Informing Colorectal Cancer Screening Decisions Using Micro-Simulation Modeling

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Informing Colorectal Cancer Screening Decisions Using Micro-Simulation Modeling

Het informeren van beslissingen over dikkedarmkankerscreening met behulp van een micro-simulatie model

Thesis

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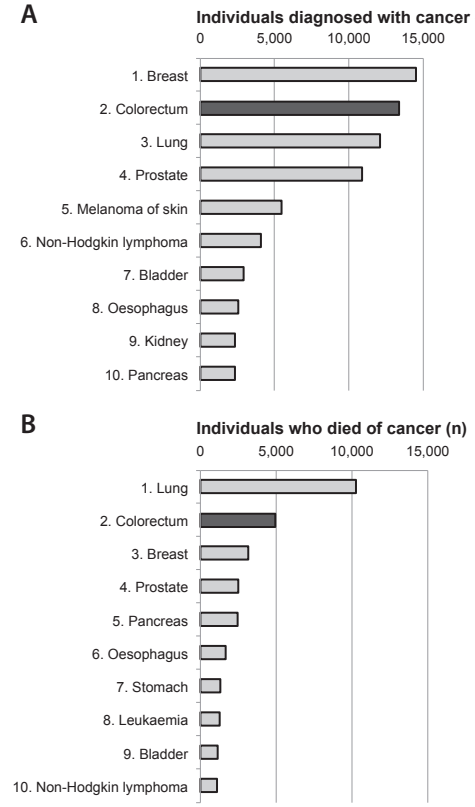
Introduction

COLORECTAL CANCER AS A PUBLIC HEALTH PROBLEM

The impact of colorectal cancer on population health

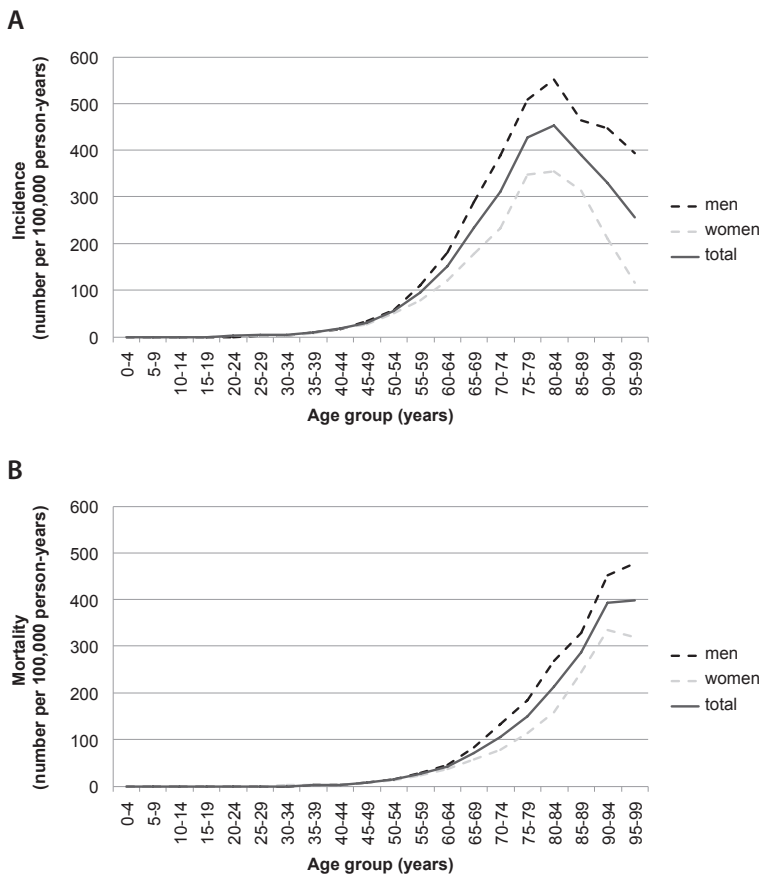
In most developed countries, colorectal cancer (CRC) is an important public health problem. In the Netherlands alone, 13,370 individuals were diagnosed with CRC in 2013.[1] In the same year, 4,940 individuals died of the disease. This makes CRC the second most common cancer and the second most common cause of cancer-related death in the Netherlands today (**Figure 1**). The lifetime risk of developing CRC in the Netherlands is 4.4%. The lifetime risk of dying of the disease is 1.8%. In the US, CRC is the fourth most common cancer and the second most common cause of cancer-related death.[2] The lifetime risks of developing CRC and dying of the disease are similar to those observed in the Netherlands: 4.5% and 1.9%, respectively.

Figure 1 The number of individuals who were diagnosed with cancer (A) and who died of cancer (B) by type of cancer in the Netherlands in 2013.[1]



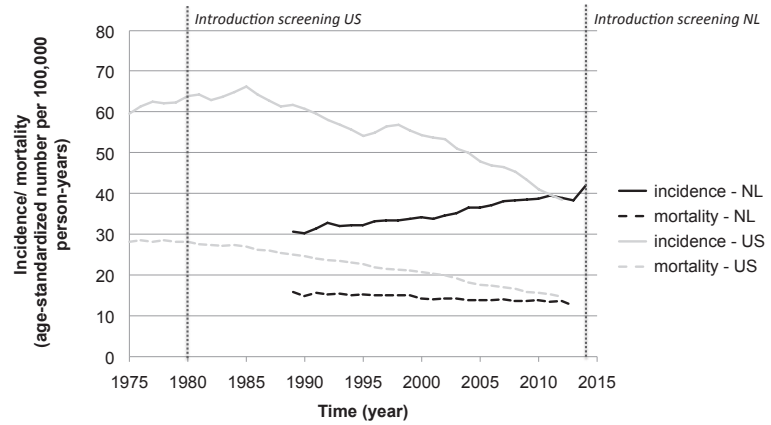
CRC incidence and mortality increase markedly with age and are higher in men than in women (**Figure 2**).[1] However, because women tend to live longer than men, the total burden of CRC in women is comparable to that in men. In 2013, 44% of CRC diagnoses and 47% of CRC deaths in the Netherlands occurred in women.

Figure 2 CRC incidence (A) and mortality (B) by gender in the Netherlands in 2013.[1]



In the Netherlands, the incidence of CRC increased substantially during the past 25 years (**Figure 3**).[1] This increase is likely to be explained by unfavorable trends in risk factors for CRC such as unhealthy dietary habits and overweight/ obesity. In the same period, CRC mortality remained relatively stable: a result of the improved treatment options that became available. In contrast with the Netherlands, in the US, CRC incidence and mortality

Figure 3 Time-trends in CRC incidence and mortality in the Netherlands and the US.[1 2]



declined during the past three decades.[2] This is likely to be explained, at least partially, by the gradual introduction of CRC screening in the US from the early 1980s onwards. In the Netherlands, screening for CRC was not implemented until 2014.

The impact of colorectal cancer on health care budgets

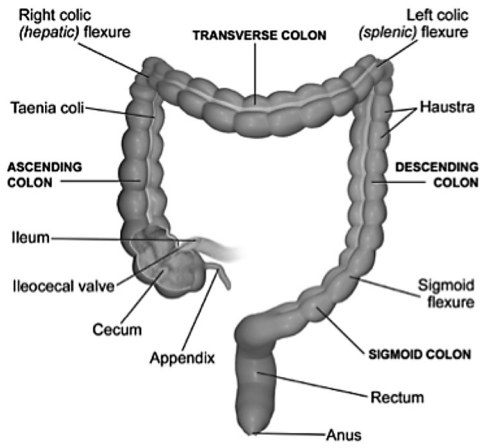
CRC does not only pose a burden on population health. It also poses a burden on health care budgets. In the Netherlands alone, the costs of CRC care were estimated to be €488 million in 2011.[3] This corresponds to 10.2% of the total costs of cancer care in that year. In the near future, the costs of CRC care are expected to rise due to the detection of prevalent cancers within the Dutch national CRC screening program. In the more distant future, the costs are expected to decline because screening also prevents cancers (see **Chapter 2** of this thesis). In the US, the costs of CRC care were estimated to be $14.1 billion in 2010, corresponding to 11.3% of the total costs of cancer care in that year.[4]

THE NATURAL HISTORY OF COLORECTAL CANCER

The colorectum

The colorectum is the final section of the gastrointestinal tract that performs the vital task of absorbing water and vitamins while converting digested food into feces. The colorectum is approximately 1.5m in length and 6-7cm in diameter. It is generally subdivided into 6 regions: the cecum, ascending colon, and transverse colon (that together comprise the proximal colon) and the descending colon, sigmoid colon, and rectum (that together comprise the distal colon) (**Figure 4**).

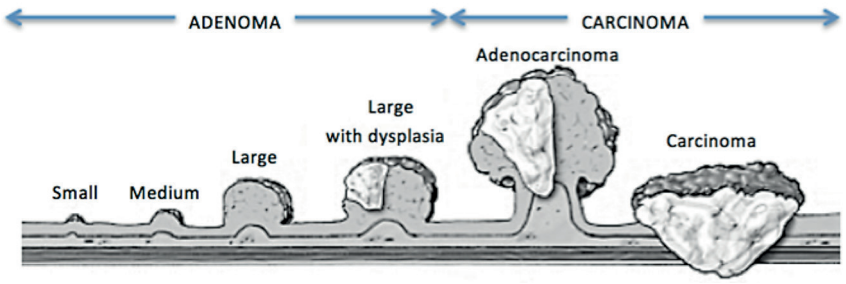
Figure 4 The colorectum.



The adenoma-carcinoma sequence

Most CRCs are believed to develop from adenomas in a process called the adenoma-carcinoma sequence (**Figure 5**).[5] Adenomas are visible lesions (i.e., polyps) of the colonic epithelium that result from a series of epithelial mutations. They can develop anywhere in the colorectum and can grow in size and develop high-grade dysplasia. Some adenomas eventually invade the mucosa and become malignant (i.e., CRC). CRC does not cause symptoms immediately: somewhere in the process of progressing from a localized stage I cancer to a metastasized stage IV cancer, symptoms will present and as a result CRC will be diagnosed.

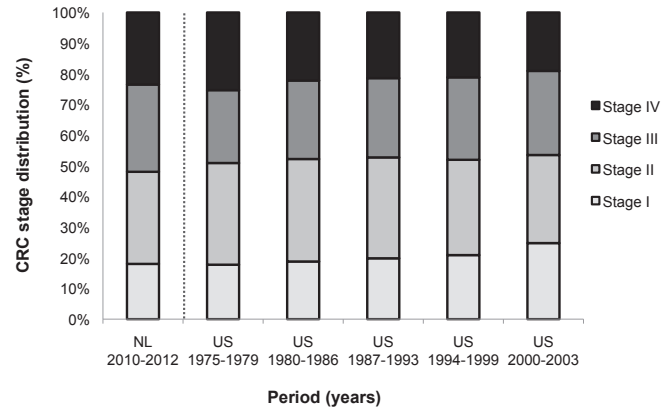
Figure 5 The adenoma-carcinoma sequence.



In most developed countries, such as the Netherlands and the US, 40%-50% of all individuals will develop at least one adenoma during life.[6] However, most of these adenomas will never develop into CRC. Adenomas that do develop into CRC take a long time to do so. Using a model-based approach, we estimated that CRC is already present in the form of a preclinical cancer for an average of 4.7 years and in the form of an adenoma for an average of 12.5 years before it gets diagnosed.

