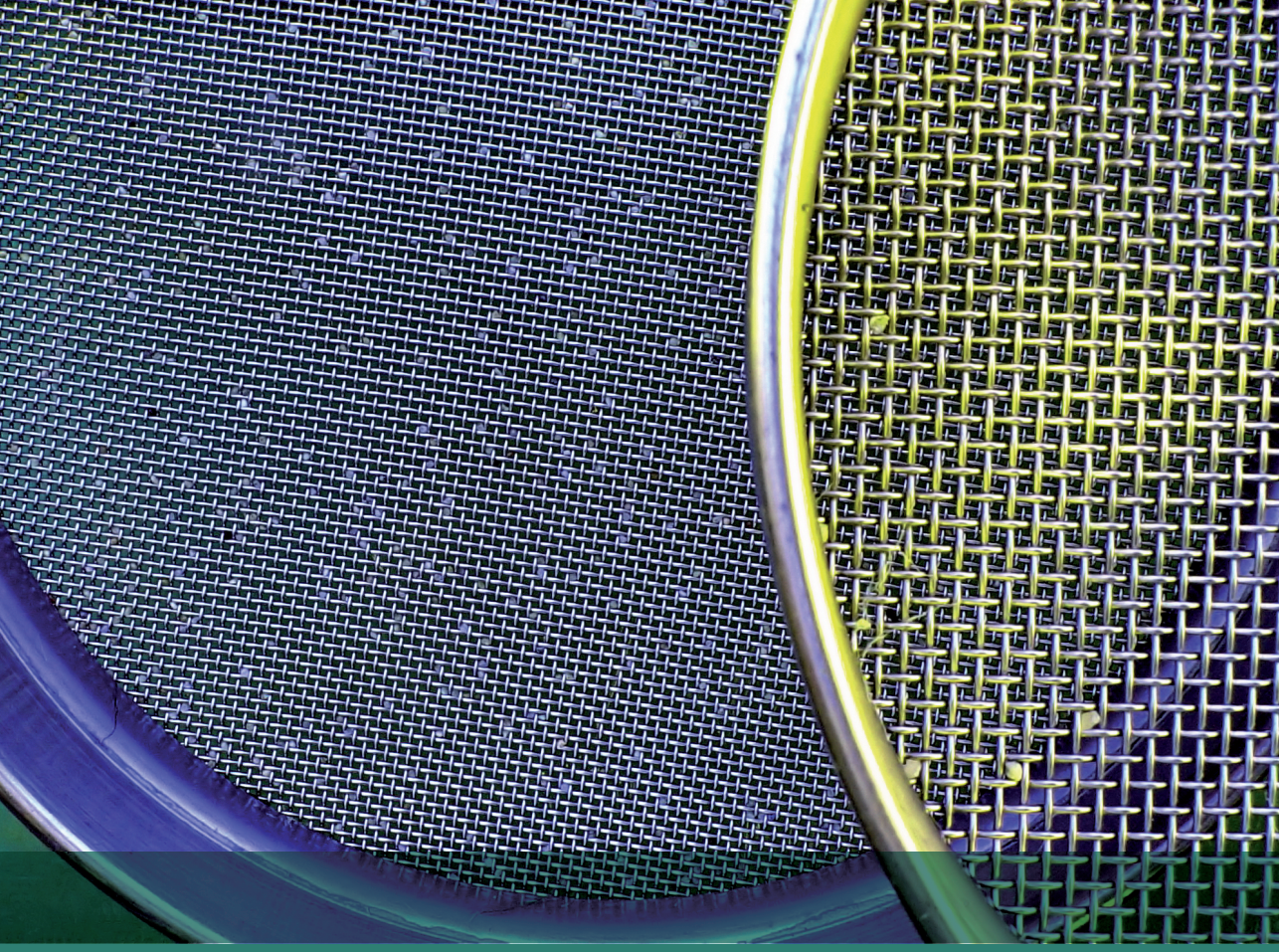

Modelling the Effects and Costs of Colorectal Cancer Screening

Simon Lucas Goede

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Modelling the Effects and Costs of Colorectal Cancer Screening

Het modelleren van effecten en kosten van darmkanker screening

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CONTENTS

Chapter 1

General introduction

1.1 COLORECTAL CANCER EPIDEMIOLOGY

Colorectal cancer (CRC) is an important public health problem with over a million new cases diagnosed every year worldwide.[1] CRC is most common in developed countries where it is the third most frequently diagnosed malignancy in men and ranks second in women. The lifetime incidence of CRC is approximately seven percent in The Netherlands.[2]

CRC incidence and mortality rates increase with age, especially above age 50. Cases with the disease before age 50 are mostly caused by hereditary disorders like familial adenomatous polyposis (FAP) and hereditary non-polyposis CRC (HNPCRC). The age-specific CRC mortality is higher in men than in women (Figure 1), but because women tend to have a longer life expectancy than men the total number of CRC deaths is comparable. In The Netherlands a total of 2,604 men and 2,484 women died of CRC in 2011.[2]

In 1989 the world age-standardised CRC incidence and mortality rates in The Netherlands and the United States (US) were roughly comparable at 30.7 and 15.9 cases/deaths per 100,000 individuals per year in The Netherlands, and 36.7 and 14.0 cases/deaths per 100,000 individuals per year in the US, respectively. However, over the past two decades the incidence rate has been increasing in The Netherlands, reaching approximately 38.6 cases per 100,000 individuals per year in 2010, while the incidence rate in the US has been decreasing steadily to approximately 25.5 cases per 100,000 per year (Figure 2). In The Netherlands the increasing trend might be explained by increases in the prevalence of risk factors such as red meat consumption and overweight.[3] In the US the trends in risk factor prevalence are more favourable. In addition, screening

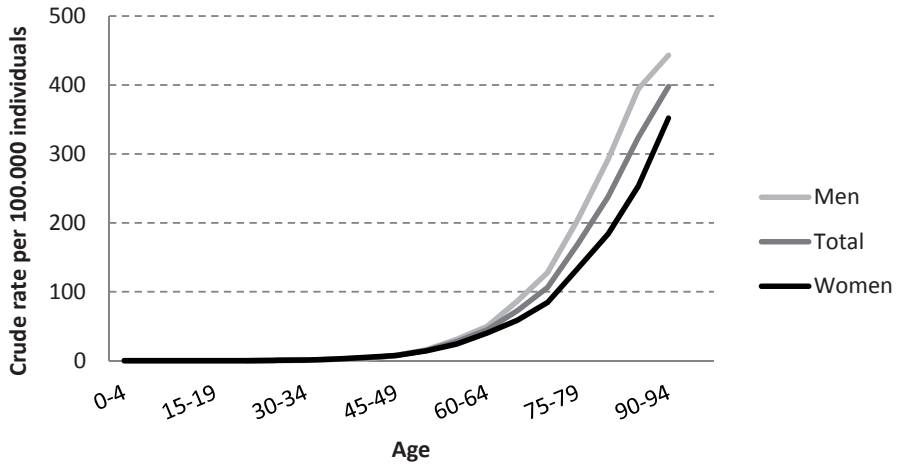

Figure 1. CRC mortality rate by age and gender in The Netherlands (data 2011).[2]

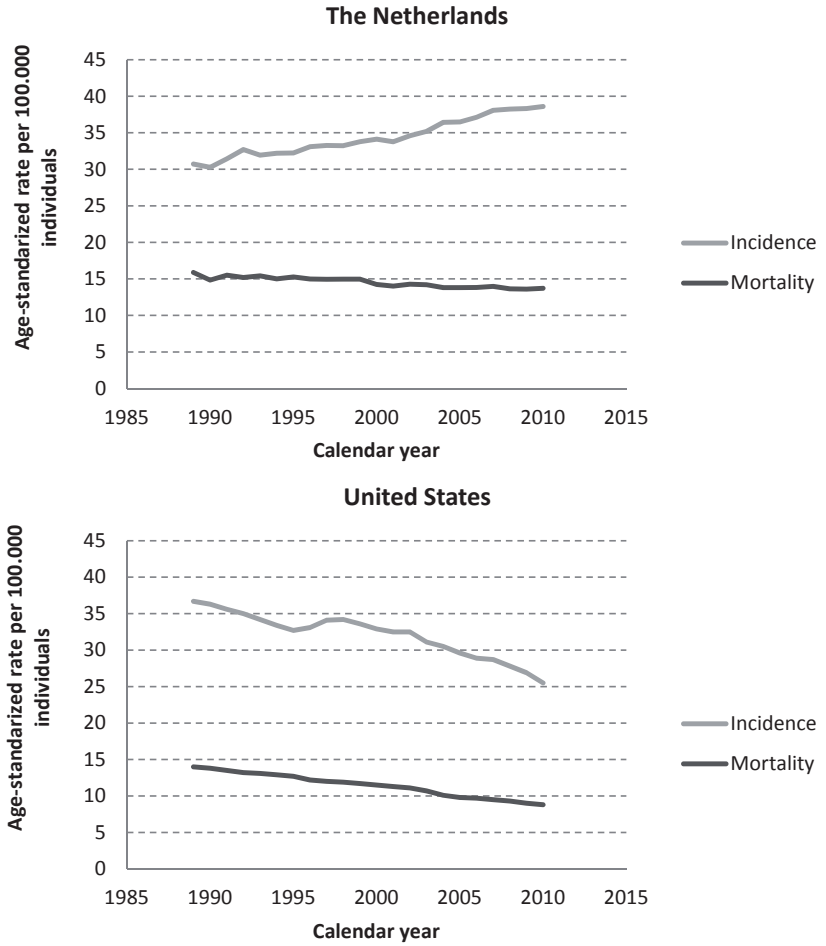

Figure 2. Annual world age-standardised CRC incidence and mortality rate per 100,000 individuals in The Netherlands and United States.[2, 9]

is responsible for a major part of the difference[4]; in the US screening for CRC was introduced more than three decades ago, with participation rates in individuals aged 50 years and older increasing from approximately 18 percent in 1987, to 58 percent in 2010.[5, 6] In the Netherlands screening has been far less common, until recently. In January 2014 a nationwide population-based screening program was introduced, which is expected to greatly impact screening participation in the near future. CRC mortality in both countries has been decreasing in recent years, because of earlier diagnosis of CRC (mainly in the US) and because of advances in surgical treatments and adjuvant therapy. [7, 8] The CRC mortality rate was 13.7 deaths per 100,000 individuals per year in The Netherlands and 8.8 per 100,000 per year in the US in 2010.[2, 9]

1.2 INTERVENTIONS TO REDUCE THE NUMBER OF COLORECTAL CANCER DEATHS

1.2.1 Primary prevention

Primary prevention strategies for CRC include the adoption of a more healthy lifestyle and applying chemoprevention (e.g. aspirin or cyclooxygenase (COX) inhibitors). Established life style related risk factors include smoking, alcohol consumption, red meat consumption and obesity, whereas physical activity, and aspirin use have a protective effect (Table 1).[10, 11] It is estimated that more than 50 percent of all CRC cases in developed countries are caused by lifestyle and environmental factors.[12] Although changing one's lifestyle is often thought hard to accomplish, changes in risk factor prevalence have contributed to approximately half the 22% CRC incidence reduction observed in the US between 1975 and the year 2000 (the other half being accomplished through screening).[4] In addition, the observed risk factor changes account for approximately one third of the 26% reduction in CRC mortality over that same time period.

Chemoprevention drugs like aspirin have been demonstrated to reduce CRC incidence and adenoma recurrence. However, they are also associated with adverse effects, mainly increased risk for bleeding and cardiovascular disease.[13, 14] Their main application is in increased risk populations like patients with a history of adenomas and individuals with familial adenomatous polyposis

Table 1. Life style related risk factors for CRC.[10, 14]

Risk factor	Relative risk (95% CI)
Alcohol	1.56 (1.42-1.70)
Red meat	1.21 (1.13-1.29)
Processed meat	1.19 (1.12-1.27)
Diabetes	1.23 (1.17-1.30)
Smoking	1.16 (1.09-1.24)
Obesity	1.19 (1.11-1.29)
Physical activity	0.81 (0.77-0.86)
Aspirin	0.75 (0.56-0.97)*

*Hazard ratio
CI: confidence interval

1.2.2 Screening

Screening tests aim to detect CRC and pre-cursor lesions (i.e. adenomas), when they are at an early stage and before individuals develop symptoms. There are two main reasons that make CRC a disease which is well suited for screening interventions. First, CRC has a long pre-clinical screen detectable phase. It has been estimated that the time for an

adenoma to develop and progress into cancer takes on average more than ten years.[15, 16] If an adenoma is detected, it can be removed and the development of CRC from that adenoma can be prevented. Second, for lesions that have already progressed into cancer, but do not yet produce symptoms, screening can detect the disease at an earlier stage. CRC development can be divided into four stages from localised disease (stage I) to distant metastasis (stage IV), and prognosis decreases with increasing stage. In the period of 2000-2004, the five year relative survival for stage I colon cancer was approximately 89 percent in The Netherlands, while the five year relative survival for stage IV colon cancer was approximately 7 percent.[17] A similar trend was observed for rectal cancer. Therefore, earlier detection of CRC through screening has the potential to significantly increase survival.

There are multiple screening tests available for early detection of CRC. They can broadly be divided into three main categories: biomarker tests, endoscopic tests, and imaging tests (Table 2). The guaiac faecal occult blood test (gFOBT) and faecal immunochemical test (FIT) are both stool-based biomarker tests. GFOBT and FIT detect small traces of blood in the stool; they can be performed at home by taking a small sample of stool, and sending the sample to a laboratory for analysis. If a test is positive the screening participant is referred to the hospital for follow-up with a colonoscopy. Several large randomised clinical trials (RCTs) have demonstrated a CRC mortality reduction from annual and biennial gFOBT screening of 11 to 33 percent.[18-22] For FIT only one RCT has been conducted, which demonstrated a 32 percent mortality from rectal cancer after a single screening round[23], and a case-control study found that FIT screening could reduce CRC mortality by 50 to 80 percent.[24, 25] In addition several trials have demonstrated increased detection rates of advanced neoplasia and comparable specificity with FIT, compared to gFOBT screening.[26-30] These data suggest the mortality reduction from FIT would be at least as good, if not better than gFOBT. There are also biomarker tests which detect markers of aberrant DNA from neoplastic cells in either stool or blood. DNA testing is relatively new, compared to gFOBT and FIT, and techniques in DNA analysis are developing rapidly. Currently there is no data demonstrating a mortality reduction from DNA testing. A recent study did evaluate the sensitivity and specificity of the latest generation stool DNA test compared to FIT screening in average risk individuals.[31] The stool DNA test had significantly higher sensitivity for advanced adenomas and CRC, but had a lower specificity than FIT (i.e. more individuals would be referred to the hospital for a colonoscopy, while they do not have any adenomas or CRC). In addition, one study evaluated the performance of a blood-based DNA test.[32] Blood-based DNA testing had a sensitivity of approximately 42 percent for CRC at a specificity of 91 percent, which is lower than the estimated sensitivity and specificity of FIT. Combined with its higher unit cost, blood-based DNA testing is not yet considered a reasonable option for population-based screening. However with improvements in

Table 2. Available CRC screening tests and evidence of their effectiveness

Screening test	Available evidence for effectiveness	References
Biomarker tests		
Guaiac faecal occult blood test	11-33% CRC mortality reduction from four different RCT's.*	Mandel, 1999[18] Scholefield, 2002[19] Kronborg, 2004[20] Lindholm, 2008[21] Shaukat, 2013[22]
Faecal immunochemical test	32% rectal cancer mortality reduction from one RCT.* 50-80% CRC mortality reduction from case-control study. Increased sensitivity at comparable specificity, compared to gFOBT.	Zheng, 2003[23] Saito, 1995[24] Saito, 2000[25] Smith, 2006[26] Allison, 2007[27] Guittet, 2007[28] Van Rossum, 2008[29] Hol, 2010[30]
Stool-based DNA	Increased sensitivity, but decreased specificity, compared to FIT.	Imperiale, 2014[31]
Endoscopic tests		
Sigmoidoscopy	22-33% CRC mortality reduction from five different RCT's.*	Thiis-Evensen, 1999[35] Atkin, 2010[36] Segnan, 2011[37] Schoen, 2012[38] Holme, 2014[39]
Colonoscopy	Two RCT's underway, no mortality data available yet. 53-68% CRC mortality reduction from two cohort studies.	Kaminski, 2012[41] Quintero, 2012[42] Zauber, 2012[43] Nishihara, 2013[44]
Imaging tests		
CT colonography	No CRC mortality data available. Sensitivity for large adenomas and CRC comparable to colonoscopy.	Sosna, 2003[45] Mulhall, 2005[46] Stoop, 2012[47]

CRC: colorectal cancer; RCT: randomised controlled trial; gFOBT: guaiac faecal occult blood test; FIT: faecal immunochemical test.
* Intention-to-treat analysis

technology this test might become interesting in the future, especially as an alternative for individuals who currently choose not to participate with stool-based screening.

With endoscopy screening a flexible tube with a fibre optic camera is inserted into the rectum. During the procedure detected lesions can be biopsied, or even completely removed. The two main types of endoscopy are sigmoidoscopy and colonoscopy. Both procedures are highly sensitive for adenomas as well as CRC, within the reach of the endoscope.[33, 34] With sigmoidoscopy only the rectum and distal part of the colon are visualised, bowel preparation is relatively easy, and during the procedure no anesthesia is required. In contrast, with colonoscopy the entire colon and rectum can be visualised, but bowel preparation is more burdensome and during the procedure anesthesia

is often administered. Five RCT's have demonstrated a 22 to 33 percent reduction in CRC mortality after one to two rounds of sigmoidoscopy screening (intention to treat analysis)[35-39], and in individuals who actually underwent a sigmoidoscopy the CRC mortality reduction was approximately 50 percent (per protocol analysis).[40] For colonoscopy screening two RCT's are underway, but no mortality data are available yet.[41, 42] However, two recent prospective cohort studies suggest a CRC mortality reduction after colonoscopy screening of 53 to 68 percent.[43, 44]

A relatively new imaging technique is CT colonography, in which a CT scanner is used to make x-ray images of the colon and rectum, which are then processed by a computer to form a three dimensional model. There is no data about CRC mortality reduction from CT colonography, but comparative studies in screening populations have demonstrated the sensitivity for large adenomas and CRC to be comparable to colonoscopy.[45-47]

Every screening test has its advantages and disadvantages. GFOBT and FIT are cheap, have high specificity, can be performed at home, and do not pose any direct risk to the participant. However, these tests mainly detect cancer at an early stage, but are not very sensitive to pre-cancerous adenomas. Stool DNA testing is potentially more sensitive than gFOBT and FIT, but is also more costly, and less specific. CT colonography and sigmoidoscopy are very sensitive and also very specific, but they require a visit to the hospital for initial screening, and if adenomas are detected, the participant needs to return for diagnostic colonoscopy. Primary screening with colonoscopy is the most sensitive, and does not require additional diagnostic testing if adenomas are detected. However, colonoscopy is also the most expensive test, in many regions there is not enough capacity in hospitals to screen all individuals in the target population with colonoscopy, the procedure is more burdensome to the patient than other screening tests, and there is a (small) risk of complications during the procedure. Altogether, there is no single screening test which is preferred over the others. When designing a population-based screening program, the benefits and harms of the different tests should be weighed, and the program should be tailored to meet local challenges and needs.

1.2.3 Treatment

Over the last two decades, treatment of CRC has improved significantly, especially for rectal cancer. Total mesorectal excision for rectal cancers has ensured significant improvements in the quality of surgical resection.[48] Pre-surgical radiotherapy for these tumours has allowed the possibility of down-staging, making more rectal cancers suitable for total mesorectal excision with a reduced local recurrence rate during long-term follow-up.[49] Advances in treatment of metastatic disease such as portal vein embolisation, have made liver resection a possibility for more patients,[50] and in order to reduce surgical stress and decrease recovery time, laparoscopy is increasingly used over open surgery.[51]

In terms of systemic management of CRC, 5-fluorouracil (5-FU) with leucovorin, has been the mainstay of chemotherapy for CRC in both the adjuvant and metastatic settings for a long time. In the late 1990s, the introduction of irinotecan and oxaliplatin as combination treatment with 5-FU/leucovorin increased the median survival of patients with metastatic CRC from 14 to 16 months.[52, 53] Sequential chemotherapy of both irinotecan and oxaliplatin with 5-FU/leucovorin further increased this survival to 21 months. Several biopharmaceuticals, in particular the monoclonal antibodies bevacizumab and cetuximab, have shown promise in clinical studies. By carefully selecting patients and combining and/or sequencing the currently available treatment options, median overall survival for patients with metastatic CRC has gradually increased from 24 to 28 months.[54, 55]

1.3 MICROSIMULATION MODELLING OF COLORECTAL CANCER SCREENING

Generally, CRC screening is associated with reduced CRC mortality by early detection of cancers, and reduced CRC incidence by detection and removal of pre-cancerous adenomas. However, screening is also associated with harms in terms of overtreatment, potential for complications and costs. When implementing a screening program is considered, the benefits and harms have to be weighted for the specific situation in question, and a screening strategy should be chosen based on the most recent scientific knowledge. RCTs provide the most robust scientific evidence, and ideally many questions regarding the effectiveness of population-based screening would be investigated using this study design. However, RCTs often require very large numbers of participants, are very costly, and take many years before final outcomes are available. Computer simulation models are often used to address these fundamental issues by extrapolating available knowledge from clinical data, and help policy makers to optimise screening recommendations to specific population settings.

In this thesis the MIcrosimulation SCreening ANalysis - colon (MISCAN-colon) model is used to estimate health effects and costs of CRC screening in the population. Besides MISCAN-colon there are MISCAN models for several other cancer sites, including lung, breast, prostate, cervix and oesophagus. The various MISCAN models have been developed at the department of Public Health, Erasmus University Medical Centre Rotterdam, The Netherlands. Our team is part of the Cancer Intervention and Surveillance Modelling Network (CISNET), a consortium of modelling groups funded by the National Cancer Institute. Within CISNET, several simulation modelling groups from different institutions collaborate to improve our understanding of cancer control interventions in prevention, screening and treatment, and their effects on population health.

Among the chapters, different versions of the MISCAN-colon model are used in order to simulate different populations. An overview of differences in model assumptions for each chapter is presented in the Model Appendix at the end of this thesis. In general, the MISCAN-colon model simulates the life histories of a large population of individuals from birth to death. CRC arises in this population according to the adenoma-carcinoma sequence (Figure 3).[15, 16] More than one adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas can progress in size from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm), but can never regress. Some adenomas may eventually become malignant; a preclinical (i.e., not detected) cancer has a chance of progressing through stages I to IV and may be detected by symptoms at any stage. After clinical diagnosis of CRC, survival depends on the stage at diagnosis. At any time during his/her life an individual may die of other causes.

Figure 4 provides an example of how an individual undergoing screening is simulated in MISCAN-colon. First, a year of birth and a year of death is generated, resulting in the life history without CRC as shown in the top line. Without CRC modeled, the individual in this example dies from other causes at age 80. Subsequently the model simulates the development of adenomas. For many individuals no adenomas are generated, for others one or more. In the example in Figure 4, the person gets one small adenoma at age 50 (second line in Figure 4). The adenoma is progressive, and after growing to medium size (6-9 mm), the adenoma transforms into stage I pre-clinical CRC. After some time the CRC causes symptoms leading to clinical diagnosis, and eventually resulting in an earlier death from CRC, at age 75. Finally, the model simulates the situation with screening. In the example one screening is performed at age 60. The adenoma is detected and

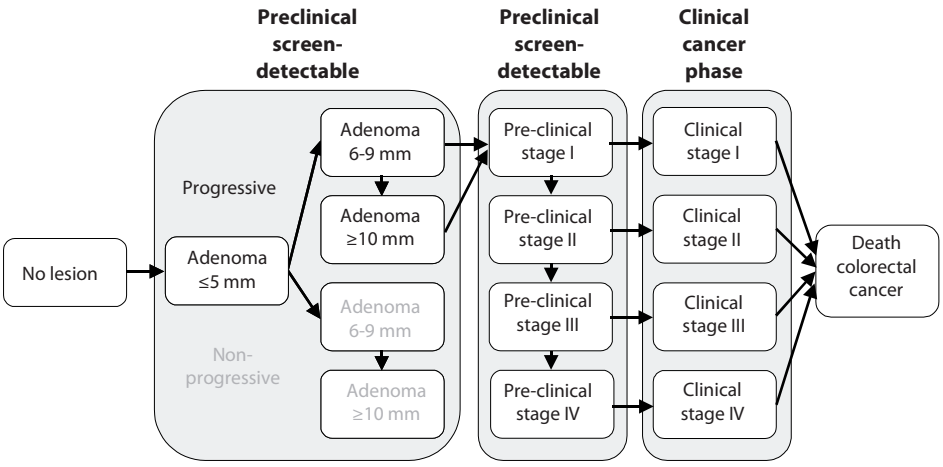

Figure 3. Schematic overview of the adenoma-carcinoma sequence in MISCAN-colon.
* At any time during his/her life an individual may die of other causes than colorectal cancer.

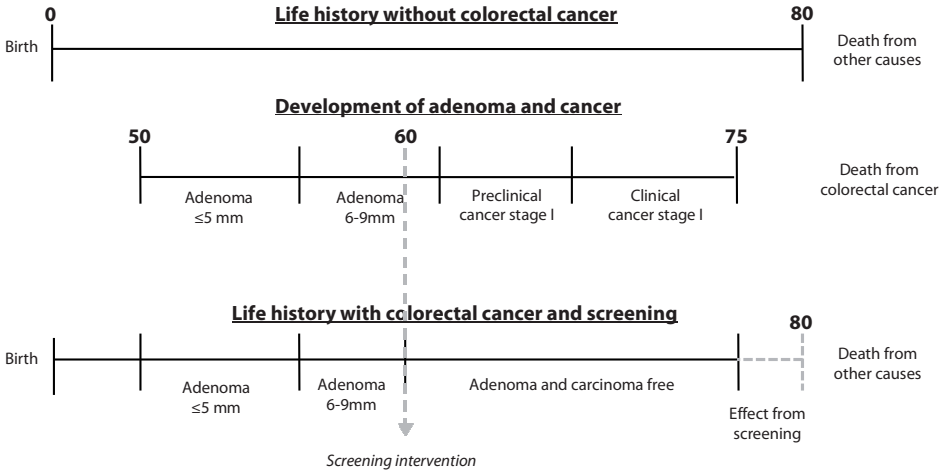

Figure 4. Example of the life history of a single individual as simulated in MISCAN-colon.

removed, and the person no longer develops cancer. This results in a combined life history for CRC and screening (bottom line). The person dies from other causes at age 80, and the benefit of screening is a gain of five life years.

1.4 RESEARCH QUESTIONS AND OUTLINE OF THIS THESIS

The aim of this thesis is to contribute to the body of knowledge about the potential effects and costs of population-based CRC screening by considering two overarching questions. In the first part we investigated what the potential impact is of current screening policies on the CRC disease burden and costs. In this part we considered the situations in the US as a whole, the states of Louisiana and New Jersey in particular, and the province of Ontario, Canada, as examples of regions with different screening policies. In the second part we investigated different strategies by which health effects and costs of CRC screening can be optimised. In this part the focus was mainly on non-invasive CRC screening tests.

In particular the following research questions will be addressed in this thesis:

Part 1: The impact of current screening policies on colorectal cancer disease burden and costs.

– What are the long-term implications of increased CRC screening participation in the US pre-Medicare population (50-64 years) on costs related to CRC in the pre-Medicare and Medicare (65+ years) populations? (Chapter 2)

- To what extent are observed disparities in CRC incidence and mortality between the states of Louisiana and New Jersey explained by differences in risk factor prevalence, screening, and survival? (Chapter 3)
- What are the additional effects of recommending colonoscopy screening for individuals with a family history of CRC within a gFOBT screening program? (Chapter 4)

Part 2: Optimising health effects and costs of non-invasive colorectal cancer screening.

- What is the cost-effectiveness of gFOBT and FIT screening in average risk individuals? (Chapter 5)
- How do participation and diagnostic yield compare of FIT screening with various intervals? (Chapter 6)
- Is providing two FIT samples on two consecutive days cost-effective, compared to providing a single sample? (Chapter 7)
- What are the requirements in test sensitivity, specificity and unit cost in order for new molecular biomarker technologies to be cost-effective compared to the FIT? (Chapter 8)

Chapter 9 concludes this thesis with a summary of answers to and discussion of the above research questions, and directions for future research.

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Part 1

The impact of current screening policies on colorectal cancer disease burden and costs

Chapter 2

Cost-savings to Medicare from Pre-Medicare colorectal cancer screening

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Submitted

ABSTRACT

Background. Many individuals have not received recommended colorectal cancer (CRC) screening before they become Medicare eligible at age 65. We aimed to estimate the long-term implications of increased CRC screening in the pre-Medicare population (50-64 years) on costs in the pre-Medicare and Medicare populations (65+ years).

Methods. We used two independently developed microsimulation models (MISCAN and SimCRC) to project CRC screening and treatment costs under two scenarios, starting in 2010: "current trends" (60% of the population up-to-date with screening recommendations) and "enhanced participation" (70% up-to-date). The population was scaled to the projected US population for each year between 2010 and 2060. Costs per year were derived by age group (50-64 and 65+ years).

Results. By 2060, the discounted cumulative total costs in the pre-Medicare population were $35.7 and $28.1 billion higher with enhanced screening participation, than in the current trends scenario ($252.1 billion with MISCAN and $239.5 billion with SimCRC, respectively). Due to CRC treatment savings with enhanced participation, cumulative costs in the Medicare population were $18.3 and $32.7 billion lower (current trends: $423.5 billion with MISCAN and $372.8 billion with SimCRC). Over the 50-year time horizon an estimated 60% (MISCAN) and 89% (SimCRC) of the increased screening costs could be offset by savings in Medicare CRC treatment costs.

Conclusions. Increased CRC screening participation in the pre-Medicare population could reduce CRC incidence and mortality, while the screening costs can be largely offset by long term Medicare treatment savings.

INTRODUCTION

Approximately 130,000 individuals were newly diagnosed with colorectal cancer (CRC) in the United States (US) in 2010.[1] Regular screening for CRC and its precursor lesions, adenomas, can prevent the disease or detect it at an earlier stage when treatment is potentially more effective. Current guidelines recommend screening for CRC beginning at age 50.[2-5] Although the proportion of individuals participating in screening is increasing, only 58% of the 50- to 75-year-old population is up-to-date with screening according to guidelines.[6]

In the US many individuals have not received recommended CRC screening when they become Medicare eligible at age 65. Some may initiate screening after becoming Medicare eligible, and others may never undergo a screening examination. In either case, Medicare will have to reimburse for the treatment of CRC that might have been prevented if screening had been done at an earlier age. Because CRC screening requires an investment in the short term with savings expected to accrue in the longer term, there may be financial incentive for public programs to support efforts to enhance screening participation before individuals turn 65. Over the past decade an increasing number of local, state and federal screening programs have been established to increase CRC screening participation.[7-9]

We aimed to estimate the long-term implications of enhanced CRC screening participation in the pre-Medicare population (50-64 years) on the distribution of costs related to CRC screening and treatment in the pre-Medicare and Medicare (age 65 and older) populations.

METHODS

We used two independently-developed microsimulation models, Microsimulation Screening Analysis Colon (MISCAN-Colon) and Simulation Model of CRC (SimCRC), to compare the annual and cumulative costs of CRC screening and treatment under current trends in screening participation (60% of the population up-to-date with screening) and under a scenario with enhanced screening participation among the pre-Medicare population (70% up-to-date). Using two models (i.e., a comparative modelling approach) serves as a sensitivity analysis on the underlying structural assumptions of the models, particularly pertaining to the natural history of CRC.

Microsimulation models

Both MISCAN and SimCRC are part of the Cancer Intervention and Surveillance Modelling Network (CISNET), a consortium funded by the National Cancer Institute. Detailed

model descriptions are provided in Appendix 1, in standardised model profiles available online[10] and in previous publications.[11-14] In brief, both models simulate the life histories of individuals from birth to death. CRC arises in the population according to the adenoma-carcinoma sequence.[15-16] More than one adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas can progress in size from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm), and some may eventually become malignant. A preclinical cancer has a chance of progressing through stages I to IV and may be detected by symptoms at any stage. After clinical diagnosis of CRC, survival depends on the stage at diagnosis. At any time during his/her life an individual may die of other causes.

The adenoma prevalence by age predicted by the models was calibrated to adenoma prevalence data from autopsy studies.[17-25] The adenoma prevalence in unscreened individuals aged 65 was 39.8% and 37.1% in MISCAN and SimCRC, respectively. The clinical CRC incidence by age and stage at diagnosis predicted by the models in the absence of screening was calibrated to data from the Surveillance, Epidemiology, and End-Results (SEER) program from 1975 to 1979, which represented an era before the introduction of screening.[26] The lifetime CRC incidence in unscreened, cancer-free individuals aged 65 was 5.8% and 5.7% in MISCAN and SimCRC, respectively. The relative survival after diagnosis of CRC by age and CRC stage was based on SEER data from individuals diagnosed in the period 2000-2003.

To ensure that differences in model results were due mainly to differences in the natural history component of the models, most inputs were standardised across the two models, including test characteristics (Appendix 1d), screening and follow-up assumptions and costs. In addition, we used a sample size of at least 600 million individuals, and used the same seeds for the random number generators in each run, in order to minimise the impact of stochastic noise on the model outcomes.

Study population

We simulated births between 1910 and 2010, resulting in a population aged 0-100 years in 2010, and 50-100 years in 2060. The size and age-composition of the population will change due to fluctuations in number of births and in life expectancy over time. In order to account for the combined effect of these population dynamics, for each year between 2010 and 2060 we scaled the number of individuals by age to the US census bureau population projections for that same period.[27] This resulted in approximately 40.2 million individuals aged 65 and older in 2010, increasing to 92.0 million in 2060.

Base-case analysis

The screening history prior to 2010 was based on 1987-2010 National Health Interview Survey (NHIS) data.[28] We assumed individuals would be screened with faecal occult

blood test (FOBT), sigmoidoscopy or colonoscopy. The overall screening participation increased over time to the point where in 2010 64% of the population aged 50 and older ever had a screening, and 58% of the population was up-to-date with screening according to guidelines.[2-5] From 2010 onward we modeled two screening scenarios: "current trends" and "enhanced participation" (Table 1). In the current trends scenario screening participation was assumed to level off at 65% ever screened and 60% up-to-date with screening by 2015.

In the enhanced participation scenario we assumed that the screening participation would increase to a level comparable with current mammography screening.[29] The screening participation was increased linearly between 2010 and 2015, to a point where 75% of the population ever had a screening, and 70% would be up-to-date with screening. Enhanced screening participation was applied to individuals aged 50-64. Individuals over age 65 in 2010, already enrolled in Medicare, would not change their screening behaviour. However, individuals who changed their screening behaviour before age 65 would continue their new behaviour as they age.

We assumed that screening in the enhanced participation scenario would be done with either FOBT or colonoscopy. Individuals previously screened with sigmoidoscopy would switch to colonoscopy from 2010 onwards. The proportions of individuals receiving FOBT and colonoscopy were assumed equal to the proportions observed in the 2010 NHIS (13% FOBT and 87% colonoscopy)[28] and were assumed to remain constant over time. Because the more sensitive Hemoccult Sensa is recommended over Hemoccult

Table 1. Screening participation among individuals aged 50 years and older in the current trends and enhanced participation scenarios.

	Current trends (%)		Enhanced participation (%)	
	2010	**2015-2060**	**2010**	**2015-2060**
Proportion of population:				
- Up-to-date with screening*	58	60	58	70
- Ever screened in lifetime	64	65	64	75
Proportion of screening participants currently screened with:				
- FOBT	13	13	13	13
- Endoscopy	87	87	87	87
Proportion of last endoscopies that were colonoscopies†	93	96	100	100
Adherence to diagnostic colonoscopy after positive FOBT or sigmoidoscopy	80	80	90	90
Adherence to surveillance colonoscopy	80	80	90	90

Abbreviations: FOBT, faecal occult blood test.

* Up-to-date with screening is defined as having had an FOBT within the past year, sigmoidoscopy in the past five years, or a colonoscopy within the past ten years.

† Endoscopy was either colonoscopy or sigmoidoscopy.

II,[2-5] we assumed that all individuals screened with FOBT as a result of the enhanced participation would receive Hemoccult Sensa.

Follow-up and surveillance

Adenomas can be detected and removed during diagnostic colonoscopy after a positive FOBT or sigmoidoscopy, or during primary colonoscopy screening. Depending on the number and size of adenomas detected, individuals would be recommended surveillance colonoscopy after five or ten years, according to current guidelines.[2-5] The adherence to diagnostic and surveillance colonoscopy was assumed to remain constant over time; 80% in the current trends scenario, and 90% under enhanced participation.

Expenditures

The analysis was conducted from a health-care system perspective and included only direct medical costs. The models capture the costs associated with screening and follow-up of positive screening tests (screening costs), and CRC-specific care by stage at diagnosis (treatment costs, Table 2). The costs for screening procedures in the Medicare population were based on Medicare payments in 2007.[37] In addition, the cost of negative screening colonoscopies were increased to reflect the removal of cost sharing for many patients as a result of the Affordable Care Act (ACA).[38]

CRC treatment costs per person, per year of care in the Medicare population were derived from a comparison of medical costs for CRC patients relative to Medicare beneficiaries without a CRC diagnosis matched by sex, age, and SEER registry area in the 1998-2003 SEER-Medicare data.[39] The costs vary by CRC stage at diagnosis and phase of care. The lifetime costs of CRC care per patient result from multiplying the cost per phase of care by the number of years lived in each phase. For example, a Medicare beneficiary diagnosed with stage III CRC and surviving one year in initial, one year in continuous and one year in terminal care before dying of CRC incurs a total of $76,304 ($26,122 + $2,132 + $48,050) for his CRC treatments.

The unit costs for screening procedures and CRC treatments in the pre-Medicare population were assumed to be 28% higher than in the Medicare population to reflect the difference in reimbursement rates between different payers; 74%, 6%, and 8% of the pre-Medicare population were insured by private insurance, Medicaid and Medicare respectively, and 12% was uninsured.[30] The reimbursement rate for these payers relative to Medicare was 140%, 100%, 90% and 90%, respectively (uninsured individuals were assumed to get Medicaid care).[31]

All cost data were inflation adjusted to 2010 US dollars by using the Consumer Price Index[40] and were assumed to remain constant over time.

Table 2. Unit costs of CRC screening and treatment, in 2010 US dollars, in the pre-Medicare and Medicare populations.

Screening costs (per procedure)	**Pre-Medicare population ($)***	**Medicare population ($)**
FOBT (Hemoccult II and Hemoccult Sensa)	6	5
FIT (only used in sensitivity analysis)	30	23
Stool DNA (only used in sensitivity analysis)†	629	493
Sigmoidoscopy without biopsy	270	211
Sigmoidoscopy with biopsy	300	235
Colonoscopy without polypectomy	876	687
Colonoscopy with polypectomy	905	710
Diagnostic test outside program	870	682
Treatment of complications from:‡		
- Colonoscopy	7,301	5,722
- Sigmoidoscopy	16,702	13,089

CRC treatment costs (per person, per year of care)§	**Pre-Medicare population ($)***				**Medicare population ($)**			
	Stage I	**Stage II**	**Stage III**	**Stage IV**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial phase	33,332	46,330	56,678	74,278	26,122	36,309	44,418	58,212
Continuing phase	2,721	2,537	3,626	11,239	2,132	1,988	2,841	8,808
Terminal phase, death CRC	61,312	61,138	64,421	86,458	48,050	47,914	50,486	67,757
Terminal phase, death other causes	15,106	13,213	17,480	46,934	11,839	10,355	13,699	36,782

Abbreviations: FOBT, faecal occult blood test; FIT, faecal immunochemical test; CRC, colorectal cancer.

* In the pre-Medicare population the reimbursement rate was assumed to be 128% of the Medicare reimbursement; 74%, 6%, and 8% of the pre-Medicare population were insured by private insurance, Medicaid and Medicare respectively, and 12% was uninsured.[31] The reimbursement rate for these payers relative to Medicare was 140%, 100%, 90% and 90% respectively (uninsured individuals were assumed to get Medicaid care).[32]

† Source for Medicare reimbursement rate of the stool DNA test: [33]

‡ Rate of serious non-fatal complications was assumed to be 2.4 per 1000 colonoscopies and 0.2 per 10.000 sigmoidoscopies.[34-36] Rate of fatal events was assumed to be 1 per 10.000 colonoscopies.[37]

§ Costs of care were divided into three phases of care: initial, continuing, and terminal care. The initial phase of care was defined as the first twelve months following diagnosis. The terminal phase of care was defined as the final twelve months of life, and the continuing phase was defined as all months between the initial and terminal phases. The terminal care phase was further subdivided into terminal care preceding CRC death and terminal care preceding death from other causes. For patients who survived less than 24 months after diagnosis, the final twelve months were allocated to the terminal phase because the care for patients with short survival is more similar

Outcomes

The main outcomes in this study were undiscounted annual costs and discounted cumulative costs for CRC screening and treatment in the US population from the year 2010 to 2060. The costs were divided into costs incurred in the pre-Medicare population (age

50-64) and Medicare population (age 65 and older). The costs in the enhanced participation scenario were compared to the costs in the current trends scenario. The proportion of screening investments offset by treatment savings, under the enhanced participation scenario, was calculated as the cumulative treatment savings in the Medicare population divided by the cumulative investment in screening costs in both the younger and older populations. All cumulative outcomes were discounted by 3% per year.[41]

Sensitivity analyses

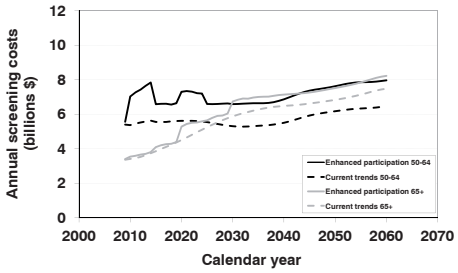
We performed a number of sensitivity analyses in order to evaluate the impact of parameter uncertainty on the model outcomes. We considered variations in screening behaviour, cost inputs, and test characteristics. In addition, we performed an analysis with a modified societal perspective, in which patient time costs were included. A detailed description of the assumptions in the sensitivity analyses is presented in Appendix 2.

RESULTS

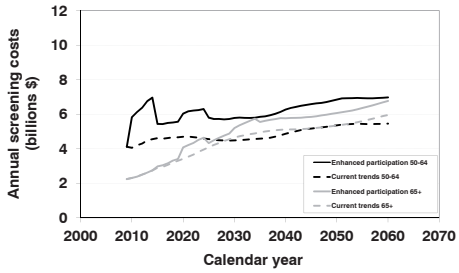
For the 50- to 64-year-old population in the current trends scenario, annual CRC screening costs increased from $5.4 billion in 2010 to $6.5 billion in 2060 (MISCAN; Figure 1A); similar results were found with SimCRC ($4.1 billion in 2010 to $5.5 billion in 2060; Figure 1B). Introducing a scenario of enhanced CRC screening participation for the pre-Medicare population, beginning in 2010, resulted in approximately $1.5 billion higher annual screening costs in 2060 in this population compared to current trends in both models. The effect of enhanced screening participation on treatment costs in the pre-Medicare population was relatively modest (Figure 1C-D); by the year 2060 annual treatment costs in the enhanced participation scenario were $0.2 billion lower compared to current trends (range reflects the use of two models).

For the Medicare population aged 65 and older in the current trends scenario, annual CRC screening costs increased from $2.3-3.4 billion in 2010 to $6.0-7.5 billion in 2060 (Figure 1A-B). Enhanced screening participation resulted in $0.7-0.8 billion higher annual screening costs in 2060. Annual CRC treatment costs in the current trends scenario increased from $7.4-7.6 billion in 2010 to $13.2-15.1 billion in 2060 (Figure 1C-D). Enhanced screening participation had a significant impact on treatment costs in the Medicare population; annual treatment costs in 2060 were $2.7-4.0 billion lower in the enhanced participation scenario compared to current trends. The lower annual treatment costs offset the increased screening costs in the Medicare population 12-14 years after the introduction of enhanced screening participation (Figure 1E-F).

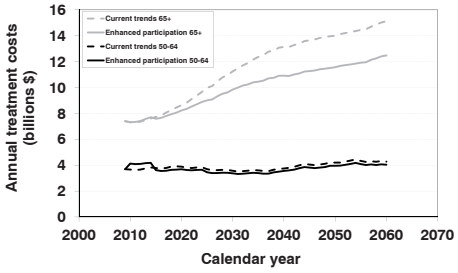
When considering discounted cumulative costs over the 50-year time horizon, the total costs in the pre-Medicare population was $35.7 billion, or 14.2% ($35.7/$252.1),



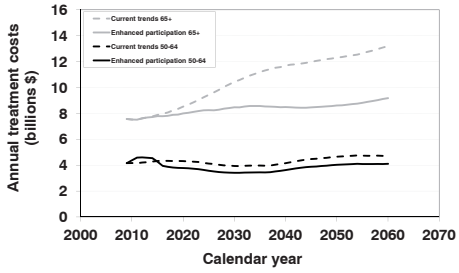
Panel A - Annual CRC screening costs (MISCAN)*



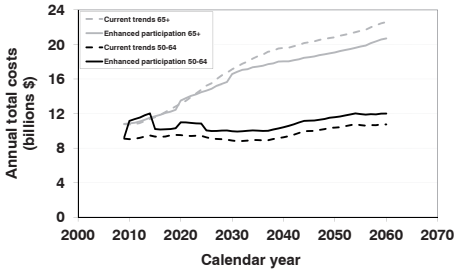
Panel B - Annual CRC screening costs (SimCRC)*



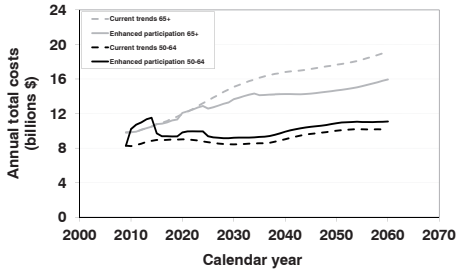
Panel C - Annual CRC treatment costs (MISCAN)†



Panel D - Annual CRC treatment costs (SimCRC)†



Panel E - Annual total CRC-related costs (MISCAN)



Panel F - Annual total CRC-related costs (SimCRC)

Figure 1. Annual CRC screening, treatment and total costs in the current trends and enhanced participation scenarios, in the US population of 50 years and older.

The black curves represent costs incurred in the pre-Medicare population (50-64 years) and the gray curves represent costs incurred in the Medicare population (65+years). All costs are undiscounted and are expressed in 2010 US dollars.

*The peaks in the annual screening costs in the enhanced participation scenario are the effect of increased colonoscopy screening in the population aged 50-64 at the start of the scenario (screening participation is increased over five years), and their subsequent screening round ten years later. Annual screening costs remain higher after that, because of new 50 year old individuals taking up screening each year.

†The increasing trend in screening and treatment costs in the Medicare population (and to a lesser extent also in the pre-Medicare population) in the current trends scenario, reflects the increasing proportion of the population reaching old age.

Abbreviations: CRC, colorectal cancer.

higher in the enhanced participation scenario compared to current trends with MISCAN (Table 3, see Appendix 3 and 4 for undiscounted results and intermediate outcomes). With SimCRC the total pre-Medicare costs were $28.1 billion, or 11.7% ($28.1/$239.5), higher in the enhanced participation scenario compared to current trends. Alternatively, in the Medicare population, the cumulative total costs in the enhanced participation scenario compared to current trends were $18.3 billion, or 4.3% ($18.3/$423.5), lower with MISCAN and $32.7 billion, or 8.8% ($32.7/$372.8), lower with SimCRC. Overall, the

Table 3. Cumulative CRC screening, treatment, and total costs (billions of 2010 US dollars) at ten year intervals in the current trends and enhanced participation scenarios (3% discounted).

	MISCAN ($)						SimCRC ($)					
	2010	**2020**	**2030**	**2040**	**2050**	**2060**	**2010**	**2020**	**2030**	**2040**	**2050**	**2060**
Current trends scenario												
Pre-Medicare population (50-64 years)												
Screening	5.4	52.8	87.7	113.0	133.8	150.3	4.1	42.7	71.6	93.5	111.6	125.8
Treatment	3.7	35.9	59.4	76.4	90.5	101.8	4.2	40.6	66.8	85.7	101.3	113.7
Total	9.0	88.7	147.1	189.4	224.3	252.1	8.2	83.3	138.4	179.1	212.9	239.5
Medicare population (65+ years)												
Screening	3.4	36.8	70.2	99.7	123.1	141.8	2.3	26.9	52.9	76.2	94.5	109.2
Treatment	7.3	74.2	137.5	195.8	243.7	281.7	7.5	75.2	135.4	188.2	230.3	263.6
Total	10.7	110.9	207.7	295.6	366.7	423.5	9.8	102.0	188.3	264.4	324.8	372.8
Total population (50+ years)												
Screening	8.8	89.6	157.9	212.7	256.8	292.1	6.4	69.5	124.5	169.7	206.1	235.0
Treatment	11.0	110.0	196.9	272.2	334.2	383.5	11.7	115.8	202.2	273.8	331.7	377.2
Total	19.8	199.6	354.9	485.0	591.0	675.6	18.1	185.3	326.7	443.5	537.7	612.2
Difference between enhanced screening and current trends scenario												
Pre-Medicare population (50-64 years)												
Screening (A)	1.7	14.5	23.3	29.5	34.5	38.5	1.8	14.3	23.1	29.2	34.2	38.2
Treatment	0.5	1.0	−0.3	−1.3	−2.1	−2.7	0.2	−0.4	−3.9	−6.4	−8.4	−10.1
Total	2.1	15.5	23.0	28.2	32.5	35.7	2.0	13.9	19.2	22.9	25.8	28.1
Medicare population (65+ years)												
Screening (B)	0.1	1.7	4.9	8.4	10.7	12.6	0.0	0.9	4.0	7.2	9.6	11.6
Treatment (C)	0.0	−1.1	−7.1	−15.9	−24.2	−30.9	0.0	−1.5	−9.4	−21.9	−34.2	−44.3
Total	0.1	0.5	−2.1	−7.5	−13.5	−18.3	0.0	−0.6	−5.4	−14.7	−24.6	−32.7
Total population (50+ years)												
Screening	1.8	16.1	28.2	37.9	45.2	51.0	1.8	15.2	27.1	36.4	43.8	49.7
Treatment	0.5	−0.1	−7.4	−17.2	−26.3	−33.6	0.2	−1.9	−13.3	−28.3	−42.7	−54.4
Total	2.3	16.0	20.8	20.7	18.9	17.4	2.0	13.3	13.8	8.2	1.2	−4.6
%offset (C/(A+B))*	-	7%	25%	42%	54%	60%	-	10%	35%	60%	78%	89%

*The percent of increased screening costs in the pre-Medicare and Medicare populations offset by Medicare treatment savings.

proportion of pre-Medicare and Medicare screening costs that were offset by Medicare treatment savings increased from 7-10% after ten years, to 25-35% after 20 years, to 60-89% after 50 years (Table 3, bottom row).

