calibration for the Canadian setting have been described elsewhere (Model Appendix).[343] In brief, MISCAN-Colon simulates the life histories of a large population of persons from birth to death, with adenoma prevalence and CRC incidence as observed in the Canadian population. By comparing all life histories with and without screening and surveillance, MISCAN-Colon quantifies the effectiveness of screening and surveillance as well as the associated costs.

Model adjustments for the Lynch syndrome population

We adjusted the MISCAN-Colon model built for the general Canadian population to reflect the LS population by assuming that, on average, adenomas progress 10 times faster (Supplementary Table A9.2). Adenoma onset was then calibrated to the age-specific cumulative CRC risk described by Bonadona et al,[343] assuming an average CRC risk of 42% at age 80 for both sexes. We assumed the same difference in relative risk between men and women as modeled for the general population (Supplementary Figure A9.1). Because LS cases have a better overall CRC survival, we adjusted survival in the MISCAN-Colon model by using a hazard ratio of overall survival of 0.65 compared with the general population. [344] We assumed no differences in CRC stage distribution or other-cause mortality between LS patients and the average-risk population.

Simulated population

For each screening and surveillance strategy, we simulated a cohort of 10 million individuals identified with LS in 2015 to generate stable model results. Their median age was 42 years, with an interquartile range of 31–55 years in accordance with the age distribution of LS-identified FDRs in a Dutch study.[342] Distribution by sex was based on the percentage of women in the 2015 Ontario population, accounting for the age distribution of the FDRs.[345]

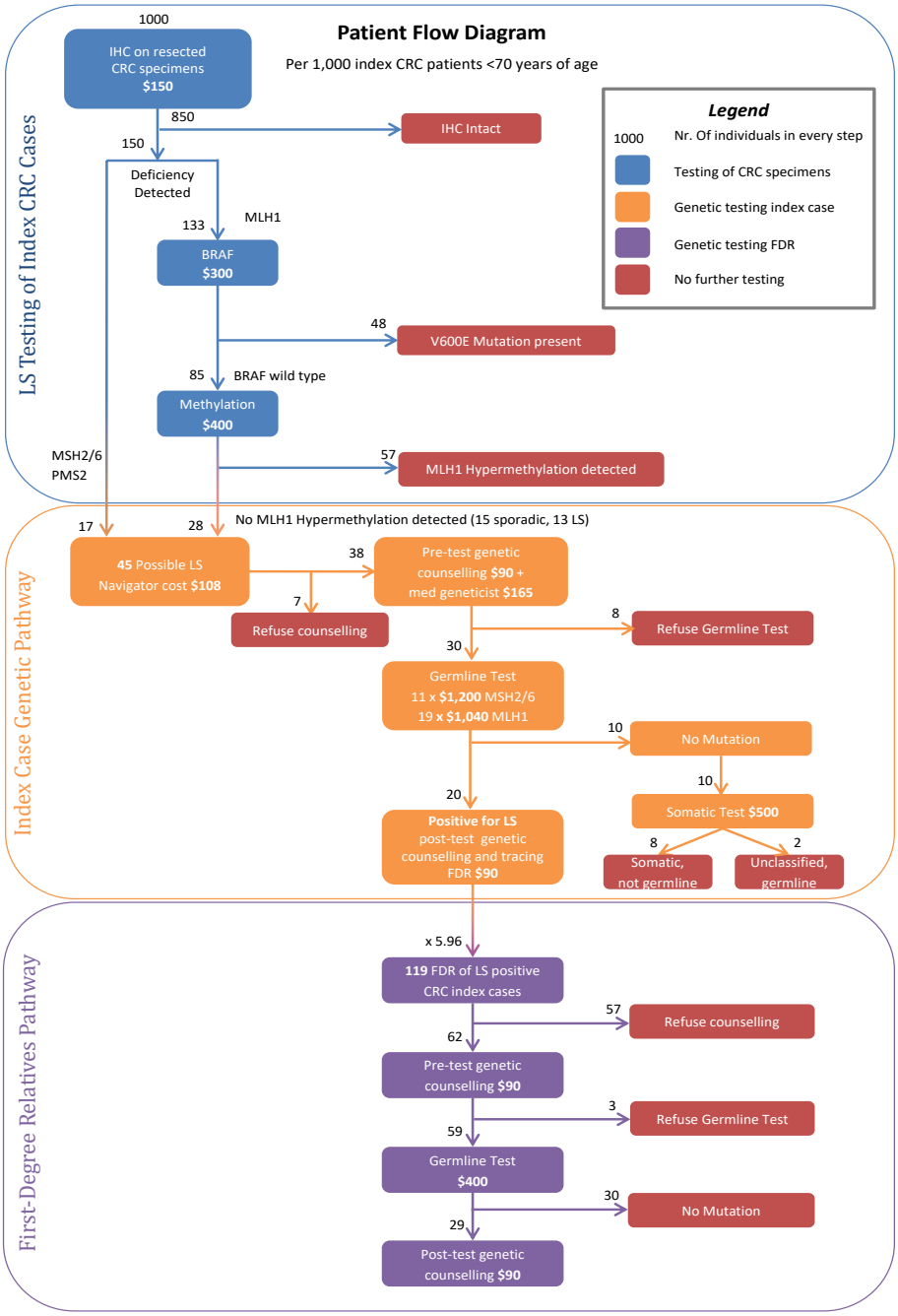


Figure 9.1: Patient flow diagram of CRC index cases and cascade testing.
CRC - colorectal cancer; FDR - first-degree relative; IHC – immunohistochemistry; LS - Lynch syndrome.

Lynch syndrome testing and colonoscopy surveillance strategies

We simulated 5 LS testing and colonoscopy strategies for LS-positive FDRs:

1. No LS testing and no colonoscopy screening.
2. No LS testing. FDRs are offered colonoscopy screening every 10 years at ages 50–80 years (ie, usual care).
3. LS testing. FDRs with LS are offered triennial colonoscopy surveillance at ages 25–59 years, extending the surveillance interval to 5 years at ages 60–80 if no adenomas are detected.[346]
4. LS testing. Similar to strategy 3, except that LS-positive FDRs are offered biennial surveillance rather than triennial surveillance.
5. LS testing. Similar to strategy 3, except that LS-positive FDRs are offered annual surveillance rather than triennial surveillance.

We assumed a 60% screening participation for the usual care strategy (strategy 2).[347] For strategies 3–5, we assumed an 80% surveillance adherence for LS-positive FDRs, [340,348-350] irrespective of the surveillance interval.

The analysis was conducted from a third-party health care payer perspective. All costs were expressed in 2018 Canadian dollars (**Figure 9.1, Supplementary Table A9.3**). Colonoscopy test characteristics have been published previously (**Supplementary Table A9.4**).[343] For 10-yearly colonoscopy screening, individuals with adenomas detected and removed at screening at any age enter a surveillance regimen, for which we assumed 100% adherence. This entails a subsequent colonoscopy in 3 years in case of high-risk findings (ie, 1 adenoma ≥10 mm or ≥3 adenomas <10 mm) and in 5 years in case of low-risk findings (ie, ≤2 adenomas <10 mm). For any of the simulated strategies, individuals with adenomas detected at their last scheduled colonoscopy will undergo such surveillance beyond age 80 until no adenomas are detected.

Outcomes

For all strategies, we evaluated the number of CRC cases and deaths, the costs of diagnosing CRC cases through symptoms, and the costs of CRC treatment. For strategy 2 (usual care), the LYG and associated costs from colonoscopy screening compared with strategy 1 (no screening) were also evaluated. For strategies 3–5 with intensified colonoscopy surveillance for LS-positive FDRs, we estimated costs for LS testing of the index cases and their FDRs, if applicable, and downstream LYG and costs of CRC surveillance of LS-positive FDRs. We used these to calculate the average cost-effectiveness ratio (compared with usual care) of LS testing followed by intensified colonoscopy surveillance for LS-positive FDRs, assuming a willingness-to-pay threshold of $100,000 per LYG. Furthermore, the incremental cost-effectiveness ratios (ICERs) of the different strategies were evaluated. Costs and LYG were discounted at an annual rate of 3% to the year in which the index case was diagnosed with CRC. The results section starts with costs of LS testing per 1000 CRC cases, but they are then converted to costs per 1000 FDRs identified with LS, and all subsequent outcomes of colonoscopy screening and surveillance are presented per 1000 FDRs with identified LS.

Sensitivity analyses

To evaluate the robustness of our results, we varied all parameters in one-way sensitivity analyses (**Supplementary Table A9.1, Supplementary Table A9.2, Supplementary Table A9.3**), in addition to evaluating a scenario in which 5-yearly colonoscopy instead of 10-yearly colonoscopy is the usual care, and a scenario in which the surveillance interval between ages 60 and 80 is not extended when no adenomas are detected. Because the progression rate of CRC in LS is uncertain, we evaluated ×0, ×2, ×5, ×10, and ×20 faster adenoma progression than the general population. For these 5 progression rates, adenoma onset was recalibrated to obtain a uniform age-specific CRC incidence.[37] Furthermore, a probabilistic sensitivity analysis was performed to evaluate the uncertainty of our estimates (**Supplementary Table A9.1, Supplementary Table A9.2, Supplementary Table A9.3**). Each of the progression assumptions was used in 20% of the runs. For the probability parameters, 1000 values were drawn from beta distributions; gamma distribution was used for all other parameters.

Results

Lynch Syndrome Testing in Index Colorectal Cancer Cases and First-Degree Relatives

Testing 1000 index CRC cases for LS through IHC and subsequent germline testing identified 20 LS cases (**Figure 9.1**) with an associated cost of $278,558 (**Supplementary Table A9.5**). The costs of cascade testing of the 119 family members of those 20 LS cases were estimated at an additional $31,716 and resulted in the identification of 29 FDRs with LS. Overall, tumor testing of 1000 index CRC cases for LS would thus cost $310,274 to identify 29 FDRs with LS, which corresponds to $10.462 million per 1000 LS-positive FDRs (**Table 9.1**).

CRC surveillance in first-degree relatives with Lynch syndrome

In the absence of CRC screening, MISCAN-Colon predicted 359 CRC cases and 165 CRC deaths per 1000 LS-positive FDRs of CRC patients diagnosed younger than the age of 70 from their LS diagnosis until death (**Table 9.1**). Associated costs of CRC diagnosis and care were estimated at $67.465 million. In the strategy without LS testing but with 10-yearly colonoscopy screening at 60% participation (usual care), the number of CRC cases and deaths was reduced to 308 (–14%) and 112 (–33%) per 1000 LS-positive FDRs, respectively. This strategy gained 334 life-years per 1000 LS-positive FDRs compared with no screening. Total costs of usual care were $63.992 million per 1000 FDRs; therefore, usual care was cost saving compared with no CRC screening.

LS testing was very cost-effective compared with no LS testing. The benefits of LS testing depend on the subsequent colonoscopy surveillance that is offered to the FDRs who are identified with LS. Compared with the care these FDRs would receive if they had not been diagnosed with LS, universal LS testing through IHC and subsequent intensified colonoscopy surveillance resulted in 722 (+116%), 741 (+122%), and 753 (+126%) LYG per 1000 FDRs with LS and increased CRC screening and surveillance costs to $4.237 million (+291%), $5.669 million (+423%), and $9.932 million (+816%) for triennial,

biennial, and annual surveillance from age 25, respectively (Table 9.1). The shorter the surveillance interval, the more CRC cases are averted, and therefore CRC care costs are lower. Strikingly, the total costs of LS testing, CRC surveillance, and CRC care of offering biennial surveillance to LS cases were lower than those of triennial surveillance. The number of LYG per 1000 LS-positive FDRs was 741 for biennial surveillance, resulting in ICER of $8785 compared with usual care. Offering LS cases annual colonoscopy surveillance minimally increased the number of LYG (753, +1.6%) and increased total costs by approximately $2.565 million (+3.8%) per 1000 LS-positive FDRs, resulting in an unfavorable ICER of $218,647 per LYG compared with biennial colonoscopy surveillance (Table 9.1).

Table 9.1: Base case results per 1,000 first-degree relatives with Lynch Syndrome.

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)	Costs CRC care[b] (million$)	Total costs[a,b] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
No LS testing or CRC screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS testing									
3-yearly colonoscopy	244	67	10.462	4.237	53.048	67.747	722	9,670	D
2-yearly colonoscopy	235	66	10.462	5.669	51.441	67.573	741	8,785	8,785
1-yearly colonoscopy	228	66	10.462	9.932	49.743	70.138	753	14,655	218,647

CRC - Colorectal Cancer; LS - Lynch Syndrome; LYG - Life-Years Gained; ACER - Average Cost-Effectiveness Ratio, ICER - Incremental Cost-Effectiveness Ratio; D - Dominated.

[a] CRC cases and deaths include those from LS diagnosis until death.

[b] Results were discounted at an annual rate of 3%.

[c] Include total costs of screening CRC index cases and their FDRs, including LS negative and non-participants.

[d] Include costs of CRC screening, diagnosis and surveillance.

[e] Compared to no LS screening.

Sensitivity analyses

The ICER of reflex tumor testing for all patients with CRC younger than age 70 followed by biennial colonoscopy compared with 10-yearly colonoscopy for FDRs identified with LS varied between being Cost Saving and $34,230 in our one-way sensitivity analyses (Supplementary Figure A9.2, Supplementary Table A9.6). The ICER of universal tumor testing followed by annual colonoscopy of FDRs with LS exceeded the threshold of $100,000 per LYG in all sensitivity and scenario analyses, except in the scenario where a cumulative CRC risk of 60% at age 80 was assumed for LS cases (Supplementary Table A9.6) and the scenario in which it assumed that the adenoma progression of LS cases is ×20 faster than the general population, which resulted in

ICERs of $95,197 and $93,835. Finally, at a willingness-to-pay threshold of $100,000, LS testing with subsequent biennial colonoscopy surveillance was the optimal strategy in 77.2% of our probabilistic sensitivity analyses (**Figure 9.2**).

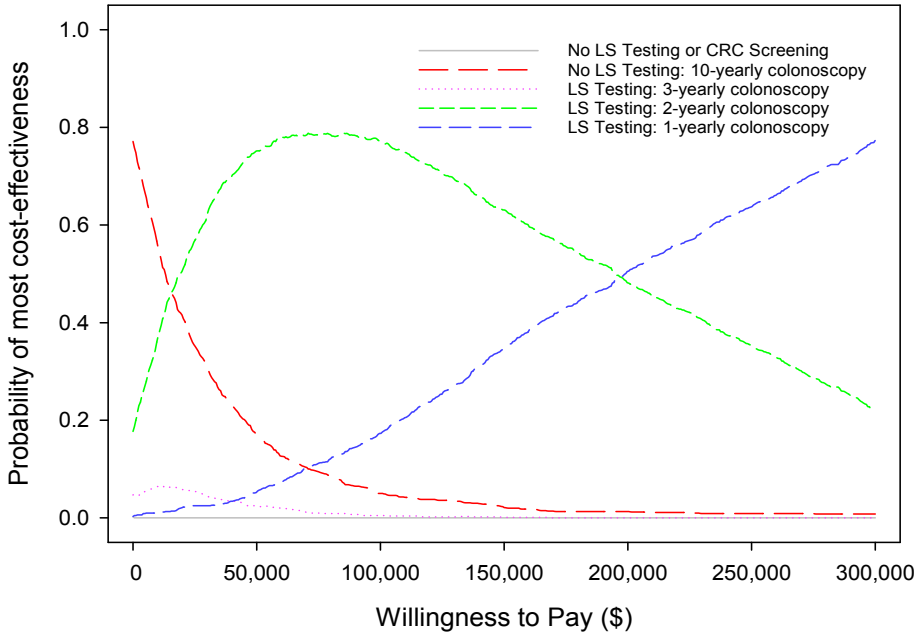


Figure 9.2: Cost-effectiveness acceptability curve of the probabilistic sensitivity analyses. CRC - colorectal cancer; LS - Lynch syndrome.

Discussion

The results of this study suggest that programmatic testing for LS with IHC in patients with CRC diagnosed younger than age 70 years followed by cascade testing is very cost-effective, and that biennial colonoscopy surveillance of identified FDRs with LS is optimal. Testing tumors of 1000 CRC patients for LS was estimated to result in the identification of 29 FDRs with LS at a cost of $310,274. Despite the high cost of LS testing, offering these FDRs with LS biennial versus 10-yearly colonoscopy screening resulted in a favorable ICER of $8785 because of a substantial increase in LYG (+122%) and cost savings in CRC care. Strikingly, because of cost savings in CRC care, the total costs of biennial surveillance were lower than those of triennial surveillance. Annual colonoscopy surveillance provided little benefit compared with biennial surveillance at a much higher cost, resulting in ICER of $218,647. LS testing with biennial colonoscopy surveillance was the optimal strategy in 77.2% of our probabilistic sensitivity analyses (willingness-to-pay threshold of $100,000), demonstrating the robustness of our conclusion.

With LS testing costs of more than $10,000 per LS-positive FDR identified, investigating the presence of LS in all CRC index cases <70 years and their FDRs is expensive. To identify 1 FDR with LS, 35 tumor samples of CRC index cases have to be analyzed by IHC, and 3 germline tests have to be performed. This emphasizes the costs of IHC testing being an important driver for the cost-effectiveness of LS testing and subsequent colonoscopy surveillance, which we also observed in our sensitivity analyses. The additional costs of offering an LS case biennial CRC surveillance were $4585 compared with 10-yearly colonoscopy. Because LS cases are at very high risk of developing CRC, substantial downstream cost savings in CRC treatment ($11,467) occur by preventing CRC cases and by diagnosing CRC cases in an earlier stage. Overall, LS testing in CRC patients younger than age 70 and subsequent biennial colonoscopy surveillance require an upfront investment that is largely offset by future savings in CRC treatment.

A recent study compared CRC incidence in LS cases between 3 countries with different colonoscopy surveillance policies (1-, 2-, and 3-year intervals) and found no difference in cumulative CRC incidence among countries.[351] Because we found only minor differences in the number of CRC cases (244–228 CRC cases per 1000 LS cases), those results are consistent with our findings. Nevertheless, because the additional costs are also small, our results demonstrate that surveillance every 2 years rather than every 3 years is worthwhile, whereas surveillance every year is not.

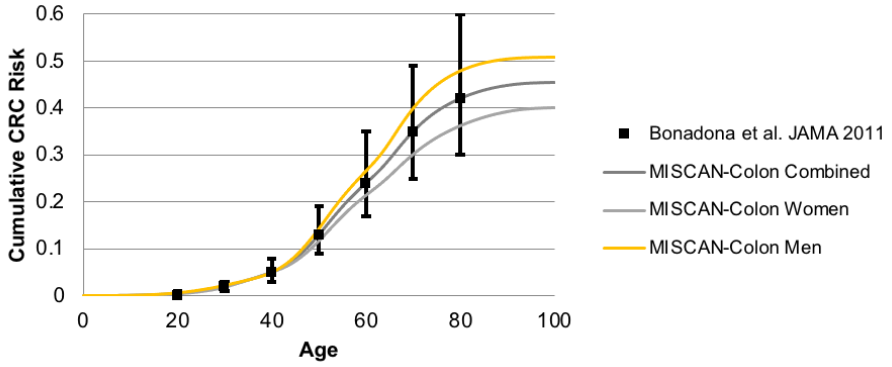
Our study has some limitations. First, we did not include any strategies in which we evaluated other methods for LS testing. Other studies have compared different strategies for LS testing and determined that screening with IHC is the most cost-effective strategy.[342,352-355] Second, not all steps in the patient flow diagram could be based on Canadian data. We varied all estimates in our sensitivity analyses and demonstrated that they did not influence our recommendation of offering biennial colonoscopy surveillance to LS cases. Third, the CRC risk for LS cases is uncertain; estimates vary greatly among studies.[37,334-338] We calibrated our model to the largest study that accounted for ascertainment bias.[37,356] Fourth, we did not evaluate gene-specific colonoscopy surveillance because of its high uncertainty in CRC risk and natural history. To address these third and fourth limitations, we performed sensitivity analyses with 30% and 60% CRC risk at age 80, which revealed that more intense colonoscopy surveillance might be optimal for LS cases with high-risk mutations, which should therefore be explored in future studies. Fifth, the natural history of CRC in LS is uncertain. We covered this uncertainty by evaluating 5 different progression assumptions. Only if we assumed that the progression of adenomas in LS is ×20 faster than the progression in the general population, the ICER of annual surveillance was below the willingness-to-pay threshold, which was $93,835 per LYG compared with biennial surveillance. Sixth, the assumptions regarding the costs for LS testing used in our study are not reflective for settings where genetic testing is performed by using multiple-gene panels. Furthermore, we did not take into account that patients with stage II CRC with adverse features may undergo IHC testing to guide chemotherapy. Lower costs for LS testing would make programmatic testing for LS even more cost-effective, and it would not influence the optimal surveillance interval. Seventh, we used LYG rather than quality-adjusted life

years gained. An important determinant of the quality of life of LS cases is the distress LS patients experience from knowing they have LS. To our knowledge, no data are available that quantify this disutility, which is why we could not incorporate it in our analyses. Last, we did not consider other LS-related cancers such as the increased risk for endometrial cancer and ovarian cancer; we assumed that apart from an increased CRC risk, LS cases have a normal life expectancy. This potentially resulted in an overestimation of LYG per CRC deaths prevented. However, an asymptomatic individual identified with LS has the additional benefit of potential earlier detection or prevention of other cancer types, and this additional benefit is also not captured in the current analysis.

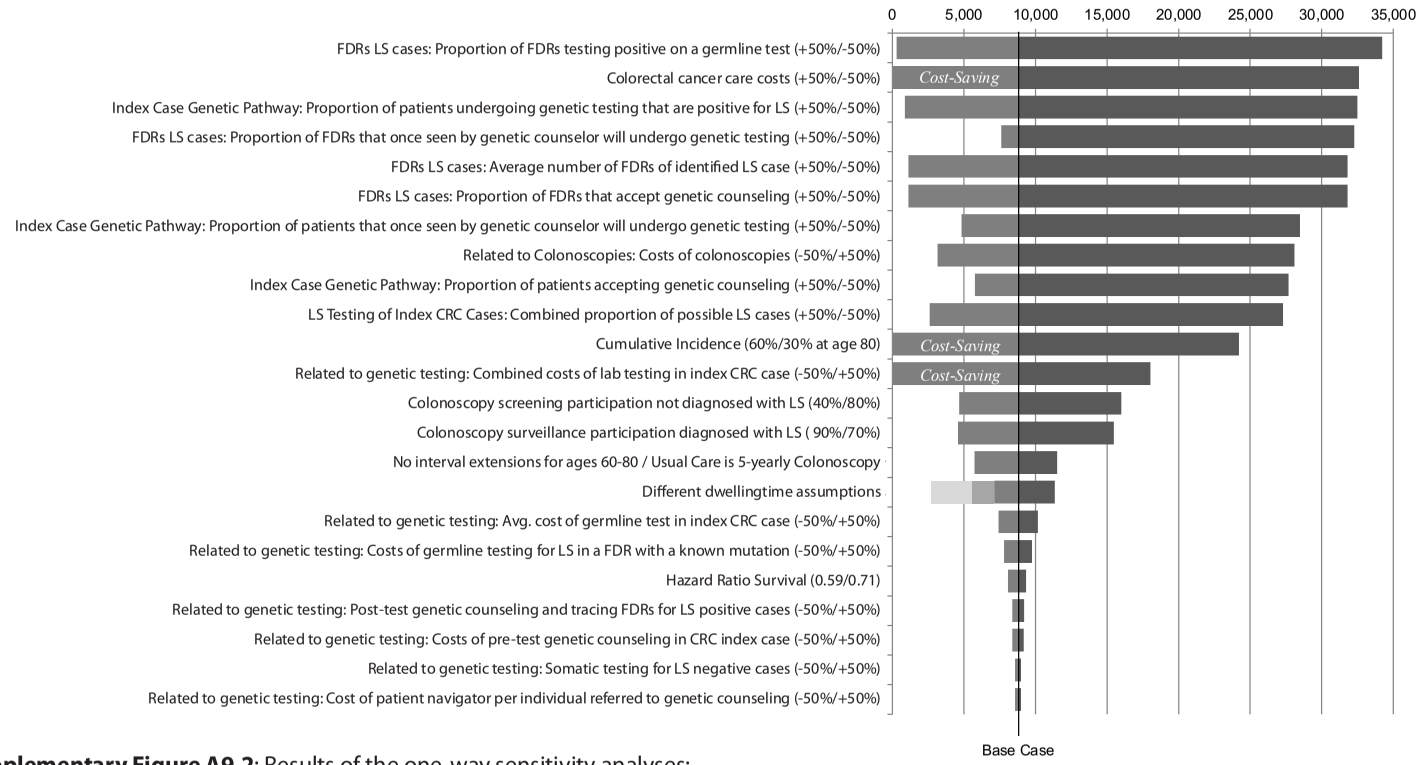
Despite these limitations, our study may be of great value to policy makers and fellow researchers. This cost-effectiveness analysis evaluates different colonoscopy surveillance intervals in LS cases identified by IHC testing. The optimal colonoscopy surveillance interval for LS cases is a topic of intense debate [351]; therefore, this study provides insights that can be used to inform surveillance guidelines internationally. In line with previous studies, LS testing with more intensive colonoscopy surveillance was very cost-effective compared with usual care.[352-355] However, we revealed that biennial colonoscopy surveillance was cost saving compared with triennial surveillance, and that annual colonoscopy was not cost-effective compared with biennial colonoscopy. Another major strength of our study is that both the costs to identify LS in CRC cases and the subsequent costs of cascade testing and colonoscopy surveillance of at-risk relatives were included in our analyses. Furthermore, we used a well-established microsimulation model that has been used to inform CRC screening guidelines in several countries, among which is the United States.[96,99] This study also evaluates universal LS testing in CRC index cases (in this case limited to patients <70 years) and subsequent cascade screening and colonoscopy surveillance in at-risk relatives for the Canadian setting. Important barriers that have been identified for implementation of a population-based program for LS screening in Canada are the education of stakeholders and concerns regarding sustaining various resources.[341] The results of this study provide data that are essential to overcome these barriers. For other countries with universal LS screening, the results of this study can be used to optimize existing programs, because it provides insight in which elements of the patient flow diagram are important drivers for the (cost-)effectiveness of LS screening.

In conclusion, we estimated that programmatic IHC testing for LS in patients with CRC diagnosed <70 years that is followed by cascade testing and subsequent biennial colonoscopy surveillance of identified FDRs is very cost-effective in Canada. These findings should urge policy makers to further explore the possibilities of implementing universal LS testing.

Appendix



Supplementary Figure A9.1: Cumulative CRC risk assumed by MISCAN-Colon was calibrated to Bonadona et al. [37]
CRC - Colorectal cancer



Supplementary Figure A9.2: Results of the one-way sensitivity analyses:
Incremental cost-effectiveness ratios ($) of LS testing and subsequent biennial colonoscopy surveillance in FDRs with LS under alternative model assumptions. Ratios plotted are compared to the previous efficient strategy.
LS - Lynch syndrome; FDR - First-degree relative; CRC - Colorectal cancer

Supplementary Table A9.1: Assumptions regarding the participation of CRC Index cases and their FDRs in every step of the patient flow diagram, and the positivity rates of the genetic tests.

Parameter	Value (range[a])	Source
LS testing of index CRC cases		
Combined proportion of possible LS cases	4.5% (2.25-6.75%)	Ontario Estimate[b]
Proportion of index CRC cases with an MLH1 deficiency, subsequently tested for *BRAF* V600E	13.3%	
Proportion of MLH1 deficient tumors with wildtype *BRAF*, subsequently tested for *MLH1* promoter hypermethylation	64%	
Proportion of MLH1 deficient *BRAF* wildtype tumors without *MLH1* promoter hypermethylation, referred to genetic counseling	33%	
Proportion of index CRC cases with an MSH2/6 or PMS2 deficiency, subsequently referred to genetic counseling	1.7%	
Index case genetic pathway		
Proportion of patients accepting genetic counseling	84% (42-100%)	357 358,359
Proportion of patients that once seen by genetic counselor will undergo genetic testing	80% (40-100%)	360-363
Proportion of patients undergoing genetic testing that are positive for LS	67% (33-100%)	
FDRs LS cases		
Average number of FDRs of identified LS case	5.96 (2.98-8.94)	342
Proportion of FDRs that accept genetic counseling	52% (26-78%)	340
Proportion of FDRs that once seen by genetic counselor will undergo genetic testing	95% (47.5-100%)	340
Proportion of FDRs testing positive on a germline test	50% (25-75%)	355
Colonoscopy participation [c]		
Colonoscopy screening participation not diagnosed with LS	60% (40-80%)[d]	347
Colonoscopy surveillance participation diagnosed with LS	80% (70-90%)[d]	340,348-350

CRC - Colorectal cancer; FDR -first-degree relative; LS - Lynch Syndrome

[a] Alternative values evaluated in sensitivity analyses. Ranges evaluated were mean*0.5 – mean*1.5.

[b] Estimates were based on experience at the Familial Gastrointestinal Cancer Registry, Mount Sinai Hospital, Toronto, Ontario

[c] In the Probabilistic Sensitivity Analysis, the participation when not being diagnosed with LS was never lower than the participation when being diagnosed with LS, using preference ordering.[243]

[d] As we are more certain of these estimated, smaller ranges were evaluated.

Supplementary Table A9.2: Natural History adjustments for the Lynch Syndrome population.

Parameter	Value (range[a])	Source
Probability of having developed colorectal cancer before age 80	42% (30-60%)	[37]
Dwelling times, faster progression compared to the general population	10x (0x/2x/5x/20x)[b]	Assumption
Hazard Ratio overall survival of CRC in LS cases versus CRC in the general population	0.65 (0.59-0.71)	[344]

CRC - Colorectal cancer; LS - Lynch Syndrome

[a] Alternative values evaluated in sensitivity analyses.

[b] In the Probabilistic Sensitivity Analysis, 0x, 2x, 5x, 10x and 20x faster dwelling times were evenly incorporated.

Supplementary Table A9.3: Assumptions regarding costs. All costs are in 2018 Canadian Dollars.

Procedure	Costs (range[a])	Source[b]
Related to genetic testing		
Combined costs of lab testing in index CRC case	224 (112-336)	Ontario Estimate
IHC MLH1, MSH2/6, PMS2	150	
BRAF V600E mutation	300	
Methylation of *MLH1* promoter	400	
Cost of patient navigator per individual referred to genetic counseling	108 (54-162)	Ontario Estimate[c]
Costs of pre-test genetic counseling in CRC index case	255 (128-383)	Ontario Estimate[d]
Avg. cost of germline test in index CRC case	1,099 (549- 1,648)	Ontario Estimate[e]
MSH2/6, PMS2	1,200	
MLH1	1,040	
Post-test genetic counseling and tracing FDRs for LS positive cases & Costs of pre-test genetic counseling of FDRs (per index CRC case with LS) & Post-test genetic counseling FDR	90 (45-135)	Ontario Estimate[f]
Somatic testing for LS negative cases	500 (250-750)	Ontario Estimate
Costs of germline testing for LS in a FDR with a known mutation	400 (200-600)	Ontario Estimate
Related to colonoscopies[g]		
Colonoscopy without polypectomy	947 (474-1,421)	[158]
Colonoscopy with polypectomy & Colonoscopy for diagnosis of CRC by symptoms	1,192 (596-1,788)	[158]

table continues

CRC care[h]				
Females (50.7%)[i]	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial	29,240 (14,620-58,481)	42,537 (21,269-85,074)	63,432 (31,746-126,865)	80,855 (40,427-161,709)
Continuing	7,664 (3,832-15,328)	10,155 (5,077-20,310)	13,269 (6,635-26,539)	40,423 (20,212-80,846)
Terminal, death CRC	324,973 (162,487-649,947)	236,714 (118,357-473,429)	144,521 (72,260-289,041)	131,414 (65,707-262,828)
Terminal, death OC	31,064 (15,532-62,129)	29,295 (14,647-58,590)	30,743 (15,371-61,486)	28,703 (14,351-57,405)
Males (49.3%)[i]	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial	33,131 (16,565-66,261)	50,829 (25,414-101,658)	70,868 (35,434-141,736)	90,642 (45,321-181.285)
Continuing	8,386 (4,193-16,773)	12,292 (6,146-16,773)	15,442 (7,721-30,884)	50,015 (25,008-100,030)
Terminal, death CRC	329,770 (164,885-659,539)	207,153 (103,577-414,307)	147,150 (73,575-294,299)	124,025 (62,013-248,050)
Terminal, death OC	33,210 (16,605-66,420)	49,954 (24,977-99.909)	36,949 (18,747-73,898)	34,412 (17,206-68,825)

CRC - Colorectal cancer; LS - Lynch syndrome; FDR - first-degree relative; OC - other causes.

[a] Alternative values evaluated in sensitivity analyses. Ranges evaluated were mean*0.5 – mean*1.5.

[b] Ontario Estimate: costs are based on experience at the Familial Gastrointestinal Cancer Registry, Mount Sinai Hospital, Toronto, Ontario

[c] Annual salary of a navigator ($70,000) was divided by the estimated number of cases per year (650).

[d] Includes 1 hour Salary for Genetic Counseler ($90) and Ontario Health Insurance Plan (OHIP) Fee Schedule code A225 ($165).

[e] 62% of individuals were tested for MLH1.

[f] Includes 1 hour Salary for Genetic Counseler ($90).

[g] Costs of colonoscopy were obtained from the 2013 Ontario Health Insurance Plan (OHIP) Schedule of Benefits and Fees,[158] and updated to 2018 Canadian dollars using the consumer price index (CPI; All-items).[364] These were varied together in the one-way sensitivity analysis.

[h] CRC care was divided in three clinically relevant phases. The initial care phase was defined as the first 12 months after diagnosis, the terminal care phase as the final 12 months of life, and the continuing care phase as all months in between. For patients surviving less than 24 months, the last 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.

The costs attributable to CRC care by sex, CRC stage, and phase of care (initial, continuing, and terminal care) included outpatient visits, hospitalizations, treatment, home care, long-term care, and rehabilitation. The costs were estimated using health care administrative data in a matched cohort study, which compared the health care costs of CRC patients with their age- and sex-matched controls, and updated to 2018 Canadian dollars using the CPI.[364]

[i] Based on the 2015 Ontario Population, accounting for the age distribution of the FDRs.

Supplementary Table A9.4: Colonoscopy test characteristics

Sensitivity	
Adenoma 1-5 mm	75%
Adenoma 6-9 mm	85%
Adenoma 10+ mm	95%
Colorectal Cancer	95%
Specificity	86%[a]
Reach (until cecum)	95%
Fatal complication risk[b]	1/14,000

[a] The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, where the non-adenomatous lesions are removed and therefore induce polypectomy and biopsy.

[b] The fatal complication risk was only included for colonoscopies with polypectomy, and was based on Rabeneck et al. [365]

Supplementary Table A9.5: Number of individuals and associated costs per 1000 CRC index cases in every step of the patient flow diagram.

Step in patient flow diagram	**No. of individuals**	**Costs ($)[a]**
LS testing of index CRC cases		
Immunohistochemistry MLH1, MSH2/6, PMS2	1000	150,000
BRAF V600E mutation	133	39,900
Methylation *MLH1* promoter	85	34,000
Total		223,900
Index case genetic pathway		
Patient navigator	45	4,848
Pre-germline testing counseling	38	9,639
Germline testing	30	33,234
Positive cases: post-germline testing counseling	20	1,796
Negative cases: somatic testing	10	5,141
Total		54,658
First-degree relatives pathway		
FDRs of LS positive CRC index cases	119	
Pre-germline testing counseling	62	5,567
Germline testing	59	23,505
Post-germline testing counseling	29	2,644
Total		31,716
Total		**310,274**

CRC - Colorectal cancer; FDR - First-degree relatives; LS - Lynch syndrome

[a] Costs are in 2018 Canadian Dollars.

Supplementary Table A9.6: Results of one-way sensitivity analyses per 1,000 LS positive first-degree relatives of CRC index cases.