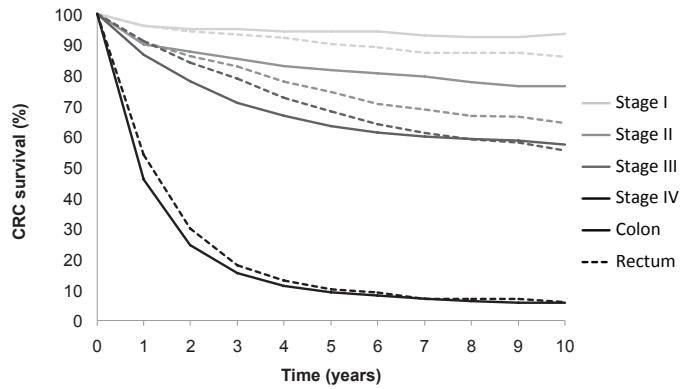
In the period 2010-2012, 18%, 30%, 28%, and 24% of CRCs in the Netherlands were diagnosed in stage I, II, III, and IV, respectively (**Figure 6**).[1] This distribution is very comparable to that observed in the US between 1975 and 1979, just before screening was introduced.[2] After the introduction of screening, the stage distribution of CRC in the US improved: in the period 2000-2003 25% of CRCs were diagnosed in stage I and only 19% of CRCs were diagnosed in stage IV.

Figure 6 The stage distribution of CRC in the Netherlands and the US.[1 2]



The probability that a patient dies of CRC depends largely on the stage of the cancer at diagnosis and the localization of the cancer in the colorectum. Of all patients diagnosed with stage I colon cancer in the Netherlands between 2003 and 2009, only 6.0% died of the disease during the first 5 years after diagnosis (**Figure 7**).[1] The corresponding percentage for patients diagnosed with stage I rectal cancer was 10.0%. Of all patients with stage IV disease approximately 90% died within 5 years after diagnosis.

Figure 7 CRC survival by stage at diagnosis and localization in the colorectum in the Netherlands between 2003 and 2009.[1]



INTERVENTIONS TO REDUCE COLORECTAL CANCER MORTALITY

Primary prevention

Primary prevention of CRC can be achieved by improving a population's lifestyle. The most important modifiable risk factors for CRC are smoking, being overweight/ obese, being physically inactive, and consuming insufficient amounts of vegetables.[8] Although lifestyle modification is challenging, we recently showed that 35% of the reduction in CRC mortality observed in the US during the past three decades could be attributed to favorable risk factor trends.[9]

Another strategy that might be used for primary prevention of CRC is chemoprevention using either aspirin or cyclooxygenase (COX) inhibitors. Both drugs have shown to reduce CRC risk.[10 11] However, since the use of aspirin and COX inhibitors is associated with gastrointestinal and cardiovascular events (COX inhibitors only),[10 11] chemoprevention is currently not recommended for average-risk individuals.[12]

Screening

Screening is defined as 'a strategy used in a population to identify an unrecognized disease in individuals without signs or symptoms'. The aim of screening is to detect disease in an earlier stage with a more favorable prognosis. CRC is particularly well suited for screening because it tends to have a long pre-clinical screen-detectable phase. During this phase, screening might prevent cancer by detecting and removing adenomas or it might detect cancer early, resulting in an improved prognosis. However, screening can also result in serious complications and overdiagnosis and overtreatment of cancers (that

is, the detection and treatment of cancers that would not have been diagnosed without screening).

There are multiple tests available for CRC screening. These tests can be subdivided into three categories: stool tests, endoscopic tests, and imaging tests. There are three types of stool tests: the guaiac fecal occult blood test (gFOBT), the fecal immunochemical test (FIT), and the stool DNA test (**Figure 8**). While the gFOBT is aimed at detecting any blood in stool, the FIT is aimed at detecting human blood only, and the stool DNA test is aimed at detecting human blood as well as mutated DNA from neoplastic cells. Whereas the FIT requires only one stool sample to be taken, the gFOBT requires two samples from 3 consecutive bowel movements, and the stool DNA test requires a full bowel movement for analysis. Moreover, whereas the gFOBT is a qualitative test (the result is either positive or negative), the FIT and stool DNA test are quantitative tests (the result is a concentration of blood in stool/ a score on a logistic regression algorithm, respectively), allowing one to vary the cut-off value for a positive test. For all tests, individuals with a positive result are referred for full endoscopic examination (i.e., a colonoscopy).

Figure 8 An example of a gFOBT (the Hemoccult II SENSA, Beckman Coulter, US) (A), a FIT (the OC-SENSOR, Eiken Chemical, Japan) (B), and a stool DNA test (the Cologuard, Exact Sciences Corporation, US) (C).

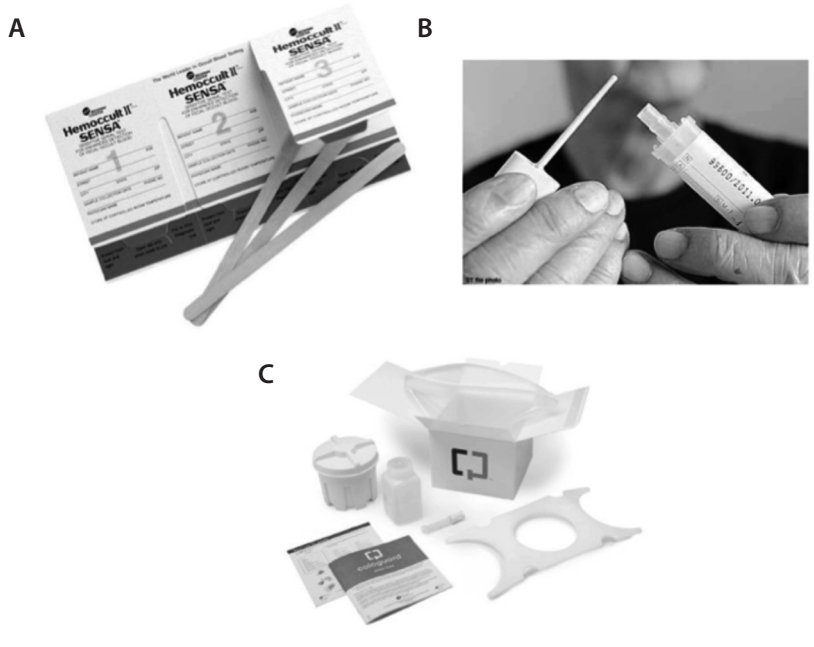


Table 1 RCTs evaluating screening using a gFOBT (Hemoccult II, Backman Coulter, US).

Trial	Age group (y)	Screening interval (y)	Screening rounds (n)	Participation first round (%)	Average length of follow up (y)	CRC mortality reduction (% (95%CI))
Denmark[13]	45-75	2	9	67[1]	17	11 (-1-22)
Sweden[14]	60-64	1-2	2-3	63	16	16 (1-29)
UK[15]	45-74	2	3-5	57	20	13 (3-22)
US[16]	50-80	1	11	75	18[2]	32 (18-44)
US[16]	50-80	2	6	78	18[2]	22 (3-38)

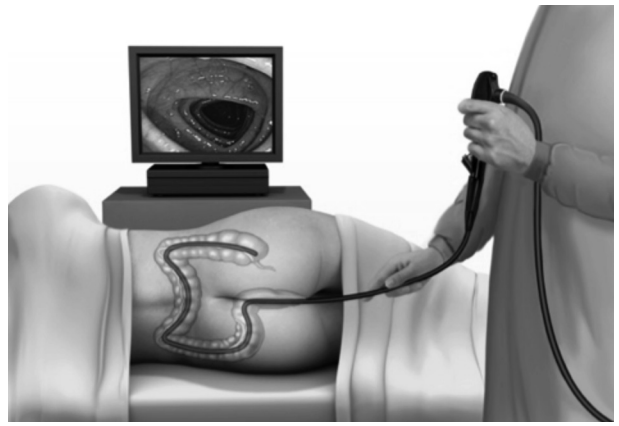
RCT = randomized controlled trial, gFOBT = guaiac fecal occult blood test, y = year, n = number,
CI = confidence interval, UK = United Kingdom, US = United States
[1] Only those participating in all previous screening rounds were re-invited for screening.
[2] Maximum length of follow-up.

The gFOBT Hemoccult II (Beckman Coulter, US) is the only stool test for which the effectiveness has been demonstrated in randomized controlled trials (RCTs) (**Table 1**). The observed reduction in CRC mortality ranged from 11% to 32%.[13-16] The effectiveness of FIT screening has never been demonstrated by means of a conventional RCT. However, several ongoing RCTs comparing gFOBT and FIT screening have demonstrated that participation in FIT screening is higher than participation in gFOBT screening and that FIT screening detects more advanced neoplasia at similar positivity rates.[17-21] FIT screening is therefore generally expected to be more effective than gFOBT screening given equal screening intensity. The effectiveness of stool DNA testing has also not been demonstrated by means of an RCT. However, a recent, large, back-to-back study in asymptomatic individuals demonstrated that stool DNA testing has a higher sensitivity for the detection of adenomas and CRC than FIT screening, but at a substantially lower specificity.[22]

Endoscopic screening involves inspecting the colorectum by inserting a flexible tube with a fiber optic camera into the anus (**Figure 9**). During the procedure adenomas and cancers can be biopsied or even completely removed. The two endoscopic procedures that can be used for CRC screening are sigmoidoscopy and colonoscopy. Both procedures are highly sensitive for detecting adenomas and cancers within the reach of the endoscope. With sigmoidoscopy only the rectum and distal part of the colon are inspected. Individuals with a positive sigmoidoscopy are referred for a colonoscopy. With colonoscopy the entire colorectum is visualized. Both procedures require a bowel preparation and can result in serious complications. However, the preparation for a colonoscopy is more burdensome than that for a sigmoidoscopy and the risks for complications are higher.

The effectiveness of one-time sigmoidoscopy screening has been demonstrated in multiple RCTs (**Table 2**). The observed reduction in CRC mortality ranged from 22% to

Figure 9 Endoscopic inspection of the colorectum.



31%.[23-26] For colonoscopy screening two RCTs are currently being conducted, but no mortality data are available yet.[27 28] Since the principle of colonoscopy screening is identical to that of sigmoidoscopy screening, and since a colonoscopy covers a larger part of the colorectum than a sigmoidoscopy, colonoscopy screening is generally expected to be more effective than sigmoidoscopy screening given equal screening intensity.

A relatively new imaging technique that can be used for CRC screening is computed tomography (CT) colonography. During this procedure two CT scans are made of the colorectum. From these scans, two-dimensional and three-dimensional images are constructed which are used to investigate the presence of lesions in the colorectum. No RCTs have yet demonstrated the effectiveness of CT colonography screening. An ongoing Dutch RCT comparing colonoscopy and CT colonography screening did demonstrate that participation in CT colonography screening is higher than participation in colonoscopy screening.[29] However, in those participating in screening, colonoscopy screening detected significantly more advanced neoplasia than CT colonography screening. Other disadvantages of CT colonography screening are that it requires a burdensome bowel preparation and that individuals with a positive test still have to undergo a colonoscopy.