Sensitivity analyses

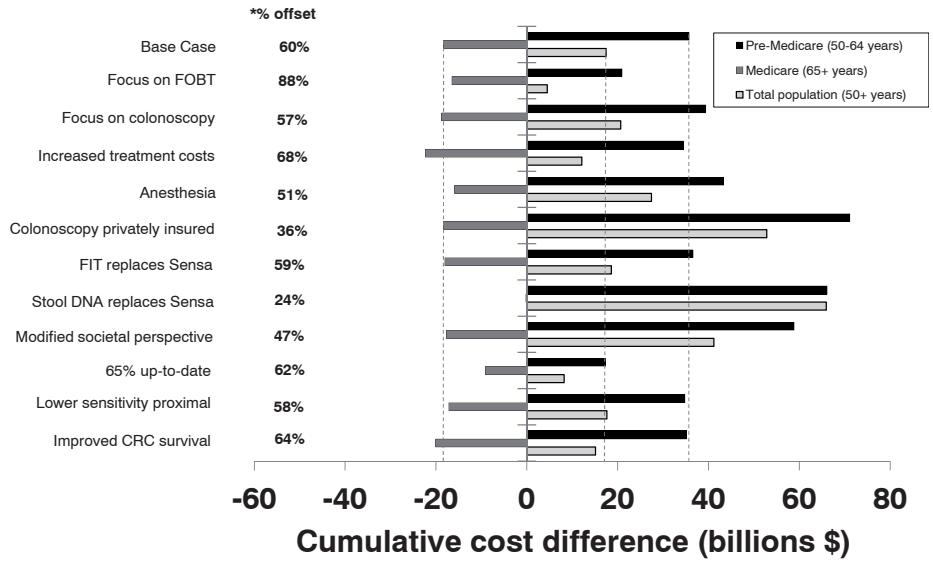
The cumulative cost difference of enhanced participation compared to current trends was robust to most alternative assumptions considered (Figure 2, see Appendix 2 for more detailed outcomes). However, when we assumed that all individuals changing their screening behaviour in the enhanced participation scenario would be screened with the Cologuard multitarget stool DNA test (with a three-year interval and Medicare reimbursement rate of $493) the proportion of cumulative screening costs offset by Medicare treatment savings after 50 years decreased from 60% (base case) to 24% with MISCAN, and from 89% to 34% with SimCRC.

In addition, the assumption that reimbursement rates for colonoscopy procedures in privately insured individuals were three times higher than the Medicare reimbursement rate, had no impact on expenditures in the Medicare population, but did decrease the proportion of cumulative screening costs offset by Medicare treatment savings from 60% (base case) to 36% with MISCAN, and from 89% to 52% with SimCRC.

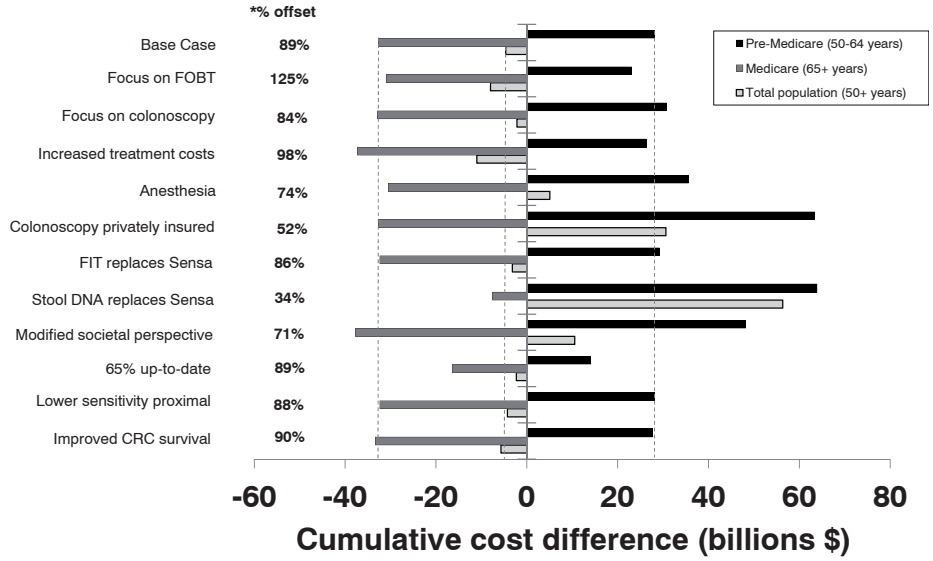
DISCUSSION

Using two independently developed microsimulation models we demonstrated the potential medical cost impact of enhancing CRC screening participation among the pre-Medicare population. While increased screening participation from 60% to 70% required a net investment in the pre-Medicare population, total costs in the Medicare population decreased, due to savings in treatment costs. According to MISCAN and SimCRC, over a 50-year time horizon the cumulative Medicare treatment savings were estimated to offset, respectively, 60% and 89% of the increased screening costs.

Two studies previously investigated the extent to which investments in pre-Medicare screening could be offset by treatment savings in the Medicare population.[45-46] Ladabaum et al.[45] found relatively fewer savings compared to our analysis, while Dobson et al.[46] found all screening costs to be offset by treatment savings before individuals reach age 75. Our study design differs from those two studies in that we take into account expected changes in the national population size and age distribution over time. The Ladabaum study considered a population with a fixed population size and age distribution, and the Dobson study considered a subgroup of the population (only those aged 50-64 years at one point in time) that was followed through time. In addition, our analysis accounted for the removal of patient cost sharing for screening endoscopies



Panel A - Outcomes for MISCAN



Panel B - Outcomes for SimCRC.

Figure 2. Results of sensitivity analyses. Cumulative cost difference (billions of 2010 US dollars, 3% discounted) of the enhanced participation scenario, compared to current trends by the year 2060.

Figure 2: legends

Base case: Under enhanced participation the proportion of individuals up-to-date with screening is increased to 70%, compared to 60% under current trends. In both scenarios 87% of screening participants receive colonoscopy and 13% receive FOBT screening.

Focus on FOBT: All individuals changing their screening behaviour in the enhanced participation scenario would be screened with Hemoccult Sensa. Individuals who were screened with Hemoccult II or endoscopy in the current trends scenario and did not change their screening behaviour, would continue to receive Hemoccult II and endoscopy screening respectively.

Focus on colonoscopy: All individuals changing their screening behaviour in the enhanced participation scenario would be screened with colonoscopy. Individuals who were screened with Hemoccult II in the current trends scenario and did not change their screening behaviour, would continue to receive Hemoccult II screening.

Increased treatment costs: Treatment costs for terminal care in all stages and initial care in stage IV CRC were increased by 30% to reflect the increasing proportion of patients receiving surgery and adjuvant chemotherapy and the increasing costs of these therapies.[42, 43]

Anesthesia: Costs of colonoscopy procedures were increased by $152 (with polypectomy) and $135 (without polypectomy) to reflect use of monitored anesthesia.†

Colonoscopy privately insured: Colonoscopy costs in the privately insured pre-Medicare population were increased to three times the Medicare reimbursement rate to reflect the higher reimbursement rate for privately insured individuals.

FIT replaces Sensa: All individuals screened with Hemoccult Sensa in the base case received FIT instead. The Medicare reimbursement rate for FIT was assumed to be $23, compared to $5 for Hemoccult Sensa.

Stool DNA replaces Sensa: All individuals changing their screening behaviour in the enhanced participation scenario would be screened with the Cologuard multitarget stool DNA test. Individuals who were screened with Hemoccult II or endoscopy in the current trends scenario and did not change their screening behaviour, would continue to receive Hemoccult II and endoscopy screening respectively. The screening interval with stool DNA was three years and the assumed Medicare reimbursement rate was $493.[33]

Modified societal perspective: Next to direct medical costs, patient time costs and beneficiary copayments were included in the analysis. An overview of cost inputs is provided in Appendix Table 2.2.

65% Up-to-date with screening: 65% of individuals were up-to-date with screening and 70% were ever screened in the enhanced participation scenario, compared to 70% and 75% respectively in the base case.

Lower sensitivity proximal lesions: The sensitivity of colonoscopy for proximal lesions was decreased to 65%, 77%, and 92% for small, medium, and large adenomas and CRC,[44] compared to 75%, 85%, and 95% for distal lesions (same as base case values for entire colon and rectum).

Improved CRC survival: CRC relative survival by age and stage at diagnosis was increased by 25% for all individuals.

Abbreviations: FOBT, faecal occult blood test; CRC, colorectal cancer; FIT, faecal immunochemical test.

*The percent of increased screening costs in the pre-Medicare and Medicare populations offset by Medicare treatment savings.

†Based on personal communication with Joel V. Brill MD, AGAF, Predictive Health LLC, Paradise Valley AZ. 2011 estimates.

for many patients resulting from the ACA, and for relative differences in reimbursement rates between Medicare and privately-insured individuals. Our study design differs in order to provide a better depiction of the projected impact from increasing screening in the pre-Medicare population on costs across payers on a national level. The Dobson study has not been peer-reviewed, but it is available in a summary format online.[46] It was presented to a Congressional committee on CRC awareness,[47] signifying the relevance of the issue to health policy.

In 2012, the Health Resources and Services Administration began requiring community health centres to track and report CRC screening rates in the Uniform Data System.[48] This system might play an important role in identifying areas where screening is particularly underused, and help prioritising targeted interventions. Federal, state and local public health programs can support public health and health systems partnership to implement evidence based interventions recommended by The Community Preventive Services Task Force, promote strategies to increase and improve the quality of CRC screening, and support the adoption of organised CRC screening systems.

Despite the randomised controlled trial data that we used for quantification of our models, there is still remaining uncertainty about the natural history of CRC and how it interacts with screening. Using two independently-developed models, but with common inputs (i.e., a comparative modelling approach), serves as a sensitivity analysis on the underlying structural assumptions of the models which cannot be directly obtained from the literature. Both models have been calibrated to CRC incidence rates from a pre-screening era (1975-1979), and both models have been extensively validated against clinical trial data on Hemoccult II screening. The main difference between the two models that explains the differences in results is the average time it takes for an adenoma to develop into clinically detectable CRC (the adenoma dwell time). If for example, a small adenoma is missed during a screening colonoscopy, a longer dwell time provides more time for that adenoma to be detected at a subsequent colonoscopy, before it progresses into CRC, and thereby preventing the costs associated with CRC treatment. Because SimCRC assumes a longer dwell time than MISCAN, the same number of additional screening procedures results in more treatment savings in SimCRC relative to MISCAN. Overall the differences in natural history assumptions between the models result in a 29%-point (89%-60%) difference in the overall proportion of pre-Medicare screening investments that is estimated to be offset by treatment savings in the Medicare population.

This study has four limitations of note. Firstly, there are no randomised controlled data available yet regarding the effect on incidence and mortality from colonoscopy screening in the general population. However, there are data available for sigmoidoscopy.[49] We assumed the sensitivity of sigmoidoscopy in the distal colon could be extrapolated to the proximal colon when using colonoscopy. Although the sensitivity analysis with reduced sensitivity for proximal lesions demonstrated limited impact of reduced sensi-

tivity, there are studies which suggest the effectiveness of colonoscopy in the proximal colon is lower compared to the distal colon and rectum[50], which might be caused by differences in progression rate or genetic characteristics of proximal cancers. If the incidence and mortality reduction from colonoscopy is lower for proximal lesions, we would have overestimated the amount of treatment savings resulting from increasing colonoscopy screening. Secondly, we did not account for potential future changes in screening recommendations. Because of advances in technology and increasing scientific knowledge, it is likely that screening recommendations pertaining to the type of screening test used, recommended screening schedule, and/or specific recommendations for different subgroups in a population would change within our time horizon. We used a long time horizon, because it takes years for screening to have an effect on treatment savings. However, because of the inability to predict future developments in screening policies we assumed no changes in policy over time. Thirdly, we did not perform a probabilistic sensitivity analysis. In order to provide stable outcomes over time and for different age groups, we needed runs with a large sample size (at least 600 million individuals). Given the time required to simulate this many individuals in each run, and the large number of draws that need to be performed in a probabilistic sensitivity analysis, such an analysis would require a huge computational effort. In addition, data on the probability distributions of most of the parameter values are lacking, which makes the interpretation of a probabilistic sensitivity analysis difficult and the outcome of limited added value. The most uncertain assumptions of the models pertain to the natural history of CRC, and we evaluated their impact by using two independently developed simulation models. Finally, our current trends scenario did not take into account that uptake and adherence with CRC screening guidelines may increase over time due to the enactment of the ACA that abolished cost sharing for preventive services like CRC screening for many patients. However, the results of our analysis of the impact of enhanced participation could shed light on the anticipated effects of this act on future CRC costs; irrespective of which payer bears the costs of screening, the majority of treatment savings will occur later in life, mainly after individuals have reached Medicare eligibility.

In conclusion, increasing screening participation in the pre-Medicare population could reduce CRC incidence and mortality, while an estimated %60 to 89% of the increased screening costs can be offset by long term savings in Medicare CRC treatment costs.

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APPENDIX

Test characteristics of screening tests.

The sensitivity and specificity of the screening tests used in the models are presented in Appendix Table 1. It is assumed that the test characteristics were independent of age and past screening. In addition, it is assumed that small adenomas do not bleed and cannot be detected by FOBT and FIT. The sensitivity of FOBT and FIT for adenomas ≤5 mm is based on the false-positive rate (that is, 1 - specificity). Hyperplastic polyps, which do not follow the adenoma-carcinoma sequence, are not modeled explicitly but are reflected in the specificity of endoscopic tests.[1] Additional biopsy costs were assumed for procedures without adenomas detected.

Appendix Table 1. Sensitivity and specificity of screening tests used in the models.

Screen test	Sensitivity (%)				Specificity (%)
	Adenoma ≤5 mm	Adenoma 6-9 mm	Adenoma ≥10 mm	Preclinical CRC	
FOBT HCII	2	5	12	40	98
FOBT Sensa	8	12	24	70	92
FIT*	5	10	22	70	95
Stool DNA*	12	26	36	92	88
Sigmoidoscopy	75	85	95	95	92
Colonoscopy	75	85	95	95	90

CRC = colorectal cancer; FOBT HCII = faecal occult blood test, Hemoccult II; FOBT Sensa = faecal occult blood test, Hemoccult Sensa; FIT = faecal immunochemical test.

* FIT and stool DNA were only used in the sensitivity analyses. The test characteristics of stool DNA were fitted to the positivity and detection rate of the Cologuard multitarget stool DNA test, developed by Exact Sciences (Madison, WI).[2]

Appendix Table 2.1. Description of assumptions in the sensitivity analyses.

Sensitivity analysis	Description
Base case	Under enhanced participation the proportion of individuals up-to-date with screening is increased to 70%, compared to 60% under current trends. In both scenarios 87% of screening participants receive colonoscopy and 13% receive FOBT screening.
Focus on FOBT	All individuals changing their screening behaviour in the enhanced participation scenario would be screened with Hemoccult Sensa. Individuals who were screened with Hemoccult II or endoscopy in the current trends scenario and did not change their screening behaviour, would continue to receive Hemoccult II and endoscopy screening respectively.
Focus on colonoscopy	All individuals changing their screening behaviour in the enhanced participation scenario would be screened with colonoscopy. Individuals who were screened with Hemoccult II in the current trends scenario and did not change their screening behaviour, would continue to receive Hemoccult II screening.
Increased treatment costs	Treatment costs for terminal care in all stages and initial care in stage IV CRC were increased by 30% to reflect the increasing proportion of patients receiving surgery and adjuvant chemotherapy and the increasing costs of these therapies.[3-4]
Colonoscopy with anesthesia	Costs of colonoscopy procedures were increased by $152 (with polypectomy) and $135 (without polypectomy) to reflect use of monitored anesthesia*
Colonoscopy privately insured	Colonoscopy costs in the privately insured pre-Medicare population were increased to three times the Medicare reimbursement rate, to reflect the higher reimbursement rate for privately insured individuals
FIT replaces Sensa	All individuals screened with Hemoccult Sensa in the base case received FIT instead. The Medicare reimbursement rate for FIT was assumed to be $23, compared to $5 for Hemoccult Sensa.
Stool DNA replaces Sensa	All individuals changing their screening behaviour in the enhanced participation scenario would be screened with stool DNA. Individuals who were screened with Hemoccult II or endoscopy in the current trends scenario and did not change their screening behaviour, would continue to receive Hemoccult II and endoscopy screening respectively. The screening interval with stool DNA was three years and the assumed Medicare reimbursement rate was $493.[5]
Modified societal perspective	Next to direct medical costs, patient time costs and beneficiary copayments were included in the analysis. An overview of cost inputs is provided in Appendix Table 2.2.
65% up-to-date with screening	65% of individuals were up-to-date with screening and 70% were ever screened in the enhanced participation scenario, compared to 70% and 75% respectively in the base case.
Lower sensitivity proximal lesions	The sensitivity of colonoscopy for proximal lesions was decreased to 65%, 77%, and 92% for small, medium, and large adenomas and CRC,[6] compared to 75%, 85%, and 95% for distal lesions (same as base case values for entire colon and rectum).
Improved CRC survival	CRC relative survival by age and stage at diagnosis was increased by 25% for all individuals.

FOBT = faecal occult blood test; CRC = colorectal cancer; FIT = faecal immunochemical test; CRC = colorectal cancer.

* Based on personal communication with Joel V. Brill MD, AGAF, Predictive Health LLC, Paradise Valley AZ. 2011 estimates.

Appendix Table 2.2. Cost inputs used in the sensitivity analysis "modified societal perspective". Unit costs of CRC screening and treatment, in 2010 US dollars, in the pre-Medicare and Medicare populations.

Screening costs (per procedure)	**Pre-Medicare population ($)***	**Medicare population ($)**
FOBT (Hemoccult II and Sensa)	24	23
Sigmoidoscopy without biopsy	48	41
Sigmoidoscopy with biopsy	725	667
Colonoscopy without polypectomy	1,332	1,143
Colonoscopy with polypectomy	831	749
Diagnostic test outside program	1,587	1,343
Treatment of complications from:†		
- Colonoscopy	1,544	1,308
- Sigmoidoscopy	9,328	7,749

CRC treatment costs (per person, per year of care‡)	**Pre-Medicare population ($)***				**Medicare population ($)**			
	Stage I	**Stage II**	**Stage III**	**Stage IV**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Initial phase	44,082	58,881	71,290	92,552	34,547	46,145	55,870	72,533
Continuing phase	3,709	3,489	4,840	14,485	2,907	2,734	3,793	11,352
Terminal phase, death CRC	76,201	75,902	80,012	105,159	59,719	59,484	62,705	82,413
Terminal phase, death other causes	23,572	21,335	26,261	59,760	18,473	16,720	20,581	46,834

FOBT = faecal occult blood test; CRC = colorectal cancer.

Direct medical costs were based on the values presented in Table 2 in the main text. The value of an hour of patient or caregiver time was assumed to be $18, the 2010 U.S. median hourly wage rate for civilians.[7] We assumed 24 hours of patient and escort time for colonoscopies and sigmoidoscopies,[8] and one hour for stool-based tests. In addition, we assumed $22.54 for bowel preparation,[9] and 25% beneficiary copayment for colonoscopies and sigmoidoscopies. CRC treatment costs in the Medicare population have been published before.[9] Estimates include beneficiary copayments, and 244, 19, and 283 hours of patient time in the initial, continuous and terminal phases of care respectively.[10-11] Treatment costs for the pre-Medicare population were inflated to account for differences in reimbursement rates between insurers in the same way as was done in the estimates of direct medical costs (Table 2 in the main text).

Appendix Table 2.3. Results of the sensitivity analysis for MISCAN. Cumulative cost difference (billions of 2010 US dollars, 3% discounted) of the enhanced participation scenario, compared to current trends by the year 2060.

	Base case	Focus on FOBT	Focus on colonoscopy	Increased treatment costs	Colonoscopy with anesthesia	Colonoscopy privately insured	FIT replaces Sensa	Stool DNA replaces Sensa	Modified societal perspective	65% up-to-date with screening	Lower sensitivity proximal lesions	Improved CRC survival
Pre-Medicare population (50-64 years)												
Screening	38.5	19.9	43.1	38.5	46.1	74.0	39.4	64.9	62.0	18.7	37.0	38.5
Treatment	−2.7	1.0	−3.7	−4.0	−2.8	−2.9	−2.7	1.2	−3.1	−1.4	−2.2	−3.3
Total	35.7	21.0	39.4	34.4	43.3	71.1	36.6	66.1	58.9	17.4	34.8	35.1
Medicare population (65+ years)												
Screening	12.6	7.8	13.7	12.6	15.1	12.6	12.8	20.7	22.0	6.3	9.8	12.6
Treatment	−30.9	−24.3	43.1	−34.9	−31.0	−30.9	−30.9	−20.9	−39.7	−15.4	−27.0	−32.6
Total	−18.3	−16.5	−18.7	−22.3	−15.9	−18.3	−18.0	0.2	−17.7	−9.1	−17.2	−20.0
Total population (50+ years)												
Screening	51.0	27.8	56.8	51.0	61.2	86.6	52.2	85.7	84.0	25.0	46.9	51.0
Treatment	−33.6	−23.3	39.4	−38.9	−33.7	−33.8	−33.6	−19.7	−42.8	−16.8	−29.2	−35.9
Total	17.4	4.5	20.7	12.1	27.4	52.8	18.6	65.9	41.2	8.2	17.6	15.1

Screening, treatment and total costs are presented for the pre-Medicare (50-64 years), Medicare (65+ years) and total (50+ years) population.

Appendix Table 2.4. Results of the sensitivity analysis for SimCRC. Cumulative cost difference (billions of 2010 US dollars, 3% discounted) of the enhanced participation scenario, compared to current trends by the year 2060.

	Base case	Focus on FOBT	Focus on colonoscopy	Increased treatment costs	Colonoscopy with anesthesia	Colonoscopy privately insured	FIT replaces Sensa	Stool DNA replaces Sensa	Modified societal perspective	65% up-to-date with screening	Lower sensitivity proximal lesions	Improved CRC survival
Pre-Medicare population (50-64 years)												
Screening	38.2	23.0	41.7	38.2	45.7	73.7	39.3	68.1	60.8	19.1	37.4	37.4
Treatment	−10.1	−6.4	−10.9	−11.9	−10.2	−10.4	−10.1	−4.2	−12.6	−5.1	−9.7	−10.1
Total	28.1	23.0	30.8	26.3	35.6	63.3	29.2	63.9	48.2	14.0	27.7	27.3
Medicare population (65+ years)												
Screening	11.6	9.3	12.3	11.6	13.9	11.6	11.9	24.1	20.0	5.8	11.2	12.1
Treatment	−44.3	−40.3	41.7	−48.9	−44.4	−44.3	−44.3	−31.7	−57.7	−22.1	−42.6	−44.5
Total	−32.7	−31.0	−32.9	−37.3	−30.5	−32.7	−32.4	−7.6	−37.7	−16.4	−31.5	−32.4
Total population (50+ years)												
Screening	49.7	32.3	53.9	49.7	59.6	85.2	51.2	92.2	80.9	24.9	48.6	49.4
Treatment	−54.4	−46.6	30.8	−60.8	−54.5	−54.6	−54.4	−35.9	−70.3	−27.2	−52.3	−54.6
Total	−4.6	−8.0	−2.2	−11.0	5.1	30.6	−3.2	56.3	10.5	−2.3	−3.7	−5.1

Screening, treatment and total costs are presented for the pre-Medicare (50-64 years), Medicare (65+ years) and total (50+ years) population.

Appendix Table 3. Cumulative CRC screening and treatment costs (billions of 2010 US dollars) at ten year intervals in the current trends and enhanced participation scenarios, in the US population of 50 years and older (undiscounted).

	MISCAN ($)						SimCRC ($)					
	2010	**2020**	**2030**	**2040**	**2050**	**2060**	**2010**	**2020**	**2030**	**2040**	**2050**	**2060**
Current trends scenario												
Pre-Medicare population (50-64 years)												
Screening	5.4	61.0	115.9	169.5	228.7	292.1	4.1	49.4	95.0	141.3	193.1	247.4
Treatment	3.7	41.5	78.5	114.5	154.8	197.8	4.2	47.0	88.1	128.1	172.7	219.9
Total	9.0	102.5	194.4	284.0	383.5	489.9	8.2	96.4	183.1	269.4	365.8	467.3
Medicare population (65+ years)												
Screening	3.4	42.8	95.8	158.5	225.0	296.8	2.3	31.4	72.6	122.1	174.2	230.7
Treatment	7.3	86.0	186.5	310.4	446.8	592.4	7.5	87.1	182.5	294.5	414.6	541.9
Total	10.7	128.9	282.3	468.9	671.8	889.2	9.8	118.5	255.1	416.6	588.9	772.6
Total population (50+ years)												
Screening	8.8	103.8	211.7	328.0	453.7	588.8	6.4	80.8	167.7	263.5	367.3	478.1
Treatment	11.0	127.5	265.0	424.9	601.7	790.2	11.7	134.1	270.6	422.5	587.4	761.8
Total	19.8	231.4	476.8	752.9	1055.3	1379.1	18.1	214.9	438.2	686.0	954.6	1239.9
Difference between enhanced screening and current trends scenario												
Pre-Medicare population (50-64 years)												
Screening (A)	1.7	16.4	30.2	43.3	57.6	72.7	1.8	16.1	29.9	42.8	57.1	72.1
Treatment	0.5	0.8	−1.2	−3.2	−5.5	−8.0	0.2	−0.9	−6.3	−11.6	−17.5	−23.9
Total	2.1	17.3	28.9	40.1	52.1	64.6	2.0	15.2	23.5	31.3	39.6	48.3
Medicare population (65+ years)												
Screening (B)	0.1	2.0	7.1	14.4	20.9	28.1	0.0	1.2	5.9	12.7	19.5	27.2
Treatment (C)	0.0	−1.5	−11.1	−30.0	−53.7	−79.2	0.0	−1.9	−14.7	−41.5	−76.7	−115.2
Total	0.1	0.5	−4.0	−15.7	−32.8	−51.1	0.0	−0.7	−8.8	−28.8	−57.2	−88.1
Total population (50+ years)												
Screening	1.8	18.5	37.3	57.7	78.6	100.8	1.8	17.3	35.7	55.5	76.6	99.3
Treatment	0.5	−0.6	−12.4	−33.3	−59.3	−87.2	0.2	−2.7	−21.0	−53.1	−94.2	−139.1
Total	2.3	17.8	24.9	24.4	19.3	13.5	2.0	14.5	14.7	2.4	−17.6	−39.8
% offset (C/(A+B))*	-	8%	30%	52%	68%	79%	-	11%	41%	75%	100%	116%

* The proportion of increased screening costs in the pre-Medicare and Medicare populations offset by savings in Medicare treatment costs.

Appendix Table 4.1. Intermediate model results from MISCAN. Cumulative number (x1,000) of tests performed and life years lived in CRC care, between 2010 and 2060.

	Pre-Medicare population (50-64 years)			Medicare population (65+ years)		
	Current trends	Enhanced participation	Difference	Current trends	Enhanced participation	Difference
FOBTs	63,633	128,287	64,654	79,477	99,684	20,208
Sigmoidoscopies	5,037	4,405	−632	5,431	4,822	−608
Colonoscopies						
- Screening	244,439	301,443	57,003	247,608	243,610	−3,998
- Diagnostic	3,983	9,291	5,309	7,819	8,497	678
- Surveillance	69,567	87,038	17,471	157,129	197,389	40,260
CRC stage at diagnosis						
- Stage I	31.8%	38.3%	6.5%	29.5%	34.7%	5.2%
- Stage II	29.1%	28.2%	−0.8%	32.5%	31.6%	−0.9%
- Stage III	21.8%	19.9%	−1.9%	20.3%	18.7%	−1.6%
- Stage IV	17.3%	13.6%	−3.7%	17.7%	15.0%	−2.7%
Life years in CRC care						
- Initial phase	2,131	2,134	4	5,283	4,539	−744
- Continuing phase	16,330	17,217	887	78,753	74,867	−3,886
- Terminal phase, death CRC	541	462	−80	2,003	1,554	−449
- Terminal phase, death other causes	172	178	6	6,900	6,414	−487
Life years in CRC care						
- Stage I	7,224	8,316	1,092	38,050	39,516	1,466
- Stage II	6,498	6,508	10	33,085	29,402	−3,682
- Stage III	4,511	4,370	−141	18,738	16,114	−2,624
- Stage IV	941	797	−144	3,066	2,341	−725

Appendix Table 4.2. Intermediate model results from SimCRC. Cumulative number (x1,000) of tests performed and life years lived in CRC care, between 2010 and 2060.

	Pre-Medicare population (50-64 years)			Medicare population (65+ years)		
	Current trends	**Enhanced participation**	**Difference**	**Current trends**	**Enhanced participation**	**Difference**
FOBTs	92,897	173,317	80,421	103,562	131,166	27,604
Sigmoidoscopies	18,953	16,647	−2,307	20,124	18,066	−2,058
colonoscopies						
- Screening	205,090	263,676	58,586	151,251	157,001	5,749
- Diagnostic	4,698	10,656	5,958	9,079	9,698	619
- Surveillance	53,970	67,236	13,266	155,157	184,671	29,513
CRC stage at diagnosis						
- Stage I	32.3%	39.0%	6.7%	28.0%	32.7%	4.7%
- Stage II	31.6%	29.9%	−1.7%	32.0%	31.0%	−0.9%
- Stage III	18.8%	16.7%	−2.1%	20.2%	18.8%	−1.5%
- Stage IV	17.4%	14.5%	−2.9%	19.8%	17.5%	−2.3%
Life years in CRC care						
- Initial phase	2,206	1,988	−218	4,556	3,416	−1,140
- Continuing phase	20,198	20,228	30	75,781	66,397	−9,384
- Terminal phase, death CRC	639	524	−115	1,811	1,289	−522
- Terminal phase, death other causes	206	200	−6	6,502	5,613	−888
Life years in CRC care						
- Stage I	9,492	10,282	789	36,990	35,219	−1,771
- Stage II	8,533	8,027	−506	32,832	26,916	−5,916
- Stage III	4,155	3,748	−407	15,902	12,480	−3,422
- Stage IV	1,068	883	−185	2,926	2,100	−825

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Chapter 3

State disparities in colorectal cancer rates - contribution of risk factors, screening and survival differences

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Submitted

ABSTRACT

Background: Considerable disparities exist in colorectal cancer (CRC) incidence and mortality rates between states in the US. We quantified how the disparity in CRC rates between Louisiana and New Jersey would be affected if differences in risk factors, screening and stage-specific CRC survival between states were eliminated.

Methods: We used the MISCAN-Colon microsimulation model to estimate CRC incidence and mortality rates in Louisiana from 1995-2009 assuming Louisiana had the same trends as observed in New Jersey for 1) smoking and obesity; 2) CRC screening; 3) stage-specific CRC survival; and 4) a combination of all three.

Results: In 2009 the observed CRC incidence and mortality rate in Louisiana were 141.4 cases and 61.9 deaths per 100,000 individuals, respectively. With the same trends in risk factors and screening as New Jersey, the CRC incidence rate in Louisiana was reduced by 3.5% and 15.2%. New Jersey trends in risk factors, screening and survival reduced the CRC mortality rate in Louisiana by 3.0%, 10.8%, and 17.4% respectively. With all trends combined, the modeled rates per 100,000 individuals in Louisiana became lower than the observed rates in New Jersey for both incidence (116.4 versus 130.0) and mortality (44.7 versus 55.8).

Conclusions: The disparity in CRC incidence and mortality rates between Louisiana and New Jersey could be eliminated if Louisiana would be able to achieve New Jersey levels of risk factors, screening and CRC relative survival. Priority should be given to enabling Southern states to achieve screening and survival rates equal to the North-eastern states.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States (U.S.). It is estimated that 136,830 CRC cases will be newly diagnosed and 50,310 persons will die of the disease in 2014.[1] While age-standardised CRC incidence and mortality rates have been decreasing in the North-eastern states of the U.S. since the late 1970s/early 1980s, the decreases began later and were slower in the Southern states.[2] As a result, CRC incidence and mortality rates are now higher in Southern states than in North-eastern states, opposite to the patterns observed prior to 1980.[2]

Most cancer control plans and policies that affect cancer prevention and access to screening in the U.S. are designed and implemented at the state level. The observed variation in CRC incidence and mortality trends between states provides important information for policy makers on the success of the implemented interventions and provides evidence that interventions in some states can be improved. Differences in risk factors, screening and treatment are the most likely candidates to explain the observed disparity in CRC incidence and mortality trends.[3] Screening has been hypothesised to be the most important driver.[2] However, the individual contributions of these factors to disparities and thus the focus for future cancer control interventions, have never been evaluated.

In this analysis, we determined to what extent attaining more favourable trends in risk factors, screening and survival could reduce observed disparities in CRC incidence and mortality rates between states. We chose Louisiana as an exemplary Southern state with unfavourable trends in CRC incidence and mortality, and New Jersey as an exemplary North-eastern state with more favourable trends. Both states are part of the National Cancer Institute's Surveillance Epidemiology and End Results Program, and have high-quality cancer registry data.

METHODS

We used the MISCAN-Colon microsimulation model[4] of the Cancer Intervention and Surveillance Modelling Network (CISNET) to quantify how the disparity in observed CRC rates between Louisiana and New Jersey would be affected if Louisiana would be able to attain trends in risk factor prevalence (i.e. smoking and obesity), screening and stage-specific relative survival for CRC as observed in New Jersey. Stage-specific survival was used as a proxy for differences in treatment between states.

MISCAN-Colon Model

The Model Appendix at the end of this thesis describes the MISCAN model. Briefly, the model simulates the life histories of a large population of individuals from birth to death and has a natural history component that tracks the progression of underlying colorectal disease in the absence of screening. As each simulated individual ages, there is a chance that one or more adenomas may develop depending on age, sex, race and individual risk. Adenomas can progress in size from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm), and some may eventually become malignant. A preclinical (i.e., not yet detected) cancer has a chance of progressing through stages I-IV and may be detected because of symptoms at any stage. With screening, adenomas and preclinical cancers may be detected depending on the sensitivity of the test and, for endoscopic tests, whether the lesion is within reach of the endoscope.

The natural history part of the model was calibrated to pre-screening data from autopsy studies (references provided in the Model Appendix) and 1995 age-specific CRC incidence from the Louisiana Tumour Registry (LTR).[5] We included only first primary cases. Autopsy only and death certificate only cases, as well as tumours of the appendix were excluded. The model uses state-specific all-cause mortality life tables from the Cancer Survival in Five Continents study (CONCORD).[6] Trends in stage-specific relative survival following CRC diagnosis from 1995 to 2009 for Louisiana and New Jersey were obtained Surveillance, Epidemiology, and End Results (SEER) data (Appendix Table 1).[7] The prevalence of smoking and obesity over time by state and by age was obtained from the Behavioural Risk Factor Surveillance System (BRFSS).[8] Smoking prevalence data was available from 1955 onwards, and obesity prevalence data was available from 1970 onwards (Appendix Table 2). We assumed smoking and obesity prevalence before these years to be equal to the 1955 and 1970 levels respectively. The prevalence of risk factors affected the risk for developing adenomas, subsequently an increase in risk factor prevalence would affect CRC incidence after an average lag time of approximately 20 years.

Estimates for the screening uptake over time were also obtained from BRFSS data (Table 1).[8] We assumed no screening prior to 1978. For years in which no data were available, trends were extrapolated linearly. The assumptions for the sensitivity and specificity of screening tests were based on a literature review.[9] We assumed that colonoscopy reached the cecum in 98% of procedures. For sigmoidoscopy, we assumed that 80% of examinations reached the junction of the sigmoid and descending colon and 40% reached the beginning of the splenic flexure.[10, 11] We assumed that 1 in 10,000 colonoscopies led to a fatal complication.[12]

The validity of the model has been tested previously using data from several large randomised screening and surveillance studies, such as the three large randomised controlled trials for faecal occult blood testing[13], the CoCap sigmoidoscopy study[14],

Table 1. Model inputs for screening participation.* Proportion of the population aged 50 years and older who ever had a CRC test, had home-based FOBT in the past 2 years or endoscopy in the past 10 years.

		1980	1985	1990	1995	2000	2005	2009
Louisiana								
All races	- Ever any test (%)	13.8	36.9	48.0	51.2	56.1	62.7	68.1
	- FOBT in past 2 years (%)	5.6	14.8	19.9	22.2	25.3	28.0	21.0
	- Colonoscopy in past 10 years (%)	6.8	18.0	25.8	31.3	36.3	43.3	54.4
Blacks	- Ever any test (%)	11.8	31.5	41.6	45.4	50.9	55.9	61.9
	- FOBT in past 2 years (%)	4.6	12.4	17.1	19.9	23.4	26.3	22.0
	- Colonoscopy in past 10 years (%)	4.8	12.8	19.3	24.9	30.6	38.3	48.5
Whites	- Ever any test (%)	14.4	38.3	49.7	52.9	57.9	64.7	70.3
	- FOBT in past 2 years (%)	5.6	14.9	20.1	22.5	26.1	28.3	20.4
	- Colonoscopy in past 10 years (%)	7.1	18.9	27.1	32.7	37.8	45.1	56.6
New Jersey								
All races	- Ever any test (%)	15.4	40.9	53.2	56.6	62.5	69.3	71.0
	- FOBT in past 2 years (%)	7.6	20.2	27.0	29.9	31.4	24.2	18.7
	- Colonoscopy in past 10 years (%)	7.6	20.4	29.1	35.2	42.1	53.2	59.9
Blacks	- Ever any test (%)	12.4	33.2	43.8	47.5	56.5	65.5	68.0
	- FOBT in past 2 years (%)	6.2	16.5	22.7	26.2	29.8	23.0	19.3
	- Colonoscopy in past 10 years (%)	4.8	12.8	19.4	24.9	32.4	50.2	57.6
Whites	- Ever any test (%)	15.9	42.5	55.2	58.5	64.9	70.7	72.6
	- FOBT in past 2 years (%)	7.7	20.7	27.8	31.1	32.0	24.9	18.7
	- Colonoscopy in past 10 years (%)	8.0	21.2	30.3	36.6	43.5	54.7	61.3

FOBT, faecal occult blood test

* Data source: Behavioural Risk Factor Surveillance System [8]. Model inputs for stage specific CRC relative survival and risk factor prevalence are presented in Appendix 1 and 2.

and the National Polyp Study.[15] Additionally, the model was able to reproduce the observed CRC incidence and mortality trends in the U.S. while accounting for secular trends in risk factor prevalence, screening practice, and chemotherapy treatment.[16]

Study Population

We used the model to simulate the Louisiana population from 1995 to 2009 (corrected for the impact of Hurricane Katrina) for both genders and all races combined. In a secondary analysis, we also simulated the black and white Louisiana populations separately. We did not analyse other racial groups or Hispanics separately due to small numbers in Louisiana. We restricted our analysis to the population aged 50 years and older, because this is the group for whom screening is recommended.[17, 18]

Base case analysis

We simulated the Louisiana population with trends in CRC risk factors, CRC screening and stage-specific relative CRC survival rates as observed in Louisiana (Run 1). Alternatively we modeled the Louisiana population assuming they had the same trends as observed in New Jersey for risk factors (Run 2), screening (Run 3), stage-specific CRC survival (Run 4), and a combination of all three (Run 5).

Based on a previously used method,[19] we calculated the expected CRC incidence/mortality rates in Louisiana for the scenarios in which risk factor, screening, and/or survival patterns were similar to those in New Jersey by applying the percent difference in age-standardised incidence/mortality rates between Run 1 and Run 2, 3, 4, or 5, respectively, to the observed CRC incidence and mortality rates for Louisiana in 2009.

The observed excess CRC risk was calculated as the absolute difference in observed CRC incidence/mortality rates between Louisiana and New Jersey in 2009 (Formula 1, Appendix 3).[20] Subsequently, the expected excess risk from each of the modeled scenarios was calculated as the absolute difference between the expected CRC incidence/mortality rate from each scenario and the observed CRC incidence/mortality in New Jersey (Formula 2-5, Appendix 3).

Sensitivity analyses

We performed three sensitivity analyses. First we performed an analysis in which Louisiana residents not only received less screening but also lower quality screening, assuming 25% lower adenoma detection rates with endoscopy. We then re-estimated the reduction in excess CRC risk due to differences in screening assuming New Jersey screening adherence and quality. Second, we explored the robustness of our results to the assumption that equal access to care resulted in the same stage-specific relative CRC survival for Louisiana and New Jersey by assuming that 25% of the difference in relative survival between states could not be taken away with equal access to care. Finally, we evaluated the impact on mortality disparity if equal access to care not only resulted in the same stage-specific relative CRC survival for Louisiana as for New Jersey, but also in the same stage distribution.

RESULTS

In 1995, the observed Louisiana CRC incidence rate (167 cases per 100,000 persons aged 50 years and older) was approximately 19% lower than the New Jersey CRC incidence (205 cases per 100,000) (Figure 1). By 2009 the ordering had reversed, with CRC incidence in Louisiana being almost 10% higher than in New Jersey. For CRC mortality a similar pattern was observed (Figure 2). The observed excess in age-standardised CRC

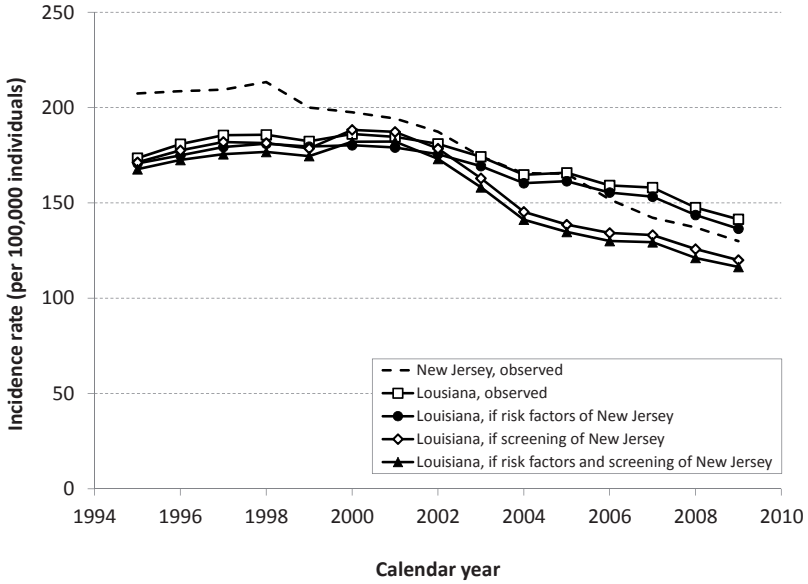

Figure 1. Age-standardised* CRC incidence rates in the 50+ year-old population from 1995 to 2009, as observed in Louisiana and New Jersey, and as expected in Louisiana if they would have had the same risk factors, and/or screening pattern as New Jersey.

*Age-standardised rate per 100,000 individuals (2000 US standard population of 50 years and older).

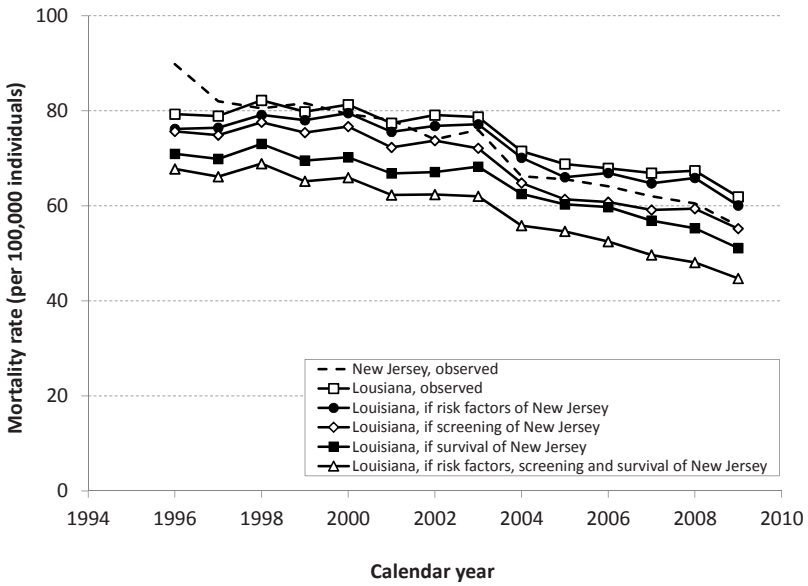

Figure 2. Age-standardised* CRC mortality rates in the 50+year old population from 1995 to 2009, as observed in Louisiana and New Jersey, and as expected in Louisiana if they would have had the same risk factors, screening pattern, and/or survival pattern as New Jersey.

*Age-standardised rate per 100,000 individuals (2000 US standard population of 50 years and older).

incidence and mortality rates in 2009 in Louisiana compared to New Jersey were 11.5 cases and 6.1 deaths per 100,000, respectively (Table 2 and 3).

If Louisiana had the same smoking and obesity pattern as observed in New Jersey, the expected CRC incidence rate would have been 136.5 per 100,000 in 2009, 3.5% lower than the observed rate for Louisiana (Figure 1 and Table 2). The expected CRC mortal-

Table 2. Base case analysis: Disparities in CRC incidence between individuals aged 50 years and older in Louisiana and New Jersey, as observed in 2009.

	All races			Blacks			Whites		
Scenario	ASR	% reduction*	Excess rate†	ASR	% reduction*	Excess rate†	ASR	% reduction*	Excess rate†
New Jersey, observed	130.0			132.0			131.2		
Louisiana, observed	141.4		11.5	174.2		42.2	131.7		0.5
- if risk factors of New Jersey	136.5	3.5%	6.5	171.3	1.6%	39.3	128.4	2.5%	−2.8
- if screening of New Jersey	120.0	15.2%	−10.0	153.8	11.7%	21.8	112.3	14.7%	−18.9
- if risk factors, screening and survival of New Jersey	116.4	17.7%	−13.6	151.1	13.2%	19.1	110.3	16.2%	−20.8

ASR, Age-standardised rate per 100,000 individuals (2000 US standard population of 50 years and older).
* Percent reduction, compared to the incidence rate observed in Louisiana in 2009.
† Excess CRC incidence rate in Louisiana compared to New Jersey

Table 3. Base case analysis: Disparities in CRC mortality between individuals aged 50 years and older in Louisiana and New Jersey in 2009.

	All races			Blacks			Whites		
Scenario	ASR	% reduction*	Excess rate†	ASR	% reduction*	Excess rate†	ASR	% reduction*	Excess rate†
New Jersey, observed	55.8			71.5			55.3		
Louisiana, observed	61.9		6.1	79.9		8.4	56.5		1.2
- if risk factors of New Jersey	60.1	3.0%	4.3	77.8	2.6%	6.3	54.8	3.0%	−0.5
- if screening of New Jersey	55.2	10.8%	−0.6	73.1	8.5%	1.6	49.3	12.7%	−6.0
- if survival of New Jersey	51.1	17.4%	−4.7	71.3	10.8%	−0.2	49.5	12.4%	−5.8
- if risk factors, screening and survival of New Jersey	44.7	27.8%	−11.1	65.3	18.3%	−6.2	43.4	23.2%	−11.9

ASR, Age-standardised rate per 100,000 individuals (2000 US standard population of 50 years and older).
* Percent reduction, compared to the mortality rate observed in Louisiana in 2009.
† Excess CRC mortality rate in Louisiana compared to New Jersey

ity rate in 2009 would have been 60.1 per 100,000 (3.0% lower than observed, Figure 2 and Table 3). However, these decreases were not large enough to offset the excess CRC burden. Louisiana would still have an excess of 6.5 cases and 4.3 deaths per 100,000 compared to New Jersey.

If Louisiana would have had the same trends in screening or the same trend in stage-specific relative CRC survival as New Jersey, CRC mortality would drop to 55.2 and 51.1 per 100,000 respectively in 2009, 10.8% and 17.4% lower than the observed rate in Louisiana. The reduction in CRC mortality from each intervention is large enough to offset the excess risk in Louisiana. With the same trends in smoking and obesity, screening, and stage-specific relative CRC survival as New Jersey combined, CRC mortality in Louisiana would have been 27.8% lower than the observed rate of 61.9 per 100,000 in Louisiana. In addition, Louisiana would have 13.6 cases and 11.1 deaths per 100,000 less as currently observed in New Jersey.

The observed disparity in CRC incidence and mortality between Louisiana and New Jersey was considerably higher for blacks (42.2 excess cases and 8.4 excess deaths per 100,000 persons) compared to whites (0.5 excess cases and 1.2 excess deaths) (Tables 2 and 3). Interestingly, the potential reduction in CRC incidence and mortality if Louisiana had similar risk factor, screening and/or survival trends as New Jersey was lower for blacks than for whites. If Louisiana blacks had similar risk factor, screening and survival patterns as New Jersey blacks, the observed CRC incidence and mortality rates were 13.2% and 18.3% lower, respectively. For whites, the respective rates would be 16.2% and 23.2% lower.