Usual care is 5-yearly colonoscopy				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
5-yearly colonoscopy	293	105		1.514
LS testing				
3-yearly colonoscopy	244	67	10.462	4.237
2-yearly colonoscopy	235	66	10.462	5.669
1-yearly colonoscopy	228	66	10.462	9.932
No interval extensions for ages 60-80				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	229	63	10.462	4.798
2-yearly colonoscopy	207	59	10.462	6.970
1-yearly colonoscopy	176	55	10.462	13.557
No decreased dwelling time				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	354	157		0.221
No LS testing				
10-yearly colonoscopy	245	93		1.380
LS testing				
3-yearly colonoscopy	150	50	10.462	4.613
2-yearly colonoscopy	140	49	10.462	6.131
1-yearly colonoscopy	131	48	10.462	10.483
Halved dwelling time				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	363	166		0.229
No LS testing				
10-yearly colonoscopy	271	102		1.275
LS testing				
3-yearly colonoscopy	179	57	10.462	4.500
2-yearly colonoscopy	167	55	10.462	5.995
1-yearly colonoscopy	155	54	10.462	10.306

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
61.690	63.204	362	-	Cost-Saving
53.048	67.747	722	12,617	D
51.441	67.573	741	11,516	11,516
49.743	70.138	753	17,728	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
51.845	67.105	739	7,672	D
49.078	66.510	772	5,741	5,741
45.493	69.513	802	11,785	100,826

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
64.196	64.417	-	-	-
55.624	57.005	363	-	Cost-Saving
43.341	58.417	727	3,880	3,880
41.932	58.525	742	4,010	7,111
40.627	61.572	753	11,716	284,648

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.431	67.66	-	-	-
59.987	61.262	371	-	Cost-Saving
47.678	62.639	766	3,486	D
45.926	62.383	785	2,705	2,705
44.151	64.919	800	8,529	176,255

table continues

5x faster dwelling time				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	362	166		0.228
No LS testing				
10-yearly colonoscopy	293	108		1.155
LS testing				
3-yearly colonoscopy	215	63	10.462	4.349
2-yearly colonoscopy	205	61	10.462	5.809
1-yearly colonoscopy	196	61	10.462	10.098
20x faster dwelling time				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	364	167		0.229
No LS testing				
10-yearly colonoscopy	335	118		1.047
LS testing				
3-yearly colonoscopy	287	74	10.462	4.157
2-yearly colonoscopy	279	73	10.462	5.572
1-yearly colonoscopy	268	73	10.462	9.809
Lower cumulative incidence (30% at age 80)				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	255	117		0.161
No LS testing				
10-yearly colonoscopy	218	79		1.046
LS testing				
3-yearly colonoscopy	172	48	10.462	4.284
2-yearly colonoscopy	166	47	10.462	5.718
1-yearly colonoscopy	161	47	10.462	10.010
Higher cumulative incidence (60% at age 80)				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	510	240		0.327
No LS testing				
10-yearly colonoscopy	444	163		1.121
LS testing				
3-yearly colonoscopy	356	99	10.462	4.135
2-yearly colonoscopy	344	97	10.462	5.562
1-yearly colonoscopy	333	98	10.462	9.768

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.227	67.455	-	-	-
61.431	62.586	353	-	Cost-Saving
50.331	65.143	747	6,491	D
48.627	64.898	766	5,599	5,599
46.972	67.532	778	11,621	208,305

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.428	67.657	-	-	-
65.172	66.219	305	-	Cost-Saving
56.789	71.408	694	13,348	D
54.881	70.915	719	11,345	11,345
52.444	72.716	739	15,000	93,835

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
47.555	47.715	-	-	-
44.488	45.534	233	-	Cost-Saving
37.525	52.271	509	24,387	D
36.380	52.560	523	24,227	24,227
35.183	55.655	531	33,911	366,988

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
99.024	99.352	-	-	-
93.110	94.231	494	-	D
78.906	93.503	1072	Cost-Saving	D
76.476	92.501	1100	Cost-Saving	Cost-Saving
73.953	94.183	1118	Cost-Saving	95,197

table continues

Lower hazard ratio overall survival (0.59)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	158		0.227
No LS testing				
10-yearly colonoscopy	308	106		1.082
LS testing				
3-yearly colonoscopy	243	64	10.462	4.228
2-yearly colonoscopy	235	63	10.462	5.657
1-yearly colonoscopy	228	63	10.462	9.910

Higher hazard ratio overall survival (0.71)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	360	173		0.228
No LS testing				
10-yearly colonoscopy	309	117		1.086
LS testing				
3-yearly colonoscopy	244	71	10.462	4.246
2-yearly colonoscopy	236	70	10.462	5.681
1-yearly colonoscopy	228	70	10.462	9.952

LS testing of index CRC cases: combined proportion of possible LS cases -50%(2.25%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	18.007	4.237
2-yearly colonoscopy	235	66	18.007	5.669
1-yearly colonoscopy	228	66	18.007	9.932

LS testing of index CRC cases: combined proportion of possible LS cases +50%(6.75%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	7.948	4.237
2-yearly colonoscopy	235	66	7.948	5.669
1-yearly colonoscopy	228	66	7.948	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
69.302	69.529	-	-	-
64.677	65.758	321	-	Cost-Saving
54.406	69.096	692	9,009	D
52.778	68.898	710	8,080	8,080
51.071	71.443	721	14,236	235,800

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
65.423	65.65	-	-	-
61.341	62.427	344	-	Cost-Saving
51.848	66.556	749	10,203	D
50.259	66.402	770	9,345	9,345
48.566	68.980	782	14,958	203,055

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	75.292	722	29,097	D
51.441	75.117	741	27,292	27,292
49.743	77.682	753	32,645	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	65.233	722	3,194	D
51.441	65.058	741	2,615	2,615
49.743	67.623	753	8,658	218,647

table continues

Index case genetic pathway: proportion of patients accepting genetic counseling -50% (42%)				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	18.17	4.237
2-yearly colonoscopy	235	66	18.17	5.669
1-yearly colonoscopy	228	66	18.17	9.932
Index case genetic pathway: proportion of patients accepting genetic counseling +50% (100%)				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	9.229	4.237
2-yearly colonoscopy	235	66	9.229	5.669
1-yearly colonoscopy	228	66	9.229	9.932
Index case genetic pathway: proportion of patients that once seen by genetic counselor will undergo genetic testing -50% (40%)				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	18.495	4.237
2-yearly colonoscopy	235	66	18.495	5.669
1-yearly colonoscopy	228	66	18.495	9.932
Index case genetic pathway: proportion of patients that once seen by genetic counselor will undergo genetic testing +50% (100%)				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	8.856	4.237
2-yearly colonoscopy	235	66	8.856	5.669
1-yearly colonoscopy	228	66	8.856	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	75.455	722	29,518	D
51.441	75.281	741	27,693	27,693
49.743	77.845	753	33,034	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	66.514	722	6,494	D
51.441	66.340	741	5,759	5,759
49.743	68.905	753	11,714	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	75.780	722	30,354	D
51.441	75.606	741	28,490	28,490
49.743	78.170	753	33,809	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	66.141	722	5,533	D
51.441	65.967	741	4,844	4,844
49.743	68.531	753	10,824	218,647

table continues

Index case genetic pathway: proportion of patients undergoing genetic testing that are positive for LS -50% (33%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	20.124	4.237
2-yearly colonoscopy	235	66	20.124	5.669
1-yearly colonoscopy	228	66	20.124	9.932

Index case genetic pathway: proportion of patients undergoing genetic testing that are positive for LS +50% (100%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	7.242	4.237
2-yearly colonoscopy	235	66	7.242	5.669
1-yearly colonoscopy	228	66	7.242	9.932

FDRs LS cases: average number of FDRs of identified LS case -50%(2.98)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	19.845	4.237
2-yearly colonoscopy	235	66	19.845	5.669
1-yearly colonoscopy	228	66	19.845	9.932

FDRs LS cases: average number of FDRs of identified LS case +50%(8.94)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	7.335	4.237
2-yearly colonoscopy	235	66	7.335	5.669
1-yearly colonoscopy	228	66	7.335	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	77.409	722	34,549	D
51.441	77.234	741	32,486	32,486
49.743	79.799	753	37,693	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	64.527	722	1,377	D
51.441	64.353	741	884	884
49.743	66.917	753	6,975	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	77.130	722	33,831	D
51.441	76.956	741	31,803	31,803
49.743	79.521	753	37,029	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	64.620	722	1,616	D
51.441	64.445	741	1,112	1,112
49.743	67.010	753	7,197	218,647

table continues

FDRs LS cases: proportion of FDRs that accept genetic counseling -50%(26%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	19.845	4.237
2-yearly colonoscopy	235	66	19.845	5.669
1-yearly colonoscopy	228	66	19.845	9.932

FDRs LS cases: proportion of FDRs that accept genetic counseling +50%(78%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	7.335	4.237
2-yearly colonoscopy	235	66	7.335	5.669
1-yearly colonoscopy	228	66	7.335	9.932

FDRs LS cases: proportion of FDRs that once seen by genetic counselor will undergo genetic testing -50%(47.5%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	20.035	4.237
2-yearly colonoscopy	235	66	20.035	5.669
1-yearly colonoscopy	228	66	20.035	9.932

FDRs LS cases: proportion of FDRs that once seen by genetic counselor will undergo genetic testing +50%(100%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	9.984	4.237
2-yearly colonoscopy	235	66	9.984	5.669
1-yearly colonoscopy	228	66	9.984	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	77.130	722	33,831	D
51.441	76.956	741	31,803	31,803
49.743	79.521	753	37,029	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	64.620	722	1,616	D
51.441	64.445	741	1,112	1,112
49.743	67.010	753	7,197	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	77.320	722	34,319	D
51.441	77.145	741	32,268	32,268
49.743	79.710	753	37,481	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.269	722	8,437	D
51.441	67.094	741	7,610	7,610
49.743	69.659	753	13,513	218,647

table continues

FDRs LS cases: proportion of FDRs testing positive on a germline test -50%(25%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	20.835	4.237
2-yearly colonoscopy	235	66	20.835	5.669
1-yearly colonoscopy	228	66	20.835	9.932

FDRs LS cases: proportion of FDRs testing positive on a germline test +50%(75%)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	7.005	4.237
2-yearly colonoscopy	235	66	7.005	5.669
1-yearly colonoscopy	228	66	7.005	9.932

Colonoscopy screening participation not diagnosed with LS = 40%

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	325	130		0.799
LS testing				
3-yearly colonoscopy	244	67	10.462	4.237
2-yearly colonoscopy	235	66	10.462	5.669
1-yearly colonoscopy	228	66	10.462	9.932

Colonoscopy screening participation not diagnosed with LS = 80%

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	291	94		1.370
LS testing				
3-yearly colonoscopy	244	67	10.462	4.237
2-yearly colonoscopy	235	66	10.462	5.669
1-yearly colonoscopy	228	66	10.462	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	78.120	722	36,379	D
51.441	77.945	741	34,230	34,230
49.743	80.510	753	39,389	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	64.290	722	767	D
51.441	64.116	741	303	303
49.743	66.680	753	6,410	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
64.351	65.150	222	-	Cost-Saving
53.048	67.747	722	5,200	D
51.441	67.573	741	4,671	4,671
49.743	70.138	753	9,401	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
61.465	62.835	445	-	Cost-Saving
53.048	67.747	722	17,727	D
51.441	67.573	741	15,985	15,985
49.743	70.138	753	23,700	218,647

table continues

Colonoscopy surveillance participation diagnosed with LS = 70%				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	258	80	10.462	3.736
2-yearly colonoscopy	251	79	10.462	4.989
1-yearly colonoscopy	244	79	10.462	8.719
Colonoscopy surveillance participation diagnosed with LS = 90%				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	229	55	10.462	4.738
2-yearly colonoscopy	220	54	10.462	6.350
1-yearly colonoscopy	212	54	10.462	11.145
Related to genetic testing: combined costs of lab testing in index CRC case -50%($112)				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	6.69	4.237
2-yearly colonoscopy	235	66	6.69	5.669
1-yearly colonoscopy	228	66	6.69	9.932
Related to genetic testing: combined costs of lab testing in index CRC case +50%($336)				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	14.235	4.237
2-yearly colonoscopy	235	66	14.235	5.669
1-yearly colonoscopy	228	66	14.235	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
54.822	69.020	632	16,866	D
53.416	68.867	649	15,478	15,478
51.930	71.111	659	21,890	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
51.274	66.475	812	5,188	D
49.467	66.279	834	4,571	4,571
47.557	69.164	847	10,072	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	D
53.048	63.975	722	Cost-Saving	D
51.441	63.801	741	Cost-Saving	Cost-Saving
49.743	66.366	753	5,660	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	71.520	722	19,383	D
51.441	71.345	741	18,039	18,039
49.743	73.910	753	23,650	218,647

table continues

Related to genetic testing: cost of patient navigator per individual referred to genetic counseling -50%($54)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.381	4.237
2-yearly colonoscopy	235	66	10.381	5.669
1-yearly colonoscopy	228	66	10.381	9.932

Related to genetic testing: cost of patient navigator per individual referred to genetic counseling +50%($162)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.544	4.237
2-yearly colonoscopy	235	66	10.544	5.669
1-yearly colonoscopy	228	66	10.544	9.932

Related to genetic testing: costs of pre-test genetic counseling in CRC index case -50%($128)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.3	4.237
2-yearly colonoscopy	235	66	10.3	5.669
1-yearly colonoscopy	228	66	10.3	9.932

Related to genetic testing: costs of pre-test genetic counseling in CRC index case +50%($383)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.625	4.237
2-yearly colonoscopy	235	66	10.625	5.669
1-yearly colonoscopy	228	66	10.625	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.666	722	9,459	D
51.441	67.491	741	8,584	8,584
49.743	70.056	753	14,460	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.829	722	9,880	D
51.441	67.655	741	8,985	8,985
49.743	70.219	753	14,849	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.585	722	9,252	D
51.441	67.411	741	8,386	8,386
49.743	69.975	753	14,267	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.910	722	10,088	D
51.441	67.735	741	9,183	9,183
49.743	70.300	753	15,042	218,647

table continues

Related to genetic testing: avg. cost of germline test in index CRC case -50%($550)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	9.903	4.237
2-yearly colonoscopy	235	66	9.903	5.669
1-yearly colonoscopy	228	66	9.903	9.932

Related to genetic testing: avg. cost of germline test in index CRC case +50%($1,649)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	11.022	4.237
2-yearly colonoscopy	235	66	11.022	5.669
1-yearly colonoscopy	228	66	11.022	9.932

Related to genetic testing: post-test genetic counseling and tracing FDRs for LS positive cases -50%($45)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.292	4.237
2-yearly colonoscopy	235	66	10.292	5.669
1-yearly colonoscopy	228	66	10.292	9.932

Related to genetic testing: post-test genetic counseling and tracing FDRs for LS positive cases +50%($135)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.633	4.237
2-yearly colonoscopy	235	66	10.633	5.669
1-yearly colonoscopy	228	66	10.633	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.188	722	8,228	D
51.441	67.013	741	7,411	7,411
49.743	69.578	753	13,320	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	68.307	722	11,111	D
51.441	68.133	741	10,158	10,158
49.743	70.698	753	15,989	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.577	722	9,231	D
51.441	67.403	741	8,367	8,367
49.743	69.968	753	14,249	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.918	722	10,108	D
51.441	67.743	741	9,202	9,202
49.743	70.308	753	15,061	218,647

table continues

Related to genetic testing: somatic testing for LS negative cases -50%($250)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.377	4.237
2-yearly colonoscopy	235	66	10.377	5.669
1-yearly colonoscopy	228	66	10.377	9.932

Related to genetic testing: somatic testing for LS negative cases +50%($750)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.547	4.237
2-yearly colonoscopy	235	66	10.547	5.669
1-yearly colonoscopy	228	66	10.547	9.932

Related to genetic testing: costs of germline testing for LS in a FDR with a known mutation -50%($200)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.062	4.237
2-yearly colonoscopy	235	66	10.062	5.669
1-yearly colonoscopy	228	66	10.062	9.932

Related to genetic testing: costs of germline testing for LS in a FDR with a known mutation +50%($600)

Strategy	CRC cases[a]	CRC deaths[a]	Costs LS testing[b,c] (million$)	Costs CRC screening[b,d] (million$)
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.862	4.237
2-yearly colonoscopy	235	66	10.862	5.669
1-yearly colonoscopy	228	66	10.862	9.932

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.662	722	9,451	D
51.441	67.488	741	8,576	8,576
49.743	70.053	753	14,452	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.832	722	9,888	D
51.441	67.658	741	8,993	8,993
49.743	70.223	753	14,857	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	67.347	722	8,640	D
51.441	67.173	741	7,803	7,803
49.743	69.738	753	13,701	218,647

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.465	-	-	-
62.908	63.992	334	-	Cost-Saving
53.048	68.147	722	10,700	D
51.441	67.973	741	9,766	9,766
49.743	70.538	753	15,609	218,647

table continues

Related to colonoscopies: costs of colonoscopies -50%($474/$596[f])				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.114
No LS testing				
10-yearly colonoscopy	308	112		0.542
LS testing				
3-yearly colonoscopy	244	67	10.462	2.119
2-yearly colonoscopy	235	66	10.462	2.835
1-yearly colonoscopy	228	66	10.462	4.966
Related to colonoscopies: costs of colonoscopies +50%($1,472/$1,788[f])				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.341
No LS testing				
10-yearly colonoscopy	308	112		1.626
LS testing				
3-yearly colonoscopy	244	67	10.462	6.356
2-yearly colonoscopy	235	66	10.462	8.504
1-yearly colonoscopy	228	66	10.462	14.898
Colorectal cancer care costs -50%				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.462	4.237
2-yearly colonoscopy	235	66	10.462	5.669
1-yearly colonoscopy	228	66	10.462	9.932
Colorectal cancer care costs +50%				
Strategy	**CRC cases[a]**	**CRC deaths[a]**	**Costs LS testing[b,c] (million$)**	**Costs CRC screening[b,d] (million$)**
No LS testing or CRC screening	359	165		0.227
No LS testing				
10-yearly colonoscopy	308	112		1.084
LS testing				
3-yearly colonoscopy	244	67	10.462	4.237
2-yearly colonoscopy	235	66	10.462	5.669
1-yearly colonoscopy	228	66	10.462	9.932

CRC - Colorectal Cancer; LS - Lynch Syndrome; LYG - Life-Years Gained; ACER - Average Cost-Effectiveness Ratio; ICER - Incremental Cost-Effectiveness Ratio; D - Dominated.

[a] CRC cases and deaths include those from LS diagnosis until death.

[b] Costs and life-years gained were discounted at an annual rate of 3%.

[c] Include total costs of screening CRC index cases and their FDRs, including LS negative and non-participants.

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.351	-	-	-
62.908	63.450	334	-	Cost-Saving
53.048	65.629	722	5,610	D
51.441	64.738	741	3,160	3,160
49.743	65.172	753	4,105	36,951

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
67.237	67.578	-	-	-
62.908	64.534	334	-	Cost-Saving
53.048	69.866	722	13,729	D
51.441	70.408	741	14,409	28,093
49.743	75.104	753	25,204	400,343

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
33.619	33.846	-	-	-
31.454	32.538	334	-	Cost-Saving
26.524	41.223	722	22,365	D
25.721	41.852	741	22,850	32,610
24.872	45.266	753	30,351	291,020

Costs CRC care[b] (million$)	Total costs[ab] (million$)	LYG[b] (y)	ACER[b,e] ($)	ICER[b] ($)
100.856	101.083	-	-	-
94.362	95.446	334	-	D
79.572	94.271	722	Cost-Saving	D
77.162	93.294	741	Cost-Saving	Cost-Saving
74.615	95.010	753	Cost-Saving	146,275

[d] Include costs of CRC screening, diagnosis and surveillance.

[e] Compared to no LS screening.

[f] Costs used for colonoscopies without polypectomy/with polypectomy.

Chapter 10

Cost-effectiveness of prophylactic hysterectomy in first-degree female relatives with Lynch syndrome of patients diagnosed with colorectal cancer in the United States: a microsimulation study

Maaike Alblas*, Elisabeth F.P. Peterse*, Mengmeng Du, Ann G. Zauber, Ewout W. Steyerberg, Nikki van Leeuwen & Iris Lansdorp-Vogelaar

Submitted

*These authors contributed equally

Abstract

Aim

To evaluate the cost-effectiveness of prophylactic hysterectomy (PH) in women with Lynch syndrome (LS).

Methods

We developed a microsimulation model incorporating the natural history for the development of hyperplasia with and without atypia into endometrial cancer (EC) based on the MISCAN-framework. We simulated women identified as first-degree relatives (FDR) with LS of colorectal cancer patients after universal testing for LS. We estimated costs and benefits of offering this cohort PH, accounting for reduced quality of life after PH and for having EC. Three minimum ages (30/35/40) and three maximum ages (70/75/80) were compared to no PH.

Results

In the absence of PH, the estimated number of EC cases was 300 per 1,000 women with LS. Total associated costs for treatment of EC were $2.7 million. Offering PH to FDRs aged 40-80 years was considered optimal. This strategy reduced the number of endometrial cancer cases to 5.4 (-98%), resulting in 516 quality-adjusted life years (QALY) gained and increasing the costs (treatment of endometrial cancer and PH) to $14.5 million (+437%) per 1,000 women. PH from earlier ages was more costly and resulted in fewer QALYs, although this finding was sensitive to disutility for PH.

Conclusions

Offering PH to 40-80 year old women with LS is expected to add 0.5 QALY per person at acceptable costs. Women may decide to have PH at age 35 years, depending on their individual disutility for PH and premature menopause.

Introduction

It has been standard policy for years to try and identify Lynch Syndrome (LS) mutation carriers among colorectal cancer (CRC) patients. Initially, this was done using family history criteria, but since the past decade, universal reflex testing of tumors of CRC patients for mismatch repair deficiency has become increasingly accepted. The aim of this practice is to identify first-degree relatives (FDR) with LS, in order to provide them with preventive interventions. [366-370] LS is a hereditary condition that causes a substantial risk of both colorectal cancer (30-60%) and endometrial cancer (17-60%).[37,371-373] It is estimated that approximately 1 in 300 individuals have LS in the United States (US). [374-376] The practice of universal testing for LS and offering FDR with LS intensive colonoscopy screening for colorectal cancer has shown to be (cost-)effective.[377,378] Yearly endometrial sampling from age 30-35 years onwards might be considered a possible screening strategy for female carriers, but there is no consensus on the effectiveness and impact on quality of life of this strategy.[379] Prophylactic hysterectomy combined with oophorectomy (further referred to as prophylactic hysterectomy, PH) when childbearing is completed has been suggested as a preventive strategy. It might prevent nearly all endometrial cancer cases and deaths in women with LS. [369,380] However, little is known about its cost-effectiveness and the optimal age range. Determining this optimal age range requires to consider different elements that are associated with PH, such as costs and quality of life. One study using a Markov model showed that offering prophylactic hysterectomy from age 40 is cost-effective, but these results were based on a single-age cohort and only a limited number of strategies (two minimum ages and no maximum age).[381] In reality, the age distribution of identified LS carriers ranges from 11 to 80.[342] This age range is of specific importance because women at higher ages should be able to weigh the benefits and harms of surgery, given that they have not developed symptomatic endometrial cancer. To our knowledge, no previous study has incorporated the age range of LS carriers in their modelling. The aim of this study was to evaluate the cost-effectiveness of offering prophylactic hysterectomy to female FDR with LS, comparing different age ranges to assess optimal age thresholds. Therefore, we developed a microsimulation model for endometrial cancer based on the MISCAN modeling framework.

Methods

Model specification and assumptions

We used the well-established MISCAN model as a framework to develop the MISCAN Endometrial model. The MISCAN model has been extensively described elsewhere.[102,103] In short, the MISCAN models simulate a large population of individuals, including life histories from birth to death. The simulations are based on input parameters, which contain both demographic information and the natural history of the specific disease. The results of the MISCAN models include information on age-specific disease incidence and mortality.

The natural history part of the model is shown in **Figure 10.1** and divides the development of endometrial cancer in three sequential phases: preclinical hyperplasia, preclinical cancer and clinical cancer.[37] We assumed two types of hyperplasia, of which endometrial hyperplasia without atypia is 6.14 times more frequent than atypical endometrial hyperplasia.[382] The progression of hyperplasia to endometrial cancer differed between hyperplasia without atypia and hyperplasia with atypia, since both have different dwelling times.[382] Dwelling times were derived from Lacey et al. and were estimated with a Weibull distribution.[382] In line with assumptions made for the development of colorectal cancer, preclinical lesions were assumed to progress 10 times faster in LS patients than in the general population.[378] The age specific onset of endometrial hyperplasia was calibrated to match the incidence of EC for LS women according to Bonadona et al.[37] (**Supplementary Figure A10.1**) The survival rates were based on SEER 18 data and were corrected for death due to other causes.[122] Upon of diagnosis of EC, death can occur due to EC or other causes.

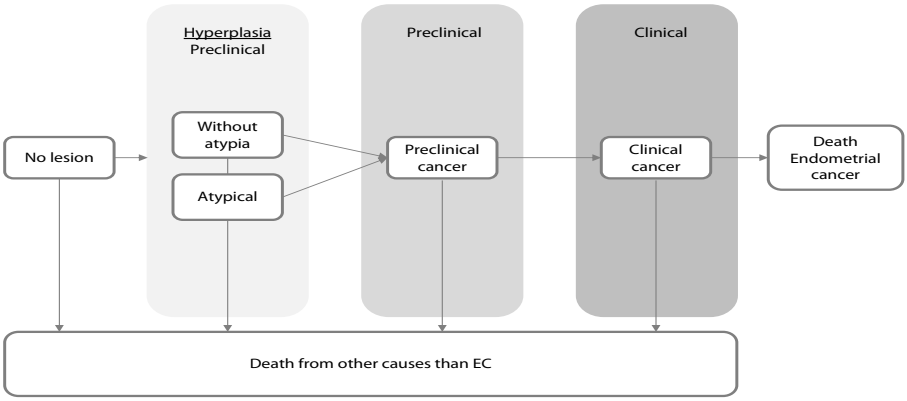


Figure 10.1: Natural history model of MISCAN Endometrium model. EC – Endometrial cancer.

Study population

For each EC prevention strategy, we simulated a population of 10 million Lynch positive women. The target population for prophylactic hysterectomy consisted of FDR with LS of colorectal cancer patients with LS (**Figure 10.2**). The age range of the population simulated matched that of FDR with LS in a Dutch study of universal testing of LS in colorectal cancer.[342] Individuals were between age 11 and 80 when they were diagnosed with LS. Their median age was 42 years, with an interquartile range of 31-55 years. In addition, benefits and costs of PH by five-year age groups were computed.

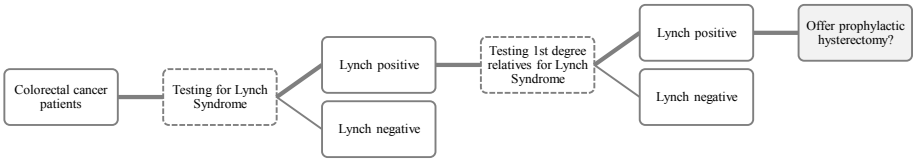


Figure 10.2: Flowchart target population for prophylactic hysterectomy

Strategies

Nine different age ranges were modelled with varying ages at which prophylactic hysterectomy was offered as young as 30, 35 or 40 years and as old as age 70, 75, or 80 years. Prophylactic hysterectomy was considered to eliminate the risk of EC completely from date of surgery. We assumed full compliance of every woman who was invited for prophylactic hysterectomy.

Data and assumptions for costs and utilities

An overview of the costs and utilities that were used in the model can be found in Table 10.1. We assumed that prophylactic hysterectomy reduced the quality of life because of surgically induced menopause. The first month after surgery, quality of life was valued at 0.56, followed by 0.74 in the second and third month after surgery.[383-386] From three months onwards, we assumed a utility of 0.88 and corrected the quality of life up to the age of 45, as it is assumed that natural menopause starts at this age which eliminates the negative side effects on quality of life of prophylactic hysterectomy.[381,384,387] We also adjusted the quality of life of women diagnosed with EC.[381,388] Furthermore, we assumed that the costs of treatment for EC are equal to the costs of prophylactic hysterectomy, as treatment of EC usually consists of a hysterectomy. Hence, we did not include chemotherapy or multiple surveillances for patients with EC.[389] The costs of (prophylactic) hysterectomy are reported as total Medicare reimbursement and include gynecologist fee, anesthesia fee for hysterectomy, pathology fee for uterus, pathology fee for lymph nodes, inpatient diagnosis-related group fees, and preoperative lab fees.[389]

Outcomes

We determined the effects of offering prophylactic hysterectomy in terms of number of EC deaths, number of prophylactic hysterectomies, life years gained (LYG) and quality –adjusted life years gained (QALYG). We calculated the associated costs for each strategy based on number of prophylactic hysterectomies and total treatment costs for endometrial cancer. We applied a 3% discount rate for both effects and costs to the year in which the women were diagnosed with LS, except for the number of EC cases and deaths. Our analyses were performed with the assumptions described in Table 10.1. We evaluated average cost-effectiveness ratios (ACERs), which are defined as the difference in costs divided by the difference in QALYG compared to the no prophylactic hysterectomy strategy. Next, the incremental cost-effectiveness ratios (ICERs) of the different strategies were evaluated to determine the optimal strategy. We assumed a willingness-to-pay threshold of 100,000 US dollars per QALY for this analysis.

Sensitivity analyses

To evaluate which assumptions were important drivers for our conclusion, we performed several sensitivity analyses (see range in Table 10.1). We varied: (1) Quality of life of endometrial cancer, prophylactic hysterectomy and health state well; (2) costs of (prophylactic) hysterectomy; (3) risk of endometrial cancer; and (4) lower life expectancy due to colorectal cancer risk in LS.

Table 10.1: Model inputs

Variable	Base case	Range	Reference
Cumulative Risk of developing EC before age 80	35%	17-60	Bonadona 2011[37]
Age distribution of FDR[a]	11-80	-	Leenen 2016[342]
Survival probability	Age specific	-	SEER 2009-2013
Ratio of prevalence of hyperplasia without atypia compared to with atypia	6.14	-	Lacey 2010[382]
Life table	Age specific	-	National Vital Statistics Reports 2012[390]
Dwelling time atypical lesions	7.77		Assumption[b]
Dwelling time lesions without atypia	114.40		Assumption[b]
Costs prophylactic hysterectomy[c]	16,273	8,137-32,546	Havrilesky 2009[389]
Costs EC[c]	16,273	8,137-32,546	Assumption[d]
Utility prophylactic hysterectomy	0.88	0.82-0.99	Roberts 2011[383] Bhattacharya 2011[385] Hurskainen 2004[386]
Utility well	1	0.8-1.0	Fryback 1993[391]

EC - Endometrial Cancer, FDRs First-degree Relatives

[a] The median age was 42 years, with an interquartile range of 31-55 years

[b] We derived dwelling times from Lacey et al 2010 with a Weibull distribution. We assumed that for women with Lynch Syndrome, dwelling times were 10 times shorter as for the general population. Values are shown as mean input parameter, dwelling times of lesions that develop into EC will be shorter.[392]

[c] Cost reported as total Medicare reimbursement in US dollars. Includes: gynecologist fee, anesthesia fee for hysterectomy, pathology fee for uterus, pathology fee for lymph nodes, inpatient diagnosis-related group fees, preoperative lab fees.

[d] We assumed that the costs of treatment for EC are equal to the costs of prophylactic hysterectomy, as treatment of EC usually consists of a hysterectomy.

Results

In the absence of prophylactic hysterectomy in FDRs with LS, the MISCAN-Endometrium model predicted 300 EC cases and 71 EC deaths per 1,000 women with LS, accounting for the age distribution of the FDR at LS diagnosis. Total associated costs for the treatment of EC were estimated at $2.7 million. Offering these women prophylactic hysterectomy greatly reduced the number of EC cases and deaths, ranging from 0 to 11 and of 0 to 2.9 per 1,000 women, respectively. Although the number of LYG

varied relatively little between the different strategies (411-435 per 1,000 women), the number of QALYG was substantially higher for strategies with age 40 as a start age (506-516 per 1,000 women) compared to age 35 (423-432 per 1,000 women) and age 30 (262-272). All strategies with prophylactic hysterectomy were cost-effective compared to no prophylactic hysterectomy, with ACERs below $50,000 when either LYG or QALYG were used as effectiveness measures (Table 10.2).

Table 10.2: Results per 1000 women diagnosed with Lynch syndrome

Strategy	EC cases	EC deaths	LYG[a,b]	QALYG[a,b]	Costs[a,] (million US$)	ACER QALYG[a,b]
No prophylactic hysterectomy	300	70.9	-	-	2.696	
30-70	5.6	2.0	426	262	14.917	$46,696
30-75	1.3	0.5	433	269	15.362	$47,012
30-80	0.0	0.0	435	272	15.553	$47,332
35-70	6.6	2.1	423	374	14.451	$31,454
35-75	2.3	2.9	430	381	14.896	$31,985
35-80	1.0	0.2	432	384	15.087	$32,298
40-70	11.0	2.9	411	506	13.834	$22,017
40-75	6.7	1.5	417	514	14.278	$22,553
40-80	5.4	1.0	420	516	14.469	$22,826

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Table 10.3: Results per age category (per 1000 women diagnosed with Lynch syndrome)

Strategy	EC cases prevented	EC deaths prevented	LYG[a, b]	QALYG[a]	Additional costs[a] (million US$)
30-34	351.8	77.9	460	-489	13.653
35-39	348.5	77.6	510	45	13.331
40-44	339.5	76.2	536	608	13.085
45-49	323.4	73.8	534	918	12.951
50-54	297.1	70.3	502	845	13.002
55-59	258.1	65.8	443	701	13.305
60-64	217.8	60.9	385	558	13.665
65-69	178.8	55.0	320	420	14.041
70-74	142.2	48.0	252	292	14.423
75-79	108.8	40.7	188	182	14.797

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained

[a] Results are 3% discounted

[b] Earlier PH adds slightly more LYG for women who would otherwise die from EC between this age group and the next. On the other hand, LYG in all women who would be diagnosed with EC after age 35 are discounted for 5 more years and therefore become smaller.

When adjusting for quality of life, only strategies in which prophylactic hysterectomy was offered to FDRs after age 40 were efficient strategies; strategies that included prophylactic hysterectomy from age 30 and age 35 were more costly and resulted in fewer quality-adjusted life years gained (**Figure 10.3**). The ICERs for ages 40-75 and ages 40-80 were $57,869 and $86,105, respectively. Assuming a willingness-to-pay threshold of $100,000, offering prophylactic hysterectomy to LS women aged 40-80 was considered optimal. Compared to no prophylactic hysterectomy, this strategy would reduce the number of endometrial cancer cases to 5.4 (-98%), resulting in 516 quality-adjusted life years gained and increasing the costs (treatment of endometrial cancer and prophylactic hysterectomy) to $14.5 million (+437%) per 1,000 women. That PH before age 40 is not cost-effective can easily be seen from **Table 10.3**. For example, offering PH to women aged 30-34 prevents 77.9 EC deaths compared to 76.2 EC deaths for PH, women aged 40-44 prevents (**Table 10.3**), which is an increase of 2.2%. The life-years with PH before age 45 on the other hand increase from approximately 2.5 years to 12.5 years, an increase of 400%. At the other extreme, **Table 10.3** also clearly outlines why PH is still worthwhile even up to age 80: in 75-79 year-olds still more than 40 EC deaths per 1,000 women can be prevented, while the disutility from PH at that age is small, because we only assume disutility in the first three months after surgery.

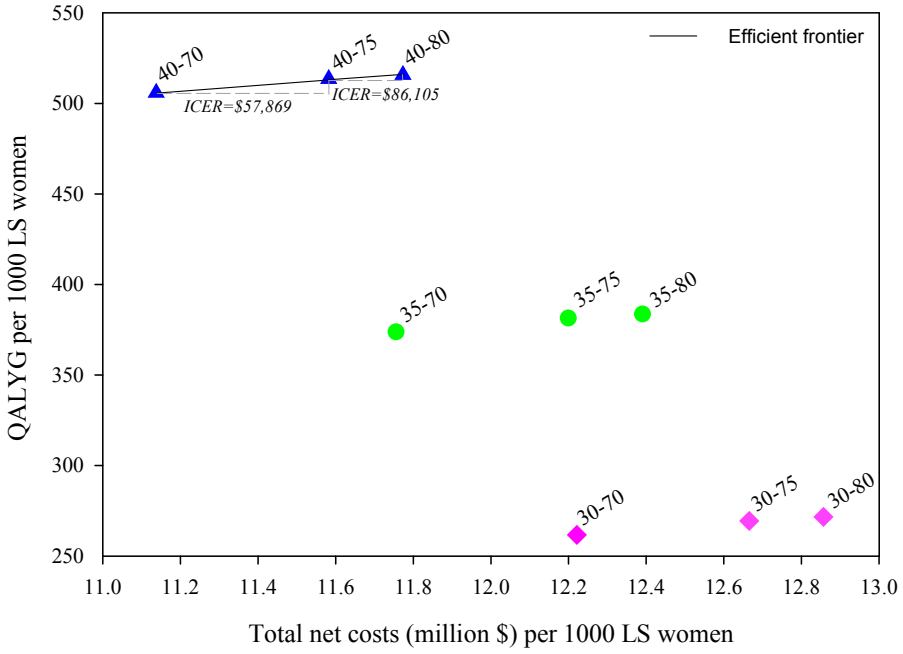


Figure 10.3: Efficiency frontier quality-adjusted life years gained.
QALYG - Quality-adjusted life-years gained; LS - Lynch syndrome

Sensitivity analyses

The findings of this study were robust for most of our assumptions (Supplementary Tables A10.1-A10.8). Only when a lower utility after PH was assumed or life-years gained were considered as the primary outcome, offering prophylactic hysterectomy before age 40 was optimal. However, there were no model-recommended strategies with starting ages below 35 years. The recommended stop age was age 80 in all analyses, except when higher hysterectomy costs were assumed (Table 10.4).