Surveillance in adenoma patients

Individuals in whom adenomas are detected and removed (either as a result of screening or during a colonoscopy indicated because of symptoms) are recommended to undergo intensive testing using colonoscopy, so-called 'colonoscopy surveillance'.[30 31] The effectiveness of colonoscopy surveillance has never been demonstrated by means of an RCT. However, since adenoma patients are at increased risk for CRC compared with the general population and since screening in the general population is effective,[32]

Table 2 RCTs evaluating screening using sigmoidoscopy.

Trial	Age group (y)	Screening interval (y)	Screening rounds (n)	Participation first round (%)	Average length of follow up (y)	CRC mortality reduction (% (95%CI))
UK[23]	55-64	NA	1	71	11	31 (18-41)
Norway[24]	50-64	NA	1	63	11	27 (6-44)
US[25]	55-74	3-5	2	84	12	26 (13-37)
Italy[26]	55-64	NA	1	58	11	22 (-8-44)

RCT = randomized controlled trial, y = year, n = number, CI = confidence interval, UK = United Kingdom

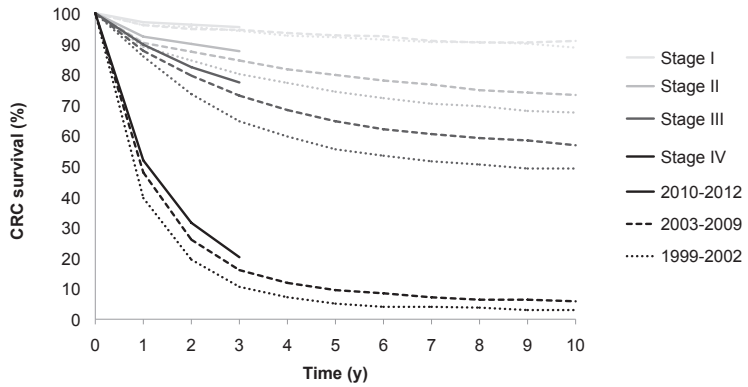
colonoscopy surveillance is also believed to be effective. Based on a large cohort study, colonoscopy surveillance is estimated to reduce the risk for CRC mortality in adenoma patients by 66% up to 75%.[33] The most recent Dutch guidelines for surveillance in adenoma patients are based on the study described in **Chapter 3** of this thesis.

CRC treatment

Depending on the stage at diagnosis and the localization of the cancer, CRC is treated by resection and chemotherapy and/ or radiation therapy. In recent years, treatment of CRC has undergone some important changes. The acceptance of total mesorectal excision as the preferred treatment option for rectal cancer has resulted in lower local recurrence rates, while the application of pre-surgical radiotherapy has increased the proportion of rectal cancers suitable for this treatment option.[34] Moreover, advances in the treatment of metastatic disease, such as portal vein embolization, have made liver resection a possibility for more patients.[35] In terms of systemic management, traditional treatment comprised 5-fluorouracil and leucovorin. This was augmented by treatment with irinotecan and oxaliplatin in the late 1990s, while more recently the monoclonal antibodies bevacizumab and cetuximab were added to regular treatment protocols.

As a result of these changes in treatment, the prognosis of CRC patients has improved over time (**Figure 10**). For Dutch CRC patients diagnosed between 1999 and 2002, 5-year survival was 92%, 74%, 56%, and 5% for stage I, II, III, and IV disease, respectively.[1] For patients diagnosed between 2003 and 2009, these percentages were 93% (+1%), 80% (+6%), 65% (+9%), and 9% (+4%). According to a recent analysis we performed, 12% of the total reduction in CRC mortality in the US in the past three decades could be explained by improvements in CRC treatment.[9]

Figure 10 Time-trends in stage-specific CRC survival in the Netherlands.[1]



THE STATUS OF COLORECTAL CANCER SCREENING

The Netherlands

In 2009, the Dutch Health Council advised the Dutch Minister of Health to implement a national CRC screening program.[36] Based on the outcomes of Dutch trials comparing gFOBT and FIT screening and subsequent modeling work,[37-39] the Council recommended biennial FIT screening between ages 55 and 75 years using a cut-off for referral to colonoscopy of 15µg hemoglobin/g feces. In response, the Minister of Health commissioned the Dutch National Institute for Public Health and the Environment to investigate the feasibility of such a CRC screening program in the Netherlands.[40] The outcomes of this study led a new Minister of Health to decide to implement a national CRC screening program in accordance with the Health Council advice in 2011.[41 42] After two years of preparation of program infrastructure, quality assurance protocols, and communication materials, the national program was first piloted in the Rotterdam-Rijnmond area in the fall of 2013 and then rolled out nationally starting in January 2014. In that year, only individuals aged 63, 65, 67, 75, and 76 years (a one-time exception) were invited. In upcoming years, the number of age groups invited for screening will be gradually expanded.

The Dutch national CRC screening program was an immediate success. Participation was higher than expected (68% instead of 60%), as was the detection rate of advanced adenomas/CRC (4.0% instead of 2.7%).[43] However, the proportion of individuals with a positive test was also considerably higher than expected (13.4% instead of 6.4%). As a result, waiting times for diagnostic colonoscopy increased. To solve this problem, the National Institute for Public Health and the Environment decided to elevate the cut-off for

referral to colonoscopy to 47µg/g in July 2014, which was the best measure to be taken according to the study described in **Chapter 2** of this thesis.[44]

The United States

In the US, screening for CRC was introduced more than three decades ago. Participation rates in individuals aged 50 years and older rose from 18% in 1987 to 58% in 2010.[45] In contrast with the Netherlands, there is no nationally organized CRC screening program in the US. Instead, most screening is carried out opportunistically. That is, the system relies on the patient and the health care provider to remember that screening should take place. Moreover, in the US, individuals are free to choose between screening tests. Medicare (i.e., a national social insurance program for individuals aged 65 years and older) started covering CRC screening using gFOBT, sigmoidoscopy, and barium enema in 1998. In 2001, colonoscopy screening was added to the menu of options. Subsequently, in 2003, Medicare began covering FIT screening. Since October 2014, Medicare also covers stool DNA testing.

All US guidelines for CRC screening recommend starting screening at age 50 years for all individuals, except the American College of Gastroenterology, which recommends starting screening at age 45 years for African Americans.[46-49] Recommendations on the appropriate age to stop screening differ between guidelines. The US Preventive Services Task Force (USPSTF) and the American College of Physicians recommend against routine screening in individuals aged older than 75 years and against screening in individuals aged older than 85 years.[46 48] The other guidelines do not specify an age to stop screening.[47 49] The screening strategies that are recommended also differ between guidelines. The USPSTF recommends annual screening with a high sensitivity gFOBT or FIT, 5-yearly sigmoidoscopy screening combined with 3-yearly screening with a high sensitivity gFOBT or FIT, or 10-yearly colonoscopy screening.[46] The American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology jointly recommend the same strategies, but also 5-yearly double-contrast barium enema, 5-yearly CT colonography, and fecal DNA testing at an unspecified interval.[47]

EVALUATING SCREENING

A three-step approach

Step 1: Effectiveness

The first step in evaluating screening is to determine whether it is effective. That is, whether screening reduces mortality due to the target disease. This can only be done by means of an RCT with disease-specific mortality as the primary endpoint. Observational studies (i.e., case-control studies and cohort studies) should be interpreted with caution, since they are prone to 'selection bias': because individuals participating in screening are

almost invariably healthier than those who do not, they are likely to have better outcomes, even in the absence of screening. Studies comparing survival rates between screen-detected and clinically detected cases of cancer are hardly informative, since (in addition to selection bias) they are prone to two other forms of bias: 'lead-time bias' and 'length bias'. Lead-time bias is caused by the fact that screening detects disease earlier in time. As a result, screen-detected cases seem to have a more favorable survival than clinically detected cases, even if screening does not postpone death. Length bias is caused by the fact that screening is more likely to detect slowly progressing disease than rapidly progressing disease. As a result, screening seems to prolong survival even if it does not.

Because cancer is relatively rare and because of the inherent time lag between a screening intervention and its effect on mortality, RCTs evaluating screening have to be large and follow-up has to be long. As a result, screening trials are relatively expensive. Still, it is important to realize that they are indispensable.

Step 2: Benefits versus harms

The second step in evaluating screening is to determine whether the benefits of screening outweigh the harms. To do this, all potential effects of screening on health (see **Table 3**) should be measured, valued, and integrated into one measure. A frequently used method to value the health effects of screening is by using utility weights. These weights correct the time spent in a certain disease state for the quality of life experienced in that state. The valued effects can be summed up to arrive at one measure for the net health effect of screening: the number of quality-adjusted life-years (QALYs) gained. A positive number of QALYs gained indicates a net health benefit; a negative number of QALYs gained indicates a net harm. An alternative to explicitly valuing and weighing effects is to present all effects to a group of decision makers and let them judge whether screening is associated with a net health benefit or harm.

Step 3: Economic evaluation

The third step in evaluating screening is to determine whether the effects of screening justify the costs (for an answer to the question of why costs should be considered see **Box 1**). In general, three types of economic evaluation are distinguished: cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses. For all types of evaluation, the costs of screening have to be determined (see **Table 4** for the cost categories that should be considered). The difference between the types of economic evaluation lies in the effects that are considered and the method that is used to value these effects. In cost-effectiveness analyses, a single effect of interest is measured. This effect (e.g. screen-detected cases, deaths prevented, life-years gained) is not valued. In cost-utility analyses multiple effects are measured. These effects are valued using utility weights and integrated in terms of QALYs gained. Screening is regarded cost-effective if the costs per QALY gained are lower than a predefined cost-effectiveness threshold (in the Netherlands a threshold of

Table 3 Potential effects of screening on health.

Positive effects on health
Screening might prevent mortality
Screening might prevent morbidity caused by (late-stage) disease
Screening might prevent morbidity caused by treatment of (late-stage) disease
True negative test results might result in justified reassurance
Screening might positively affect risk behavior
Negative effects on health
The screening test might be burdensome and possibly harmful
A possible diagnostic test might be burdensome and possibly harmful
Awaiting test results might cause psychological distress
False negative test results might result in false reassurance and diagnostic delay
False positive test results might result in unnecessary diagnostic tests
Screening might result in overdiagnosis and overtreatment of disease
Screening will result in disease diagnoses earlier in life
Screening might negatively affect risk behavior

Box 1 Why costs should also be considered.

The basic economic problem is that wants are infinite, while the resources required to obtain these wants are limited. This problem, called 'scarcity', implies that choices on how to deploy resources have to – and will be – made. It is important to realize that all choices involve a trade-off. The so-called 'opportunity costs' of a choice are the benefits of the next best alternative that is forgone because of a choice being made. If these opportunity costs exceed the benefits of the choice that was made, the net result of a choice will be a loss of the outcome that one wants to achieve, and hence, should not have been made. An example: If a government only has sufficient resources to implement either CRC screening or HPV vaccination, and if the potential health effects of CRC screening exceed the potential health effects of HPV vaccination, the government should choose not to implement HPV vaccination, even though it might be very effective, as the choice to implement HPV vaccination would mean that CRC could not be implemented and, hence, affect population health.

€20,000 per QALY gained is often used; in the US thresholds of $50,000 and $100,000 per QALY gained are often used). In cost-benefit analyses the effects of screening are valued in money terms, so as to make them commensurate with costs. Therefore potentially this is the broadest form of analysis. However, measurement problems often mean that the

Table 4 Potential effects of screening on costs.