Sensitivity analyses

Our findings were robust for assumptions concerning quality of endoscopy, residual survival differences and stage distribution (Table 4). Lower-quality endoscopy slightly increased the potential reduction in excess mortality from 27.8% to 33.7%. Residual differences in stage-specific relative CRC survival between Louisiana and New Jersey decreased potential reduction in CRC mortality to 24.0%. Stage distribution had virtually no effect.

DISCUSSION

This study shows that removing differences in smoking and obesity, screening, and stage-specific relative CRC survival would eliminate observed disparities in CRC incidence and mortality rates between Louisiana and New Jersey. Eliminating differences in screening had the biggest impact on CRC incidence: the observed CRC incidence in Louisiana could be reduced by 15.2% by increasing CRC screening up to the level of New

Table 4. Sensitivity analyses: Disparities in CRC mortality between individuals aged 50 years and older in Louisiana and New Jersey in 2009, under alternative model assumptions.

	Lower quality endoscopies			Residual survival difference			Same survival and stage distribution		
Scenario	ASR	% reduction*	Excess rate†	ASR	% reduction†	Excess rate*	ASR	% reduction*	Excess rate†
New Jersey, observed	55.8			55.8			55.8		
Louisiana, observed	61.9		6.1	61.9		6.1	61.9		6.1
- if risk factors of New Jersey	60.2	2.7%	4.4	60.1	3.0%	4.3	60.1	3.0%	4.3
- if screening of New Jersey	50.8	17.9%	−5.0	55.2	10.8%	−0.6	55.2	10.8%	−0.6
- if survival of New Jersey	50.7	18.1%	−5.1	53.6	13.3%	−2.2	50.8	17.9%	−5.0
- if risk factors, screening and survival of New Jersey	41.1	33.7%	−14.7	47.0	24.0%	−8.8	44.6	27.9%	−11.2

ASR, Age-standardised rate per 100,000 individuals (2000 US standard population of 50 years and older).
* Percent reduction, compared to the mortality rate observed in Louisiana in 2009.
† Excess CRC mortality rate in Louisiana compared to New Jersey

Jersey. Treatment had the largest impact on CRC mortality, the observed CRC mortality could be reduced by 17.4% by improving the stage-specific relative CRC survival to the level of New Jersey. Eliminating differences in the prevalence of smoking and obesity had a relatively modest impact on CRC incidence (3.5% reduction) and mortality (3.0% reduction).

Together, eliminating differences in risk factors, screening and survival not only completely eliminates the excess CRC incidence and mortality in Louisiana but reverses the pattern. This may sound surprising, but given that in the early 1990's New Jersey had higher incidence and mortality rates than Louisiana[2], it makes sense that the background CRC risk in Louisiana is actually lower than in New Jersey.

The disparity in CRC incidence and mortality rates between Louisiana and New Jersey mainly exists for blacks, and not for whites (Tables 2 and 3). When simply looking at the 2009 rates, one could argue that the disparity between the two states is therefore a result of a difference in population distribution by race. However, when looking at trends since 1995 it is clear that population distribution is not the explanation. For both races, the trend was less favourable (even unfavourable for blacks) in Louisiana than in New Jersey. This finding is corroborated by our modelling, showing that CRC incidence and mortality rates in Louisiana could be reduced to a similar extent in blacks and whites if risk factors, screening and survival were the same as in New Jersey. Interestingly, the potential reduction was even somewhat higher in whites than in blacks. This finding is

probably explained by the increase in CRC incidence and mortality in Louisiana blacks in the late 1990's, which cannot be explained by the factors investigated in this study. This means that other factors (e.g. other risk factors or environmental factors) are responsible for this increase and therefore for the difference in CRC incidence and mortality between Louisiana and New Jersey blacks. Removing differences in smoking, obesity, screening, and survival cannot eliminate this difference. Consequently, some excess CRC incidence in blacks remained in Louisiana compared to New Jersey.

In our primary analysis, we considered uptake of screening, assuming equal access to and quality of screening, between Louisiana and New Jersey. The lower population density and larger geographic area of Louisiana might make achieving equal access more difficult. In addition, quality of endoscopy has been shown to be dependent on the skill of the endoscopist performing the procedure, with colonoscopy being performed by gastroenterologists being more sensitive for cancer than colonoscopy by non-gastroenterologists.[21] The number of certified gastroenterologists differs widely between states in the U.S. In Louisiana there were only 3.9 gastroenterologists per 100,000 residents in 2013 compared to 6.7 in New Jersey.[22] This pattern is mirrored in the other Southern and North-eastern states.[23]

Three limitations are noteworthy. First, we did not incorporate all known risk factors for CRC into the model, because data were not available. Therefore the simulated CRC incidence and mortality rates do not correspond with the observed rates. Instead, we assumed that the simulated relative benefit of New Jersey risk factor, screening and stage-specific relative CRC survival patterns over Louisiana would be applicable to the observed CRC incidence and mortality. Second, relative survival estimates by state were estimated using SEER*Stat.[7] SEER*Stat uses U.S. life tables to estimate expected mortality in the absence of cancer. Louisiana death rates are higher than overall U.S. death rates, while New Jersey rates are lower.[24] As a result, we may have underestimated the relative CRC survival in Louisiana and overestimated it for New Jersey. Consequently, the impact of eliminating differences in relative CRC survival may have been overestimated. Finally, we have not explicitly considered state differences in treatment but used state differences in stage-specific relative CRC survival as a proxy. Data on use and quality of CRC treatment by state are sparse, especially for the population below 65 years old. If part of the state differences in survival cannot be explained by differences in the (quality of) treatment, for example because Louisiana residents could have more comorbidities and are therefore unable to receive guideline therapy, we have overestimated the potential for reducing disparities in CRC mortality. We explored the impact of our assumption in a sensitivity analysis and found that the effect was limited.

Removing differences in risk factors, screening and stage-specific relative CRC survival can eliminate state disparities in CRC incidence and mortality. Measures should therefore be taken to eliminate the gaps between states, especially in screening use and

survival. The Patient Protection and Affordable Care Act (ACA, Pub.L. 111-148, 2010) may be an important step towards this elimination although Louisiana has yet to expand the state Medicaid program. The ACA aims to improve access to quality health care for all Americans. Furthermore, all new health plans must cover certain preventive services including CRC screening without charging a deductible, co-pay or coinsurance. Several studies have shown that in situations with equal access to care, such as military medical centres, Department of Defence facilities or clinical trials, no differences in screening uptake or CRC treatments exist.[25-30] A notable example is universal CRC screening coverage in Delaware that eliminated the black-white disparities in CRC mortality rates.[31]

In conclusion, this study shows that the disparities in CRC incidence and mortality rates between states can be completely eliminated by removing differences in risk factors, screening and survival. Priority should be given to enabling Southern states to achieve equal screening and survival as North-eastern states.

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APPENDIX

Appendix Table 1.

Appendix Table 1.1. Estimates from SEER for the 5-year relative survival after colorectal cancer diagnosis by stage, anatomic sub site, period and race (Lousisiana).

	1995-1999					2000-2004					2005-2008				
Subgroup	**20-49**	**50-59**	**60-69**	**70-79**	**80+**	**20-49**	**50-59**	**60-69**	**70-79**	**80+**	**20-49**	**50-59**	**60-69**	**70-79**	**80+**
Stage I, colon															
Louisiana, total population	88%	91%	88%	88%	77%	92%	92%	92%	87%	73%	92%	93%	89%	87%	74%
Louisiana, blacks	82%	90%	79%	73%	60%	87%	88%	88%	85%	53%	86%	94%	86%	79%	52%
Louisiana, whites	90%	92%	91%	90%	81%	96%	93%	93%	87%	77%	96%	92%	90%	89%	77%
Stage I, rectum															
Louisiana, total population	89%	90%	84%	75%	78%	90%	87%	85%	79%	55%	88%	85%	79%	83%	44%
Louisiana, blacks	95%	81%	76%	65%	53%	86%	87%	76%	70%	50%	86%	83%	70%	58%	35%
Louisiana, whites	87%	93%	86%	76%	81%	91%	87%	87%	81%	53%	88%	86%	81%	88%	43%
Stage II-III, colon															
Louisiana, total population	71%	66%	67%	65%	55%	74%	73%	67%	64%	60%	74%	73%	75%	66%	59%
Louisiana, blacks	72%	65%	62%	64%	41%	66%	69%	58%	63%	45%	68%	64%	74%	56%	43%
Louisiana, whites	71%	67%	69%	66%	59%	78%	75%	70%	65%	64%	78%	79%	74%	70%	63%
Stage II-III, rectum															
Louisiana, total population	66%	69%	60%	54%	53%	65%	69%	63%	54%	43%	71%	73%	60%	60%	57%
Louisiana, blacks	61%	62%	65%	45%	26%	56%	65%	53%	50%	29%	49%	58%	51%	42%	16%
Louisiana, whites	68%	72%	60%	57%	56%	68%	71%	66%	54%	45%	80%	80%	64%	64%	63%
Stage IV, colon and rectum															
Louisiana, total population	9%	9%	9%	6%	4%	15%	12%	11%	6%	5%	18%	13%	13%	6%	8%
Louisiana, blacks	5%	7%	5%	4%	4%	15%	8%	6%	4%	2%	21%	10%	11%	0%	7%
Louisiana, whites	10%	10%	10%	6%	3%	16%	14%	13%	7%	6%	16%	14%	14%	6%	8%

Appendix Table 1.2. Estimates from SEER for the 5-year relative survival after colorectal cancer diagnosis by stage, anatomic sub site, period and race (New Jersey).

	1995-1999					2000-2004					2005-2008				
Subgroup	**20-49**	**50-59**	**60-69**	**70-79**	**80+**	**20-49**	**50-59**	**60-69**	**70-79**	**80+**	**20-49**	**50-59**	**60-69**	**70-79**	**80+**
Stage I, colon															
New Jersey, total population	93%	93%	89%	91%	83%	94%	95%	93%	93%	87%	93%	97%	94%	91%	84%
New Jersey, blacks	85%	87%	79%	83%	63%	86%	91%	86%	88%	80%	82%	93%	87%	81%	66%
New Jersey, whites	95%	94%	90%	92%	84%	95%	96%	94%	93%	88%	95%	97%	95%	92%	85%
Stage I, rectum															
New Jersey, total population	94%	91%	90%	83%	71%	92%	91%	89%	84%	77%	89%	91%	89%	86%	67%
New Jersey, blacks	100%	92%	77%	72%	69%	71%	85%	75%	43%	69%	91%	84%	83%	43%	27%
New Jersey, whites	92%	90%	92%	83%	71%	94%	91%	90%	87%	78%	89%	91%	89%	89%	70%
Stage II-III, colon															
New Jersey, total population	70%	68%	68%	67%	60%	79%	76%	75%	67%	62%	77%	78%	77%	67%	64%
New Jersey, blacks	57%	63%	58%	53%	57%	68%	68%	75%	66%	41%	65%	68%	76%	67%	49%
New Jersey, whites	73%	68%	70%	68%	60%	81%	77%	76%	67%	63%	80%	79%	77%	66%	64%
Stage II-III, rectum															
New Jersey, total population	69%	70%	64%	62%	56%	76%	77%	76%	61%	57%	76%	82%	78%	62%	58%
New Jersey, blacks	65%	67%	44%	50%	48%	51%	67%	80%	34%	43%	49%	74%	84%	32%	78%
New Jersey, whites	69%	71%	66%	63%	55%	77%	78%	76%	63%	57%	79%	82%	76%	65%	56%
Stage IV, colon and rectum															
New Jersey, total population	10%	10%	8%	7%	3%	18%	14%	12%	8%	5%	24%	16%	13%	9%	5%
New Jersey, blacks	5%	9%	7%	6%	0%	9%	5%	8%	3%	0%	18%	5%	6%	7%	0%
New Jersey, whites	11%	10%	9%	7%	3%	20%	16%	13%	9%	5%	24%	20%	15%	9%	5%

Appendix Table 2.

Appendix Table 2.1. Estimates from BRFSS for smoking prevalence by age, period and race (Louisiana).

	Calendar year											
Age	**1955**	**1960**	**1965**	**1970**	**1975**	**1980**	**1985**	**1990**	**1995**	**2000**	**2005**	**2009**
All races												
18-24	47.7%	44.4%	41.0%	37.7%	34.3%	30.9%	27.6%	24.2%	25.8%	29.2%	26.8%	21.9%
25-34	55.5%	52.3%	49.1%	45.9%	42.7%	39.5%	36.3%	33.1%	29.9%	27.9%	26.4%	25.8%
35-44	55.0%	51.5%	48.1%	44.6%	41.1%	37.7%	34.2%	30.7%	29.9%	29.9%	26.8%	22.8%
45-54	48.4%	46.0%	43.5%	41.1%	38.7%	36.2%	33.8%	30.8%	27.5%	26.8%	26.0%	25.4%
55-64	39.7%	38.3%	36.9%	35.5%	34.1%	32.8%	30.1%	25.5%	23.4%	21.8%	20.3%	19.0%
65+	16.9%	16.6%	16.3%	16.1%	15.8%	15.6%	15.3%	13.4%	11.5%	10.6%	10.4%	10.7%
Blacks												
18-24	47.1%	43.4%	39.8%	36.2%	32.6%	29.0%	24.2%	14.7%	12.3%	16.1%	18.0%	16.3%
25-34	56.3%	52.9%	49.5%	46.1%	42.7%	39.4%	35.6%	30.2%	24.8%	20.5%	21.1%	22.5%
35-44	49.3%	47.1%	44.8%	42.6%	40.4%	38.2%	35.9%	33.7%	30.5%	29.3%	21.7%	20.0%
45-54	50.9%	48.3%	45.7%	43.2%	40.6%	38.0%	35.4%	32.8%	30.2%	30.2%	27.9%	25.5%
55-64	30.3%	30.9%	31.5%	32.1%	32.7%	33.3%	32.8%	28.0%	24.4%	23.5%	22.8%	24.0%
65+	12.1%	12.9%	13.8%	14.6%	15.5%	16.3%	16.8%	16.0%	14.5%	13.2%	11.6%	11.4%
Whites												
18-24	45.6%	43.1%	40.5%	38.0%	35.5%	32.9%	30.4%	27.9%	29.2%	32.6%	28.7%	21.9%
25-34	52.6%	49.9%	47.1%	44.4%	41.7%	38.9%	36.2%	33.5%	30.8%	29.3%	28.0%	25.1%
35-44	55.7%	52.2%	48.7%	45.2%	41.6%	38.1%	34.6%	31.1%	29.8%	31.0%	27.4%	22.7%
45-54	48.7%	46.3%	43.9%	41.5%	39.0%	36.6%	34.2%	31.2%	27.8%	26.2%	26.2%	24.0%
55-64	40.4%	38.7%	37.1%	35.5%	33.8%	32.2%	29.8%	24.5%	23.2%	22.3%	20.5%	17.4%
65+	15.3%	15.6%	15.8%	16.1%	16.4%	16.6%	15.0%	13.3%	11.6%	10.7%	9.7%	9.7%

Appendix Table 2.2. Estimates from BRFSS for obesity prevalence by age, period and race (Louisiana).

	Calendar year								
Age	**1970**	**1975**	**1980**	**1985**	**1990**	**1995**	**2000**	**2005**	**2009**
All races									
18-24	5.8%	4.7%	3.6%	5.2%	7.6%	9.9%	13.3%	16.6%	19.2%
25-34	5.0%	5.1%	5.2%	5.3%	7.6%	16.4%	21.2%	26.0%	29.9%
35-44	9.3%	10.5%	11.6%	12.7%	15.0%	18.2%	24.5%	29.9%	33.6%
45-54	11.4%	13.1%	14.8%	16.4%	19.1%	23.1%	28.2%	32.2%	35.0%
55-64	10.4%	11.8%	13.1%	14.6%	17.4%	21.0%	28.8%	34.3%	37.6%
65+	10.1%	11.6%	13.0%	14.5%	15.9%	18.9%	22.4%	25.9%	28.5%
Blacks									
18-24	6.9%	7.1%	7.2%	7.3%	11.2%	15.9%	22.8%	24.7%	25.9%
25-34	8.5%	9.4%	10.3%	11.2%	13.7%	23.9%	32.7%	38.5%	43.0%
35-44	16.6%	17.9%	19.2%	20.5%	21.8%	26.9%	36.3%	43.8%	48.2%

	Calendar year								
Age	**1970**	**1975**	**1980**	**1985**	**1990**	**1995**	**2000**	**2005**	**2009**
45-54	24.8%	25.5%	26.2%	26.9%	27.6%	31.2%	37.6%	43.1%	46.8%
55-64	22.4%	23.7%	25.0%	26.4%	27.7%	31.3%	38.9%	45.5%	49.3%
65+	18.7%	20.6%	22.4%	24.3%	26.1%	28.7%	33.0%	38.0%	41.3%
Whites									
18-24	4.1%	4.0%	3.9%	4.3%	6.5%	8.8%	11.9%	15.1%	17.6%
25-34	5.4%	5.7%	6.1%	6.7%	8.3%	14.2%	18.7%	23.7%	27.7%
35-44	8.0%	9.3%	10.6%	11.9%	13.9%	16.8%	21.8%	27.8%	32.7%
45-54	9.0%	10.8%	12.6%	14.5%	17.1%	20.9%	26.0%	30.6%	33.8%
55-64	9.4%	10.6%	11.8%	13.4%	16.4%	19.5%	26.8%	32.9%	36.1%
65+	8.0%	9.3%	10.6%	11.8%	13.1%	15.9%	20.0%	24.6%	27.1%

Appendix Table 2.3. Estimates from BRFSS for smoking prevalence by age, period and race (New Jersey).

	Calendar year											
Age	**1955**	**1960**	**1965**	**1970**	**1975**	**1980**	**1985**	**1990**	**1995**	**2000**	**2005**	**2009**
All races												
18-24	45.3%	42.1%	38.9%	35.7%	32.5%	29.3%	26.2%	23.0%	24.5%	25.5%	22.3%	17.6%
25-34	47.9%	45.1%	42.4%	39.6%	36.9%	34.1%	31.3%	28.6%	25.8%	24.6%	21.8%	18.7%
35-44	43.4%	40.6%	37.9%	35.2%	32.4%	29.7%	26.9%	24.2%	23.6%	22.7%	20.0%	16.8%
45-54	36.5%	34.7%	32.8%	31.0%	29.1%	27.3%	25.5%	23.2%	20.7%	24.2%	20.1%	16.9%
55-64	33.8%	32.7%	31.5%	30.3%	29.1%	27.9%	25.6%	21.8%	19.9%	18.1%	16.3%	14.8%
65+	14.8%	14.6%	14.4%	14.1%	13.9%	13.7%	13.5%	11.8%	10.1%	9.6%	9.0%	8.0%
Blacks												
18-24	47.0%	43.4%	39.8%	36.2%	32.5%	28.9%	24.2%	14.7%	12.3%	15.7%	16.4%	13.8%
25-34	53.5%	50.3%	47.1%	43.9%	40.7%	37.5%	33.9%	28.7%	23.6%	20.1%	19.2%	18.2%
35-44	44.9%	42.8%	40.8%	38.8%	36.7%	34.7%	32.7%	30.6%	27.8%	26.7%	18.7%	16.3%
45-54	45.3%	43.0%	40.7%	38.4%	36.1%	33.8%	31.5%	29.2%	26.9%	30.0%	24.4%	19.7%
55-64	28.6%	29.2%	29.8%	30.3%	30.9%	31.5%	31.0%	26.5%	23.1%	22.3%	20.4%	20.0%
65+	11.6%	12.4%	13.2%	14.0%	14.9%	15.7%	16.2%	15.4%	14.0%	13.1%	10.7%	9.3%
Whites												
18-24	39.7%	37.5%	35.3%	33.1%	30.9%	28.6%	26.4%	24.2%	25.4%	27.7%	23.6%	17.9%
25-34	43.7%	41.4%	39.1%	36.9%	34.6%	32.3%	30.1%	27.8%	25.5%	25.0%	22.9%	19.5%
35-44	44.2%	41.4%	38.6%	35.8%	33.0%	30.2%	27.4%	24.6%	23.7%	24.6%	21.3%	17.8%
45-54	37.8%	35.9%	34.0%	32.2%	30.3%	28.4%	26.5%	24.2%	21.5%	22.6%	20.8%	17.8%
55-64	33.3%	31.9%	30.6%	29.2%	27.9%	26.5%	24.6%	20.2%	19.1%	18.5%	16.5%	14.0%
65+	12.8%	13.1%	13.3%	13.5%	13.7%	13.9%	12.5%	11.2%	9.8%	9.3%	8.1%	7.7%

Appendix Table 2.4. Estimates from BRFSS for obesity prevalence by age, period and race (New Jersey).

	Calendar year								
Age	**1970**	**1975**	**1980**	**1985**	**1990**	**1995**	**2000**	**2005**	**2009**
All races									
18-24	2.2%	1.8%	1.4%	2.0%	3.0%	3.9%	10.4%	13.8%	15.0%
25-34	6.3%	6.5%	6.6%	6.7%	9.6%	12.5%	14.6%	18.3%	22.2%
35-44	6.8%	7.6%	8.4%	9.2%	10.9%	13.1%	18.4%	22.8%	23.4%
45-54	7.1%	8.2%	9.3%	10.3%	12.0%	14.5%	20.5%	25.7%	27.0%
55-64	11.8%	13.3%	14.8%	16.5%	19.6%	23.8%	25.2%	28.0%	31.0%
65+	8.3%	9.5%	10.7%	11.9%	13.1%	15.5%	18.5%	21.5%	24.0%
Blacks									
18-24	3.9%	4.0%	4.0%	4.1%	6.2%	8.9%	19.0%	20.8%	20.2%
25-34	8.6%	9.5%	10.4%	11.2%	13.8%	18.7%	25.6%	29.8%	32.7%
35-44	12.7%	13.7%	14.7%	15.6%	16.6%	20.5%	29.7%	35.3%	35.6%
45-54	17.6%	18.1%	18.6%	19.1%	19.6%	22.2%	30.3%	35.4%	36.4%
55-64	21.3%	22.6%	23.9%	25.1%	26.4%	29.8%	34.4%	38.0%	39.5%
65+	15.2%	16.7%	18.2%	19.7%	21.2%	23.3%	28.2%	32.0%	33.5%
Whites									
18-24	2.4%	2.3%	2.3%	2.5%	3.8%	5.1%	9.7%	12.6%	14.1%
25-34	5.6%	6.0%	6.3%	7.0%	8.6%	11.5%	14.3%	18.2%	21.6%
35-44	6.3%	7.4%	8.4%	9.4%	11.0%	13.3%	17.5%	22.3%	24.8%
45-54	6.6%	8.0%	9.3%	10.6%	12.6%	15.4%	20.5%	25.1%	26.9%
55-64	9.3%	10.5%	11.7%	13.2%	16.2%	19.2%	23.2%	27.3%	29.8%
65+	6.8%	7.8%	8.9%	10.0%	11.0%	13.4%	16.8%	20.6%	22.5%

Appendix 3. Formulas for Calculation of Excess CRC Risk Explained by Disparities in Risk Factor Prevalence, Screening and Survival.

The observed excess in CRC incidence and mortality rates were calculated as:

$$\Delta_{obs} = r_{obs\,LA} - r_{obs\,NJ} \quad [1]$$

where Δ_{obs} is the observed excess in CRC incidence (mortality) between Louisiana and New Jersey, and $r_{obs\,LA}$ is the observed CRC incidence (mortality) in Louisiana and $r_{obs\,NJ}$ the observed CRC incidence (mortality) in New Jersey.

The expected excess CRC risk if Louisiana would have had the same risk factor prevalence as New Jersey was calculated as:

$$\Delta_{rf} = r_{rf\,LA} - r_{obs\,NJ} \quad [2]$$

where Δ_{rf} is the expected excess in CRC incidence (mortality) if Louisiana had New Jersey trends in risk factor prevalence and $r_{rf\,LA}$ is the expected CRC incidence (mortality) in Louisiana if they had had New Jersey trends in risk factor prevalence.

The expected excess CRC risk if Louisiana would have had the same screening as New Jersey was calculated as:

$$\Delta_{scr} = r_{scr\,LA} - r_{obs\,NJ} \quad [3]$$

where Δ_{scr} is the expected excess in CRC incidence (mortality) if Louisiana had New Jersey trends in screening rates and $r_{scr\,LA}$ is the expected CRC incidence (mortality) in Louisiana if they had had New Jersey trends in screening rates.

The expected excess in CRC mortality if Louisiana would have had the same stage-specific relative CRC survival as New Jersey was calculated as:

$$\Delta_{surv} = r_{surv\,LA} - r_{obs\,NJ} \quad [4]$$

where Δ_{surv} is the expected excess in CRC mortality if Louisiana had New Jersey trends in stage-specific relative CRC survival rates and $r_{surv\,LA}$ is the expected CRC mortality rate in Louisiana if they had New Jersey trends in stage-specific relative CRC survival rates.

The expected excess CRC risk if Louisiana would have had the same risk factor prevalence, screening and stage-specific relative CRC survival as New Jersey was calculated as:

$$\Delta_{rf+scr+surv} = r_{rf+scr+surv\,LA} - r_{obs\,NJ} \quad [5]$$

where $\Delta_{rf+scr+surv}$ is the expected excess in CRC incidence (mortality) if Louisiana had New Jersey trends in risk factor prevalence, screening and stage-specific relative CRC survival and $r_{rf+scr+surv\,LA}$ is the expected CRC incidence (mortality) rate in Louisiana if they had New Jersey trends in risk factor prevalence, screening and stage-specific relative CRC survival rates.

Chapter 4

The impact of stratifying by family history in colorectal cancer screening programs

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ABSTRACT

In the province-wide colorectal cancer (CRC) screening program in Ontario, Canada, individuals with a family history of CRC are offered colonoscopy screening and those without are offered guaiac faecal occult blood testing (gFOBT, Hemoccult II). We used microsimulation modelling to estimate the cumulative number of CRC deaths prevented and colonoscopies performed between 2008 and 2038 with this family history-based screening program, compared to a regular gFOBT program. In both programs, we assumed screening uptake increased from 30% (participation level in 2008 before the program was launched) to 60%. We assumed that 11% of the population had a family history, defined as having at least one first-degree relative diagnosed with CRC. The programs offered screening between age 50-74 years, every two years for gFOBT, and every ten years for colonoscopy. Compared to opportunistic screening (2008 participation level kept constant at 30%), the gFOBT program cumulatively prevented 6,700 more CRC deaths and required 570,000 additional colonoscopies by 2038. The family history-based screening program increased these numbers to 9,300 and 1,100,000, a 40% and 93% increase, respectively. If biennial gFOBT was replaced with biennial faecal immunochemical test (FIT), annual Hemoccult Sensa or five-yearly sigmoidoscopy screening, both the added benefits and colonoscopies required would decrease. A biennial gFOBT screening program that identifies individuals with a family history of CRC and recommends them to undergo colonoscopy screening would prevent 40% (range in sensitivity analyses: 20-51%) additional deaths while requiring 93% (range: 43-116%) additional colonoscopies, compared to a regular gFOBT screening program.

INTRODUCTION

Colorectal cancer (CRC) is the second most diagnosed malignancy in Western Countries,[1] and its incidence is likely to increase because most cases are diagnosed later in life and life expectancy is increasing in many countries. Screening for CRC and its precursor lesions, adenomas, can prevent the disease or detect it at an earlier and more curable stage. Several trials have proven that screening reduces CRC incidence and mortality,[2, 3] and that screening is cost-effective.[4]

Based on recommendations from the Canadian Task Force on Preventive Health Care and Health Canada's National Committee on Colorectal Cancer Screening in 2008 the ColonCancerCheck screening program was launched in Ontario, Canada.[5] ColonCancerCheck is a population-based screening program, which includes individuals aged 50-74 years old. At launch, the program relied on family physicians to identify eligible patients in their practices and to recommend screening, and on a public awareness campaign encouraging eligible individuals to discuss CRC screening with their family physicians. Several components including mailed invitations (newly eligible individuals), recall letters (previous screening participants), and annually recurring public awareness campaigns are being planned and introduced in a phased implementation.[5, 6]

At the family physician visit, individuals are risk stratified based on their family history of CRC. Individuals with a positive family history, defined as having at least one first-degree relative with a diagnosis of CRC, are recommended to undergo ten-yearly colonoscopy screening. Individuals without family history are offered biennial screening with the Hemoccult II guaiac faecal occult blood test (gFOBT).

To our knowledge the ColonCancerCheck is the first population-based screening program which actively identifies individuals with a family history in order to provide them with a more sensitive test. We aimed to estimate the effects of this family history-based screening approach on the cumulative number of CRC deaths prevented and colonoscopies performed, compared to a screening program where only gFOBT is recommended.

METHODS

The MISCAN-colon microsimulation model was used to simulate two program screening scenarios in Ontario: a program in which everyone was offered gFOBT screening and a program in which those with a family history of CRC were offered colonoscopy screening. The program outcomes were compared to a scenario that reflects the opportunistic screening participation observed in Ontario in 2008, prior to the launch of the ColonCancerCheck program (i.e. the "opportunistic screening" scenario).

MISCAN-Colon Microsimulation Model

The MISCAN-colon microsimulation model has been described in detail in the Model Appendix (at the end of this thesis) and in previous publications.[7-9] In brief, the model simulates the life histories of individuals from birth to death. CRC arises in the population according to the adenoma-carcinoma sequence.[10] More than one adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas can progress in size from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm), and some may eventually become malignant. A preclinical (i.e., not detected) cancer has a chance of progressing through stages I-IV and may be detected by symptoms at any stage. After clinical diagnosis of CRC, survival depends on the stage at diagnosis. At any time during his/her life an individual may die of other causes. With screening, an individual with a positive test will be referred for diagnostic colonoscopy for possible removal of adenomas and detection of cancers. This way CRC mortality can be reduced.

For this analysis the age-specific CRC incidence and stage distribution of the total population (i.e. average risk and family history populations combined) were calibrated to 2001 incidence data from the Canadian Cancer Registry, which was before the introduction of screening.[11] In the runs for the analysis we assumed that the CRC stage distribution in the absence of screening was similar between both risk groups, only the CRC incidence in each risk group was adjusted based on their relative risk for CRC (see section "study population"). The model used all-cause mortality estimates from the 2000-2002 Ontario life tables.[11] Because age- and stage-specific data on CRC relative survival were not available for Canada, we assumed the same age- and stage-specific survival as observed in the Surveillance, Epidemiology, and End-Results (SEER) database in the US, in the period 2000-2003.[12] We assumed that survival did not differ between individuals with and without family history. We did not include historical changes in risk factor prevalence or CRC relative survival, therefore any simulated changes in CRC incidence and mortality are attributable solely to changes in screening behaviour.

Study population

Table 1 provides an overview of the main estimates and assumptions in the model. We simulated the Ontario population aged 50 years and older. The population was followed from 2008-2038, with new 50-year-olds entering the population each year. The age distribution was based on the observed age distribution in Ontario in 2008. [11] We modeled two subpopulations; individuals with and without a family history, defined as having at least one first-degree relative with a diagnosis of CRC. We assumed that 11% of the total population had a family history[13] and that their relative risk (RR) for developing adenomas and CRC was on average 2.24 times higher than that of the general population.[14] The model allowed for individual variability of CRC risk within each subpopulation. As the general population includes those with and without a fam-

Table 1. Overview of the main assumptions in the base case and sensitivity analyses.

Variable	Base case analysis	Sensitivity analyses
Proportion of population with a family history of CRC	11%[13]	8% (low value), and 14% (high value)
RR of those with a family history of CRC compared to general population	Average RR = 2.24[14]	1.62 (low value), and 2.86 (high value)
CRC relative survival	Based on data from SEER[12], assumed to be similar for average and increased risk individuals	10% improved survival for increased risk individuals[15]
Adherence to diagnostic and surveillance colonoscopies	71%[5] and 80% (assumption) respectively	85% uptake for both diagnostic and surveillance colonoscopies
Dependency of gFOBT results in sequential screening rounds	None	74% of the large adenomas (≥10 mm) that are not detected, will not be detected in the next screening round[16]
Screening history (1990-2008)	Screening uptake gradually increased to 30% in 2008. We assumed individuals with a family history received ten-yearly colonoscopy, and average risk individuals received biennial gFOBT. [5]	15% of the population (both average and increased risk) who did not participate in CRC screening before the program, get a colonoscopy unrelated to CRC screening 5-10 years before the start of the screening program
Screening uptake during program (2008-2038)	- Average risk population: Increasing gradually from 30% to 60% over approximately 10 years. - Increased risk population: Increasing gradually from 30% to 60% over approximately 10 years.	Varying for both populations independently from 30% to 100%, at 10% increments.
Average risk screening during program (between age 50-74 years)	Biennial gFOBT (Hemoccult II)	Either annual gFOBT, biennial FIT50, biennial FIT100, 5-yearly sigmoidoscopy, annual Hemoccult Sensa, or 10-yearly colonoscopy
Increased risk screening during program (between age 50-74 years)	10-yearly colonoscopy	-

RR: relative risk; CRC: colorectal cancer; SEER: Surveillance, Epidemiology, and End-Results database; gFOBT: guaiac faecal occult blood test; FIT50: faecal immunochemical test, 50 ng Hb/ml cut-off value; FIT100: faecal immunochemical test, 100 ng Hb/ml cut-off value.

ily history of CRC, the persons without a family history would have slightly lower than average risk for developing CRC. The model adjusts risk downward modestly for these "average risk" individuals (average RR=0.85).

The screening history prior to the start of the program was based on observed screening rates in Ontario.[5] It was assumed that in the average risk population individuals between 50-74 years old would be able to participate in CRC screening with biennial gFOBT, and would only get a colonoscopy after a positive gFOBT result. After

age 74 individuals would stop screening, and new individuals turning age 50 would potentially start screening. The screening participation was assumed to increase steadily over time. In 2003, 15% of the 50-74 year old average risk individuals had a gFOBT within the past two years, this increased to 20% in 2005, and 30% in 2008. For the increased risk population we assumed individuals between age 50-74 years would be able to participate in ten-yearly colonoscopy screening. The proportion of increased risk individuals who had a colonoscopy within the past ten years was assumed to increase over time similarly to the gFOBT participation in the average risk population, i.e. 15% in 2003, 20% in 2005, and 30% in 2008. We assumed no significant screening in either risk group prior to 1995.

Base case analysis

In both program scenarios we assumed that participants were screened between age 50-74, and that the screening uptake in the average risk and increased risk populations would increase, over approximately 10 years, from 30% (observed 2008 participation level[5]) to 60% (comparable to current mammography screening in Ontario[17]):

1) gFOBT program: A screening program that offers biennial gFOBT screening to all participants and does not actively identify increased risk individuals. We assumed that 30% of the increased risk population would receive colonoscopy screening, consistent with the colonoscopy uptake prior to the start of the program.
2) Family history-based program: A screening program that identifies individuals with a family history of CRC (i.e. because of a CRC diagnosis in at least one first degree relative) and invites them to undergo ten-yearly colonoscopy screening. Although colonoscopy is more invasive than gFOBT, which could negatively affect screening uptake, for the base case analysis we assumed the increased risk individuals would obtain similar uptake as the average risk individuals, because they were identified as being at increased risk for CRC.[18, 19] As in the gFOBT program, average risk individuals were recommended to undergo biennial gFOBT screening.

The two program screening scenarios were compared to a scenario that reflects the opportunistic screening participation observed in Ontario in 2008, prior to the launch of the ColonCancerCheck program (opportunistic screening scenario), that is, 30% gFOBT screening in the average risk population and 30% colonoscopy screening in the increased risk population.

In all scenarios, approximately 10% of the average risk gFOBT participants ever had a positive gFOBT result and received colonoscopy screening as part of the surveillance program (i.e. with 30% gFOBT screening participation approximately 3% of the average risk population would be in colonoscopy surveillance). Among increased risk gFOBT participants (only applicable to the gFOBT program scenario) approximately 13% ever

had a positive gFOBT result and received colonoscopy screening as part of the surveillance program.

Adenomas could be detected and removed during diagnostic colonoscopy after a positive gFOBT or during colonoscopy screening (increased risk individuals only). Depending on the number and size of adenomas detected, the individual would be recommended for surveillance colonoscopy after three or five years. If no adenomas were detected the individuals would be recommended to undergo colonoscopy after ten years.[20] We assumed that once individuals entered surveillance they would remain in surveillance for the rest of their lives (i.e. they would not stop screening at age 74). Adherence to diagnostic colonoscopy after a positive gFOBT, and to surveillance colonoscopy after detection and removal of adenomas were assumed to be 71% and 80% respectively.[5] These rates were assumed to be equal for average and increased risk individuals, and to remain constant over time. Individuals who did not adhere to the recommendation to undergo diagnostic colonoscopy, would return to screening. Individuals who did not adhere to the recommendation for surveillance colonoscopy would receive another recommendation for surveillance colonoscopy after three or five years (depending on the findings at the previous colonoscopy).

Sensitivity analyses

In order to investigate the robustness of our results to model assumptions, we evaluated several sensitivity analyses (Table 1). The following assumptions had an effect during the screening program (2008-2038), as well as the screening history: 1) the proportion of individuals at increased risk was varied by 30% (low value: 8%; high value: 14%); 2) the RR of CRC in the increased risk population compared to the general population was varied by 50% (low value: RR=1.62; high value: RR=2.86); 3) the uptake rate for both diagnostic and surveillance colonoscopies was increased to 85% (base case value: 71% and 80% respectively); 4) age- and stage-specific CRC relative survival in individuals with a family history was increased by 10%; 5) 15% of the population (in the average risk as well as the increased risk population) who did not participate in CRC screening before the program, but who would start screening during the program, would get a colonoscopy unrelated to CRC screening 5-10 years before the start of the screening program; 6) dependency of gFOBT results in sequential screening rounds were assumed for 74% of the large adenomas (≥10mm), because individuals with a false negative test result are likely to have a higher than average probability to have another false negative test result at a successive screening round.[16]

The following assumptions only had an effect during the screening programs (2008-2038): 7) the family history assessment was only able to identify 50% if the increased risk individuals (those individuals with a false negative family history assessment were assumed to receive gFOBT instead of colonoscopy screening) 8) biennial gFOBT screen-

ing was replaced by either annual gFOBT, biennial faecal immunochemical test (FIT) at a cut-off level of 50 or 100 ng Hb/ml, five-yearly sigmoidoscopy, or annual Hemoccult Sensa; 9) all screening participants, including those at average risk, were screened with ten-yearly colonoscopy; 10) screening uptake in the average risk and increased risk populations during the screening programs was varied independently from 30% to 100% at ten percent increments.

Outcomes

The main outcomes of the analysis are the cumulative number of CRC deaths prevented and colonoscopies performed in the population aged 50 years and older, in the program screening scenarios between 2008 and 2038, compared to opportunistic screening. In addition, we provide age adjusted annual CRC incidence and mortality rates as intermediate outcomes.

All simulation runs were performed using common random seeds, and a large sample size (600 million) in order to minimise the impact of stochastic variations on model outcomes.

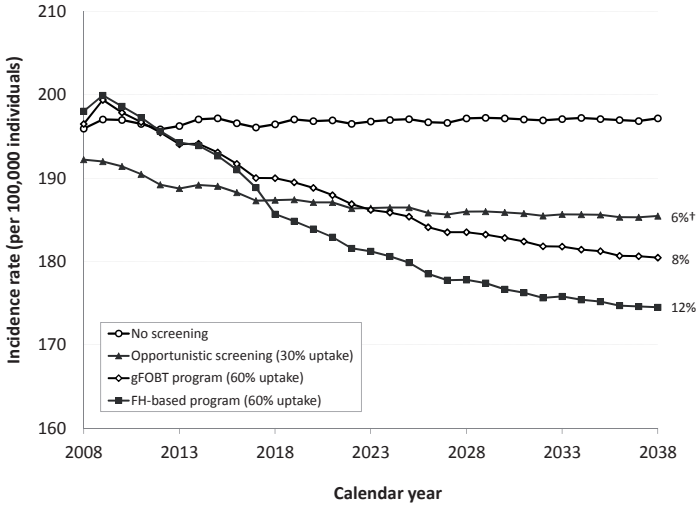

Figure 1. Age adjusted* CRC incidence rate per 100,000 individuals aged 50 years and older, after implementing screening programs with and without family history-based screening in Ontario.
CRC: colorectal cancer; gFOBT: guaiac faecal occult blood test; FH: family history.
* The data are age adjusted to the 1991 Canadian Standard Population aged 50 years and older.
In the model we did not take into account historical changes in risk factor prevalence or CRC relative survival, therefore any simulated changes in CRC incidence and mortality are attributable solely to changes in screening behaviour. The no screening scenario provides an estimate of background CRC risk in the absence of screening.
† Numbers behind the curves indicate the CRC incidence reduction of the screening scenarios compared the no screening in the year 2038.

RESULTS

In all scenarios screening participation was increasing slowly in the years before 2008, reaching 30% uptake with ten-yearly colonoscopy in the increased risk population and 30% uptake with biennial gFOBT in the average risk population. In the opportunistic screening scenario screening participation was assumed to level off from 2008 onwards. As a result, the age-adjusted CRC incidence rate in this scenario was first decreasing following 2008, and with a lag time levelled off at 185.5 cases per 100,000 individuals per year in 2038 (Figure 1). Assuming that the gFOBT and family history-based screening programs increased screening uptake from 30% to 60% resulted in an increase in CRC incidence in the first years of the programs, reflecting the detection of prevalent cancers in screened individuals. After approximately ten years the CRC incidence rate dropped below that of the opportunistic screening scenario, resulting in 180.5 and 174.5 cases per 100,000 per year in 2038, in the gFOBT and family history-based programs respectively. In the opportunistic screening scenario the CRC mortality rate declined from 71.0 to 66.7 deaths per 100,000 individuals per year in 2038. With the gFOBT and family

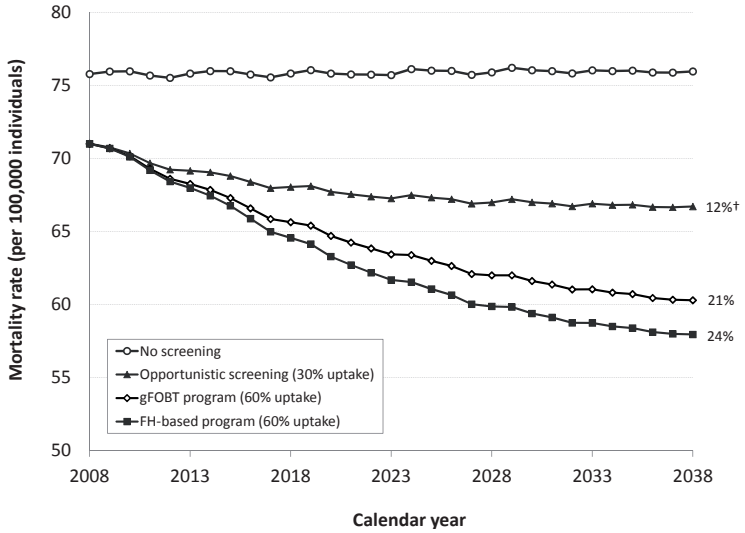

Figure 2. Age adjusted* CRC mortality rate per 100,000 individuals aged 50 years and older, after implementing screening programs with and without family history-based screening in Ontario.
CRC: colorectal cancer; gFOBT: guaiac faecal occult blood test; FH: family history.
* The data are age adjusted to the 1991 Canadian Standard Population aged 50 years and older.
In the model we did not take into account historical changes in risk factor prevalence or CRC relative survival, therefore any simulated changes in CRC incidence and mortality are attributable solely to changes in screening behaviour. The no screening scenario provides an estimate of background CRC risk in the absence of screening.
† Numbers behind the curves indicate the CRC mortality reduction of the screening scenarios compared the no screening in the year 2038.

history-based screening programs the mortality rate declined to 60.3 and 57.9 deaths per 100,000 per year, in 2038 (Figure 2).

The cumulative number of CRC deaths prevented reached 6,700 by 2038 in the gFOBT program, compared to opportunistic screening (Figure 3). The family history-based program resulted in 9,300 deaths prevented by 2038, a 40% increase compared to the gFOBT program. In order to achieve this effect the cumulative number of colonoscopies performed compared to opportunistic screening increased by 93% from 570,000 in the gFOBT program, to 1,100,000 in the family history-based program (Figure 4).

Sensitivity Analyses

The results were robust to varying model assumptions. In most sensitivity analyses the family history-based program provided 20-51% more deaths prevented than the gFOBT program, compared to opportunistic screening, while requiring 43-116% more colonoscopies (Table 2). However, the results were sensitive to gFOBT screening interval and main screening modality. Annual gFOBT screening or replacing Hemoccult II by FIT, Hemoccult Sensa, or sigmoidoscopy reduced both the additional benefit and colonoscopies required of family history-based compared to non-family history-based screening: 3-16% additional deaths prevented (base case: 40%) and 11-55% additional colonoscopies required (base case: 93%).

In the base case analysis, we assumed 60% screening uptake with colonoscopy in individuals with a family history (the same uptake rate as gFOBT screening in average risk individuals). If colonoscopy uptake in the family history-based program was 40% or less, this program became less effective than the gFOBT program (6,400 versus 6,700 deaths prevented compared to opportunistic screening, Appendix Table 1).

DISCUSSION

Our results suggest that a family-history based CRC screening approach where individuals at increased risk are offered colonoscopy screening, could prevent approximately 40% (range: 20-51%) more deaths within 30 years, than a program that only recommends biennial gFOBT (Hemoccult II) screening. In order to achieve this effect, 93% (range: 43-116%) more colonoscopies would be required. In a screening program that performs gFOBT annually, or uses FIT, Hemoccult Sensa, or sigmoidoscopy instead of Hemoccullt II, a family history-based screening approach would still be more effective but the added benefits and added colonoscopy demand are reduced.

In the opportunistic screening scenario there is a lag time between the levelling off of the screening uptake rate and the levelling off of the CRC incidence and mortality. This lag time results from the increasing trend in screening participation before 2008 and the

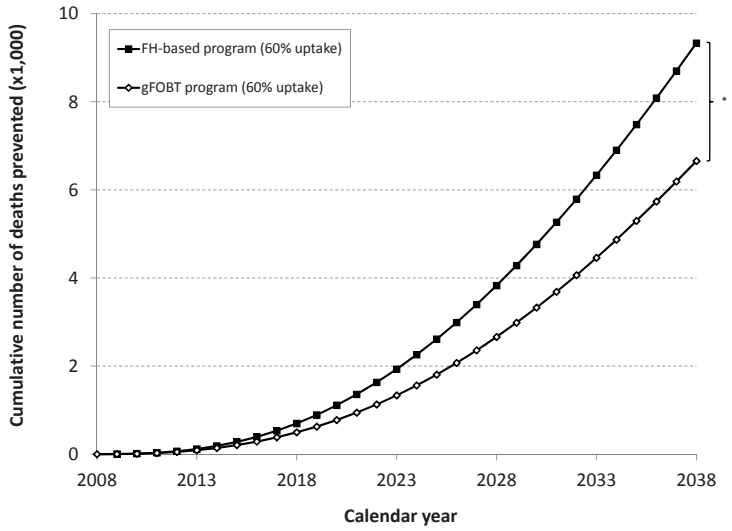

Figure 3. Cumulative number of CRC deaths prevented in the population aged 50 years and older, after implementing screening programs with and without family history-based screening in Ontario, compared to opportunistic screening.
CRC: colorectal cancer; gFOBT: guaiac faecal occult blood test; FH: family history.
* Added effect the family history-based program, compared to the gFOBT program: 2,700 additional CRC deaths were prevented by 2038.

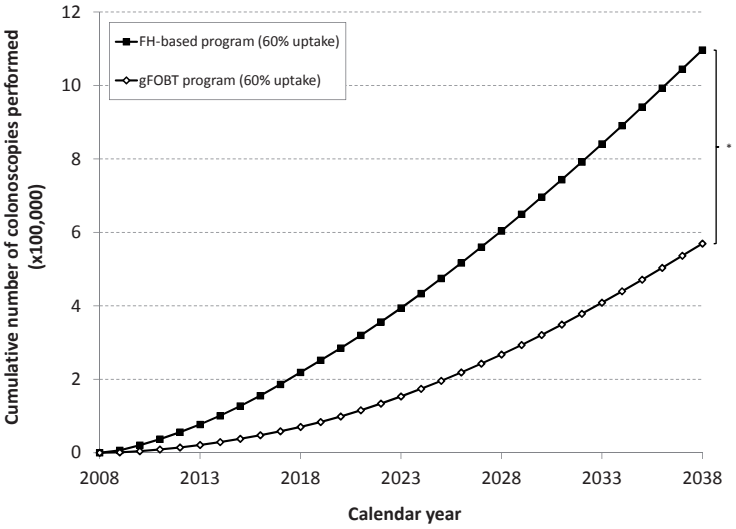

Figure 4. Cumulative number of colonoscopies performed in the population aged 50 years and older, after implementing screening programs with and without family history-based screening in Ontario, compared to opportunistic screening.
CRC: colorectal cancer; gFOBT: guaiac faecal occult blood test; FH: family history.
* Added effect the family history-based program, compared to the gFOBT program: 530,000 additional colonoscopies were performed by 2038.