Table 10.4: Model-recommended strategies with a willingness-to-pay threshold of $100,000 based on varying input parameters in sensitivity analyses

	Model-recommended strategies
Base case	40-80
Base case without adjustment for quality of life	35-80
(Prophylactic) hysterectomy costs	
- 50%	40-80
+ 100%	40-70
Utility endometrial cancer	
0.68	40-80
Utility prophylactic hysterectomy	
0.82	40-80
0.99	35-80
Risk of endometrial cancer	
17%	40-80
60%	40-80
Accounting for reduced life expectancy due to increased colorectal cancer risk in LS[a]	40-80

QALYG - Quality-adjusted life-years gained; LYG - life years gained

[a] MISCAN-Colon was used to generate lifetables that accounted for the increased colorectal cancer mortality of LS women, assuming LS women participated in biennial colonoscopy surveillance from age 25 to age 80.[378]

Discussion

We evaluated the cost-effectiveness of offering prophylactic hysterectomy to asymptomatic women diagnosed with LS by reflex testing and subsequent cascade testing of FDR with colorectal cancer. Our results show that offering prophylactic hysterectomy to these women is cost-effective at currently accepted standards, and is most cost-effective when offered between age 40 and 80. Depending on an individual disutility for PH and premature menopause, women may decide to undergo PH at age 35 when the perceived impact of PH and premature menopause is small.

Obviously, earlier stop ages were optimal when higher costs of hysterectomy were assumed. The increase in benefits of offering prophylactic hysterectomy to LS women

until age 80 rather than age 70 or 75 was relatively small. This may be explained by the median age of diagnosis of endometrial cancer in patients with LS, which is 48 years,[393] while 98% may be diagnosed before the age of 65 years.[393] This may support stopping prophylactic hysterectomy before age 70 to prevent potential unnecessary surgery. However, as long as the relative increase in costs is also small, offering prophylactic hysterectomy until age 80 may be considered.

Altering the input parameters for quality of life after PH resulted in the recommendation to start prophylactic hysterectomy at an age younger than 40 years. Women will go into premature menopause as a result of prophylactic hysterectomy, which can result in depression, anxiety, sexual dysfunction and lower self-confidence.[394] We must acknowledge the presence of individual variation in the impact of PH on quality of life during premature menopause. Little is known on this individual variation and specific data on utilities after prophylactic surgery instead of curative surgery is currently lacking. Therefore, empirical data regarding quality of life after prophylactic hysterectomy and the resulting premature menopause are needed to make the quality of life adjustments that are made in our model more robust.

An important strength of this study is that it comprehensively compares the cost-effectiveness of offering prophylactic hysterectomy to women diagnosed with LS for different minimum and maximum ages in a mixed population of different ages. Our results are in line with the results from a prior Markov decision model by Kwon et al.,[381] who also showed that offering prophylactic hysterectomy from age 40 was the best strategy. Like us, Kwon et al.[381] also showed that the results are highly depended on the inclusion of quality of life in the analyses. In our analyses, starting with prophylactic hysterectomy at age 30 until age 80 prevented all endometrial cancer cases and deaths due to endometrial cancer, leading to a high number of LYG. However, this strategy comes at a high prize in terms of costs and quality of life. Hence, any strategy that starts at the age of 30 or even age 35 was dominated by strategies that start prophylactic hysterectomy at age 40. In addition, the age when women have their first child is increasing, which might cause women to complete their family at an older age.[395] As a consequence, women may postpone prophylactic hysterectomy. Yang et al.[396] identified prophylactic hysterectomy from age 30 as optimal strategy, compared to annual examination. However, no other start ages were tested, which complicates the comparison with the results from our study.

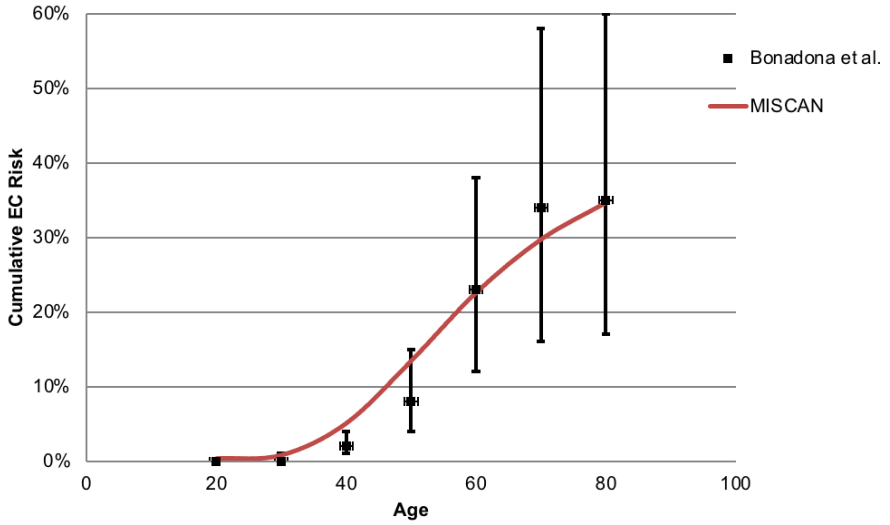
Some limitations of our study should be acknowledged. First, we used the utilities and costs of hysterectomy combined with oophorectomy in our analyses, while we did not incorporate ovarian cancer in our microsimulation model. We have chosen to do so because prophylactic hysterectomy combined with oophorectomy has been recommended as preventive strategy in female patients with LS, given their elevated risk of ovarian cancer (2-39% life time risk).[380] As we now do account for the burden of oophorectomy in our analysis, our estimated ICERs are likely to be underestimated. Second, we assumed that every woman who was invited for prophylactic hysterectomy would undergo this procedure. The model therefore predicted the maximum achievable benefits of prophylactic hysterectomy. Although this implies that the predicted benefits

are unrealistic, guidelines should be made based on the benefits that would accrue under perfect rates of adherence to recommendations. Moreover, any change in rates of adherence will have no effects on the ratios that were calculated in our analyses, as the costs and benefits that were used are proportional. Research has shown that FDR of patients with LS underutilize genetic screening, with uptake varying from 15% to 53%.[397] A study on the uptake of bilateral risk-reducing mastectomy and bilateral risk-reducing salpingo-oophorectomy amongst BRCA1/2 mutation carriers showed that uptake was 40% and 45% respectively, and was related to lifetime risk and age.[398] Third, we did not consider other LS-related cancers, such as colorectal or ovarian cancer; due to the lack of data we assumed that apart from an increased EC risk, LS cases have a normal life expectancy. Although the risk of colorectal cancer can be greatly reduced by intensive colonoscopy surveillance,[339] this potentially resulted in an overestimation of life-years gained per EC death prevented. However, our sensitivity analysis showed that our findings were robust when we corrected life expectancy for the increased colorectal cancer mortality in LS. Third, the natural history of EC in women with LS is largely unknown. In line with analyses performed for colorectal cancer in LS, we assumed that dwelling times are ten times shorter for women with LS compared to the general population. Lastly, the risk of EC in LS women is uncertain, as estimates vary greatly among studies.[37] We calibrated our model to the largest study that accounted for ascertainment bias,[37,371,372] and explored higher and lower risk levels in sensitivity analyses. Our results demonstrate that the optimal age range depends on the assumed EC risk for LS cases, which is why future studies are needed to determine the exact risk of EC in LS women.

Current guidelines in the United States recommend to offer prophylactic hysterectomy to women from age 40 or when childbearing has completed.[368] This is in line with the results from our study and underlines the importance of identifying LS mutation carriers among colorectal cancer patients and subsequent cascade testing to improve future prospects of these patients in terms of life expectancy and quality of life. However, standards and protocols vary between centers and countries, which may lead to undesired variation.[399] This variation may be caused by conflicting recommendations and protocols on the optimal screening and preventive strategy for LS.[400] Additional information regarding costs and effects of prophylactic hysterectomy, as provided by our study, may aid in the development of uniform protocols and recommendations for the identification of LS mutation carriers. Moreover, our results can inform physicians and women with LS regarding the decision whether or not to perform prophylactic hysterectomy and from which age, which is important in determining the optimal strategy given the preference-sensitive nature of the decisions these patients are facing.

In summary, our study suggests that offering prophylactic hysterectomy to women diagnosed with LS is cost-effective, and is most cost-effective when offered from age 40 until age 80. Individual variation in impact of PH and premature menopause on quality of life must be taken into account and may cause women to start PH earlier. These findings can be used to inform policy makers and clinicians regarding decisions about offering prophylactic hysterectomy to LS women.

Appendix



Supplementary Figure A10.1: Cumulative endometrial cancer risks by MISCAN Endometrium, calibrated to Bonadona et al.

Supplementary Table A10.1 : Results sensitivity analysis: -50% hysterectomy costs (per 1000 women diagnosed with Lynch syndrome

Strategy	EC cases	EC deaths	LYG[a]	QALYG[a]	Costs[a,] (million US$)	ACER QALYG[a,b]	ICER QALYG
No prophylactic hysterectomy	300	70.9	-	-	1.35		
40-70	11.0	2.9	411	530	6.92	$11,009	$11.009
40-75	6.7	1.5	417	541	7.14	$11,277	$28,936
35-70	6.6	2.1	423	375	7.23	$15,728	Dominated
40-80	5.4	1.0	420	544	7.23	$11,414	$43,055
35-75	2.3	2.9	430	385	7.45	$15,994	Dominated
30-70	5.6	2.0	426	245	7.46	$23,349	Dominated
35-80	1.0	0.2	432	388	7.54	$16,150	Dominated
30-75	1.3	0.5	433	255	7.68	$23,508	Dominated
30-80	0.0	0.0	435	258	7.78	$23,667	Dominated

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Supplementary Table A10.2: Results sensitivity analysis: +100% hysterectomy costs (per 1000 women diagnosed with Lynch syndrome)

Strategy	EC cases	EC deaths	LYG[a]	QALYG[a]	Costs[a,] (million US$)	ACER QALYG[a,b]	ICER QALYG
No prophylactic hysterectomy	300	70.9	-	-	5.39		
40-70	11.0	2.9	411	530	27.67	$44,034	$49,364
40-75	6.7	1.5	417	541	28.56	$45,106	$115,739
35-70	6.6	2.1	423	375	28.90	$62,908	Dominated
40-80	5.4	1.0	420	544	28.94	$45,653	$172,210
35-75	2.3	2.9	430	385	29.79	$63,970	Dominated
30-70	5.6	2.0	426	245	29.83	$93,392	Dominated
35-80	1.0	0.2	432	388	30.17	$64,596	Dominated
30-75	1.3	0.5	433	255	30.72	$94,025	Dominated
30-80	0.0	0.0	435	258	31.11	$94,663	Dominated

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Supplementary Table A10.3: Results sensitivity analysis: utility endometrial cancer 0.68 (per 1000 women diagnosed with Lynch syndrome)

Strategy	EC cases	EC deaths	LYG[a]	QALYG[a]	Costs[a,] (million US$)	ACER QALYG[a,b]	ICER QALYG
No prophylactic hysterectomy	300	70.9	-	-	2.70		
40-70	11.0	2.9	411	830	13.83	$24,972	$24,972
40-75	6.7	1.5	417	843	14.28	$25,563	$62,807
35-70	6.6	2.1	423	684	14.45	$37,690	Dominated
40-80	5.4	1.0	420	847	14.47	$25,867	$92,560
35-75	2.3	2.9	430	697	14.90	$38,246	Dominated
30-70	5.6	2.0	426	557	14.92	$61,292	Dominated
35-80	1.0	0.2	432	701	15.09	$38,595	Dominated
30-75	1.3	0.5	433	570	15.36	$61,341	Dominated
30-80	0.0	0.0	435	574	15.55	$61,650	Dominated

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Supplementary Table A10.4 : Results sensitivity analysis: utility prophylactic hysterectomy 0.82 (per 1000 women diagnosed with Lynch syndrome)

Strategy	EC cases	EC deaths	LYG[a]	QALYG[a]	Costs[a,] (million US$)	ACER QALYG[a,b]	ICER QALYG
No prophylactic hysterectomy	300	70.9	-	-	2.70		
40-70	11.0	2.9	411	468	13.83	$25,638	$25,638
40-75	6.7	1.5	417	478	14.28	$26,198	$57,847
35-70	6.6	2.1	423	261	14.45	$51,605	Dominated
40-80	5.4	1.0	420	481	14.47	$26,497	$86,097
35-75	2.3	2.9	430	271	14.90	$51,807	Dominated
30-70	5.6	2.0	426	92	14.92	$205,248	Dominated
35-80	1.0	0.2	432	274	15.09	$52,127	Dominated
30-75	1.3	0.5	433	102	15.36	$188,364	Dominated
30-80	0.0	0.0	435	106	15.55	$185,093	Dominated

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Supplementary Table A10.5: Results sensitivity analysis: utility prophylactic hysterectomy 0.99 (per 1000 women diagnosed with Lynch syndrome)

Strategy	EC cases	EC deaths	LYG[a]	QALYG[a]	Costs[a,] (million US$)	ACER QALYG[a,b]	ICER QALYG
No prophylactic hysterectomy	300	70.9	-	-	2.70		
40-70	11.0	2.9	411	734	13.83	$17,488	$17,488
40-75	6.7	1.5	417	744	14.28	$17,970	$57,911
35-70	6.6	2.1	423	745	14.45	$18,331	Dominated
40-80	5.4	1.0	420	747	14.47	$18,203	$86,119
35-75	2.3	2.9	430	755	14.90	$18,799	Dominated
30-70	5.6	2.0	426	741	14.92	$19,326	Dominated
35-80	1.0	0.2	432	758	15.09	$19,028	$139,171
30-75	1.3	0.5	433	751	15.36	$19,788	Dominated
30-80	0.0	0.0	435	754	15.55	$20,017	Dominated

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Supplementary Table A10.6: Results sensitivity analysis: risk endometrial cancer 17% (per 1000 women diagnosed with Lynch syndrome)

Strategy	EC cases	EC deaths	LYG[a]	QALYG[a]	Costs[a,] (million US$)	ACER QALYG[a,b]	ICER QALYG
No prophylactic hysterectomy	284	69.0	-	-	2.46		
40-70	6.3	2.2	363	442	13.88	$27,439	$27,439
40-75	1.8	0.6	370	453	14.33	$27,912	$54,544
35-70	6.0	2.1	363	272	14.48	$44,723	Dominated
40-80	0.4	0.1	372	456	14.53	$28,282	$87,295
30-70	5.9	2.1	364	143	14.93	$45,017	Dominated
35-75	1.5	2.2	371	283	14.93	$79,556	Dominated
35-80	0.1	0.0	373	286	15.13	$45,355	Dominated
30-75	1.4	0.5	371	154	15.38	$78,287	Dominated
30-80	0.0	0.0	373	157	15.58	$78,407	Dominated

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Supplementary Table A10.7: Results sensitivity analysis: risk endometrial cancer 60% (per 1000 women diagnosed with Lynch syndrome)

Strategy	EC cases	EC deaths	LYG[a]	QALYG[a]	Costs[a,] (million US$)	ACER QALYG[a,b]	ICER QALYG
No prophylactic hysterectomy	609.7	136.3	-	-	5.61		
40-70	16.7	4.5	863	1365	13.98	$6,225	$8,395
40-75	9.9	2.2	875	1382	14.21	$6,324	$14,735
40-80	7.9	1.4	878	1387	14.30	$7,482	$24,016
35-70	10.2	3.3	882	1203	14.65	$6,375	Dominated
35-75	3.5	4.5	893	1221	14.88	$7,575	Dominated
35-80	1.5	0.2	897	1225	14.98	$8,780	Dominated
30-70	8.8	3.1	886	1063	15.16	$7,628	Dominated
30-75	2.0	0.8	897	1081	15.39	$8,865	Dominated
30-80	0.0	0.0	900	1085	15.49	$8,919	Dominated

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Supplementary Table A10.8 : Results sensitivity analysis: Accounting for reduced life expectancy due to increased colorectal cancer risk in LS (per 1000 women diagnosed with Lynch syndrome)

Strategy	EC cases	EC deaths	LYG[a]	QALYG[a]	Costs[a,] (million US$)	ACER QALYG[a,b]	ICER QALYG
No prophylactic hysterectomy	297.5	69.9	-	-	2.7		
40-70	10.9	2.9	404	520	13.83	$22,503	$22,467
40-75	6.7	1.5	411	530	14.27	$23,036	$57,788
35-70	6.5	2.1	417	364	14.45	$32,429	Dominated
40-80	5.4	1.0	413	533	14.45	$23,309	$86,163
35-75	2.3	2.9	424	374	14.89	$32,948	Dominated
30-70	5.5	1.9	420	234	14.92	$48,831	Dominated
35-80	1.0	0.2	426	377	15.08	$33,260	Dominated
30-75	1.3	0.5	426	244	15.36	$49,093	Dominated
30-80	0.0	0.0	429	247	15.54	$49,404	Dominated

EC deaths - endometrial cancer deaths; LYG - life years gained; QALYG - quality-adjusted life years gained; ACER - Average Cost-Effectiveness Ratio

[a] Results are 3% discounted

[b] Compared to no prophylactic hysterectomy

Chapter 11

General discussion

Colorectal cancer screening has the potential to prevent many colorectal cancer cases and deaths. In this thesis, we aimed to guide colorectal cancer screening policies using microsimulation modeling. Our analyses attempted to optimize colorectal cancer screening guidelines (Part I, Chapters 2-4), evaluate the cost-effectiveness of interventions that potentially increase screening participation (Part II, Chapters 5-8) and improve the detection and clinical management of Lynch syndrome patients (Part III, Chapter 9-10). The main findings from the studies presented in this thesis are summarized below. Subsequently, methodological considerations, practical implications and future perspectives are discussed. This Chapter ends with conclusions and recommendations based on the studies described in this thesis.

Main findings

Informing screening guidelines

Colorectal cancer screening has been recommended by expert panels in the US for more than two decades.[115] Recommendation panels regularly re-evaluate their guidelines due to epidemiological trends, newly developed tests and new evidence regarding the effectiveness or screening. Although overall colorectal cancer incidence has been declining for several decades, the incidence of colorectal cancer has been increasing since the mid-1980s in individuals below the age of 50 years.[16] This fueled debate regarding the age to start screening. In 2018, the American Cancer Society (ACS) re-evaluated their colorectal cancer screening guidelines in light of the increasing incidence in the prescreening ages, for which they commissioned decision-analytic modeling from our group.

Does the optimal screening strategy for the general population change when incorporating contemporary trends in colorectal cancer incidence?

In **Chapter 2**, we evaluated the optimal age to start screening, age to stop screening and the screening interval incorporating contemporary trends in young adults. The original version of the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model, which was calibrated to 1975-1979 data, was adjusted by incorporating an incidence multiplier of 1.59 across all ages. This multiplier was based on the comparison of colorectal cancer incidence in the 1935 birth cohort (40-year-olds in 1975) and the 1975 birth cohort (40-year-olds in 2015). We evaluated 132 screening strategies, which differed with respect to test modality, ages to start screening (40/45/50 years), ages to stop screening (75/80/85 years) and screening intervals (depending on screening modality). We used the number of colonoscopies as a proxy for resource utilization, and efficiency ratios (Δ colonoscopies / Δ life-years gained) to select model-recommended screening strategies. Our analyses demonstrated that because of the higher incidence, the benefits of screening for colorectal cancer increased, and consequently the balance of burden (colonoscopies) to benefit (life-years gained) improved. With the updated model, the efficiency ratio of 10-yearly colonoscopy screening from ages 45 to 75 years was 32 colonoscopies per life-year gained, which was lower than previously accepted

efficiency ratio thresholds. For the current 40-year-olds, the model-recommendable strategies were screening every 10 years with colonoscopy, every year with the Fecal Immunochemical Test (FIT), every 5 years with sigmoidoscopy or every 5 years with computed tomographic colonography (CTC) from ages 45 to 75 years. Therefore, the optimal screening strategies for the general population changed by incorporating contemporary trends in colorectal cancer incidence, now favoring colorectal cancer screening initiation at age 45 years rather than 50 years.

What is the potential benefit and burden from earlier screening for black men and women versus whites?

As colorectal cancer risk varies by race and sex, the influence of race and sex on optimal colorectal cancer screening strategies was explored in **Chapter 3** using the MISCAN-Colon model and the SimCRC model, developed by the University of Minnesota and Massachusetts General Hospital. As there was controversy around the mechanism for the increase in colorectal cancer incidence, two risk scenarios were evaluated: one based on the original race- and sex-specific models and one incorporating race- and sex-specific incidence rate ratios. Using a similar selection algorithm as used in Chapter 2, model-recommendable screening strategies for white females, black females, white males and black males were evaluated. When using the original models, colonoscopy screening every 10 years from ages 50 to 75 years for whites and ages 45 to 75 years for blacks was optimal with MISCAN-Colon based on the efficiency ratio. However, colonoscopy screening from ages 45 to 75 years every 15 years was recommended by SimCRC for all population subgroups. Both models recommended annual FIT screening and CTC screening every 5 years as alternatives to colonoscopy screening. In the scenario where the increased risk was incorporated, both models recommended screening between age 45 and 75 years for all four demographic subgroups. Recommended screening modalities for all demographic subgroups were colonoscopy every 10 years, FIT every year, sigmoidoscopy every 5 years, and CTC every 5 years, except for white males, in whom MISCAN-Colon recommended colonoscopy every 5 years. Therefore, our analyses suggested that there is not a very strong rationale for an earlier start age of colorectal cancer screening in blacks than in whites, particularly if lifetime risks have increased similar to observed trends under age 40 years. For blacks and whites, recommendable strategies generally did not differ for men and women.

How do the rising colorectal cancer incidence and the increasing colorectal cancer treatment costs impact the optimal screening strategy from a cost-effectiveness perspective?

Cost-effectiveness analyses are commonly used to compare screening strategies, in which the incremental cost-effectiveness ratio (ICER) is used to evaluate which screening strategy is deemed optimal given the willingness-to-pay threshold. For all efficient strategies, the ICER represent the additional costs of saving one additional (healthy) life year compared to the next less effective efficient strategy. Costs were not included in the analyses presented in Chapters 2 and 3, as the ACS chose not to

apply cost as a decision-making criterion. Therefore, in **Chapter 4**, we evaluated the impact of the rising colorectal cancer incidence and the increasing colorectal cancer treatment costs on the cost-effectiveness of colorectal cancer screening. Four scenarios were evaluated, differing with respect to colorectal cancer incidence (with or without the incidence multiplier described above) and treatment costs (2007-2013 or 1998-2003 Centers for Medicare and Medicaid Services(CMS) costs). Costs were evaluated from a healthcare sector perspective, with commercial cost estimates for individuals below age 65 years and CMS cost estimates for individuals ages 65 years and above. Our results demonstrated that the total costs of colorectal cancer in the absence of screening increased from $2.57 million to $5.87 million per 1,000 40-year-olds, an increase of 128% compared to 1975-1979 incidence and 1998-2003 cost estimates. All strategies which used primary FIT screening are now cost-saving compared to no screening, as well as the large majority of guaiac fecal occult blood test strategies, 3 sigmoidoscopy screening strategies with an interval of 10 years, and colonoscopy screening from ages 50 to 75 years every 15 years. Annual FIT screening from ages 40 to 85 years resulted in the highest benefit at acceptable incremental costs, with an ICER of $26,777 per quality-adjusted life-year gained (QALYG). When the cost-effectiveness of colonoscopy-based screening strategies was compared, the cost-effectiveness of screening from ages 45 to 75 years every 10 years was $38,695 per QALYG with the incidence multiplier and new treatment costs, which is lower than the estimate of $61,702 for colonoscopy screening every 10 years from ages 50 to 75 years without the incidence multiplier and old treatment costs. Therefore, as a result of the increasing incidence and treatment costs, the cost-effectiveness of colorectal cancer screening greatly improved, which further supports screening initiation at age 45 years rather than age 50 years in the US.

Interventions to improve adherence

In addition to having optimal screening guidelines, the effectiveness of any screening program greatly depends on the willingness of the target population to adhere to the guidelines. Previous analyses from our group estimated that approximately 58% of colorectal cancer deaths that will occur in 2020 can be attributed to the nonuse of screening.[401] Therefore, many studies in the past decade tested interventions intended to increase colorectal cancer screening completion. In the second part of this thesis, we evaluated the cost-effectiveness of four potential interventions.

Under what circumstances is waiving all coinsurance for colorectal cancer screening in Medicare beneficiaries cost-effective?

The 2010 provisions of the Affordable Care Act require health plans to cover recommended preventive services without charging a deductible, copayment or coinsurance. However, due to a "loophole" in this legislation, financial barriers for colorectal cancer screening persist. Colonoscopies in which lesions are removed and colonoscopies that are performed as a diagnostic follow-up after a positive stool-based test are coded as "diagnostic" rather than "preventive", and are therefore subject to a 20% coinsurance. In **Chapter 5**, we evaluated the cost-effectiveness of waiving these coinsurance requirements from a CMS perspective, both within a colonoscopy and a

FIT setting. Our results suggested that if waiving the coinsurance increases colonoscopy screening participation by 5 percentage-points, the number of colorectal cancer deaths would decrease by 6.4% while the total costs would increase by 1.2%. Given the uncertainty regarding the effect of this waiver on participation, we also determined the threshold increase in participation needed for this waiver to be cost-effective. Waiving all coinsurance would be cost-effective if it increased screening participation from 60% to 60.4% for a colonoscopy setting and from 60% to 60.3% in a setting where FIT is used as a primary screening modality. Therefore, the health benefits of the waiver would likely outweigh the additional costs.

For individuals who are unwilling to undergo FIT or colonoscopy screening, which screening strategy is a cost-effective alternative?

Other possible barriers for individuals to participate in screening are fear and disgust of the screening test. Therefore, new tests that try to circumvent these barriers have the potential to increase screening acceptance. In **Chapter 6**, we determined which currently available alternative screening test to FIT and colonoscopy is most promising from a cost-effectiveness perspective. The cost-effectiveness of screening with capsule endoscopy every 5 or 10 years, CTC screening every 5 years, the multi-target stool DNA (mtSDNA) test every 1 or 3 years, and the methylated *SEPT9* DNA plasma assay (m*SEPT9*) every 1 or 2 years was compared from a societal perspective. None of these alternative tests were cost-effective compared to FIT or colonoscopy screening. When colonoscopy and FIT were not considered, CTC every 5 years, annual m*SEPT9* and annual mtSDNA were efficient strategies with ICERs of $1,092, $63,253 and $214,974 per QALYG, respectively. Under the assumption of perfect adherence, annual screening with the m*SEPT9* resulted in higher benefits but 63% more colonoscopies and 26% higher costs than annual FIT screening. Therefore, our results suggested that for individuals that are unwilling to be screened with FIT or colonoscopy, annual screening with the m*SEPT9* is the test of choice given its cost-effectiveness profile compared to the other alternative tests.

What are the optimal screening strategies for women willing to obtain some, but not all, US Preventive Services Task Force (USPSTF)-recommended screenings?

For women above the age of 50 years in the US, not only screening for colorectal cancer is recommended, but also for cervical cancer, breast cancer and, for those with heavy smoking histories, lung cancer. Only one in three women obtain all guideline-recommended cancer screening. Women might be time-limited or overwhelmed. Therefore, in **Chapter 7**, we sought to quantify optimal cancer screening strategies for women who were unwilling or unable to obtain all guideline-recommended screenings. For this study, we utilized the MISCAN models developed for breast cancer, cervical cancer, colorectal cancer and lung cancer.[246,270,272] We stratified women based on their eligibility for lung cancer screening, and evaluated 45 different screening strategies combining breast, cervical, colorectal and/or lung cancer screenings, restricted to 1, 2, 3, or 4 screenings per year. Our results suggested that it is possible to reduce screening

intensity to one test per year in women ineligible for lung cancer screening and to two tests per year in women eligible for lung cancer screening while maintaining 94% and 97% of life-years gained, respectively, compared to full compliance to all USPSTF cancer screening guidelines. Screening for a variety of cancers, but less often than recommended, was more effective than to screen only for specific cancers. For women eligible for lung cancer screening, lung cancer screening should be the top priority, as strategies omitting it provided ≤25% life-years gained compared to full compliance to all USPSTF cancer screening guidelines.

Would it be cost-effective to include the FIT kit in the screening invitation letter in France?

US studies suggest that mailing stool-based tests to individuals eligible for colorectal cancer screening is the most effective way to increase screening participation.[312] Several countries with organized screening programs, such as the Netherlands, already disseminate FIT kits using this method. However, in France, a letter is sent by mail that invites individuals to collect the FIT kit at their general practitioner's office. In 2016, only 29% of French individuals invited for colorectal cancer screening participated, which is much lower than participation in surrounding countries/regions such as the Netherlands (73%), Basque country (72%) and Flanders (55%).[402] In **Chapter 8**, we estimated the potential benefits and costs of including the FIT in the invitation letter in France. We simulated the French population ages 35 to 75 years in 2018, incorporating historical screening, and followed them for a life time. If participation increased to 60% as a result of the change in invitation method, there were 11% fewer colorectal cancer deaths, 6% fewer cases, 42% more QALYG and a 2.2% increase in costs, resulting in an ICER of €1,510 per QALYG. Mailing out the FIT needs to increase participation by only 0.5 percentage point for it to be cost-effective (willingness-to-pay threshold of €30,000 per QALYG). Therefore, including the FIT in the invitation letter is likely a very cost-effective intervention to increase participation in colorectal cancer screening in France.

Screening and subsequent steps for Lynch syndrome patients

Approximately 3% of all colorectal cancer patients have a germline mutation in one of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2* or *EPCAM*). These individuals have Lynch syndrome, which is the most common familial colorectal cancer syndrome. By sequencing the DNA of first-degree relatives of Lynch syndrome patients (= cascade testing), individuals that carry these mutations can be identified before clinical manifestation. These asymptomatic first-degree relatives with Lynch syndrome have an increased risk to develop several cancers, among them colorectal cancer (42% before age 80 years), and, for women, endometrial cancer (35% before age 80 years).[37] Identifying mutation carriers before they develop symptoms gives them the opportunity to take preventive measurements that can reduce cancer incidence and mortality.

Is it cost-effective to screen colorectal cancer cases for Lynch syndrome, and what is the optimal surveillance interval for first-degree relatives identified through cascade testing?

The province of Ontario, Canada, was considering to implement Lynch syndrome testing for all colorectal cancer cases under age 70 years using immunohistochemistry. In **Chapter 9**, we developed a patient flow diagram to determine costs and yield of immunohistochemical testing for Lynch syndrome in colorectal cases and, for those found to have Lynch syndrome, their first-degree relatives, accounting for realistic uptake. Subsequently, we compared costs and benefits of annual, biennial, and triennial surveillance in asymptomatic Lynch syndrome cases. We estimated that testing 1,000 colorectal cancer cases would result in identifying 20 colorectal cancer cases and 29 asymptomatic first-degree relatives with Lynch syndrome at a cost of CA$310,274. The benefit of identifying these asymptomatic mutation carriers depends on the colonoscopy surveillance interval offered to these individuals. Offering these first-degree relatives biennial colonoscopy surveillance was optimal from a cost-effectiveness perspective, as it resulted in a favorable ICER of CA$8,785 per life-year gained due to a substantial increase in life-years gained (+122%). The total costs of biennial surveillance were lower than those of triennial surveillance due to cost savings in colorectal cancer care. Annual colonoscopy surveillance provided little benefit compared to biennial surveillance at a much higher cost, resulting in an ICER of CA$218,647 per life-year gained. Therefore, the results of our study suggested that immunohistochemical testing for Lynch syndrome in colorectal cancer cases followed by cascade testing is very cost-effective, and that biennial colonoscopy surveillance is optimal for asymptomatic Lynch syndrome cases.

What are the optimal age thresholds for offering prophylactic hysterectomy to asymptomatic women identified with Lynch syndrome from a cost-effectiveness perspective?

Another preventive measure that can be taken by women with Lynch syndrome is prophylactic hysterectomy. In **Chapter 10**, we evaluated the costs and benefits of this preventive measure. The MISCAN Endometrial model was developed, which incorporated the natural history for the development of hyperplasia with and without atypia into endometrial cancer. We simulated women identified with Lynch syndrome through the steps described in Chapter 9. We estimated costs and benefits of offering this cohort prophylactic hysterectomy, accounting for a reduced quality of life after prophylactic hysterectomy due to premature menopause, and for having endometrial cancer. Three minimum ages (30/35/40 years) and three maximum ages (70/75/80 years) were compared. When adjusting for quality of life, only strategies with a minimum age of 40 years were efficient. Lower minimum ages increased the total costs and resulted in fewer QALYG in women with Lynch syndrome. Prophylactic hysterectomy for women aged 40-70 years, 40-75 years and 40-80 years resulted in ICERs of $22,017, $57,869 and $86,105 per QALYG, respectively. Therefore, prophylactic hysterectomy for women with Lynch syndrome aged 40 to 80 years is optimal from a cost-effectiveness perspective. However, women may consider performing prophylactic hysterectomy at age 35 years, as

the optimal age range was heavily depended on the impact of prophylactic hysterectomy on quality of life, which differs vastly between patients

Methodological considerations

All studies presented in this thesis used the MISCAN-colon model to simulate the effects of colorectal cancer screening policy changes. In addition, the study described in Chapter 7 used three other MISCAN cancer models. The value of these models has been internationally recognized as policy makers from around the globe request analyses with these MISCAN models to inform their cancer screening programs. The MISCAN-colon model has been used to guide public health research and policies for over two decades. However, the findings presented in this thesis should be interpreted in light of several limitations.

Limitations in the model structure of MISCAN-colon

There are two major limitations regarding the structure of the MISCAN-colon model. First, the natural history module of MISCAN-colon only includes the adenoma-carcinoma sequence as a carcinogenic pathway. The serrated pathway, which may account for up to one-third of all colorectal cancers, has not been incorporated. There is great uncertainty regarding the progression risk, detectability and recurrence risk of sessile serrated lesions, which is why incorporating this pathway is challenging and would require making several assumptions. Nevertheless, not incorporating this pathway might have impacted the results presented in this thesis. In Chapters 2, 3, 4 and 6 of this thesis, different screening modalities were compared. These tests might have different test sensitivities for the lesions in the serrated pathway. In particular, it has been described that the multi-target stool DNA test has an increased sensitivity for sessile serrated lesions compared to the FIT,[72,403] which was not captured in our analyses. This potentially underestimates the cost-effectiveness of the multi-target stool DNA test compared to the other evaluated screening modalities. Second, the progression rates of adenomas do not vary by location in MISCAN-colon. This implies that the distribution of adenomas and cancers by location are identical. However, from autopsy studies, we know that the fraction of distal adenomas (approximately 40%) is smaller than the fraction of distal cancers (63%), suggestion a faster adenoma progression rate for distal compared to proximal adenomas. As we simulate a relatively high proportion of adenoma in the distal colon or rectum, our estimates of the (cost-)effectiveness of sigmoidoscopy screening in Chapters 2-4 might be too optimistic.

Uncertainty in model parameters

As for any type of modeling analysis, the accuracy of our predictions depends on the accuracy of the data used to inform our model. Unfortunately, not all parameters in the model can be directly informed by empirical data. For those parameters, we have to make assumptions. Six assumptions that potentially impact the results from our analyses are noteworthy. First, the current background risk of colorectal cancer in the general US population is uncertain. MISCAN-Colon has been calibrated to 1975-1979 data.