Costs
Costs of screening tests
Costs of diagnostic tests
Costs of complications of screening tests or diagnostic tests
Costs of overdiagnosis and overtreatment of cancers/ precursor stages of cancer
Savings
Savings due to the prevention of (late stage) cancer

range of effects that can be valued in money terms is fairly limited. Thus whilst in theory it is a broad form of evaluation, in practice many of the cost-benefit analyses published to date are more restricted than cost-utility or cost-effectiveness analyses.

The World Health Organization criteria for screening

Already in the late 1960s, medical officer James Maxwell Glover Wilson and clinical chemist Gunner Jungner were commissioned by the World Health Organization to write a book that sets out the principles and practice of screening for disease in a clear and simple way. [50] At that time, there were many technological advances in medicine, which made screening a topic of growing importance and controversy. Although the authors merely hoped to stimulate discussion, many still view their 10 'principles of early disease detection' (see **Box 2**) as the gold standard for the evaluation of screening.

In 2008, the criteria by Wilson and Jungner were revisited (see **Box 2**).[51] More emphasis was put on the need for evidence on the effectiveness of screening (Step 1 from the 3-step approach) and on the importance of balancing the benefits of screening against the harms (Step 2 from the 3-step approach). However, the criterion that the costs of case finding should be economically balanced in relation to expenditure on medical care as a whole (Step 3 from the 3-step approach) was abandoned.

MODELING

The need for modeling

As said before, RCTs are indispensable for evaluating screening. However, they also have their limitations. First, RCTs are relatively expensive and time consuming. As a result, the number of RCTs that have evaluated CRC screening is limited. Second, RCTs usually have a limited follow-up time. As a result, they cannot be used to determine lifetime health effects and costs, which is necessary to determine the (cost-)effectiveness of screening.

Box 2 World health organization criteria for screening.

The criteria by Wilson and Jungner (1968):

1) The condition sought should be an important health problem;
2) There should be an accepted treatment for patients with recognized disease;
3) Facilities for diagnosis and treatment should be available;
4) There should be a recognizable latent or early symptomatic stage;
5) There should be a suitable test or examination;
6) The test should be acceptable to the population;
7) The natural history of the condition, including development from latent to declared disease, should be adequately understood;
8) There should be an agreed policy on whom to treat as patients;
9) The costs of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to expenditure on medical care as a whole; and
10) Case finding should be a continuing process and not a "once and for all" project.

The revisited criteria (2008):

1) The screening program should respond to a recognized need.
2) The objectives of screening should be defined at the outset.
3) There should be a defined target population.
4) There should be scientific evidence of screening program effectiveness.
5) The program should integrate education, testing, clinical services and program management.
6) There should be quality assurance, with mechanisms to minimize potential risks of screening.
7) The program should ensure informed choice, confidentiality and respect for autonomy.
8) The program should promote equity and access to screening for the entire target population.
9) Program evaluation should be planned from the outset.
10) The overall benefits of screening should outweigh the harm.

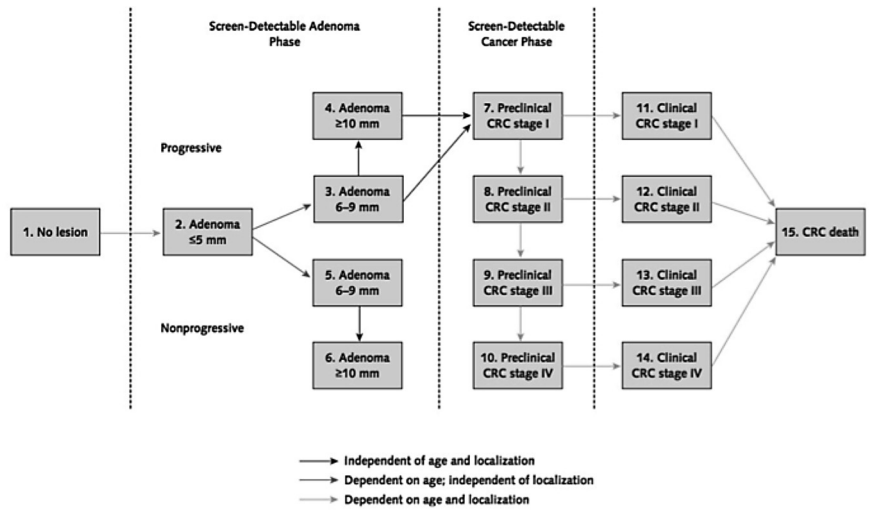
Third, the effectiveness of screening might differ from setting to setting. For example, a sigmoidoscopy screening trial in Norway showed a 63% participation rate,[24] while in the Netherlands a participation rate of only 32% was observed.[19] Finally, country-level resource demands for a certain screening program cannot easily be inferred from an RCT. To summarize: RCTs alone do not answer the question of which screening strategy is optimal given a certain context.

Decision models provide a useful tool to extrapolate evidence from RCTs and address the question of which screening strategy is optimal given local conditions with respect to CRC risk, life expectancy, costs, resource availability, and population preferences.

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Center (Rotterdam, the Netherlands). The general model structure is shown in **Figure 11**. In brief, MISCAN-Colon simulates the life histories of a large population of persons from birth to death. As each simulated person ages, one or more adenomas may develop. These adenomas can progress from small (≤5mm in diameter) to medium (6-9mm) to large size (≥10mm). Some adenomas can develop into preclinical cancer, which may progress through stages I to IV. During each stage, CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the localization of the cancer, and the person's age.

Figure 11 The general model structure of MISCAN-Colon.



Screening will alter some of the simulated life histories: some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favorable chance of survival. However, screening can also result in serious complications and overdiagnosis and overtreatment of CRC. By comparing all life histories with screening with the corresponding life histories without screening, MISCAN-Colon quantifies the effectiveness, as well as the costs of screening.

All studies in this thesis are conducted using MISCAN-Colon. For more detailed information on MISCAN-Colon we refer to the **Model Appendix** included at the end of this thesis.

AN IMPORTANT TREND IN SCREENING: PERSONALIZATION

The effectiveness of screening depends on the characteristics of the screening strategy that is applied, that is, the screening test that is used, the screening interval that is applied, and the ages at which screening is started and stopped. However, the effectiveness of screening also depends on characteristics on the individual being screened, such as sex, race, screening history, exposure to risk factors for the target disease, and comorbidity status, which together determine an individual's risk for the target disease and life-expectancy. While much effort has been put in extrapolating evidence from RCTs to determine optimal screening strategies for "average individuals" (i.e., individuals at average risk for the target disease with an average life expectancy), so far, relatively little effort has been put in specifying optimal screening strategies for individuals that differ from the "average individual" in important respects. Hence, until now, both high-risk individuals with a favorable life expectancy and low-risk individuals with an unfavorable life expectancy were recommended "average individual"-screening. This has resulted in underuse of screening (i.e., the denial of cost-effective screening) for some and overuse of screening (i.e., screening that is not cost-effective or even harmful) for others. In order to target screening at those individuals most likely to benefit, screening recommendations should be tailored according to individual patient characteristics. This process is called personalization. **Chapters 5-8** of this thesis deal with personalization of CRC screening recommendations for US elderly individuals. **Chapter 3** of this thesis deals with personalization of recommendations for colonoscopy surveillance in Dutch adenoma patients.

RESEARCH QUESTIONS AND OUTLINE OF THIS THESIS

The aim of the first study described in this thesis (**Chapter 2**) was to demonstrate how models can be used to help policy makers make better decisions about CRC screening programs. The aim of the subsequent study (**Chapter 3**) was to help Dutch clinicians make better decisions about surveillance in adenoma patients. The aim of the last 5 studies described in this thesis (**Chapters 4-8**) was to help US clinicians make better decisions about CRC screening in the wide variety of patients they encounter.

More specifically, we addressed the following questions:

- How can models be used to inform policy decisions regarding screening programs? (**Chapter 2**)
- What is the appropriate interval for a first surveillance colonoscopy in adenoma patients given the characteristics of adenomas removed and the sex and age of the patient? (**Chapter 3**)

- Is more intensive colonoscopy screening than recommended favorable for Medicare beneficiaries and, if so, is it efficient from a societal perspective? (**Chapter 4**)
- Should CRC screening be considered in elderly individuals without previous screening? If so, up to what age and which screening test should be used at what age? (**Chapter 5**)
- Why should decisions on cancer screening be personalized and how can personalized screening recommendations be derived? (**Chapter 6**)
- What is the appropriate age to stop colonoscopy screening given an individual's sex, race, screening history, background risk for CRC, and comorbidity status? (**Chapter 7**)
- What could be the effect of personalizing colonoscopy screening in the Medicare population on population health and Medicare spending? (**Chapter 8**)

Chapter 9 contains a general discussion of the studies described in this thesis.

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2

The value of models in informing resource allocation in colorectal cancer screening: the case of the Netherlands

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ABSTRACT

In May 2011, the Dutch government decided to implement a national programme for colorectal cancer (CRC) screening using biennial faecal immunochemical test screening between ages 55 and 75.(1) Decision modelling played an important role in informing this decision, as well as in the planning and implementation of the programme afterwards. In this overview, we illustrate the value of models in informing resource allocation in CRC screening using the role that decision modelling has played in the Dutch CRC screening programme as an example.

BACKGROUND

More than 1 million people worldwide are diagnosed with colorectal cancer (CRC) each year.(2) Half of these patients die from the disease, making CRC the fourth leading cause of cancer death in the world.(2) Randomised controlled trials (RCTs) have shown that screening can prevent many of these deaths by detecting CRC in an earlier stage or by detecting and removing its precursor lesion: the adenoma.(3, 4)

Although RCTs are the gold standard for determining the effectiveness of screening, they also have their limitations. First, RCTs are expensive and time consuming. As a result, the number of RCTs that have evaluated CRC screening is limited. Until now, only guaiac faecal occult blood test (gFOBT) and sigmoidoscopy screening have been evaluated by means of an RCT. Screening modalities such as the faecal immunochemical test (FIT) and colonoscopy, although expected to be more effective, have not. For the same reasons, so far, direct comparisons between different CRC screening modalities, as well as comparisons between different screening strategies using the same screening modality (except annual vs biennial gFOBT screening), have never been made. Second, RCTs usually have a limited follow-up time. As a result, they cannot be used to determine lifetime health effects and costs, which is necessary to determine the (cost-)effectiveness of screening. Third, the effectiveness of screening might differ from setting to setting. For example, a sigmoidoscopy screening trial in Norway showed a 63% attendance rate,(5) while in the Netherlands an attendance rate of only 32% was observed.(6) This will impact the comparative (cost-) effectiveness of sigmoidoscopy screening compared with FIT screening, for example. Finally, country-level resource demands for a certain screening programme cannot easily be inferred from an RCT. To summarise: RCTs alone do not answer the question of which screening strategy is optimal for a certain country. This might explain the large differences between the screening programmes that are currently implemented in the European Union (**Table 1**).

Decision models provide a useful tool to extrapolate evidence from RCTs and address the question of which screening strategy is optimal given local conditions with respect to CRC risk, life expectancy, resource availability and population preferences, which is the central question in the decision phase of a CRC screening programme. This is the phase in which models have been most frequently used. However, modelling is also valuable in the phases afterwards: during the planning, implementation and evaluation of a screening programme. In this paper, we will illustrate the value of models during the whole cycle of a screening programme using the role of the MISCAN-Colon model in the Dutch CRC screening programme as an example.