Table 2. Overview of the sensitivity analyses. Cumulative number of CRC deaths prevented and colonoscopies performed by 2038 in the screening programs with and without family history-based screening in Ontario, compared to opportunistic screening.*

	Additional CRC deaths prevented (x1,000)			**Additional colonoscopies performed (x100,000)**		
Scenario	gFOBT program (A)	FH-based program (B)	Difference (B-A)	gFOBT program (A)	FH-based program (B)	Difference (B-A)
Base case	6.7	9.3	2.7 (40%)	5.7	11.0	5.3 (93%)
RR for CRC among those with a family history: 2.24 → 1.62	6.6	8.6	1.9 (29%)	5.7	10.8	5.1 (90%)
RR for CRC among those with a family history: 2.24 → 2.86*	6.7	10.1	3.4 (50%)	5.7	11.0	5.4 (95%)
Proportion at increased risk: 11% → 8%†	6.4	8.3	1.9 (31%)	5.6	9.4	3.8 (68%)
Proportion at increased risk: 11% → 14%†	6.9	10.3	3.4 (49%)	5.8	12.5	6.7 (116%)
Uptake rate diagnostic and surveillance colonoscopies: 71%/80% → 85%/85%	7.7	10.2	2.5 (32%)	6.6	11.9	5.3 (80%)
10% increased CRC survival for all increased risk individuals	6.5	8.9	2.4 (37%)	5.7	11.0	5.3 (93%)
15% of the population get a colonoscopy unrelated to CRC screening before the start of the screening program	5.1	7.4	2.3 (44%)	5.1	10.0	5.0 (98%)
Sensitivity of FH assessment: 100% → 50%	6.7	8.0	1.3 (20%)	5.7	8.3	2.6 (46%)
Dependency of gFOBT test results between screening rounds	5.7	8.6	2.9 (51%)	4.9	10.4	5.5 (111%)
Biennial gFOBT replaced by:						
• Annual gFOBT	10.5	12.2	1.7 (16%)	10.5	15.0	4.6 (44%)
• Biennial FIT50	12.7	13.9	1.1 (9%)	12.5	16.6	4.1 (33%)
• Biennial FIT100	11.0	12.6	1.6 (14%)	8.4	13.1	4.7 (55%)

• 5-yearly sigmoidoscopy	10.7	12.3	1.6 (15%)	8.4	12.5	4.1 (48%)
• Annual Hemoccult Sensa	15.6	16.0	0.4 (3%)	24.9	27.7	2.8 (11%)
10-yearly colonoscopy screening for all (including average risk individuals)	-	17.3	-	-	50.6	-

CRC: colorectal cancer; gFOBT: guaiac faecal occult blood test; FH: family history; FIT50: faecal immunochemical test, 50 ng Hb/ml cut-off value; FIT100: faecal immunochemical test, 100 ng Hb/ml cut-off value

Legend:

Base case: base case scenario.

RR for CRC among those with a family history: 2.24 → 1.62: relative risk of individuals with a family history of CRC is assumed 1.62 compared to the general population (base case value: 2.24).

RR for CRC among those with a family history: 2.24 → 2.86: the relative risk of individuals with a family history of CRC is assumed 2.86 compared to the general population (base case value: 2.24).

Proportion at increased risk: 11% → 8%: 8% of the population is considered to be at increased risk because of a family history of CRC (base case value: 11%).

Proportion at increased risk: 11% → 14%: 14% of the population is considered to be at increased risk because of a family history of CRC (base case value: 11%).

Uptake rate diagnostic and surveillance colonoscopies: 71%/80% → 85%/85%: the uptake rate of both diagnostic and surveillance colonoscopies was increased to 85% (base case value: 71% and 80% respectively).

10% increased CRC survival for all increased risk individuals: age- and stage-specific CRC relative survival in individuals with a family history is improved by 10%.

15% of the population get a colonoscopy unrelated to CRC screening before the start of the screening program: 15% of the population who did not participate in CRC screening prior to the program (but who would start screening during the program) get a colonoscopy unrelated to CRC screening 5-10 years before the start of the screening program.

Sensitivity of FH assessment: 100% → 50%: the family history assessment was only able to identify 50% if the increased risk individuals (those individuals with a false negative family history assessment were assumed to receive gFOBT instead of colonoscopy screening).

Dependency of gFOBT test results between screening rounds: 74% of all large adenomas (≥10 mm) that are not detected by gFOBT, will not be detected in the next screening round.[16]

Biennial gFOBT replaced by: annual gFOBT/biennial FIT50/biennial FIT100/5-yearly sigmoidoscopy/annual Hemocccult Sensa: biennial gFOBT screening was replaced by either annual gFOBT, biennial faecal immunochemical test (FIT) at a cut-off level of 50 ng Hb/ml, biennial FIT at a cut-off level of 100 ng Hb/ml, five-yearly sigmoidoscopy, or annual Hemoccult Sensa.

10-yearly colonoscopy screening for all (including average risk individuals): all screening participants are screened with 10-yearly colonoscopy screening.

* Results include events in the population aged 50 years and older.

†[x]→[y]: [x] represents the base case value, and [y] represents the alternative value assumed in the sensitivity analysis.

time it takes for the removal of adenomas and early detection of CRC to have an effect on CRC incidence and mortality.

The benefits of the CRC screening programs are directly related to the additional number of colonoscopies performed. Implementing a family history-based screening program, and similarly, reducing the gFOBT screening interval or replacing gFOBT by FIT or sigmoidoscopy will increase the number of colonoscopies required. In many health care systems colonoscopy capacity is limited and in order to prevent unacceptably long waiting lists, the introduction of a large scale screening program requires careful planning up front and a phased rollout in the target population.

Although this study focused on the added benefits of family history-based screening, compared to a regular gFOBT program, one could argue that increasing gFOBT uptake in the general population has a larger potential for health benefits than providing a more sensitive test in the family history population (which is only about 11% of the general population). Based on the data from Appendix Table 1 we estimated that compared to 60% screening uptake in the gFOBT program (6,700 additional deaths prevented compared to opportunistic screening), providing colonoscopy to increased risk individuals (also with 60% uptake) was approximately as effective as increasing the gFOBT screening participation in the general population to 70% (9,300 versus 8,900 additional deaths prevented respectively).

To our knowledge only one published study had estimated the added benefits of family history-based screening within a population-based screening program.[21] Ramsey et al. modelled several scenarios where individuals with a family history were screened with colonoscopy from younger ages and/or with shorter screening intervals than the average risk population. The study estimated fewer additional CRC deaths prevented with family history screening than our current analysis. The difference is mainly explained by the screening test used; in the study of Ramsey et al. all individuals in usual care (including average risk) were screened with colonoscopy between age 50 and 80 years. Colonoscopy is a more sensitive test than gFOBT, leaving less room for additional health benefits from family history screening. Furthermore, Ramsey et al. used a narrower definition of a positive family history; one first degree relative diagnosed with CRC before age 60 or two or more affected first degree relatives of any age. Using this definition, only two percent of the population had a positive family history, compared to 11% in our analysis.

We have focused on family history, because this was the strategy used in the province-wide screening program in Ontario. However, several other risk factors, in addition to family history, are also associated with an increased risk for CRC.[22] Researchers have proposed risk prediction models to help customise screening recommendations.[23-28] Although most of these models look promising, none has been implemented in population-based screening. Inclusion of one or more risk factors into a risk stratified

screening program, or considering different levels of risk within the family history population (e.g. individuals with more than one first degree relative with CRC), might provide greater health benefits compared to the findings in our analysis. However, such strategy would make the program more complicated and if more individuals will be identified as being at increased risk the colonoscopy demand will also increase.

Several limitations need to be acknowledged. First, there are no randomised controlled trial data available yet for the effect of colonoscopy screening on CRC incidence and mortality, but there is data available for sigmoidoscopy.[29] We assumed that the effectiveness of sigmoidoscopy in the distal colon and rectum could be extrapolated to the proximal colon when using colonoscopy. However, it has been suggested that colonoscopy effectiveness might be lower in the proximal colon, because proximal lesions are more often flat and might have a higher probability to progress into CRC.[30] This would mean we might have overestimated the mortality reduction from screening increased risk individuals with colonoscopy instead of gFOBT.

Second, we assumed that the increased risk in individuals with a family history is solely the result of an increased adenoma incidence. In reality, reduced adenoma dwell time and/or a greater proportion of adenomas that progress to cancer may also play a role. If this were the case, the added benefits of colonoscopy screening in increased risk individuals might be reduced.

Third, we only modeled CRC screening between age 50-74. However, for people at increased risk of colorectal cancer due to a family history, the ColonCancerCheck program recommends screening with colonoscopy beginning at age 50 or 10 years earlier than the age at which their relative was diagnosed, whichever occurs first.[5] Since we did not take into account the effects of the family-history based program in individuals who will participate in screening before age 50, we have underestimated both the number of colonoscopies performed and number of deaths prevented of the family history-based program compared to the gFOBT program.

Fourth, we assumed that the family physician was able to identify all individuals with a family history of CRC in clinical assessment. Using this approach we are able to demonstrate the potential added health benefits of a stratified screening approach. However, family history assessments by the physician do not identify all individuals at increased risk in the general population.[31] If the family history assessment would only manage to identify 50% of the individuals at increased risk, both the number of CRC deaths prevented and number of colonoscopies performed would decreased by a similar proportion (see sensitivity analyses). In addition, most population-based screening programs will identify individuals at increased risk at least to some degree. For instance, on the patient information website about the national FIT screening program in The Netherlands it is recommended to seek medical advice if there is a family history of

cancer.[32] This might reduce the added effects of family history-based screening within gFOBT programs.

Finally, we did not include costs in our analysis. Screening with both gFOBT and colonoscopy have been demonstrated to be very cost-effective in the general population.[4] Unless the process of family history assessment is very costly, we anticipate that colonoscopy screening of individuals with a family history would be cost-effective. However, for healthcare systems considering implementing a screening program a cost-effectiveness analysis would still be necessary before family history risk assessment would be incorporated. In addition, even if a family history-based screening program is cost-effective it would require a considerable upfront financial investment which may become a barrier given the currently available health care budget.

In Ontario the family history assessment is performed during one consultation with the family physician (approximately 10 minutes) and the reimbursement rate for a consultation is approximately 32 Canadian dollars.[33] There is currently no data available about the acceptance rate to colonoscopy screening after an individual has been identified to have an increased risk for CRC.

In conclusion, a biennial gFOBT screening program that identifies individuals with a family history of CRC (approximately 11% of the general population) and recommends them to undergo colonoscopy screening would prevent 40% (range: 20-51%) additional deaths while requiring 93% (range: 43-116%) additional colonoscopies, compared to a regular gFOBT program. In order to increase the health benefits of a gFOBT screening program, a strategy incorporating family history risk assessment comparable to the Ontario province-wide CRC screening program should be considered.

Acknowledgements

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APPENDIX

Appendix Table 1.

Appendix Table 1.1. Cumulative number of CRC deaths prevented (x1,000) in Ontario by 2038, in the programs with and without family history-based screening, compared to opportunistic screening.*

Screening participation in average risk population	Screening participation in increased risk population: 30%	40%	50%	60%	70%	80%	90%	100%
30%	0·0	0·6	1·1	1·7	2·2	2·8	3·3	3·9
	0·0	1·4	2·9	4·3	5·8	7·2	8·7	10·1
40%	1·7	2·2	2·8	3·3	3·9	4·4	5·0	5·5
	1·7	3·1	4·6	6·0	7·4	8·9	10·3	11·8
50%	3·3	3·9	4·4	5·0	5·5	6·1	6·6	7·2
	3·3	4·8	6·2	7·7	9·1	10·6	12·0	13·4
60%	5·0	5·6	6·1	6·7	7·2	7·8	8·3	8·9
	5·0	6·4	7·9	9·3	10·8	12·2	13·7	15·1
70%	6·7	7·2	7·8	8·3	8·9	9·4	10·0	10·5
	6·7	8·1	9·6	11·0	12·4	13·9	15·3	16·8
80%	8·3	8·9	9·4	10·0	10·5	11·1	11·6	12·2
	8·3	9·8	11·2	12·7	14·1	15·6	17·0	18·4
90%	10·0	10·6	11·1	11·7	12·2	12·8	13·3	13·9
	10·0	11·4	12·9	14·3	15·8	17·2	18·7	20·1
100%	11·7	12·2	12·8	13·3	13·9	14·4	15·0	15·5
	11·7	13·1	14·6	16·0	17·4	18·9	20·3	21·8

Family history-based program

	No
	Yes

CRC: colorectal cancer; gFOBT: guaiac faecal occult blood test.

* Screening participation in 2008 was assumed 30% in both the increased risk and average risk populations, increased risk receiving ten-yearly colonoscopy, and average risk receiving biennial gFOBT screening. In the gFOBT program (no family history-based screening), colonoscopy screening uptake in the increased risk population was assumed to remain at 30%. The additional screening participants as a result of the program were assumed to receive gFOBT. In the average risk population all screening participants received gFOBT. In the family history-based program all increased risk individuals received colonoscopy screening, and all average risk individuals received gFOBT screening.

Appendix Table 1.2. Cumulative number of colonoscopies performed (x100,000) in Ontario by 2038, in the programs with and without family history-based screening, compared to opportunistic screening.*

Screening participation in average risk population	Screening participation in increased risk population							
	30%	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**	**100%**
30%	0·0	0·3	0·6	0·9	1·2	1·5	1·8	2·1
	0·0	2·1	4·1	6·2	8·2	10·3	12·3	14·4
40%	1·6	1·9	2·2	2·5	2·8	3·1	3·4	3·7
	1·6	3·7	5·7	7·8	9·8	11·9	13·9	16·0
50%	3·2	3·5	3·8	4·1	4·4	4·7	5·0	5·3
	3·2	5·3	7·3	9·4	11·4	13·5	15·5	17·6
60%	4·8	5·1	5·4	5·7	6·0	6·3	6·6	6·9
	4·8	6·9	8·9	11·0	13·0	15·1	17·1	19·2
70%	6·4	6·7	7·0	7·3	7·6	7·9	8·2	8·5
	6·4	8·4	10·5	12·6	14·6	16·7	18·7	20·8
80%	8·0	8·3	8·6	8·9	9·2	9·5	9·8	10·1
	8·0	10·0	12·1	14·2	16·2	18·3	20·3	22·4
90%	9·6	9·9	10·2	10·5	10·8	11·1	11·4	11·7
	9·6	11·6	13·7	15·8	17·8	19·9	21·9	24·0
100%	11·2	11·5	11·8	12·1	12·4	12·7	13·0	13·3
	11·2	13·2	15·3	17·4	19·4	21·5	23·5	25·6

Family history-based program

No

Yes

CRC: colorectal cancer; gFOBT: guaiac faecal occult blood test.

* Screening participation in 2008 was assumed 30% in both the increased risk and average risk populations, increased risk receiving ten-yearly colonoscopy, and average risk receiving biennial gFOBT screening. In the gFOBT program (no family history-based screening), colonoscopy screening uptake in the increased risk population was assumed to remain at 30%. The additional screening participants as a result of the program were assumed to receive gFOBT. In the average risk population all screening participants received gFOBT. In the family history-based program all increased risk individuals received colonoscopy screening, and all average risk individuals received gFOBT screening.

Part 2

Optimising health effects and costs of non-invasive colorectal cancer screening

Chapter 5

Harms, benefits and costs of faecal immunochemical testing versus guaiac faecal occult blood testing for colorectal cancer screening

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Submitted

ABSTRACT

Background. The ColonCancerCheck screening program in Ontario, Canada, recommends biennial Hemoccult II guaiac faecal occult blood test (gFOBT) screening between age 50-74 years for individuals at average risk of colorectal cancer (CRC). Faecal immunochemical test (FIT) screening is generally considered more sensitive, but also less specific and would therefore require more colonoscopies. The aim of this study is to estimate whether the benefits of FIT screening outweigh the harms and costs, compared to gFOBT screening.

Methods. We used microsimulation modelling to estimate quality adjusted life years (QALY) gained and costs of gFOBT and FIT, compared to no screening, in a cohort of screening participants. We compared strategies for different age groups (start and stop age), screening intervals, and FIT cut-off levels at various levels of colonoscopy capacity.

Results. FIT is more effective and less costly, when compared to gFOBT. Without expanding colonoscopy demand compared to the current strategy in Ontario, biennial FIT (with a cut-off level of 200 ng Hb/ml) between age 50-74 years is the most effective strategy (31 QALY gained per 1000 participants, compared to no screening) and is highly cost-effective. Without restrictions in colonoscopy capacity, and assuming a willingness-to-pay threshold of CAN$50,000 per QALY gained, FIT (with cut-off level 50) every 1.5 years between age 45-84 years would be the preferred strategy (47 QALY gained per 1000 participants).

Interpretation. Compared to gFOBT screening, switching to FIT at a high cut-off level could increase the health benefits of a CRC screening program without considerably increasing colonoscopy demand.

INTRODUCTION

In most developed countries, including Canada, colorectal cancer (CRC) is the second leading cause of cancer deaths and the third most commonly diagnosed cancer.[1, 2] Screening for CRC and its precursor lesions, adenomas, can detect colorectal neoplasia at an earlier stage when treatment is potentially more effective, resulting in reduced CRC incidence and mortality.[3, 4]

Like a number of regions around the world,[5, 6] the province-wide ColonCancer-Check screening program in Ontario, uses the Hemoccult II guaiac faecal occult blood test (gFOBT) to screen individuals at average risk of CRC.[7] Faecal immunochemical testing (FIT) offers several advantages over gFOBT, including greater sensitivity, no need for dietary restrictions and automated processing of test kits.[8] However, depending on the cut-off level used FIT also has a lower specificity, which is associated with increased colonoscopy demand and number of false positive test results.

At the time of the funding announcement and public launch of the ColonCancerCheck program, the evidence base to support FIT was increasing, but FIT was not yet endorsed by the Canadian Task Force on Preventive Health Care.[9] Hence the implementation of gFOBT by the program. Currently the evidence base has increased sufficiently for the program to reconsider FIT as a screening option. In order to inform this decision, the aim of the present study is to compare the harms, benefits and costs of gFOBT and FIT screening in average risk individuals.

METHODS

We used the MISCAN-Colon microsimulation model to estimate the quality adjusted life years (QALY) gained and costs of gFOBT and FIT screening with varying screening age ranges and intervals, and various FIT cut-off levels in a cohort of average risk Ontarians. Cost-efficient strategies were determined for different levels of available colonoscopy capacity.

MISCAN-colon microsimulation model

The MISCAN-colon model and the data sources that inform the quantifications of the model are described in detail in the Model Appendix at the end of this thesis and in previous publications.[10-12] In brief, the MISCAN-colon model simulates the life histories of individuals from birth to death. CRC arises in the population according to the adenoma-carcinoma sequence.[13, 14] More than one adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas can progress in size from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm), and some may eventually

become malignant. A preclinical (i.e., not detected) cancer has a chance of progressing through stages I to IV and may be detected by diagnostic work-up of symptoms at any stage. After the diagnosis of CRC, survival depends on the stage at diagnosis. At any time during their life individuals may die of other causes.

With screening, an individual with a positive test will be referred for diagnostic colonoscopy for possible removal of adenomas and detection of cancers. In this way CRC incidence and mortality can be reduced. The life years gained (LYG) by screening are calculated as the difference in model-predicted life years lived in the population with and without CRC screening.

The validity of the MISCAN-colon model has been successfully tested on the results of large screening and surveillance studies, such as the randomised trials of gFOBT in Minnesota, Funen, and Nottingham,[12] the CoCap sigmoidoscopy study,[15] and the National Polyp Study.[16] In addition, the model was able to explain observed CRC incidence and mortality trends in the United States when accounting for risk factor trends, screening practice, and chemotherapy use.[17]

Study Population

We modeled a cohort of 40-year-old screening participants at average risk of CRC which was followed until death. The CRC incidence and stage distribution were calibrated to incidence data from the Canadian Cancer Registry for 2001, which was prior to the introduction of screening.[18] The model used all-cause mortality estimates from the 2009-2011 Ontario life tables.[19] Because stage-specific data on CRC relative survival were not available for Canada, we assumed similar relative survival as observed in the Surveillance, Epidemiology, and End-Results (SEER) database in the US, in the period 2000-2003.[20]

Screening Strategies

We considered screening schedules for both gFOBT and FIT varying by age to start screening (40, 45, 50, 55, 60 or 65 years), age to stop screening (70, 75, 80 or 85 years), screening interval (1, 1.5, 2, or 3 years), and FIT cut-off level (50, 75, 100, 150 and 200 ng Hb/ml). The combinations of these variables resulted in 576 unique screening strategies.

After a positive test result individuals were referred for diagnostic colonoscopy. Depending on the number and size of adenomas detected, the individual would be recommended for surveillance colonoscopy based on current guidelines [21-24].

Test characteristics

The test characteristics of gFOBT (Hemoccult II) were based on a prior calibration of the MISCAN-Colon model to three large gFOBT trials (Table 1).[12] It was assumed that, the probability a CRC bleeds and thus the sensitivity of gFOBT for CRC depends on the time

Table 1. Test characteristics of the screening tests used in the model.

Screen test	Specificity (%)	Sensitivity* (%)					
		Adenoma			CRC		
		Small (≤5mm)	Medium (6-9mm)	Large (≥10mm)	Early preclinical†	Late preclinical†	Average
gFOBT	98	2	3	8	20	52	33
FIT 50	96	4	15	37	52	83	65
FIT 75	97	3	9	31	48	81	62
FIT 100	98	2	7	28	43	77	57
FIT 150	98	2	5	25	41	76	56
FIT 200	99	1	4	21	40	76	55
Colonoscopy‡	90	75	85	95	95	95	95

CRC, colorectal cancer; gFOBT, guaiac faecal occult blood test; FIT, faecal immunochemical test.

* Sensitivity is presented per participant for faecal occult blood tests and per lesion for colonoscopy.

† It was assumed that the probability a CRC bleeds and thus the sensitivity of gFOBT and FIT for CRC depend on the time until clinical diagnosis, based on a prior calibration of the MISCAN-Colon model to three gFOBT trials.[12] This result is to be expected when cancers that bleed do so increasingly over time, starting in occult fashion and progressing to grossly visible.

‡ Colonoscopy was only used during follow-up and surveillance after a positive gFOBT or FIT. The lack of specificity of colonoscopy reflects the detection of hyperplastic polyps, which do not follow the adenoma-carcinoma sequence.[29] Additional biopsy costs were assumed for procedures where biopsies were performed and in which, in retrospect, no adenomas were detected.

until clinical diagnosis, i.e. cancers that bleed do so increasingly over time, starting in occult fashion and ending as grossly visible. The test characteristics of FIT (OC-Sensor Micro; Eiken Chemical Co, Tokyo, Japan) were fitted to the FIT positivity rates and detection rates of adenomas and CRC observed in the first screening round of two Dutch randomised trials.[25-27] We considered FIT cut-off levels of 50, 75, 100, 150 and 200 ng Hb/ml, yielding different combinations of sensitivity and specificity. The test characteristics of colonoscopy were based on a systematic review of polyp miss rates in tandem colonoscopy studies.[28] The lack of specificity of colonoscopy reflects the detection of hyperplastic polyps, which do not follow the adenoma-carcinoma sequence.[29] Additional biopsy costs were assumed for procedures where biopsies were performed and in which, in retrospect, no adenomas were detected.

Health-related quality of life

Health benefits were expressed in quality adjusted life years (QALY) gained. In the model, health-related quality of life declines with increasing age based on a large longitudinal study on the quality of life of Canadians.[30] We incorporated utility losses associated with colonoscopy and its associated complications and CRC using a multiplicative approach (Table 2). Losses in health utility (i.e. loss of quality of life) associated with

Table 2. Utility weights used in the model.

Variable	Utility loss			
Screening, per event				
gFOBT	-			
FIT	-			
Colonoscopy, no polypectomy	0.0055			
Colonoscopy, polypectomy	0.0055			
Complication, bleeding*	0.0384			
Complication, perforation*	0.0384			
Treatment, per person year of CRC care[31]†	*Initial care*	*Continuous care*	*Terminal care, death CRC*	*Terminal care, death other causes*
Stage I	0.15	0.10	0.29	0.10
Stage II	0.15	0.10	0.29	0.10
Stage III	0.15	0.10	0.29	0.10
Stage IV	0.34	0.29	0.29	0.29

gFOBT: guaiac faecal occult blood test; FIT: faecal immunochemical test; CRC: colorectal cancer.
*We assumed a utility loss equivalent to 2 days of life per colonoscopy performed (0.0055 QALYs) and 2 weeks of life for non-lethal complications (0.0384 QALYs). We assumed complications with bleeding in 1.64 per 1,000 procedures, and complications with perforation in 0.85 per 1,000 procedures.[32] In addition, we assumed 1/14,000 colonoscopies resulted in fatal complications.[32]
† 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.

CRC were based on a recent literature review (Table 2).[31] We assumed a utility loss equivalent to 2 days of life per colonoscopy performed (0.0055 QALYs), 2 weeks of life for non-lethal complications (0.0384 QALYs).

Costs

The analysis was conducted from a third party health-care payer perspective. All costs were expressed in 2013 Canadian dollars (Table 3). The cost of gFOBT included costs of test kit, dispensing fee, postage, lab processing, communicating results to the participants and collecting data for the screening registry, and was obtained from the ColonCancerCheck program. Since FIT is currently not funded in Ontario, the costs of test kit and processing are unknown. Therefore we estimated the costs of the FIT test kit and processing based on the difference between gFOBT and FIT in a Dutch screening trial[33, 34], and applied this difference to the cost of gFOBT in Ontario. We assumed that the dispensing fee and communication of the test results would be identical to gFOBT. The costs attributable to CRC care by CRC stage and phase of care (initial, continuing,

Table 3. Cost estimates used in the model (2013 Canadian dollars).

Variable	Cost (CAN$)				Source
Fixed program costs per year (assumed identical for gFOBT and FIT screening)	Year 1: 6,592,000, Year 2: 15,151,000, Year 3: 13,536,000, Year 4: 10,876,000, Year 5: 11,071,000, Year 6+: 10,652,000				ColonCancerCheck program*
Screening, per event					
gFOBT	28.23				ColonCancerCheck program*
FIT†	31.11				ColonCancerCheck program*, [33, 34]
GP visit after positive stool test	34.73				[35]
Colonoscopy, no polypectomy	872				[35, 36]
Colonoscopy, polypectomy	1,097				[35, 36]
Complication, bleeding‡	3,521				[37]
Complication, perforation‡	34,412				[37]
Treatment, per person year of CRC care§	*Initial care*	*Continuous care*	*Terminal care, death CRC*	*Terminal care, death other causes*	
Stage I	27,453	3,135	322,472	33,542	Matched cohort study using health care administrative data (manuscript in preparation)
Stage II	44,500	6,648	219,717	42,262	
Stage III	64,998	10,187	146,543	35,942	
Stage IV	83,540	42,208	129,842	34,276	

gFOBT: guaiac faecal occult blood test; FIT: faecal immunochemical test; GP: general practitioner; CRC: colorectal cancer.

* The fixed program costs include costs for the screening registry, program infrastructure, communications and advertising, and sending activity reports to primary care physicians. Personal communication with co-author Dr. Linda Rabeneck, Vice President Prevention and Cancer Control at Cancer Care Ontario.

† FIT is currently not funded in Ontario, therefore the costs of test kit and processing are unknown. We estimated the costs of FIT test kit and processing based on the difference between gFOBT and FIT in a Dutch screening trial[33, 34], and applied this difference to the cost of gFOBT in Ontario.

‡ We assumed complications with bleeding in 1.64 per 1,000 procedures, and complications with perforation in 0.85 per 1,000 procedures.[32] In addition, we assumed 1/14,000 colonoscopies resulted in fatal complications.[32]

§ 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.

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 (manuscript in preparation).

Cost-effectiveness analyses

For each screening strategy we estimated the number of QALYs gained and costs, compared to no screening. Strategies that were more costly and less effective than other strategies were ruled out by simple dominance. Strategies that were more costly and less effective than a mix of other strategies were ruled out by extended dominance. The remaining strategies that had not been ruled out were referred to as "efficient" strategies. The incremental cost-effectiveness ratio (ICER) of an efficient strategy was determined by comparing its additional costs and effects to those of the next less costly and less effective efficient strategy.

Sensitivity analyses

We performed several sensitivity analyses assuming: 1) dependency of test results between screening rounds (74% of large adenomas could not be detected because they did not bleed [38]); 2) half and double the base case rate of colonoscopy complications; 3) 25% increased CRC relative survival; 4) FIT unit costs of 43.87 CAN$ (based on the difference in reimbursement rate between FIT and gFOBT in the US Medicare program[39]); 5) half and double the base case value for colonoscopy costs; 6) higher and lower CRC treatment costs (based on upper and lower bounds of 95% confidence interval, see Appendix Table 1 for exact values).

Outcomes

The main outcomes of the analysis were QALYs and costs per 1,000 participants, and number of colonoscopies per 1,000 participants per year, compared to no screening. Costs and QALYs were discounted by 3% per year[40], the number of colonoscopies were undiscounted.

RESULTS

The current screening strategy in Ontario, biennial gFOBT between age 50-74 years, yielded 20 QALY at a cost of CAN$43,600 per 1,000 screening participants, compared to no screening (Figure 1). When colonoscopy capacity is not a limiting factor, increasing the screening age range to 40-85 years with annual gFOBT could provide a maximum of 37 QALY at a cost of CAN$288,400 per 1,000 participants. For each gFOBT screening strategy there was a FIT strategy that provided more QALY at lower costs, therefore FIT dominated gFOBT. The FIT strategies on the efficient frontier provided 40 to 51 QALY, at a cost of -CAN$500,200 to -CAN$19,100 per 1,000 participants, compared to no screening. Assuming a willingness-to-pay threshold of CAN$50,000 per QALY gained, FIT every 1.5 years between age 45-84 years would be the preferred strategy, providing 47 QALY per 1,000 participants.

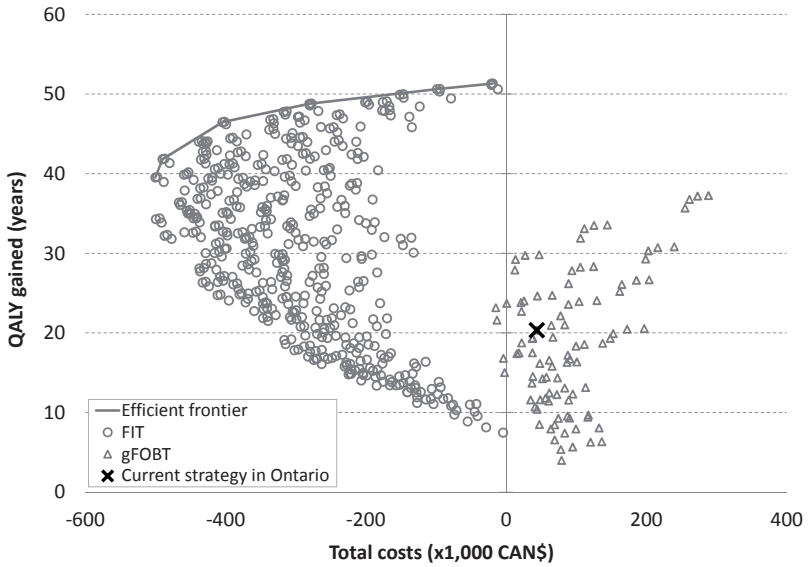

Figure 1. Discounted total costs and discounted QALYs gained, per 1,000 participants, of the gFOBT and FIT screening strategies compared to no screening.
QALY: quality adjusted life year; gFOBT: guaiac faecal occult blood test; FIT: faecal immunochemical test.
Current screening strategy in Ontario: biennial gFOBT, between age 50-74.
Strategies are varied by age at starting screening, age at stopping screening, screening interval, and FIT cut-off level. The cost-effective strategies are connected by the efficient frontier. Costs (expressed in 2013 Canadian dollars) and QALYs are discounted by 3% per year.

With unrestricted colonoscopy capacity almost all cost-effective strategies used FIT with a cut-off level of 50 ng Hb/ml (Table 4, see Table 5 for intermediate outcomes). The number of colonoscopies required for the strategies on the efficient frontier ranged from 35 to 69 per 1,000 participants per year. This is a two- to four-fold increase over the colonoscopy demand of the current screening strategy in Ontario (17 colonoscopies per 1,000 participants per year). However, when colonoscopy capacity was restricted to 40, 30, 20, or 17 colonoscopies per year FIT remained cost-effective over gFOBT. At 17 colonoscopies per 1,000 participants per year, biennial FIT with a cut-off level of 200 ng Hb/ml, between age 50-74 still provided 31 QALY at a cost of -CAN$289,700, compared to 20 QALY at a cost of CAN$43,600 for gFOBT (Figure 2).

Sensitivity analyses

The higher cost-effectiveness of FIT compared to gFOBT screening strategies was robust to alterations in our model assumptions. None of the sensitivity analyses resulted in a gFOBT strategy on the efficient frontier (Appendix Table 2). Varying colonoscopy costs had the largest impact on costs-effectiveness. When colonoscopy costs were 200% of the base case value the ICER ranged from -CAN$800 for biennial FIT100 between age

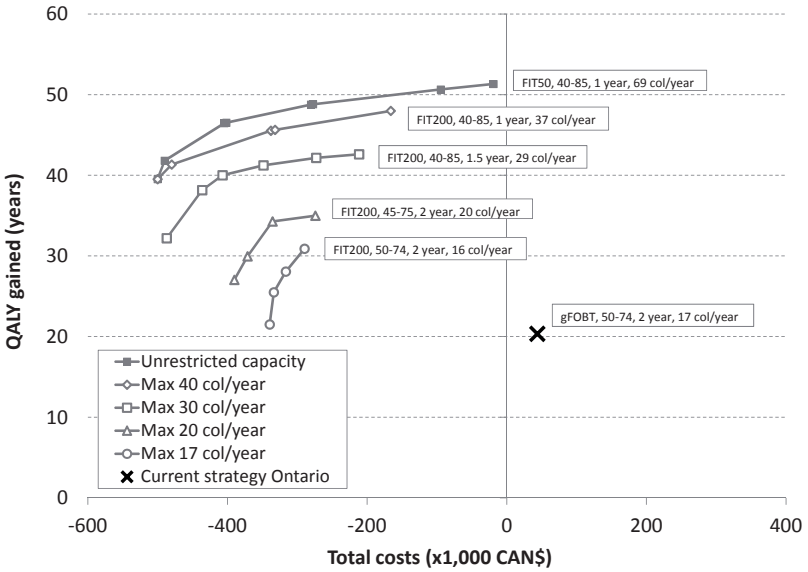

Figure 2. Efficient frontiers for different levels of colonoscopy capacity. Costs and QALYs gained per 1,000 participants, compared to no screening.
QALY: quality adjusted life year; gFOBT: guaiac faecal occult blood test; FIT: faecal immunochemical test; Col/year: number of colonoscopies required per 1,000 participants per year.
Strategies are varying by age at starting screening, age at stopping screening, screening interval, and FIT cut-off level. For each level of available colonoscopy capacity (maximal 17, 20, 30, 40 colonoscopies per 1,000 participants per year and unrestricted colonoscopy capacity) the cost-effective strategies are connected by their respective efficient frontier. The text boxes beside each frontier present the screening strategy (test, age range, interval and colonoscopy

60-74 years (providing 21 QALY) to CAN$491,200 for annual FIT50 between age 40-85 (providing 51 QALY).

INTERPRETATION

Our study shows that compared to the current CRC screening strategy in Ontario (biennial gFOBT between age 50-74 years), replacing gFOBT by FIT with a cut-off level of 200 ng Hb/ml provides more QALY at lower costs, without increasing the number of colonoscopies required. When the colonoscopy capacity would be expanded greater health benefits and cost-reductions could be achieved by lowering the FIT cut-off level and expanding the number of screening rounds. Without restriction in colonoscopy capacity and assuming a willingness-to-pay threshold of CAN$50,000 per QALY, FIT50 between age 40-84 years with a 1.5 year interval would be the most effective strategy providing 47 QALY compared to no screening.

Table 4. Overview of the current gFOBT screening strategy in Ontario, and efficient FIT screening strategies, compared to no screening. Outcomes per 1,000 participants.

Screen test	Start age (years)	Stop age (years)	Interval (years)	Col/year (N)	QALY (years)	Costs (CAN$)	ICER (CAN$)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	20.3	43,600	dominated
Cost-effective screening strategies							
Unrestricted colonoscopy capacity							
FIT 50	50	80	2	35.0	39.5	−500,200	−12,700
FIT 50	50	80	1.5	40.9	41.8	−490,000	4,400
FIT 50	45	79.5	1.5	48.8	46.5	−404,700	18,400
FIT 50	45	84	1.5	49.3	46.5	−401,700	46,200
FIT 50	45	80	1	58.6	48.8	−280,600	53,800
FIT 50	45	85	1	59.1	48.8	−277,500	88,000
FIT 75	40	85	1	58.8	50.6	−94,600	99,500
FIT 50	40	85	1	69.1	51.3	−19,100	111,500
Maximal 40 colonoscopies per 1,000 participants per year							
FIT 50	50	80	2	35.0	39.5	−500,200	−12,700
FIT 50	50	74	1.5	39.3	41.3	−480,000	11,200
FIT 150	45	80	1	36.2	45.5	−337,900	33,900
FIT 150	45	85	1	36.8	45.6	−331,900	53,800
FIT 200	40	85	1	37.3	48.0	−166,200	70,500
Maximal 30 colonoscopies per 1,000 participants per year							
FIT 50	55	79	2	28.5	32.2	−487,100	−15,100
FIT 100	50	80	1.5	28.7	38.2	−436,300	8,500
FIT 150	50	75	1	29.1	40.0	−407,200	15,800
FIT 150	45	84	1.5	29.2	41.2	−348,600	47,700
FIT 200	45	70	1	28.4	42.2	−273,000	80,500
FIT 200	40	85	1.5	29.3	42.6	−211,600	141,000
Maximal 20 colonoscopies per 1,000 participants per year							
FIT 50	55	70	3	19.9	27.0	−390,300	−14,400
FIT 150	55	79	1.5	19.5	30.0	−371,400	6,500
FIT 200	50	74	1.5	19.6	34.3	−335,500	8,300
FIT 200	45	75	2	19.9	35.0	−274,200	86,400
Maximal 17 colonoscopies per 1,000 participants per year							
FIT 50	60	75	3	16.8	21.5	−339,600	−15,800
FIT 75	55	73	3	16.8	25.5	−333,700	1,500
FIT 200	55	74.5	1.5	16.0	28.1	−316,500	6,700
FIT 200	50	74	2	16.4	30.9	−289,700	9,400

Col/year: number of colonoscopies required per 1,000 participants per year; QALY: quality adjusted life year gained; ICER: incremental cost-effectiveness ratio.
The number of colonoscopies per year are undiscounted. Costs and QALYs are discounted by 3% per year.

Table 5. Undiscounted intermediate model outcomes per 1,000 participants, compared to no screening.

Screen test (age range, interval)	Total tests (N)	Positive tests (N)	Col/year (N)	CRC cases (N)	CRC deaths (N)	LYG (years)	QALY (years)
Current screening strategy in Ontario							
gFOBT (50-74, 2)	10346	258	16.9	−12.6	−10.8	122.5	65.2
Cost-effective screening strategies (unrestricted colonoscopy capacity)							
FIT 50 (50-80, 2)	9778	529	35.0	−29.8	−19.3	215.9	123.4
FIT 50 (50-80, 1.5)	11695	609	40.9	−32.6	−20.2	225.8	130.3
FIT 50 (45-79.5, 1.5)	13094	659	48.8	−34.3	−20.7	240.6	141.5
FIT 50 (45-84, 1.5)	13574	684	49.3	−34.7	−21.1	242.5	141.8
FIT 50 (45-80, 1)	16107	779	58.6	−37.3	−21.6	250.9	148.3
FIT 50 (45-85, 1)	16543	800	59.1	−37.6	−21.8	252.1	148.5
FIT 75 (40-85, 1)	21469	746	58.8	−36.4	−21.8	257.7	152.1
FIT 50 (40-85, 1)	17791	839	69.1	−38.9	−22.2	261.4	154.9

Col/year: number of colonoscopies required per 1,000 participants per year; CRC: colorectal cancer; LYG: life year gained; QALY: quality adjusted life year gained.

The fact that screening FIT is less costly than gFOBT (and even cost-saving compared to no screening) results from the combination of increased sensitivity for adenomas and high costs for CRC treatments. GFOBT mainly detects CRC. While early detection of CRC does reduce mortality, it does not reduce CRC treatment costs by a large amount. On the other hand FIT, even at the cut-off level of 200 ng Hb/ml, is more than twice as sensitive for large adenomas than gFOBT, and therefore prevents more CRC and subsequent treatments. At the 200 cut-off level, the specificity of FIT is similar to gFOBT resulting in similar colonoscopy demand.

Most previous cost-effectiveness analyses found FIT screening to be cost-effective, but FIT was generally also more costly than gFOBT.[34, 41-46] However, most studies used outdated estimates of CRC treatment costs[47] and only considered a single, or a very limited number of screening strategies. Our findings are in line with the study by Heitman et al. which reported FIT screening with medium and high performance characteristics to be more effective and less costly than gFOBT.[48] Heitman et al. used an indirect method to estimate current CRC treatment costs in Canada. In our analysis we used recent CRC treatment data as observed with a fully allocated costing approach and included costs of recently introduced biologic therapies (manuscript in preparation). Our study adds to the results of Heitman et al. that benefits and costs differ widely among different FIT screening strategies and the preferred screening strategy (start and stop age, screening intervals and FIT cut-off level) depends on available colonoscopy capacity and willingness-to-pay threshold.

Our study has two limitations of note. First, there is considerable uncertainty in assumptions used in the model. We evaluated the impact of uncertainty on several pa-

rameters in one-way sensitivity analyses. One of the most uncertain assumptions is that all CRCs arise from adenoma precursors. We did consider a sensitivity analysis with the assumption that 74% of large adenomas did not bleed (and were therefore undetectable) by gFOBT and FIT[38], which did not greatly affect the relative cost-effectiveness of FIT compared to gFOBT. We did not perform a probabilistic sensitivity analysis. Given the large number of strategies that has to be evaluated for each draw, such an analysis would require a huge computational effort. We believe that simulating the range of varying strategies is one of the strengths of this analysis, because we were primarily interested in the comparison between different gFOBT and FIT screening strategies allowing for varying screening age ranges, intervals and FIT cut-off levels. Second, we assumed full adherence to screening, follow-up and surveillance invitations, in order to represent the cost-effectiveness for participants who follow program recommendations. On a population level, screening adherence will be less than 100%, which will impact the cost-effectiveness ratios. However, it has been demonstrated that adherence to FIT is greater than to gFOBT screening.[26, 27] Therefore the difference in cost-effectiveness between the two tests is likely to be even greater when screening adherence is taken into account.

This study has been performed in the setting of the ColonCancerCheck program in Ontario, Canada. In addition to Ontario, there are a number of regions around the world which use gFOBT in their CRC screening programs.[5, 6] Provided that the relative difference between the costs of screening tests and CRC care is not radically different from Ontario, the results from this study can be generalised to these other jurisdictions.

In conclusion, FIT is more effective and less costly than gFOBT screening in average risk individuals. The optimal FIT strategy depends on the available colonoscopy capacity. Compared to gFOBT screening, introducing FIT at a high cut-off level could increase the health benefits of a CRC screening program without considerably increasing colonoscopy demand.

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APPENDIX

Appendix Table 1.

Appendix Table 1. CRC treatment costs used in the sensitivity analyses.

Treatment, per person year of CRC care*	Initial care (CAN$)	Continuous care (CAN$)	Terminal care, death CRC (CAN$)†	Terminal care, death other causes (CAN$)
Decreased CRC treatment costs, based on lower bound of the 95% confidence interval				
- Stage I	26,211	2,464	251,516	23,149
- Stage II	43,065	5,860	181,918	32,620
- Stage III	63,726	9,305	126,704	29,925
- Stage IV	81,283	39,317	120,518	30,696
Decreased CRC treatment costs, based on lower bound of the 95% confidence interval				
- Stage I	29,796	3,805	393,429	43,934
- Stage II	47,034	7,436	257,516	51,905
- Stage III	67,370	11,068	166,383	41,959
- Stage IV	86,896	45,098	139,165	37,857

CRC: colorectal cancer.

* 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 (manuscript in preparation)

† The number of cases in terminal care with death from CRC, especially in stage I and II, were small hence the large range in costs between the lower and upper estimates of treatment costs.

All cost estimates were expressed in 2013 Canadian dollars.

Appendix Table 2.

Appendix Table 2. Outcomes from the base case and sensitivity analyses (per 1,000 participants).

Appendix Table 2.1. Base case

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	20.3	43,600	dominated
Cost-efficient screening strategies							
FIT 50	50	80	2	35.0	39.5	−500,200	−12,700
FIT 50	50	80	1.5	40.9	41.8	−490,000	4,400
FIT 50	45	79.5	1.5	48.8	46.5	−404,700	18,400
FIT 50	45	84	1.5	49.3	46.5	−401,700	46,200
FIT 50	45	80	1	58.6	48.8	−280,600	53,800
FIT 50	45	85	1	59.1	48.8	−277,500	88,000
FIT 75	40	85	1	58.8	50.6	−94,600	99,500
FIT 50	40	85	1	69.1	51.3	−19,100	111,500

Appendix Table 2.2. Non-bleeding adenomas: 74% of large adenomas could not be detected by gFOBT and FIT[1]

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	15.1	16.8	202,900	dominated
Cost-efficient screening strategies							
FIT 50	55	75	1	36.6	32.0	–252,900	–7,900
FIT 50	50	75	1	46.4	39.4	–212,700	5,500
FIT 50	45	75	1	56.0	44.5	–76,900	26,500
FIT 50	45	80	1	57.0	44.7	–70,200	37,000
FIT 50	40	80	1	67.2	47.4	160,000	85,200
FIT 50	40	85	1	67.6	47.4	165,600	280,700

Appendix Table 2.3. Rate of fatal complications: 1 per 28,000 colonoscopies (50% of base case value)[2]

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	20.5	43,700	dominated
Cost-efficient screening strategies							
FIT 50	50	80	2	35.0	39.8	–500,100	–12,600
FIT 50	50	80	1.5	41.0	42.1	–490,000	4,400
FIT 50	45	79.5	1.5	48.8	46.9	–404,500	18,000
FIT 50	45	84	1.5	49.3	47.0	–401,600	44,000
FIT 50	45	80	1	58.6	49.3	–280,600	50,600
FIT 50	45	85	1	59.1	49.4	–277,400	86,600
FIT 75	40	85	1	58.8	51.3	–94,500	95,300
FIT 50	40	85	1	69.1	52.1	–18,800	97,700

Appendix Table 2.4. Rate of fatal complications: 1 per 7,000 colonoscopies (200% of base case value)[2]

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	20.1	43,500	dominated
Cost-efficient screening strategies							
FIT 50	50	80	2	35.0	39.0	–500,400	–12,800
FIT 50	50	80	1.5	40.9	41.2	–490,200	4,600
FIT 50	45	79.5	1.5	48.8	45.6	–405,000	19,500
FIT 50	45	84	1.5	49.3	45.7	–402,100	47,600
FIT 50	45	80	1	58.6	47.7	–281,100	59,000
FIT 50	45	85	1	59.1	47.7	–277,900	89,600
FIT 100	40	85	1	50.8	49.0	–147,100	107,800
FIT 75	40	85	1	58.8	49.4	–95,000	118,300
FIT 50	40	85	1	69.0	49.8	–19,500	181,000

Appendix Table 2.5. CRC relative survival: 25% improved survival, compared to base case values for all CRC stages

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	16.1	–181,500	dominated
Cost-efficient screening strategies							
FIT 50	50	80	1.5	40.9	33.6	–898,600	–26,700
FIT 50	45	79.5	1.5	48.8	37.0	–862,400	10,800
FIT 50	45	84	1.5	49.3	37.0	–860,700	40,900
FIT 50	45	80	1	58.6	39.1	–764,700	46,600
FIT 50	45	85	1	59.1	39.1	–762,500	79,900
FIT 100	40	85	1	50.8	40.2	–633,500	118,700
FIT 75	40	85	1	58.8	40.5	–587,200	134,300
FIT 50	40	85	1	69.0	40.9	–516,800	187,400

Appendix Table 2.6. Increased cost of FIT: CAN$43.87 per test (based on reimbursement rate in US Medicare program)[3]

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	20.3	43,600	dominated
Cost-efficient screening strategies							
FIT 50	55	79	1.5	33.0	34.3	–436,200	–12,700
FIT 50	50	80	2	35.0	39.5	–432,600	700
FIT 50	50	80	1.5	40.9	41.8	–407,600	10,900
FIT 50	45	79.5	1.5	48.8	46.5	–301,400	22,900
FIT 50	45	80	1	58.6	48.8	–150,900	65,000
FIT 50	40	80	1	68.7	51.3	137,400	114,200
FIT 50	40	85	1	69.1	51.3	140,800	124,300

Appendix Table 2.7. Decreased colonoscopy costs, 50% of base case value

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	20.3	–132,300	dominated
Cost-efficient screening strategies							
FIT 50	50	85	1	50.0	44.1	–951,900	–21,600
FIT 50	45	84	1.5	49.3	46.5	–947,300	1,900
FIT 50	45	85	1	59.1	48.8	–935,200	5,300
FIT 50	40	85	1	69.1	51.3	–828,700	42,300

Appendix Table 2.8. Increased colonoscopy costs, 200% of base case value

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	20.3	395,500	dominated
Cost-efficient screening strategies							
FIT 100	60	74	2	13.9	20.8	−16,200	−800
FIT 150	60	75	1.5	14.2	22.0	−13,900	2,000
FIT 200	60	75	1	15.5	23.6	−9,300	2,800
FIT 200	55	74.5	1.5	16.0	28.1	8,800	4,100
FIT 150	55	74.5	1.5	18.4	29.2	14,600	5,000
FIT 200	55	75	1	20.2	31.8	37,300	8,800
FIT 150	50	80	1.5	24.1	36.6	112,300	15,700
FIT 200	50	80	1	26.4	39.3	170,900	21,400
FIT 150	50	80	1	30.3	40.6	219,100	39,300
FIT 200	45	80	1	31.4	44.4	372,500	40,200
FIT 150	45	80	1	36.2	45.5	454,700	72,600
FIT 200	40	80	1	36.8	47.9	665,300	89,500
FIT 150	40	80	1	42.5	49.0	797,400	118,500
FIT 150	40	85	1	43.1	49.1	813,400	174,500
FIT 100	40	85	1	50.8	50.0	1,019,100	228,200
FIT 75	40	85	1	58.8	50.6	1,267,400	377,300
FIT 50	40	85	1	69.1	51.3	1,600,100	491,200

Appendix Table 2.9. Decreased CRC treatment costs, based on lower bound of the 95% confidence interval

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
gFOBT	50	74	2	16.9	20.3	8,800	dominated
FIT 50	50	80	1.5	40.9	41.8	−633,300	−15,100
FIT 50	45	79.5	1.5	48.8	46.5	−566,200	14,500
FIT 50	45	84	1.5	49.3	46.5	−563,800	37,200
FIT 50	45	80	1	58.6	48.8	−464,500	44,100
FIT 50	45	85	1	59.1	48.8	−462,000	69,100
FIT 50	40	85	1	69.1	51.3	−217,900	97,100

Appendix Table 2.10. Increased CRC treatment costs, based on upper bound of the 95% confidence interval

Screen test	Start age	Stop age	Interval	Col/year	QALY (years)	Costs ($)	ICER ($)
Current screening strategy in Ontario							
gFOBT	50	74	2	16.9	20.3	78,200	dominated
Cost-efficient screening strategies							
FIT 50	55	79	2	28.5	32.2	–385,600	–12,000
FIT 50	50	80	2	35.0	39.5	–378,800	900
FIT 50	50	80	1.5	40.9	41.8	–352,200	11,600
FIT 50	45	79.5	1.5	48.8	46.5	–249,500	22,200
FIT 50	45	84	1.5	49.3	46.5	–246,000	55,400
FIT 50	45	80	1	58.6	48.8	–104,300	62,900
FIT 100	40	85	1	50.8	50.0	10,400	94,400
FIT 75	40	80	1	58.3	50.6	71,500	99,800
FIT 75	40	85	1	58.8	50.6	76,100	100,000
FIT 50	40	85	1	69.1	51.3	171,400	140,700

Col/year: colonoscopies per year; QALY: quality adjusted life years; ICER: incremental cost-effectiveness ratio.