In response to the increasing incidence observed in the prescreening ages, which has been identified as a cohort effect,[16] we assumed a 59% increase in background colorectal cancer incidence compared to 1975-1979 data across all ages in Chapters 2, 3, 4 and 6; the analyses presented in Chapter 5 were finalized before the landmark publication of the increasing incidence. The assumed background colorectal cancer incidence is an important driver of the cost-effectiveness of screening. In retrospect, we likely underestimated the benefits of the coinsurance waiver in Chapter 5. The true magnitude of the increase in colorectal cancer incidence above the age of 50 years is uncertain, and will be difficult to assess due to the high uptake of screening in these ages. Second, the risk of developing colorectal cancer and endometrial cancer for Lynch syndrome patients is uncertain, and varies greatly between studies. In Chapters 9 and 10, we calibrated our models to the largest study that accounted for ascertainment bias.[37] However, results of Chapters 9 and 10 indicate that the assumed risks impact the cost-effectiveness of screening and subsequence steps for Lynch syndrome patients. Third, the version of the MISCAN-colon model used in the Chapter 3 assumed a difference in background colorectal cancer risk between whites and blacks. However, a recent comprehensive review of the literature from our collaborators 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.[404] This further questions differential screening recommendations by race even without assumed increases in risk since the 1990s. Fourth, studies suggest that test performance in repeat stool-based screening is not independent like we assumed in all analyses presented in this thesis.[238,405] If adenomas do not bleed over several years, they will cause systematic false-negative FIT results. A previous analysis from our group showed that the impact of assuming correlation of outcomes in repeat FIT screening rounds is likely to be modest.[238] However, systematic false-negativity might not be restricted to stool-based screening tests. The proportion of adenomas and cancers that are systematically missed by the different screening modalities might impact their relative (cost-)effectiveness. Fifth, no studies provide information on long-term adherence patterns required to accurately model realistic adherence. Given the limited evidence to inform long-term adherence patterns and the variability in estimates of short-term adherence rates, simulating the impact of imperfect adherence required numerous assumptions. Reflecting the goal of estimating the impact of screening among average risk persons who are willing to be screened for colorectal cancer, we assumed perfect adherence in the studies described in Chapter 2, 3, 4 and 6. This implies that the estimated effects of colorectal cancer screening are unrealistic. Lastly, important drivers of the cost-effectiveness of colorectal cancer screening are the costs of the screening tests and the costs of treatment. Not all cost parameters could be based on national US estimates. For example, we assumed costs from a CMS perspective in Chapters 5 and 6. Those costs are substantially lower than those for individuals with private insurance. We tried to account for this in the analyses presented in Chapter 4 by using a multiplier for individuals below age 65 years. However, this multiplier is based on costs of screening tests only, not treatment.

Considerations with outcome metrics used

The optimal measures to compare the effects of colorectal cancer screening policies are somewhat arbitrary. First, the optimal measure of benefit is debatable. According to panel recommendations,[109] the QALYG is the optimal measure of benefit. However, in Chapters 2, 3, 7 and 9, we did not account for quality of life, and used life-years gained as a measure of benefit. Accounting for quality of life requires making several subjective assumptions about, for example, the burden of a particular screening test, as these are often unknown. Using (quality-adjusted) life-years gained as the primary measure of benefit accounts for a larger gain in life expectancy from, for example, preventing a colorectal cancer death in a 53-year-old individual compared to a 73-year-old individual. However, it also implies that, when assuming an average life expectancy of 83, saving three 73-year-olds gets the same weight as saving one 53-year-old. This may be ethically questionable. Using cases and deaths prevented gives the same value to every life saved, might be easier to interpret for clinicians and patients, and these were also provided as secondary outcomes for most analyses. Second, the measure of cost or burden varied between the different studies presented in this thesis. Panel recommendations suggest reporting costs both from a health care sector perspective and from a societal perspective.[109] In practice, performing analyses from a societal perspective can be challenging and requires a lot of assumptions. We attempted obtaining cost estimates from a societal perspective for Chapter 6, but only analyzed a health care sector perspective in Chapters 4, 5, 8, 9 and 10. As per the request of the ACS, the number of required colonoscopies was used as the measure of the burden of screening in Chapters 2 and 3. This was chosen because colonoscopy is the only burden shared by all modalities. However, this does not assign any burden to a non-colonoscopy screening test, making comparisons across different modalities impossible. Especially when individuals need to undergo bowel preparation for their primary screening test (as with sigmoidoscopy and CTC) this burden is not negligible. Lastly, the incremental burden-to-benefit ratios used in this thesis have limitations. In Chapters 2 and 3, the efficiency ratio ((Δ colonoscopies / Δ life-years gained) was used. This ratio does not have a commonly accepted threshold. The ICER, used in other Chapters of this thesis, also has limitations. The so-called willingness-to-pay threshold is not set in stone. Furthermore, ICERs are influenced by the other strategies evaluated in a study. This is illustrated by comparing results in Chapters 4 and 6, where 10-yearly colonoscopy screening was cost-effective compared to FIT in the latter, but not in the former due to the limited number of strategies evaluated in Chapter 6.

Practical implications

Despite the limitations described in the section above, the studies presented in this thesis may be of great value to policy makers.

Start colorectal cancer screening at age 45 years in the US

The studies presented in Chapters 2 and 3 of this thesis were instrumental for the 2018 colorectal cancer screening guidelines from the ACS. Based on the results from our

modeling analyses, the increased disease burden in individuals below age 50 years and the reasonable expectation that screening will perform similarly in individuals aged 45-49 as in those above age 50, the ACS included a qualified recommendation to start screening at age 45 years.[78] It has been estimated that if the current age-specific screening rates shift to 5 years earlier, this change in legislation will prevent 29,400 colorectal cancer cases and 11,100 colorectal cancer deaths over the next 5 years.[152]

The recommendation to start screening at age 45 years in the US has sparked intense debate. Despite the substantial health benefits, opponents argue that it may divert limited resources away from higher-priority areas, such as unscreened elderly patients.[406] Although colonoscopy constraints may not be a problem for the US as a whole,[407] they most likely are for some areas or individuals. Furthermore, colorectal cancer health disparities might increase. As the colonoscopy demand of the commercially insured 45 to 49-year-olds expands, adults with Medicaid or Medicare insurance may be given lower priority as those reimbursements rates are lower.[408] Insurers are currently not required to cover colorectal cancer screening below age 50 years, which means that the 45-year-olds that currently get screened are likely those with a high socioeconomic status. A potential solution for areas with a limited colonoscopy capacity would be to use FIT as a primary screening test rather than colonoscopy. This is supported by our analyses presented in Chapter 4, which demonstrate that annual FIT screening from ages 45 to 80 years results in a higher number of (QA)LYG than colonoscopy screening every 10 years from ages 50 to 75 at a lower cost and colonoscopy demand.

Despite the fact that the ACS is the only organization that recommends colorectal cancer screening initiation at age 45 years for average-risk individuals, CRC test use among 45 to 49-year-olds has been increasing. According to data from the National Health Interview Survey (NHIS), utilization rates in this age group increased from 4.8% in the first quarter to 11.7% in the last quarter of 2018, coinciding with the release of the ACS guidelines.[183] The USPSTF is currently updating their colorectal cancer screening guidelines.[409] A potential change in their guidelines will probably have an even larger impact on screening rates due to the mandate for insurers to cover USPSTF recommendations graded A or B. Similar to their previous updates in 2008 and 2016, the USPSTF requested analyses from all three CISNET modeling groups to help inform their updated guidelines.

Remove financial barriers for screening participation

In most countries, there is some financial barrier for screening participation, either in the form of copays or deductibles. In the Netherlands, the deductible applies to the diagnostic follow-up colonoscopy after a positive FIT. Individuals in the Netherlands have deductibles between €385 to €885 depending on their health care plan, suggesting a potential financial barrier for individuals to get a follow-up colonoscopy. In the US, due to a "loophole" in the law, screening colonoscopies with polyp removal or follow-up for another test can be coded as "diagnostic" rather than "screening" and are therefore subjected to both the Part B deductible ($198) and a 20% coinsurance (approx. $150) in Medicare beneficiaries.

Our analyses in Chapter 5 demonstrate that removing this coinsurance requirement in the US is most likely a cost-effective way to increase screening participation. Given the waiver may primarily affect the out-of-pocket costs of Medicare beneficiaries from low socioeconomic status background, who more often lack supplemental insurance, it may also contribute to reducing colorectal cancer health disparities in the US. Results of our study have been used by advocates to convince members of congress to change this legislation. Flyers describing the main findings of our study were distributed at the 11th call-on congress, an annual event organized by Fight Colorectal Cancer. Bills have been introduced since the 2011-12 sessions of Congress to address this loophole. The current bills (H.R.1570 and S.668) were introduced in March 2019 in the house and the senate, respectively, but haven't moved forward as of today.

Send out the FIT by mail to those eligible for screening

Our analyses in Chapter 8 suggest that including the FIT kit in the invitation letter in France is very likely a cost-effective way to increase screening participation. Our study is not only informative for France, but also for other countries facing similar screening barriers. Mailing the FIT kits has been suggested as a way to improve colorectal cancer screening worldwide.[410] In the US, where there is largely opportunistic screening, sending out the FIT by mail to those eligible has been identified as the most effective way to increase screening participation.[312] Furthermore, participation among beneficiaries of the Kaiser Permanente Northern California health plan increased from 40% in 2006 to 83% in 2015 following a switch towards programmatic screening using mailed-out FITs.[411] Extending programmatic screening using FIT outreach would also imply an increased uptake of FIT screening compared to other screening modalities, which is supported by our results in Chapter 4 favoring FIT screening from a cost-effectiveness perspective.

Discuss alternative screening options for those not willing to participate

Chapter 6 suggests that for individuals that are not willing to be screened with colonoscopy or FIT, screening with the m*SEPT9* is a cost-effective alternative. This implies that colorectal cancer screening guidelines should be reevaluated, as from a cost-effectiveness perspective, there is no rationale to recommend the CTC, capsule endoscopy and mtSDNA while not recommending the m*SEPT9* as an alternative to FIT or colonoscopy. The m*SEPT9* has the potential to attract the population that currently does not want to participate in screening. It just requires a blood sample, and might be administered during primary care visits. Some individuals might prefer this test over collecting a stool sample or a more invasive test. A previous study identified an increased uptake of a blood-based test compared to a stool-based test among individuals overdue for screening,[239] and another study found that among people who declined stool-based tests, there was a 25% uptake of a blood-based test,[240] demonstrating its potential. However, the m*SEPT9* might not be the best alternative in every setting. For example, due to its relatively low specificity, it requires a high number of follow-up colonoscopies, which might not be warranted in settings with a limited capacity.

One potential reason for women not to participate in colorectal cancer screening might be that they are overwhelmed by the number of recommended cancer screenings. Our

results from Chapter 7 suggest that less frequent screening than recommended can still result in the majority of the benefits if 1) those who are eligible participate in lung cancer screening and 2) women select screening for a variety of cancers although less frequently than recommended rather than screening only for some cancers. According to 2015 NHIS data, current percentages up to date are 4% for lung (in those eligible), 57% for colorectal, 87% for cervical and 71% for breast cancer screening in those above age 50 years, which does not align with predicted benefits. Lung cancer screening has the highest benefits for those eligible, and the benefits of colorectal cancer screening exceed those of breast cancer screening and cervical cancer screening. Therefore, physicians should be discussing priorities and less-intensive cancer screening schedules for women if this helps increasing their likelihood of participating in those cancer screenings that, given their screening history, result in the highest expected benefit.

Implement Lynch syndrome testing for all colorectal cancer cases below age 70 years

Our analyses presented in Chapter 9 suggest that implementing Lynch syndrome testing for colorectal cancer cases below age 70 years using immunohistochemistry and subsequently testing first-degree relatives if positive for Lynch syndrome is very cost-effective. Our study used data from Ontario, Canada, as they considered implementing screening for Lynch syndrome. Important barriers that have been identified for the implementation in Canada are the education of stakeholders and concerns regarding resources such as laboratory costs and workload for pathologists.[341] Our study provides data that may help overcome these barriers.

Although implementation of a population-based program for Lynch syndrome screening is recommended by expert panels,[340] it is still not universally implemented in many countries worldwide. A recent survey performed among institutions in the US, Canada, Europe and Australia suggest an encouraging 86% uptake, of which 76% used primary immunohistochemistry.[412] Results of our study urge policymakers and clinicians worldwide to increase the implementation of universal Lynch syndrome testing using primary immunohistochemistry.

Offer Lynch syndrome cases biennial colonoscopy surveillance and prophylactic hysterectomy

Chapters 9 and 10 suggest that Lynch syndrome patients should undergo biennial colonoscopy surveillance and prophylactic hysterectomy from a cost-effectiveness perspective. These preventive measures greatly reduce colorectal and endometrial cancer mortality in Lynch syndrome patients. The study presented in Chapter 9 was the first cost-effectiveness analysis that evaluated different colonoscopy surveillance intervals in Lynch syndrome cases identified by primary immunohistochemical testing. No randomized-controlled trials have been performed that compare different surveillance intervals, and it is difficult to compare interval cancer rates between observational studies due to different methodologies.[368] Therefore, the optimal colonoscopy surveillance interval for Lynch syndrome patients is a topic of intense debate.[351] Our modeling study provides insights that can be used to inform surveillance guidelines internationally.

Current guidelines recommend to offer prophylactic hysterectomy to women with Lynch syndrome from age 40 or when childbearing has completed.[368] This is in line with the results from our study presented in Chapter 10, suggesting prophylactic hysterectomy for women aged 40 to 80 years is cost-effective. Our study further underlines the importance of implementing universal Lynch syndrome screening of colorectal cancer patients and subsequent cascade testing to improve future prospects of these patients in terms of life expectancy and quality of life. Furthermore, our results can inform physicians and women with Lynch syndrome regarding the decision whether or not to perform prophylactic hysterectomy and from which age, which is especially helpful given the preference-sensitive nature of the decisions these patients are facing.

Future perspectives

Colorectal cancer screening is a rapidly evolving field. Four areas are of particular interest with respect to the studies presented in this thesis. The character of the increase in colorectal cancer incidence in prescreening ages has only been recognized a few years ago, fueling many ongoing studies. Our understanding of the role of the serrated polyp pathway in colorectal cancer is rapidly increasing. Furthermore, our knowledge about (genetic) risk factors for colorectal cancer has substantially increased in recent years, potentially opening the door for personalized screening. Lastly, with the increased implementation of routine screening for Lynch syndrome, we better understand the cancer risks associated with the different mismatch repair mutations. These research areas, their expectations for the near future and potential contributions of microsimulation modeling are described below.

The driver(s) of the increasing colorectal cancer incidence observed in the prescreening ages

While most experts agree that the trends in colorectal cancer incidence are concerning and warrant investigation, there is disagreement on the underlying causes. Several studies mention the increase in obesity, a known risk factor, as a possible explanation, but there is contrasting evidence about this hypothesis. A large prospective female US cohort study found an association between obesity and early-onset colorectal cancer.[413] However, two recent retrospective studies did not confirm this association and pointed towards an important role for non-modifiable risk factors,[414] alcohol consumption and specific dietary components.[415] Furthermore, a recent analysis looking at US state variation demonstrated no correlation between obesity and heavy alcohol consumption trends and early-onset colorectal cancer trends.[416] Importantly, the increase in colorectal cancer incidence is stronger in whites than in blacks,[16] whereas obesity prevalence has risen more rapidly in blacks than in whites.[417] A limitation of these studies is that risk factor trends are assessed in isolation, while a more comprehensive approach is needed.[99] A complicating factor is that in the US, the increase is stronger in rectal cancer compared to distal colon cancers and proximal colon cancers,[16] while in Europe it is the other way around.[12] This suggests that underlying causes might differ by country.

Microsimulation modeling provides a window into unobserved data, and is a useful tool to inform ongoing debates. For example, our models can be used to evaluate if background colorectal risk is also increasing in individuals above age 50 years by adjusting for the increased uptake of screening in those ages. Furthermore, we can estimate what fraction of the increasing incidence can be explained by specific risk factors by incorporating those into our model, accounting for their prevalence over time and relative risk estimates. Understanding the etiology of the increasing incidence is critical for accurate assessment of the benefits, harms and costs of colorectal cancer screening.

The sessile serrated polyp pathway for colorectal cancer

The sessile serrated polyp pathway to colorectal cancer was postulated more than two decades ago. It accounts for up to 30% of all colorectal cancers.[418] However, unlike adenomatous polyps (their more common counterparts), we have only recently been able to gather data about their outcomes and natural history. Researchers in our group recently conducted a systematic review to determine the prevalence, clinical features, and progression risk of sessile serrated polyps.[419] Interestingly, sessile serrated polyps are more likely to be located in the proximal colon compared to typical adenomas. Furthermore, among individuals with a sessile serrated polyp, a smaller proportion is diagnosed with multiple sessile serrated polyps compared to individuals with a typical adenoma. However, approximately half of individuals with a sessile serrated polyp also have conventional adenomas. Another interesting finding is the apparent lack of a relationship between age and sessile serrated polyp prevalence, which is in sharp contrast to the strong positive correlation between age and adenoma prevalence.

Despite the remaining uncertainty, we have now gained sufficient knowledge about the sessile serrated polyp pathway to start including it into our microsimulation model. The inclusion of this carcinogenic pathway in our model will help unravel its natural history. For example, it can be used to explore to what extent the apparent faster disease progression of sessile serrated polyps stems from poorer visibility, and how the progression risk relates to its size and multiplicity. Including this pathway in our model may have important implications for our estimates on the (cost-)effectiveness of colorectal cancer screening, and on the relative performance of different screening tests.

Personalizing colorectal cancer screening based on risk factors

The majority of individuals who participate in screening (approximately 94%) will never develop colorectal cancer, but do experience the burden and potential harms. Ideally, we would be able to identify those individuals that will benefit from resource-demanding colorectal cancer screening strategies. The most comprehensive risk prediction model today has been developed by the Fred Hutchinson Cancer Research Center, Seattle, WA, US. This colorectal cancer risk prediction model was generated using data from 40,000 colorectal cancer patients and 46,000 controls, and includes family history, 63 genetic, and 19 environmental (including lifestyle) factors.[420] In addition, it has been validated against a community-based cohort of >100,000 participants (manuscript in preparation), and has a current discriminative accuracy of 0.652. As the optimal age to start and stop screening, screening interval

and screening test are influenced by individual risk, this risk prediction model can be utilized to personalize screening recommendations. For example, in an individual with an unhealthy lifestyle and many high-risk alleles in his DNA, the screening recommendation might be a colonoscopy every 5 years from ages 40 to 80, while an individual with a healthy lifestyle and few high-risk alleles, screening every 2 years from ages 60 to 70 with a stool-based test might provide the best benefit-to-harm ratio.

The translation of genetic- and environmental risk factors to risk-tailored screening recommendations can be performed using microsimulation modeling.[118] Interestingly, previous exploratory analyses from our group suggested that with an AUC of 0.65 based on genetics only, risk-stratified colorectal cancer screening can be cost-effective when the costs of a polygenic test are below $291.[421] Risk-differentiation based on both environmental and genetic risk information can likely achieve even better results. In an ongoing collaboration with the Fred Hutchinson Cancer Research Center, we combine the strengths of their unparalleled risk prediction model and our microsimulation model. This collaboration has the potential to accelerate the translation of contemporary genetic and epidemiologic research into changes in clinical practice and advances in public health.

Another option for personalizing screening recommendations in FIT-based programs, is by using absolute hemoglobin levels as risk predictors. Results from the Dutch program (cut-off = 47 μg/g feces) revealed that individuals with a hemoglobin level between 15 and 47 μg/g feces in the first round were 23 times more likely to have an advanced neoplasia detected in the second round compared to those with 0 μg.[230] This demonstrates that the amount of hemoglobin detected in the stool is a strong predictor for future cancer risk. While using hemoglobin levels does not allow for personalization of the start age of screening, it has the advantage that this information is already present in registries and does not require additional resources. Our group will develop a risk prediction model based on age, sex, geographical location and fecal hemoglobin concentration and identify optimal risk-based screening strategies using our microsimulation model. Subsequently, a randomized controlled trial will be performed within the Dutch colorectal cancer screening program to demonstrate feasibility, acceptability and superiority of risk-tailored screening compared to uniform screening.

Mutation-specific surveillance of Lynch syndrome patients

The risks of developing colorectal cancer, endometrial cancers and various other cancers for Lynch syndrome patients depend on which mismatch repair gene is mutated.[369] The lifetime risk to develop colorectal cancer is estimated between 30% and 74% for *MLH1* and *MSH2* gene mutation carriers, between 10% and 22% for *MSH6* gene mutation carriers, and between 15% and 20% in *PMS2* mutation carriers. Furthermore, risk in males is higher than in females. How carcinogenic pathways differ by mutation is poorly understood. A recent study identified that *CTNNB1* is frequently mutated in tumors of *MLH1* mutation carriers, whereas *APC* is more frequently mutated in tumors of *MSH2* mutation carriers.[422] Interestingly, in this study that included 2747 Lynch syndrome patients, *MSH2* mutation carriers had an increased risk of developing (advanced) adenomas compared to *MLH1* mutation carriers, but their incident colorectal cancer

risk was the same.[422] Based on these findings, the authors hypothesized that *MSH2*-associated cancers may have developed from an accelerated adenoma-carcinoma sequence, whereas a substantial proportion of *MLH1*-associated cancers may have derived without prior polyp formation through an immediate invasive pathway arising from mismatch-repair deficient crypts.[423] This implies that the effectiveness of colonoscopy surveillance might depend on which mismatch repair gene is mutated.

Apart from the recent UK guidelines that recommend colonoscopy surveillance from age 25 years for *MLH1* and *MSH2* mutation carriers and from age 35 years for *MSH6* and *PMS2* mutation carriers,[424] surveillance guidelines in general are not mutation-specific. Offering colonoscopy surveillance every two years to *MSH6* and *PMS2* mutation carriers while offering colonoscopy surveillance every five years to individuals with a family history in whom no driver mutation has been identified (lifetime risk between 14% and 30%) seems illogical, as their lifetime risk is comparable. Microsimulation models can be a useful tool to translate the most recent knowledge about gene-specific cancer risk and natural history to personalize surveillance start ages, stop ages and intervals in Lynch syndrome patients. In the analyses presented in Chapter 9, we evaluated a range of 30%-60% risk of developing colorectal cancer before age 80, and revealed that an individual's optimal surveillance interval is strongly influenced by an individual's lifetime risk. We anticipate that gene-specific surveillance recommendations will be implemented in the future.

Conclusions

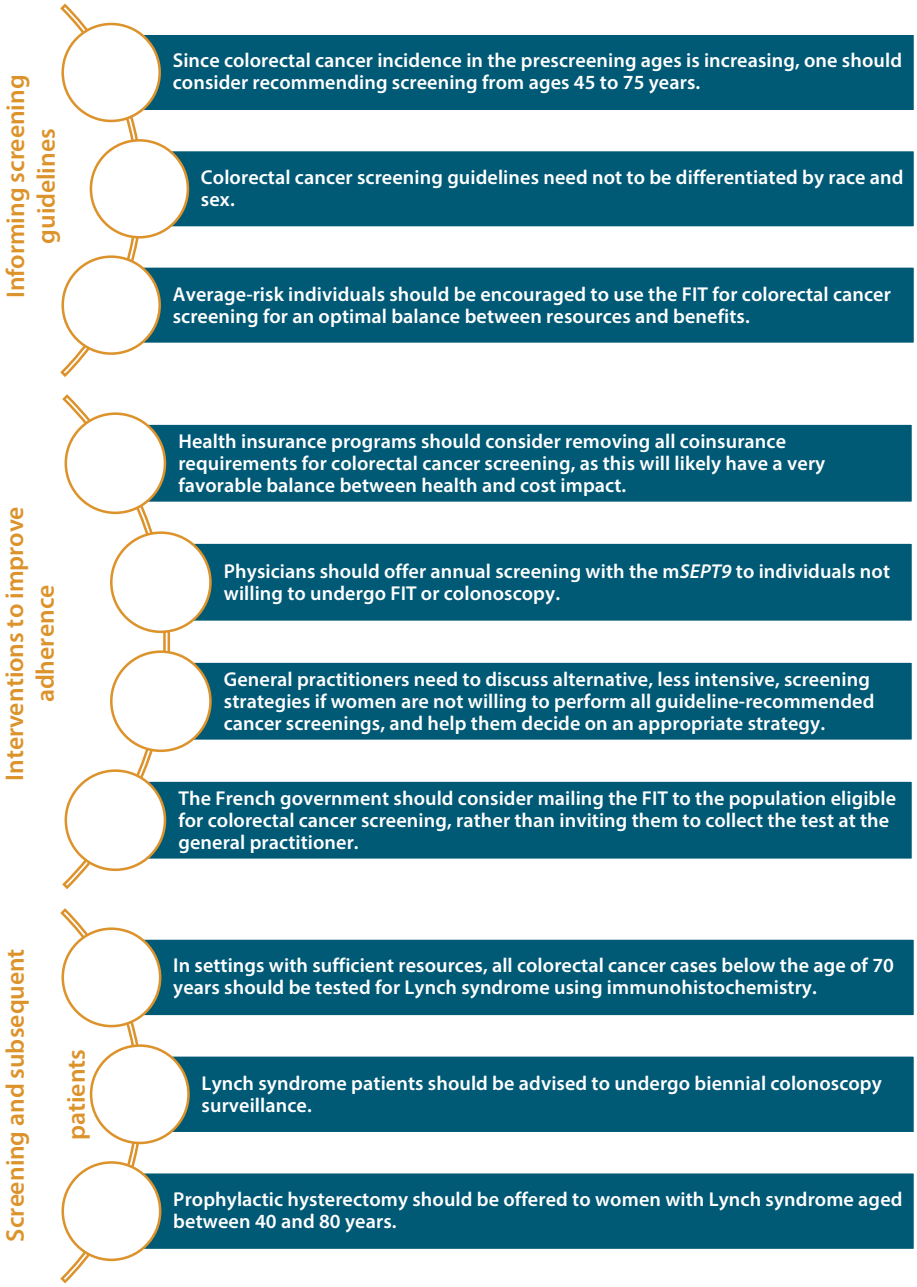
Considering all of the above, the following conclusions can be drawn based on the studies presented in this thesis:

- As a result of the increase in colorectal cancer incidence observed in young adults, screening initiation at age 45 years rather than age 50 years in the US has a favorable balance between screening benefits, burden and costs.
- The optimal screening ages for individuals in the US are not influenced by race and sex under assumed increases in background risk.
- The increase in colorectal cancer incidence in young adults and the increase in colorectal cancer treatment costs greatly improved the cost-effectiveness of colorectal cancer screening.
- Only colorectal cancer screening strategies that use FIT as a primary screening test are cost-effective.
- Waiving the coinsurance for all colonoscopy procedures has a favorable balance of health and cost impact.
- For individuals that are not willing to participate in colorectal cancer screening using FIT and colonoscopy, annual screening with the m*SEPT9* is the test of choice given its cost-effectiveness profile compared to the other alternative tests.
- Women unable or unwilling to obtain all guideline-recommended cancer screenings may be able to reduce screening intensity with limited impact on overall benefits, but should go for lung cancer screening if eligible.

- Lung cancer screening in eligible women has greater benefit than colorectal, cervical and breast cancer screening.
- It is more valuable for women to obtain a variety of cancer screenings even if less-often than recommended, than to screen for some cancers but skip others entirely.
- Including the FIT in the invitation letter is a very cost-effective intervention to increase colorectal cancer screening participation.
- Immunohistochemical testing for Lynch syndrome in persons younger than 70 years with a colorectal cancer diagnosis, and then testing first-degree relatives of those found to have Lynch syndrome, provides a good balance between costs and long-term benefits.
- Colonoscopy surveillance every 2 years is the optimal surveillance interval for patients with Lynch syndrome.
- Prophylactic hysterectomy in Lynch syndrome women aged between 40 and 80 years is cost-effective from a population perspective.
- The earliest age to recommend prophylactic hysterectomy in women with Lynch syndrome depends on the impact of a prophylactic hysterectomy on an individual's quality of life.

Recommendations

The studies presented in this thesis suggest the following recommendations for clinical practice.



Model appendix

Microsimulation model structure

MISCAN-Colon is a stochastic, semi-Markov, microsimulation model for colorectal cancer (CRC) programmed in Delphi (Borland Software Corporation, Scotts Valley, California, United States). It can be used to explain and predict trends in CRC incidence and mortality and to quantify the effects and costs of primary prevention of CRC, screening for CRC, and surveillance after polypectomy. The term 'microsimulation' implies that the individuals are moved through the model one at a time, rather than as proportions of a cohort. The term 'semi-Markov' implies that MISCAN-Colon, unlike traditional Markov models, does not assume annual state transitions; instead it generates durations in states, allowing future state transitions to depend on past transitions, and thereby increases model flexibility and computational performance. The term 'stochastic' implies that the model determines the states and corresponding durations by drawing from probability distributions, rather than using fixed values. Hence, the results of the model are subject to random variation. MISCAN-Colon consists of three modules: a demography module, natural history module, and screening module.

Demography module

Using birth- and life-tables representative for the population under consideration, MISCAN-Colon draws a date of birth and a date of non-CRC death for each individual simulated. The maximum age an individual can achieve is assumed to be 100 years.

Natural history module

Transitions

As each simulated person ages, one or more adenomas may develop (**Figure 1**). These adenomas can be either progressive or non-progressive. Both progressive and non-progressive adenomas can grow in size from small (≤5mm), to medium (6-9mm), to large (≥10mm); however, only progressive adenomas can develop into preclinical cancer. A preclinical cancer may progress through stages I to IV without symptoms, or be diagnosed during each stage CRC because of symptoms. After clinical diagnosis, CRC survival is simulated using age-, stage-, and localization-specific survival estimates for clinically diagnosed CRC. These survival estimates are country-specific,[134,318] although US survival estimates are used for the Canadian model due to the lack of data. For individuals with synchronous CRCs at time of diagnosis, the survival of the most advanced cancer is used. The date of death for individuals with CRC is set to the earliest simulated death due either to CRC or another cause ('Demography module').

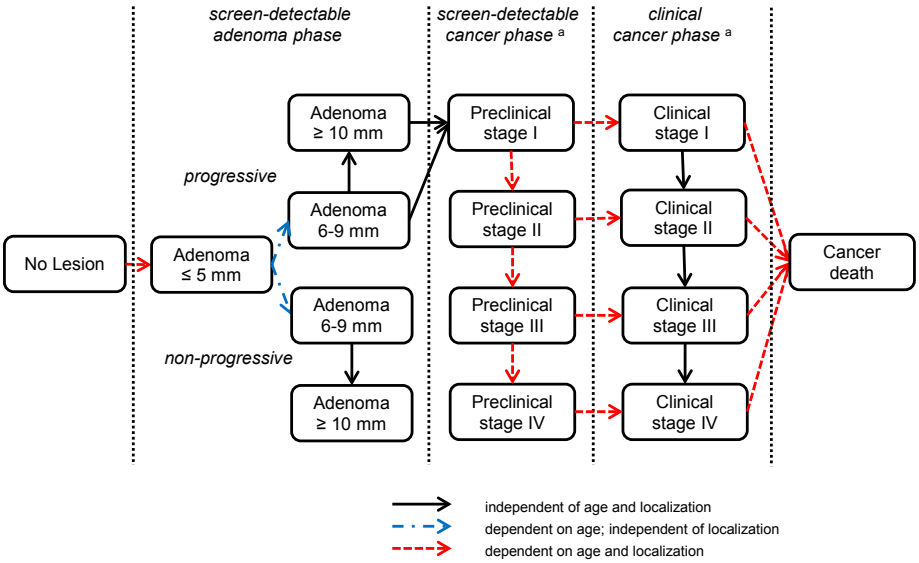


Figure 1: The stages of disease in the semi-Markov model.
[a] Cancer stages were based on the 5th edition Cancer Staging Manual from the American Joint Committee on Cancer[425]

Transition rates and durations

An individual's risk of developing adenomas depends on the individual's age and a personal Gamma-distributed risk index (non-homogeneous Poisson process). As a result of the latter most individuals develop no adenomas, whilst some develop many. We assumed that the distribution of adenomas over the colon and rectum equals the distribution of cancers as observed in the population under consideration before the introduction of screening.[37,426,427] The age-specific onset of adenomas and the dispersion of the personal risk index were calibrated to data on the prevalence and multiplicity distribution of adenomas as observed in autopsy studies (Figure 2).[123-132] In chapters 2, 3, 4, and 6, adenoma onset across all ages was multiplied to account for the increase in CRC incidence observed in young adults in the US, as indicated. The age-specific probability of adenoma-progressivity and the age- and localization-specific transition probabilities between preclinical cancer stages and between preclinical and clinical cancer stages were simultaneously calibrated to country-specific data on the age-, stage-, and localization-specific incidence of CRC as observed before the introduction of screening (Figures 3 & 4).[426-429]

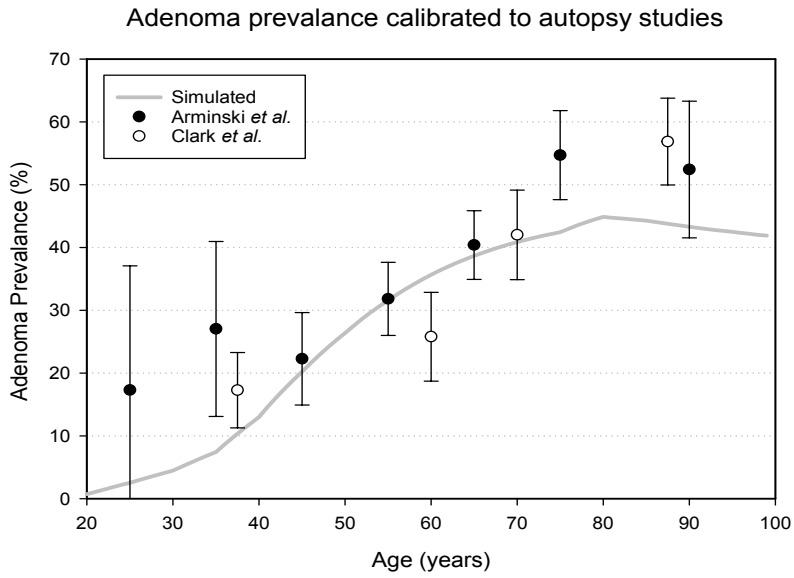


Figure 2: Simulated versus observed adenoma prevalence in selected autopsy studies (with 95% confidence intervals).[a]

[a] Observed results are only shown for the two largest studies on which the model has been calibrated. MISCAN-Colon has additionally been calibrated to 8 other autopsy studies.

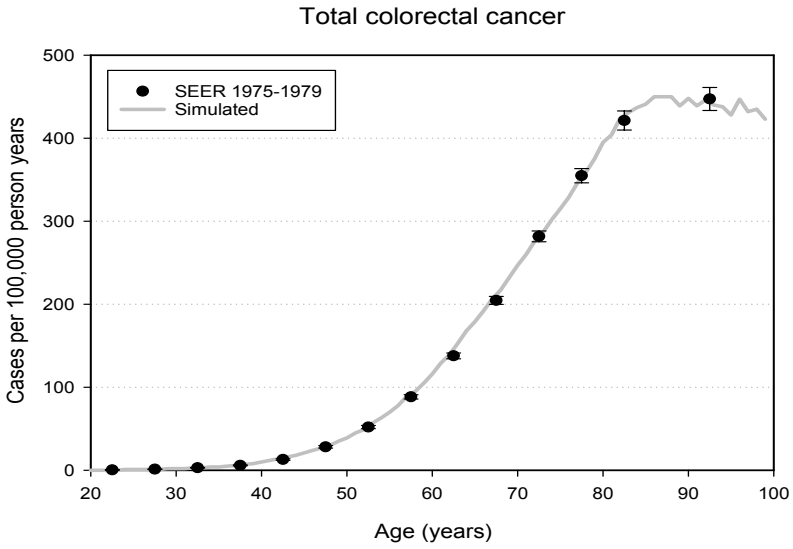
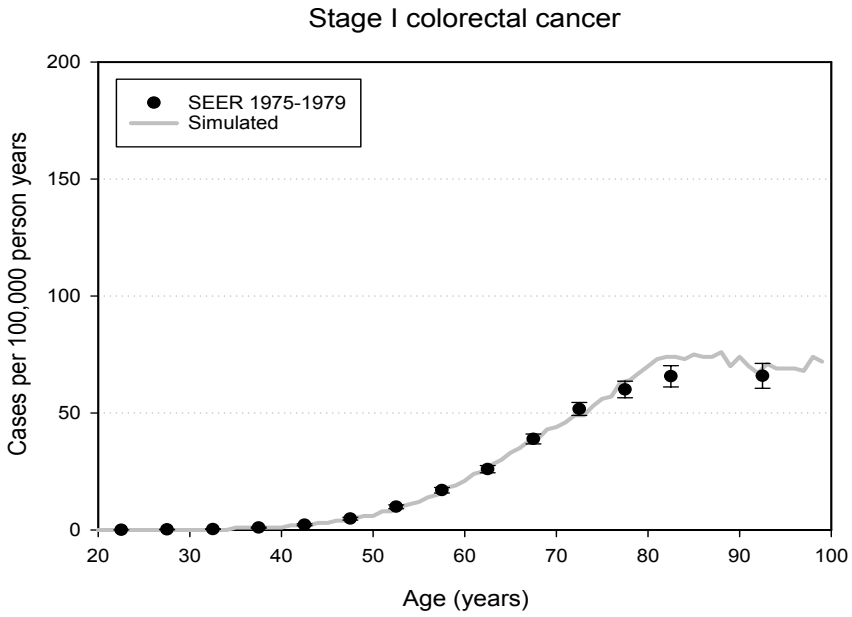
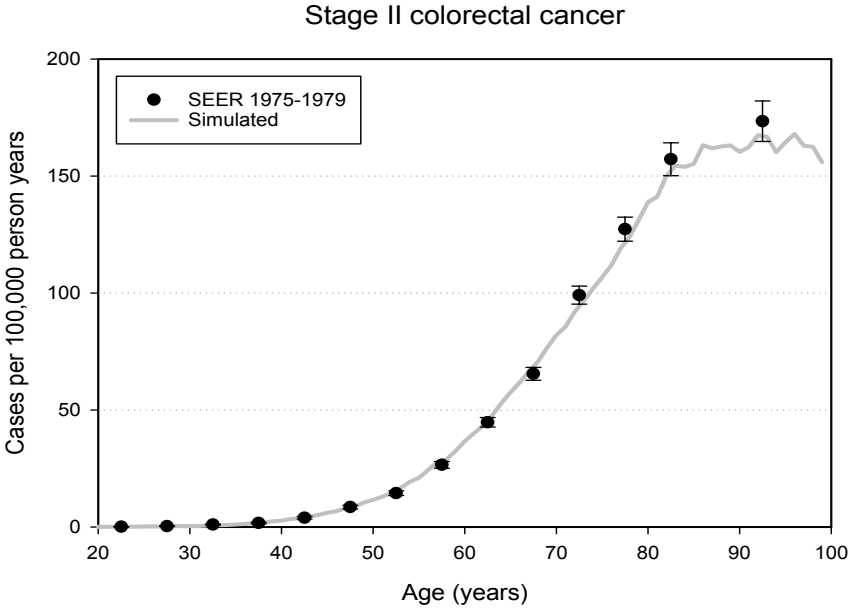


Figure 3: Simulated versus observed colorectal cancer incidence in the US, based on 1975-1979 Surveillance Epidemiology and End Results program data.