MISCAN-Colon decision model

The Dutch CRC screening programme has been co-informed by MISCAN-Colon. MISCAN-Colon is a microsimulation model for CRC developed at the Department of

Table 1 Colorectal cancer screening programmes in the European Union.

Country	Programme number	Test	Screening interval (yrs)	Start age (yrs)	Stop age (yrs)
Belgium	1	gFOBT	nd	50	74
Croatia	1	gFOBT	2	50	74
Czech Republic[1]	1	gFOBT	1	50	54
		gFOBT	2	55	nd
	2	gFOBT	1	50	54
		COL	10	55	nd
Denmark	1	gFOBT	2	50	74
Estonia	1	FOBT	2	50	74
Finland	1	gFOBT	2	60	69
France	1	gFOBT	2	50	74
Germany[1]	1	gFOBT	1	50	54
		gFOBT	2	55	nd
	2	gFOBT	1	50	54
		COL	10	55	nd
Hungary	1	FIT	2	50	70
Ireland	1	FIT	2	55	74
Italy[1]	1	FIT	2	50	70
	2	SIG	once only	58-60	58-60
Latvia	1	gFOBT	1	50	nd
Malta	1	FIT	2	60	64
Netherlands	1	FIT	2	55	75
Poland	1	COL	10	50	66
Portugal	1	FOBT	2	50	70
Slovenia	1	FIT	2	50	69
Spain	1	FIT	2	50	69
Sweden	1	gFOBT	2	60	69
UK	1	gFOBT	2	50	74

FOBT = fecal occult blood test; gFOBT = guaiac fecal occult blood test; FIT = fecal immunochemical test; SIG = sigmoidoscopy; COL = colonoscopy; nd = no data

[1] In the Czech Republic and Germany 2 screening programmes are offered from age 55 onwards: 2-yearly gFOBT and 10-yearly colonoscopy screening. In Italy 2 screening programmes are offered: 2-yearly FIT screening and a once only screening sigmoidoscopy. This table is based on data obtained from a paper by Altobelli and colleagues.[60]

Public Health of the Erasmus University Medical Center (Rotterdam, the Netherlands). The model's structure, underlying assumptions and calibration are described extensively in a standardized model profile (available at http://cisnet.cancer.gov/colorectal/profiles.html) and previous publications.(7, 8) In brief, MISCAN-Colon 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.(9, 10) More than one adenoma can occur in an individual, and each adenoma can independently develop into CRC. Adenomas may progress in size from small (≤5 mm) to medium (6–9 mm) to large (≥10 mm), and some adenomas will eventually become malignant. Cancer can progress from a localised stage I cancer to a metastasised stage IV cancer. However, during each stage, there is a probability of the cancer being diagnosed due to symptoms. At any time during the development of the disease, the process may be interrupted because the individual dies of another cause. Screening will alter some of the simulated life histories: some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favourable survival. However, screening can also result in serious complications and overdiagnosis and overtreatment of CRC (ie, the detection and treatment of cancers that would not have been diagnosed without screening). By comparing all life histories with screening with the corresponding life histories without screening, MISCAN-Colon quantifies the benefits of screening, as well as the associated harms and costs.

MISCAN-Colon was calibrated to data on the age-specific, stage-specific and localisation-specific incidence of CRC in the Netherlands(11) and the age-specific prevalence and multiplicity distribution of adenomas as observed in autopsy and colonoscopy studies.(12–22) Furthermore, MISCAN-Colon was calibrated to the reductions in CRC incidence and mortality observed in RCTs evaluating the effectiveness of screening with either gFOBTs or flexible sigmoidoscopy and showed good concordance with these trials results.(8, 23, 24)

The value of MISCAN-Colon in informing the Dutch CRC screening programme

The run-up to the Dutch CRC screening programme is characterized by a long history of decision-making and planning by various stakeholders. **Figure 1** gives an overview of the most important milestones in this process. The process and milestones as well as the role MISCAN-Colon has played in this process are described in more detail below.

Decision phase

The discussion on population screening for CRC was initiated in the Netherlands by a report of the Dutch Health Council in 2001.(25) This report not only recommended that feasibility studies and screening trials should be conducted, but also that a simulation model should be developed in order to make well-founded judgements about screening strategies. In 2003 and 2004, more landmark reports were published stressing the need to

Figure 1 Overview of the most important milestones in the run-up to the Dutch national colorectal cancer screening programme.

DECISION PHASE	2001	The Dutch Health Council publishes a signalling report stressing the need for a national CRC screening programme
	2002	More landmark reports stressing the need for a national CRC screening programme are published
	2003	
	2004	
	2005	The Netherlands Organization for Health Research and Development and the Dutch Cancer Society organise a consensus development meeting on CRC screening
	2006	Screening trials comparing FIT and gFOBT screening are conducted in the Amsterdam, Rotterdam, and Nijmegen areas. MISCAN-colon is used to determine the optimal screening strategy for the Dutch setting
	2007	
	2008	
	2009	The Dutch Health Council recommends to implement a national CRC screening programme
PLANNING PHASE	2010	The Dutch Minister of Health postpones a final decision on implementing a national CRC screening programme. A feasibility study is performed by the National Institute for Public Health and the Environment. MISCAN-Colon is used to predict the annual resource requirement for a national CRC screening programme.
	2011	The Dutch Minister of Health decides to implement a national CRC screening programme.
	2012	The infrastructure, quality assurance protocols, and communication materials for the national CRC screening programma are being prepared under supervision of the National Institute for Public Health and the Environment.
	2013	The screening programme is piloted in the Rotterdam-Rijnmond area.
IMPLEMENTATION PHASE	2014	The screening programme is rolled out nationally. Based on a MISCAN-Colon analysis, the cut-off for referral is elevated to 275ng/mL (47µg/g).
	2015	
	2016	The age range of individuals invited to the programme will be gradually expanded to 55-75.
	2017	

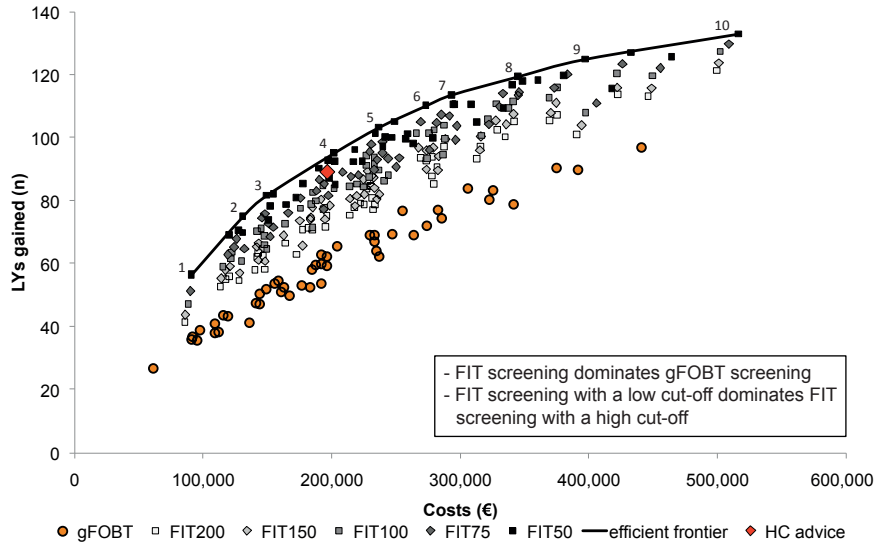
implement a national CRC screening programme.(26–28) In response to these signals, the Netherlands Organisation for Health Research and Development and the Dutch Cancer Society joined forces and organised a consensus development meeting in February 2005 in which both public health researchers (in favour of faecal occult blood test (FOBT) screening) and clinicians (in favour of endoscopy screening) participated. During this meeting, consensus was reached to perform population screening with FOBT biennially with the specific test (FIT or gFOBT), the cut-off for referral to colonoscopy in case of a FIT and the age range for screening to be decided within 2–3 years based upon further research.(29)

In 2006 and 2007, screening trials were conducted in the Amsterdam, Rotterdam and Nijmegen areas to compare attendance rates and detection rates of advanced neoplasia for different FOBTs. More than 30 000 individuals aged between 50 and 74 were randomly selected from the municipal registries and randomised to receive either a gFOBT

(Hemoccult II, Beckman Coulter, USA) or a FIT (OC-Sensor, Eiken, Japan). For the FIT, a cut-off for referral to colonoscopy of 50 ng/mL buffer (10 mg/g faeces) was applied, which allowed us to also calculate positivity and detection rates for higher cut-offs. All three regions showed higher attendance and detection rates for FIT compared with gFOBT screening.(30, 31) FIT detection rates were higher at lower cut-offs, but applying a low cut-off also required substantially more colonoscopies. What could not be estimated from the trials was whether the health benefit of detecting more advanced neoplasia justified the additional upfront costs of colonoscopies. To answer that question, MISCAN-Colon was developed and adjusted to reproduce the positivity and detection rates of gFOBT and FIT screening as observed in the Dutch screening trials. The model was subsequently used to predict the costs and effects of different screening strategies, varying the test and cut-off for referral to colonoscopy, as well as the age range and screening interval to determine the optimal FOBT screening strategy for the Dutch setting.

Figure 2 presents the outcomes of this analysis.(32) Each symbol in the graph represents a screening strategy. The higher the symbol in the graph, the more effective the strategy, the more to the right, the more expensive. The strategies lying on the top-left, which are connected by the solid line, form the efficient frontier, that is, the economically rational subset of choices.(33) Symbols lying beneath the efficient frontier represent strategies that are not as effective for the given amount of money as a point lying on the efficient frontier.

Figure 2 The costs and life-years gained associated with FOBT-based screening programmes in the Dutch setting (MISCAN-Colon predictions).1



These strategies are 'dominated' by (combinations of) other strategies. All gFOBT strategies clearly lie beneath the efficient frontier, and hence, are dominated by FIT strategies. In other words, FIT screening is more effective than gFOBT screening at lower cost. The strategies that form the efficient frontier all consist of FIT screening with a cut-off for referral to colonoscopy of 50 ng/mL (10 mg/g), indicating that screening using this low cut-off does not only result in more life-years (LYs) gained, but that the higher upfront costs of colonoscopies are also more than compensated for by higher future savings on CRC treatment.

Table 2 gives an overview of the FIT strategies on the efficient frontier. The strategy with the lowest costs per LY gained was 3-yearly screening between ages 60 and 69; next came lowering the start age to 55. The age range recommended by the Council of Europe (50–75) was not among the cost-effective options. As said, each of these strategies is an economically rational choice. Which strategy to choose depends on the willingness-to-pay for a LY gained. Generally in the Netherlands, a threshold between €20 000 and €40 000 per quality-adjusted life-year gained is used for preventive interventions. All efficient strategies resulted in costs per LY gained well beneath that threshold, making the most intensive strategy (ie, annual screening between ages 45 and 80) still an appropriate choice in the Dutch setting.