The number of colonoscopies per year are undiscounted.

Costs (expressed in 2013 Canadian dollars) and QALYs are discounted by 3% per year.

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Chapter 6

Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening

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ABSTRACT

Objective: Colorectal cancer screening by means of faecal immunochemical tests (FITs) requires successive screening rounds for an optimal preventive effect. However, data on the influence of screening interval length on participation and diagnostic yield are lacking. We therefore performed repeated FIT screening in a population-based trial comparing various repeated intervals.

Design: A total of 7,501 Dutch individuals aged 50-74 years were randomly selected and invited for two 1-sample FIT screening rounds (haemoglobin (Hb) concentration ≥ 50 ng/mL, corresponding to 10 µg Hb/g faeces) with intervals of one (group I), two (II), or three years (III), respectively.

Results: In group I, participation was 64.7% in the first and 63.2% in the second screening round. The corresponding percentages for groups II and III were 61.0% vs. 62.5%, and 62.0% vs. 64.0%. Triennial screening resulted in a higher participation to the second screening round compared with individuals who were invited every year (p=0.04). The overall positivity rate in the second screening round was significantly lower compared with the first round (6.0% vs. 8.4%, OR 0.69; 95% CI, 0.58-0.82) and did not depend on interval length (p=0.23). Similarly, the overall detection rate of advanced neoplasia was significantly lower in the second round compared with the first screening round (1.9% vs. 3.3%, OR 0.57; 95% CI, 0.43-0.76) and did also not depend on interval length (p=0.62). The positive predictive value of the FIT did not significantly change over time (41% vs. 33%; p=0.07).

Conclusion: The total number of advanced neoplasia found at repeated FIT screening is not influenced by the interval length within a one to three years range. Furthermore, this trial shows a stable and acceptably high participation to the second screening round. This implies that screening intervals can be tailored to local resources.

INTRODUCTION

Colorectal cancer (CRC) is a major health problem in the Western world which fulfils the conditions for population-based screening.[1] There is considerable evidence that annual to biennial screening of asymptomatic average-risk individuals using a guaiac-based faecal occult blood test (gFOBT) can detect cancers at an early, curable stage, which results in a 15-33% reduction of CRC-related deaths.[2-5] Based on these results, repeated FOBT screening has been advocated in international guidelines.[6-8] Recent studies have indicated that faecal immunochemical testing (FIT) is superior to gFOBT screening both with respect to participation and diagnostic yield.[9-11] Introduction of FIT-based screening is therefore widely considered and implemented in the USA, Canada, and many countries throughout Europe. Unfortunately, a single FIT test is insufficient for the detection of all advanced neoplasia (i.e., all patients with CRC or an advanced adenoma, usually defined as an adenoma of 10 mm or larger, an adenoma with 25% or more villous histology, or with high-grade dysplasia) due to a suboptimal sensitivity for such lesions.[12] This necessitates successive screening rounds, which may result in a similar preventive effect as a screening strategy with an invasive, highly sensitive test such as colonoscopy.[13] However, there are no data on the comparison of different intervals for FIT screening and their impact on participation and detection of advanced neoplasia, two factors which both highly determine the efficacy of a screening programme.

The aim of this study was therefore to compare the participation and diagnostic yield of repeated FIT testing with screening intervals of various lengths ranging from one to three years in a population-based colorectal cancer screening trial.

METHODS

Study population

Details about the design of our ongoing population-based CRC screening programme have been described.[9, 14, 15] In short, demographic data of all individuals between 50–74 years living in the southwest of the Netherlands were obtained from municipal population registers. Random samples were taken from the target population by a computer-generated algorithm (Tenalea, Amsterdam, the Netherlands). Selection was performed per household and occurred before invitation. Since there is no CRC screening programme in the Netherlands, the target population invited for this trial was screening-naïve when first approached. Exclusion criteria were asked for on the informed consent form that had to be completed by the screenee. Exclusion criteria were a history of CRC; inflammatory bowel disease; an estimated life expectancy of less

than 5 years; a colonoscopy, sigmoidoscopy or double-contrast barium enema within the previous 3 years; and inability to give informed consent. Recruitment took place between November 2006 and December 2010.

Interventions

With each screening round, one FIT (OC-Sensor Micro, Eiken Chemical Co., Tokyo, Japan) was sent by mail to collect a single sample of one bowel movement. The test was considered positive when the haemoglobin (Hb) concentration in the FIT sample was ≥ 50 ng/mL, which corresponds to 10 µg Hb/g faeces. Details about the study design have been described elsewhere. [9, 14-16] All study subjects were divided over three groups to undergo repeated FIT testing at various screening intervals. The groups were designated in relation to the interval length, expressed in years, between the consecutive FITs.

Study groups

Groups I-III: Repeated 1-sample FIT screening

Subjects assigned to groups I-III were offered repeated 1-sample FIT screening at intervals of respectively one, two, or three years (Figure 1). In order to complete the repeated FIT screening trial, we started with recruitment of subjects who were scheduled for a longer interval. Recruitment for groups II and III took place between November 2006 and December 2007. Individuals selected for group I received their first invitation between May and November 2008. In each group, invitees who fulfilled the exclusion criteria after the first invitation, those who tested positive during the first screening round, individuals who had become 75 years of age or older, and those who had moved out of the region or had died were not approached for the second screening round.

Reference group 0: Once only 2-sample FIT screening

Subjects assigned to Reference group 0 were offered once only 2-sample FIT screening (Figure 1). All subjects who were randomly selected for this group simultaneously received two FIT kits. Explicit instructions were given to obtain a single stool sample per FIT and use both FITs on two consecutive days while noting the sampling date on both test tubes. Recruitment took place between October 2008 and June 2009. Results concerning this once only 2-sample FIT group have been published before.[15] Only those data relevant for the current comparison with repeated FIT testing with longer screening intervals are presented in this paper.

Follow-up evaluation

Subjects with a positive FIT were scheduled for colonoscopy within four weeks. All colonoscopies were performed by experienced endoscopists. The maximum reach of

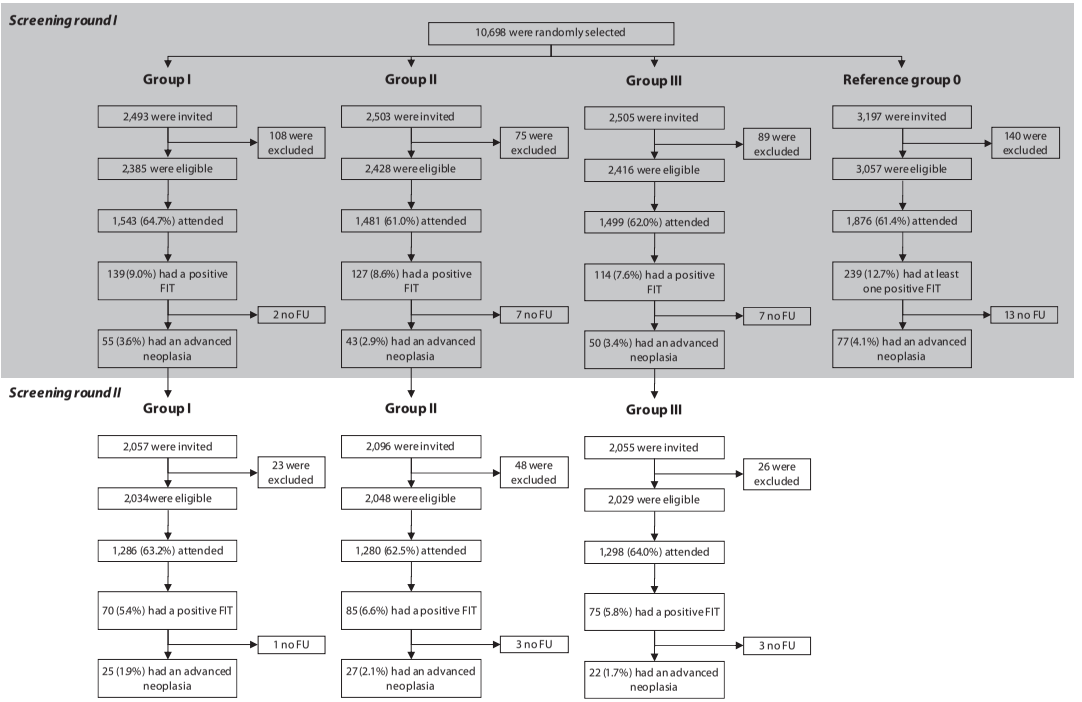

Figure 1. Trial profile

Group I: Invitees were invited for a second 1-sample FIT screening round after 1 year; **Group II**: Invitees were invited for a second 1-sample FIT screening round after 2 years; **Group III**: Invitees were invited for a second 1-sample FIT screening round after 3 years; **Reference group 0**: Invitees were invited for their first 2-sample FIT screening round.

Screenees with a positive test result in the first screening round, subjects who fulfilled the exclusion criteria of the first round, individuals who had moved out of the region, had died, or turned over 75 years were *not invited* for a second FIT-based screening round. FIT = faecal immunochemical test (OC-Sensor Micro), cut-off value 50 ng Hb/mL; FU = follow-up after a positive test result (i.e. colonoscopy); Advanced neoplasia was defined as a colorectal cancer and an adenoma 10 mm or larger, or an adenoma with 25% or more villous component, and/or high-grade dysplasia.

the endoscope, adequacy of bowel preparation, as well as characteristics and location of any polyps were recorded. All removed polyps were evaluated by experienced gastrointestinal pathologists.[17, 18] Patients with a positive colonoscopy entered a surveillance programme, whereas patients with a negative colonoscopy were referred back to the screening programme but were considered not to require FIT screening for ten years. [6, 19]

Screen-detected and interval carcinomas

Except for individuals who moved out of the Netherlands, all recruited participants were followed for the development of CRC. Screen-detected cancers were defined as cancers identified at colonoscopy performed after a positive test result. Interval cancers were defined as colorectal cancers diagnosed within the time period between two consecutive screening rounds. Interval cancers were identified through record linkage with the Dutch Comprehensive Cancer Centre (www.iknl.nl).

Power calculation

The primary outcome measurement was the participation rate for each screening strategy. The sample size was chosen based on a presumed 50-60% participation rate to yield an 80% power to determine second round participation rates for each group with a confidence interval of ± 2.5%.

Statistical analysis

Differences in proportions between the screening interval groups were tested using the χ^2 test. Differences in means between the various groups were tested using the Student t-test. The participation rate was calculated by dividing the number of participants by all eligible subjects (defined as all invitees minus the individuals who fulfilled the exclusion criteria). The positivity rate (PR) was defined as the proportion of participants having a positive test result, the positive predictive value (PPV) as the proportion of participants with a positive test result having advanced neoplasia, and the detection rate (DR) as the proportion of participants having an advanced neoplasia. Participants with more than one lesion were classified according to the most advanced lesion found.

A logistic regression model was fitted to the data to determine differences in second round participation between the three interval groups (i.e. groups I-III). In a subgroup analysis, we extended this model by adding (non-)participation in the first screening round as a separate parameter. In a subsequent multivariate logistic regression model, the variables age, sex, and socio-economic status (SES) were added. A second logistic regression model was fitted to the data to determine differences in PR, PPV, and DR between groups I-III. Because participants with a positive screening test followed by colonoscopy during the first round were not invited for the second screening round,

participants could only have one positive FIT result. This allowed us to combine the test outcomes from both rounds in a simple logistic regression analysis without using multi-level techniques. A third logistic regression model was used to determine the differences in second round PR and DR (subdivided into (non)-participant of the first screening round) between the three interval groups. All p-values were two-sided and considered significant if < 0.05. Statistical analysis was performed with SPSS 15.0 for Windows. Finally, we performed an analysis in which the once only 2-sample FIT group was considered to be a 1-sample group which was re-invited for a second screening round after an interval of zero years (i.e. Reference group 0). The 2-sample FIT data presented under the subheading 'First sample / Screening round I' were obtained when the average of the PR and DR of the first and second performed test was taken as reference. The data presented as 'Second sample / Screening round II' were acquired when the same data of both performed tests were used to determine the added value of a second test. Additionally, for these analyses only individuals who participated twice were considered appropriate. This comparison is presented in Table 3.

RESULTS

Participation rate

During the first screening round of groups I-III, a total of 7,501 asymptomatic average-risk subjects were invited (Table 1) of which 272 (3.6%) were excluded from analyses after the invitation had been sent (223 individuals met one of the exclusion criteria, 41 had moved away, and 8 had died) (Figure 1). From the remaining, a total of 4,523 subjects responded to the first round invitation: the participation rate in group I was 64.7% (95% CI, 62.8-66.6), in group II 61.0% (95% CI, 59.0-62.9), and in group III 62.0% (95% CI, 60.1-64.0). A total of 1,021 (13.6%) individuals were not re-invited for the second screening round (380 subjects had tested positive during the first screening, 342 individuals had become 75 years of age or older, 88 individuals had died, and the remaining 211 subjects had moved out of the region). Therefore, 6,208 individuals were approached for the second screening round of which 97 (1.6%) invitees fulfilled the exclusion criteria (Figure 1). In group I, the participation rate in the second round slightly decreased to 63.2% (95% CI, 61.1-65.3). For the biennial and triennial screening groups, participation increased towards 62.5% (95% CI, 60.4-64.6) and 64.0% (95% CI, 61.9-66.0), respectively. In a multivariate analysis, in which we corrected for participation in the first screening round, the interval length was associated with second round participation (p-value = 0.04). Higher second round participation was achieved with biennial screening (odds ratio (OR) 1.18; 95% CI, 0.98-1.43) and triennial screening (OR 1.26; 95% CI, 1.04-1.52) compared with annual screening.

Table 1. Baseline characteristics (first screening round)

	Repeated 1-sample FIT screening			Once only 2-sample FIT screening	
	Group I	**Group II**	**Group III**	**Reference group 0**	***P* value**
Invited subjects (n)	2,493	2,503	2,505	3,197	
Median age	60.0	60.0	60.0	62.0	0.001
(yrs-IQR)	(55.0-66.0)	(55.0-66.0)	(55.0-65.5)	(56.0-68.0)	
Sex (male; n-%)	1,223 (49.1)	1,254 (50.1)	1,254 (50.1)	1,593 (49.8)	0.87
SES (n-%)					0.99
High	993 (39.8)	1,019 (40.7)	1,019 (40.7)	1,280 (40.0)	
Intermediate	509 (20.4)	503 (20.1)	503 (20.1)	640 (20.0)	
Low	991 (39.8)	981 (39.2)	983 (39.2)	1,277 (39.9)	

Group I: Individuals were invited for two 1-sample FIT screening rounds after an interval of 1 year; **Group II**: Individuals were invited for two 1-sample FIT screening rounds after an interval of 2 years; **Group III**: Individuals were invited for two 1-sample FIT screening rounds after an interval of 3 years; **Reference group 0**: Individuals were invited for one 2-sample FIT screening round.
IQR = interquartile range; SES = socio-economic status, which was based on the data of Statistics Netherlands (www.cbs.nl), providing average SES per postal code area, each representing small neighborhoods.

Of first round participants, 89.8% (1,166/1,299; 95% CI, 88.0-91.3) also attended the second screening round after an interval of one year, 90.9% (1,123/1,235; 95% CI, 89.2-92.4) after an interval of two years, and 91.3% (1,138/1,247; 95% CI, 89.6-92.7) participated again after a triennial screening interval (Table 2). The same calculations were made for the non-participants of the first screening round: the proportion of eligible previous non-participants attending the second screening round was respectively 16.3% (120/735; 95% CI, 13.8-19.2), 19.3% (157/813; 95% CI, 16.7-22.2), and 20.5% (160/782; 95% CI, 17.8-23.4), for groups I, II, and III. No interaction was found between the parameters "first round participation" and "interval length" (p-value = 0.86), indicating that the differences in second round participation for participants and non-participants in the first screening round (expressed in ORs) were the same in the three interval groups.

Finally, a separate analysis was made for the cumulative participation rate after two 1-sample FIT screening rounds. In the group with an interval of one year, 69.7% (1,663/2,385; 95% CI, 67.9-71.5) of all eligible subjects participated at least once. This was 67.5% (1,638/2,428; 95% CI, 65.6-69.3) in the biennial screening group and 68.7% (1,659/2,416; 95% CI, 66.8-70.5) in the triennial screening group. The interval length was not associated with the cumulative participation rate after two successive screening rounds (p-value = 0.24).

Proportion of positive tests

At a Hb concentration ≥ 50 ng/mL, a total of 380/4,523 (8.4%, 95% CI, 7.6-9.2) first round participants tested positive.

In the second screening round, a total of 230/3,864 (6.0%, 95% CI, 5.2-6.7) screened individuals tested positive. In a multivariate model, the overall PR was significantly lower in the second round compared with the first screening round (OR 0.69; 95% CI, 0.58-0.82). Among subjects who had tested negative during the first screening, the PRs in the second screening round were not significantly different between the three interval groups, being 5.1% (95% CI, 4.0-6.6) for group I, 6.8% (95% CI, 5.4-8.4) for group II, and 5.6% (95% CI, 4.4-7.1) for group III (p-value = 0.23; Table 2).

Table 2. Overview of participation and FIT performance characteristics per screening round

	Group I	**Group II**	**Group III**	***P* value**
Screening round I				
Eligible invitees (n)	2,385	2,428	2,416	
Participation rate (n-%))	1,543 (64.7)	1,481 (61.0)	1,499 (62.0)	
Positivity rate (n-%)	139 (9.0)	127 (8.6)	114 (7.6)	
Detection rate of	55 (3.6)	43 (2.9)	50 (3.4)	
Advanced neoplasia (n-%)	51 (3.3)	33 (2.2)	42 (2.8)	
Advanced adenoma (n-%)	4 (0.3)	10 (0.7)	8 (0.5)	
Colorectal cancer (n-%)				
Screening round II				
Eligible invitees (n)	2,034	2,048	2,029	
Participation rate (n-%)	1,286 (63.2)	1,280 (62.5)	1,298 (64.0)	0.04
Participant round I (n-%)	*1,166 (89.8)*	*1,123 (90.9)*	*1,138 (91.3)*	
Non-participant round I (n-%)	*120 (16.3)*	*157 (19.3)*	*160 (20.5)*	
Positivity rate (n-%)	70 (5.4)	85 (6.6)	75 (5.8)	0.40
Participant round I (n-%)	*60 (5.1)*	*76 (6.8)*	*64 (5.6)*	
Non-participant round I (n-%)	*10 (8.3)*	*9 (5.7)*	*11 (6.9)*	
Detection rate of				
Advanced neoplasia (n-%)	25 (1.9)	27 (2.1)	22 (1.7)	0.77
Advanced adenoma (n-%)	24 (1.9)	23 (1.8)	20 (1.5)	
Colorectal cancer (n-%)	1 (0.1)	4 (0.3)	2 (0.2)	
Detection rate of				
Advanced neoplasia (n-%)	25 (1.9)	27 (2.1)	22 (1.7)	0.77
Participant round I (n-%)	*19 (1.6)*	*23 (2.1)*	*18 (1.6)*	
Non-participant round I (n-%)	*6 (5.0)*	*4 (2.5)*	*4 (2.5)*	

Group I: Individuals were invited for two 1-sample FIT screening rounds after an interval of 1 year; **Group II**: Individuals were invited for two 1-sample FIT screening rounds after an interval of 2 years; **Group III**: Individuals were invited for two 1-sample FIT screening rounds after an interval of 3 years.
Screenees with a positive test result in the first screening round, subjects who fulfilled the exclusion criteria of the first round, individuals who had moved out of the region, had died, or turned over 75 years were *not invited* for a second FIT-based screening round. FIT = faecal immunochemical test (OC-Sensor Micro), haemoglobin concentration ≥ 50 ng/mL; Advanced neoplasia was defined as a colorectal cancer and an adenoma 10 mm or larger, or an adenoma with 25% or more villous component, and/or high-grade dysplasia.

Follow-up and test performance characteristics

Of the 380 screenees in groups I-III who tested positive during the first screening round (Table 2), 364 (96%) underwent a successful colonoscopy. The remaining 16 subjects either refused a colonoscopy or turned out to have too severe co-morbidity to benefit from an invasive endoscopic procedure. Colonoscopy resulted in the detection of advanced lesions in 148 (PPV 41%; 95% CI, 35.7-45.8) patients, consisting of 126 advanced adenomas and 22 CRCs of which 17 (77%) were classified as early stage (Stage I: 14; Stage II: 3) and 5 (23%) as advanced (Stage III: 5). In the second screening round, 223 (97%) of the 230 positive screenees underwent colonoscopy, revealing advanced lesions in 74 (PPV 33%; 95% CI, 27.3-39.6) patients, consisting of 67 advanced adenomas and 7 CRCs of which 6 were early stage (Stage I: 5; Stage II: 1) and one was Stage III. The difference in PPV between the first and second round of FIT screening was not statistically significant (p-value = 0.07).

Overall, 148 of 4,523 participants in the first screening round were diagnosed with an advanced neoplasia, corresponding with a DR of 3.3% (95% CI, 2.8-3.8), without significant differences between the three groups (p-value = 0.60; Table 2). In the second screening round, the overall DR of advanced colonic lesions dropped to 1.9% (95% CI, 1.5-2.4), significantly lower than in the first round (OR 0.57; 95% CI, 0.43-0.76). In addition, significantly fewer CRCs were found during the second screening (0.18%; OR 0.37; 95% CI, 0.16-0.86) compared with the first screening round (0.49%). Among first round participants, the overall DR with a second FIT was 1.8% (95% CI, 1.4-2.3; Table 3, Second sample / Screening round II), without significant differences between the three groups, being 1.6% (95% CI, 1.0-2.5) in group I, 2.1% (95% CI, 1.4-3.1) in group II, and 1.6% (95% CI, 1.0-2.5) in group III (p-value = 0.62; Table 2). In contrast, among non-participants in the first screening round, the second round DR was 3.2% (95% CI,1.9-5.3) which is as expected similar to the 3.3% among the participants in the first screening round, and significantly higher than the second round DR among those who had participated in the first screening round (p-value = 0.02).

Looking at the once only 2-sample FIT group, the DR of advanced neoplasia of a single test was 3.3% (95% CI, 2.6-4.2) (Table 3, One sample / Screening round I). The additional second FIT sample enabled detection of 16 additional advanced neoplasia in 1,876 participants, corresponding with an additional DR of 0.9% (95% CI, 0.5-1.4) (Table 3, Second sample / Screening round II) and thus an overall DR of 4.1% (95% CI, 3.3-5.1).

Interval carcinomas

After record linkage with the Dutch Comprehensive Cancer Centre, 32 CRCs were found in the total study population. Twenty-nine CRCs (90.6%) were screen-detected tumours (Table 2), of which 22 (76%) were detected during first and 7 (24%) during second round screening. The other three (9.4%) were interval cancers. Two of those were detected in

Table 3. Overview of positivity rate and detection rate per screening round for either 2-sample FIT screening (i.e. Reference group 0) or 1-sample FIT screening (i.e. Groups I-III)

	Groups I-III	Reference group 0
One sample / Screening round I		
Screened individuals (n)	4,523	1,876
Positivity rate (n-%)	380 (8.4)	167 (8.9)
Detection rate of		
Advanced neoplasia (n-%)	148 (3.3)	62 (3.3)
Advanced adenoma (n-%)	126 (2.8)	51 (2.7)
Colorectal cancer (n-%)	22 (0.5)	11 (0.6)
Second sample / Screening round II		
Screened individuals (n)	3,427	1,876
Positivity rate (n-%)	200 (5.8)	73 (3.9)
Detection rate of		
Advanced neoplasia (n-%)	60 (1.8)	16 (0.9)
Advanced adenoma (n-%)	54 (1.6)	14 (0.8)
Colorectal cancer (n-%)	6 (0.2)	2 (0.1)

Individuals were invited for two 1-sample FIT screening rounds after an interval of one (group I), two (group II), or three years (group III). However, since no statistically significant differences were found between the three groups, corresponding data were pooled (i.e. **Groups I-III**). For the 'Second sample / Screening round II' comparison *only individuals who participated twice* were included. Furthermore, for this comparison the 2-sample FIT group was considered to be a 1-sample FIT group which was re-invited for a second screening after a virtual interval of zero years (i.e. **Reference group 0**). The 2-sample FIT data presented under the subheading 'First sample / Screening round I' were obtained when the average of the first and second performed test was taken as reference. The data presented as 'Second sample / Screening round II' were acquired when the same data of both performed tests were used to determine the added value of one extra test.

the 4,143 first round participants with a negative test: one Stage III tumour (FIT result at baseline, 24 ng Hb/mL) was detected nine months after baseline screening, and one Stage II cancer (7 ng Hb/mL) was discovered two years and five months after stool sampling. The third and last CRC was diagnosed at Stage I in one of 117 subjects with a positive first round test (960 ng Hb/mL) but negative follow-up colonoscopy. The tumour was located at 50 cm of the anal verge. Reassessment of the original colonoscopy report and pictures revealed no explanation for missing this lesion.

These results imply that in the first screening round 0% (0/4) of all CRCs diagnosed in group I were interval cancers. The corresponding percentages for interval cancers were 9.1% (1/11) for the biennial screening and 20.0% (2/10) for the triennial screening group, respectively.

DISCUSSION

The effectiveness of FIT-based screening in decreasing colorectal cancer-related mortality has not been studied in large long-term prospective randomised controlled trials. Although such trials would be highly valuable, they may never be conducted. CRC screening programmes using FITs are therefore based on evidence from prospective randomised controlled trials showing that annual or biennial gFOBT screening led to a 15-33% reduction in CRC mortality,[2-5] combined with observations from other randomised trials that FIT screening compared with gFOBT is associated with higher participation and diagnostic yield.[9, 11] This forms the basis for the assumption that repeated FIT screening will eventually have a larger impact on CRC-related mortality than gFOBT screening. This is further supported by modelling results.[13, 20] The effectiveness of a FIT-based screening programme is however highly dependent on adherence to repeat testing. This trial demonstrates that participation slightly increases with second round screening when performed with biennial or triennial intervals. This increased participation was seen both among first round participants as well as first round non-participants, in particular in the triennial screening group. This underlines the importance of re-inviting previous non-participants to increase the effectiveness of screening. Unfortunately, this is not routinely applied in CRC screening programmes.[21] Optimising participation rates must be a priority in any screening programme and requires scrutiny of health promotion campaigns, invitation techniques, the test kit, and involvement of general practitioners.[14, 22-24]

Besides pursuing high participation to repeated screening, the detection rate of advanced neoplasia is of similar importance for the effectiveness of screening. Repeated screening rounds enable to cover a larger proportion of the population and help to detect more subjects with advanced lesions, both because of the gradual progression and the intermittent bleeding pattern of advanced neoplasia.[15] As a consequence, CRC screening requires successive screening rounds for an optimal preventive effect. This trial first demonstrates that repeated FIT screening enables a higher population coverage and a higher detection rate of advanced neoplasia, even when compared with single round 2-sample FIT screening.[15] The cumulative coverage of the target population was 67.5-69.7% in the repeated 1-sample FIT screening groups compared with 61.4% in the once only 2-sample FIT group, and the cumulative DR of advanced neoplasia ranged from 5.3-5.7% in the repeated 1-sample FIT screening groups compared with 4.1% in the once only 2-sample FIT group. Second, our study demonstrates that second round FIT screening yields fewer advanced neoplasia compared with baseline screening. This finding confirms that FIT screening has a considerable yield of advanced neoplasia already with single round screening.[10, 25] Third, our study shows that there is no association between the interval length within a one to three years range and

the DR of advanced neoplasia at the second screening round. This finding was, to some extent, against our assumption that a longer screening interval would result in more newly bleeding advanced neoplasia at the second screening round. Our current findings support the concept of slow progression of sporadic colorectal neoplasia. Finally, these findings could also be an expression that non-bleeding advanced neoplasia persist in not bleeding for a long time. This issue needs further research.

We performed additional analyses for the positivity rate and detection rate, including only participants who attended both screening rounds (Table 3). Since the DRs in the three interval groups did not differ, corresponding data were pooled (i.e. Groups I-III) and compared with 2-sample FIT screening where the second test was performed after a virtual interval of zero years. The pooled data showed that 1.8 advanced neoplasia per 100 participants were detected during the second screening of the 1-3 yearly screening interval groups, versus 0.9 after an interval of zero years, i.e. the second test of the once only 2-sample FIT screening on two consecutive days. These figures imply that 50% of detected advanced neoplasia with second round screening could have been detected at baseline, but were -at that time- not bleeding (consistently) enough to be detected by one FIT. Moreover, the fact that the second round DRs did not differ between groups I-III suggests that even a triennial screening interval might be too short to detect genuine newly developed or at least newly bleeding advanced neoplasia. This is consistent with the long so-called polyp dwell time, i.e. the average time for transformation from a small adenoma to an invasive CRC which is estimated to be on average at least 10 years.[1] In this respect, it is important to note that the sensitivity of FIT for the detection of low concentrations of blood in stool samples, in particular at a low cut-off value which was used in this trial, leads to considerably higher detection of advanced neoplasia than screening with gFOBT. For instance, in our previous randomised comparative trial, gFOBT and FIT screening led to the detection of respectively 6 vs. 20 subjects with an advanced neoplasia per 1,000 screenees invited.[10] The majority of these subjects had advanced adenomas, not cancer. This learns that adenomas can bleed prior to becoming an invasive cancer, and single FIT sampling at a low cut-off detects part of these lesions. Therefore, while current international CRC screening guidelines recommend that FOBT screening should apply fixed one year intervals with a single test,[6-8] our data suggest that FIT screening may progress to faecal sampling with longer intervals. This strategy may be further improved by using 2 FIT samples in every screening round, with optimization of the number of days or bowel movements between FIT sampling.[15] If this is true, such a multiple sample strategy with longer screening intervals could become more advantageous than a one sample FIT strategy with a shorter interval.

To our knowledge, this is the first study to evaluate the second round participation and diagnostic yield of a FIT-based CRC screening trial comparing different interval lengths between successive screening rounds. Moreover, in screening for CRC comparatively

little is known about the outcome measures of the first versus subsequent screening rounds. Most available studies were conducted with the gFOBT, which has been used for more than forty years.[26-30] Additionally, the majority of FIT-related data that have been published so far have not been tabulated by screening round and therefore do not allow analysis of participation and diagnostic yield per screening round.[31-35] One exception is an Italian study in which all individuals were invited for biennial 1-sample FIT screening.[36] Our main results concerning second round participation and diagnostic yield are in line with these Italian results. However, when the same Hb concentration threshold was used (i.e. 100 ng/mL), we observed a lower first round PR and a higher DR of colorectal cancer. Potential explanations for the lower number of detected cancers in the Italian study included the younger population (aged 50–69 years vs. 50–74 years) and the lower proportion of positive screenees undergoing follow-up colonoscopy (86% vs. 96% respectively). It is difficult to explain differences in PR since the brand name of the used FIT kit was not provided, neither were additional baseline characteristics of the target population given.

This study had some limitations. First, the invitations for the first screening round were not sent at the same time. Since the recruitment of all groups took place in the same screening-naïve population, more awareness about CRC and CRC screening could have been obtained over time. This implies that the participation rate of group I at first screening and group III at second screening could have been affected the most by this potential bias as these were invited later in time. This increased awareness about CRC screening would then explain the higher first round participation seen in the annual FIT screening group compared with groups II and III, although this contrasts with the lower second round participation in this same group. Second, this trial was powered on participation and therefore lacks power to detect small differences in second round PRs and DRs between the different interval length groups. Additionally, although no significant differences were found in the total number and stage of advanced neoplasia between the three interval groups, this has to be confirmed with further studies.

In conclusion, this comparative population-based CRC screening trial demonstrates that the association, if any, between longer screening intervals and larger numbers of advanced neoplasia detected at repeated FIT screening is limited. Furthermore, this trial shows a stable and acceptably high participation to the second screening round within a one to three years range. This implies that screening intervals can be tailored to local resources.

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Chapter 7

Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening

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ABSTRACT

Objective. The sensitivity and specificity of a single faecal immunochemical test (FIT) are limited. The performance of FIT screening can be improved by increasing the screening frequency or by providing more than one sample in each screening round. We aimed to evaluate if 2-sample FIT screening is cost-effective compared to 1-sample FIT.

Design. The MISCAN-colon microsimulation model was used to estimate costs and benefits of strategies with either 1- or 2-sample FIT screening. The FIT cut-off level varied between 50 and 200 ng haemoglobin/ml, and the screening schedule was varied with respect to age range and interval. In addition, different definitions for positivity of the 2-sample FIT were considered: a) at least one positive sample, b) two positive samples, or c) the mean of both samples being positive.

Results. Within an exemplary screening strategy, biennial FIT from age 55-75 years, 1-sample FIT provided 76.0-97.0 life years gained (LYG) per 1,000 individuals, at a cost of €259,000-264,000 (range reflects different FIT cut-off levels). 2-Sample FIT screening with at least one sample being positive provided 7.3-12.4 additional LYG compared to 1-sample FIT at an extra cost of €50,000-59,000. However, when all screening intervals and age ranges were considered, intensifying screening with 1-sample FIT provided equal or more LYG at lower costs compared to 2-sample FIT.

Conclusion. If attendance to screening does not differ between strategies it is recommended to increase the number of screening rounds with 1-sample FIT screening, before considering to increase the number of FIT samples provided per screening round.

INTRODUCTION

In industrialised countries colorectal cancer (CRC) is the third most commonly diagnosed malignancy in men and ranks second in women.[1] The majority of CRC cases are diagnosed later in life. Because life expectancy increases in many countries and the costs of CRC treatment rapidly rise, it is expected that CRC will place an increasing burden on national healthcare systems.

Screening for CRC and its premalignant lesions (i.e. adenomatous polyps) can detect the disease at an earlier and more curable stage. Faecal occult blood tests (FOBTs) have been developed to detect microscopic bleeding from colorectal neoplasms before there are any clinical signs or symptoms. At least three randomised controlled trials proved the effectiveness of FOBT screening, demonstrating a mortality reduction of 15-33%.[2-4] Subsequently, several screening trials have confirmed the superiority of faecal immunochemical test (FIT) screening over the more traditionally used guaiac-based FOBTs (i.e. non-rehydrated Hemoccult-II test) both with respect to attendance as well as detection rate of advanced neoplasia.[5-11] Most of these trials used screening strategies with a single FIT sample.

Since not all advanced neoplasia will be detected by means of 1-sample FIT screening, providing two FIT samples collected on consecutive days could increase the effectiveness of a screening program. On the one hand, referring a screenee for a diagnostic colonoscopy when at least one sample is positive, increases sensitivity since some colorectal neoplasms bleed intermittently and can therefore be missed with 1-sample FIT screening.[12] On the other hand, referring a screenee when both samples are positive can increase specificity since only colonic lesions with a more consistent bleeding pattern will be detected which will lead to less false positive test results. However, in either way, providing two FIT samples within one screening round will also increase screening costs because twice the number of samples needs to be analysed.

The aim of this study was to evaluate the cost-effectiveness of 1-sample and 2-sample FIT screening strategies with variable intervals, age ranges and cut-off levels in order to assess if the increased performance of a second FIT sample outweighs the increased costs compared to 1-sample FIT screening.

METHODS

We used the MISCAN-Colon microsimulation model to estimate the additional life-years gained and costs of 2-sample FIT screening over 1-sample FIT for the screening strategy of biennial FIT from age 55 to 75. This screening strategy has intermediate screening intensity and was previously found to be cost-effective.[13] Additional life-years gained

can also be achieved by increasing the intensity of 1-sample FIT screening instead of adding a second sample. We therefore also compared the costs and life-years gained of 1-sample FIT screening with that of 2-sample FIT for a range of screening strategies.

MISCAN-colon microsimulation model

The MISCAN-colon model and the data sources that inform the quantifications of the model are described in detail in the Model Appendix at the end of the thesis, in previous publications,[14-18] and in a standardised model profile available online.[19] In brief, the MISCAN-colon model simulates the relevant life histories of a large population of individuals from birth to death. CRC arises in this population according to the adenoma-carcinoma sequence.[20, 21] More than one adenoma can occur in an individual and each adenoma can independently develop into a CRC. Adenomas progress in size from small (≤5 mm) to medium (6–9 mm) to large (≥10 mm). Although most adenomas will never turn into cancer, some will eventually become malignant, transforming to stage I CRC and some may even progress into stage IV. In every stage, there is a probability of the CRC being diagnosed due to the development of symptoms versus symptomless progressing into the next stage. If CRC has developed, the survival rate after clinical diagnosis depends on the stage in which the cancer was detected. The 5-year survival rate is on average 90% if the disease is diagnosed while still localised, 68% for regional disease, and less than 10% for disseminated disease. At any time during the development of the disease, the process may be interrupted because a person dies of other causes.

With FIT screening lesions can be detected before clinical diagnosis; a screened individual with a positive test result will be referred for a colonoscopy for detection and removal of adenomas and early-stage cancers. In this way, CRC incidence and/or CRC-related mortality can be reduced. The life years gained by screening are calculated as the difference in model-predicted life years lived in the population with and without CRC screening.

Study Population

In this study we modelled the age distribution of the Dutch population in 2010 (Statistics Netherlands, www.cbs.nl) and all individuals were followed until death. The CRC incidence rate was based on the observed incidence rate in the Netherlands in 1999-2003, which was before the onset of opportunistic screening (Comprehensive Cancer Centre (CCC), www.ikcnet.nl). The observed CRC incidence in the population included cases from higher risk groups. Survival rates after clinical diagnosis of CRC was based on relative survival data from 1985-2004 from the South of the Netherlands,[22] since nationwide data were not available. The survival for individuals aged 75 years and older was adjusted to fit the observed age-increasing mortality/incidence ratio (CCC).

Screening Strategies

CRC screening was simulated in the population starting in 2010. Individuals were offered FIT screening according to different screening schedules varying by:

- Age to start screening at respectively 45, 50, 55, and 60 years
- Age to stop screening at respectively 70, 75, and 80 years
- Screening interval with respectively 1, 1.5, 2, and 3 years

Separate simulations were performed in which individuals were invited for a) 1-sample FIT screening; b) 2-sample FIT screening with referral if at least one sample tested positive; c) 2-sample FIT screening with referral only if both samples tested positive; or d) 2-sample FIT screening with referral if the mean of both samples was positive. The cut-off level for a positive test result varied between 50, 75, 100, 150 and 200 ng Hb/ml. These different screening schedules with varying start and stop ages, intervals, cut-off levels and samples resulted in a total of 960 different screening strategies.

After a positive test result, individuals were referred for colonoscopy. If no adenomas were found during the procedure, the individual was assumed to be at low-risk for CRC and did not return to the screening program until after ten years. If one or more adenomas were found, they were removed and the individual entered a surveillance program according to the Dutch guidelines for follow-up after polypectomy,[23] i.e. a colonoscopy after six years in case of one or two adenomas and after three years in case of three or more adenomas. We assumed that surveillance colonoscopies would be performed until the stop age for screening.

Attendance rates

We modelled attendance rates in the first screening round as observed in two Dutch population-based CRC screening trials[9, 11, 12]; 60% for both 1- and 2-sample FIT screening, and we assumed these rates to remain stable over time. For subsequent screening rounds, we assumed that 80% of the individuals that attended the previous screening round would attend again.[24, 25] Furthermore, we assumed that 10% of the individuals never attended FIT screening[26] and that these never-attenders had a higher risk of CRC than the general population (RR=1.15).[2] Attendance to diagnostic colonoscopies following a positive FIT and subsequent surveillance colonoscopies was assumed to be 85% and 80% respectively.[27]

Test characteristics

Test characteristics of the 1-sample and 2-sample FIT tests were fitted to the positivity rates (PR) and detection rates (DR) of advanced neoplasia observed in the first screening round of two Dutch randomised trials [Table 1].[9-12] Advanced neoplasia included CRC and advanced adenomas, of which the latter was defined as adenomas ≥10 mm in size, with ≥25% villous component, and/or high-grade dysplasia.

Table 1. Test characteristics of 1-sample and 2-sample FIT used in the model.

Cut-off level (ng Hb/mL)	Specificity (per person, %)	Sensitivity (per lesion, %)[1]				
		Adenoma			CRC early preclinical[2]	CRC late preclinical[2]
		≤5mm	6-9mm	≥10mm		
1-sample FIT						
50	95.79	0.0	9.6	16.1	65.0	90.0
75	97.05	0.0	5.7	14.4	58.5	87.0
100	97.76	0.0	4.4	13.1	52.0	83.5
150	98.34	0.0	2.9	12.3	50.5	83.0
200	98.70	0.0	2.5	10.3	50.0	82.5
2-sample FIT, at least one sample positive						
50	93.01	0.0	14.2	16.7	75.0	93.5
75	94.90	0.0	8.4	15.5	71.0	92.0
100	96.03	0.0	6.9	14.4	66.0	90.0
150	97.03	0.0	5.2	14.3	66.0	90.0
200	97.65	0.0	4.9	12.5	66.0	90.0
2-sample FIT, mean of both samples positive						
50	95.51	0.0	12.6	17.0	67.0	90.0
75	96.90	0.0	7.5	15.1	61.0	87.5
100	97.66	0.0	5.4	13.8	54.0	84.0
150	98.31	0.0	3.3	12.8	51.0	83.0
200	98.63	0.0	2.1	10.7	49.0	81.5
2-sample FIT, both samples positive						
50	98.40	0.0	3.8	12.0	34.0	70.0
75	98.94	0.0	1.8	10.0	29.0	65.0
100	99.21	0.0	0.9	8.8	24.0	59.0
150	99.43	0.0	0.1	7.1	20.0	53.0
200	99.49	0.0	0.0	5.2	16.0	47.5

[1] Excluding the probability that an adenoma or cancer is found due to a lack of specificity

[2] It was assumed that the probability a CRC bleeds and thus the sensitivity of FIT for CRC depends on the time until clinical diagnosis, in concordance with findings for gFOBT, which were based on a prior calibration of the MISCAN-Colon model to three FOBT trials.[16] This result is to be expected when cancers that bleed do so increasingly over time, starting "occultly" and ending as clinically visible. This interpretation also holds for FIT.

The test characteristics used in the model were fitted to the PR and DR of advanced neoplasia and CRC from two Dutch randomised controlled trials.[9-12] Sensitivity for adenomas smaller than 5 mm was assumed to be 0% for all tests, at any cut-off level.

To estimate the 2-sample FIT test characteristics the following approach was applied; we used the average PR and DR of the first and second performed test from the 2-sample FIT group as reference and calculated the relative difference in performance when both samples were evaluated. Subsequently, we added this relative difference to

the PR and DR derived from the original 1-sample FIT trials. An example of this method of calculation is presented in Figure 1. The main reasons for this approach were: 1) the larger sample size of the 1-sample FIT group provides more statistical power for the estimates of test sensitivity and specificity; 2) to avoid possible bias caused by the fact that the PR and DR of the 1-sample and 2-sample FIT groups were calculated from different cohorts that were not 1:1 randomised before invitation[10, 12]; 3) in this way we used paired observations, which gives a better estimate of the additional performance of a second FIT sample.

The sensitivity of diagnostic colonoscopies was assumed to be 75% for adenomas 1-5 mm, 85% for adenomas 6-9 mm, and 95% for adenomas ≥10 mm and CRC.[28]

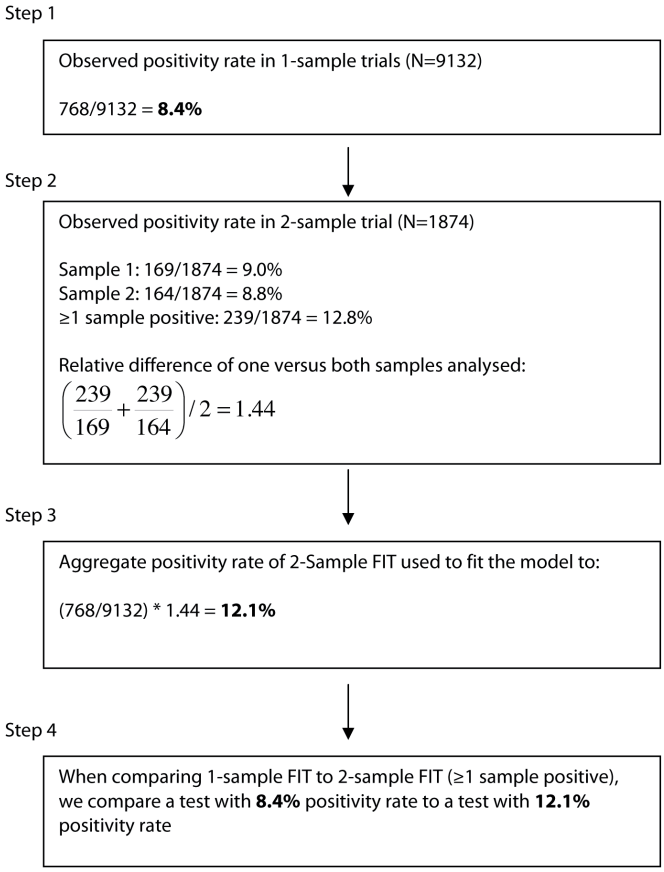

Figure 1. Example of calculation of the added performance of 2-sample FIT compared to 1-sample FIT screening.
* This example provides the calculation of the positivity rate of 2-sample FIT with at least one sample positive at a cut-off level of 50 ng Hb/ml. The method of calculation is similar for both positivity rate and detection rate, as well as for the different 2-sample FIT positivity criteria (i.e. at least one sample positive, both samples positive and the mean of both samples positive).

Costs

The analysis was conducted from a health-care system perspective. In the base case analyses, we included screening and treatment costs as presented in Table 2. Base case organisational costs for 1-sample FIT screening were based on the Dutch cervical cancer screening program, adjusted for differences with FIT screening. Costs for the test kits were based on prices from the manufacturer. Costs for analysis of the tests included material and personnel needed during the process of registration, analysis and authorization of returned tests.[29] The additional costs associated with 2-sample FIT screening included double costs for FIT test kits and packaging material, and double costs for materials needed during the analysis of returned samples. Although double the number of FIT samples would need to be analysed, the costs of personnel needed for the analysis only increased by a factor of 1.5 since some tasks (e.g. patient registration) do not require double the amount of work compared to analysing samples with 1-sample FIT screening. Colonoscopy costs were based on an internal six months study at the Erasmus MC (data not shown). Costs for complications after colonoscopy were based on DBC-rates (Diagnosis Treatment Combination), derived from the Dutch Health Care Authority (http://ctg.bit-ic.nl/Nzatarieven/top.do).

Costs for treatment of CRC were divided into three clinically relevant phases of care: initial treatment, continuous care and terminal care. Initial treatment costs were based on DBC-rates, except for oxaliplatin. The costs for oxaliplatin were derived from the Dutch Health Care Insurance Board (www.medicijnkosten.nl). We assumed that during the continuous care phase, individuals would follow the Dutch CRC treatment

Table 2. Summary of model assumptions of the base case and sensitivity analyses.

Variable	Base case analysis	Sensitivity analyses
Quality of life loss		
Colonoscopy	-	1 day lost per colonoscopy
CRC from diagnosis onwards (1-utility)	-	Initial treatment[33]: - Stage I: 0.26 during first year - Stage II: 0.3 during first year - Stage III: 0.4 during first year - Stage IV: 0.75 during first year Continuous care[34]: 0.15 in years between initial and terminal phase Terminal care death by CRC: 0.75 in last year before dying of CRC Terminal care death by other cause: 0.35 in last year before dying of other causes
Adherence to:		
- *Screening tests*	60%	100% adherence to all tests.
- *Diagnostic tests*	85%	
- *Surveillance tests*	80%	

Table 2. (continued)

Variable	Base case analysis				Sensitivity analyses	
Correlation of FOBT results	-				74% of the large adenomas (≥10 mm) that are not detected, will not be detected in the next screening round[35]	
Colonoscopy capacity	Not limited				Limited to either 40, 20, 10 and 5 colonoscopies per 1,000 individuals per year	
					Low value	*High value*
Fatal complications after colonoscopy	1 per 10,000 colonoscopies				No fatal complications	- 1 per 1,000 colonoscopies with polypectomy - 1 per 10,000 colonoscopies without polypectomy
Relative increase in test performance between 1-sample and 2-sample FIT	Average of the first and second sample used as comparator				Relative increase in test performance 50% smaller	Relative increase in test performance 50% greater
FIT costs	*1-sample FIT*		*2-sample FIT*			
Costs per invitation (organization and test kit)	€15.51		€17.76		Difference between 1- and 2-sample FIT 50% smaller	Difference between 1- and 2-sample FIT 200% greater
Costs per attendee (personnel and materials for analysis)	€4.37		€8.19			
Colonoscopy costs						
Without polypectomy	€303				50%	200%
With polypectomy	€393					
Costs complications after colonoscopy[1]	€1,250				50%	200%
Treatment costs [2]	*Initial treatment*	*Continuous care*	*Terminal care death CRC*	*Terminal care death other causes*		
Stage I	€12,100	€340	€17,500	€4,400	50%	200%
Stage II	€16,600	€340	€17,500	€4,000		
Stage III	€20,600	€340	€18,500	€5,200		
Stage IV	€24,600	€340	€25,000	€14,000		

[1] The assumed complication rate is 2.4 per 1,000 colonoscopies

[2] 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.

guidelines (www.oncoline.nl) and costs for periodic control were based on DBC-rates. Terminal care costs were based on a Dutch last year of life cost analysis. These were estimated at €19,700 for patients that ultimately died from CRC.[30] We assumed that these costs increased with stage at diagnosis, at a rate observed for US patients.[31, 32] Dutch terminal care costs for individuals that died from CRC were approximately 40% of the US costs. We assumed that terminal care costs of CRC patients that die from other causes were also 40% of the US cost.