Stage I colorectal cancer
SEER 1975-1979
Simulated
Cases per 100,000 person years
Age (years)
0
50
100
150
200
20
30
40
50
60
70
80
90
100


Stage II colorectal cancer
SEER 1975-1979
Simulated
Cases per 100,000 person years
Age (years)
0
50
100
150
200
20
30
40
50
60
70
80
90
100

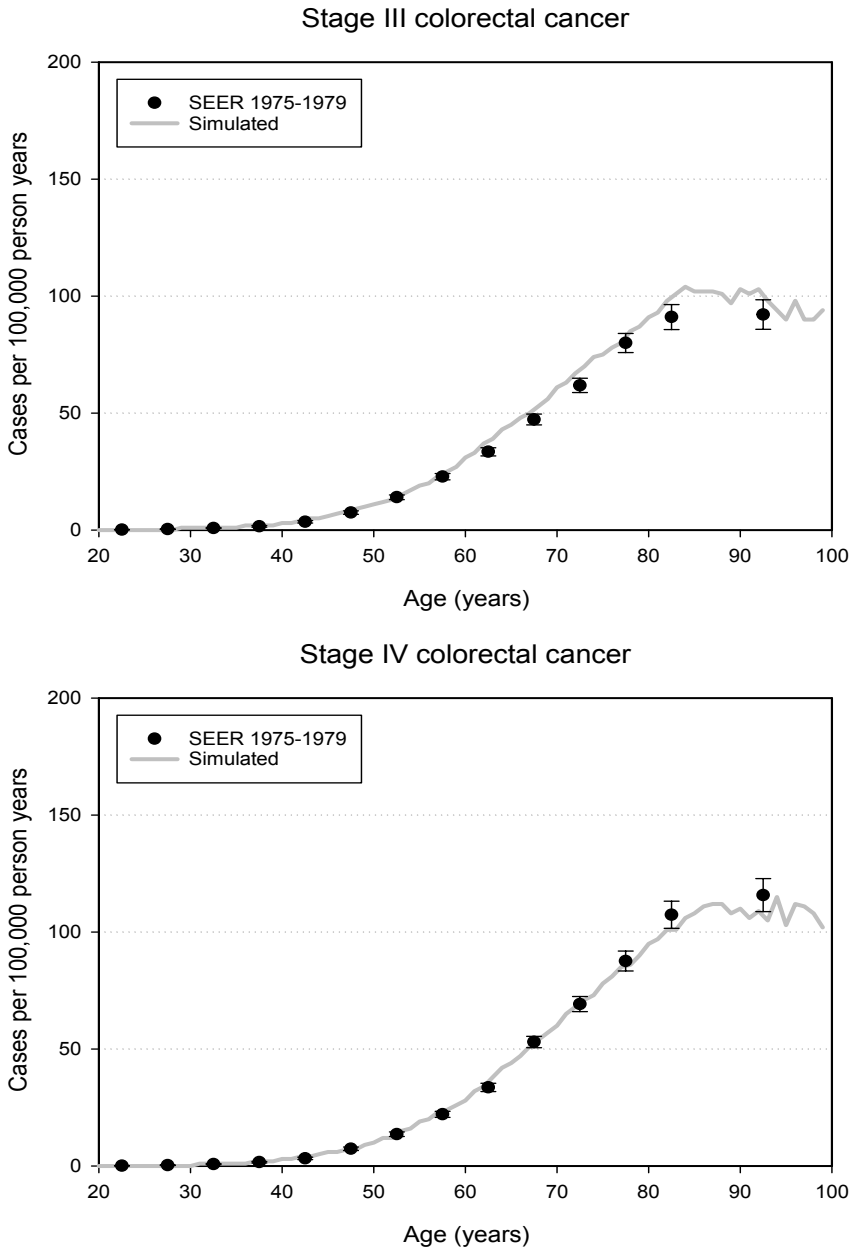


Figure 4: Stage-specific simulated versus observed colorectal cancer incidence in the US, based on 1975-1979 Surveillance Epidemiology and End Results program data.

The average durations between the preclinical cancer stages were calibrated to the rates of screen-detected and interval cancers observed in randomized controlled trials evaluating screening using guaiac fecal occult blood tests.[53,430,431] This exercise has been described extensively elsewhere.[184] The average duration from the emergence of an adenoma until progression into preclinical cancer (i.e. the adenoma dwell-time) was calibrated to the rates of interval cancers (including surveillance detected cancers) observed in a randomized controlled trial evaluating once-only sigmoidoscopy screening (**Figure 5**),[184] and validated against the NORCCAP trial (**Figure 6**).[432] We assumed an equal overall dwell-time for adenomas developing into CRC from a medium size (30% of all CRCs) and from a large size (70% of all CRCs). All durations in the adenoma and preclinical cancer phase were drawn from Exponential distributions. Durations of the disease stages within the adenoma and preclinical cancer phase, respectively, were assumed to be perfectly correlated (i.e. if a small adenoma grows into a medium-sized adenoma rapidly, it will also grow into a large adenoma or develop into CRC rapidly). However, durations in the adenoma phase were assumed to be uncorrelated with durations in the preclinical cancer phase (i.e. a rapidly growing adenoma does not necessarily develop into a rapidly progressing cancer). The proportion of medium sized, non-progressive adenomas growing large and the average duration in the medium size, non-progressive adenoma state were calibrated to size-specific adenoma detection rates observed in a Dutch randomized controlled trial on colonoscopy screening (*not shown*). All calibrations were performed using the Nelder-Mead search algorithm to minimize deviances from observed values based on log-likelihood functions (Poisson likelihood for incidence, Binomial likelihood for adenoma prevalence, and Multinomial likelihood for cancer stages).

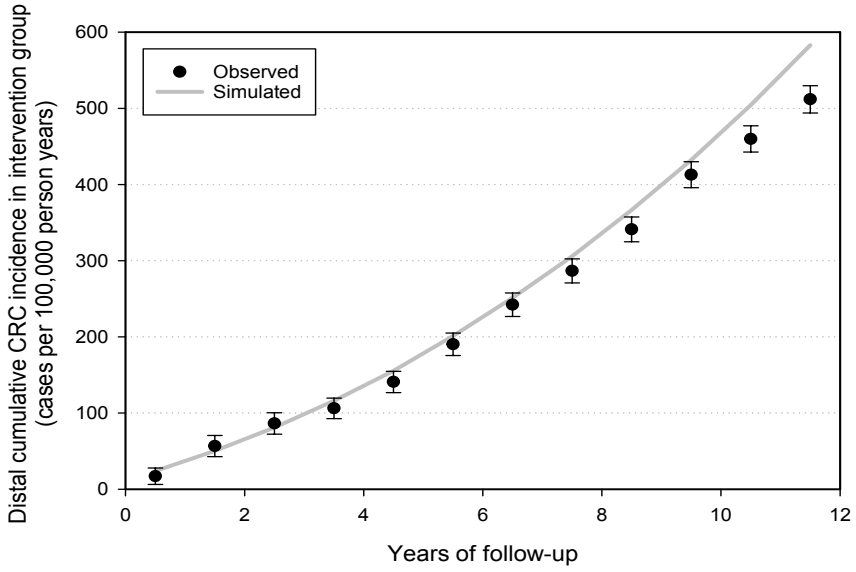


Figure 5: Simulated versus observed distal colorectal cancer incidence in the intervention group of the UK Flexible Sigmoidoscopy Trial.

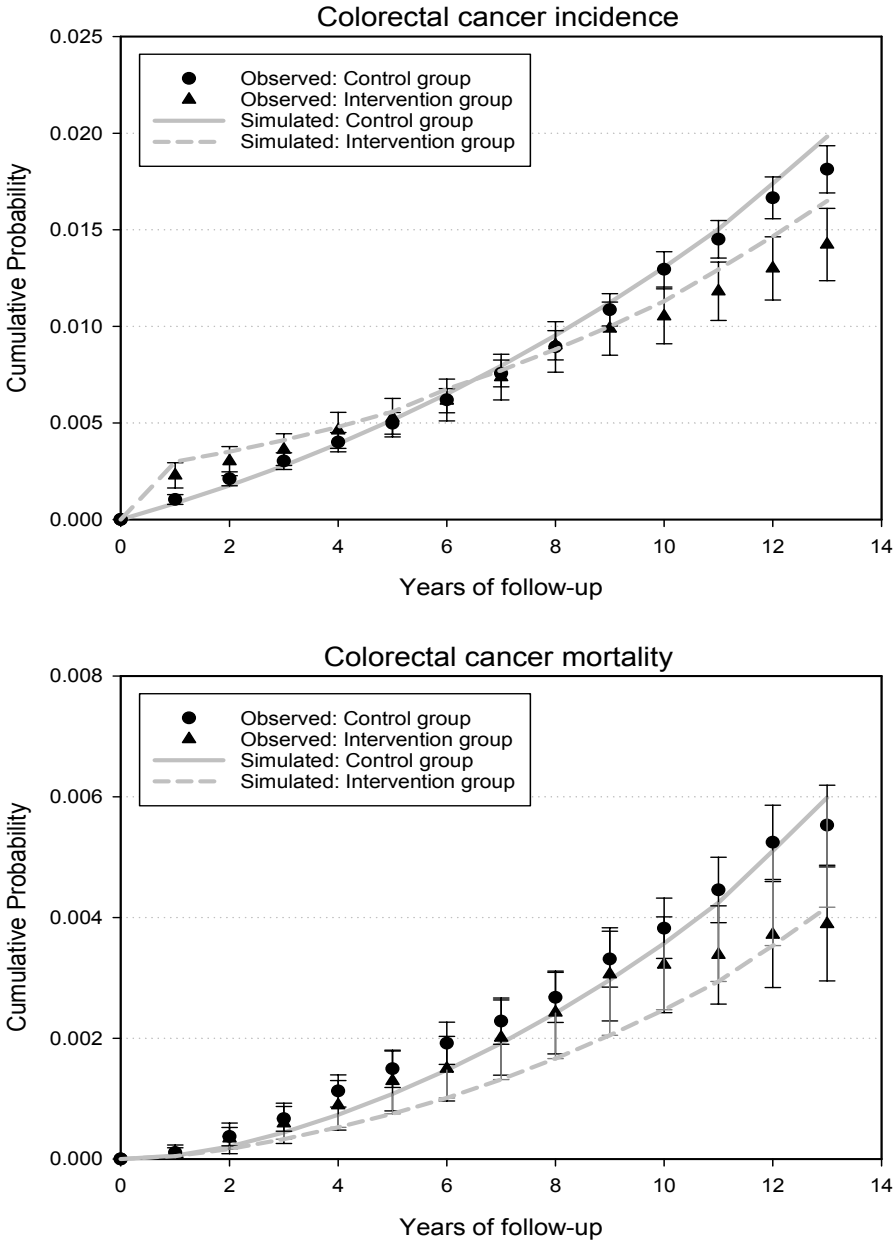


Figure 6: Simulated versus observed colorectal cancer incidence and mortality separately for the intervention and the control group of the NORCCAP trial. [136]

Screening module

Screening will alter some of the simulated life histories: some cancers will be prevented by the detection and removal of adenomas, while other cancers will be detected in an earlier stage with a more favorable survival. As the stage-specific survival of screen-detected CRC as observed in randomized controlled trials on guaiac fecal occult blood testing was substantially more favorable than that of clinically detected CRC, even after correcting for lead-time bias,[184] we assigned those screen-detected cancers that would have been clinically detected in the same stage the survival corresponding to a one stage less progressive cancer. Hence, a cancer screen-detected in stage II, that would also have been clinically diagnosed in stage II, is assigned the survival of a clinically diagnosed stage I cancer. The only exceptions were screen-detected stage IV cancers. These cancers were always assigned the survival of a clinically diagnosed stage IV cancer.

Besides positive health effects of screening, the model also allows for the evaluation of colonoscopy-related complications and over-diagnosis and over-treatment of CRC (i.e. the detection and treatment of cancers that would not have been diagnosed without screening).

Integrating modules

The demography module generates a date of birth and a date of non-CRC death for each individual simulated, creating a life-history without adenomas or CRC. Then, in Patient A in **Figure 7**, the natural history module generates an adenoma. This adenoma progresses into preclinical cancer, which, in the absence of screening, is diagnosed because of symptoms in stage II and results in CRC death before non-CRC death would have occurred. In the screening module a screening examination is simulated, indicated by the blue arrow. During this examination the adenoma is detected, and as a result both CRC and CRC death are prevented. Hence, integrating all 3 modules for Patient A, screening prolongs life by the amount indicated by the green arrow. Patient B also develops an adenoma, and although this adenoma does progress into preclinical cancer, Patient B would never have been diagnosed with CRC in a scenario without screening (see *Life history 2*). However, during the screening examination simulated in the screening module, indicated by the blue arrow, CRC is screen-detected in stage I. Hence, in this patient screening results in over-diagnosis of CRC: it detects a cancer that would never have been diagnosed in a scenario without screening. Hence, integrating all 3 modules in this patient, screening does not prolong life but results in additional LYs with CRC care (over-treatment), as indicated by the red arrow.

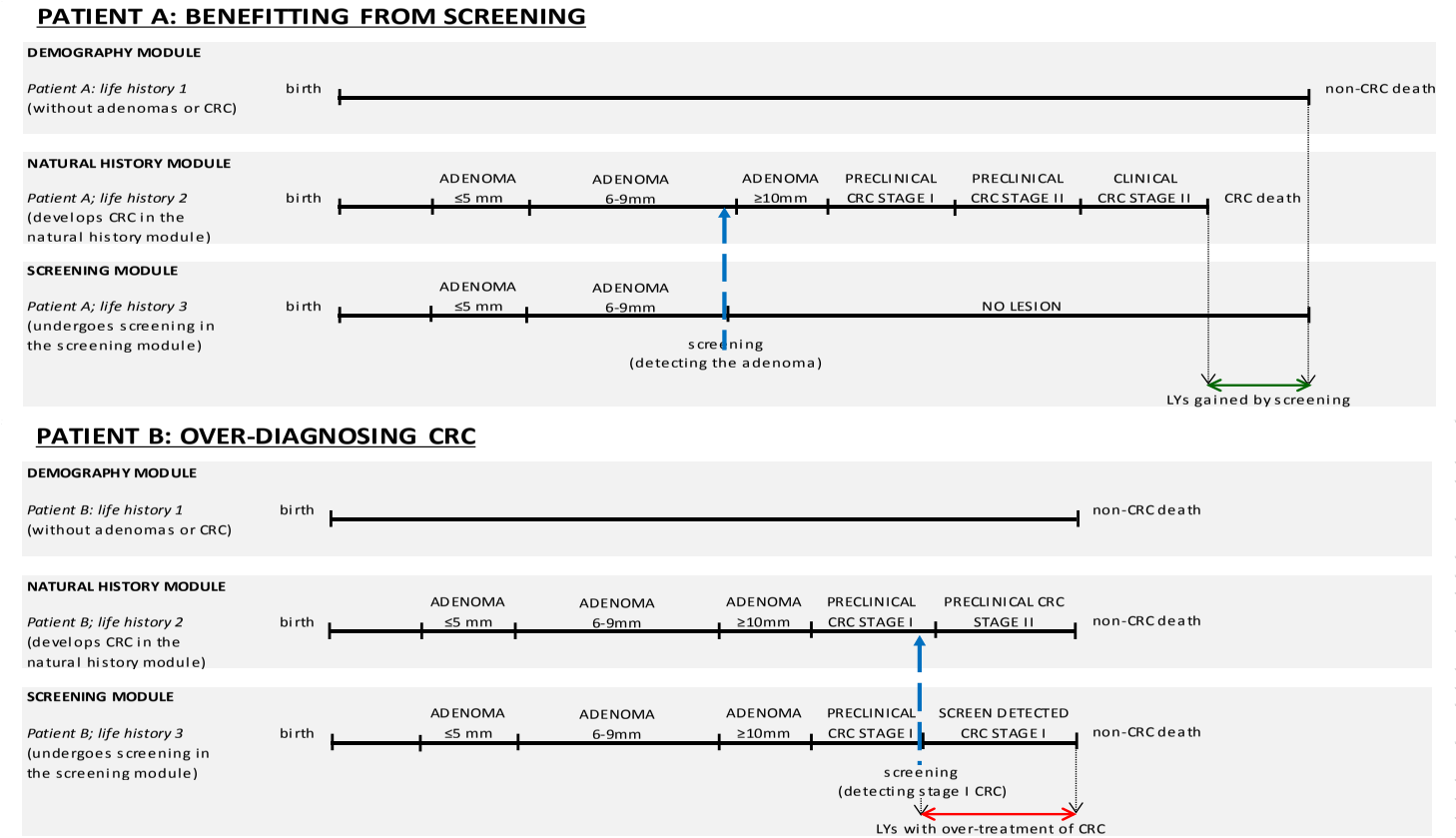


Figure 7: Integrating MISCAN modules for two example patients.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2017;66(4):683-691.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020.
4. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (2012-2016), National Cancer Institute, DCCPS, Surveillance Research Program. released April 2019, based on the November 2018 submission.
5. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016). www.cdc.gov/cancer/dataviz. Accessed January 15, 2020.
6. Weiser MR. AJCC 8th Edition: Colorectal Cancer. *Ann Surg Oncol.* 2018;25(6):1454-1455.
7. Cronin KA, Lake AJ, Scott S, et al. Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. *Cancer.* 2018;124(13):2785-2800.
8. Toes-Zoutendijk E, Kooyker AI, Elferink MA, et al. Stage distribution of screen-detected colorectal cancers in the Netherlands. *Gut.* 2018;67(9):1745-1746.
9. Young JP, Win AK, Rosty C, et al. Rising incidence of early-onset colorectal cancer in Australia over two decades: report and review. *J Gastroenterol Hepatol.* 2015;30(1):6-13.
10. Brenner DR, Heer E, Sutherland RL, et al. National Trends in Colorectal Cancer Incidence Among Older and Younger Adults in Canada. *JAMA Netw Open.* 2019;2(7):e198090.
11. Araghi M, Soerjomataram I, Bardot A, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. *Lancet Gastroenterol Hepatol.* 2019;4(7):511-518.
12. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut.* 2019;68(10):1820-1826.
13. Feletto E, Yu XQ, Lew JB, et al. Trends in Colon and Rectal Cancer Incidence in Australia from 1982 to 2014: Analysis of Data on Over 375,000 Cases. *Cancer Epidemiol Biomarkers Prev.* 2019;28(1):83-90.
14. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. *Gut.* 2019;68(12):2179-2185.
15. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(3):177-193.
16. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. *J Natl Cancer Inst.* 2017;109(8).
17. Austin H, Henley SJ, King J, Richardson LC, Eheman C. Changes in colorectal cancer incidence rates in young and older adults in the United States: what does it tell us about screening. *Cancer Causes Control.* 2014;25(2):191-201.
18. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Rates of colon and rectal cancers are increasing in young adults. *Am Surg.* 2003;69(10):866-872.

19. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. *JAMA Surg.* 2015;150(1):17-22.
20. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. *Cancer Epidemiol Biomarkers Prev.* 2009;18(6):1695-1698.
21. Singh KE, Taylor TH, Pan CG, Stamos MJ, Zell JA. Colorectal Cancer Incidence Among Young Adults in California. *J Adolesc Young Adult Oncol.* 2014;3(4):176-184.
22. Meester RGS, Mannalithara A, Lansdorp-Vogelaar I, Ladabaum U. Trends in Incidence and Stage at Diagnosis of Colorectal Cancer in Adults Aged 40 Through 49 Years, 1975-2015. *JAMA*. 2019;321(19):1933-1934.
23. American Cancer Society. *Colorectal Cancer Facts & Figures 2017-2019*. Atlanta: American Cancer Society;2017.
24. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. *Eur J Cancer.* 2006;42(2):216-227.
25. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. *Am J Gastroenterol.* 2001;96(10):2992-3003.
26. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer.* 2015;112(3):580-593.
27. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. *PLoS One.* 2013;8(1):e53916.
28. Chan DS, Lau R, Aune D, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One*. 2011;6(6):e20456.
29. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA*. 2008;300(23):2765-2778.
30. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2012;104(20):1548-1561.
31. Aune D, Lau R, Chan DS, et al. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. *Ann Oncol.* 2012;23(1):37-45.
32. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet.* 2010;376(9754):1741-1750.
33. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis.* 2013;19(4):789-799.
34. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ.* 2015;350:g7607.
35. Patel SG, Ahnen DJ. Familial colon cancer syndromes: an update of a rapidly evolving field. *Curr Gastroenterol Rep.* 2012;14(5):428-438.
36. Sinicrope FA. Lynch Syndrome-Associated Colorectal Cancer. *N Engl J Med.* 2018;379(8):764-773.
37. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*. 2011;305(22):2304-2310.
38. Dekker E, Bleijenberg AGC, Balaguer F, et al. Update on the World Health Organization Criteria for Diagnosis of Serrated Polyposis Syndrome. *Gastroenterology.* 2020.
39. Jones S, Chen WD, Parmigiani G, et al. Comparative lesion sequencing provides insights

into tumor evolution. *Proc Natl Acad Sci U S A.* 2008;105(11):4283-4288.
40. Kuntz KM, Lansdorp-Vogelaar I, Rutter CM, et al. A systematic comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression. *Med Decis Making.* 2011;31(4):530-539.
41. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol.* 2012;107(9):1315-1329; quiz 1314, 1330.
42. Snover D, Ahnen DJ, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated ("hyperplastic") polyposis. In: Bozman FT, Carneiro F, Hruban RH, Theise ND, eds. *WHO classification of tumours. Pathology and genetics. Tumours of the digestive system*. 4th ed. Berlin: Springer-Verslag; 2010.
43. Holme O, Bretthauer M, Eide TJ, et al. Long-term risk of colorectal cancer in individuals with serrated polyps. *Gut.* 2015;64(6):929-936.
44. Cenaj O, Gibson J, Odze RD. Clinicopathologic and outcome study of sessile serrated adenomas/polyps with serrated versus intestinal dysplasia. *Mod Pathol.* 2018;31(4):633-642.
45. Erichsen R, Baron JA, Hamilton-Dutoit SJ, et al. Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps. *Gastroenterology.* 2016;150(4):895-902 e895.
46. Anderson JC, Butterly LF, Robinson CM, Weiss JE, Amos C, Srivastava A. Risk of Metachronous High-Risk Adenomas and Large Serrated Polyps in Individuals With Serrated Polyps on Index Colonoscopy: Data From the New Hampshire Colonoscopy Registry. *Gastroenterology.* 2018;154(1):117-127 e112.
47. Burnett-Hartman AN, Chubak J, Hua X, et al. The association between colorectal sessile serrated adenomas/polyps and subsequent advanced colorectal neoplasia. *Cancer Causes Control.* 2019;30(9):979-987.
48. He X, Hang D, Wu K, et al. Long-term Risk of Colorectal Cancer After Removal of Conventional Adenomas and Serrated Polyps. *Gastroenterology.* 2020;158(4):852-861 e854.
49. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology.* 2010;138(6):2088-2100.
50. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol.* 2019;16(12):713-732.
51. Holme O, Bretthauer M, Fretheim A, Odgaard-Jensen J, Hoff G. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. *Cochrane Database Syst Rev.* 2013(9):CD009259.
52. Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet.* 2017;389(10076):1299-1311.
53. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. *J Natl Cancer Inst.* 1999;91(5):434-437.
54. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut.* 2012;61(7):1036-1040.
55. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. *N Engl J Med.* 2013;369(12):1106-1114.
56. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by

screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med.* 1993;328(19):1365-1371.
57. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg.* 2008;95(8):1029-1036.
58. Holme O, Loberg M, Kalager M, et al. Long-Term Effectiveness of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality in Women and Men: A Randomized Trial. *Ann Intern Med.* 2018;168(11):775-782.
59. Pitkaniemi J, Seppa K, Hakama M, et al. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. *BMJ Open Gastroenterol.* 2015;2(1):e000034.
60. Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. *Scand J Gastroenterol.* 2004;39(9):846-851.
61. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. *J Natl Cancer Inst.* 2011;103(17):1310-1322.
62. Thiis-Evensen E, Kalager M, Bretthauer M, Hoff G. Long-term effectiveness of endoscopic screening on incidence and mortality of colorectal cancer: A randomized trial. *United European Gastroenterol J.* 2013;1(3):162-168.
63. Chiu HM, Chen SL, Yen AM, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. *Cancer.* 2015;121(18):3221-3229.
64. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med.* 2012;366(8):687-696.
65. Ventura L, Mantellini P, Grazzini G, et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. *Dig Liver Dis.* 2014;46(1):82-86.
66. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut.* 2010;59(1):62-68.
67. Wolff WI, Shinya H. Polypectomy via the fiberoptic colonoscope. Removal of neoplasms beyond reach of the sigmoidoscope. *N Engl J Med.* 1973;288(7):329-332.
68. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med.* 2012;366(25):2345-2357.
69. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med.* 2003;349(23):2191-2200.
70. Van Gossum A, Munoz-Navas M, Fernandez-Urien I, et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. *N Engl J Med.* 2009;361(3):264-270.
71. Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al. Real-Time Monitoring of Results During First Year of Dutch Colorectal Cancer Screening Program and Optimization by Altering Fecal Immunochemical Test Cut-Off Levels. *Gastroenterology.* 2017;152(4):767-775 e762.
72. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med.* 2014;370(14):1287-1297.
73. Deng L, Ismond K, Liu Z, et al. Urinary Metabolomics to Identify a Unique Biomarker Panel for Detecting Colorectal Cancer: A Multicenter Study. *Cancer Epidemiol Biomarkers Prev.* 2019;28(8):1283-1291.

74. Doubeni CA, Corley DA, Zauber AG. Colorectal Cancer Health Disparities and the Role of US Law and Health Policy. *Gastroenterology.* 2016;150(5):1052-1055.
75. Kim SY, Kim HS, Park HJ. Adverse events related to colonoscopy: Global trends and future challenges. *World J Gastroenterol.* 2019;25(2):190-204.
76. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016;315(23):2564-2575.
77. European Colorectal Cancer Screening Guidelines Working G, von Karsa L, Patnick J, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. *Endoscopy.* 2013;45(1):51-59.
78. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin.* 2018;68(4):250-281.
79. Stefanek ME. Uninformed compliance or informed choice? A needed shift in our approach to cancer screening. *J Natl Cancer Inst.* 2011;103(24):1821-1826.
80. Dube C. Organized Screening Is Better Than Opportunistic Screening at Decreasing the Burden of Colorectal Cancer in the United States. *Gastroenterology.* 2018;155(5):1302-1304.
81. Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol.* 2017;112(7):1016-1030.
82. Joseph DA, King JB, Richards TB, Thomas CC, Richardson LC. Use of Colorectal Cancer Screening Tests by State. *Prev Chronic Dis.* 2018;15:E80.
83. Sauer AG, Liu B, Siegel RL, Jemal A, Fedewa SA. Comparing cancer screening estimates: Behavioral Risk Factor Surveillance System and National Health Interview Survey. *Prev Med.* 2018;106:94-100.
84. Gingold-Belfer R, Leibovitzh H, Boltin D, et al. The compliance rate for the second diagnostic evaluation after a positive fecal occult blood test: A systematic review and meta-analysis. *United European Gastroenterol J.* 2019;7(3):424-448.
85. Murphy CC, Sandler RS, Grubber JM, Johnson MR, Fisher DA. Underuse and Overuse of Colonoscopy for Repeat Screening and Surveillance in the Veterans Health Administration. *Clin Gastroenterol Hepatol.* 2016;14(3):436-444 e431.
86. Laiyemo AO, Pinsky PF, Marcus PM, et al. Utilization and yield of surveillance colonoscopy in the continued follow-up study of the polyp prevention trial. *Clin Gastroenterol Hepatol.* 2009;7(5):562-567; quiz 497.
87. Colquhoun P, Chen HC, Kim JI, et al. High compliance rates observed for follow up colonoscopy post polypectomy are achievable outside of clinical trials: efficacy of polypectomy is not reduced by low compliance for follow up. *Colorectal Dis.* 2004;6(3):158-161.
88. Wender RC, Doroshenk M, Brooks D, Hotz J, Smith RA. Creating and Implementing a National Public Health Campaign: The American Cancer Society's and National Colorectal Cancer Roundtable's 80% by 2018 Initiative. *Am J Gastroenterol.* 2018;113(12):1739-1741.
89. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg.* 2011;128(1):305-310.
90. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ.*

2008;86(4):317-319.
91. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease] Principios y metodos del examen colectivo para identificar enfermedades. *Bol Oficina Sanit Panam.* 1968;65(4):281-393.
92. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol.* 2012;13(1):55-64.
93. van Hees F, Zauber AG, van Veldhuizen H, et al. The value of models in informing resource allocation in colorectal cancer screening: the case of The Netherlands. *Gut.* 2015;64(12):1985-1997.
94. Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. *Comput Biomed Res.* 1999;32(1):13-33.
95. Habbema JD, van Oortmarssen GJ, Lubbe JT, van der Maas PJ. The MISCAN simulation program for the evaluation of screening for disease. *Comput Methods Programs Biomed.* 1985;20(1):79-93.
96. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. *JAMA.* 2016;315(23):2595-2609.
97. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2008;149(9):659-669.
98. Meester RGS, Peterse EFP, Knudsen AB, et al. Optimizing colorectal cancer screening by race and sex: Microsimulation analysis II to inform the American Cancer Society colorectal cancer screening guideline. *Cancer.* 2018;124(14):2974-2985.
99. Peterse EFP, Meester RGS, Siegel RL, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: Microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. *Cancer.* 2018;124(14):2964-2973.
100. American Cancer Society, Cancer Statistics Center. 2017; https://cancerstatisticscenter.cancer.org/?_ga=1.33682849.1877282425.1465291457#/cancer-site/Colorectum. Accessed February 21, 2017.
101. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin.* 2008;58(3):130-160.
102. van Hees F, Habbema JD, Meester RG, Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG. Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis. *Ann Intern Med.* 2014;160(11):750-759.
103. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JD, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. *J Natl Cancer Inst.* 2009;101(20):1412-1422.
104. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. *Ann Intern Med.* 2009;150(12):849-857, W152.
105. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of

perforation after colonoscopy and sigmoidoscopy: a population-based study. *J Natl Cancer Inst.* 2003;95(3):230-236.
106. Surveillance Epidemiology and End Results Program. SEER*Stat Software, version 8.3.4. Surveillance Research Program. 2014; http://seer.cancer.gov/seerstat/. Accessed August 24, 2017.
107. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology.* 2012;143(3):844-857.
108. Mark DH. Visualizing cost-effectiveness analysis. *JAMA.* 2002;287(18):2428-2429.
109. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA.* 2016;316(10):1093-1103.
110. Atreja A, Bellam N, Levy SR. Strategies to enhance patient adherence: making it simple. *MedGenMed.* 2005;7(1):4.
111. Murphy CC, Lund JL, Sandler RS. Young-Onset Colorectal Cancer: Earlier Diagnoses or Increasing Disease Burden? *Gastroenterology.* 2017;152(8):1809-1812 e1803.
112. Siegel RL, Miller KD, Jemal A. Colorectal Cancer Mortality Rates in Adults Aged 20 to 54 Years in the United States, 1970-2014. *JAMA.* 2017;318(6):572-574.
113. Centers for Disease Control and Prevention. National Health interview Survey (NHIS) 2015; http://www.cdc.gov/nchs/nhis.htm.
114. Colquhoun P, Chen HC, Kim JI, et al. High compliance rates observed for follow up colonoscopy post polypectomy are achievable outside of clinical trials: efficacy of polypectomy is not reduced by low compliance for follow up. *Colorectal Disease.* 2004;6(3):158-161.
115. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology.* 1997;112(2):594-642.
116. Eddy D. ACS report on the cancer-related health checkup. *CA Cancer J Clin.* 1980;30(4):193-240.
117. U.S. Department of Health and Human Services. United States Life Tables 2010. *National Vital Statistics Reports.* 2014;63(7).
118. Saini SD, van Hees F, Vijan S. Smarter screening for cancer: possibilities and challenges of personalization. *JAMA.* 2014;312(21):2211-2212.
119. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol.* 2009;104(3):739-750.
120. Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients From the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology.* 2017;153(1):307-323.
121. U.S. Preventive Services Task Force. Modeling Report. 2016; https://www.uspreventiveservicestaskforce.org/Page/Document/modeling-report1/colorectal-cancer-screening2. Accessed March 6, 2017.
122. Cancer Intervention and Surveillance Modeling Network (CISNET). Colorectal Cancer Model Profiles. 2013; http://cisnet.cancer.gov/colorectal/profiles.html/. Accessed January 1, 2013.
123. Arminski TC, McLean DW. Incidence and Distribution of Adenomatous Polyps of the Colon and Rectum Based on 1,000 Autopsy Examinations. *Dis Colon Rectum.* 1964;7:249-261.

124. Blatt LJ. Polyps of the colon and rectum: incidence and distribution. *Dis Colon Rectum.* 1961;4:277-282.
125. Bombi JA. Polyps of the colon in Barcelona, Spain. An autopsy study. *Cancer.* 1988;61(7):1472-1476.
126. Chapman I. Adenomatous polypi of large intestine: incidence and distribution. *Ann Surg.* 1963;157:223-226.
127. Clark JC, Collan Y, Eide TJ, et al. Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. *Int J Cancer.* 1985;36(2):179-186.
128. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. *Gut.* 1992;33(11):1508-1514.
129. Johannsen LG, Momsen O, Jacobsen NO. Polyps of the large intestine in Aarhus, Denmark. An autopsy study. *Scand J Gastroenterol.* 1989;24(7):799-806.
130. Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM. Adenomatous lesions of the large bowel: an autopsy survey. *Cancer.* 1979;43(5):1847-1857.
131. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. *Cancer.* 1982;49(4):819-825.
132. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. *Gut.* 1982;23(10):835-842.
133. Surveillance Epidemiology and End Results Program. SEER*Stat Software, version 5.3.1. Surveillance Research Program. 2014; http://seer.cancer.gov/seerstat/. Accessed January 1, 2015.
134. Rutter CM, Johnson EA, Feuer EJ, Knudsen AB, Kuntz KM, Schrag D. Secular trends in colon and rectal cancer relative survival. *J Natl Cancer Inst.* 2013;105(23):1806-1813.
135. Rutter CM, Knudsen AB, Marsh TL, et al. Validation of Models Used to Inform Colorectal Cancer Screening Guidelines: Accuracy and Implications. *Med Decis Making.* 2016;36(5):604-614.
136. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. *JAMA.* 2014;312(6):606-615.
137. Reumkens A, Rondagh EJ, Bakker CM, Winkens B, Masclee AA, Sanduleanu S. Post-Colonoscopy Complications: A Systematic Review, Time Trends, and Meta-Analysis of Population-Based Studies. *Am J Gastroenterol.* 2016;111(8):1092-1101.
138. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Am J Gastroenterol.* 2015;110(1):72-90.
139. Bailey CE, Hu CY, You YN, et al. Increasing Disparities in the Age-Related Incidences of Colon and Rectal Cancers in the United States, 1975-2010. *JAMA Surg.* 2014:1-6.
140. Surveillance, Epidemiology, and End Results Program. SEER*Stat Database: incidence—SEER 9 regs research data, Nov 2013 sub (1973- 2011) <Katrina/Rita population adjustment>—linked to county attributes—total U.S., 1969- 2012 counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission. https://seer.cancer.gov/data/. Accessed Accessed May 25, 2016.
141. Ransohoff DF, Lang CA. Screening for colorectal cancer with the fecal occult blood test: a background paper. American College of Physicians. *Ann Intern Med.* 1997;126(10):811-822.
142. National Center for Health Statistics. 2010, 2013, and 2015 National Health Interview Survey. http://www.cdc.gov/nchs/nhis.htm. Accessed Jan 26th, 2018.

143. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, et al. Individualizing colonoscopy screening by sex and race. *Gastrointest Endosc.* 2009;70(1):96-108, 108 e101-124.
144. van Hees F, Saini SD, Lansdorp-Vogelaar I, et al. Personalizing colonoscopy screening for elderly individuals based on screening history, cancer risk, and comorbidity status could increase cost effectiveness. *Gastroenterology.* 2015;149(6):1425-1437.
145. Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. *Arch Intern Med.* 2012;172(7):575-582.
146. Liang PS, Dominitz JA. Editorial: Bowel Preparation: Is Fair Good Enough? *Am J Gastroenterol.* 2014;109(11):1725-1727.
147. Jensen CD, Corley DA, Quinn VP, et al. Fecal Immunochemical Test Program Performance Over 4 Rounds of Annual Screening: A Retrospective Cohort Study. *Ann Intern Med.* 2016;164(7):456-463.
148. Winawer SJ, Fischer SE, Levin B. Evidence-Based, Reality-Driven Colorectal Cancer Screening Guidelines: The Critical Relationship of Adherence to Effectiveness. *JAMA.* 2016;315(19):2065-2066.
149. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
150. Cress RD, Morris C, Ellison GL, Goodman MT. Secular changes in colorectal cancer incidence by subsite, stage at diagnosis, and race/ethnicity, 1992-2001. *Cancer.* 2006;107(5 Suppl):1142-1152.
151. Siegel RL, Ward EM, Jemal A. Trends in colorectal cancer incidence rates in the United States by tumor location and stage, 1992-2008. *Cancer Epidemiol Biomarkers Prev.* 2012;21(3):411-416.
152. Ladabaum U, Mannalithara A, Meester RGS, Gupta S, Schoen RE. Cost-Effectiveness and National Effects of Initiating Colorectal Cancer Screening for Average-Risk Persons at Age 45 Years Instead of 50 Years. *Gastroenterology.* 2019;157(1):137-148.
153. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. *Epidemiol Rev.* 2011;33:88-100.
154. Peterse EFP, Meester RGS, Gini A, et al. Value Of Waiving Coinsurance For Colorectal Cancer Screening In Medicare Beneficiaries. *Health Aff (Millwood).* 2017;36(12):2151-2159.
155. van Hees F, Zauber AG, Klabunde CN, Goede SL, Lansdorp-Vogelaar I, van Ballegooijen M. The appropriateness of more intensive colonoscopy screening than recommended in Medicare beneficiaries: a modeling study. *JAMA Intern Med.* 2014;174(10):1568-1576.
156. Van Hees F, Zauber AG, Van Veldhuizen H, et al. The value of models in informing resource allocation in colorectal cancer screening: the case of the Netherlands. *Gut.* 2015;64(12):1985-1997.
157. Cenin DR, St John J, Slevin T, Ledger MJ, Lansdorp-Vogelaar I. Optimising the expansion of the national bowel cancer screening program. *The Medical journal of Australia.* 2014;201(8):456.
158. Goede SL, Rabeneck L, van Ballegooijen M, et al. Harms, benefits and costs of fecal immunochemical testing versus guaiac fecal occult blood testing for colorectal cancer screening. *PLoS One.* 2017;12(3):e0172864.
159. Arias E, Heron M, Xu J. United States Life Tables, 2013. *Natl Vital Stat Rep.* 2017;66(3):1-64.
160. van Hees F, Habbema JD, Meester RG, Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG. Should colorectal cancer screening be considered in elderly persons without previous screening?: a cost-effectiveness analysis. *Ann Intern Med.* 2014;160(11):750-759.

161. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst.* 2011;103(2):117-128.
162. Mariotto AB, Enewold L, Zhao J, Zeruto CA, Yabroff KR. Medical Care Costs Associated with Cancer Survivorship in the United States. *Cancer Epidemiol Biomarkers Prev.* 2020;29(7):1304-1312.
163. Ladabaum U, Levin Z, Mannalithara A, Brill JV, Bundorf MK. Colorectal testing utilization and payments in a large cohort of commercially insured US adults. *Am J Gastroenterol.* 2014;109(10):1513-1525.
164. Centers for Medicare & Medicaid Services. 2017 Clinical Laboratory Fee Schedule. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched. Accessed October 3, 2019.
165. Centers for Medicare & Medicaid Services. 2017 Physician Fee Schedule. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched. Accessed October 3, 2019.
166. Ladabaum U, Mannalithara A, Brill JV, Levin Z, Bundorf KM. Contrasting Effectiveness and Cost-Effectiveness of Colorectal Cancer Screening Under Commercial Insurance vs. Medicare. *Am J Gastroenterol.* 2018;113(12):1836-1847.
167. Jonas DE, Russell LB, Sandler RS, Chou J, Pignone M. Patient time requirements for screening colonoscopy. *Am J Gastroenterol.* 2007;102(11):2401-2410.
168. Swan JS, Kong CY, Hur C, et al. Comparing morbidities of testing with a new index: screening colonoscopy versus core-needle breast biopsy. *J Am Coll Radiol.* 2015;12(3):295-301.
169. Kirkegaard P, Edwards A, Larsen MB, Andersen B. Waiting for diagnostic colonoscopy: a qualitative exploration of screening participants' experiences in a FIT-based colorectal cancer screening program. *Patient Prefer Adherence.* 2018;12:845-852.
170. Mandelblatt JS, Stout NK, Schechter CB, et al. Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies. *Ann Intern Med.* 2016;164(4):215-225.
171. Ness RM, Holmes AM, Klein R, Dittus R. Utility valuations for outcome states of colorectal cancer. *Am J Gastroenterol.* 1999;94(6):1650-1657.
172. Naber SK, Knudsen AB, Zauber AG, et al. Cost-effectiveness of a multitarget stool DNA test for colorectal cancer screening of Medicare beneficiaries. *PLoS One.* 2019;14(9):e0220234.
173. Centers for Disease Control and Prevention. National Health interview Survey (NHIS) 2015; http://www.cdc.gov/nchs/nhis.htm. Accessed Agust 1, 2020.
174. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med.* 2014;371(9):796-797.
175. Centers for Disease C, Prevention. Vital signs: colorectal cancer screening test use--United States, 2012. *MMWR Morb Mortal Wkly Rep.* 2013;62(44):881-888.
176. Sabatino SA, White MC, Thompson TD, Klabunde CN, Centers for Disease Control and Prevention. Cancer screening test use - United States, 2013. *MMWR Morb Mortal Wkly Rep.* 2015;64(17):464-468.
177. National Colorectal Cancer Roudtable. 80% by 2018. http://nccrt.org/what-we-do/80-percent-by-2018/. Accessed August 1, 2020.
178. Venook A. Critical evaluation of current treatments in metastatic colorectal cancer. *Oncologist.* 2005;10(4):250-261.

179. Peterse EFP, Meester RGS, de Jonge L, et al. Comparing the cost-effectiveness of innovative colorectal cancer screening tests. *J Natl Cancer Inst.* 2020.
180. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Results of screening colonoscopy among persons 40 to 49 years of age. *N Engl J Med.* 2002;346(23):1781-1785.
181. Rundle AG, Lebwohl B, Vogel R, Levine S, Neugut AI. Colonoscopic screening in average-risk individuals ages 40 to 49 vs 50 to 59 years. *Gastroenterology.* 2008;134(5):1311-1315.
182. Chen CH, Tsai MK, Wen CP. Extending Colorectal Cancer Screening to Persons Aged 40 to 49 Years With Immunochemical Fecal Occult Blood Test: A Prospective Cohort Study of 513,283 Individuals. *J Clin Gastroenterol.* 2016;50(9):761-768.
183. Fedewa SA, Siegel RL, Goding Sauer A, Bandi P, Jemal A. Colorectal cancer screening patterns after the American Cancer Society's recommendation to initiate screening at age 45 years. *Cancer.* 2020;126(6):1351-1353.
184. Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, Zauber A, Habbema JD. A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials. *Cancer.* 2009;115(11):2410-2419.
185. Lo SH, Halloran S, Snowball J, Seaman H, Wardle J, von Wagner C. Predictors of repeat participation in the NHS bowel cancer screening programme. *Br J Cancer.* 2015;112(1):199-206.
186. Kapidzic A, van Roon AHC, van Leerdam ME, et al. Attendance and diagnostic yield of repeated two-sample faecal immunochemical test screening for colorectal cancer. *Gut.* 2015.
187. American Cancer Society. Cancer Statistics Center, Colorectum: at a glance [Internet]. Atlanta (GA): ACS; c 2017 [cited 2017 Oct 11]. Available from: https://cancerstatisticscenter.cancer.org/?_ga=1.33682849.1877282425.1465291457#!/cancersite/Colorectum.
188. Jones RM, Woolf SH, Cunningham TD, et al. The relative importance of patient-reported barriers to colorectal cancer screening. *Am J Prev Med.* 2010;38(5):499-507.
189. Senore C, Inadomi J, Segnan N, Bellisario C, Hassan C. Optimising colorectal cancer screening acceptance: a review. *Gut.* 2015;64(7):1158-1177.
190. Sommers BD, Gunja MZ, Finegold K, Musco T. Changes in Self-reported Insurance Coverage, Access to Care, and Health Under the Affordable Care Act. *Jama.* 2015;314(4):366-374.
191. Fedewa SA, Goodman M, Flanders WD, et al. Elimination of cost-sharing and receipt of screening for colorectal and breast cancer. *Cancer.* 2015;121(18):3272-3280.
192. Hamman MK, Kapinos KA. Affordable Care Act Provision Lowered Out-Of-Pocket Cost And Increased Colonoscopy Rates Among Men In Medicare. *Health Aff (Millwood).* 2015;34(12):2069-2076.
193. Hamman MK, Kapinos KA. Colorectal Cancer Screening and State Health Insurance Mandates. *Health Econ.* 2016;25(2):178-191.
194. Richman I, Asch SM, Bhattacharya J, Owens DK. Colorectal Cancer Screening in the Era of the Affordable Care Act. *J Gen Intern Med.* 2016;31(3):315-320.
195. Wharam JF, Zhang F, Landon BE, LeCates R, Soumerai S, Ross-Degnan D. Colorectal Cancer Screening in a Nationwide High-deductible Health Plan Before and After the Affordable Care Act. *Med Care.* 2016;54(5):466-473.
196. Howard DH, Guy GP, Jr., Ekwueme DU. Eliminating cost-sharing requirements for colon cancer screening in Medicare. *Cancer.* 2014;120(24):3850-3852.
197. Cancer Intervention and Surveillance Modeling Network: CISNET Model Profiles. https://cisnet.cancer.gov/resources/profiles.html. Accessed July 30, 2019.

198. CMS.gov Clinical laboratory fee schedule files [Internet]. Baltimore (MD): Centers for Medicare and Medicaid Services; [last modified 2016 Sep 29; cited 2017 Sep 27]. Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files.html.
199. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. *J Natl Cancer Inst.* 2008;100(9):630-641.
200. Centers for Disease Control and Prevention. Vital signs: colorectal cancer screening test use—United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(44):881–8. .
201. Khatami S, Xuan L, Roman R, et al. Modestly increased use of colonoscopy when copayments are waived. *Clin Gastroenterol Hepatol.* 2012;10(7):761-766 e761.
202. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res.* 2008;8(2):165-178.
203. Oliphant R, Brewster DH, Morrison DS. The changing association between socioeconomic circumstances and the incidence of colorectal cancer: a population-based study. *Br J Cancer.* 2011;104(11):1791-1796.
204. Henry J. Kaiser Family Foundation. Status of state action on the Medicaid expansion decision [Internet]. Menlo Park (CA): KFF; 2017 Jan 1 [cited 2017 Sep 27]. Available from: http://www.kff.org/health-reform/state-indicator/state-activityaround-expanding-medicaid-underthe-affordable-care-act.
205. Cooper GS, Kou TD, Schluchter MD, Dor A, Koroukian SM. Changes in receipt of cancer screening in Medicare beneficiaries following the Affordable Care Act. J Natl Cancer Inst. 2015;108(5).
206. Han X, Robin Yabroff K, Guy GP, Jr., Zheng Z, Jemal A. Has recommended preventive service use increased after elimination of cost-sharing as part of the Affordable Care Act in the United States? *Prev Med.* 2015;78:85-91.
207. Mehta SJ, Jensen CD, Quinn VP, et al. Race/Ethnicity and Adoption of a Population Health Management Approach to Colorectal Cancer Screening in a Community-Based Healthcare System. *J Gen Intern Med.* 2016;31(11):1323-1330.
208. Medina GG, McQueen A, Greisinger AJ, Bartholomew LK, Vernon SW. What would make getting colorectal cancer screening easier? Perspectives from screeners and nonscreeners. *Gastroenterol Res Pract.* 2012;2012:895807.
209. Meissner HI, Klabunde CN, Breen N, Zapka JM. Breast and colorectal cancer screening: U.S. primary care physicians' reports of barriers. *Am J Prev Med.* 2012;43(6):584-589.
210. Subramanian S, Bobashev G, Morris RJ. When budgets are tight, there are better options than colonoscopies for colorectal cancer screening. *Health Aff (Millwood).* 2010;29(9):1734-1740.
211. Schoen C, Osborn R, Squires D, Doty MM. Access, affordability, and insurance complexity are often worse in the United States compared to ten other countries. *Health Aff (Millwood).* 2013;32(12):2205-2215.
212. HealthyPeople.gov. Disparities [Internet]. Washington (DC): Department of Health and Human Services; [last updated 2017 Sep 26; cited 2017 Sep 27]. Available from: https://www.healthypeople.gov/2020/about/foundation-health-measures/Disparities.
213. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol.* 2006;101(2):343-350.

214. American Cancer Society. Cancer Statistics Center. 2016; https://cancerstatisticscenter.cancer.org/?_ga=1.33682849.1877282425.1465291457#/cancer-site/Colorectum. Accessed March 2, 2020, 2020.
215. Simon JB. Occult blood screening for colorectal carcinoma: a critical review. *Gastroenterology.* 1985;88(3):820-837.
216. Wolff WI. Colonoscopy: history and development. *Am J Gastroenterol.* 1989;84(9):1017-1025.
217. Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, Wilschut JA, Zauber AG, van Ballegooijen M. Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. *Ann Intern Med.* 2010;153(6):368-377.
218. Ladabaum U, Mannalithara A. Comparative Effectiveness and Cost Effectiveness of a Multitarget Stool DNA Test to Screen for Colorectal Neoplasia. *Gastroenterology.* 2016;151(3):427-439 e426.
219. Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, et al. Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the medicare population. *J Natl Cancer Inst.* 2010;102(16):1238-1252.
220. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut J, Habbema JD. At what costs will screening with CT colonography be competitive? A cost-effectiveness approach. *Int J Cancer.* 2009;124(5):1161-1168.
221. Ladabaum U, Allen J, Wandell M, Ramsey S. Colorectal cancer screening with blood-based biomarkers: cost-effectiveness of methylated septin 9 DNA versus current strategies. *Cancer Epidemiol Biomarkers Prev.* 2013;22(9):1567-1576.
222. Hassan C, Zullo A, Winn S, Morini S. Cost-effectiveness of capsule endoscopy in screening for colorectal cancer. *Endoscopy.* 2008;40(5):414-421.
223. Potter NT, Hurban P, White MN, et al. Validation of a real-time PCR-based qualitative assay for the detection of methylated SEPT9 DNA in human plasma. *Clin Chem.* 2014;60(9):1183-1191.
224. Food and Drug Administration. PMA P130001: FDA Summary of Safety and Effectiveness Data. 2016; https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130001B.pdf. Accessed January 27, 2020, 2020.
225. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut.* 2014;63(2):317-325.
226. Rex DK, Adler SN, Aisenberg J, et al. Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population. *Gastroenterology.* 2015;148(5):948-957 e942.
227. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med.* 2008;359(12):1207-1217.
228. Schroy PC, 3rd, Coe A, Chen CA, O'Brien MJ, Heeren TC. Prevalence of advanced colorectal neoplasia in white and black patients undergoing screening colonoscopy in a safety-net hospital. *Ann Intern Med.* 2013;159(1):13-20.
229. Liang PS, Wheat CL, Abhat A, et al. Adherence to Competing Strategies for Colorectal Cancer Screening Over 3 Years. *Am J Gastroenterol.* 2016;111(1):105-114.
230. Kooyker AI, Toes-Zoutendijk E, Opstal-van Winden AWJ, et al. The second round of the Dutch colorectal cancer screening program: Impact of an increased fecal immunochemical test cut-off level on yield of screening. *Int J Cancer.* 2019.
231. Centers for Disease Control and Prevention. National Health interview Survey (NHIS)

2015; http://www.cdc.gov/nchs/nhis.htm. Accessed April 3, 2019, 2019.
232. Ahmed D, Danielsen SA, Aagesen TH, et al. A tissue-based comparative effectiveness analysis of biomarkers for early detection of colorectal tumors. *Clin Transl Gastroenterol.* 2012;3:e27.
233. Alarid-Escudero F, Enns EA, Kuntz KM, Michaud TL, Jalal H. "Time Traveling Is Just Too Dangerous" but Some Methods Are Worth Revisiting: The Advantages of Expected Loss Curves Over Cost-Effectiveness Acceptability Curves and Frontier. *Value Health.* 2019;22(5):611-618.
234. Baio G. BCEA: A R Package to Perform Bayesian Cost-Effectiveness Analysis. *Value Health.* 2014;17(7):A550.
235. Jalal H, Pechlivanoglou P, Krijkamp E, Alarid-Escudero F, Enns E, Hunink MGM. An Overview of R in Health Decision Sciences. *Med Decis Making.* 2017;37(7):735-746.
236. Food and Drug Administration. Epi proColon PAS. 2020; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?c_id=3927&t_id=505162. Accessed April 8, 2020, 2020.
237. DeVos T, Molnar B. Screening for Colorectal Cancer Based on the Promoter Methylation Status of the Septin 9 Gene in Plasma Cell Free DNA. *Journal of Clinical Epigenetics.* 2017;3:1.
238. van der Meulen MP, Lansdorp-Vogelaar I, van Heijningen EM, Kuipers EJ, van Ballegooijen M. Nonbleeding adenomas: Evidence of systematic false-negative fecal immunochemical test results and their implications for screening effectiveness-A modeling study. *Cancer.* 2016;122(11):1680-1688.
239. Liles EG, Coronado GD, Perrin N, et al. Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: A randomized trial. *Cancer Treatment and Research Communications.* 2017;10:27-31.
240. Symonds EL, Cock C, Meng R, Cole SR, Fraser RJ, Young GP. Uptake of a colorectal cancer screening blood test in people with elevated risk for cancer who cannot or will not complete a faecal occult blood test. *Eur J Cancer Prev.* 2017.
241. Yabroff KR, Davis WW, Lamont EB, et al. Patient time costs associated with cancer care. *J Natl Cancer Inst.* 2007;99(1):14-23.
242. Yabroff KR, Warren JL, Knopf K, Davis WW, Brown ML. Estimating patient time costs associated with colorectal cancer care. *Med Care.* 2005;43(7):640-648.
243. Goldhaber-Fiebert JD, Jalal HJ. Some Health States Are Better Than Others: Using Health State Rank Order to Improve Probabilistic Analyses. *Med Decis Making.* 2016;36(8):927-940.
244. Taksler GB, Rothberg MB. Assessing Years of Life Lost Versus Number of Deaths in the United States, 1995-2015. *Am J Public Health.* 2017;107(10):1653-1659.
245. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2014;160(5):311-320.
246. Burger EA, de Kok I, Groene E, et al. Estimating the Natural History of Cervical Carcinogenesis Using Simulation Models: A CISNET Comparative Analysis. *J Natl Cancer Inst.* 2019.
247. Richards TB, Doria-Rose VP, Soman A, et al. Lung Cancer Screening Inconsistent With U.S. Preventive Services Task Force Recommendations. *Am J Prev Med.* 2019;56(1):66-73.
248. Hall IJ, Tangka FKL, Sabatino SA, Thompson TD, Graubard BI, Breen N. Patterns and

Trends in Cancer Screening in the United States. *Prev Chronic Dis.* 2018;15:E97.
249. Barlow WE, Beaber EF, Geller BM, et al. Evaluating Screening Participation, Follow-up, and Outcomes for Breast, Cervical, and Colorectal Cancer in the PROSPR Consortium. *J Natl Cancer Inst.* 2020;112(3):238-246.
250. McLachlan SA, Clements A, Austoker J. Patients' experiences and reported barriers to colonoscopy in the screening context--a systematic review of the literature. *Patient Educ Couns.* 2012;86(2):137-146.
251. Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. *JAMA.* 2014;311(13):1327-1335.
252. Keating NL, Pace LE. Breast Cancer Screening in 2018: Time for Shared Decision Making. *JAMA.* 2018;319(17):1814-1815.
253. Brenner AT, Malo TL, Margolis M, et al. Evaluating Shared Decision Making for Lung Cancer Screening. *JAMA Intern Med.* 2018;178(10):1311-1316.
254. Redberg RF. Failing Grade for Shared Decision Making for Lung Cancer Screening. *JAMA Intern Med.* 2018;178(10):1295-1296.
255. Hoffmann TC, Del Mar C. Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med.* 2015;175(2):274-286.
256. Hudson B, Zarifeh A, Young L, Wells JE. Patients' expectations of screening and preventive treatments. *Ann Fam Med.* 2012;10(6):495-502.
257. Metcalfe KA, Narod SA. Breast cancer risk perception among women who have undergone prophylactic bilateral mastectomy. *J Natl Cancer Inst.* 2002;94(20):1564-1569.
258. Hoffmann TC, Del Mar C. Clinicians' Expectations of the Benefits and Harms of Treatments, Screening, and Tests: A Systematic Review. *JAMA Intern Med.* 2017;177(3):407-419.
259. Kim DK, Riley LE, Hunter P. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2018. *MMWR Morb Mortal Wkly Rep.* 2018;67(5):158-160.
260. Piette JD, Richardson C, Valenstein M. Addressing the needs of patients with multiple chronic illnesses: the case of diabetes and depression. *Am J Manag Care.* 2004;10(2 Pt 2):152-162.
261. Pentakota SR, Rajan M, Fincke BG, et al. Does diabetes care differ by type of chronic comorbidity?: An evaluation of the Piette and Kerr framework. *Diabetes Care.* 2012;35(6):1285-1292.
262. Aung E, Donald M, Coll J, Dower J, Williams GM, Doi SA. The impact of concordant and discordant comorbidities on patient-assessed quality of diabetes care. *Health Expect.* 2015;18(5):1621-1632.
263. Taksler GB, Pfoh ER, Stange KC, Rothberg MB. Association Between Number of Preventive Care Guidelines and Preventive Care Utilization by Patients. *Am J Prev Med.* 2018;55(1):1-10.
264. Taksler GB, Keshner M, Fagerlin A, Hajizadeh N, Braithwaite RS. Personalized estimates of benefit from preventive care guidelines: a proof of concept. *Ann Intern Med.* 2013;159(3):161-168.
265. Owens DK, Goldhaber-Fiebert JD. Prioritizing guideline-recommended interventions. *Ann Intern Med.* 2013;159(3):223-224.
266. Maciosek MV, LaFrance AB, Dehmer SP, et al. Updated Priorities Among Effective Clinical Preventive Services. *Ann Fam Med.* 2017;15(1):14-22.

267. Isham G, Sanchez E, Jones WA, Teutsch S, Woolf S, Haddix A. Prevention Priorities: Guidance for Value-Driven Health Improvement. *Ann Fam Med.* 2017;15(1):6-8.
268. O'Connor PJ, Sperl-Hillen JM, Margolis KL, Kottke TE. Strategies to Prioritize Clinical Options in Primary Care. *Ann Fam Med.* 2017;15(1):10-13.
269. Cancer Intervention and Surveillance Modeling Network: Modeling to guide public health research and priorities. https://cisnet.cancer.gov. Accessed July 30, 2019.
270. van den Broek JJ, van Ravesteyn NT, Heijnsdijk EA, de Koning HJ. Simulating the Impact of Risk-Based Screening and Treatment on Breast Cancer Outcomes with MISCAN-Fadia. *Med Decis Making.* 2018;38(1_suppl):54S-65S.
271. Tan SY, van Oortmarssen GJ, de Koning HJ, Boer R, Habbema JD. The MISCAN-Fadia continuous tumor growth model for breast cancer. *J Natl Cancer Inst Monogr.* 2006(36):56-65.
272. Ten Haaf K, van Rosmalen J, de Koning HJ. Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. *Cancer Epidemiol Biomarkers Prev.* 2015;24(1):154-161.
273. Meza R, ten Haaf K, Kong CY, et al. Comparative analysis of 5 lung cancer natural history and screening models that reproduce outcomes of the NLST and PLCO trials. *Cancer.* 2014;120(11):1713-1724.
274. Holford TR, Levy DT, McKay LA, et al. Patterns of birth cohort-specific smoking histories, 1965-2009. *Am J Prev Med.* 2014;46(2):e31-37.
275. Holford TR, Clark L. Chapter 4: Development of the counterfactual smoking histories used to assess the effects of tobacco control. *Risk Anal.* 2012;32 Suppl 1:S39-50.
276. Cancer Intervention and Surveillance Modeling Network: Modeling to guide public health research and priorities. 2015; http://cisnet.cancer.gov/. Accessed August 24, 2015.
277. Giovannucci E, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. *J Natl Cancer Inst.* 1994;86(3):192-199.
278. International Collaboration of Epidemiological Studies of Cervical C, Appleby P, Beral V, et al. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *Int J Cancer.* 2006;118(6):1481-1495.
279. Mandelblatt JS, Near AM, Miglioretti DL, et al. Common Model Inputs Used in CISNET Collaborative Breast Cancer Modeling. *Med Decis Making.* 2018;38(1_suppl):9S-23S.
280. Ten Haaf K, Tammemagi MC, Bondy SJ, et al. Performance and Cost-Effectiveness of Computed Tomography Lung Cancer Screening Scenarios in a Population-Based Setting: A Microsimulation Modeling Analysis in Ontario, Canada. *PLoS Med.* 2017;14(2):e1002225.
281. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. *JAMA.* 2018;320(7):706-714.
282. National Health Interview Survey. https://www.cdc.gov/nchs/nhis/index.htm. Accessed June 30, 2020.
283. Behavioral Risk Factor Surveillance System. https://www.cdc.gov/brfss/index.html. Accessed June 30, 2020.
284. Kapidzic A, van Roon AH, van Leerdam ME, et al. Attendance and diagnostic yield of repeated two-sample faecal immunochemical test screening for colorectal cancer. *Gut.* 2017;66(1):118-123.

285. Oeffinger KC, Fontham ET, Etzioni R, et al. Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society. *JAMA*. 2015;314(15):1599-1614.
286. Rebolj M, Parmar D, Maroni R, Blyuss O, Duffy SW. Concurrent participation in screening for cervical, breast, and bowel cancer in England. *J Med Screen.* 2020;27(1):9-17.
287. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *N Engl J Med.* 2020;382(6):503-513.
288. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365(5):395-409.
289. Wille MM, Dirksen A, Ashraf H, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. *Am J Respir Crit Care Med.* 2016;193(5):542-551.
290. Infante M, Cavuto S, Lutman FR, et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. *Am J Respir Crit Care Med.* 2015;191(10):1166-1175.
291. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev.* 2012;21(3):308-315.
292. Kinsinger LS, Anderson C, Kim J, et al. Implementation of Lung Cancer Screening in the Veterans Health Administration. *JAMA Intern Med.* 2017;177(3):399-406.
293. DeRigne L, Stoddard-Dare P, Collins C, Quinn L. Paid sick leave and preventive health care service use among U.S. working adults. *Prev Med.* 2017;99:58-62.
294. Jaen CR, McIlvain H, Pol L, Phillips RL, Jr., Flocke S, Crabtree BF. Tailoring tobacco counseling to the competing demands in the clinical encounter. *J Fam Pract.* 2001;50(10):859-863.
295. Jaen CR, Stange KC, Nutting PA. Competing demands of primary care: a model for the delivery of clinical preventive services. *J Fam Pract.* 1994;38(2):166-171.
296. Jaen CR, Stange KC, Tumiel LM, Nutting P. Missed opportunities for prevention: smoking cessation counseling and the competing demands of practice. *J Fam Pract.* 1997;45(4):348-354.
297. Nutting PA, Baier M, Werner JJ, Cutter G, Conry C, Stewart L. Competing demands in the office visit: what influences mammography recommendations? *J Am Board Fam Pract.* 2001;14(5):352-361.
298. Leppin AL, Montori VM, Gionfriddo MR. Minimally Disruptive Medicine: A Pragmatically Comprehensive Model for Delivering Care to Patients with Multiple Chronic Conditions. *Healthcare (Basel).* 2015;3(1):50-63.
299. Fineberg HV. The paradox of disease prevention: celebrated in principle, resisted in practice. *JAMA.* 2013;310(1):85-90.
300. Licher S, Heshmatollah A, van der Willik KD, et al. Lifetime risk and multimorbidity of non-communicable diseases and disease-free life expectancy in the general population: A population-based cohort study. *PLoS Med.* 2019;16(2):e1002741.
301. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin.* 2018;68(1):31-54.
302. Gini A, Meester RGS, Keshavarz H, et al. Cost-Effectiveness of Colonoscopy-Based Colorectal Cancer Screening in Childhood Cancer Survivors. *J Natl Cancer Inst.* 2019;111(11):1161-

1169.
303. Draft Recommendation Statement. Lung Cancer: Screening. https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/lung-cancer-screening-2020. Accessed July 16, 2020.
304. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiology and Prevention Biomarkers.* 2009;18(6):1688-1694.
305. Fitzpatrick-Lewis D, Ali MU, Warren R, Kenny M, Sherifali D, Raina P. Screening for Colorectal Cancer: A Systematic Review and Meta-Analysis. *Clin Colorectal Cancer.* 2016;15(4):298-313.
306. Ran T, Cheng CY, Misselwitz B, Brenner H, Ubels J, Schlander M. Cost-Effectiveness of Colorectal Cancer Screening Strategies-A Systematic Review. *Clin Gastroenterol Hepatol.* 2019.
307. von Karsa L, Patnick J, Segnan N. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Executive summary. *Endoscopy.* 2012;44 Suppl 3:SE1-8.
308. Navarro M, Nicolas A, Ferrandez A, Lanas A. Colorectal cancer population screening programs worldwide in 2016: An update. *World Journal of Gastroenterology.* 2017;23(20):3632.
309. Leuraud K, Jezewski-Serra D, Viguier J, Salines E. Colorectal cancer screening by guaiac faecal occult blood test in France: Evaluation of the programme two years after launching. *Cancer epidemiology.* 2013;37(6):959-967.
310. France Sp. EVALUATION DES PROGRAMMES DE DÉPISTAGE DES CANCERS-INDICATEURS DÉVALUATION. 2011; http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Cancers/Evaluation-des-programmes-de-depistage-des-cancers/Evaluation-du-programme-de-depistage-du-cancer-colorectal/Indicateurs-d-evaluation/Taux-de-participation-au-programme-de-depistage-organise-du-cancer-colorectal-2016-2017 (accessed 04 April 2018). Accessed April 4, 2018, 2018.
311. Toes-Zoutendijk E, Portillo I, Hoeck S, et al. Comparison of Fit-Based Colorectal Cancer Screening Programs. Digestive Disease Week; 2018; Walter E. Washington Convention Center, Washington.
312. Dougherty MK, Brenner AT, Crockett SD, et al. Evaluation of Interventions Intended to Increase Colorectal Cancer Screening Rates in the United States: A Systematic Review and Meta-analysis. *JAMA Intern Med.* 2018;178(12):1645-1658.
313. Piette C, Durand G, Bretagne JF, Faivre J. Additional mailing phase for FIT after a medical offer phase: The best way to improve compliance with colorectal cancer screening in France. *Dig Liver Dis.* 2017;49(3):308-311.
314. EU-TOPIA. WP4- Model development. n.d.; http://eu-topia.org/workpackages/wp4-model-development/ (accessed 04 Dec 2018). Accessed December 4, 2018, 2018.
315. Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JDF. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. *Computers and Biomedical Research.* 1999;32(1):13-33.
316. Defossez G, Le GuyaderPeyrou S, Uhry Z, et al. *Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018.* Santé Publique France, Registres des cancers Francim, Hospices civils de Lyon, Institut National du Cancer;July 2019. Volume 1 - Tumeurs solides.
317. Bouvier AM, Trétarre B, Delafosse P, et al. *Étude réalisée à partir des registres des cancers du*

réseau Francim. Santé Publique France, Registres des cancers Francim, Hospices civils de Lyon, Institut National du Cancer;April 2018.
318. Rollot F, Chauvenet M, Roche L, et al. Long-term net survival in patients with colorectal cancer in France: an informative contribution of recent methodology. *Dis Colon Rectum.* 2013;56(10):1118-1124.
319. Santé publique France. Données issues des structures départementales du dépistage organisé du cancer colorectal. 2017-2018.
320. Denis B, Gendre I, Perrin P. Participation in four rounds of a French colorectal cancer screening programme with guaiac faecal occult blood test: a population-based open cohort study. *Journal of medical screening.* 2015;22(2):76-82.
321. Atkin WS, Valori R, Kuipers EJ, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Colonoscopic surveillance following adenoma removal. *Endoscopy.* 2012;44 Suppl 3:SE151-163.
322. Van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, Van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *The American journal of gastroenterology.* 2006;101(2):343-350.
323. Lejeune C, Arveux P, Dancourt V, Bejean S, Bonithon-Kopp C, Faivre J. Cost-effectiveness analysis of fecal occult blood screening for colorectal cancer. *Int J Technol Assess Health Care.* 2004;20(4):434-439.
324. ATIH. Tarifs MCO et HAD. 2018; https://www.atih.sante.fr/tarifs-mco-et-had (accessed 13 May 2019). Accessed 13/05, 2018.
325. International Monetary Fund IFSadf. Inflation, consumer prices (annual %). 2018; https://data.worldbank.org/indicator/FP.CPI.TOTL.ZG (accessed 02 May 2018), 2018.
326. Trouvez l'offre qu'il vous faut. 2019; https://www.laposte.fr/professionnel/ (accessed 04 Sept 2018). Accessed 0409, 2019.
327. Ramsey SD, Andersen MR, Etzioni R, et al. Quality of life in survivors of colorectal carcinoma. *Cancer.* 2000;88(6):1294-1303.
328. Health WCoMa. *Macroeconomics and health : investing in health for economic development / report of the Commission on Macroeconomics and Health.* Geneva: World Health Organization: WHO Commission on Macroeconomic and Health; 20/12/2001 2001. 9241545526.
329. Sabatino SA, Lawrence B, Elder R, et al. Effectiveness of interventions to increase screening for breast, cervical, and colorectal cancers: nine updated systematic reviews for the guide to community preventive services. *Am J Prev Med.* 2012;43(1):97-118.
330. Van Roosbroeck S, Hoeck S, Van Hal G. Population-based screening for colorectal cancer using an immunochemical faecal occult blood test: a comparison of two invitation strategies. *Cancer epidemiology.* 2012;36(5):e317-e324.
331. Church TR, Yeazel MW, Jones RM, et al. A randomized trial of direct mailing of fecal occult blood tests to increase colorectal cancer screening. *J Natl Cancer Inst.* 2004;96(10):770-780.
332. Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al. Real-time monitoring of results during first year of Dutch colorectal cancer screening program and optimization by altering fecal immunochemical test cut-off levels. *Gastroenterology.* 2017;152(4):767-775. e762.
333. Sicsic J, Franc C. Obstacles to the uptake of breast, cervical, and colorectal cancer screenings: what remains to be achieved by French national programmes? *BMC Health Serv Res.* 2014;14:465.

334. Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. *J Natl Cancer Inst.* 2010;102(3):193-201.
335. Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat.* 2013;34(3):490-497.
336. Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. *Gastroenterology.* 2008;135(2):419-428.
337. Stoffel E, Mukherjee B, Raymond VM, et al. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. *Gastroenterology.* 2009;137(5):1621-1627.
338. Choi YH, Cotterchio M, McKeown-Eyssen G, et al. Penetrance of colorectal cancer among MLH1/MSH2 carriers participating in the colorectal cancer familial registry in Ontario. *Hered Cancer Clin Pract.* 2009;7(1):14.
339. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology.* 2000;118(5):829-834.
340. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med.* 2009;11(1):42-65.
341. Palter VN, Baker NA, Rabeneck L, et al. A framework to build capacity for a reflex-testing program for Lynch syndrome. *Genet Med.* 2019;21(6):1381-1389.
342. Leenen CH, Goverde A, de Bekker-Grob EW, et al. Cost-effectiveness of routine screening for Lynch syndrome in colorectal cancer patients up to 70 years of age. *Genet Med.* 2016;18(10):966-973.
343. Goede SL, Rabeneck L, Lansdorp-Vogelaar I, et al. The impact of stratifying by family history in colorectal cancer screening programs. *Int J Cancer.* 2015;137(5):1119-1127.
344. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol.* 2005;23(3):609-618.
345. Statistics Canada. Table 17-10-0005-01 Ontario population estimates on July 1st 2015, by age and sex. https://www150.statcan.gc.ca. Accessed August 16, 2018.
346. eviQ. Risk management for Lynch syndrome. https://www.eviq.org.au/cancer-genetics/adult/risk-management/1410-risk-management-for-lynch-syndrome##cancer-risk-management. Accessed July 1 2019.
347. Singh H, Bernstein CN, Samadder JN, Ahmed R. Screening rates for colorectal cancer in Canada: a cross-sectional study. *CMAJ Open.* 2015;3(2):E149-157.
348. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, Peltomaki P, Aaltonen LA, Mecklin JP. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. *J Clin Oncol.* 2009;27(28):4793-4797.
349. Newton K, Green K, Lalloo F, Evans DG, Hill J. Colonoscopy screening compliance and outcomes in patients with Lynch syndrome. *Colorectal Dis.* 2015;17(1):38-46.
350. Stoffel EM, Mercado RC, Kohlmann W, et al. Prevalence and predictors of appropriate colorectal cancer surveillance in Lynch syndrome. *Am J Gastroenterol.* 2010;105(8):1851-1860.
351. Engel C, Vasen HF, Seppala T, et al. No Difference in Colorectal Cancer Incidence or Stage at Detection by Colonoscopy Among 3 Countries With Different Lynch Syndrome Surveillance Policies. *Gastroenterology.* 2018.

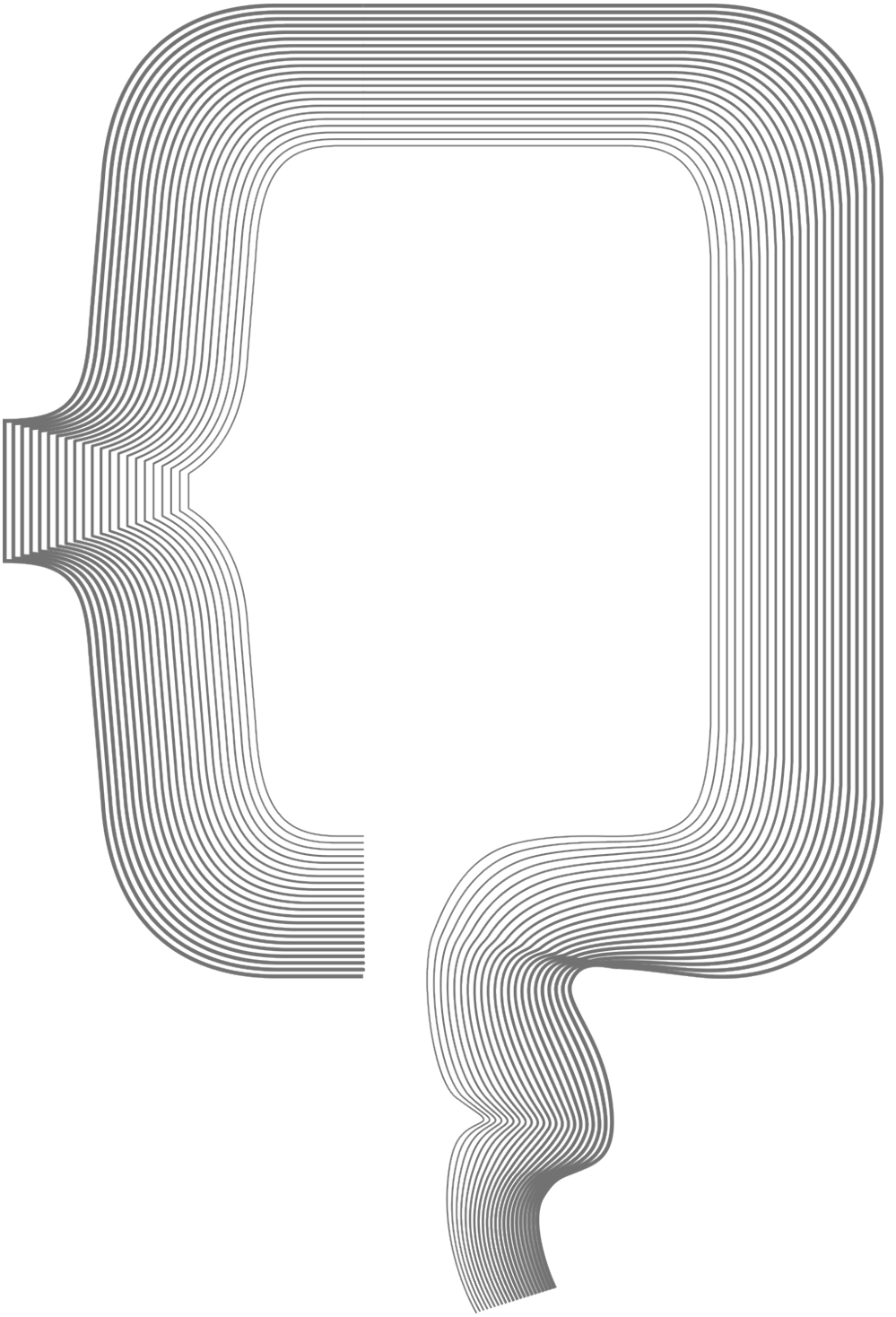
352. Barzi A, Sadeghi S, Kattan MW, Meropol NJ. Comparative effectiveness of screening strategies for Lynch syndrome. *J Natl Cancer Inst.* 2015;107(4).
353. Severin F, Stollenwerk B, Holinski-Feder E, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. *Genet Med.* 2015;17(10):765-773.
354. Chen YE, Kao SS, Chung RH. Cost-Effectiveness Analysis of Different Genetic Testing Strategies for Lynch Syndrome in Taiwan. *PLoS One.* 2016;11(8):e0160599.
355. Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. *Ann Intern Med.* 2011;155(2):69-79.
356. Carayol J, Khlat M, Maccario J, Bonaiti-Pellie C. Hereditary non-polyposis colorectal cancer: current risks of colorectal cancer largely overestimated. *J Med Genet.* 2002;39(5):335-339.
357. Schofield L, Grieu F, Goldblatt J, Amanuel B, Iacopetta B. A state-wide population-based program for detection of lynch syndrome based upon immunohistochemical and molecular testing of colorectal tumours. *Fam Cancer.* 2012;11(1):1-6.
358. Ward RL, Hicks S, Hawkins NJ. Population-based molecular screening for Lynch syndrome: implications for personalized medicine. *J Clin Oncol.* 2013;31(20):2554-2562.
359. Ngeow J, Eng C. Population-based universal screening for Lynch syndrome: ready, set... How? *J Clin Oncol.* 2013;31(20):2527-2529.
360. Hadley DW, Jenkins J, Dimond E, et al. Genetic counseling and testing in families with hereditary nonpolyposis colorectal cancer. *Arch Intern Med.* 2003;163(5):573-582.
361. Heald B, Plesec T, Liu X, et al. Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing lynch syndrome in a large academic medical center. *J Clin Oncol.* 2013;31(10):1336-1340.
362. Gritz ER, Peterson SK, Vernon SW, et al. Psychological impact of genetic testing for hereditary nonpolyposis colorectal cancer. *J Clin Oncol.* 2005;23(9):1902-1910.
363. Murakami Y, Okamura H, Sugano K, et al. Psychologic distress after disclosure of genetic test results regarding hereditary nonpolyposis colorectal carcinoma. *Cancer.* 2004;101(2):395-403.
364. Statistics Canada. Table 18-10-0005-01 Consumer Price Index, annual average, not seasonally adjusted. https://www150.statcan.gc.ca. Accessed October 22, 2018.
365. Rabeneck L, Paszat LF, Hilsden RJ, et al. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. *Gastroenterology.* 2008;135(6):1899-1906, 1906 e1891.
366. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. *J Clin Oncol.* 2015;33(2):209-217.
367. Rubenstein JH, Enns R, Heidelbaugh J, Barkun A, Clinical Guidelines C. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. *Gastroenterology.* 2015;149(3):777-782; quiz e716-777.
368. Vasen HF, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut.* 2013;62(6):812-823.
369. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal

cancer. *Gastroenterology.* 2014;147(2):502-526.
370. Kastrinos F, Ojha RP, Leenen C, et al. Comparison of Prediction Models for Lynch Syndrome Among Individuals With Colorectal Cancer. LID - 10.1093/jnci/djv308 [doi] LID - djv308 [pii]. (1460-2105 (Electronic)).
371. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer.* 1999;81(2):214-218.
372. Dunlop MG, Farrington SM, Carothers AD, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum Mol Genet.* 1997;6(1):105-110.
373. Cenin DR, Naber SK, Lansdorp-Vogelaar I, et al. Costs and outcomes of Lynch syndrome screening in the Australian colorectal cancer population. *J Gastroenterol Hepatol.* 2018;33(10):1737-1744.
374. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2017;26(3):404-412.
375. Boland CR, Shike M. Report from the Jerusalem workshop on Lynch syndrome-hereditary nonpolyposis colorectal cancer. *Gastroenterology.* 2010;138(7):2197.e2191-2197.e21977.
376. Hampel H, de la Chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means? *Cancer Prev Res (Phila).* 2011;4(1):1-5.
377. Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. *Genetics In Medicine.* 2010;12:93.
378. Peterse EFP, Naber SK, Daly C, et al. Cost-effectiveness of Active Identification and Subsequent Colonoscopy Surveillance of Lynch Syndrome Cases. *Clin Gastroenterol Hepatol.* 2019.
379. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the Care of Individuals With an Inherited Predisposition to Lynch SyndromeA Systematic Review. *Jama.* 2006;296(12):1507-1517.
380. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med.* 2006;354(3):261-269.
381. Kwon JS, Sun CC, Peterson SK, et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. *Cancer.* 2008;113(2):326-335.
382. Lacey JV, Jr., Sherman ME, Rush BB, et al. Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J Clin Oncol.* 2010;28(5):788-792.
383. Roberts TE, Tsourapas A, Middleton LJ, et al. Hysterectomy, endometrial ablation, and levonorgestrel releasing intrauterine system (Mirena) for treatment of heavy menstrual bleeding: cost effectiveness analysis. *BMJ (Clinical research ed).* 2011;342:d2202-d2202.
384. Miller JD, Lenhart GM, Bonafede MM, Lukes AS, Laughlin-Tommaso SK. Cost-Effectiveness of Global Endometrial Ablation vs. Hysterectomy for Treatment of Abnormal Uterine Bleeding: US Commercial and Medicaid Payer Perspectives. *Popul Health Manag.* 2015;18(5):373-382.
385. Bhattacharya S, Middleton LJ, Tsourapas A, et al. Hysterectomy, endometrial ablation and Mirena(R) for heavy menstrual bleeding: a systematic review of clinical effectiveness and cost-effectiveness analysis. *Health Technol Assess.* 2011;15(19):iii-xvi, 1-252.

386. Hurskainen R, Teperi J, Rissanen P, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up. *Jama.* 2004;291(12):1456-1463.
387. Fryback DG, Dasbach Ej Fau - Klein R, Klein R Fau - Klein BE, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. (0272-989X (Print)).
388. Sun C.C., Peterson S.K., White K.G., et al. Preferences for cancer prevention strategies (CPS) in women with hereditary nonpolyposis colectal cancer (HNPCC). *Journal of Clinical Oncology.* 2006;24:1018-1018.
389. Havrilesky LJ, Maxwell GL, Myers ER. Cost-effectiveness analysis of annual screening strategies for endometrial cancer. *Am J Obstet Gynecol.* 2009;200(6):640 e641-648.
390. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2012. *Natl Vital Stat Rep.* 2013;62(9):1-68.
391. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making.* 1993;13(2):89-102.
392. van Ballegooijen M, Rutter CM, Knudsen AB, et al. Clarifying differences in natural history between models of screening: the case of colorectal cancer. *Med Decis Making.* 2011;31(4):540-549.
393. Vasen HF, Watson P, Mecklin JP, et al. The epidemiology of endometrial cancer in hereditary nonpolyposis colorectal cancer. *Anticancer Res.* 1994;14(4B):1675-1678.
394. Deeks AA, Gibson-Helm M, Teede H, Vincent A. Premature menopause: a comprehensive understanding of psychosocial aspects. *Climacteric.* 2011;14(5):565-572.
395. Mathews TJ, Hamilton BE. Delayed childbearing; more women are having their first child later in life. 2009.
396. Yang KY, Caughey AB, Little SE, Cheung MK, Chen L-M. A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) Families. *Familial Cancer.* 2011;10(3):535-543.
397. Sharaf RN, Myer P, Stave CD, Diamond LC, Ladabaum U. Uptake of Genetic Testing by Relatives of Lynch Syndrome Probands: A Systematic Review. *Clinical Gastroenterology and Hepatology.* 2013;11(9):1093-1100.
398. Evans DGR, Lalloo F, Ashcroft L, et al. Uptake of Risk-Reducing Surgery in Unaffected Women at High Risk of Breast and Ovarian Cancer Is Risk, Age, and Time Dependent. *Cancer Epidemiology Biomarkers & Prevention.* 2009;18(8):2318-2324.
399. Daly C, Rotenberg C, Facey M, Baker NA, Baxter NN. Reflex Lynch syndrome screening by example: A review of existing programs. *Journal of Clinical Oncology.* 2015;33(3_suppl):543-543.
400. Rahm AK, Cragun D, Hunter JE, et al. Implementing universal Lynch syndrome screening (IMPULSS): protocol for a multi-site study to identify strategies to implement, adapt, and sustain genomic medicine programs in different organizational contexts. *BMC Health Serv Res.* 2018;18(1):824.
401. Meester RG, Doubeni CA, Lansdorp-Vogelaar I, et al. Colorectal cancer deaths attributable to nonuse of screening in the United States. *Ann Epidemiol.* 2015;25(3):208-213 e201.
402. Toes-Zoutendijk E, Portillo I, Hoeck S, et al. Participation in faecal immunochemical testing-based colorectal cancer screening programmes in the northwest of Europe. *J Med Screen.* 2019:969141319879712.
403. Bosch LJW, Melotte V, Mongera S, et al. Multitarget Stool DNA Test Performance

in an Average-Risk Colorectal Cancer Screening Population. *Am J Gastroenterol.* 2019;114(12):1909-1918.
404. Rutter CM, Knudsen AB, Lin JS, Bouskill K. Lack of evidence for racial differences in the natural history of colorectal cancer: A narrative review. (under review).
405. Hubbard RA, Johnson E, Hsia R, Rutter CM. The cumulative risk of false-positive fecal occult blood test after 10 years of colorectal cancer screening. *Cancer Epidemiol Biomarkers Prev.* 2013;22(9):1612-1619.
406. Ladabaum U, Mannalithara A, Meester RG, Gupta S, Schoen REJG. Cost-Effectiveness and National Effects of Initiating Colorectal Cancer Screening for Average-Risk Persons at Age 45 Years Instead of 50 Years. 2019.
407. Joseph DA, Meester RG, Zauber AG, et al. Colorectal cancer screening: estimated future colonoscopy need and current volume and capacity. 2016;122(16):2479-2486.
408. Liang PS, Allison J, Ladabaum U, et al. Potential Intended and Unintended Consequences of Recommending Initiation of Colorectal Cancer Screening at Age 45 Years. *Gastroenterology.* 2018;155(4):950-954.
409. U.S. Preventive Services Task Force. Colorectal Cancer: Screening. 2020; https://www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/colorectal-cancer-screening3. Accessed July 15th, 2020.
410. Kaminski MF, Robertson DJ, Senore C, Rex DK. Optimizing the Quality of Colorectal Cancer Screening Worldwide. *Gastroenterology.* 2020;158(2):404-417.
411. Levin TR, Corley DA, Jensen CD, et al. Effects of Organized Colorectal Cancer Screening on Cancer Incidence and Mortality in a Large Community-Based Population. *Gastroenterology.* 2018;155(5):1383-1391 e1385.
412. Hissong E, Crowe EP, Yantiss RK, Chen YT. Assessing colorectal cancer mismatch repair status in the modern era: a survey of current practices and re-evaluation of the role of microsatellite instability testing. *Mod Pathol.* 2018;31(11):1756-1766.
413. Liu PH, Wu K, Ng K, et al. Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women. *JAMA Oncol.* 2019;5(1):37-44.
414. Gausman V, Dornblaser D, Anand S, et al. Risk Factors Associated With Early-onset Colorectal Cancer. *Clin Gastroenterol Hepatol.* 2019.
415. Rosato V, Bosetti C, Levi F, et al. Risk factors for young-onset colorectal cancer. *Cancer Causes Control.* 2013;24(2):335-341.
416. Siegel RL, Medhanie GA, Fedewa SA, Jemal A. State Variation in Early-Onset Colorectal Cancer in the United States, 1995-2015. *J Natl Cancer Inst.* 2019;111(10):1104-1106.
417. Ljungvall A, Zimmerman FJ. Bigger bodies: long-term trends and disparities in obesity and body-mass index among U.S. adults, 1960-2008. *Soc Sci Med.* 2012;75(1):109-119.
418. Crockett SD, Nagtegaal ID. Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia. *Gastroenterology.* 2019;157(4):949-966 e944.
419. Meester RGS, van Herk M, Lansdorp-Vogelaar I, Ladabaum U. Prevalence and Clinical Features of Sessile Serrated Polyps: A Systematic Review. *Gastroenterology.* 2020;159(1):105-118 e125.
420. Jeon J, Du M, Schoen RE, et al. Determining Risk of Colorectal Cancer and Starting Age of Screening Based on Lifestyle, Environmental, and Genetic Factors. *Gastroenterology.* 2018;154(8):2152-2164 e2119.
421. Naber SK, Kundu S, Kuntz KM, et al. Cost-Effectiveness of Risk-Stratified Colorectal Cancer

Screening Based on Polygenic Risk: Current Status and Future Potential. *JNCI Cancer Spectr.* 2020;4(1):pkz086.
422. Engel C, Ahadova A, Seppala T, et al. Associations of Pathogenic Variants in MLH1, MSH2, and MSH6 With Risk of Colorectal Adenomas and Tumors and With Somatic Mutations in Patients With Lynch Syndrome. *Gastroenterology.* 2020.
423. Ahadova A, Gallon R, Gebert J, et al. Three molecular pathways model colorectal carcinogenesis in Lynch syndrome. *Int J Cancer.* 2018;143(1):139-150.
424. Monahan KJ, Bradshaw N, Dolwani S, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut.* 2020;69(3):411-444.
425. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 5th ed. Philadelphia: Lippincott - Raven Publishers; 1997: http://cancerstaging.org/references-tools/deskreferences/Documents/AJCC5thEdCancerStagingManual.pdf.
426. Mehta SJ, Jensen CD, Quinn VP, Schottinger JE, Zauber AG, Meester R, et al. Race/ethnicity and adoption of a population health management approach to colorectal cancer screening in a community-based healthcare system. J Gen Intern Med. 2016;31(11):1323–30.
427. Lyon: International Agency for Research on Cancer. Cancer Incidence in Five Continents, Vol. XI (electronic version). http://ci5.iarc.fr. Accessed February 4, 2019, 2018.
428. Drouillard A, Bouvier AM, Rollot F, Faivre J, Jooste V, Lepage C. Conditional net survival: Relevant prognostic information for colorectal cancer survivors. A French population-based study. *Dig Liver Dis.* 2015;47(7):597-601.
429. Statistics Canada. Table 103–0550—New cases for ICD-O-3 primary sites of cancer (based on the July 2011 CCR tabulation file), by age group and sex, Canada, provinces and territories, annual, CANSIM (database). . 2011; http://www5.statcan.gc.ca/cansim/a01?lang=eng. Accessed April 1, 2012.
430. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet.* 1996;348(9040):1472-1477.
431. Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut.* 2002;50(1):29-32.
432. Buskermolen M, Gini A, Naber SK, Toes-Zoutendijk E, de Koning HJ, Lansdorp-Vogelaar I. Modeling in Colorectal Cancer Screening: Assessing External and Predictive Validity of MISCAN-Colon Microsimulation Model Using NORCCAP Trial Results. *Med Decis Making.* 2018;38(8):917-929.



Summary

Colorectal cancer is one of the leading causes of cancer death, and is an increasing public health concern for many countries worldwide. Screening can prevent colorectal cancer death through removal of premalignant lesions or through early detection of colorectal cancer. The aim of this thesis was to estimate population-level effects (including benefits, harms and costs) of colorectal cancer screening policy changes or interventions. These studies can aid in optimizing colorectal cancer screening programs.

All nine studies presented in this thesis made use of the microsimulation screening analysis model for colorectal cancer (MISCAN-Colon). This model is based on simulation and mathematical techniques within a logical framework to integrate and synthesize known biological, epidemiological, clinical, behavioral and/or economic information. Its value has been internationally recognized, and policy makers from multiple countries requested analyses using MISCAN-Colon to address their colorectal cancer screening policy questions.

Informing screening guidelines

The first part of this thesis is comprised of studies that were commissioned by the American Cancer Society for their 2018 colorectal cancer screening guideline. These studies compare the benefits, harms and burden of over one hundred screening strategies, differing in terms of the screening test used, age to start screening, age to stop screening and the screening interval. The key difference between these analyses and those performed previously by our group was the incorporation of the most recent trends in colorectal cancer incidence - an alarming increase was observed in colorectal cancer diagnoses before the age of 50 years. **Chapter 2** demonstrated that as a result of these epidemiological trends, the balance between the benefits and the burden of screening improved, now favoring initiation of screening at age 45 years rather than age 50 years. Model-recommendable strategies for average-risk individuals were screening every 10 years with colonoscopy, every year with the fecal immunochemical test (FIT), every 5 years with sigmoidoscopy and every 5 years with computed tomographic colonography until age 75 years. **Chapter 3** built upon the analyses performed in Chapter 2 by exploring the influence of race and sex on the optimal colorectal cancer screening strategies. These analyses were not only performed using the MISCAN-Colon model, but also by using the simulation model of colorectal cancer (SimCRC). Two different scenarios regarding colorectal cancer risk were evaluated: one in which age-, race-, and sex-specific risks were assumed to remain stable over time and another in which risks increased proportionally to trends observed in young-onset cases. Results from this modeling study suggest that if lifetime risk increases proportionally to trends observed in younger ages, screening should be recommended from the age of 45 years

for all population subgroups. Under the assumption of stable risk, models agreed about the age to start screening in black Americans (age 45 years) but disagreed about the age to start screening in white Americans (age 50 vs 45 years). Based on the results from the modeling analyses presented in Chapters 2 & 3, the increased disease burden in individuals below age 50 years and the reasonable expectation that screening will perform similarly in individuals aged 45-49 as in those above age 50, the American Cancer Society included a qualified recommendation to start screening at age 45 years. This change in the US colorectal cancer screening guideline has the potential to save thousands of lives each year in the US.

In the analyses performed in Chapters 2 & 3, costs were not taking into account as the American Cancer Society does not apply cost as a decision-making criterion for their recommendations. In **Chapter 4**, we explored how the increasing incidence as well as increasing treatment costs of colorectal cancer impacted the cost-effectiveness of screening. We demonstrated that the benefits of starting screening at age 45 years rather than age 50 years outweigh the additional costs. As a results of the increased treatment costs, several colorectal cancer screening strategies were cost-saving compared to no screening. Only FIT and colonoscopy were efficient screening modalities, but the additional costs of gaining one additional quality-adjusted life-year of colonoscopy screening compared to FIT screening exceeded the willingness-to-pay threshold. Annual screening from ages 40 to 85 years with FIT would be optimal from a cost-effectiveness perspective. These results favor FIT rather than colonoscopy as a primary screening test.

Interventions to improve adherence

The benefits of screening cannot only be improved by optimization of the guidelines, but also by improving adherence to the guidelines. Among individuals ages 50 to 75 years, current colorectal cancer screening participation reached a plateau of approximately 60% in the US. Therefore, the second part of this thesis explored the cost-effectiveness of several interventions that have the potential to increase colorectal cancer screening participation rates.

In **Chapter 5**, we addressed a financial barrier for colorectal cancer screening in the US. There is a so-called "loophole" in the current legislation that allows insurers to charge a 20% coinsurance for follow-up colonoscopy performed after a positive non-colonoscopy test and for screening colonoscopies in which polyps are removed. We estimated that waiving coinsurance would be cost-effective from a Medicare perspective if it would increase screening rates from 60.0% to 60.4%. Therefore, the waiver would likely have a very favorable balance of health and cost impact. This study is used by colorectal cancer screening advocates to influence politicians and change legislation.

In **Chapter 6** the cost-effectiveness of newly developed colorectal cancer screening tests was compared. These tests have the potential of attracting individuals who do not want to participate in colorectal cancer screening using FIT or colonoscopy. We evaluated

capsule endoscopy, computed tomographic colonography, the multi-target stool DNA test and the methylated SEPT9 DNA plasma assay (m*SEPT9*), and compared their effectiveness to colonoscopy and FIT screening. Our study revealed that among these innovative alternative strategies, annual screening with m*SEPT9*, a blood-based test, is cost-effective. Other efficient strategies were computed tomographic colonography screening every 5 years and annual multi-target stool DNA screening, which were not optimal given the willingness-to-pay threshold. m*SEPT9* had similar benefits as FIT screening, but resulted in 63% more colonoscopies and 26% higher costs. Therefore, screening with the m*SEPT9* should only be recommended if an individual is not willing to undergo FIT or colonoscopy screening.

In **Chapter 7**, we considered a holistic framework of cancer screening. For women in the US, screening is not only recommended for colorectal cancer, but also for breast, cervical, and, for those with heavy smoking histories, lung cancer. However, only one out of three women participates in all guideline-recommended cancer screenings. Therefore, we aimed to evaluate optimal screening strategies in women willing to obtain some, but not all, recommended screenings by combining results from MISCAN models of these four cancer types. We demonstrated that it is possible to reduce screening intensity to one or two cancer screenings per year for women ineligible or eligible for lung cancer screening, respectively, while maintaining ≥94% of the benefits. Screening for a variety of cancers, although less frequent than recommended, was more effective than screening for specific cancers but omitting others. For eligible women, lung cancer screening was essential; strategies omitting it provided ≤25% of maximum benefits. Our study suggests that women who prefer to reduce cancer screening intensity may be able to do so with a small loss in benefits, provided they choose an optimal less-intensive strategy. Offering women the option to lower screening intensity has the potential to increase their participation.

Chapter 8 focused on the French colorectal cancer screening program. Interestingly, its current participation rate is below 35%, which is much lower than participation rates in neighboring European countries. A potential explanation for this low participation rate is the need for participants to visit their general practitioner to collect a FIT. In other countries, such as the Netherlands, the FIT is mailed directly to the homes of those eligible for colorectal cancer screening. Therefore, we estimated the potential benefits and costs of including the FIT in the invitation letter in France. Our results suggest that including the FIT in the invitation letter is cost-effective if it increases screening participation by 0.5 percentage point. It can be expected that the impact of this intervention on participation is considerably higher than this threshold, suggesting that including the FIT in the invitation letter in France would have a favorable balance between its benefits and costs.

Screening and subsequent steps for Lynch syndrome patients

The last part of this thesis focused on Lynch syndrome patients. Approximately 42% of individuals with Lynch syndrome develop colorectal cancer before the age of 80 years, and approximately 35% of women develop endometrial cancer. Therefore, it is

important to identify asymptomatic individuals with Lynch syndrome as preventative measures can be taken to reduce cancer incidence and mortality.

In **Chapter 9**, we evaluated the benefits and costs of screening all colorectal cancer patients below the age of 70 years for Lynch syndrome using immunohistochemistry in a Canadian setting. Screening colorectal cancer patients for Lynch syndrome can ultimately identify asymptomatic relatives who benefit from intensive colonoscopy surveillance. Our study predicted that testing 1,000 colorectal cancer patients would result in the identification of 29 asymptomatic relatives with Lynch syndrome. Offering these relatives biennial colonoscopy surveillance instead of usual care (had they not been diagnosed with Lynch syndrome) decreased their probability to die from colorectal cancer by 40%. The long-term benefits of identifying these relatives outweigh the additional cost of Lynch syndrome screening. Furthermore, our study revealed that biennial colonoscopy surveillance for individuals with Lynch syndrome is optimal; the optimal surveillance interval has been a topic of intense debate. These results were especially informative for policy makers in the province of Ontario, Canada, who were considering introducing Lynch syndrome screening for all colorectal cancer cases below the age of 70 years.

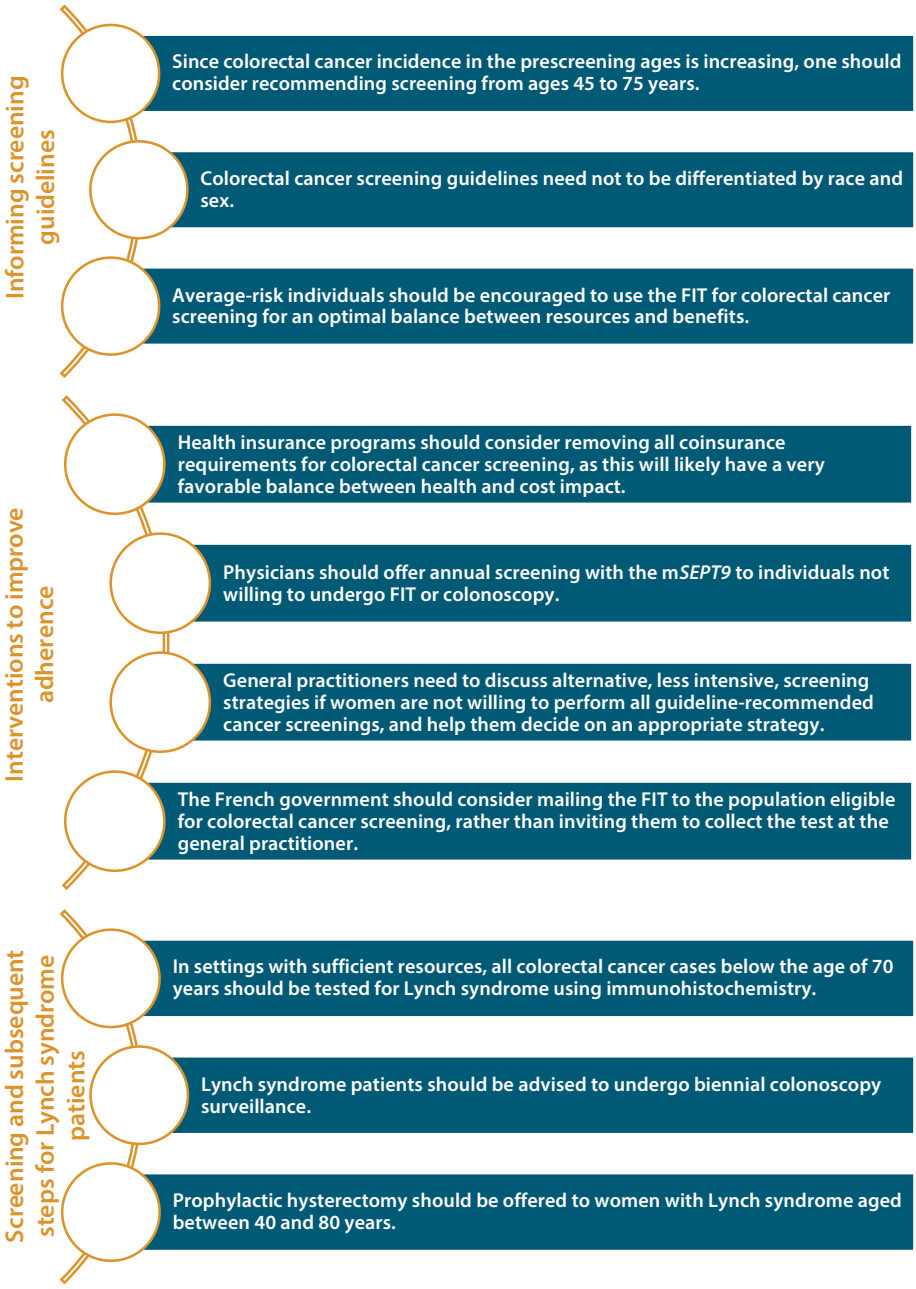
Chapter 10 builds upon the analyses performed in Chapter 9, by estimating the benefits and costs of offering prophylactic hysterectomy to the asymptomatic female relatives identified with Lynch syndrome. The MISCAN Endometrial model was developed to compare different age ranges of prophylactic hysterectomy. From a cost-effectiveness perspective, prophylactic hysterectomy should be offered to women with Lynch syndrome aged 40-80 years. However, the optimal age range depended on an individual's quality of life after a prophylactic hysterectomy. The impact of a prophylactic hysterectomy on a woman's quality of life varies from woman to woman. Therefore, women with Lynch syndrome may consider performing prophylactic hysterectomy at age 35 years. Results of this study can inform physicians and women with Lynch syndrome regarding the decision whether or not to perform prophylactic hysterectomy, and at what age.

Conclusions and recommendations

The following conclusions can be drawn based on the studies presented in this thesis:

- As a result of the increase in colorectal cancer incidence observed in young adults, screening initiation at age 45 years rather than age 50 years in the US has a favorable balance between screening benefits, burden and costs.
- The optimal screening ages for individuals in the US are not influenced by race and sex under assumed increases in background risk.
- The increase in colorectal cancer incidence in young adults and the increase in colorectal cancer treatment costs greatly improved the cost-effectiveness of colorectal cancer screening.
- Only colorectal cancer screening strategies that use FIT as a primary screening test are cost-effective.
- Waiving the coinsurance for all colonoscopy procedures has a favorable balance of health and cost impact.
- For individuals that are not willing to participate in colorectal cancer screening using FIT and colonoscopy, annual screening with the m*SEPT9* is the test of choice given its cost-effectiveness profile compared to the other alternative tests.
- Women unable or unwilling to obtain all guideline-recommended cancer screenings may be able to reduce screening intensity with limited impact on overall benefits, but should go for lung cancer screening if eligible.
- Lung cancer screening in eligible women has greater benefit than colorectal, cervical and breast cancer screening.
- It is more valuable for women to obtain a variety of cancer screenings even if less-often than recommended, than to screen for some cancers but skip others entirely.
- Including the FIT in the invitation letter is a very cost-effective intervention to increase colorectal cancer screening participation.
- Immunohistochemical testing for Lynch syndrome in persons younger than 70 years with a colorectal cancer diagnosis, and then testing first-degree relatives of those found to have Lynch syndrome, provides a good balance between costs and long-term benefits.
- Colonoscopy surveillance every 2 years is the optimal surveillance interval for patients with Lynch syndrome.
- Prophylactic hysterectomy in Lynch syndrome women aged between 40 and 80 years is cost-effective from a population perspective.
- The earliest age to recommend prophylactic hysterectomy in women with Lynch syndrome depends on the impact of a prophylactic hysterectomy on an individual's quality of life.

The conclusions derived in this thesis support the following recommendations.



Nederlandse samenvatting

Darmkanker is een van de voornaamste doodsoorzaken aan kanker en vormt een toenemende bedreiging voor de volksgezondheid. Darmkankersterfte kan worden voorkomen door screening, doordat screening goedaardige voorlopers van darmkanker kan opsporen en screening de ziekte in een vroeg stadium kan detecteren. Het doel van dit proefschrift was het schatten van de effecten op populatieniveau (voordelen, nadelen, kosten) van beleidswijzigingen en interventies rondom darmkankerscreening. De studies beschreven in dit proefschrift zijn gericht op het optimaliseren van darmkankerscreeningprogramma's.

In alle studies beschreven in dit proefschrift is gebruik gemaakt van het rekenmodel MISCAN-Colon. Dit model is gebaseerd op simulaties en wiskundige technieken, en is gebaseerd op de meest recente biologische, epidemiologie, klinische, gedragsmatige en economische inzichten die betrekking hebben op darmkankerscreening. Dit model is wereldwijd bekend onder onderzoekers in het veld, en beleidsmakers van vele landen vragen om analyses met MISCAN-Colon voor het implementeren en/of optimaliseren van hun bevolkingsonderzoeken.