This MISCAN-Colon analysis was an important component of the 2009 Health Council advice on CRC screening.(34) The Health Council advised the Minister of Health to implement biennial FIT screening between ages 55 and 75 using a cut-off for referral to colonoscopy of 75 ng/mL (15 mg/g). Based on the outcomes of the cost-effectiveness analysis, a different age range was chosen than recommended by the European Council (ie, 55–75 instead of 50–75) and a different cut-off was chosen than recommended by the FIT manufacturer (ie, 75 ng/mL (15 mg/g) instead of 100 ng/mL (20 mg/g)). The Health Council recognised that applying a lower cut-off for referral to colonoscopy was more cost-effective and that the willingness-to-pay threshold allowed for more intensive FIT screening. However, their choice also reflects the anticipated lack of colonoscopy capacity in the Netherlands to implement such a colonoscopy-intensive programme.(34)

Planning phase

In January 2010, the Minister of Health responded to the Health Council advice. He acknowledged the value of a nationwide CRC screening programme, but felt forced to postpone a final decision on its implementation.(35) The financial climate at that time put the government in a situation of radical cost reductions, so there was no budget for a national CRC screening programme. In addition, the minister considered the anticipated shortage of colonoscopy capacity(36) an important bottleneck that needed to be resolved before a national CRC screening programme could be implemented and emphasised the need for a system for quality assurance. He therefore commissioned the National Institute for Public Health and the Environment to investigate the feasibility of a national CRC

Table 2 The efficient FIT-based screening programmes in the Dutch setting.[1]

Nr	Screening test	Cut-off value (ng/mL)	Screening interval (yrs)	Start age (yrs)	Stop age (yrs)	Number of screens (n)	Costs (€)	LYs gained (n)	Incremental costs per LY gained (€/ LY gained)
1	FIT	50	3	60	69	4	91,000	57	1,600
2	FIT	50	3	55	70	6	131,000	75	2,200
3	FIT	50	3	55	73	7	149,000	82	2,800
4	FIT	50	2	55	75	11	201,000	95	3,900
5	FIT	50	1.5	55	74.5	14	237,000	103	4,300
6	FIT	50	1.5	55	79	17	273,000	110	5,300
7	FIT	50	2	50	80	16	293,000	114	5,800
8	FIT	50	1.5	50	80	21	344,000	119	8,900
9	FIT	50	1.5	45	79.5	24	397,000	125	9,400
10	FIT	50	1	45	80	36	515,000	133	14,900

FOBT = fecal occult blood test; CRC = colorectal cancer; LY = life-year

[1]Costs and LYs gained per 1,000 individuals aged 45-80 in 2005, compared with no screening, and 3% discounted. Results for all screening programmes are shown in **Figure 2**.

screening programme in the Netherlands. The purpose of this feasibility study was to ascertain the prerequisites for a CRC screening programme and to determine how such a programme could be introduced successfully. The study should identify potential problems with implementation and suggest how to deal with them, including issues of capacity, communication, quality assurance, flexibility in the light of new technological developments, link with further diagnostics and care, as well as monitoring and evaluation.(37)

To investigate the issue of capacity, the National Institute for Public Health and the Environment requested Erasmus MC to predict the resource requirements for a national CRC screening programme using MISCAN-Colon.(38) The model was used to simulate the Dutch population from 2013 up to 2042 under the implementation of a national CRC screening programme as proposed by the Health Council, including a phased roll-out from 2013 to 2018 (**Figure 3**).

Figure 3 The phased roll-out of the Dutch national colorectal cancer screening programme as recommended by the Dutch Health Council.

	AGE (years)					
	Calendar year					
Birth year	2013	2014	2015	2016	2017	2018
1963	50	51	52	53	54	55
1962	51	52	53	54	55	56
1961	52	53	54	55	56	57
1960	53	54	55	56	57	58
1959	54	55	56	57	58	59
1958	55	56	57	58	59	60
1957	56	57	58	59	60	61
1956	57	58	59	60	61	62
1955	58	59	60	61	62	63
1954	59	60	61	62	63	64
1953	60	61	62	63	64	65
1952	61	62	63	64	65	66
1951	62	63	64	65	66	67
1950	63	64	65	66	67	68
1949	64	65	66	67	68	69
1948	65	66	67	68	69	70
1947	66	67	68	69	70	71
1946	67	68	69	70	71	72
1945	68	69	70	71	72	73
1944	69	70	71	72	73	74
1943	70	71	72	73	74	75
1942	71	72	73	74	75	76
1941	72	73	74	75	76	77
1940	73	74	75	76	77	78
1939	74	75	76	77	78	79
1938	75	76	77	78	79	80

Assuming attendance, positivity and detection rates for FIT screening with a cut-off of 75 ng/mL (15 mg/g), the model predicted the annual numbers of FIT analyses, colonoscopies, histopathological examinations, surgical procedures, as well as the numbers of CRC deaths prevented, and the costs of screening from the anticipated start of the programme in 2013 until 2042 when resource requirements and screening benefits were expected to stabilise (**Figure 4**).(37, 38) A comparison of required and available endoscopy capacity showed that in 2016, 2017 and 2018 there would be a shortage of endoscopy capacity (**Figure 5**). The professional groups proposed that increasing colonoscopy efficiency and increasing the intake to training programmes could overcome the expected shortage in these years.

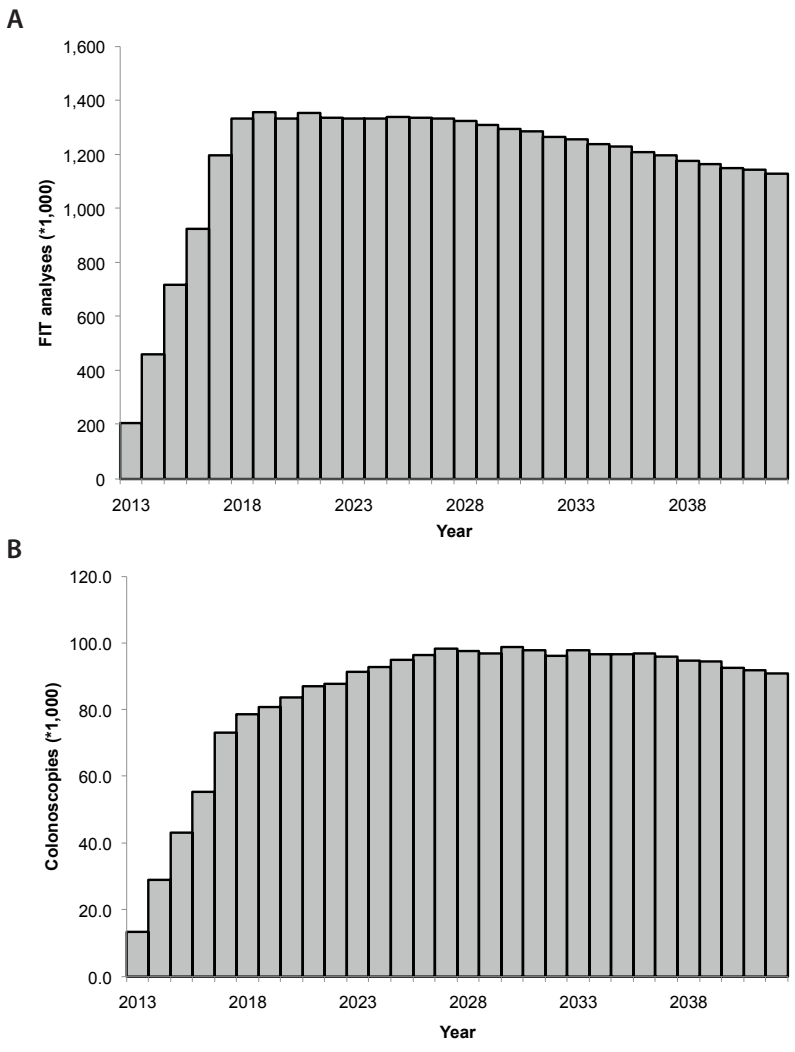
Implementation phase

Based on the outcomes of the feasibility study, a new Minister of Health decided in May 2011 to implement a national CRC screening programme in accordance with the Health Council advice.(1) After 2 years of preparation of programme infrastructure, quality assurance protocols and communication materials, the national programme was first piloted in the Rotterdam-Rijnmond area in the fall of 2013 and then gradually rolled out nationally starting in January 2014. Based on the outcome of a public tender, the FOB-Gold (Sentinel, Italy) was chosen as the preferred test. The cut-off for referral to colonoscopy was set at 88 ng/mL (15 mg/g), which corresponds with the 75 ng/mL (15 mg/g) of the OC-Sensor as recommended by the Dutch Health Council. Because of the slight delay in the start of the programme (January 2014 instead of September 2013), not only individuals aged 63, 65, 67 and 75 but also individuals aged 76 were invited in 2014, thereby assuring that these individuals, originally scheduled for screening in 2013, still got a chance to participate in screening at least once.

Because the information technology (IT)-system especially developed for the CRC screening programme allowed for continuous monitoring of the programme, attendance, positivity and detection rates could be tracked real time. The programme was an immediate success. Attendance to the programme was higher than expected (68% vs 60%),(39) as was the detection rate of advanced adenomas/CRC (4.0% vs 2.7%).(34, 40) However, the positivity rate was also considerably higher than expected (13.4% vs 6.4%) and the observed positive predictive value for detecting an advanced adenoma/CRC was substantially lower than expected (30.0% vs 42.5%).(37, 40) Consequently, colonoscopy capacity became an important bottle neck and waiting times for diagnostic colonoscopy increased.

Several steps were taken to address this problem. In a first step, positivity and detection rates at several cut-offs as observed in the national programme were compared with those observed in the Rotterdam screening trial. This comparison showed that applying the same cut-off level resulted in a higher positivity and a higher detection rate in the national programme than in the trial (**Figure 6A, B**). The correlation between the positivity rate and the detection rate, however, was strikingly similar (**Figure 6C**). Based on a

Figure 4 The resource demands (A–D), health effects (E) and costs (F) of the Dutch national colorectal cancer screening programme between 2013 and 2042 (MISCAN-Colon predictions).[1]



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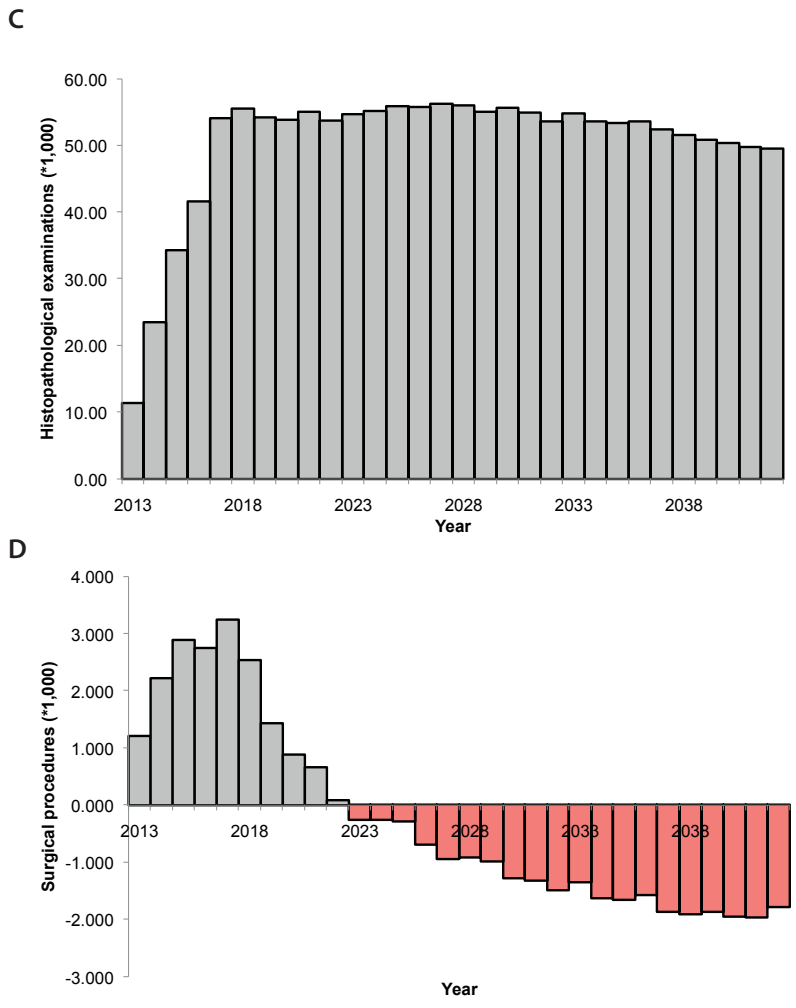