Cost-effectiveness analyses

For all screening strategies we used the MISCAN-colon model to estimate costs and number of life years gained due to screening to the situation without screening. Costs and life years gained were discounted by 3% per year.[36] Strategies that were more costly and less effective than other strategies were ruled out by simple dominance. Strategies that were more costly and less effective than a mix of other strategies were ruled out by extended dominance. The remaining strategies are not dominated and are known as "efficient". On a plot of life years gained versus costs, the line that connects the efficient strategies is called the efficient frontier, which implies that all dominated strategies lie below this line. The incremental cost-effectiveness ratio (ICER) of an efficient strategy was determined by comparing its additional costs and effects to those of the next less costly and less effective efficient strategy.

Sensitivity analyses

We performed several sensitivity analyses on different parameters, which are summarised in Table 2. We started with sensitivity analyses with respect to the additional performance and costs of 2-sample FIT over 1-sample FIT. Furthermore, we adjusted for reduced quality of life due to screening as well as CRC treatment. Correlated FIT test results were assumed because individuals with a false negative test result are likely to have a higher than average probability to have another false negative test result at a successive screening round. We used the results of a population-based CRC screening program in Italy to estimate the correlation between false negative FIT results for cancers and advanced adenomas in subsequent screening rounds.[35] Effects of limited colonoscopy capacity were evaluated by only considering strategies in which colonoscopy demand did not exceed 40, 20, 10, or 5 colonoscopies per 1,000 individuals per year. In order to assess the cost-effectiveness of the different strategies for individuals who adhere to the CRC screening guidelines, we simulated all screening strategies with 100% attendance to screening, diagnostic and surveillance colonoscopies. In addition, we performed sensitivity analyses on lower and higher values than the base case analysis for fatal complication rates with colonoscopy and for unit costs of FIT, colonoscopy, complications and treatment. We decided not to perform a probabilistic sensitivity

analysis after having weighed the limited added value against the computational effort required (see Discussion).

RESULTS

The strategy of biennial 1-sample FIT screening from age 55 to 75 years yielded 76.0-97.0 life years gained (LYG) per 1,000 individuals aged 45 years and older, compared to no screening (the range in life years gained reflects different FIT cut-off levels). The associated costs ranged from €259,000 to €264,000 per 1,000 individuals, corresponding with €2,690-€3,473 per LYG compared to no screening (Figure 2). The 2-sample FIT

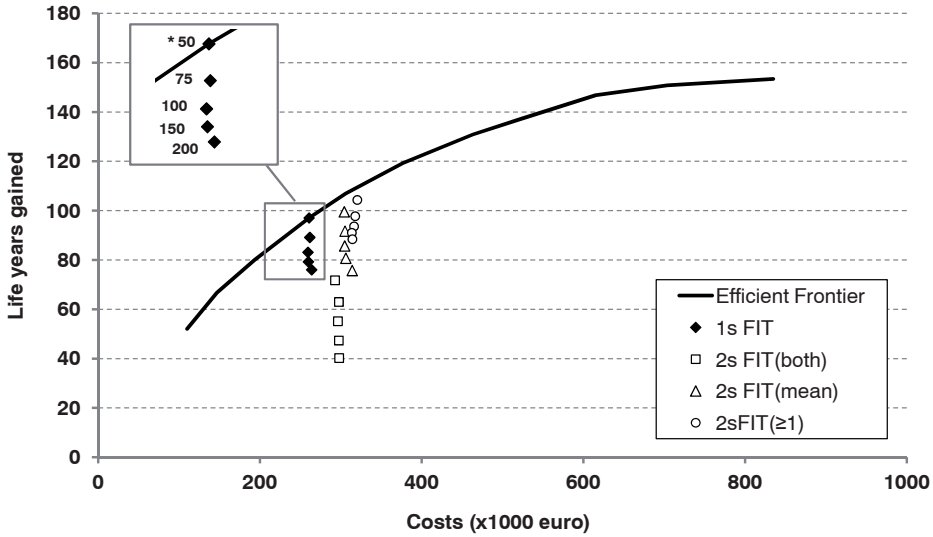

Figure 2. Costs and life years gained compared to no screening per 1,000 individuals in 2005 (start of the programme) for 1-sample and 2-sample FIT screening at different cut-off values. All data points represent biennial FIT screening from age 55 to 75.

* Per screening test (i.e. 1- or 2-sample FIT), the data points represent the results at cut-off values of 50, 75, 100, 150 and 200 ng Hb/ml. For each test, a higher cut-off level is associated with fewer life years gained, i.e. the data point at the bottom represents the result at a cut-off value of 200 ng Hb/ml, whereas the data point at the top represents the result at a cut-off value of 50 ng Hb/ml.

1sFIT = 1-sample FIT; 2sFIT(both) = 2-sample FIT, referral to colonoscopy restricted to subjects with both samples positive; 2sFIT(mean) = 2-sample FIT, referral to colonoscopy restricted to subjects for whom the mean of both samples is positive; 2sFIT(≥1) = 2-sample FIT, referral to colonoscopy of all subjects with at least one sample positive; The most efficient strategies, i.e. those strategies which for a given amount of costs yield the largest number of life-years saved, are connected by the efficient frontier (Efficient frontier). The screening interventions were modelled from the year 2005, all individuals were invited for screening until they reached the end age for screening, and health care costs for each individual were calculated until death. Costs and life years gained were discounted at an annual rate of 3%.

screening strategies with the mean of both test results being positive and at least one test result being positive provided respectively between –0.3-2.6 and 7.3-12.4 more LYG than 1-sample FIT screening at additional costs of respectively €43,000-€50,000 and €50,000-€59,000 per 1,000 individuals. The corresponding incremental cost-effectiveness ratios (ICERs) ranged from €16,818-€31,930 and €4,024-€8,041 per additional LYG. The 2-sample FIT screening strategies with two positive outcomes were less effective (i.e. less LYG per 1,000 individuals) and more costly than 1-sample FIT screening and were therefore dominated from a cost-effectiveness standpoint (see Appendix Table 1 for detailed results on effects and costs for the different biennial FIT screening strategies with the age range of 55 to 75 years).

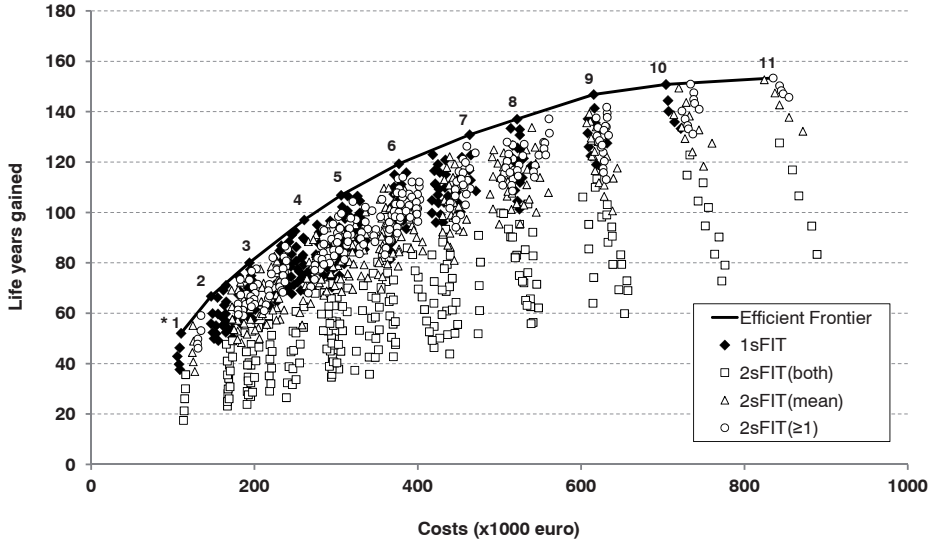

Figure 3. Costs and life years gained compared to no screening per 1,000 individuals in 2005 (start of the programme), for 1-sample and 2-sample FIT screening at different cut-off values. The data represents all simulated screening strategies, which includes varying screening age ranges and intervals.

* The numbers of the strategies on the efficient frontier correspond to the cost-efficient strategies presented in Table 3.

1sFIT = 1-sample FIT; 2sFIT(both) = 2-sample FIT, referral to colonoscopy restricted to subjects with both samples positive; 2sFIT(mean) = 2-sample FIT, referral to colonoscopy restricted to subjects for whom the mean of both samples is positive; 2sFIT(≥1) = 2-sample FIT, referral to colonoscopy of all subjects with at least one sample positive; The most efficient strategies, i.e. those strategies which for a given amount of costs yield the largest number of life-years saved, are connected by the efficient frontier (Efficient frontier). Strategies with the least intensive screening schedule (i.e. small age range, and long screening interval) are located at the bottom left of the graph, whereas strategies with the most intensive screening schedule (i.e. large age range and short screening interval) are located at the top right of the graph.

The screening interventions were modelled from the year 2005, all individuals were invited for screening until they reached the end age for that particular screening strategy, and health care costs for each individual were calculated until death. Costs and life years gained were discounted at an annual rate of 3%.

When all simulated screening strategies were considered (i.e. by varying not only the cut-off level, but also the screening age range and interval), the number of LYG compared to no screening ranged between 17.5-153.4 per 1,000 individuals, and costs ranged between €105,000-€889,000 per 1,000 individuals (Figure 3). The LYG and costs of the strategies on the efficient frontier are presented in Table 3. Although the ICER of biennial 2-sample FIT screening between age 55 and 75 (mean of both samples being positive, or at least one sample being positive) compared to 1-sample FIT seemed reasonable, Table 3 shows that most 2-sample FIT strategies are not cost-effective. When comparing the additional effect of providing two samples per screening round to the effect of providing 1-sample FIT more frequently (i.e. with a larger age range and/or shorter interval), the latter provided more LYG at equal or less costs than the 2-sample FIT strategies. This effect is also demonstrated in Figure 2, because the strategies of biennial 2-sample FIT are located below the efficient frontier. The 2-sample FIT screening strategies with the mean from both test results being positive or at least one positive test outcome were therefore ruled out by extended dominance and were considered

Table 3. Costs per life-year gained compared with no screening and incremental cost-effectiveness ratio of the cost-effective screening strategies, in a population with realistic attendance[1] to the screening program.

Strategy[2]	Test (cut-off)	Start age (y)	Stop age (y)	Interval (y)	LYG (y)	Costs (€)	Costs /LYG(€)	ICER[3] (€)
1	1s FIT (50)	60	69	3	52	110,000	2,115	2,115
2	1s FIT (50)	60	70	2	67	147,000	2,200	2,500
3	1s FIT (50)	60	74	2	80	194,000	2,420	3,524
4	1s FIT (50)	55	75	2	97	261,000	2,688	3,956
5	1s FIT (50)	55	74.5	1.5	107	306,000	2,865	4,613
6	1s FIT (50)	55	79	1.5	119	377,000	3,159	5,678
7	1s FIT (50)	50	80	1.5	131	463,000	3,541	7,480
8	1s FIT (50)	55	80	1	137	522,000	3,806	9,427
9	1s FIT (50)	50	80	1	147	615,000	4,191	9,590
10	1s FIT (50)	45	80	1	151	704,000	4,667	22,099
11	2s FIT ≥1s pos. (50)	45	80	1	153	835,000	5,444	51,336

[1] Attendance rate was 60% for screening, 85% for diagnostic colonoscopies, and 80% for surveillance colonoscopies.

[2] The strategy number corresponds to the strategies on the efficient frontier in Figure 3.

[3] The ICER of an efficient strategy is determined by comparing its additional costs and effects to those of the next less costly and less effective efficient strategy.

Costs and life-years gained are expressed per 1,000 individuals aged 45 years and older in 2005. The strategies are in ascending order from least to most costly. LYG = Life-years gained; ICER = Incremental cost-effectiveness ratio

The screening interventions were modelled from the year 2005, all individuals were invited for screening until they reached the end age for that particular screening strategy, and health care costs for each individual were calculated until death. Costs and life years gained were discounted at an annual rate of 3%.

not cost-effective compared to 1-sample FIT screening. Although Figure 2 demonstrates this effect for biennial FIT screening, the principle applies to all screening intervals, including annual screening.

Sensitivity analyses

The higher cost-effectiveness of more frequent 1-sample FIT screening compared to 2-sample FIT strategies was robust to alterations in our model assumptions. However, decreasing the cost difference between 1-sample and 2-sample FIT by 50% resulted in multiple 2-sample FIT strategies to become efficient next to 1-sample FIT. In addition, limited colonoscopy capacity did not affect the preference of 1-sample FIT over 2-sample FIT strategies, with the exception of the most stringent scenario. In case the colonoscopy demand was not allowed to exceed 5 colonoscopies per 1,000 individuals per year, 2-sample FIT strategies with both samples being positive were preferred over 1-sample FIT.

DISCUSSION

Our analysis demonstrates that for a given screening schedule (i.e. age range and screening interval), 2-sample FIT strategies with the mean from both test results being positive or at least one positive test outcome provide more LYG at acceptable costs than 1-sample FIT screening. However, when all simulated screening strategies are considered (i.e. including varying age ranges and screening intervals), increasing the screening intensity of 1-sample FIT testing (i.e. greater age range and/or shorter screening interval) is more cost-effective than providing two FITs within one screening round.

This study was based on data from a randomised trial in which the attendance and diagnostic yield of 1- and 2-sample FIT were compared.[12] Considering only the relation between positivity rate and detection rate of advanced adenomas it seems to be recommendable to choose for FIT screening with either one or two samples based on the available colonoscopy capacity. However, the current analysis demonstrates that including the costs for screening and treatment of CRC over multiple screening rounds, affects the relation between 1- and 2-sample FIT. Although a number of 2-sample FIT screening strategies (e.g. with at least one sample, or the mean of both samples being positive) are close to the cost-efficiency frontier, increasing the number of 1-sample FIT screening rounds was found to be a more cost-effective way of gaining health benefits.

Other cost-effectiveness analyses determining the optimal number of FIT samples are limited. Two Japanese studies compared the costs of FIT screening with either one, two or three FITs, per cancer detected in a single screening round.[37, 38] In all three sampling strategies individuals were referred for diagnostic colonoscopy if at least one

sample was positive. In both studies it was concluded that 2-sample FIT screening with at least one test being positive would be the most desirable strategy from a diagnostic accuracy and cost-effectiveness stand-point. A more recent French study did include multiple screening rounds in their cost-effectiveness model and also evaluated the effect of different cut-off levels.[39] The authors concluded that 3-sample FIT screening with a cut-off level of 50 ng Hb/ml was the most cost-effective strategy to be preferred. The results of our current analysis do agree with these studies about the added value of multiple FIT sampling within a given screening schedule. More than one FIT sample can provide additional health benefits at acceptable costs. Unfortunately, the study did not provide information comparing the added effect of multiple FIT samples per screening round to the effect of increasing screening intensity with 1-sample FIT.

Several limitations need to be acknowledged. Firstly, we based our analysis on data from one screening round. Therefore we could not estimate the correlation of test outcomes between successive screening rounds. Individuals with a false negative test result (e.g. because the lesion did not bleed) in one screening round may have a higher than average probability to have another false negative test result at a successive screening round. Therefore, we performed a sensitivity analysis based on Italian results [35] in which correlation of systematic false negative test outcomes was assumed for advanced adenomas and CRCs. The analysis showed that the cost-effectiveness of 2-sample FIT decreased less than the cost-effectiveness of 1-sample FIT strategies, but 1-sample FIT screening remained dominant. Nevertheless, we need further data from repeat screening rounds in The Netherlands to get a good estimate of systematic false negative rates in the population we modelled.

Secondly, we assumed the screening attendance rate to be independent of screening intensity and number of FIT samples performed. In the first screening round of one of the Dutch trials, [10-12] screening attendance rate was not significantly different between the 2-sample FIT and 1-sample FIT study arm (61.3% vs 61.5%; P=0.837). However, it could be hypothesised that, e.g. adherence in case of a more intense screening schedule with 1-sample FIT would decrease compared to less intense screening schedules with 2-sample screening. This would negatively affect the cost-effectiveness of more intensive screening strategies relative to 2-sample testing and might alter our conclusions.

Thirdly, we based our analyses on a screening naïve population. Depending on the amount of prior screening, CRC incidence in the population and the resulting cost-effectiveness could be lower. However, this would affect the strategies we compared in a similar way. If any, the effect of prior screening would make 1-sample FIT screening more preferable, since a lower CRC incidence would reduce the added value of a second FIT sample.

Finally, we did not perform a probabilistic sensitivity analysis. Given the large number of strategies that has to be evaluated for each draw, such an analysis would

require a huge computational effort. We believe that simulating the range of varying strategies is one of the strengths of this analysis, because we were primarily interested in the comparison of different FIT screening strategies with varying numbers of samples provided, FIT cut-off levels, screening intervals and age ranges. Regardless, data on the probability distributions of most of the parameter values are lacking, which makes the interpretation of a probabilistic sensitivity analysis difficult and the outcome of limited added value. One of the most uncertain assumptions of the model is that all CRCs arise from adenoma precursors. For FIT screening, this assumption will have limited impact because FIT has a low sensitivity for adenomas. In addition, the assumption of non-bleeding (and therefore for FIT undetectable) adenomas was evaluated in the sensitivity analysis by assuming correlation between false-negative results.

In conclusion, our analysis provides new insights for decision makers; in a situation where attendance to screening does not differ between strategies, intensifying screening with 1-sample FIT was found to be more cost-effective than providing two FIT samples within one screening round. It is therefore recommended to increase the number of screening rounds with 1-sample FIT screening, before considering to increase the number of FIT samples provided per screening round.

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APPENDIX

Appendix Table 1.

Appendix Table 1. Summary results of biennial 1- and 2-sample FIT screening strategies with the age range of 55-75 years.

				Costs per 1,000 individuals (x1,000 €) (3% discount)						
Screen test and cut-off level*	Incidence reduction (0% discount)	Mortality reduction (0% discount)	Life years gained (3% discount)	Total	FIT	Diagnostic colonoscopy after positive FIT	Surveillance colonoscopy	Clinical diagnostic colonoscopy	Complications after colonoscopy	Treatment of CRC
1sFIT										
50	12.83%	28.34%	97.0	261	186	143	71	−10.4	1.7	−130
75	10.39%	25.98%	89.2	262	191	114	58	−9.8	1.4	−93
100	9.08%	24.22%	83.1	259	193	98	51	−9.3	1.2	−74
150	7.74%	22.92%	79.3	260	196	83	45	−9.0	1.0	−55
200	6.47%	21.94%	76.0	264	197	72	39	−8.7	0.9	−36
2sFIT (both)										
50	8.58%	21.38%	71.8	293	244	83	46	−8.3	1.0	−73
75	6.47%	18.60%	63.0	298	248	64	36	−7.4	0.8	−43
100	5.29%	16.39%	55.2	296	250	53	30	−6.6	0.6	−30
150	3.90%	13.92%	47.4	298	252	41	23	−5.8	0.5	−13
200	2.88%	11.71%	40.3	298	253	34	18	−5.1	0.4	−2
2sFIT (mean)										
50	13.95%	29.27%	99.5	304	230	153	77	−10.7	1.9	−147
75	11.35%	26.81%	91.7	305	237	121	63	−10.0	1.5	−107
100	9.78%	24.92%	85.7	305	240	103	55	−9.5	1.2	−85
150	8.11%	23.36%	80.7	306	244	86	46	−9.1	1.0	−62
200	6.48%	21.78%	75.7	314	246	73	39	−8.6	0.9	−36
2sFIT (≥1)										
50	15.25%	30.62%	104.4	320	223	188	85	−11.0	2.2	−166
75	12.69%	28.65%	97.8	318	230	153	71	−10.6	1.8	−127
100	11.29%	27.29%	93.6	316	234	132	64	−10.2	1.6	−105
150	10.00%	26.36%	91.0	314	238	113	57	−9.9	1.4	−87
200	8.93%	25.59%	88.4	314	241	100	52	−9.8	1.2	−70

* 1sFIT = 1-sample FIT; 2sFIT(both) = 2-sample FIT, both samples positive; 2sFIT(mean) = 2-sample FIT, mean of both samples positive; 2sFIT(≥1) = 2-sample FIT, at least one sample positive.

Chapter 8

Requirements for colorectal cancer screening with new biomarkers: a cost-effectiveness analysis

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ABSTRACT

Background. There is increasing interest in developing molecular biomarkers for non-invasive colorectal cancer (CRC) screening. We evaluated under which conditions biomarker-based screening could be cost-effective, compared to current faecal immunochemical test (FIT) screening, in average risk individuals.

Methods. The MISCAN-colon microsimulation model was used to estimate the relative impact of various CRC screening test characteristics on life years gained (LYG) and costs. We modelled FIT, as well as a range of hypothetical and two recently described biomarker tests (Cologuard® and PHACTR3 promoter methylation combined with FIT), while varying the screening age range and interval. For each biomarker test we calculated the threshold unit cost allowed to be cost-effective.

Results. Biennial FIT screening between age 55-75 years resulted in 84,9 LYG at a cost of €122,000 per 1,000 participants. Maximising the sensitivity alternatively for CRC or advanced adenomas increased the number of LYG to a similar extent, but the upper limit threshold cost was considerably higher with adenoma sensitivity (€43, versus €18 for CRC). Considering a unit cost of €7 for FIT, Cologuard® and PHACTR3+FIT were cost-effective at unit costs up until approximately €11. With a hypothetical perfect specificity and sensitivity for CRC the threshold costs for biomarker tests never exceeded €51.

Conclusion. Given the considerable sensitivity of FIT for CRC, improving on the sensitivity for adenomas is crucial for alternative tests to become competitive. In case of greatly improved all-over performance the unit cost of a biomarker test should, for cost-effectiveness, not exceed approximately seven times the unit cost of FIT.

INTRODUCTION

In developed countries, colorectal cancer (CRC) is the third most commonly diagnosed malignancy in men and ranks second in women.[1] Screening for CRC and its precursor lesions, adenomas, can detect the disease at an earlier stage when treatment is potentially more effective. Guaiac faecal occult blood tests (gFOBT) and faecal immunochemical tests (FIT) detect traces of blood in stool, and are widely used for non-invasive screening.[2] However, even the newer versions have a limited sensitivity, especially for adenomas. It is estimated that FIT misses 27-47% of CRCs and 70-80% of advanced adenomas per screening round.[3, 4]

Improved performance of non-invasive screening could be obtained by testing for disease specific molecules like DNA in stool or blood, added to or replacing FIT.[5] Molecular biomarkers have been investigated extensively, and ongoing technical innovations have improved the feasibility to use such tests for mass-screening. Exact Sciences Corp. (Madison, WI) has developed a multi-target stool DNA test, which consists of multiple DNA mutation and methylation markers, and also includes a measure of haemoglobin. Recently data were published from the first screening trial, reporting 42% sensitivity for advanced adenomas and 92% sensitivity for CRC, at a specificity for neoplastic findings of 88%.[6] Although the sensitivity for CRC of this particular test is higher than FIT, in order to be considered for implementation in population-based screening programs, as are operational in several European countries, any new test should be both effective and cost-effective compared to current screening options.

Research and analysis methods in biomarkers for CRC are still developing, and test performance and costs are not yet settled. Therefore the aim of this study was to provide insight in the requirements for test sensitivity, specificity and unit cost in order for new technologies to be cost-effective compared to FIT screening in the general population.

Methods

We used the MISCAN-Colon microsimulation model to estimate life years gained (LYG) and costs of various screening scenarios. Firstly, we explored the potential impact of maximising specificity, adenoma sensitivity and CRC sensitivity on cost-effectiveness, by modelling a single screening schedule based on FIT, and varying test characteristics one by one. Secondly, we modelled a range of hypothetical biomarker tests, with varying specificity and sensitivity for adenomas and CRC. For each biomarker test variant we varied the screening age range and interval, and calculated costs per LYG assuming a unit cost of €50, €100 and €300 per test. Thirdly, for each biomarker test variant we calculated the threshold unit cost allowed to be cost-effective compared to FIT screening.

MISCAN-Colon microsimulation model

The MISCAN-colon model and the data sources that informed the quantifications of the model are described in detail in the Model Appendix at the end of this thesis, and in previous publications.[7-11] In brief, the MISCAN-colon model simulates the life histories of individuals from birth to death. CRC arises in the population according to the adenoma-carcinoma sequence.[12, 13] More than one adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas can progress in size from small (≤5 mm) to medium (6-9 mm) to large (≥10 mm), and some may eventually become malignant. A preclinical (i.e., not detected) cancer has a chance of progressing through stages I to IV and may be detected by symptoms at any stage. After clinical diagnosis of CRC, survival depends on the stage at diagnosis. At any time during his/her life an individual may die of other causes.

With stool- or blood-based screening, an individual with a positive test will be referred for diagnostic colonoscopy for possible removal of adenomas and detection of cancers. In this way CRC mortality can be reduced. The life years gained by screening are calculated as the difference in model-predicted life years lived in the population with and without CRC screening.

Study population

We modelled a cohort of individuals at average risk of CRC. The age-specific all-cause mortality was based on the 2010 Dutch life tables. The simulated CRC incidence rate and CRC stage distribution were calibrated to observed data in The Netherlands from 1999-2003, which was before the onset of opportunistic screening.[14] Survival rates after clinical diagnosis of CRC before age 75 were based on CRC relative survival data from 1985-2004.[15] The survival for individuals diagnosed at age 75 and older was based on the under 75 survival rates, and adjusted to fit the observed age-increasing mortality/incidence ratio.

Test characteristics

The test characteristics of FIT were fitted to the positivity and detection rates of adenomas and CRC observed in the first screening round of two Dutch randomised trials (Table 1).[16-18] In addition, based on a prior calibration of the MISCAN-Colon model to three gFOBT trials, it was assumed that, the probability a CRC bleeds and thus the sensitivity of FIT for CRC depends on the time until clinical diagnosis, i.e. cancers that bleed do so increasingly over time, starting "occultly" and ending as clinically visible.[9] We modelled FIT with a cut-off level of 50 ng Hb/ml, because this was previously found to be the most cost-effective.[19]

For the first part of the analysis (maximising sensitivity and specificity) we considered hypothetical tests based on the FIT, but with the sensitivity for adenomas and/or CRC, and specificity alternatively increased to 100%.

In the second and third part of the analysis (varying screening age range, interval and test costs, and threshold costs for biomarker tests) we considered various biomarker test variants with sensitivities for CRC ranging from 60% (slightly lower than FIT) to 100%, at 10% increments. The low end sensitivity for adenomas was based on the sensitivity observed with FIT, and was varied by the same proportions as the sensitivity for CRC. For example, when increasing the sensitivity for CRC from 70% to 80%, the sensitivity for adenomas was also increased by a factor of 1.14 (80/70). In the model, the "lack of specificity" was defined as the probability of a positive test result irrespective of hav-

Table 1. Overview of test characteristics used in the model.

Screen test (reference)	Model specificity (per person, %)	Model sensitivity (per lesion, %)*					
		Adenoma			CRC		
		Small (≤5mm)	Medium (6-9mm)	Large (≥10mm)	Early preclinical†	Late preclinical†	Average
FIT‡	96	0	11	34	50	83	64
Biomarker test variants							
Sensitivity CRC 60%	88-100§	0	11	32	45	80	60
Sensitivity CRC 70%	88-100§	0	12	37	58	87	70
Sensitivity CRC 80%	88-100§	0	14	42	71	92	80
Sensitivity CRC 90%	88-100§	0	16	48	85	96	90
Sensitivity CRC 100%	88-100§	0	18	53	100	100	100
Cologuard®[6]‡	88	0	16	28	87	97	91
PHACTR3+FIT[20]‡	94	0	9	24	91	98	94
Colonoscopy‖	90	75	85	95	95	95	95

CRC, colorectal cancer; FIT, faecal immunochemical test; PHACTR3, Phosphatase and actin regulator 3

* Excluding to probability that an adenoma or cancer is detected because of a lack of specificity. An example of lack of specificity is that a person with a non-bleeding adenoma can get a positive FIT (with possible detection during follow-up colonoscopy) not because of the adenoma, but because of bleeding from a diverticulum.

† It was assumed that the probability a CRC bleeds and thus the sensitivity of FIT for CRC depends on the time until clinical diagnosis, in concordance with findings for gFOBT, which were based on a prior calibration of the MISCAN-Colon model to three gFOBT trials.[9] This result is to be expected when cancers that bleed do so increasingly over time, starting "occultly" and ending as clinically visible.

‡ The test characteristics of FIT were fitted to the positivity and detection rates of adenomas and CRC from two Dutch randomised trials.[16-18] In a similar way, the test characteristics of Cologuard® and PHACTR3+FIT were fitted to the positivity and detection rates reported by Imperiale et al.[6], and Bosch et al.[20] For all tests we assumed that the sensitivity for small adenomas was 0%, and that small adenomas would only be detected because of a lack of specificity of the test.

§ We modelled five different sets of sensitivities for the biomarker test. All five sets of sensitivities were modelled with specificities ranging from 88% to 100%, at 2% increments, yielding a total of 35 (5x7) different sets of test characteristics for the hypothetical biomarker tests variants.

‖ Colonoscopy was only used during follow-up and surveillance after a positive FIT or biomarker test.

ing adenomas or not. For example, a person with a non-bleeding adenoma can get a positive FIT (with possible detection during follow-up colonoscopy) not because of the adenoma, but because of bleeding from a diverticulum. For the biomarker test variants the specificity (one minus the lack of specificity) was varied from 88% to 100% at 2% increments. Varying both sensitivity and specificity resulted in 35 (5x7) different sets of test characteristics (Table 1).

Based on existing data, we modelled two additional, more realistic, biomarker tests: 1) Cologuard®, a multimarker faecal DNA test developed by Exact Sciences Corp., Madison, WI, USA[6]; and 2) a combination of the DNA methylation marker Phosphatase and actin regulator 3 (PHACTR3) and FIT, developed at the VU University Medical Centre, Amsterdam, The Netherlands.[20]

The sensitivity of diagnostic and surveillance colonoscopies was assumed to be 75% for adenomas ≤5 mm, 85% for adenomas 6-9 mm, and 95% for adenomas ≥10 mm and CRC.[21] We did not explicitly model a separate pathway for traditional and sessile serrated adenomas. The average time it takes for an adenoma to develop into CRC was calibrated to the UK flexible sigmoidoscopy screening trial[22] which included both traditional adenomas, as well as sessile serrated adenomas. The different types of adenomas are therefore included in the modelled mix of slow and rapid progressing lesions. However, we assume that the sensitivity of colonoscopy was only dependent on adenoma size. Hyperplastic polyps are reflected by the lack of specificity of colonoscopy.[23] We assumed additional biopsy costs for procedures where biopsies were performed and in which, in retrospect, no adenomas were detected.

Screening scenarios

In the first part of the analysis (maximising sensitivity and specificity), we modelled the screening schedule recommended in the Dutch population-based screening program; biennial screening between age 55 and 75. In the second and third part of the analysis (varying screening age range, interval and test costs, and threshold costs for biomarker tests) we considered different screening schedules by varying age to start screening (45, 50, 55, or 60 years), age to stop screening (70, 75, or 80 years), and screening interval (1, 1.5, 2, 3, 5, 7, or 10 years). These screening age ranges and intervals result in 84 (4x3x7) different screening schedules, and combining them with the different biomarker test variants resulted in more than 3000 unique screening scenarios.

In order to focus on the relation between test performance and cost, we simulated individuals who follow the screening, follow-up and surveillance recommendations. Individuals with a positive test result would be referred for diagnostic colonoscopy. If no adenomas were found during the procedure the individual was assumed to be at low-risk for CRC and returned to the regular screening program after ten years. If one or more adenomas were found, they would be removed and the individual would enter

surveillance according to the Dutch guidelines for follow-up after polypectomy used until recently,[24] which indicates colonoscopy after six years in case of one or two adenomas and after three years in case of three or more adenomas.

Costs

The analysis was conducted from a modified societal perspective. This means that next to direct medical costs, patient time costs were also included.[25] Costs for FIT screening, complications after colonoscopy and treatment of CRC have been published previously.[19] Using the medical cost price index from the Dutch Health Care Authority, we updated those costs to the year 2013.[26] In addition, the costs for colonoscopy procedures were based on a recent internal study at the Dutch Erasmus Medical Centre (unpublished data), in the setting of a dedicated screening centre. We assumed that the biomarker tests would have organizational costs (i.e. costs for the mailing of invitations, reminders and test results, gathering of address information of eligible participants, and overhead of the screening organization) equal to those of FIT screening. Although current DNA-based tests require whole stool samples for analysis, which are more expensive to return than a FIT test, for the sake of the present study we assumed that smaller samples will be sufficient in the near future. In the analyses preceding the calculation of threshold unit costs, the costs for the biomarker test kit and the analysis of the test was assumed to be either €50, €100 or €300 for all biomarker test variants. An overview of cost inputs used in the model is presented in Table 2.

Cost-effectiveness and threshold costs

To start with, we estimated costs and LYG of our scenario's compared to no screening, discounted by three percent per year.[30] Subsequently, based on these results, we compared between scenario's. Scenarios that were more costly and less effective than other scenarios (simple dominance) or than a mix of other scenario's (extended dominance) were ruled out. The remaining scenarios are not dominated and are known as "efficient". On a plot of costs versus LYG, the line that connects the efficient scenarios is called the efficient frontier, which implies that all dominated scenarios lie below this line. The incremental cost-effectiveness ratio (ICER) of an efficient scenario was determined by comparing its additional costs and effects to those of the next less costly and less effective efficient scenario.

In the analysis of threshold unit costs, for each biomarker test variant an efficient frontier was determined from the variety of screening age ranges and intervals considered. Subsequently, for each scenario on the efficient frontier we calculated the cost per biomarker test that is allowed for that scenario to be on the efficient frontier of FIT. The resulting cost level may vary over the screening intensities, and we considered the highest value as the threshold unit cost for the particular test variant. For biomarker

Table 2. Cost inputs used in the model, modified societal perspective.*

Variable	**Cost (€)**			
CRC screening, per procedure	*FIT*		*Biomarker*	
	Attenders†	*Non-attenders†*	*Attenders†*	*Non-attenders†*
Organizational costs	14.61	14.61	14.61	14.61
Test kit	2.48	2.48	2.48	2.48
Analysis of the test	4.81	0.00	‡	0.00
Subtotal (test kit + analysis of test)	*7.29*	*2.48*	*‡*	*2.48*
Patient time cost	15.93	0.00	15.93	0.00
Total screen costs, per person invited	37.83	17.09	130.54	17.09
Follow-up/surveillance, per procedure				
Colonoscopy, no polypectomy	447			
Colonoscopy, polypectomy	584			
Colonoscopy, diagnosis clinical CRC	688			
Colonoscopy, complications§	3,156			
CRC treatment, per patient per year‖	*Stage I*	*Stage II*	*Stage III*	*Stage IV*
Initial treatment	17,219	22,177	26,585	30,992
Continuous care	685	685	685	685
Terminal care, death CRC	23,786	23,786	24,888	32,050
Terminal care, death other causes	9,352	8,912	10,234	19,930

CRC, colorectal cancer; FIT, faecal immunochemical test

* For the calculation of patient time costs we assumed an average hourly wage of €15.93.[27] We assumed 1, 16, and 112 hours of patient time per procedure for FIT and biomarker testing, colonoscopy (including bowel preparation), and colonoscopy complications respectively. For CRC treatment we assumed 244, 19, and 283 hours of patient time per year of care in initial treatment, continuous care, and terminal care respectively.[28, 29]

† In the base case analysis we assumed all individuals would attend all screening, follow-up and surveillance invitations. In the sensitivity analysis with different attendance rate between FIT and biomarker screening we assumed invitation costs for non-attenders, but no cost of test analysis and no patient time.

‡ The unit cost of the biomarker test variants (test kit and analysis of the test) were determined in the threshold analysis.

§ We assumed a complication rate of 2.4 per 1,000 colonoscopies

‖ 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.

scenarios that were more effective than the most effective FIT scenario, the threshold cost for the biomarker scenario was calculated based on a maximal willingness-to-pay of €50,000 per additional LYG relative to the most effective FIT scenario.

Outcomes

The outcomes are costs and LYG per 1,000 individuals compared to no screening, and threshold unit cost required for equal cost-effectiveness compared to FIT.

Sensitivity analyses

We considered several sensitivity analyses, summarised in Appendix Table 1, to investigate the robustness of the estimated threshold unit costs to varying model assumptions. First, we adjusted for quality of life effects of CRC screening and treatment. Second, we evaluated the effect of limited colonoscopy capacity by considering only scenarios in which colonoscopy demand did not exceed alternatively 40, 30, 20, or 10 colonoscopies per 1,000 individuals per year. Third, we considered a scenario in which screening uptake with FIT was 60%[16-18] and screening uptake using the biomarker test variants would be either 20% point higher or lower than FIT. Fourth, we assumed an ICER of €100,000 per additional LYG as the upper limit for any scenario to be considered cost-effective. Fifth, we alternatively increased and decreased the costs of colonoscopy, colonoscopy complications and CRC treatment. Finally, we replaced all CRC screening and treatment costs from The Netherlands, with US costs. For this analysis we used cost estimates as published by Zauber and colleagues,[31] and we adjusted them to 2013 US dollars using the Consumer Price Index.[32]

RESULTS

Maximising sensitivity and specificity

Relative to no screening, biennial FIT between ages 55-75 years (the screening schedule recommended in the Dutch population-based screening program) provided 84.9 LYG per 1,000 screening participants. This effect was achieved at an overall cost of €122,000 per 1,000 participants (Figure 1). When taking this screening schedule as a reference, a test with a theoretical maximal sensitivity for CRC of 100% (instead of 64% in case of FIT) would increase the number of LYG to 92.4, at a cost of €129,000. Similarly, a test with a theoretical 100% sensitivity for large adenomas (100% instead of 34% in case of FIT) would result in 93.8 LYG, at a cost of only €24,000.

Increasing the sensitivity of the screening tests allows for a higher cost per test, while still being equally cost-effective as FIT. The threshold cost rose from €7 (unit cost of FIT) to €18 and €43 for the tests with 100% sensitivity for CRC and large adenomas respectively (Figure 2). In the extreme case of a test that is able to detect 100% of all lesions, including adenomas <10mm, the threshold cost was €53.

Decreasing the specificity of the hypothetical test to 90%, compared to 96% for FIT, increased the number of individuals referred to colonoscopy and increased the number

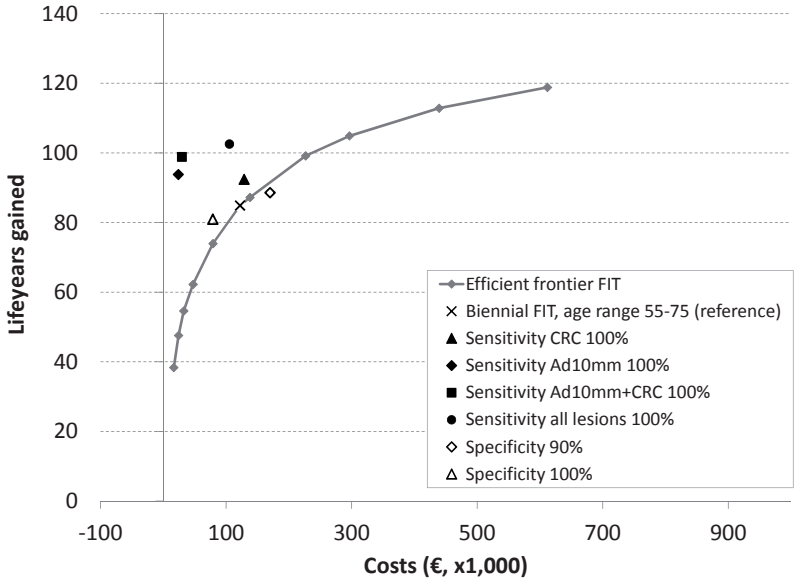

Figure 1. Upper limits of effects on costs and life years gained per 1,000 individuals of theoretically increasing test sensitivity and specificity, with biennial screening between age 55-75 years.
FIT, faecal immunochemical test; CRC, colorectal cancer; Ad, adenoma.
Legend: Efficient frontier FIT, Efficient frontier of the FIT screening scenarios; Biennial FIT, age range 55-75 (reference), Reference screening scenario of biennial FIT between age 55-75 years; Sensitivity CRC/Ad10mm/Ad10mm+CRC 100%, A theoretical test with the specificity and sensitivity for small adenomas (<10mm) identical to FIT, but with 100% sensitivity for CRC, large adenomas (≥10mm), or CRC and large adenomas respectively; Sensitivity all lesions 100%, A theoretical test with the specificity of FIT, but with 100% sensitivity for all lesions; Specificity 90%/100%, A theoretical test with the same sensitivity as FIT, but with 90%, or 100% specificity respectively.
The scenarios on the FIT efficient frontier were previously found to be cost-effective.[19] From the bottom left to the top right of the graph increase in screening age range and decrease in screening interval.
Decreasing the specificity of the theoretical test, compared to FIT, increased the number of individuals referred to colonoscopy and increased the number of LYG (by increasing the possibility of detecting non-bleeding adenomas). Alternatively, increasing the specificity reduced the number of LYG compared to the FIT reference scenario.
All costs and life years gained are discounted by 3% per year.

of LYG from 84.9 to 88.6 per 1,000 screening participants (by increasing the possibility of detecting non-bleeding adenomas). However, the additional costs due to the additional colonoscopies resulted in a threshold cost of only €2 (Figure 2). Alternatively, increasing the specificity to 100% decreased the number of LYG, but increased the threshold cost to €13 per test.

Varying screening age range, interval and test costs

Next to increasing the sensitivity and/or specificity of screening tests, varying the screening age ranges and intervals also affects the effectiveness of a screening program.

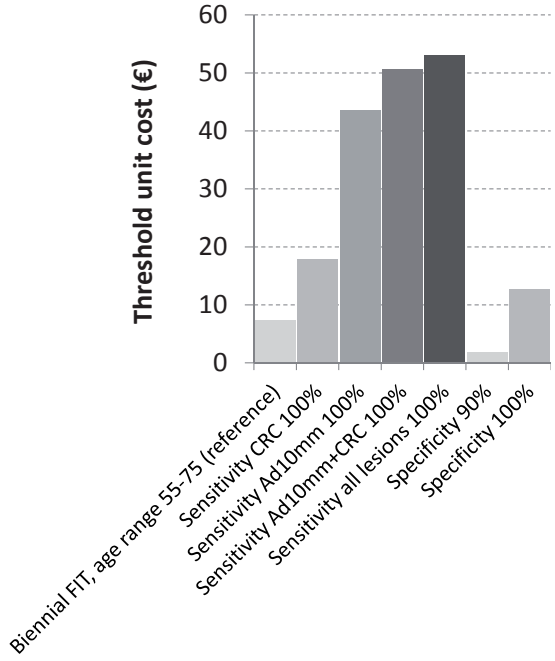

Figure 2. Upper limits of effects on the threshold unit cost of varying theoretically increasing test sensitivity and specificity, with biennial screening between age 55-75 years.
FIT, faecal immunochemical test; CRC, colorectal cancer; Ad, adenoma.
Legend: Efficient frontier FIT, Efficient frontier of the FIT screening scenarios; Biennial FIT, age range 55-75 (reference), Reference screening scenario of biennial FIT between age 55-75 years; Sensitivity CRC/Ad10mm/Ad10mm+CRC 100%, A theoretical test with the specificity and sensitivity for small adenomas (<10mm) identical to FIT, but with 100% sensitivity for CRC, large adenomas (≥10mm), or CRC and large adenomas respectively; Sensitivity all lesions 100%, A theoretical test with the specificity of FIT, but with 100% sensitivity for all lesions; Specificity 90%/100%, A theoretical test with the same sensitivity as FIT, but with 90%, or 100% specificity respectively.

For example, a higher sensitivity would allow for longer screening intervals at equal LYG. Figure 3 presents the costs and LYG of two more realistic biomarker test variants, based on Cologuard® and PHACTR3+FIT, while allowing for alternative screening age ranges and intervals. In this figure the unit cost of the biomarker tests was varied from €50, to €100 and €300 per test. At these cost levels all biomarker screening scenarios were located below the efficient frontier of FIT, indicating that for each biomarker screening scenario, there was a FIT scenario resulting in the same number of LYG at equal or lower costs. This finding was independent of whether un-intensive (lower left part of the frontier) or intensive (upper right part) screening was considered.

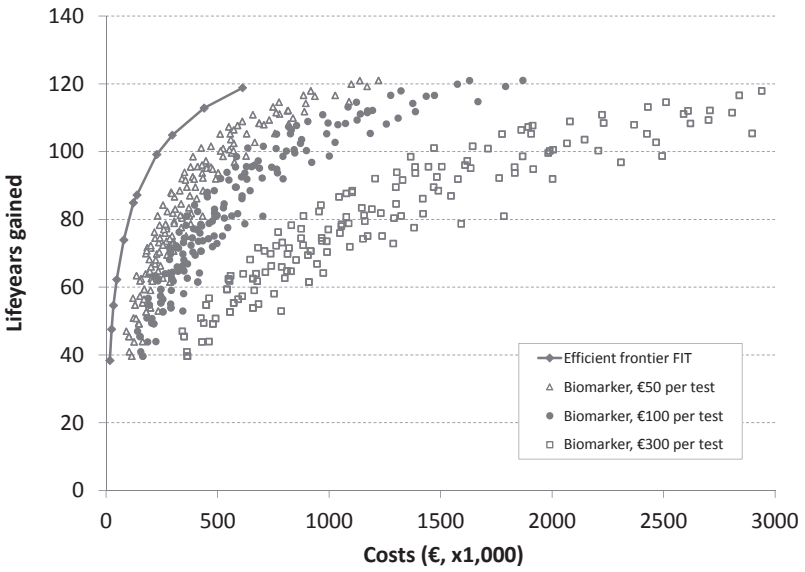

Figure 3. Costs and life years gained per 1,000 individuals of potentially more realistic biomarker test variants, when varying screening age ranges, intervals and unit costs.
FIT, faecal immunochemical test.
The test characteristics of the biomarker scenarios were based on the Cologuard® and PHACTR3+FIT tests (see Table 1 for details). For each test we considered different screening schedules by varying age to start screening (45, 50, 55, or 60 years), age to stop screening (70, 75, or 80 years), and screening interval (1, 1.5, 2, 3, 5, 7, or 10 years).
The scenarios on the FIT efficient frontier were previously found to be cost-effective.[19] For all tests, in general, the scenarios from the bottom left to the top right of the graph increase in screening intensity by increasing age range and decreasing in screening interval.
All costs and life years gained are discounted by 3% per year.

Threshold costs for biomarker tests

The threshold unit cost allowed for equal cost-effectiveness compared to FIT are presented in Table 3. The (maximal) threshold cost for Cologuard® was €11.05. This value was attained by screening biennially between age 50 and 80 years (at higher or lower screening intensity the unit costs had to be even lower for the test to become cost-effective). For PHACTR3+FIT the threshold cost of €11.39 was attained by annual screening between age 45 and 80.

Considering the range of hypothetical biomarker test variants described in Table 1, threshold costs varied considerably. Thresholds below the €7 for FIT showed in instances where test specificity would be sacrificed to get good sensitivity, resulting in increased colonoscopy demand. On the other hand, the threshold cost for a very good performing test with 53% and 100% sensitivity for large adenomas and CRC, and 100% specificity was €50.23 (Table 3).

Table 3. Threshold unit costs of the biomarker test variants allowed for equal cost-effectiveness compared to FIT.

Specificity any lesion (%)	Sensitivity CRC (%)*	Threshold unit cost (€)†	Specificity any lesion (%)	Sensitivity CRC (%)*	Threshold unit cost (€)†
FIT (comparator)		**7.29**		90	**31.63**
88	60	**Neg.**		100	**43.63**
	70	**6.21**	96	60	**5.89**
	80	**14.75**		70	**14.19**
	90	**25.06**		80	**23.07**
	100	**37.81**		90	**33.64**
90	60	**Neg.**		100	**45.50**
	70	**8.71**	98	60	**8.27**
	80	**16.66**		70	**16.80**
	90	**27.44**		80	**25.25**
	100	**40.13**		90	**35.25**
92	60	**1.02**		100	**47.96**
	70	**9.20**	100	60	**10.98**
	80	**18.64**		70	**18.58**
	90	**29.46**		80	**27.12**
	100	**41.72**		90	**36.38**
94	60	**3.11**		100	**50.23**
	70	**12.00**	Cologuard®		**11.05**
	80	**20.90**	*PHACTR3*+FIT		**11.39**

CRC, colorectal cancer; FIT, faecal immunochemical test; PHACTR3, Phosphatase and actin regulator 3; Neg., calculated threshold cost was a negative value.

† Although the average sensitivity for CRC is used to identify different biomarker test variants, the sensitivity for adenomas is varied accordingly (see Table 1).

* The presented unit costs include costs for the test kit and the analysis of the test.