Richtlijnen van darmkankerscreening informeren

Het eerste gedeelte van dit proefschrift bestaat uit studies die gedaan zijn in opdracht van de American Cancer Society, die in 2018 nieuwe richtlijnen voor darmkankerscreening opgesteld heeft. Deze studies vergelijken de voor- en nadelen van meer dan honderd verschillende screeningsstrategieën, die verschillen in de screeningstest die gebruikt wordt en de leeftijden waarop gescreend wordt (startleeftijd, stopleeftijd en interval). Het belangrijkste verschil tussen deze analyses en analyses die eerder door onze groep gedaan zijn, is dat in deze analyses de meest recente trends in darmkankerincidentie meegenomen worden – er is namelijk een alarmerende toename in het aantal darmkankerdiagnoses onder leeftijd 50. In **Hoofdstuk 2** laten we zien dat door deze epidemiologische trends, de balans tussen de voor- en nadelen van screening verbetert, waardoor het nu gunstig is om op leeftijd 45 te beginnen met screening in plaats van op leeftijd 50. 10-jaarlijkse coloscopiescreening, jaarlijkse screening met de faeces-immunochemische test op occult bloed (FIT), 5-jaarlijkse screening met sigmoïdoscopie en 5-jaarlijkse screening met de CT-colografie, allen tot leeftijd 75, zijn volgens het model de beste strategieën om te implementeren. **Hoofdstuk 3** bouwt verder op deze analyses door de invloed van geslacht en etniciteit op de optimale darmkankerscreeningsstrategieën te evalueren. Deze analyses werden niet alleen met behulp van MISCAN-Colon gedaan, maar ook met het rekenmodel SimCRC. Twee verschillende scenario's met betrekking tot de incidentie van darmkanker werden doorgerekend: één waarbij het aangenomen werd dat leeftijd- etniciteit- en geslachtsspecifieke darmkankerincidentie stabiel blijft over de

tijd, en één waarbij het risico op darmkanker toeneemt in lijn met trends geobserveerd in jongvolwassenen. Resultaten van deze modelstudie suggereren dat als het risico op darmkanker inderdaad toeneemt, screening vanaf leeftijd 45 aangeboden moet worden aan de gehele bevolking, onafhankelijk van etniciteit en geslacht. In het scenario waarin aangenomen werd dat het risico op darmkanker stabiel blijft, identificeerde de twee modellen dezelfde optimale startleeftijd voor Afro-Amerikanen (45 jaar), maar een verschillende optimale startleeftijd voor Euro-Amerikanen (50/45 jaar). Mede gebaseerd op de analyses van hoofdstukken 2 en 3 heeft de American Cancer Society een aanbeveling gedaan om individuen met gemiddeld risico vanaf leeftijd 45 te screenen. Deze verandering in de richtlijnen kan mogelijk duizenden sterfgevallen als gevolg van darmkanker per jaar voorkomen in de Verenigde Staten.

In de analyses van hoofdstukken 2 en 3 werden kosten niet meegenomen omdat de American Cancer Society deze buiten beschouwing wil laten bij het opstellen van de screeningsrichtlijnen. In **Hoofdstuk 4** kijken we naar de effecten van de toenemende incidentie en behandelkosten op de kosteneffectiviteit van darmkankerscreening. Deze analyses wijzen uit dat de gezondheidswinst van het aanbieden van darmkankerscreening vanaf leeftijd 45 in plaats van vanaf leeftijd 50 opweegt tegen de additionele kosten. Doordat de behandelkosten van darmkanker toe zijn genomen, zijn er meerdere screeningsstrategieën kostenbesparend ten opzichte van geen screening. Zowel FIT en coloscopiescreening bleken efficiënte screeningstesten, maar de kosten om een extra levensjaar te winnen met coloscopiescreening ten opzichte van FIT-screening waren hoger dan de drempelwaarde voor kosteneffectiviteit. Op basis van kosteneffectiviteit zou jaarlijkse screening met FIT van leeftijd 40 tot 85 jaar optimaal zijn. Deze resultaten pleiten voor het gebruik van FIT-screening in plaats van coloscopiescreening.

Interventies voor het verhogen van deelname

De gezondheidswinst van darmkankerscreening kan niet alleen verbeterd worden door richtlijnen te optimaliseren, maar ook door de deelname aan screening te verbeteren. In Amerika neemt ongeveer 60% van de individuen tussen leeftijd 50 en 75 deel aan darmkankerscreening. Daarom focust het tweede gedeelte van de proefschrift op de kosteneffectiviteit van verschillende interventies die mogelijk de deelname aan darmkankerscreening kunnen verhogen.

Hoofdstuk 5 heeft betrekking op een financiële barrière voor participatie aan screening. In principe is screening voor Amerikanen gratis, maar door een maas in de wet kunnen zorgverzekeraars een eigen bijdragen van 20% in rekening brengen voor coloscopieën die gedaan worden na een positieve ontlastingstest, en voor screeningscoloscopieën waarbij een poliep verwijderd wordt. Resultaten van onze studie suggereren dat, vanuit het perspectief van Medicare, het verwijderen van de 20% eigen bijdrage al kosteneffectief zou zijn als dit de deelname aan screening zou verhogen van 60.0% naar 60.4%. Daarom is het zeer aannemelijk dat de gezondheidswinst van het opheffen van de eigen bijdrage opweegt tegen de kosten. Deze studie wordt door voorstanders van

darmkankerscreening gebruikt om politici te overtuigen om de wetgeving aan te passen. Nieuwe screeningstesten hebben de potentie om mensen die niet gescreend willen worden met FIT of coloscopie alsnog deel te laten nemen aan het Amerikaanse bevolkingsonderzoek. In **Hoofdstuk 6** werd de kosteneffectiviteit van nieuwe darmkankerscreeningstesten vergeleken. De nieuwe testen die we mee hebben genomen in deze studie zijn de videocapsule-endoscopie, de CT-colografie, de multi-target fecale DNA-test en de gemethyleerde Septin-9 test (m*SEPT9*). De kosteneffectiviteit van deze nieuwe testen werd ook vergeleken met die van FIT en coloscopie. Onze studie liet zien dat van deze nieuwe testen, jaarlijkse screening met de m*SEPT9*, een test die zoekt naar kankermarkers in het bloed, het meest veelbelovend is. Andere efficiënte screeningsopties waren screening elke 5 jaar met CT-colografie en jaarlijkse screening met de multi-target fecale DNA-test, maar de extra kosten van deze strategieën wogen niet op tegen de extra opbrengsten en ze worden daarom niet kosteneffectief geacht. De voordelen van jaarlijkse screening met de m*SEPT9* zijn vergelijkbaar met die van jaarlijkse FIT-screening, maar deze strategie resulteerde wel in 63% meer coloscopieën en 26% hogere kosten. Daarom moet screening met de m*SEPT9* alleen aangeboden worden aan individuen die niet gescreend willen worden met FIT of coloscopie.

In **Hoofdstuk 7** hebben we een meer holistisch benadering van kankerscreening meegenomen. Aan vrouwen in de Verenigde Staten wordt naast screening op darmkanker ook screening op borstkanker, baarmoederhalskanker en, aan vrouwen die erg veel roken/gerookt hebben, longkanker aangeboden. Slechts één op de drie vrouwen neemt deel aan al deze bevolkingsonderzoeken. Daarom hebben wij in deze studie gekeken wat optimale screeningsstrategieën zijn voor vrouwen die wel wat screening, maar niet alle aanbevolen screenings willen ondergaan. We hebben dit gedaan door resultaten van vier verschillende MISCAN modellen te combineren. De resultaten van deze studie demonstreren dat het aantal screenings gereduceerd kan worden tot maximaal 2 of 1 per jaar, respectievelijk voor vrouwen die wel of niet in aanmerking komen voor longkankerscreening, terwijl ≥94% van de gezondheidswinst behouden kan blijven. Screenen voor verschillende kankers, ook al wordt het screeningsinterval hierdoor langer, levert meer gezondheidswinst op dan het volledig deelnemen aan sommige maar niet alle bevolkingsonderzoeken. Voor vrouwen die in aanmerking komen is longkankerscreening essentieel: strategieën zonder longkankerscreening behaalden ≤25% van de gezondheidswinst. Samenvattend toont onze studie aan dat het mogelijk is voor vrouwen om hun screeningsintensiteit te verlagen met maar een beperkt gezondheidsverlies, mits zij een optimaal afwisselend schema kiezen. Door vrouwen de optie te geven minder vaak gescreend te worden zijn er mogelijk meer vrouwen bereid om deel te nemen.

Hoofdstuk 8 heeft betrekking op het bevolkingsonderzoek darmkanker in Frankrijk. De huidige deelname aan dit bevolkingsonderzoek is onder de 35%, wat veel lager is dan de deelname in omliggende Europese landen. Een mogelijke verklaring hiervoor is dat in Frankrijk de bevolking opgeroepen wordt een FIT op te halen bij de huisarts, terwijl in andere landen, waaronder Nederland, een FIT met de post naar het huisadres verstuurd wordt. Daarom hebben we de mogelijke gezondheidswinst en bijkomende kosten van het per post versturen van de FIT in Frankrijk geschat. Onze resultaten suggereren

dat het per post versturen van de FIT kosteneffectief is als het de deelname aan het bevolkingsonderzoek met 0,5 procentpunt verhoogd. Het ligt in lijn der verwachting dat het effect van deze maatregel op participatie vele malen groter is, en daarom heeft deze maatregel waarschijnlijk een gunstige kosten-batenbalans.

Screening en vervolgstappen voor Lynch syndroom patiënten

Het laatste gedeelte van dit proefschrift richt zich op patiënten met Lynch-syndroom. Individuen gediagnostiseerd met Lynch-syndroom hebben ongeveer 42% kans op het ontwikkelen van darmkanker voor leeftijd 80. Daarnaast hebben vrouwen ongeveer 35% kans op het krijgen van endometriumkanker. Het is daarom van belang om individuen met Lynch-syndroom te identificeren voordat zij kanker ontwikkelen zodat preventieve maatregelen genomen kunnen worden.

In **Hoofdstuk 9** wordt voor de Canadese setting de kosteneffectiviteit berekend van het screenen op Lynch-syndroom van alle darmkankerpatiënten jonger dan 70 jaar door middel van immunohistochemie. Het screenen van darmkankerpatiënten kan uiteindelijk leiden tot het identificeren van asymptomatische familieleden, die baat hebben bij intensieve coloscopiesurveillance. Onze studie voorspelde dat het testen van 1000 darmkankerpatiënten leidt tot het identificeren van 29 asymptomatische familieleden met Lynch-syndroom. Door deze familieleden elke twee jaar coloscopiesurveillance aan te bieden in plaats van de normale darmkankerscreening, verlaagde de kans van deze familieleden om te sterven aan darmkanker met 40%. De langetermijneffecten van het identificeren van deze familieleden wegen op tegen de kosten van het screenen op Lynch-syndroom van alle darmkankerpatiënten onder leeftijd 70. Daarnaast toonde onze studie aan dat het optimale surveillance-interval twee jaar is; in het veld wordt momenteel uitvoerig gediscussieerd over het optimale surveillance-interval. Onze resultaten waren met name informatief voor beleidsmakers in Ontario, Canada, waar overwogen werd deze vorm van screening op het Lynch-syndroom in te voeren.

Hoofdstuk 10 bouwt voort op de analyses van hoofdstuk 9 door de gezondheidswinst en kosten te schatten van het aanbieden van profylactische hysterectomie aan asymptomatische vrouwelijke familieleden van darmkankerpatiënten die gediagnostiseerd zijn met Lynch-syndroom. Het MISCAN-endometriummodel werd ontwikkeld om de optimale leeftijdsgroep voor profylactische hysterectomie te bepalen.

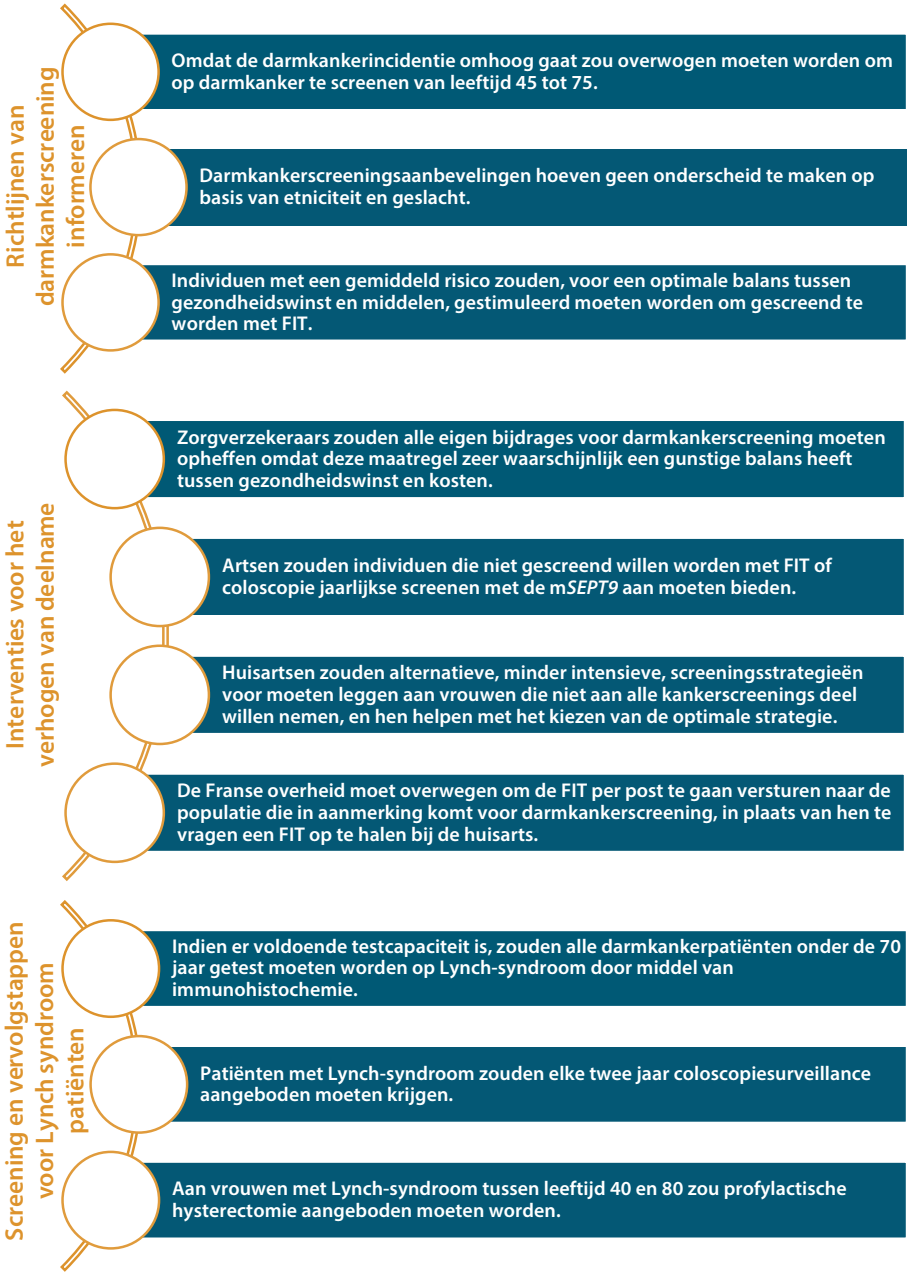
Vanuit het oogpunt van kosteneffectiviteit is het optimaal om vrouwen met Lynch-syndroom tussen de 40 en 80 jaar profylactische hysterectomie aan te bieden. Echter, de optimale leeftijdsgroep hangt sterk af van de kwaliteit van leven van een individu nadat het profylactische hysterectomie heeft ondergaan; vrouwen kunnen overwegen al profylactische hysterectomie te ondergaan op leeftijd 35 als ze de negatieve effecten van het vervroegd in de overgang raken acceptabel vinden. Resultaten van deze studie informeren artsen en vrouwen met Lynch-syndroom over de beslissing over het al dan niet ondergaan van profylactische hysterectomie, en op welke leeftijd.

Conclusies en aanbevelingen

De volgende conclusies kunnen getrokken worden op basis van de studies in dit proefschrift:

- Doordat de darmkankerincidentie toeneemt in Amerikaanse jongvolwassenen weegt de gezondheidswinst van het starten met screening op leeftijd 45 in plaats van leeftijd 50 op tegen de lasten en de kosten.
- De optimale screeningsstrategie voor Amerikanen is onafhankelijk van etniciteit en geslacht als de darmkankerincidentie toeneemt.
- De toenemende darmkankerincidentie en behandelkosten zorgen voor een verbeterde kosteneffectiviteit van darmkankerscreening.
- Van alle testen voor darmkankerscreening biedt FIT de meest gunstige verhouding tussen kosten en opbrengsten
- Het opheffen van de eigen bijdrage voor alle coloscopieën in de setting van darmkankerscreening heeft een gunstige balans tussen gezondheidswinst en kosten.
- Voor individuen die niet deel willen nemen aan FIT of coloscopiescreening is jaarlijkse screening met de m*SEPT9* op basis van kosteneffectiviteit het beste alternatief.
- Vrouwen die niet aan alle kankerscreenings kunnen of willen deelnemen, kunnen hun screeningsintensiteit verlagen met beperkte impact op de totale gezondheidswinst van kankerscreening, mits vrouwen die daarvoor in aanmerking komen longkankerscreening ondergaan.
- Longkankerscreening levert voor vrouwen die daarvoor in aanmerking komen meer gezondheidswinst op dan screening op darmkanker, borstkanker of baarmoederhalskanker.
- Het screenen op meerdere kankers, zelfs als dit minder frequent is dan aanbevolen wordt, levert meer gezondheidswinst op dan het screenen op specifieke kankers maar niet op alle kankers.
- Het per post versturen van de FIT is een zeer kosteneffectieve interventie om de deelname aan darmkankerscreening te verbeteren.
- Het testen op Lynch-syndroom van alle darmkankerpatiënten onder leeftijd 70, en, wanneer positief, het testen van familieleden, heeft een gunstige balans tussen gezondheidswinst en kosten.
- Twee jaar is het optimale coloscopiesurveillance-interval voor patiënten met Lynch-syndroom.
- Het aanbieden van profylactische hysterectomie aan vrouwen met Lynch-syndroom tussen leeftijd 40 en 80 is kosteneffectief op populatieniveau.
- Vanaf welke leeftijd profylactische hysterectomie aangeboden zou moeten worden, hangt af van de impact van profylactische hysterectomie op de kwaliteit van leven van de betreffende vrouw.

De conclusies van dit proefschrift suggereren de volgende aanbevelingen voor de praktijk.



About the author

Elisabeth Francisca Patricia Peterse was born on the 29th of January 1991 in Diessen, the Netherlands. In 2009, she completed pre-university education (atheneum) at the Odulphuslyceum in Tilburg. In that same year, she started to attend the Bachelor's program Biomedical Sciences at Leiden University. During her Bachelor's, Elisabeth studied at the Karolinska Institute in Stockholm, Sweden, for half a year as part of an Erasmus exchange program. In 2011, she enrolled in the MSc/PhD-track and started extracurricular research at the Department of Pathology, Leiden University Medical Center (LUMC). After receiving her Bachelor's degree in 2012, Elisabeth continued her studies by attending the Master's program Biomedical Sciences at Leiden University. She did a 5-month internship at the Ludwig Institute for Cancer Research, University of Oxford, United Kingdom. Upon her return, Elisabeth continued her MSc/PhD research in the LUMC. After receiving her Master of Science degree with distinction in 2014, she received personal funding to continue her PhD titled: "Targeting Chondrosarcoma and Osteosarcoma Cell Metabolism", which she completed in 2018. In 2016, she decided to change fields and started her second PhD at the department of Public Health, Erasmus University Medical Center, Rotterdam. In 2018, Elisabeth graduated from her Master's degree in Health sciences with specialization Public Health at the Netherlands Institute for Health Sciences. From May 2019 to March 2020, she was a visiting scientist at the Fred Hutchinson Cancer Research Center in Seattle, WA, US. When she returned to the Netherlands, she finished her second PhD, of which the results are presented in this thesis. Since October 2020, Elisabeth is working at Pharmerit – an OPEN Health Company.

PhD portfolio

Name PhD student:	Elisabeth Francisca Patricia Peterse
Erasmus MC department:	Public Health
Research School:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	2016-2021
Promotor:	Prof. dr. Harry J. de Koning
Co-promotors:	Dr. Iris Lansdorp-Vogelaar & Dr. Reinier G.S. Meester

Courses	**Year**	**ECTS**
NIHES: Master of Science in Health Sciences, specialization Public Health	2016-2018	70
Biostatistical Methods II: Classical Regression Models	2016	4.3
Principles of Research in Medicine and Epidemiology	2016	0.7
Methods of Public Health	2016	0.7
Introduction to Public Health	2016	0.7
Methods of Health Services Research	2016	0.7
Primary and Secondary Prevention Research	2016	0.7
Social Epidemiology	2016	0.7
Public Health Research Methods	2017	5.7
Integration Module	2017	0.3
International Comparison of Health Care Systems	2017	1.4
Health Economics	2017	0.7
Joint Models for Longitudinal and Survival Data	2017	0.7
Planning and Evaluation of Screening	2017	1.4
From Problem to Solution in Public Health	2017	1.1
Courses for the Quantitative Researcher	2017	1.4
Site Visit to the Municipal Health Service Rotterdam	2018	0.3
Advanced topics in Decision-making in Medicine	2018	2.4
Advanced Decision Science Modeling	2018	1.4
Erasmus MC: Scientific Integrity	2016	0.4
Society for Medical Decision Making: Hands-on Model Calibration in R	2019	0.3
Erasmus MC: Female Talent Class	2019	2.0
Presentations	**Year**	**ECTS**
Oral Presentations		
Cancer Intervention and Surveillance Modeling Network, Rockville, MD.	2016	0.5
Southeastern Colorectal Cancer Consortium, San Juan, PR.	2017	0.5
Digestive Disease Week, Chicago, IL.	2017	0.5
Cancer Intervention and Surveillance Modeling Network, Stanford, CA.	2017	0.5
International Cancer Screening Network Meeting, Bethesda, MD.	2017	0.5
Cancer Intervention and Surveillance Modeling Network, Rockville, MD.	2017	0.5
Cancer Intervention and Surveillance Modeling Network, Ann Arbor, MI.	2018	0.5

World Endoscopy Organization, Washington D.C.	2018	0.5
Digestive Disease Week, Washington D.C.	2018	0.5
Comprehensive Colorectal Cancer Risk Prediction To Inform Personalized Screening Meeting, Seattle, WA.	2018	0.5
Society for Medical Decision Making, Portland, OR.	2019	0.5
Comprehensive Colorectal Cancer Risk Prediction To Inform Personalized Screening Meeting, Seattle, WA.	2019	0.5
Poster Presentations		
Society for Medical Decision Making, Leiden.	2018	0.5

Conferences and meetings	**Year**	**ECTS**
NvvO milestone day, Amsterdam.	2016	0.3
Cancer Intervention and Surveillance Modeling Network, Rockville, MD.	2016	0.7
World Endoscopy Organization, Vienna	2016	0.3
Southeastern Colorectal Cancer Consortium, San Juan, PR.	2017	0.7
World Endoscopy Organization, Chicago, IL.	2017	0.3
Digestive Disease Week, Chicago, IL.	2017	1.0
Cancer Intervention and Surveillance Modeling Network, Stanford, CA.	2017	0.5
International Cancer Screening Network Meeting, Bethesda, MD.	2017	0.7
Cancer Intervention and Surveillance Modeling Network, Rockville, MD.	2017	0.7
Cancer Intervention and Surveillance Modeling Network, Ann Arbor, MI.	2018	0.5
World Endoscopy Organization, Washington D.C.	2018	0.3
Digestive Disease Week, Washington D.C.	2018	1.0
Cancer Intervention and Surveillance Modeling Network, Rockville, MD.	2018	0.7
Comprehensive Colorectal Cancer Risk Prediction To Inform Personalized Screening Meeting, Seattle, WA.	2018	0.5
Society for Medical Decision Making, Leiden.	2018	0.4
Cancer Intervention and Surveillance Modeling Network, Seattle, WA.	2019	0.5
ENCODE 2019: Research applications and users meeting	2019	1.0
Society for Medical Decision Making, Portland, OR.	2019	1.0
Cancer Intervention and Surveillance Modeling Network, Rockville, MD.	2019	0.7
Comprehensive Colorectal Cancer Risk Prediction To Inform Personalized Screening Meeting, Seattle, WA.	2019	0.5
Cancer Intervention and Surveillance Modeling Network, Online	2020	0.3

Teaching	**Year**	**ECTS**
Supervision Bachelor Student, Erasmus MC, Rotterdam.	2017-2018	5.0
Supervision Community Project, third year Medicine students, Erasmus MC, Rotterdam.	2017+2018	2.8
Workshop on MISCAN-Colon, Erasmus MC, Rotterdam.	2017+2018	1.0
Supervision PhD Student, Erasmus MC, Rotterdam.	2017-2019	15.0
Supervision Master Student, Erasmus MC, Rotterdam.	2018	3.0
Teacher in course "Secondary Prevention" for third year Medicine students, Erasmus MC, Rotterdam.	2018+2019	1.2
Teacher in course "Planning and Evaluation of Screening" for NIHES Master students, Erasmus MC, Rotterdam.	2019	1.0

Supervision PhD Student	2020	2.5
Grant writing	**Year**	**ECTS**
Colorectal Cancer Screening Coverage: Impacts on Decision Making and Health, NCI Grant.	2017	1.0
Rubicon, NWO Grant.	2019	3.0
Nijbakker-Morra Foundation, Travel Grant.	2019	1.0
René Vogels foundation, Travel Grant.	2019	1.0
Obesity, sedentary behaviors, and diet quality for prevention and early detection of early-onset colorectal neoplasia, NCI Grant.	2019	1.0
Advancing equity in colorectal cancer genetic risk prediction through expansion of racial/ethnic minority representation, NCI Grant.	2019	1.0
CISNET-Colon "Comparative Modeling of Colorectal Cancer: Informing Health Policies and Prioritizing Future Research, NCI Grant.	2019	1.0
Others	**Year**	**ECTS**
Meetings ORCA study, Gastroenterology Department, Erasmus MC, Rotterdam.	2017-2019	1.0
MISCAN education and documentation working group	2017-2019	5.6
Reviewer for Cancer, American Journal of Preventive Medicine, Gut.	2017-2020	1.0
Organizing the participation of the screen section to the National Econometricians Day.	2018+2019	4.0
Organizing committee International Cancer Screening Network, Rotterdam.	2018-2019	1.0
Visiting Scientist, 11 months, Fred Hutchinson Cancer Research Center, Seattle, WA.	2019-2020	-
Research Seminars at the Department of Public Health, Erasmus MC, Rotterdam.	2016-2020	-

List of publications

This thesis

1. Peterse EFP, Knudsen AB, Lietz A, Kolb JM, Scott FI, Zauber AG, Lansdorp-Vogelaar I, The impact of the increased colorectal cancer treatment costs and incidence in young adults on the cost-effectiveness of colorectal cancer screening. *Submitted.*
2. Alblas M*, Peterse EFP*, Du M, Zauber AG, Steyerberg EW, van Leeuwen N, Lansdorp-Vogelaar I, Cost-effectiveness of prophylactic hysterectomy in first-degree female relatives with Lynch syndrome of patients diagnosed with colorectal cancer in the United States: a microsimulation study. *Submitted.*
3. Taksler GB, Peterse EFP, Willems I, ten Haaf K, Jansen EEL, de Kok IMCM, van Ravesteyn NT, de Koning HJ, Lansdorp-Vogelaar I. Prioritizing Cancer Screenings in Women with Restrictive Preferences. *Submitted.*
4. Peterse EFP, Osoro CB, Bardou M, Lansdorp-Vogelaar I. Comparative effectiveness and cost-effectiveness of mailed-out fecal immunochemical tests versus collection at general practitioner. *Submitted.*
5. Peterse EFP, Meester RGS, de Jonge L, Omidvari AH, Alarid-Escudero F, Knudsen AB, Zauber AG, Lansdorp-Vogelaar I. Comparing the cost-effectiveness of innovative colorectal cancer screening tests. *Journal of the National Cancer Institute*. 2020; Epub.
6. Peterse EFP, Naber SK, Daly C, Pollett A, Paszat LF, Spaander MCW, Aronson M, Gryfe R, Rabeneck L, Lansdorp-Vogelaar I, Baxter NN. Cost-effectiveness of Active Identification and Subsequent Colonoscopy Surveillance of Lynch Syndrome Cases. *Clinical Gastroenterology and Hepatology*. 2020;18:2760-2767.
7. Peterse EFP, Meester RGS, Siegel RL, Chen JC, Dwyer A, Ahnen DJ, Smith RA, Zauber AG, Lansdorp-Vogelaar I. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: Microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. *Cancer*. 2018;124:2964-2973.
8. Meester RGS, Peterse EFP, Knudsen AB, de Weerdt AC, Chen JC, Lietz AP, Dwyer A, Ahnen DJ, Siegel RL, Smith RA, Zauber AG, Lansdorp-Vogelaar I. Optimizing colorectal cancer screening by race and sex: Microsimulation analysis II to inform the American Cancer Society colorectal cancer screening guideline. *Cancer*. 2018;124:2974-2985.
9. Peterse EFP, Meester RGS, Gini A, Doubeni CA, Anderson DS, Berger FG, Zauber AG, Lansdorp-Vogelaar I. Value Of Waiving Coinsurance For Colorectal Cancer Screening In Medicare Beneficiaries. *Health Affairs (Millwood)*. 2017;36:2151-2159.

*These authors contributed equally

Other

10. Vuik FER, Nieuwenburg SAV, Moen S, Schreuders EH, Oudkerk Pool MD, Peterse EFP, Spada C, Epstein O, Fernandez-Urien I, Hofman A, Kuipers EJ, Spaander MCW. Population-based prevalence of gastrointestinal abnormalities at colon capsule endoscopy. *Clinical Gastroenterology and Hepatology*. 2020; Epub
11. Archambault AN, Su YR, Jeon J, Thomas M, Lin Y, Conti DV, Win AK, Sakoda LC, Lansdorp-Vogelaar I, Peterse EFP, …., Gallinger SJ, Jenkins MA, Newcomb PA, Gruber SB, Schoen RE, Hampel H, Corley DA, Hsu L, Peters U, Hayes RB. Cumulative Burden of Colorectal Cancer-Associated Genetic Variants Is More Strongly Associated With Early-Onset vs Late-Onset Cancer. *Gastroenterology*. 2020;158:1274-1286 e1212.
12. Peterse EFP*, Niessen B*, Addie RD, de Jong Y, Cleven AHG, Kruisselbrink AB, van den Akker B, Molenaar RJ, Cleton-Jansen AM, Bovee J. Targeting glutaminolysis in chondrosarcoma in context of the IDH1/2 mutation. *British Journal of Cancer*. 2018;118:1074-1083.
13. Peterse EFP, van den Akker B, Niessen B, Oosting J, Suijker J, de Jong Y, Danen EHJ, Cleton-Jansen AM, Bovee J. NAD Synthesis Pathway Interference Is a Viable Therapeutic Strategy for Chondrosarcoma. *Molecular Cancer Research*. 2017;15:1714-1721.
14. Peterse EFP, van Leeuwen TN, Cleton-Jansen AM. A researcher's perspective on the quantity of osteosarcoma in vitro studies. *Journal of Bone Oncology*. 2017;7:29-31.
15. van Maldegem AM, Bovee JV, Peterse EFP, Hogendoorn PC, Gelderblom H. Ewing sarcoma: The clinical relevance of the insulin-like growth factor 1 and the poly-ADP-ribose-polymerase pathway. *European Journal of Cancer*. 2016;53:171-180.
16. Peterse EFP, Bovee JV. CORR Insights((R)): Transcriptional Profiling Identifies the Signaling Axes of IGF and Transforming Growth Factor-beta as Involved in the Pathogenesis of Osteosarcoma. *Clinical Orthopaedics and Related Research*. 2016;474:190-192.
17. Peterse EFP, Cleven AH, De Jong Y, Briaire-de Bruijn I, Fletcher JA, Danen EH, Cleton-Jansen AM, Bovee JV. No preclinical rationale for IGF1R directed therapy in chondrosarcoma of bone. *BMC Cancer*. 2016;16:475.
18. Baranski Z, de Jong Y, Ilkova T, Peterse EFP, Cleton-Jansen AM, van de Water B, Hogendoorn PC, Bovee JV, Danen EH. Pharmacological inhibition of Bcl-xL sensitizes osteosarcoma to doxorubicin. *Oncotarget*. 2015;6:36113-36125.
19. Kuijjer ML, Peterse EFP, van den Akker BE, Briaire-de Bruijn IH, Serra M, Meza-Zepeda LA, Myklebost O, Hassan AB, Hogendoorn PC, Cleton-Jansen AM. IR/IGF1R signaling as potential target for treatment of high-grade osteosarcoma. *BMC Cancer*. 2013;13:245.
20. Zeron-Medina J, Wang X, Repapi E, Campbell MR, Su D, Castro-Giner F, Davies B, Peterse EFP, Sacilotto N, Walker GJ, Terzian T, Tomlinson IP, Box NF, Meinshausen N, De Val S, Bell DA, Bond GL. A polymorphic p53 response element in KIT ligand influences cancer risk and has undergone natural selection. *Cell*. 2013;155:410-422.

*These authors contributed equally

Dankwoord

Een tweede PhD, waarom zou je dat doen? Vele doctoren die zich door hun PhD en proefschrift heen geworsteld hebben moeten hier absoluut niet aan denken. Toch heb ik er nooit aan getwijfeld om op MGZ te starten en vervolgens mijn PhD af te ronden. In eerste instantie kwam dit door de maatschappelijke relevantie van het werk, maar later heeft de fantastisch werksfeer er voor gezorgd dat ik altijd met veel plezier naar mijn werk kwam. Hiervoor wil ik een aantal personen in het bijzonder bedanken.

Mijn co-promotor dr. Iris Lansdorp-Vogelaar. Iris, jij hebt mij vier jaar lang talloze mogelijkheden geboden om me te blijven ontwikkelen. Het trainen van leiderschaps-vaardigheden, het geven van onderwijs, het begeleiden van (PhD) studenten, het vertegenwoordigen van onze groep op (internationale) meetings, en elf maanden onderzoek doen in het buitenland zijn kansen die zeker niet elke PhD student krijgt. Door mij het vertrouwen te geven ben ik enorm gegroeid, niet alleen als onderzoeker maar ook als persoon. Ik ben je hiervoor ontzettend dankbaar.

Dr. Reinier Meester, mijn co-promotor en dagelijkse begeleider. Reinier, jij hebt inhoudelijk onwijs veel bijgedragen aan dit proefschrift. Ik kon altijd bij je terecht voor vragen over de optimale opzet van een studie en voor technische tips om berekeningen sneller te kunnen doen. Ik heb met veel bewondering gekeken naar de feedback die jij op al mijn stukken gegeven hebt. Mijn proefschrift had zonder jou absoluut niet het huidige niveau bereikt.

Mijn promotor, prof. dr. Harry J. de Koning. Harry, door het goede team wat jij om je heen verzameld hebt ben jij maar zijdelings betrokken geweest bij de totstandkoming van dit proefschrift. Toch zijn er een aantal moeilijke momenten geweest in mijn PhD waarbij Iris en ik bij jou aan hebben moeten kloppen. Op die momenten heb ik het gevoel gehad dat je blindelings achter me bent gaan staan, en daar wil ik je enorm voor bedanken.

All the members of the CISNET-colorectal team. Your expertise in microsimulation modeling for colorectal cancer is unprecedented. It was an outstanding opportunity for me to be part of this amazing group of researchers. On top of that, our semi-annual meetings were always great fun and something to look forward to. A special thanks goes to drs. Ann and Peter Zauber. Dear Ann and Peter, you are without a doubt among the kindest people I have ever met. You welcomed me into your home with open arms when I stayed in the US in between meetings. I will cherish those memories forever.

My collaborators and former colleagues from the Fred Hutchinson Cancer Research Center. Riki, I am extremely grateful that you gave me the opportunity to be part of you research team for one year. Your ambition and enthusiasm has been inspiring. Kelsey,

I really enjoyed our lunch breaks and drinks. Thank you for all the fun we had, and for your patience when explaining American football. Sepi, our coffee breaks at *Vivace* always brightened my day. Thank you so much for your warmth and openness.

My peers in the GI-team, Amir, Andrea, Annemieke, Arthur, Brechtje, Carlijn, Dayna, Esther, Isarah, Lucie, Maaike A, Maaike B and Steffie, and other members of the screen section, especially Amarens, Erik B, Erik J, Inge, Lindy, Lisanne, Nadine and Valerie. We were a very social group, with many fun activities outside of work. Ski trips, quizzes, volleyball, sightseeing, dinners and drinks, there was always something going on. I always felt very lucky to be part of this team.

Mijn kamergenootjes, Andrée, Erik, Laura, Mark, Sophie en Suzanne. Bij ons in de kamer kon iedereen zichzelf zijn, was er altijd tijd voor koffie, een sappige roddel en een luisterend oor. Ondanks dat we overgingen naar flexwerken, en later iedereen elders is gaan werken, zijn we elkaar op blijven zoeken. We hebben elkaar er doorheen gesleept.

Mijn lieve familie en vrienden. Van jullie krijg ik altijd positieve energie. Ik wil jullie bedanken voor jullie onvoorwaardelijke steun. Tenslotte wil ik graag mijn “vriend” Bram bedanken. Bram, je stimuleert me altijd om het beste uit mezelf te halen. Samen zijn we het avontuur aangegaan om een jaar in Seattle te gaan wonen. Ik kijk uit naar de vele avonturen die ongetwijfeld nog komen gaan.