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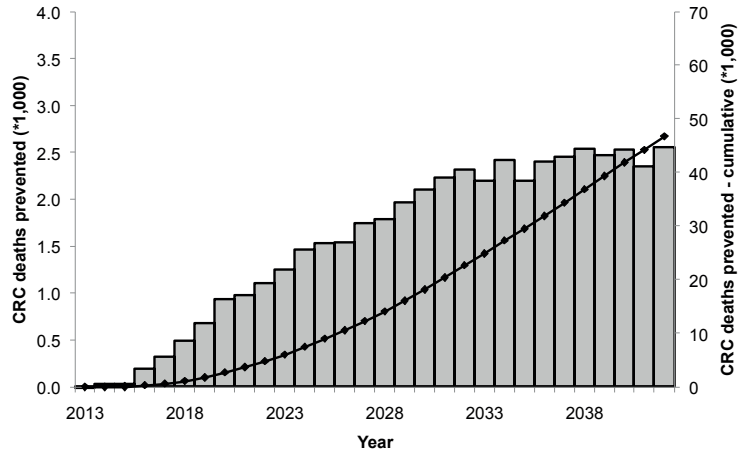

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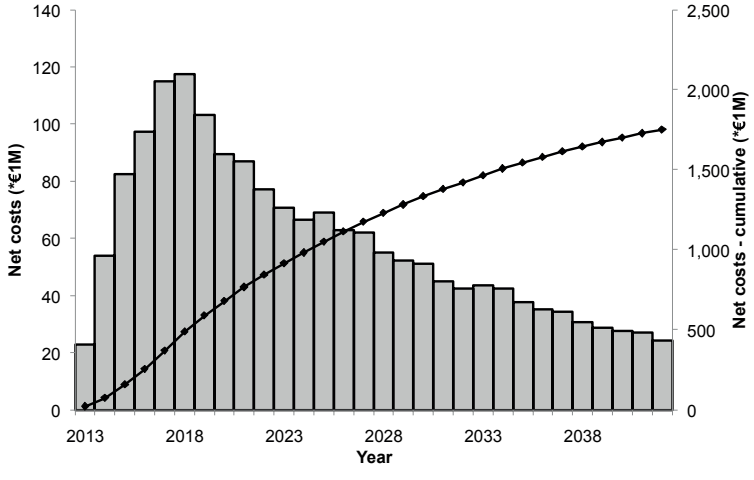


[1] We simulated the Dutch population on 1 January 2013. In this population, we simulated screening as recommended by the Dutch Health Council (ie, biennial FIT screening (OC-Sensor, Eiken, Tokyo, Japan) between ages 55 and 75 with a cut-off for referral to colonoscopy of 75 ng/mL (ie, 15 µg/g)) and applied the roll-out scheme shown in **Figure 3**. We assumed that no opportunistic screening took place before 2013 and that no such screening would take place after 2013, neither in a scenario with, nor in a scenario without a screening programme. We assumed that the age-specific risks for CRC, the age-specific risks for other cause mortality and the age-specific, stage-specific and localisation-specific CRC survival probabilities remained constant over time.

[2] We assumed that 10% of the target population will never participate in screening. In the remainder of the population, we assumed a 67% attendance rate at first invitation to arrive at a 60% overall attendance rate as observed in the Rotterdam pilot study. In those attending, we assumed an 80% attendance rate in the subsequent screening round; in those not attending, we assumed a 40% attendance rate, again arriving at an average attendance rate of 60% in the total target population. We assumed that all returned FITs could be analysed and that no one had to return multiple FITs.

[3] We considered three categories of colonoscopies: (1) diagnostic colonoscopies after a positive FIT; (2) surveillance colonoscopies after the detection and removal of adenomas and (3) colonoscopies during which CRC is clinically detected. We assumed that 85% of those with a positive FIT underwent a diagnostic colonoscopy, as was observed in the Rotterdam pilot study. Moreover, we assumed that 80% of those referred for a surveillance colonoscopy—according to a slightly de-intensified version of the 2002 Dutch surveillance guidelines—underwent this colonoscopy. Finally, we took into account that screening reduces the number of clinically detected cancers and corresponding colonoscopies.

[4] We considered three categories of histopathological examinations: (1) examinations of adenomas, cancers and hyperplastic polyps detected during a diagnostic or surveillance colonoscopy; (2) examinations of surgically removed adenomas and cancers; and (3) examinations of clinically detected cancers. We assumed that each hyperplastic polyp, adenoma and cancer detected during a diagnostic or surveillance colonoscopy resulted in one histopathological examination. Moreover, we assumed that each surgically removed adenoma and cancer resulted in one additional examination. We assumed that all cancers, except 58% of all stage I cancers, and 3.9% of all large adenomas (≥10 mm) required surgery. Finally, we took into account that screening reduces the number of clinically detected cancers and corresponding histopathological examinations.

[5] We assumed that all adenomas and cancers that had to be surgically removed required one surgical procedure. Since screening eventually prevents cancers, the screening programme results in a reduction in surgical procedures from year 2023 onward.

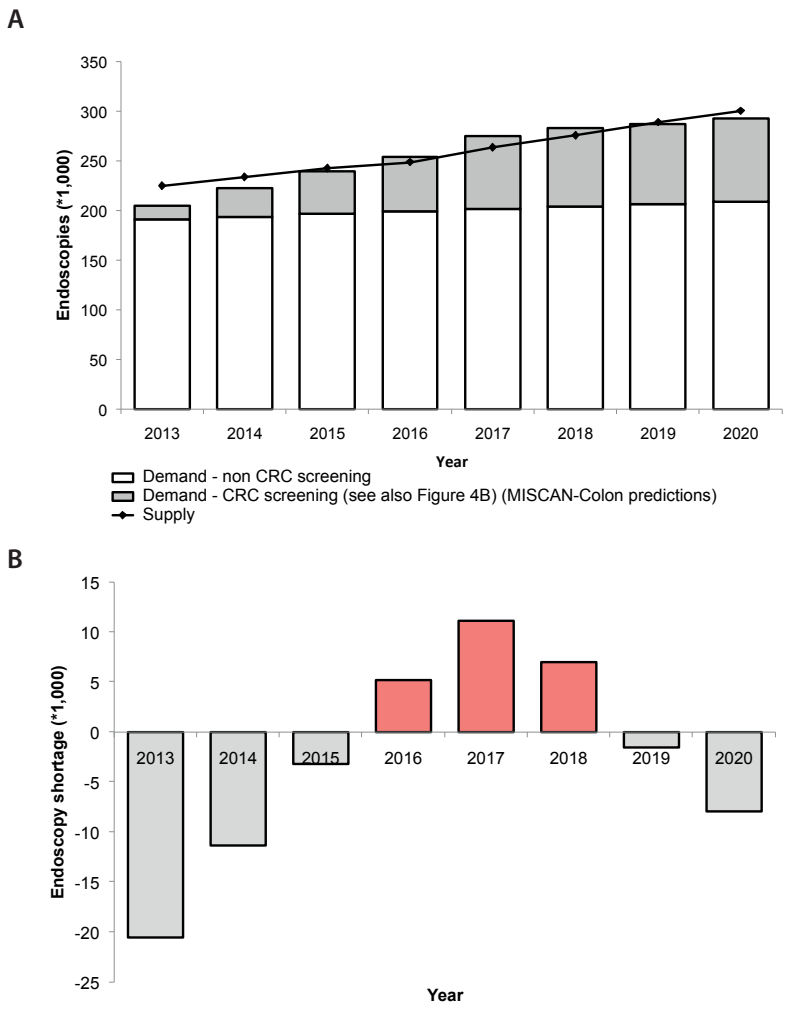
[6] We calculated costs from a third-party payer perspective and took into account the costs of (1) FITs (ie, the costs of the test kit, analysis, organisation of the programme and telephonic consultations by primary care physicians in case of a positive FIT), (2) all colonoscopies (see footnote 3), (3) all histopathological examinations (see footnote 4), (4) complications of colonoscopy, (5) surgical removal of adenomas and (6) short-term and long-term CRC care. Since screening eventually prevents cancers, the costs of the screening programme decrease over time. For all calculations, see van Veldhuizen et al.(37) for more details.

CRC, colorectal cancer; FIT, faecal immunochemical test.

MISCAN-Colon analysis in which we corrected for the difference in the age distribution between the individuals screened within the Rotterdam screening trial and the national programme, who were substantially older, it was concluded that the test characteristics corresponding to a cut-off level of 75 ng/mL (15 mg/g) as observed in the trial could be reproduced by elevating the cut-off level in the national programme to 275 ng/mL (47 mg/g).