Sensitivity analyses of threshold costs

The estimated threshold costs for the biomarker test variants were robust (threshold costs never exceeding €100) to most alternative assumptions considered, and assuming US costs levels for screening and treatment procedures approximately doubled the threshold cost; $104.98 for the test with 53% and 100% sensitivity for large adenomas and CRC, and 100% specificity, compared to €50.23 with Dutch cost inputs (Appendix Table 1).

However, the results were sensitive to assuming a limited colonoscopy capacity. The maximal colonoscopy demand in the base case analysis was approximately 55 per 1,000 individuals (annual screening with a low specificity test). When the analysis was limited to scenario's with a colonoscopy demand not exceeding 10 colonoscopies per 1,000 individuals per year, the test variants with 88-92% specificity were not cost-effective

compared to FIT (with 94% specificity) at any unit cost. In contrast, with higher specificity levels the threshold costs strongly increased, up until €213.97-€436.77 for biomarker tests with 100% specificity (€10.98-€50.23 in the base case analysis).

In addition, the analyses were sensitive to differences in screening uptake between FIT and the biomarker tests; a 20% point lower screening uptake with biomarker screening (test with 53% and 100% sensitivity for large adenomas and CRC, and 100% specificity) compared to FIT decreased threshold costs from €50.23 to €18.01, while a 20% point greater screening uptake resulted in a threshold cost of €238.08.

DISCUSSION

This study demonstrates that, when taking FIT as a reference, maximising the sensitivity for adenomas has a larger potential impact on cost-effectiveness than maximising the sensitivity for CRC. The threshold unit cost of the biomarker test variants allowed for equal cost-effectiveness compared to FIT (the latter with a sensitivity of 34% for large adenomas (≥10mm), 64% for CRC, specificity of 96%, and a unit cost of €7.29), ranged from €1.02 for a test with 32% and 60% sensitivity for large adenomas and CRC, and 92% specificity to €50.23 for a test with 53% and 100% sensitivity for large adenomas and CRC, and 100% specificity. The results were sensitive to reduced colonoscopy capacity, and (large) differences in screening uptake between FIT and the biomarker tests.

The finding that maximising the adenoma sensitivity has a bigger impact on effectiveness than CRC sensitivity is tied to the lower sensitivity of FIT for adenomas than for CRC, which provides more room for improving adenoma rather than CRC detection. In addition, the preclinical duration of adenomas is longer than that of CRC, and earlier detection of CRC has a smaller impact on treatment costs than preventing CRC through the removal of adenomas. Improving the sensitivity and specificity did not greatly increase the threshold cost compared to FIT mainly because CRC is a slow growing disease, and the time for progressive adenomas to develop and progress into cancer takes on average more than 10 years.[12, 13] Although FIT has imperfect "per test sensitivity", it can be performed multiple times at relatively low costs, resulting in fairly good "program sensitivity".

We did not model location dependency for the sensitivity of FIT screening. It has been suggested that FIT might be less sensitive for proximal lesions, compared to distal ones, and that this effect would be less pronounced with faecal DNA-based screening.[33, 34] However, other data suggest there is no such difference for FIT.[35, 36] Either way, we did model multiple biomarker test variants with a range of improved overall sensitivity for adenomas and CRC, and this can also represent improved sensitivity in, for example, proximal lesions.

The analysis was sensitive to differences in screening uptake between FIT and the biomarker test. If the biomarker test would be able to increase screening uptake by 20% point relative to FIT the threshold would increase from €50.23 to €238.08 (variant with 53% and 100% sensitivity for large adenomas and CRC, and 100% specificity). For a stool-based biomarker test such a difference in screening uptake is unlikely since the method of sample collection is very similar to FIT. A blood-based biomarker provides a different test modality, which could potentially be more acceptable for individuals who currently choose not to participate in stool-based screening. However, current blood-based biomarker tests have fairly low sensitivity.[37]

At the individual level a very sensitive, but expensive, biomarker test could be an option, if the individual wants to bear the costs. It should be noted that, unless the individual is seeking for a less invasive test, using colonoscopy might be a more logical choice for such a person.

In theory the threshold costs of biomarker tests could improve beyond the test characteristics we modelled if a test would be able to discriminate between progressive and non-progressive adenomas, thereby reducing the number of colonoscopies required for removing lesions which would not develop into CRC, while still being able to detect adenomas that do have the potential to develop into CRC.[38] When modelling a test with 100% sensitivity for progressive adenomas of any size, 0% sensitivity for all non-progressive adenomas, and 100% specificity the threshold cost for biennial screening between age 55 and 75 was approaching €200.

Several studies have evaluated the cost-effectiveness of specific biomarker tests.[39-45] The majority of the studies considered various versions of the faecal DNA test developed at Exact Sciences and unit costs, including laboratory analysis, varied between $50.9 US (Taiwanese population) and $825 US (US population). One study evaluated a blood-based methylated Septin 9 DNA assay at a cost of $150 per test.[45] In general DNA testing was found to be cost-effective compared to no screening, but was not cost-effective compared to other screening options, including Hemoccult II, FIT and colonoscopy. Our study adds to previous publications by providing researchers and manufacturers with data to determine the requirements of their test to be cost-effective compared to current alternatives. This is important, because analysis methods in DNA testing are still developing, and test performance and costs are not yet settled. In our analysis the threshold cost of currently available DNA tests was less than $20 compared to FIT in the US setting (Appendix Table 1). Two publications investigating earlier versions of the Exact Sciences test reported threshold costs of $34-60, compared to gFOBT (Hemoccult Sensa), and FIT with similar sensitivity and specificity as Hemoccult Sensa.[42, 43] The specificity of the DNA test in both studies was comparable with FIT.

Screening scenarios for various common cancer sites like breast, cervix, lung, prostate and oesophagus have reported ICERs ranging between $3,000-90,000.[46-51] In most

cost-effectiveness analyses an ICER of $50,000 or $100,000 is considered the maximal willingness-to-pay for an additional LYG, although studies from the UK often use £20,000 or £30,000 per LYG as the upper limit based on guidelines from the National Institute for Health and Clinical Excellence (NICE).[52] In the current analysis the maximal willingness-to-pay did not greatly affect the threshold costs of the biomarker test variants; in a sensitivity analysis increasing the maximal willingness-to-pay from €50,000 to €100,000 per additional LYG did not increase the threshold unit costs for any of the biomarker variants by more than €17.

This study has two potential limitations. First, we did not explicitly model distinct pathways for traditional and sessile serrated adenomas. The average time it takes for an adenoma to develop into CRC was calibrated to the UK flexible sigmoidoscopy screening trial[22] and included both traditional adenomas, as well as sessile serrated adenomas. Therefore the different types of adenomas are included in the modelled mix of slow and rapid progressing lesions. We would underestimate the relative effectiveness of biomarkers compared to FIT only if the biomarker sensitivity for serrated adenomas would be greater than FIT and these lesions would have higher malignant potential than adenomas in general. Limited evidence suggests that FIT might be less sensitive for serrated adenomas, because they are often flat and therefore less likely to bleed.[53, 54]

Second, we based our stage specific CRC survival estimates on data from the south of the Netherlands (period 1985-2004), while recently data became available with national coverage and from a more recent time period (1989-2008). Compared to the current model, the five year relative survival has increased less than four percent. In a sensitivity analysis, we estimated that even a 25% increase in the relative survival for all stages would not change the calculated threshold unit costs by more than €1.60.

Our results suggest that when improving the performance of non-invasive biomarker tests, researchers should focus on increasing adenoma sensitivity next to the sensitivity for CRC. Although the latter is likely more difficult to achieve without losing too much specificity, improving adenoma sensitivity has equal if not greater potential to increase health benefits from screening, at more favourable costs. Meanwhile, in order to be considered in population-based screening programs, reducing the unit cost should also be a priority. It was recently announced that Cologuard® will be reimbursed by the Centres for Medicare and Medicaid Services (CMS) at $502 per test, while we estimated that even the best performing test need to cost less than $105 in the US setting (€50 in the Dutch setting, with its lower endoscopy costs) in order to be cost-effective.

In conclusion, given the considerable sensitivity of FIT for CRC, improving the sensitivity for adenomas is crucial for alternative tests to become competitive. In case of greatly improved all-over performance the unit cost of a biomarker test should, for cost-effectiveness, not exceed approximately seven times the unit cost of FIT.

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APPENDIX

Appendix Table 1.

Appendix Table 1.1. Overview of assumptions in the sensitivity analyses of threshold unit costs.

Variable	Base case analysis	Sensitivity analysis
Adjusting for quality of life loss (1-utility) [1, 2]	-	- Colonoscopy: 1 day lost per procedure - Initial, continuous and terminal care (for death from other causes): - Stage I: 0.12 in each year - Stage II:0.18 in each year - Stage III: 0.24 in each year - Stage IV: 0.70 in each year - Terminal care death from CRC: 0.70 in last year of life
Limited colonoscopy capacity	Not limited	Limited to either 40, 30, 20 or 10 colonoscopies per 1,000 individuals per year
Screening uptake FIT versus biomarker	No difference, 100% for all tests	- Low value: FIT 60%, biomarker 40% - High value: FIT 60%, biomarker 80%
Maximal ICER considered to be cost-effective	€50,000	€100,000
Colonoscopy costs, incl. complications	See Table 2 in main text	- Low value: 50% of base case value - High value: 200% of base case value
CRC treatment costs	See Table 2 in main text	- Low value: 50% of base case value - High value: 200% of base case value
US costs	-	See Table A2.2

* Only relevant for biomarker strategies which are more effective than the most effective FIT strategy.

Appendix Table 1.2. US cost estimates used in one of the sensitivity analyses (expressed in 2013 US dollars).

Variable	Modified societal cost (US $)*			
CRC screening, per procedure†	*FIT*	*Biomarker*		
Organisational costs	0	0		
Test kit + analysis of test	25.28	Determined in threshold analysis		
Patient time cost	22.01	22.01		
Total screen costs, per participant	47.29	Determined in threshold analysis		
Follow-up/surveillance, per procedure				
Colonoscopy, no polypectomy	1,105			
Colonoscopy, polypectomy	1,315			
Colonoscopy, complications†	8,243			
CRC treatment, per year‡	*Stage I*	*Stage II*	*Stage III*	*Stage IV*
Initial treatment	37,224	49,775	60,299	78,331
Continuous care	3,093	2,914	4,065	12,222
Terminal care death CRC	64,437	64,183	67,669	88,996
Terminal care death other causes	19,804	17,907	22,085	50,494

* For the calculation of patient time costs we assumed an average hourly wage of $22.01.[3] We assumed 1, 16, and 112 hours of patient time per procedure for FIT and biomarker testing, colonoscopy (including bowel preparation), and colonoscopy complications respectively . For CRC treatment we assumed 244, 19, and 283 hours of patient time per year of care in initial treatment, continuous care, and terminal care respectively.[4, 5]
† Because most screening in the US is performed opportunistically, we assumed no organizational costs. The cost of the FIT test kit and analysis is based on Medicare reimbursement rate.
‡ We assumed a complication rate of 2.4 per 1,000 colonoscopies
§ 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.

Appendix Table 1.3. Overview of maximal threshold unit costs of selected biomarker test variants from the sensitivity analyses.

Screening test		Base Case (€)	Adjusted for quality of life losses (€)	ICER 100,000 euro (€)	Colonoscopy capacity 40 per 1,000 individuals (€)	Colonoscopy capacity 30 per 1,000 individuals (€)	Colonoscopy capacity 20 per 1,000 individuals (€)	Colonoscopy capacity 10 per 1,000 individuals (€)
Specificity any lesion (%)	Sensitivity CRC (%)*							
88	60	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	80	14.75	14.52	17.88	14.55	12.15	5.99	neg.
	100	37.81	34.27	42.73	37.81	28.97	22.22	neg.
90	60	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	80	16.66	16.57	21.71	16.36	13.49	13.49	neg.
	100	40.13	36.33	51.92	40.13	31.18	28.78	neg.
92	60	1.02	1.27	1.02	1.02	1.02	1.02	neg.
	80	18.64	18.74	24.29	18.64	18.11	15.57	neg.
	100	41.72	40.75	57.07	41.72	39.83	31.04	neg.
94	60	3.11	3.18	3.11	3.11	3.11	3.11	2.05
	80	20.90	20.79	28.84	20.92	20.16	18.31	11.99
	100	43.63	46.29	60.42	49.60	89.20	67.52	32.73
96	60	5.89	5.97	5.89	5.89	5.89	5.89	5.16
	80	23.07	27.01	34.44	31.96	52.48	42.12	27.60
	100	45.50	50.71	62.54	57.31	111.21	152.53	54.46
98	60	8.27	8.38	8.27	13.82	33.04	52.73	26.03
	80	25.25	32.25	38.57	33.04	70.29	131.95	114.19
	100	47.96	55.11	64.65	58.84	106.92	219.26	290.97
100	60	10.98	10.92	10.98	13.56	36.83	80.47	213.97
	80	27.12	35.82	39.59	33.88	66.56	134.12	328.60
	100	50.23	59.08	66.15	60.13	104.98	207.06	436.77
Cologuard®		11.05	7.87	18.35	7.86	2.76	neg.	neg.
PHACTR3+FIT		11.39	3.51	19.88	7.62	16.09	neg.	neg.
88	60	neg.	173.97	14.39	neg.	neg.	11.48	neg.

Appendix Table 1.3 (continued)

Screening test		Base Case (€)	Adjusted for quality of life losses (€)	ICER 100,000 euro (€)	Colonoscopy capacity 40 per 1,000 individuals (€)	Colonoscopy capacity 30 per 1,000 individuals (€)	Colonoscopy capacity 20 per 1,000 individuals (€)	Colonoscopy capacity 10 per 1,000 individuals (€)
Specificity any lesion (%)	Sensitivity CRC (%)*							
	80	neg.	237.25	26.73	neg.	13.60	21.93	14.27
	100	0.41	310.62	43.68	26.06	38.10	37.88	47.01
90	60	neg.	162.28	12.15	neg.	neg.	10.00	neg.
	80	neg.	223.52	24.60	1.10	16.21	21.47	23.36
	100	3.01	300.51	43.68	36.87	41.64	38.15	56.39
92	60	neg.	146.12	9.86	neg.	neg.	9.57	6.37
	80	neg.	208.98	22.58	10.78	18.53	20.19	32.68
	100	5.75	288.21	43.70	46.48	44.42	41.50	64.69
94	60	neg.	132.55	8.11	neg.	2.20	7.21	14.69
	80	neg.	194.79	21.39	21.40	21.75	20.36	41.97
	100	8.93	277.24	42.75	56.76	47.69	43.80	74.98
96	60	neg.	118.84	6.35	5.91	5.63	8.50	23.87
	80	0.05	181.86	21.48	32.21	25.65	23.41	51.01
	100	11.94	265.97	41.12	66.90	50.85	45.27	83.43
98	60	neg.	104.24	4.48	18.39	10.96	6.43	33.64
	80	3.00	168.43	20.78	42.82	29.02	25.76	60.77
	100	14.90	251.91	39.40	75.88	53.14	46.47	93.74
100	60	neg.	90.48	2.80	30.78	16.37	6.74	42.89
	80	5.68	154.37	18.45	53.34	32.41	26.32	70.14
	100	18.01	238.08	37.40	85.26	55.62	47.44	104.98
Cologuard®		neg.	225.82	22.84	neg.	10.68	13.79	3.90
PHACTR3+FIT		neg.	162.95	14.68	9.18	13.44	9.91	18.07

CRC = colorectal cancer; Neg.: calculated threshold cost was a negative value.

* Although the average sensitivity for CRC is used to identify different biomarker test variants, the sensitivity for adenomas is varied accordingly (see Table 1 in main text). All costs and LYG are discounted by 3% per year

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Chapter 9

General discussion

9.1 ANSWERS TO SPECIFIC RESEARCH QUESTIONS

In this thesis we have investigated the potential effects and costs of population-based colorectal cancer (CRC) screening by estimating the impact of current screening policies on the CRC disease burden and costs, and by investigating different strategies by which health effects and costs of CRC screening can be optimised. In this chapter, we will answer the specific research questions formulated in chapter 1, based on the results described in this thesis. Next, we will discuss the interpretation of the findings and suggest directions for future research. This chapter will end with our conclusions and recommendations.

9.1.1 The impact of current screening policies on CRC disease burden and costs

What are the long-term implications of increased CRC screening participation in the US pre-Medicare population (50-64 years) on costs related to CRC in the pre-Medicare and Medicare (65+ years) populations?

An investment in screening pre-Medicare eligible individuals is not very attractive to private payers, because savings in treatment costs accrue mostly when individuals have reached Medicare eligibility. However, increased screening participation in the pre-Medicare population could reduce CRC incidence and mortality, while 60% to 89% of the additional screening costs could be offset by long term savings in CRC treatment costs in the Medicare population.

Current guidelines in the United States (US) recommend screening for CRC beginning at age 50,[1-4] but many individuals have not received recommended CRC screening when they become eligible for the publicly funded Medicare health insurance at age 65. We used two CISNET models (MISCAN-colon and SimCRC) to quantify the annual CRC screening and treatment costs in the pre-Medicare and Medicare populations. Compared to a situation in which trends in CRC screening participation continued as currently observed, increasing the screening participation from 60% to 70% resulted in a 12-14% increase in cumulative total costs in the pre-Medicare population over 50 years (range reflects the use of two models). Due to CRC treatment savings with enhanced participation, cumulative total costs in the Medicare population decreased by 4-9%. Overall, it was estimated that over the 50 year time horizon 60-89% of the additional CRC screening costs could be offset by Medicare treatment savings.

One of the main sources of uncertainty driving the difference in outcomes between te models is the average time it takes for an adenoma to develop into clinically detectable CRC. Based on the difference in this adenoma dwell time, one model estimates a smaller preventive effect from removing adenomas, and therefore less treatment savings than the other model.

To what extent are observed disparities in CRC incidence and mortality between the states of Louisiana and New Jersey explained by differences in risk factor prevalence, screening, and survival?

The prevalence of the risk factors smoking and obesity only had a minor impact on the disparity in CRC incidence and mortality rates between Louisiana and New Jersey, while the impact of screening and survival were more substantial. If Louisiana would be able to attain a combined level of risk factor prevalence, screening and survival comparable to that observed in New Jersey, the disparity in CRC incidence and mortality rates between the states would be eliminated.

While age-standardised CRC incidence and mortality rates have been decreasing in the North-eastern states of the US since the late 1970s/early 1980s, the decreases began later and were slower in the Southern states.[5] As a result, CRC incidence and mortality rates are currently higher in Southern states than in the North-eastern states, opposite to the patterns observed prior to 1980. Most policies that affect cancer control and access to screening in the US are designed and implemented at the state level.[6] The observed variation in CRC incidence and mortality trends between states provides important information for policy makers on the success of the implemented interventions and provides evidence that interventions in some states can be improved.

We estimated that if the Southern state of Louisiana would be able to attain trends in risk factor prevalence or screening similar to those observed in the North-eastern state of New Jersey, CRC incidence would decrease by 3.5% and 15.2% respectively. In addition, attaining New Jersey trends in risk factor prevalence, screening or CRC relative survival would decrease CRC mortality rates in Louisiana by 3.0%, 10.8%, and 17.4% respectively. When all trends were combined the modeled rates per 100,000 individuals in Louisiana became lower than the observed rates in New Jersey for both incidence (116.4 versus 130.0) and mortality (44.7 versus 55.8).

What are the additional effects of recommending colonoscopy screening for individuals with a family history of CRC within a gFOBT screening program?

A screening program in which average risk individuals are offered biennial guaiac faecal occult blood test (gFOBT) screening and individuals with a family history of CRC are recommended 10-yearly colonoscopy screening could in the long term cumulatively prevent 40% more CRC deaths, compared to a program in which only gFOBT screening is offered. In order to attain this effect, approximately 93% more colonoscopies need to be performed.

In Ontario, Canada, a province-wide CRC screening program was launched in 2008.[7] In this program, individuals eligible for screening are encouraged to visit their family physician, who risk stratifies persons based on their family history of CRC. Individuals with at least one first-degree relative with a diagnosis of CRC (approximately 11% of the screening eligible population) are recommended to undergo 10-yearly colonoscopy screening. Individuals without family history are offered biennial screening with gFOBT.

Compared to opportunistic screening only (observed 2008 participation level kept constant at 30%), we estimated that a gFOBT program that increased the screening participation to 60% cumulatively prevented 6,700 additional CRC deaths and required 570,000 additional colonoscopies by 2038. A family history-based program, also assuming 60% screening participation, would increase these numbers to 9,300 and 1,100,000, a 40% (range in sensitivity analyses: 20–51%) and 93% (range: 43–116%) increase respectively. If biennial gFOBT was replaced with biennial faecal immunochemical test (FIT), annual Hemoccult Sensa or five-yearly sigmoidoscopy screening, both the difference in CRC deaths prevented as well as the difference in colonoscopies required between programs with and without family history-based screening would decrease.

There are several regions in the world where gFOBT screening programs are currently implemented.[8, 9] Given that a family history assessment is fairly easily performed by the family physician, and that the proportion of individuals at increased risk because of a family history is relatively small, our results suggest that a family history-based screening approach is a good strategy to improve the health benefits in a gFOBT screening program. Although costs were not included in this analysis, screening with both gFOBT and colonoscopy have been demonstrated to be very cost-effective in the general population.[10] Therefore, unless the process of family history assessment is very costly, we anticipate that colonoscopy screening of individuals with a family history would be cost-effective.

9.1.2 Optimising health effects and costs of non-invasive CRC screening

What is the cost-effectiveness of gFOBT and FIT screening in average risk individuals?

Compared to a screening program of biennial gFOBT screening between age 50 and 74, replacing gFOBT by FIT with a high cut-off level could provide more quality adjusted life years gained (QALY) at lower costs and without increasing colonoscopy demand. When colonoscopy capacity is not limited FIT screening with lower cut-off levels is even more cost-effective.

Like a number of regions around the world,[8, 9] the CRC screening program in Ontario, Canada, uses the Hemoccult II gFOBT to screen individuals at average risk of CRC.[7] FIT offers several advantages over gFOBT, including greater sensitivity, no need for dietary

restrictions and automated processing of test kits.[11] However, depending on the cut-off level used FIT is also associated with a lower specificity, increasing the colonoscopy demand and number of false positive test results. Therefore, we estimated the harms, benefits and costs of gFOBT and FIT screening for different levels of colonoscopy demand.

Compared to no screening, biennial gFOBT screening between age 50-74 years (current strategy in Ontario) provided 20 QALY at a cost of $43,600 per 1,000 individuals, and required 17 colonoscopies per 1,000 individuals per year. Replacing gFOBT by FIT with a cut-off level of 200 ng Hb/ml provided 31 QALY and saved $289,700 per 1,000 individuals, compared to no screening, without increasing the number of colonoscopies required. When the colonoscopy capacity would be expanded greater health benefits and cost-reductions could be achieved by lowering the FIT cut-off level and expanding the number of screening rounds. Without restriction in colonoscopy capacity and assuming a willingness-to-pay threshold of CAN$50,000 per QALY, FIT50 between age 40-84 years with a 1.5 year interval would be the most effective strategy providing 47 QALY compared to no screening.

In regions where gFOBT screening has been introduced, switching to FIT with a high cut-off level could increase the health benefits of the program and reduce overall costs, without the need to increase colonoscopy capacity. However, building up colonoscopy capacity is recommended, because decreasing the cut-off level of FIT provides more QALYs at more favourable cost-effectiveness ratios than FIT screening with higher cut-off levels.

How do participation and diagnostic yield compare of FIT screening with various intervals?

In a Dutch population-based FIT screening trial, the positivity rate and detection rate of advanced neoplasia were significantly lower in the second screening round, compared to the first screening round. There was no association between detection rate of advanced neoplasia in the second screening round and the interval length (1, 2 or 3 years) between the first and second screening round. For all intervals the second round participation was stable and acceptably high.

One of the strategies to tailor the colonoscopy demand of a FIT screening program to local colonoscopy availability is to vary the interval between screening rounds. However, data on the impact of screening interval on detection rate of advanced neoplasia, positivity rate and screening participation are lacking.

We determined the diagnostic yield and participation rate of repeated FIT screening with intervals of 1, 2 and 3 years in a Dutch population-based CRC screening trial.

The number of individuals invited for the second screening round were 2,057, 2,096, 2,055 respectively. The overall positivity rate in the second screening round was significantly lower compared with the first round (6.0% vs 8.4%) and did not depend on interval length (p=0.23). Similarly, the overall detection rate of advanced neoplasia was significantly lower in the second round compared with the first screening round (1.9% vs 3.3%) and also did not significantly depend on interval length (p=0.62). The participation of the 1-year interval group was 64.7% in the first screening round and 63.2% in the second. The corresponding percentages for the 2-year and 3-year interval groups were 61.0% vs 62.5% and 62.0% vs 64.0%. In a multivariate analysis correcting for first round participation, biennial and triennial screening were associated with a higher participation rate in the second screening round relative to annual screening. The cumulative screening participation after two rounds was 69.7%, 67.5% and 68.7% in the 1-, 2-, and 3-year interval groups respectively and did not significantly differ between screening interval groups.

The results from this screening trial suggest that varying the screening interval does not greatly affect diagnostic yield nor participation rate of a screening program and could therefore be considered as a viable strategy to tailor the colonoscopy demand of the program to local capacity.

Is providing two FIT samples on two consecutive days cost-effective, compared to providing a single sample?

For a given screening age range and interval, 2-sample FIT screening could provide additional life years gained (LYG) compared to 1-sample FIT screening at acceptable costs. However, intensifying screening with 1-sample FIT provides equal or more LYG at lower costs, compared to screening by means of 2-sample FIT.

Although FIT has improved test characteristics over gFOBT, not all advanced neoplasia will be detected by means of 1-sample FIT screening.[12, 13] Providing two FIT samples collected on consecutive days could increase the effectiveness of a screening program. On the one hand, referring a screenee for a diagnostic colonoscopy when at least one sample is positive, increases sensitivity since some colorectal neoplasms bleed intermittently and can therefore be missed with 1-sample FIT screening.[14] On the other hand, referring a screenee when both samples are positive can increase specificity since only colonic lesions with a more consistent bleeding pattern will be detected which will lead to less false positive test results.

With the screening strategy currently employed in the Dutch population-based screening program (biennial FIT from age 55-75 years) 1-sample FIT provided 76.0-97.0 LYG per 1,000 individuals, at a cost of €259,000-264,000 (range reflects different FIT cut-

off levels). Two-sample FIT screening with at least one sample being positive provided 7.3-12.4 additional LYG compared to 1-sample FIT at an extra cost of €50,000-59,000. However, when alternative screening intervals and age ranges were considered, intensifying screening (i.e. decreasing the interval or extending the age range) with 1-sample FIT provided equal or more LYG at lower costs compared to 2-sample FIT screening.

Screening adherence does influence the balance of cost-effectiveness between different screening strategies. So far there is no evidence of a significant difference in screening adherence between 1- and 2-sample screening,[14] as well as between different screening intervals (Chapter 6).[15] In order to improve the effectiveness of their CRC screening program, decision makers are therefore recommended to increase the number of screening rounds with 1-sample FIT screening, before considering to increase the number of FIT samples provided per screening round.

What are the requirements in test sensitivity, specificity and unit cost in order for new molecular biomarker technologies to be cost-effective compared to the FIT?

Compared to FIT, maximising the test sensitivity for adenomas has a larger potential for improving the cost-effectiveness of a screening program than maximising the sensitivity for CRC. The threshold unit cost of a biomarker test with greatly improved performance was maximally seven times the unit cost of FIT, in order to be cost-effective.

Currently FOBT's in general and FIT in particular are widely used non-invasive CRC screening tests.[8] FOBT's detect small traces of blood in stool and because test sensitivity and specificity are suboptimal, there is a strong rationale to test for disease specific molecules like DNA in stool or blood, added to or replacing FIT in an effort to improve overall test performance. The introduction of "next generation" DNA sequencing technologies have markedly reduced DNA sequencing costs, which could make sensitive biomarker tests potentially cost-effective.

By modelling biennial FIT screening between age 55 and 75 (current screening strategy in the Dutch population-based screening program) and varying test characteristics one by one, we demonstrated that maximising the test sensitivity for large adenomas (≥10mm) resulted in more LYG and lower costs than maximising the sensitivity for CRC. Subsequently, we calculated the threshold unit cost for a range of hypothetical and two recently described biomarker tests that is required to be cost-effective. Compared to FIT screening (with a cut-off level of 50 ng Hb/ml and a unit cost of €7.29), the threshold unit cost ranged from €1.02 for a test with 32% and 60% sensitivity for large adenomas and CRC, and 92% specificity to €50.23 for a test with 53% and 100% sensitivity for large adenomas and CRC, and 100% specificity. The results were sensitive to restrictions in colonoscopy capacity and differences in screening uptake between FIT and the biomarker test.

9.2 INTERPRETATION OF THE FINDINGS

With this thesis we aimed to contribute to the body of knowledge about the potential effects and costs of population-based CRC screening by considering two overarching questions. The first question concerned the potential impact of current screening policies in the US and Canada on the CRC disease burden and costs. The second question concerned different strategies by which health effects and costs of non-invasive CRC screening can be optimised.

Part 1: The impact of current screening policies on CRC disease burden and costs

There are two main ways of providing CRC screening in a population: via opportunistic screening or via programmatic screening. In the US mainly the opportunistic approach is used. No single test is regarded as the best option, and no invitations are sent to individuals to undergo screening. It is left up to the general practitioners to discuss with their patients whether or not to participate in CRC screening and if so which test to use.

As was demonstrated in Chapter 3, there are large differences in CRC incidence and mortality between richer and poorer states in the US. The observed disparities between different states could be greatly reduced, if not eliminated, by ensuring better access to screening and treatment in areas where the disease burden is highest. Since screening participation is strongly associated with health insurance status[16], improving insurance coverage (especially in poorer populations) is of great importance. The implementation of the Patient Protection and Affordable Care Act (ACA, Pub. L. 111-148, 2010) aims to improve access to quality health care for all Americans and may be an important step towards improving access to care in underserved regions of the US. In addition, public programs like the Colorectal Cancer Control Program[17] that subsidise screening procedures in underserved populations could further decrease (monetary) barriers to undergo screening. The long term net costs of such programs are likely more favourable than projected in Chapter 2, because screening procedures in underserved populations can be reimbursed at Medicare rates instead of the generally higher reimbursement rates for privately insured individuals, while the savings in (Medicare) treatment costs later in life remain comparable.

Besides monetary barriers, there are several limiting factors that could inhibit underserved populations from increasing their screening rates and access to CRC care. For instance the less wealthy Southern States of the US have generally larger geographic areas and lower population densities, as well as a lower number of certified gastroenterologists compared to North-eastern states.[18]

In The Netherlands variations in CRC incidence among different regions of the country are much less pronounced.[19] Two likely explanations are the mandatory health insurance in the country and the fact that screening for CRC was rare until the introduction

of the nationwide FIT screening program in 2014. Because the type of health assurance is not dependent on age, like in the US, the distribution of costs and savings associated with the screening program are different; the government is funding the initial screening tests, while the health insurance companies (apart from a temporary increase in costs in the first years of the program) stand to accrue all treatment savings.

Like in The Netherlands, in Ontario, Canada a population-based screening program was introduced. As was demonstrated in Chapter 4, the dual strategy of providing gFOBT to average risk individuals and colonoscopy to those with a family history of CRC could provide substantial increases in CRC deaths prevented with a reasonable amount of additional colonoscopies required, compared to a situation in which only gFOBT screening is recommended. These results are in part generalizable to The Netherlands; with FIT screening the additional number of CRC deaths prevented is lower, both in relative and absolute terms, but the additional number of colonoscopies required is also lower.

Currently the screening program in The Netherlands is being rolled out to more age groups over a period of six years. In this period colonoscopy demand is increasing each year, and implementing additional interventions that further increase colonoscopy demand is not practical. Whether or not a family history-based approach would be advisable once the current program is fully implemented would require further studies in which, amongst others, the cost-effectiveness of family history-based screening is directly compared to varying the FIT screening age range and/or interval. In Ontario individuals need to visit their family doctor to collect their gFOBT kit. In this situation asking the individual about their family history does not really increase up-front costs nor influence screening participation relative to a situation in which only gFOBT is provided. However, in The Netherlands FIT kits are sent out to participants by mail. If in this setting individuals would need to visit their family doctor for a family history assessment, the upfront costs would increase and the added complexity might negatively affect overall screening participation.

Part 2: Optimising health effects and costs of non-invasive CRC screening

Although colonoscopy is the gold standard of CRC screening tests when it comes to sensitivity for adenomas and CRC, there are several disadvantages associated with it, such as high costs and resource requirements, potential for serious complications, and lower acceptance among screening participants. This prompted many organised screening programs to provide non-invasive tests as the primary means of screening.

Based on the findings from Chapter 5 it was suggested that from the two most widely available non-invasive screening tests, FIT is more cost-effective than gFOBT. For gFOBT screening there is solid evidence for the long term effects of multiple screening rounds on CRC incidence and mortality.[20-24] However, for FIT screening there is much less data about the CRC incidence and mortality reduction. Instead, the added effectiveness

in the model has been estimated based on the added detection rate of adenomas in first round screening trials.[14, 25, 26] While there is a good rationale to assume that increased adenoma detection will also lead to increased CRC mortality reduction, this needs to be validated. A good data source would be the observed numbers of interval CRC over multiple rounds of screening. With the introduction of the nationwide FIT screening program in The Netherlands, this data will become available over the coming years.

In regions where gFOBT is currently used in screening programs (e.g. The ColonCancerCheck program in Ontario) it is recommended to switch to FIT. In most regions the available colonoscopy capacity is limited, therefore transitioning to a situation that increases colonoscopy demand requires careful planning in order to prevent unacceptable long waiting lists. According to our results introducing FIT at a high cut-off level (200 ng Hb/ml) can increase the health benefits of a screening program, without increasing colonoscopy demand. This suggests that replacing gFOBT by FIT can be done alongside or even before increasing the current colonoscopy capacity. Subsequently, building up colonoscopy capacity to allow FIT screening with lower cut-off levels is expected to provide even more health benefits and is also more cost-effective.

Next to the observation that the interval between two FIT screening rounds does not affect overall screening participation (Chapter 6), for the effectiveness of a screening program it is also important that participation remains high over successive screening rounds. Recently, data from the third screening round in the CORERO trial found that screening participation even increased in the third screening round (from 62.6% and 63.2% in the first and second screening round, to 68.3% in the third round).[27] It is thought that increased awareness of CRC and FIT screening leading up to the introduction of the nationwide FIT screening program is contributing to this observation. In addition, data from repeated 2-sample FIT screening supported the findings from Chapter 7 by demonstrating that, although repeated 2-sample FIT screening was associated with a stable and high participation rate, the cumulative detection rate of advanced neoplasia did not significantly differ from that of repeated 1-sample FIT screening.[28]

Improving the sensitivity of a test beyond that of FIT is possible with novel biomarkers.[29] In Chapter 8 we have demonstrated that in order to be cost-effective compared to FIT, the unit cost of a (hypothetical) biomarker test with greatly improved overall performance should not exceed approximately seven times the unit cost of FIT (approximately €50 in the Dutch setting, and $105 in the US setting). This is much lower than the recently approved Medicare reimbursement rate of $493 for the Cologuard multitarget stool DNA test.[30] Although cost-effectiveness was not a requirement for reimbursement in the US, the high unit costs is likely a barrier for implementation in population-based screening programs in most other regions of the world. Although the

technology to detect molecular markers like DNA is quickly becoming less costly, it will take time before biomarker tests will obtain competitive cost levels.

The Cologuard test has sacrificed some specificity in order to improve its sensitivity relative to FIT. In the future, rather than improving sensitivity, the potential added value of biomarker tests might be more in preventing overtreatment by discriminating between adenomas that would eventually progress into CRC, and adenomas that will not. In such a case the number of colonoscopies performed will be reduced without sacrificing the life years gained (and associated savings in treatment costs), resulting in threshold costs much higher than the currently estimated €50. In addition, biomarker tests that detect markers in blood, instead of stool might also be of interest, since blood-based testing could potentially be more acceptable for individuals who currently choose not to participate in either endoscopic or stool-based screening. However, current blood-based DNA tests still have fairly low sensitivity.[31]

9.3 FUTURE DIRECTIONS

In the past two decades our understanding about the CRC disease process and the effects of screening on CRC development have greatly improved. With the increasing number of countries implementing CRC screening programs this trend is likely to continue in the future. We think that in the coming years the following areas will be of major importance in expanding our knowledge about the effectiveness of CRC screening in general and modelling of CRC screening in particular:

Continued model validation

Any simulation model is only as good as the data that goes into it. Therefore it is very important that we keep validating our models or update our data sources when results from new studies become available. In the past, several natural history assumptions in MISCAN-colon have been validated on the results of large screening and surveillance studies, such as the randomised trials of gFOBT in Minnesota, Funen, and Nottingham,[32] the CoCap sigmoidoscopy study,[33] and the National Polyp Study.[34] More recently we have used data from the UK flexible sigmoidoscopy study to estimate the average time for an adenoma to develop into pre-clinical CRC, and used data from the Dutch COCOS trial to update the size distribution of adenomas in the model.

In the near future the COCOS trial could also be used to create a separate pathway for sessile serrated lesions, besides the traditional adenoma-carcinoma pathway. This is of interest, because sessile serrated lesions are often flat or depressed making them more difficult to detect with endoscopy, while it is estimated that they might account for up to one-third of all CRC cases.[35, 36] Sessile serrated lesions could also affect the

relative effectiveness of FIT and biomarker tests because they have different molecular features than traditional adenomas[36], and might be less likely to bleed.[35] There is very limited data indicating potential differences in dwell time and/or progression rate between adenoma types. The similar ratio between the prevalence of traditional and serrated adenomas and their relative contribution to the development of CRC suggests no great difference.[37]

The potential for adenomas to regress is another topic that requires further study. Based on data from the National Polyp Study, it has been suggested that some adenomas could have the potential to regress over time.[34] Currently the MISCAN-colon model does not simulate adenoma regression, however it could affect the costs of screening. The potential for adenomas to regress would require the model to assume a higher incidence of newly developing adenomas in order to fit the observed adenoma prevalence data by age. Subsequently when screening is simulated, more individuals would be detected with adenomas (which would potentially have regressed without screening), resulting in more individuals in surveillance.

Increasing transparency of simulation models

With our simulation modelling studies we aim to inform public health policy and improve clinical practice. However, due to the complexity of most models readers often used to experience them as a "black box". Improving the transparency of model structures and data sources would enable readers to better understand the strengths and weaknesses of the models. More transparency could also shed light on potential explanations for observed differences in, for example, cost-effectiveness ratios for CRC screening strategies as reported in the literature.[10, 38] Within the CISNET consortium the development of the CISNET model registry (https://resources.cisnet.cancer.gov/registry) is a good example of an effort to improve transparency and comparability between models. On the website of the registry individuals can compare differences in model structure and output variables between CISNET models of the same cancer site, and even between models that simulate different cancers.

Effectiveness of FIT screening

FIT (as well as gFOBT) has imperfect sensitivity for adenomas, because adenomas often bleed inconsistently or do not bleed at all. An individual with a false negative FIT test result is likely to have a higher than average probability to have another false negative test result in sequential screening rounds, which would limit the effectiveness of a FIT screening program. Based on data from the second screening round from the CORERO trial (of which the clinical results have been presented in chapter 6 of this thesis) we will be able to estimate the proportion of lesions that are systematically missed by FIT screening. In addition, based on the number of interval cancers observed among

individuals who have participated in FIT screening, we could estimate the potential CRC incidence and mortality reduction from FIT screening.

Potential improvements to biomarker-based screening

So far most novel biomarker tests have focused on increasing the sensitivity for adenomas and CRC. In Chapter 8 we have demonstrated that increasing the sensitivity of biomarker tests compared to FIT, does not greatly increase the threshold unit cost allowed for such tests in order to be cost-effective. Based on the difference between adenoma prevalence from autopsy studies and observed CRC incidence in the general population it is thought that the majority of adenomas are non-progressive (i.e. will never develop into CRC). A very sensitive screen test will therefore result in the detection and subsequent removal of a large number of lesions which would have never resulted in CRC if left untreated. Reducing the amount of overtreatment could greatly reduce colonoscopy demand and costs, without reducing the health benefits of a screening program. By focusing on discriminating between progressive and non-progressive lesions, molecular biomarker tests could become an interesting screening option even if the unit cost of the test is still considerably higher than FIT. Biomarker tests might be very suited for this, because they can measure molecules that are more specific to the CRC disease process than haemoglobin which is measured by FIT and gFOBT.

Monitoring and evaluation of the Dutch nationwide screening program

In early 2014 the national CRC screening program was launched in The Netherlands. With over 2.2 million individuals in the target age range (55-75 years), the program is an enormous undertaking, requiring close coordination between the regional screening organizations, general practitioners, colonoscopy centres and pathology centres. Monitoring and evaluating the progress and results of the program is vital to obtain maximum effectiveness and assure high quality care. Modelling of different aspects of the program can provide critical insights about potential changes to the program. A very fitting example was the greater than expected number of positive samples in the first months of the program which was, at least in part, the result of a higher participation rate than observed in the pilot program combined with the higher than anticipated average age of the invited individuals. Based on calculations performed with the MISCAN model, the FIT cut-off level was (temporarily) increased to prevent waiting lists for follow-up colonoscopies.

Personalising screening

Currently the majority of CRC screening programs are based on a one-size-fits-all principle. The ColonCancerCheck progam in Ontario (Chapter 4 of this thesis) is an example of personalising CRC screening based on a person's risk for CRC. There are several other

easily identifiable risk factors for CRC like overweight, physical activity, smoking and red meat consumption. Combining risk factors into a personal risk profile to recommend a particular screening strategy on a personal level might improve the ratio of harms and benefits, as well as the cost-effectiveness of screening. One could even take into account multiple diseases for which screening programs are available, and optimise the different types of screening and screening strategies. Quantifying the added benefits and costs for such personalised interventions would be the first priority.

9.4 CONCLUSIONS AND RECOMMENDATIONS

Based on the results presented in this thesis we conclude that:

- In the United States, increased CRC screening in the pre-Medicare population could reduce CRC incidence and mortality, while a large part of the investments can be offset by long term savings in Medicare CRC treatment costs.
- Differences in CRC screening and treatment are contributing the most to the observed disparities in CRC incidence and mortality rates between the states of Louisiana and New Jersey. Disparities in risk factor prevalence play a relatively minor role.
- Colonoscopy screening for individuals at increased risk of CRC because of a family history of the disease is an effective strategy to increase the health benefits from a gFOBT screening program. In a FIT screening program, there are both fewer additional health benefits to be gained and fewer additional colonoscopies required.
- The detection rate of advanced neoplasia and positivity rate are not significantly influenced by the interval (1, 2, or 3 years) between successive FIT screening rounds. In addition, for all intervals the second round screening participation was stable and acceptably high. Varying the screening interval is therefore considered a viable strategy to tailor the colonoscopy demand of a FIT screening program to the available colonoscopy capacity.
- In order to be cost-effective compared to FIT, the unit cost of a new biomarker test with greatly improved overall performance should not exceed approximately seven times the unit cost of FIT.

In addition, our results support the following recommendations:

- In regions where gFOBT screening programs are implemented policymakers should consider switching to FIT with a high cut-off level to start with, because this provides more health benefits at lower costs, without increasing colonoscopy demand. Subsequently, building up colonoscopy capacity to allow FIT screening with lower cut-off levels provides even more health benefits and is also more cost-effective.

- Determining whether or not family history-based screening is cost-effective compared to increasing the number of FIT screening rounds for all requires further study.
- It is recommended to increase the number of screening rounds with 1-sample FIT, before considering to increase the number of FIT samples provided per screening round.
- In order to improve the performance of non-invasive screening tests, researchers should focus on increasing adenoma sensitivity, next to the sensitivity for CRC.

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Model appendix

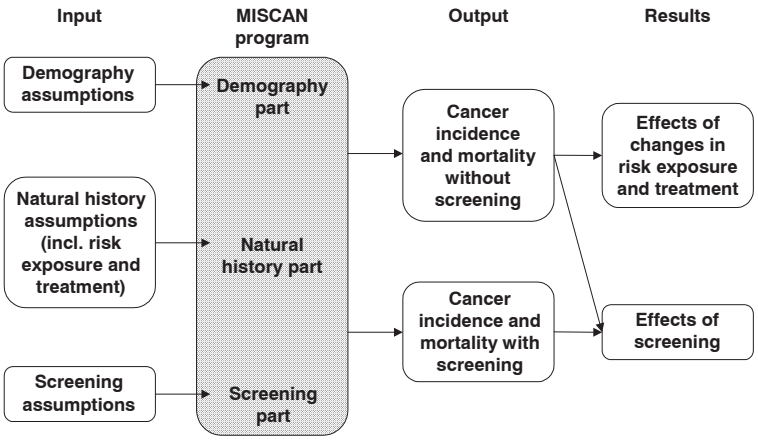
MODEL OVERVIEW

The MISCAN-Colon model is a semi-Markov micro-simulation model. The population is simulated individual by individual, and each person can evolve through discrete disease states. However, instead of modelling yearly transitions with associated transition probabilities, the MISCAN-Colon model generates durations in states. This improves model performance. With the assumption of exponential distribution of the duration in each state, this way of simulating leads to the same results as a Markov model with yearly transition probabilities. The advantage of the MISCAN approach is that durations in a certain state need not necessarily be a discrete value but can be continuous. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, adenoma incidence and transitions from one state of disease to another.

The basic structure of MISCAN-Colon is illustrated in Appendix Figure 1. Appendix Figure 1 clearly demonstrates that MISCAN-Colon consists of three parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is useful to consider them separately.



Appendix Figure 1. Structure of MISCAN-Colon

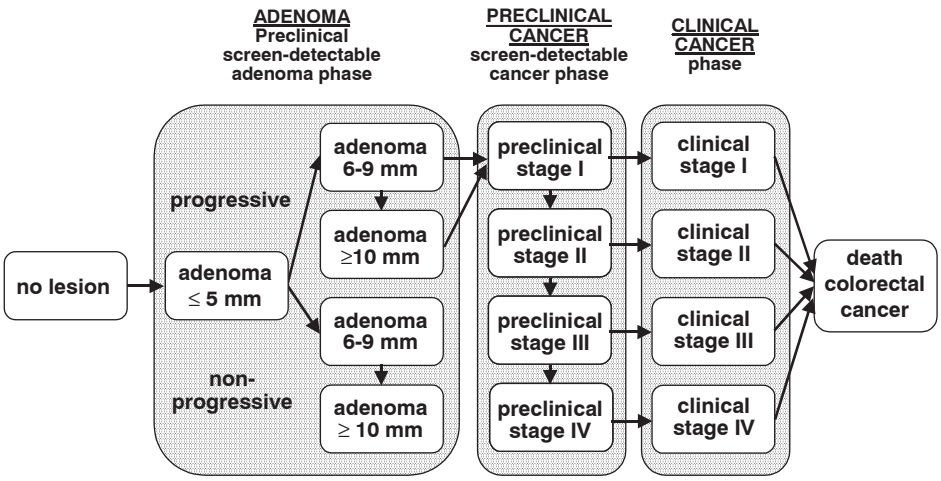
Demography part

The demography part of the model simulates individual life histories without colorectal cancer to form a population. For each person, a date of birth and a date of death of other

causes than colorectal cancer are simulated. The distribution of births and deaths can be adjusted to represent the population simulated. For example, a population of Caucasian females will have higher death ages than a population of African American males.

Natural history part

The Natural History part of MISCAN-Colon simulates the development of colorectal cancer in the population. We assume all colorectal cancers develop according to the adenoma-carcinoma sequence of Morson[1] and Vogelstein[2] (Appendix Figure 2). For each individual in the simulated population a personal risk index is generated. Subsequently, adenomas are generated in the population according to this personal risk index and an age specific incidence rate of adenomas. This results in no adenomas for most persons and one or more adenomas for others. The distribution of adenomas over the colorectum is simulated according to the observed distribution of colorectal cancer incidence. Each of the adenomas can independently develop into colorectal cancer. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (10+ mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. The survival after clinical diagnosis depends on the stage of the cancer.



Appendix Figure 2. Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for colorectal cancer. Adenomas are categorised by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age.

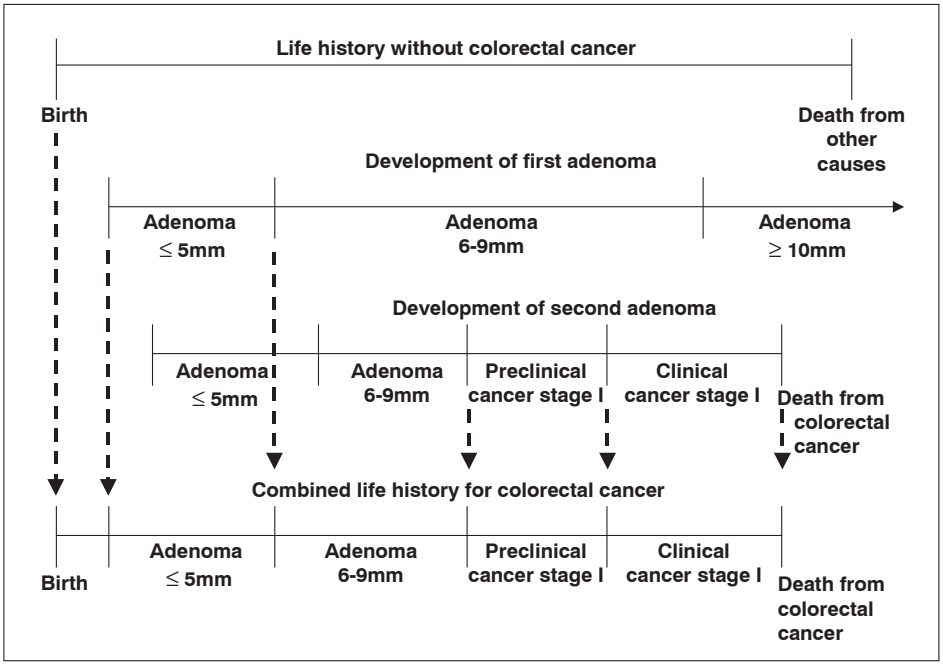
Screening part

Screening interrupts the development of CRC. With screening, adenomas may be detected and removed and cancers may be found, usually in an earlier stage than with clinical diagnosis. In this way screening prevents CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening. The effects of different screening policies can be compared by applying them to identical natural histories.

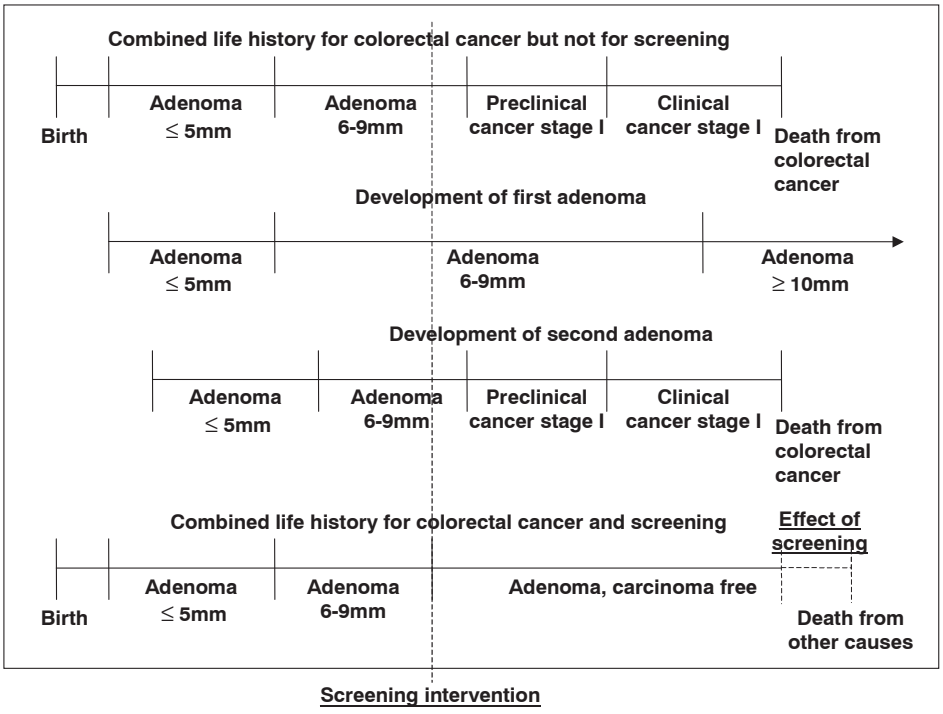
Integration of the three model components

For each individual, the demography part of the model simulates a time of birth and a time of death of other causes than colorectal cancer, creating a life history without colorectal cancer (top line in Appendix Figure 3a). Subsequently adenomas are simulated for that individual. For most individuals no adenomas are generated, for other multiple. In the example in Appendix Figure 3, the person gets two adenomas (2nd and 3rd line in Appendix Figure 3a). The first adenoma arises at a certain age, grows into 6-9 mm and eventually becomes larger than 10 mm. However, this adenoma does not become cancer before the death of the person. The second adenoma is a progressive adenoma. After having grown to 6-9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and diagnosis and eventually resulting in an earlier death from CRC. The life history without CRC and the development of the two adenomas in Appendix Figure 3 together lead to the combined life history with CRC depicted in the bottom line. Because this person dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly.

After the life history of a person is adjusted for colorectal cancer, the history will now be adjusted for the effects of screening. The effect of screening on life history is explained in Appendix Figure 3b.The top line in this figure is the combined life history for colorectal cancer from Appendix Figure 3a. The development of the separate adenomas is repeated in the second and third line. In this picture there is one screening intervention. During the screening both prevalent adenomas are detected and removed. This results in a combined life history for colorectal cancer and screening (bottom line). From the moment of screening the adenomas are removed and this individual becomes adenoma and carcinoma free. He does not develop cancer because the precursor lesion has been removed. Therefore the person dies at the moment of death from other causes and the effect of screening is the difference in life-years in the situation without screening and the situation with screening. Of course many other possibilities could have occurred: a person could have developed new adenomas after the screening moment, or an adenoma could have been missed by the screening test, but in this case this individual really benefited from the screening intervention.



Appendix Figure 3a. Modelling natural history into life history



Appendix Figure 3b. Modelling screening into life history

MODEL QUANTIFICATION

The quantification of the demography and natural history parameters in the model may vary depending on the population simulated. Below an example of the model quantification is provided for the Dutch population as was used in Chapter 8. At the end of this Model Appendix an overview is provided of the differences in model quantification between all chapters in this thesis.

Demography parameters

In all runs a cohort of individuals was modelled with age specific all cause morality based on the 2010 Dutch life tables.

Natural history parameters

The parameters for natural history model that could not be directly estimated from data or fit to reference data, were established based on expert opinion. At two expert meetings at the NCI on June 5–7, 1996, and May 12–13, 1997, a model structure was devised in agreement with the currently accepted model of the adenoma–carcinoma sequence. It was assumed that all cancers are preceded by adenomas.

The average duration between onset of a progressive adenoma and the transition to preclinical cancer was calibrated to data from the UK flexible sigmoidoscopy screening trial.[3] The duration of cancer in preclinical stages was estimated based on the results of three large randomised controlled screening trials.[3] This resulted in an average duration of 2.5 years, 2.5 year, 3.7 years, and 1.5 year, for stages I-IV respectively, with a total average duration of 6.7 years because not every cancer reaches stage IV before clinical diagnosis. All durations were governed by an exponential probability distribution. Durations in each of the invasive cancer stages as well as durations in the stages of the non-invasive adenomas were assumed to be 100% associated with each other, but the durations in invasive stages as a whole were independent of durations in non-invasive adenoma stages that precede cancer. These assumptions resulted in an exponential distribution of the total duration of progressive non-invasive adenomas and of the total duration of preclinical cancer, which has also been used in other cancer screening models.[4-5]

It was assumed that 30% of the cancers arise from adenomas of 6–9 mm and that 70% arise from larger adenomas. Initially, the preclinical incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localization in the Netherlands in 1999-2003, which was before the onset of opportunistic screening. [6] The size distribution of adenomas over all ages was assumed to be 73% for stages less than or equal to 5 mm, 15% for stages 6–9 mm, and 12% for stages greater than or equal to 10 mm.[7] The preclinical incidence of non-progressive adenomas that will

never grow into cancer was varied until the simulated prevalence of all adenomas was in agreement with data from autopsy studies.[8-17]

The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of colorectal cancers in the Netherlands in 1999-2003.[6] The stage-specific survival after the clinical diagnosis of colorectal cancer before age 75 is taken from the Comprehensive Cancer Centre South (CCC) from 1989-2003.[6] The survival for individuals aged 75 years and older was adjusted to fit the observed age-increasing mortality/incidence ratio. Appendix Table 1 contains a summary of the model input values and its data-sources.

Appendix Table 1. Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2.67	Fit to multiplicity distribution of adenomas in autopsy studies [8-17]
Adenoma incidence in general population	Age dependent:	Fit to adenoma prevalence in autopsy studies [8-17] and to CRC incidence in 1999-2003 per 100,000:[6]
	0-19 years: 0.2% per year	<20 years: 0.2
	20-24 years: 0.3% per year	20-24 years: 0.5
	25-29 years: 0.3% per year	25-29 years: 1.3
	30-34 years: 0.5% per year	30-34 years: 2.6
	35-39 years: 1.2% per year	35-39 years: 5.6
	40-44 years: 2.8% per year	40-44 years: 11.0
	45-49 years: 3.1% per year	45-49 years: 23.9
	50-54 years: 3.3% per year	50-54 years: 50.7
	55-59 years: 3.3% per year	55-59 years: 85.4
	60-64 years: 3.3% per year	60-64 years: 142.3
	65-69 years: 3.3% per year	65-69 years: 201.4
	70-74 years: 3.3% per year	70-74 years: 275.5
	75-79 years: 3.7% per year	75-79 years: 347.7
	80-84 years: 0.3% per year	80-84 years: 389.3
	85-100 years: 0.2% per year	85+ years: 332.4
Probability that a new adenoma is progressive	Dependent on age at onset: 0–45 years: linearly increasing from 0 to 22% 45–65 years: linearly increasing from 22% to 93% 65–100 years: linearly increasing from 93% to 99%	Fit to adenoma prevalence in autopsy studies, [8-17] CRC incidence in 1999-2003.[6]
Regression of adenomas	No significant regression of adenomas	Expert opinion

Appendix Table 1 (continued)

Model parameter	Value	Source
Mean duration of preclinical cancer	6.7 years	Estimated from FOBT trials.[3]
Percent of non-progressive adenomas that stay 6-9mm	25%	Fit to size distribution of adenomas in colonoscopy trial (percentages corrected for colonoscopy sensitivity):[7] 1-5mm: 73% 6-9 mm: 15% 10+ mm: 12%
Percent of non-progressive adenoma that become 10mm or larger	75%	Fit to size distribution of adenomas in colonoscopy trial (percentages corrected for colonoscopy sensitivity):[7] 1-5mm: 73% 6-9 mm: 15% 10+ mm: 12%
Percent of cancers that develops from 6-9mm adenoma and from 10+mm adenoma	30% of cancer develops from 6-9 mm, 70% from 10+mm	Expert opinion
Localization distribution of adenomas and cancer	Rectum: 26% Distal colon: 42% Proximal colon: 32%	Directly estimated from CRC incidence data.[6]
10-year survival after clinical diagnosis of CRC	Dependent on age, stage and localization	Directly estimated from CCC South 1989-2003 for diagnosis before age 75 and fitted on mortality from CCC 1999-2003.[6]

CRC = colorectal cancer; FOBT = faecal occult blood test; CCC = Comprehensive Cancer Centre

Screening test characteristics

Among the chapters in this thesis several different screening tests were simulated. Unless explicitly stated otherwise, the sensitivity and specificity that were assumed for each test are presented in Appendix Table 2.

The test characteristics of the Hemoccult II guaiac faecal occult blood test (gFOBT) were based on a prior calibration of the MISCAN model to three large gFOBT screening trials[3] It was assumed that the probability a CRC bleeds, and thus the sensitivity of the test for CRC, depends on the time until clinical diagnosis, hence the distinction between 'early' and 'late' preclinical CRC. This is to be expected when cancers that bleed do so increasingly over time, starting with occult blood loss and progressing to clinically visible bleeding. In addition, it is assumed that small adenomas do not bleed and therefore cannot be detected by the test. The sensitivity for adenomas ≤5 mm is based on the false-positive rate (i.e., 1 - specificity).

The test characteristics of the faecal immunochemical test (FIT) and the stool DNA test were fitted to the observed positivity and detection rates of adenomas and CRC in the first round of two randomised screening trials from the Netherlands[18-20], and a

Appendix Table 2. Sensitivity and specificity of screening tests used in the model.

Screen test	Sensitivity (%)					Specificity (%)
	Adenoma ≤5 mm	Adenoma 6-9 mm	Adenoma ≥10 mm	Early preclinical CRC	Late preclinical CRC	
gFOBT HCII	1	2	8	19	51	99
gFOBT Sensa	8	12	20	56	85	92
FIT50	4	15	37	52	83	96
FIT100	2	7	28	43	77	98
Stool DNA	12	26	36	88	97	88
Sigmoidoscopy	75	85	95	95	95	92
Colonoscopy	75	85	95	95	95	90

CRC = colorectal cancer; FOBT = faecal occult blood test; HCII = Hemoccult II; FIT50/100 = faecal immunochemical test with a cut-off level of either 50 or 100 ng Hb/ml.

screening trial from the US[21] respectively. Like with the Hemoccult II test, for all stool-based tests it was assumed that the sensitivity for CRC depends on the time until clinical diagnosis, and the sensitivity of adenomas ≤5 mm is only based on the false-positive rate of the test.

For colonoscopy procedures we assumed a cecal intubation rate of 95%.[22-24] The sensitivity of colonoscopy for each lesion within the reach of the endoscope was based on back-to-back colonoscopy studies.[25] After a positive test, all lesions are removed within a short time. The percentage of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after colonoscopy has been estimated from Kaiser data: 10%.[26] This percentage was assumed to be independent of the screening round. Removal of an adenoma always prevents the development of any subsequent cancer that may have arisen from this adenoma. Risks of complications reported in organised screening programs [27-29] are lower than those reported for general practice colonoscopies.[30-31] The major complications of colonoscopy are perforations (which can occur with or without polypectomy), serosal burns, bleeds requiring transfusion and bleeds not requiring transfusion.[27-31] We estimated a rate of death of 1 per 30,000 for colonoscopies with a polypectomy.[32-33]

For sigmoidoscopy, we assumed that 80% of examinations reached the junction of the sigmoid and descending colon and 40% reached the beginning of the splenic flexure.[34-35] The sensitivity of the test for adenomas and CRC was assumed similar to that of colonoscopy.

MODEL OUTPUTS

The model generates the following output, both undiscounted and discounted:

Demography

1. Life-years lived in the population by calendar year and age
2. Deaths from other causes than colorectal cancer by calendar year and age

Natural history

1. Colorectal cancer cases by calendar year, stage and age
2. Colorectal cancer deaths by calendar year and age
3. Life-years lived with colorectal cancer by calendar year, stage and age
4. Total number of life years with surveillance for adenoma patients
5. Total number of life years with initial therapy after screen-detected or clinical invasive cancer by stage
6. Total number of life years with continuing therapy after screen-detected or clinical invasive cancer by stage
7. Total number of life years with terminal care before death from other causes by stage
8. Total number of life years with terminal care before death from colorectal cancer by stage

Screening

1. Number of invitations for screen-tests, screen-tests, diagnostic tests, surveillance and opportunistic screen tests by calendar year
2. Number of positive and negative test results per preclinical state and per year
3. Total number of life years lived, life years lost due to cancer, number of specific deaths and non-specific deaths
4. Number of screenings that prevented cancer by year of screening
5. Number of screenings that detected cancer early by year of screening
6. Number of surveillance tests that prevented cancer by year of surveillance
7. Number of surveillance tests that detected cancer early by year of surveillance
8. Number of life years gained due to screening by year of screening

Appendix Table 3. Differences in model assumptions for demography and natural history as made in the different chapters of this thesis.

Variable	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 7	Chapter 8
Demography						
Population modelled	US average risk population in 2010[36]	Louisiana total, black and white average risk populations in 2010[37]	Ontario population with and without family history[38]*	Ontario average risk cohort 40 year olds	Dutch average risk population in 2010[39]	Dutch average risk cohort 40 year olds
Natural history						
Distribution of risk for adenomas over the general population, age specific adenoma incidence and probability that a new adenoma is progressive	Fitted to adenoma multiplicity from autopsy studies[8-17] and CRC incidence from SEER 1975-1979[40]	Fitted to adenoma multiplicity from autopsy studies[8-17] and CRC incidence from state cancer registry 1995[41]	Fitted to adenoma multiplicity from autopsy studies[8-17] and CRC incidence from Canadian cancer registry 2001[42]	Fitted to adenoma multiplicity from autopsy studies[8-17] and CRC incidence from Canadian cancer registry 2001[42]	Fitted to adenoma multiplicity from autopsy studies[8-17] and CRC incidence from IKC 1999-2003[6]	Fitted to adenoma multiplicity from autopsy studies [8-17] and CRC incidence from IKC 1999-2003[6]
Localization distribution of adenomas and CRC, and stage distribution of CRC at diagnosis	CRC incidence from SEER 1975-1979[40]	CRC incidence from state cancer registry 1995[41]	CRC incidence from Canadian cancer registry 2001[42]	CRC incidence from Canadian cancer registry 2001[42]	CRC incidence from IKC 1999-2003[6]	CRC incidence from IKC 1999-2003[6]
CRC relative survival	US survival from SEER 2000-2003[40]	State specific, from SEER 1995-2009[40]	US survival from SEER 2000-2003[40]	US survival from SEER 2000-2003[40]	Dutch survival from IKZ 1985-2004[43]	Dutch survival from IKZ 1985-2004[43]
Mean duration of preclinical CRC phase†	6.7 years[3]	6.7 years[3]	6.7 years[3]	6.7 years[3]	6.7 years[3]	6.7 years[3]
Mean duration of adenoma phase	Calibrated to UKFSS trial[44]	Calibrated to UKFSS trial[44]	Calibrated to UKFSS trial[44]	Calibrated to UKFSS trial[44]	20 years, expert opinion	Calibrated to UKFSS trial[44]
Regression of adenomas	No significant regression, expert opinion	No significant regression, expert opinion	No significant regression, expert opinion	No significant regression, expert opinion	No significant regression, expert opinion	No significant regression, expert opinion

Appendix Table 3 (continued)

Variable	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 7	Chapter 8
Percent of non-progressive adenomas that stay 6-9mm	25%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]	25%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]	25%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]	25%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]	50%[45]	25%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]
Percent of non-progressive adenomas that become 10mm or larger	75%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]	75%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]	75%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]	75%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]	50%[45]	75%, calibrated to adenoma prevalence in colonoscopy arm of COCOS trial[7]
Percent of cancers that develop from 6-9mm adenoma	30%, expert opinion	30%, expert opinion	30%, expert opinion	30%, expert opinion	30%, expert opinion	30%, expert opinion
Percent of cancers that develop from 10+mm adenoma	70%, expert opinion	70%, expert opinion	70%, expert opinion	70%, expert opinion	70%, expert opinion	70%, expert opinion

* The natural history component of the model was calibrated to the CRC incidence in the total population. We assumed the difference in CRC incidence between the population with and without a family history of CRC was caused by a difference in adenoma incidence. The relative risk in the family history population was 2.24 compared to the general population.[46] The relative risk in the population without family history was adjusted downwards accordingly.

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Summary

Colorectal cancer (CRC) is an important public health problem with over a million new cases diagnosed every year worldwide. CRC is most common in developed countries where it is the third most frequently diagnosed malignancy in men and ranks second in women. CRC incidence and mortality rates increase with age, especially above age 50. In The Netherlands the lifetime incidence of CRC is approximately seven percent.

CRC is a disease that is preventable; it is estimated that more than 50 percent of all CRC cases in developed countries are caused by lifestyle and environmental factors. Established life style related risk factors include smoking, alcohol consumption, red meat consumption and obesity, whereas physical activity, and aspirin use have a protective effect.

When a CRC is diagnosed, a patient will be treated by surgical removal of the tumour and/or by administering chemotherapy. Although significant advances in CRC treatment have been made over the past two decades, survival is still largely dependent on the stage of the disease at diagnosis. In The Netherlands, in the period of 2000-2004, the five year relative survival for stage I colon cancer was approximately 89 percent, while the five year relative survival for stage IV colon cancer was only seven percent. A similar trend was observed for rectal cancer.

Screening tests can be used to remove CRC pre-cursor lesions (i.e. adenomas), potentially preventing CRC, or to detect CRC at an earlier stage in order to improve prognosis. There are several screening tests available, each with its own advantages and disadvantages, and they can broadly be divided into three categories: stool-based, endoscopic and imaging tests. For guaiac faecal occult blood tests (gFOBT) and sigmoidoscopy the potential for incidence and mortality reduction has been demonstrated is large randomised screening trials.

Several regions around the world have implemented policies and programs in order to stimulate CRC screening on a population level. In 2014 the first nationwide screening program was introduced in The Netherlands.

There are a large number of parameters that can influence the effectiveness of a screening program. Computer simulation models can be used to combine and extrapolate existing clinical data, and help evaluate and optimise the harms, benefits and costs of CRC screening. In this thesis we have used the MISCAN-colon microsimulation model from the Cancer Intervention and Surveillance Modelling Network (CISNET) to evaluate various CRC screening policies in order to inform health policy.

Current guidelines in the United States recommend screening for CRC beginning at age 50, but many individuals have not received recommended CRC screening when they become eligible for the publicly funded Medicare health insurance at age 65. In **Chapter 2**, we estimated the long-term implications of increased CRC screening participation in the pre-Medicare population (50-64 years) on costs in the pre-Medicare and Medicare populations (65+ years). We used two CISNET models (MISCAN-colon and SimCRC) and

compared a situation in which trends in CRC screening participation continued as currently observed (60% of individuals up-to-date with screening) to a situation in which screening participation was enhanced (70% up-to-date). The enhanced participation scenario resulted in a 12-14% increase in cumulative total costs in the pre-Medicare population over 50 years (range reflects the use of two models). Due to CRC treatment savings with enhanced participation, cumulative total costs in the Medicare population decreased by 4-9%. Overall, it was estimated that over the 50 year time horizon 60-89% of the additional CRC screening costs could be offset by Medicare treatment savings.

In **Chapter 3** we compared the observed CRC incidence and mortality between different states in the US. While CRC incidence and mortality rates have been decreasing in the North-eastern states of the US since the late 1970s/early 1980s, the decreases began later and were slower in the Southern states. As a result, CRC incidence and mortality rates are currently higher in Southern states than in the North-eastern states, opposite to the patterns observed prior to 1980. We estimated that if the Southern state of Louisiana would be able to attain trends in risk factor prevalence or screening similar to those observed in the North-eastern state of New Jersey, CRC incidence would decrease by 3.5% and 15.2% respectively. In addition, attaining New Jersey trends in risk factor prevalence, screening or CRC relative survival would decrease CRC mortality rates in Louisiana by 3.0%, 10.8%, and 17.4% respectively. When all trends were combined the modeled rates per 100,000 individuals in Louisiana became lower than the observed rates in New Jersey for both incidence (116.4 versus 130.0) and mortality (44.7 versus 55.8).

In Ontario, Canada, a province-wide CRC screening program was launched in 2008. In this program, individuals eligible for screening are encouraged to visit their family physician, who risk stratifies persons based on their family history of CRC. Individuals with at least one first-degree relative with a diagnosis of CRC (approximately 11% of the screening eligible population) are recommended to undergo 10-yearly colonoscopy screening. Individuals without family history are offered biennial screening with gFOBT. In **Chapter 4** it was estimated that compared to opportunistic screening only (approximately 30% of individuals participating in screening), a gFOBT program that increased the screening participation to 60%, cumulatively prevented 6,700 additional CRC deaths and required 570,000 additional colonoscopies after 30 years. The family history-based program, also assuming 60% screening participation, would increase these numbers to 9,300 and 1,100,000, a 40% (range in sensitivity analyses: 20–51%) and 93% (range: 43–116%) increase respectively. In a faecal immunochemical test (FIT) screening program both the additional number of CRC deaths prevented and the additional number of colonoscopies are lower. Given that a family history assessment is fairly easily performed by the family physician, and that the proportion of individuals at increased risk because of a family

history is relatively small, our results suggest that a family history-based screening approach is a good strategy to improve the health benefits in a gFOBT screening program.

FIT screening offers several advantages over gFOBT, including greater sensitivity, no need for dietary restrictions and automated processing of test kits. However, depending on the cut-off level used FIT is also associated with a lower specificity, potentially increasing the colonoscopy demand and number of false positive test results. In **Chapter 5** we compared the cost-effectiveness of gFOBT and FIT screening in the average risk population of Ontario, while varying the screening age range, interval and FIT cut-off level. Compared to no screening, biennial gFOBT screening between age 50-74 years provided 20 quality adjusted life years (QALY) at a cost of $43,600 per 1,000 individuals, and required 17 colonoscopies per 1,000 individuals per year. Replacing gFOBT by FIT with a cut-off level of 200 ng Hb/ml provided 31 QALY and saved $289,700 per 1,000 individuals, compared to no screening, without increasing the number of colonoscopies required. When the colonoscopy capacity would be expanded greater health benefits and cost-reductions could be achieved by lowering the FIT cut-off level and expanding the number of screening rounds. Without restriction in colonoscopy capacity and assuming a willingness-to-pay threshold of CAN$50,000 per QALY, FIT50 between age 40-84 years with a 1.5 year interval would be the most effective strategy providing 47 QALY compared to no screening. For regions where gFOBT screening is performed it is recommended to switch to FIT with a high cut-off level initially. Subsequently, building up colonoscopy capacity to allow for a decreased cut-off level of FIT would provide additional QALYs at more favourable cost-effectiveness ratios. Determining whether or not implementing family history-based screening in a gFOBT program as described in Chapter 4 would be cost-effective compared to switching to FIT for all would require further studies.

In **Chapter 6** we determined the positivity rate, diagnostic yield and participation rate of repeated FIT screening with intervals of 1, 2 and 3 years in a Dutch population-based CRC screening trial. The overall positivity rate in the second screening round was significantly lower compared with the first round (6.0% vs 8.4%) and did not depend on interval length. Similarly, the overall detection rate of advanced neoplasia was significantly lower in the second round compared with the first screening round (1.9% vs 3.3%) and also did not depend on interval length. The participation of the 1-year interval group was 64.7% in the first screening round and 63.2% in the second. The corresponding percentages for the 2-year and 3-year interval groups were 61.0% vs 62.5% and 62.0% vs 64.0%. In a multivariate analysis correcting for first round participation, biennial and triennial screening were associated with a higher participation rate in the second screening round relative to annual screening. The cumulative screening participation after two rounds was 69.7%, 67.5% and 68.7% in the 1-, 2-, and 3-year interval groups respectively and did not significantly differ between screening interval groups.

These results suggest that varying the screening interval can be considered as a viable strategy to tailor the colonoscopy demand of the program to local capacity.

A single FIT has imperfect sensitivity for adenomas. Part of this lack in sensitivity is thought to arise because some adenomas bleed intermittently and therefore providing two FIT samples, collected on consecutive days, is expected to increase the effectiveness of a screening program. In **Chapter 7** we performed a cost-effectiveness analysis to determine whether the additional benefits of 2-sample FIT screening outweigh its additional costs. With the screening strategy currently employed in the Dutch population-based screening program (biennial FIT from age 55-75 years) 1-sample FIT provided 76.0-97.0 life years gained (LYG) per 1,000 individuals, at a cost of €259,000-264,000 (range reflects different FIT cut-off levels). Two-sample FIT screening with at least one sample being positive provided 7.3-12.4 additional LYG compared to 1-sample FIT at an extra cost of €50,000-59,000. However, when alternative screening intervals and age ranges were considered, intensifying screening (i.e. decreasing the interval or extending the age range) with 1-sample FIT provided equal or more LYG at lower costs compared to 2-sample FIT screening. In order to improve the effectiveness of a CRC screening program, it is therefore recommended to increase the number of screening rounds with 1-sample FIT screening, before considering to increase the number of FIT samples provided per screening round.

An alternative way to increase test sensitivity, instead of providing two FIT samples per screening round, is to test for disease specific molecules like DNA, added to or replacing FIT. The introduction of "next generation" DNA sequencing technologies has markedly reduced DNA sequencing costs, which could make sensitive biomarker tests potentially cost-effective. In **Chapter 8** we evaluated a range of hypothetical, as well as two recently described, biomarker tests with varying sensitivity and specificity. For each test we calculated the threshold unit cost that is allowed for that particular test to be as cost-effective as FIT. By modelling biennial FIT screening between age 55 and 75 (current screening strategy in the Dutch population-based screening program) and varying test characteristics one by one, we demonstrated that maximising the test sensitivity for large adenomas (≥10mm) resulted in more LYG and allowed for higher unit costs than maximising the sensitivity for CRC. When optimising the screening age range and interval, a biomarker test with greatly improved overall performance should, for cost-effectiveness, not exceed approximately seven times the unit cost of FIT (i.e. the maximal threshold cost was approximately €50 per test).

In the General Discussion of this thesis (**Chapter 9**) we answered the specific research questions and their implications. In addition, directions for further research were suggested and an overview of the main conclusions and recommendations were presented.

Samenvatting

Darmkanker (DK) is een belangrijk gezondheidsprobleem; jaarlijks worden wereldwijd meer dan een miljoen mensen gediagnosticeerd met de ziekte. DK komt vooral voor in Westerse landen en is daar de op twee na meest voorkomende kanker bij mannen en op een na meest voorkomende kanker bij vrouwen. De incidentie en mortaliteit aan DK neemt toe met de leeftijd, vooral bij mensen boven de 50 jaar. In Nederland krijgt ongeveer zeven procent van alle mensen de ziekte in zijn of haar leven.

DK is een ziekte die voor een groot deel is te voorkomen; er is geschat dat meer dan 50 procent van alle gevallen veroorzaakt wordt door factoren die te maken hebben met de levensstijl en/of de leefomgeving. Bekende levensstijl gerelateerde risicofactoren zijn onder andere roken, alcohol consumptie, rood vlees consumptie en overgewicht, terwijl fysieke activiteit en aspirine gebruik een beschermend effect hebben.

Wanneer DK gediagnosticeerd wordt kan de patiënt behandeld worden door middel van chirurgische verwijdering van de tumour en/of toediening van chemotherapie. Hoewel de behandeling van DK significant verbeterd is in de afgelopen twee decennia, is de overleving na diagnose nog steeds voornamelijk afhankelijk van de stadium waarin de ziekte gediagnosticeerd wordt. In de periode 2000-2004 was in Nederland de vijfjaarsoverleving voor stadium I colon kanker ongeveer 89 procent, terwijl de vijfjaarsoverleving voor stadium IV colon kanker slechts zeven procent was. Een soortgelijke trend is geobserveerd voor rectale kankers.

Screenen op DK en voorlopers van DK (adenomen) kan de ziekte mogelijk voorkomen of detecteren in een vroeg stadium, waarbij de kans op overleving groter is. Er bestaan verschillende screen tests met elk zijn voor- en nadelen. De tests kunnen grofweg ingedeeld worden in drie categorieën: ontlastingstests, endoscopische tests en beeldvormende tests. Voor screenen met de guaiac-gebaseerde feces occult bloed test (gFOBT) en met sigmoïdoscopie is de potentie tot incidentie en mortaliteitsreductie aangetoond in grote gerandomiseerde screening studies.

In verschillende landen en regio's over de wereld zijn DK screening programma's ingesteld om deelname aan DK screening in de populatie te bevorderen. In 2014 is in Nederland het landelijk bevolkingsonderzoek naar DK van start gegaan.

Er zijn een groot aantal parameters die van invloed zijn op de effectiviteit van een screening programma. Computer simulatie modellen bieden de mogelijkheid om bestaande klinische data te combineren en te extrapoleren om zodoende de balans tussen de voordelen, nadelen en kosten van screening te optimaliseren. In dit proefschrift hebben we voornamelijk gebruik gemaakt van het MISCAN-colon microsimulatie model van het Cancer Intervention and Surveillance Modelling Network (CISNET) om nieuwe inzichten te krijgen in het effect van verschillende strategieën in DK screening.

In de huidige richtlijnen in de Verenigde Staten (VS) wordt aanbevolen om de starten met DK screening vanaf 50-jarige leeftijd, echter veel mensen hebben nog geen screening ondergaan wanneer ze, vanaf 65-jarige leeftijd, in aanmerking komen voor

de door de overheid gesubsidieerde Medicare zorgverzekering. In **Hoofdstuk 2** hebben we geschat wat de lange termijn effecten zijn van het bevorderen van de screening deelname in de pre-Medicare populatie (50-64 jaar) op de kosten in de pre-Medicare en Medicare populaties (65+ jaar). Voor deze analyse hebben we gebruik gemaakt van twee CISNET modellen (MISCAN-colon en SimCRC). We vergeleken een situatie waarin het screening gedrag door ging zoals op dit moment geobserveerd in de VS (60% van de populatie neemt deel aan screening), met een situatie waarin de screening deelname toe nam tot 70%. De hogere screening deelname resulteerde in een 12-14% toename van de cumulatieve totale kosten in de pre-Medicare populatie (de spreiding geeft het gebruik van twee modellen aan). Echter, door besparingen in DK behandelen daalde de totale kosten in de Medicare populatie met 4-9%, ten opzichte van het scenario met de huidige screening deelname. Geschat wordt dat op de lange termijn 60-89% van de toename in screening kosten in de pre-Medicare populatie gecompenseerd kan worden door besparingen in DK behandelingen in de Medicare populatie.

In **Hoofdstuk 3** hebben we de DK incidentie en mortaliteit vergeleken tussen twee verschillende staten in de VS. De incidentie en mortaliteit in veel noordoostelijke staten in de VS zijn dalende sinds het begin van de jaren 80, echter de daling begon later en was minder snel in de zuidelijke staten. Dit heeft geresulteerd in een lagere DK incidentie en mortaliteit in de noordoostelijke staten ten opzichte van de zuidelijke staten, terwijl dit tegenovergesteld was in de periode voor de jaren 80. Met het MISCAN model hebben we berekend dat de DK incidentie in de zuidelijke staat Louisiana zou afnemen met 3.5% en 15.2% indien de populatie dezelfde trends zou hebben in respectievelijk de prevalentie van risico factoren en screening deelname als de populatie van New Jersey (een noordoostelijke staat). Indien Louisiana dezelfde trends zou hebben als New Jersey voor de prevalentie van risico factoren, screening deelname of overleving na diagnose van DK, dan zou de mortaliteit in Louisiana afnemen met respectievelijk 3.0%, 10.8%, en 17.4%. Indien alle trends gecombineerd worden, zou de ziektelast van DK in Louisiana lager uitkomen dan op dit moment geobserveerd in New Jersey, zowel voor het jaarlijks aantal nieuwe gevallen (116 versus 130 per 100.000 mensen) als het jaarlijks aantal sterfgevallen (44 versus 56 per 100.000 mensen).

In Ontario, Canada, is in 2008 een populatie breed screening programma gestart. In het programma worden mensen in de doelgroep gestimuleerd om de huisarts te bezoeken voor een familie anamnese. Indien de persoon minimaal een eerstegraads familielid met een diagnose van DK heeft (ongeveer 11% van de doelgroep) wordt tienjaarlijkse coloscopie screening aanbevolen en indien dit niet het geval is wordt tweejaarlijkse gFOBT screening aanbevolen. In **Hoofdstuk 4** hebben we berekend hoeveel DK sterfgevallen voorkomen worden en hoeveel additionele coloscopieën vereist zijn in dit op familiegeschiedenis gebaseerde screening programma (met 60% deelname) ten opzichte van een situatie zonder familie geschiedenis (gFOBT voor iedereen, ook met

60% deelname) en een situatie zonder programma (30% deelname aan opportunistische screening, zoals geobserveerd in Ontario voor de invoering van het programma). Ten opzichte van geen programma kan een gFOBT programma over 30 jaar cumulatief 6,700 sterfgevallen voorkomen met 570,000 additioneel benodigde coloscopieën. In het programma met familiegeschiedenis kunnen 9,300 sterfgevallen worden voorkomen met 1,100,000 additionele colocopieën; een toename van respectievelijk 40% (spreiding in sensitiviteitsanalyses: 20–51%) en 93% (spreiding: 43–116%). In programma's waarbij de feces immunochemische test (FIT) gebruikt wordt zal risico stratificatie op basis van familiegeschiedenis minder toename in voorkomen sterfgevallen geven, maar ook minder toename in additioneel benodigde coloscopieën. Gegeven dat het afnemen van een familiegeschiedenis weinig werk vereist voor de huisarts en dat het aantal mensen met een familiegeschiedenis relatief klein is, suggereren onze resultaten dat een screening programma op basis van familiegeschiedenis een te overwegen strategie is om de effectiviteit van een gFOBT programma te verhogen.

DK screening met FIT heeft een aantal voordelen ten opzichte van screenen met gFOBT, waaronder hogere test sensitiviteit, geen benodigde dieet voorschriften en de mogelijkheid tot geautomatiseerd analyseren van de tests. Echter, afhankelijk van de gehanteerde afkapwaarde heeft FIT ook een lagere specificiteit wat een groter aantal fout positieve testuitslagen geeft en een grotere coloscopievraag. In **Hoofdstuk 5** hebben we de kosteneffectiviteit vergeleken van gFOBT en FIT screening met verschillende leeftijdsgrenzen, intervallen en FIT afkapwaardes, in de populatie van Ontario. Ten opzichte van geen screening, geeft twee-jaarlijkse gFOBT screening tussen leeftijd 50 en 74 jaar 20 "quality adjusted life years" (QALY). Deze strategie kost $42,600 per 1,000 deelnemers en vereist 17 coloscopieën per 1,000 deelnemers per jaar. Indien bij deze strategie gFOBT vervangen wordt door FIT met een afkapwaarde van 200 ng Hb/ml is de gezondheidswinst 31 QALY en wordt $289,700 per 1,000 deelnemers bespaart ten opzichte van geen screening. Dit terwijl de coloscopievraag even groot is als bij de gFOBT strategie. Indien de coloscopie capaciteit groot genoeg is om de FIT afkapwaarde te verlagen en het aantal screening rondes te verhogen zou dit een nog grotere gezondheidswinst geven bij een gunstiger kosteneffectiviteitratio. Zonder beperking in coloscopie capaciteit en een kosteneffectiviteitdrempel van $50,000 per additioneel gewonnen QALY is FIT 50 met een 1.5 jaars screening interval, tussen leeftijd 40 en 84 de meest effectieve strategie; een winst van 47 QALY ten opzichte van geen screening. Voor regio's waar gFOBT screening wordt gebruikt, wordt aanbevolen in eerste instantie over te stappen op FIT screening met een hoge afkapwaarde. Daarna zou de coloscopie capaciteit verhoogd moeten worden om op termijn de FIT afkapwaarde te kunnen verlagen voor een nog grotere gezondheidswinst bij een gunstiger kosteneffectiviteitratio. Om te kunnen bepalen of het implementeren van familiehistorie in een gFOBT screening

programma zoals beschreven in Hoofdstuk 4 kosteneffectief is ten opzichte van overstappen naar FIT is nader onderzoek vereist.

In **Hoofdstuk 6** hebben we bepaald wat de diagnostische opbrengst en deelnamegraad was bij mensen die, met een interval van 1, 2, of 3 jaar, voor een tweede ronde FIT screening uitgenodigd zijn in een Nederlands DK proefbevolkingsonderzoek. Voor alle drie de groepen was zowel de positiviteitsgraad, als de detectiegraad van geavanceerde neoplasie significant lager in de tweede ronde ten opzichte van de eerste ronde (respectievelijk 6.0% versus 8.4% en 1.9% versus 3.3%) en deze observatie was onafhankelijk van de interval lengte. De deelnamegraad in de 1-jaar interval groep was 64.7% in de eerste ronde en 63.2% in de tweede ronde. Voor de 2-jaar en 3-jaar interval groepen was de deelnamegraad in eerste en tweede ronde 61.0% versus 62.5% en 62.0% versus 64.0%. In een multivariate analyse, gecorrigeerd voor de deelnamegraad in de eerste ronde, waren 2- en 3-jaarlijkse screening geassocieerd met een significant hogere deelname in de tweede ronde ten opzichte van 1-jaarlijkse screening. De cumulatieve deelnamegraad na twee ronden was 69.7%, 67.5% en 68.7% in respectievelijk de 1-, 2- en 3-jaar interval groep en was niet significant verschillend tussen de groepen. Deze resultaten suggereren dat het variëren van het interval tussen twee opeenvolgende screening ronden een goede manier is om de coloscopie vraag van een FIT screening programma af te stemmen op de lokaal beschikbare coloscopie capaciteit.

Een FIT test heeft imperfecte sensitiviteit, vooral voor adenomen. Een deel van het gebrek aan sensitiviteit wordt veroorzaakt doordat adenomen niet of onregelmatig bloeden. Het aanbieden van twee FIT samples per screening ronde, afgenomen op twee opeenvolgende dagen, zou een grotere kans geven adenomen te detecteren en daarmee de effectiviteit van een screening programma kunnen verhogen. In **Hoofdstuk 7** hebben we in een kosteneffectiviteitsanalyse onderzocht in hoeverre de toename in gezondheidswinst van 2-sample FIT screening opweegt tegen de additionele kosten ten opzichte van 1-sample FIT screening. Met het screening schema uit het Nederlandse DK bevolkingsonderzoek (twee-jaarlijkse screening tussen leeftijd 55 en 75 jaar) geeft 1-sample FIT screening 76.0-97.0 "life years gained" (LYG) per 1,000 mensen, bij kosten variërend van €259,000 tot €264,000 (de spreiding geeft het effect van verschillende FIT afkapwaardes aan). 2-Sample FIT screening met minimaal een positief sample geeft 7.3-12.4 additionele LYG ten opzichte van 1-sample FIT screening en kost €50,000 tot €59,000 extra. Echter, wanneer een intensiever screening schema gebruikt wordt (dat wil zeggen een korter screening interval en/of bredere leeftijdsgrenzen) met 1-sample screening levert dit gelijke of grotere gezondheidswinst op bij een minder sterke toename in kosten. Indien men de effectiviteit van een FIT screening programma wil verhogen is het daarom aan te raden eerst het aantal screening ronden met 1-sample FIT screening te verhogen, voordat twee FIT samples per ronde aangeboden gaat worden.

Een alternatieve manier om de sensitiviteit te verhogen, in plaats van het aanbieden van twee FIT samples, is het testen op specifieke aan de ziekte gerelateerde moleculen zoals afwijkend DNA, toegevoegd aan, of in plaats van FIT. De introductie van "next generation" DNA analyse technieken hebben de kosten voor DNA analyse drastisch verlaagd, waardoor een zeer sensitieve moleculaire biomarker test een potentieel kosteneffectieve screening optie wordt. In **Hoofdstuk 8** hebben we verschillende hypothetische en twee recent beschreven biomarker testen gemodelleerd. Voor elke test variant hebben we uitgerekend hoeveel de test mag kosten om even kosteneffectief te zijn als FIT. Door twee-jaarlijkse FIT screening te modelleren tussen leeftijd 55 en 75 en verschillende testeigenschappen een voor een te variëren ten opzichte van FIT hebben we aangetoond dat het maximaliseren van de sensitiviteit voor grote adenomen (≥10mm) meer LYG gaf en hogere test kosten toeliet dan het maximaliseren van de sensitiviteit voor DK. Wanneer het screening interval en de leeftijdsgrenzen geoptimaliseerd worden voor elke test mag een biomarker test met bijna perfecte test sensitiviteit en specificiteit ongeveer zeven maal duurder zijn dan de huidige FIT test (dat wil zeggen deze biomarker test mag ongeveer €50 kosten).

In de overkoepelende discussie (**Hoofdstuk 9**) hebben we de specifieke onderzoeksvragen die behandeld zijn in dit proefschrift besproken. Tevens hebben we in dit hoofdstuk suggesties gegeven voor toekomstig onderzoek en presenteren we een overzicht van de belangrijkste conclusies en bevindingen.

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About the author

CURRICULUM VITAE

Simon Lucas Goede was born on May 6th 1983, in Ruinerwold, The Netherlands. In 2001 he completed his secondary school education (Atheneum) at the Scholengemeenschap Tabor in Hoorn. That same year he started studying Human Movement Sciences at the Vrije Universiteit (VU) in Amsterdam. In 2006 he obtained his Master of Science degree with a specialization in biomechanics and physiology in sports. He wrote his Master's thesis about the biomechanical factors affecting cross-county ski performance. As part of this thesis he wrote a computer simulation model with which the effects of the various biomechanical factors on performance could be quantified. During his research internship at the VU he assessed the effect of time trial distance on anaerobic work during cycling. He did a second internship at TNO Industry and Technology in Eindhoven, where he performed a positioning analysis based on wind tunnel data, used for the development of a track racing bicycle and contributed to the development of a prototype power meter for racing bicycles. From 2006 to 2009 he worked as a project assistant at NOC*NSF in Arnhem where he provided sport technical support to various projects in preparation of the 2008 Olympic Games. Since 2009 he was appointed as a researcher at the department of Public Health at the Erasmus University Medical Centre in Rotterdam. During his time at Erasmus he obtained a Master of Science degree in Health Sciences (specialization: Public Health) at the Netherlands Institute of Health Sciences (NIHES), and performed research with the MISCAN-Colon microsimulation model on the effects of colorectal cancer screening on population health and costs. The results of his research are presented in this thesis.

LIST OF PUBLICATIONS

In this thesis:

S. Lucas Goede, Karen M. Kuntz, Marjolein van Ballegooijen, Amy B. Knudsen, Iris Lansdorp-Vogelaar, Florence K. Tangka, David H. Howard, Joseph Chin, Ann G. Zauber, Laura C. Seeff. Cost-savings to Medicare from Pre-Medicare Colorectal Cancer Screening. Submitted.

Iris Lansdorp-Vogelaar, S. Lucas Goede, Jiemin Ma, Wu Xiau-Cheng, Karen Pawlish, Marjolein van Ballegooijen, Ahmedin Jemal. State disparities in colorectal cancer rates - contribution of risk factors, screening and survival differences. Submitted.

S. Lucas Goede, Linda Rabeneck, Iris Lansdorp-Vogelaar, Ann G. Zauber, Lawrence F. Paszat, Jeffrey S. Hoch, Jean H.E. Yong, Frank van Hees, Jill Tinmouth, Marjolein van Ballegooijen. The Impact of Stratifying by Family History in Colorectal Cancer Screening Programs. Int J Cancer. 2015 Feb. doi: 10.1002/ijc.29473. [Epub ahead of print]

S. Lucas Goede, Linda Rabeneck, Marjolein van Ballegooijen, Ann G. Zauber, Lawrence F. Paszat, Jeffrey S. Hoch, Jean H.E. Yong, Sonja Kroep, Jill Tinmouth, Iris Lansdorp-Vogelaar. Harms, benefits and costs of fecal immunochemical testing versus guaiac fecal occult blood testing for colorectal cancer screening. Submitted.

Van Roon AH, Goede SL, van Ballegooijen M, van Vuuren AJ, Looman CW, Biermann K, Reijerink JC, Mannetje H', van der Togt AC, Habbema JD, van Leerdam ME, Kuipers EJ. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. Gut. 2013 Mar;62(3):409-15.

Goede SL, van Roon AH, Reijerink JC, van Vuuren AJ, Lansdorp-Vogelaar I, Habbema JD, Kuipers EJ, van Leerdam ME, van Ballegooijen M. Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening. Gut. 2013 May;62(5):727-34.

S. Lucas Goede, Iris Lansdorp-Vogelaar, Linda J.W. Bosch, Veerle Melotte, Beatriz Carvalho, Manon van Engeland, Gerrit A. Meijer, Harry J. de Koning, Marjolein van Ballegooijen. Requirements for colorectal cancer screening with new biomarkers: a cost-effectiveness analysis. Submitted.

Other publications:

Meester RG, Doubeni CA, Zauber AG, Goede SL, Levin TR, Corley DA, Jemal A, Lansdorp-Vogelaar I. Public health impact of achieving 80% colorectal cancer screening rates in the United States by 2018. Cancer. 2015 Mar. doi: 10.1002/cncr.29336. [Epub ahead of print]

Meester RG, Doubeni CA, Lansdorp-Vogelaar I, Goede SL, Levin TR, Quinn VP, Ballegooijen Mv, Corley DA, Zauber AG. Colorectal cancer deaths attributable to nonuse of screening in the United States. Ann Epidemiol. 2015 Mar;25(3):208-213.e1. doi: 10.1016/j.annepidem.2014.11.011. [Epub ahead of print]

Else-Mariëtte B. van Heijningen, Iris Lansdorp-Vogelaar, Ewout W. Steyerberg, S. Lucas Goede, Evelien Dekker, Wilco Lesterhuis, Frank ter Borg, Juda Vecht, Pieter Spoelstra, Leopold Engels, Clemens J.M. Bolwerk, Robin Timmer, Jan H. Kleibeuker, Jan J. Koornstra, Harry J. de Koning, Ernst J. Kuipers, Marjolein van Ballegooijen. Adherence to surveillance guidelines after removal of colorectal adenomas: A large, community-based study. Gut. 2015 Jan. doi: 10.1136/gutjnl-2013-306453. [Epub ahead of print].

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 Oct;174(10):1568-76.

Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010 Feb;116(3):544-73.

PhD PORTFOLIO

Name PhD student:	Simon Lucas Goede
Erasmus MC Department:	Public Health
Research School:	Netherlands Institute for Health Sciences
PhD period:	2009-2015
Promotor:	Prof.dr. H.J. de Koning
Supervisor:	Dr. I. Lansdorp-Vogelaar

PhD training	Year	Workload
General academic skills		
- Master of Health Sciences, specialization: Public Health. Netherlands Institute for Health Sciences (NIHES), Erasmus MC, Rotterdam, the Netherlands	2009-2012	70.0 ECTS*
Presentations		
- Research meetings at department of Public Health, Erasmus MC, Rotterdam	2009-2014	40 hours
- Cancer Intervention and Surveillance Modelling Network (CISNET) meetings, National Cancer Institute, Bethesda, Maryland	2009-2010	40 hours
- Centre for Translational Molecular Medicine (CTMM) annual meetings, Utrecht (posters)	2010-2013	80 hours
- American College of Gastroenterology, San Antonio, Texas	2010	20 hours
- Digestive Diseases Week, San Diego, California (poster)	2012	20 hours
- International Cancer Screening Network, Sydney, Australia	2012	20 hours
- Integraal Kankercentrum Nederland, Symposium Effecten Darmkankerscreening, Sittard	2012	20 hours
- DeCoDe general assembly, Breukelen	2012-2013	40 hours
(Inter)national conferences		
- American College of Gastroenterology, San Antonio, Texas	2010	32 hours
- International Cancer Screening Network, Sydney, Australia	2012	24 hours
Seminars and workshops		
- Seminars at department of Public Health, Erasmus MC, Rotterdam	2009-2014	100 hours
- Symposium Cancer Screening: Trials and modelling to guide public health policies, Rotterdam	2009	8 hours
- Symposium Patients, People and Populations – 40 Years of Epidemiology at Erasmus MC, Rotterdam	2009	8 hours
- Nederlandse Vereniging voor Oncologie 68ste Oncologiedag - Colorectale kanker, Utrecht	2010	8 hours
- Nationaal symposium: Colorectaal carcinoom en de toegevoegde waarde van colonscreening, Oegstgeest	2011	8 hours

- Nationaal symposium: Invoering van colonscreening, een scherpe blik vooruit, Zeist	2012	8 hours
- Symposium De waarde van gezondheid: waar ligt de grens?, Rotterdam	2012	8 hours
- Symposium Effecten Darmkankerscreening, Sittard	2012	8 hours

* 1 ECTS = 28 hours

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