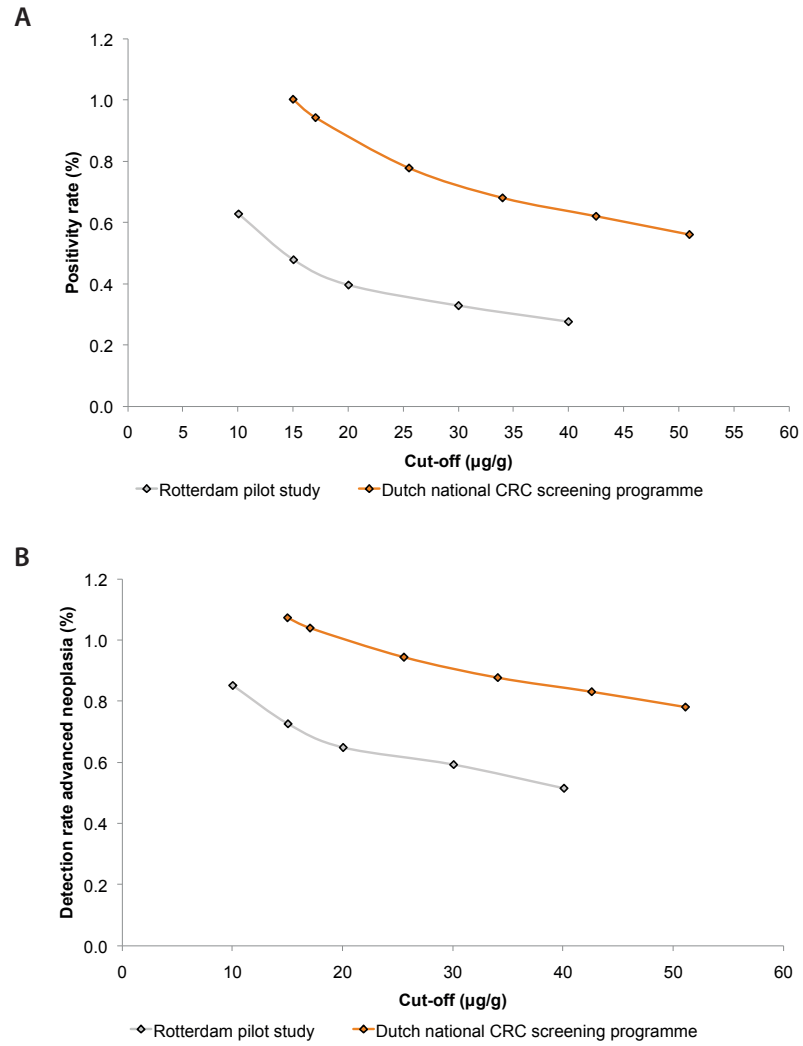
In a second step, MISCAN-Colon was used to quantify the impact of the modified roll-out, the higher-than-expected attendance and the higher-than-expected positivity rate on the anticipated colonoscopy demand for 2014 and to determine which measure could best be taken to reduce this demand. Also screening 76 year olds in 2014 was found to increase the anticipated colonoscopy demand for 2014 from 28 000 to 33 000 (**Figure 7**). The higher attendance rate further increased this demand to 38 000 colonoscopies. However, the higher positivity rate resulted in the largest increase in colonoscopy demand

Figure 5 The endoscopy demand and supply (A) and resulting endoscopy shortage (B) in the Netherlands between 2013 and 2020.[1]



[1] We simulated the Dutch national CRC screening programme applying the phased roll-out scheme shown in **Figure 3** to estimate the endoscopy demand for the Dutch national CRC screening programme (see also **Figure 4B**). The endoscopy demand outside the programme and the endoscopy supply were determined by independent management consulting firm Berenschot (http://www.berenschot.com/).
CRC, colorectal cancer.

Figure 6 The differences in the associations between the cut-off for referral to colonoscopy and the positivity rate (A); the cut-off for referral to colonoscopy and the detection rate of advanced neoplasia[1] (B); and the positivity rate and the detection rate of advanced neoplasia (C) between the Rotterdam pilot study and the first half year of the Dutch national colorectal cancer screening programme.[2]



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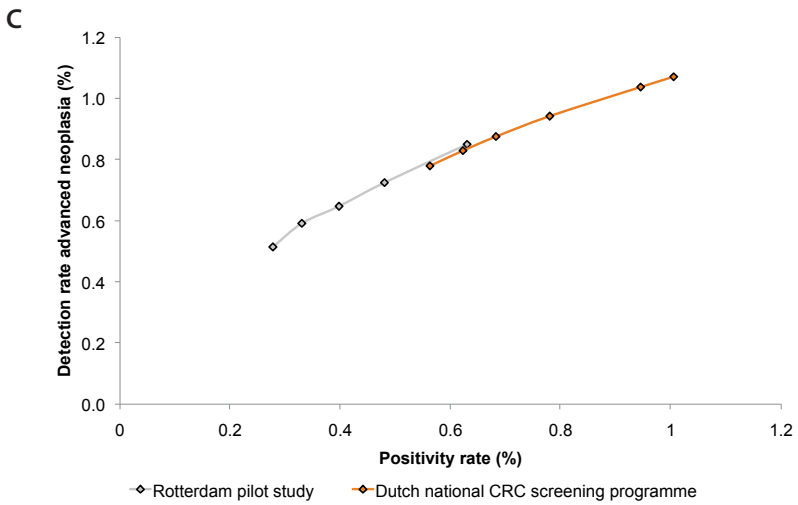


[1] The detection rate of advanced neoplasia was defined as the proportion of individuals with an analysable FIT that were diagnosed with CRC or an advanced adenoma (ie, an adenoma with a diameter ≥10 mm, and/or with a ≥25% villous component and/or high-grade dysplasia).

[2] In the Rotterdam pilot study, individuals aged between 50 and 74 were included, whereas the Dutch national CRC screening programme data are largely based on individuals aged 75 and 76. This is likely to explain part of the observed differences.

for 2014: up to 64 000 colonoscopies. By 2030, the higher attendance and positivity rate would result in a doubling of colonoscopy demand compared with what was anticipated based on the feasibility study.

To reduce colonoscopy demand for 2014, two measures could be taken: screening could be postponed until 2016 in one or more of the age groups scheduled for screening in 2014 or the cut-off for referral to colonoscopy could be elevated in all age groups. To determine which of these measures was best suited to reduce colonoscopy demand for 2014, MISCAN-Colon was used to estimate the associated loss in benefit from screening and the reductions in colonoscopy demand for 2014. The best measure to reduce colonoscopy demand for 2014 was defined as the measure that resulted in the largest reduction in colonoscopy demand per CRC death not prevented.

Postponing screening in 75-year-old and 76-year-old individuals, which implies not screening them at all, reduced colonoscopy demand by 21 and 22 colonoscopies per CRC death not prevented, respectively (**Table 3**). Postponing screening in 63-year-old, 65-year-old and 67-year-old individuals was somewhat more efficient, reducing colonoscopy

Figure 7 The cumulative effects of modifying the roll-out of the Dutch national colorectal cancer screening programme, the higher-than-expected attendance and the higher-than-expected positivity and detection rates on colonoscopy demand (MISCAN-Colon predictions).

[1] The original estimates were based on adherence, positivity and detection rates as observed in the Dutch screening trials and the original phased roll-out scheme (see Figure 3). See also Figure 4B.

[2] Because the Dutch national colorectal cancer screening programme started in 2014 instead of 2013, the roll-out of the programme was modified. In 2014, not only individuals aged 63, 65, 67 and 75 but also individuals aged 76 were invited for screening.

[3] In the first half of 2014, the attendance rate to screening was higher than expected based on the screening trials: 68% instead of 60%.

[4] In the first half of 2014, when a cut-off of 88 ng/mL (15 mg/g) was used, the positivity rate and detection rate of advanced adenomas/CRC were higher than expected based on the screening trials: 13.4% instead of 6.4% and 4.0% instead of 2.7%, respectively. The positive predictive value for detecting an advanced adenoma/CRC was substantially lower than expected: 30.0% instead of 42.5%. FIT88, FIT screening with a cut-off for referral to colonoscopy of 88 ng/mL (15 mg/g).

demand by 54, 60 and 53 colonoscopies per CRC death not prevented, respectively. However, temporarily elevating the cut-off for referral in all age groups to 275 ng/mL (47 mg/g) reduced colonoscopy demand by 68 colonoscopies per CRC death not prevented and was most efficient. The National Institute for Public Health and the Environment therefore decided to increase the cut-off for referral to colonoscopy to 275 ng/mL (47 mg/g), starting on 23 July 2014.(40) MISCAN-Colon predicted that applying this higher cut-off will result in a similar number of CRC deaths prevented as anticipated based on the 2010–2011 feasibility study (**Figure 8**).

Table 3 The efficiency of measures to reduce colonoscopy demand in 2014.[1]

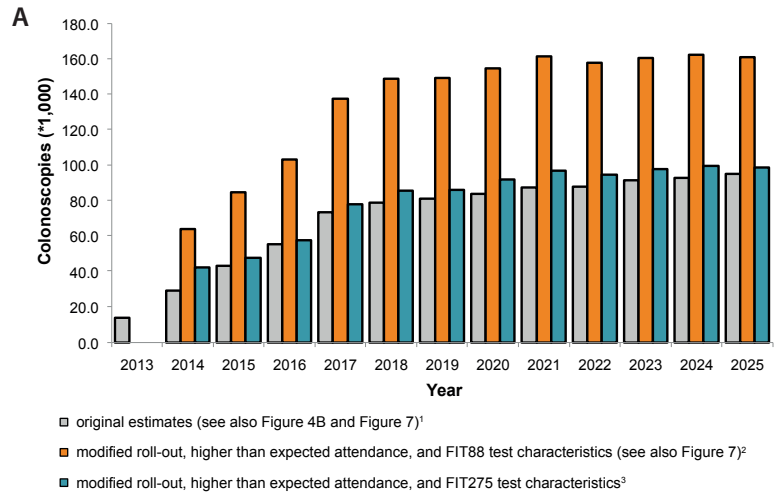
Measure	Colonoscopies performed	ΔColonoscopies performed	CRC deaths prevented	ΔCRC deaths prevented	ΔColonoscopies performed/ ΔCRC deaths prevented
no measure (see also Figure 7)	64	-	7.71	-	-
postpone screening 63 year-olds	49	14	7.44	0.26	54
postpone screening 65 year-olds	49	15	7.46	0.25	60
postpone screening 67 year-olds	48	16	7.41	0.30	53
postpone screening 75 year-olds[2]	54	9	7.26	0.45	21
postpone screening 76 year-olds[2]	55	9	7.30	0.41	22
elevate the FIT cut-off to 275 ng/mL in 2014	36	28	7.30	0.40	68

CRC = colorectal cancer; LY = life-year

[1] We modeled the cohort of screen-eligible individuals in the Netherlands in 2014 (i.e. those aged 63, 65, 67, 75, and 76 years) using the observed attendance rate in the first half of 2014 and FIT test characteristics that were calibrated to the observed positivity and detection rates in the first half of 2014 (see also the Figure 7 legend). We modeled a scenario without measures, 5 scenarios in which screening was postponed in 1 of the age-groups, and a scenario in which the cut-off for referral to colonoscopy was elevated to 275ng/mL. For each scenario, we determined the colonoscopy demand for 2014 as well as the life-time number of CRC deaths prevented. The efficiency of each measure was expressed in terms of the reduction in colonoscopy demand per CRC death that could not be prevented.

[2] Postponing screening in 75 year-old and 76 year-old individuals implies not screening them at all.

Figure 8 The effects of applying a cut-off for referral to colonoscopy of 275 ng/mL (47 mg/g) rather than 88 ng/mL (15 mg/g) from the second half of 2014 onward on the colonoscopy demand (A) and health effects (B) of the Dutch national colorectal cancer screening programme (MISCAN-Colon predictions).



[1] The original estimates were based on adherence, positivity and detection rates as observed in the Dutch screening trials and the original phased roll-out scheme (see **Figure 3**). See also **Figure 4**.

[2] In the first half of 2014, the roll-out of the screening programme was modified and attendance, positivity and detection rates for advanced adenomas/CRC were higher than expected. For details on model assumptions, see **Figure 7** legend.

[3] In this scenario, we maintained the modified roll-out and higher attendance rate; however, we simulated screening using a cut-off for referral to colonoscopy of 275 ng/mL (47 mg/g), rather than 88 ng/mL (15 µg/g) from July 1st 2014 onward. At this cut-off level, the positivity rate during the first half of 2014 would have been 7.9%, the detection rate of advanced adenomas/CRC would have been 3.0% and the positive predictive value for the detection of advanced adenomas/CRC would have been 38.3%.

CRC, colorectal cancer; FIT88, FIT screening with a cut-off for referral to colonoscopy of 88 ng/mL (15 mg/g); FIT275, FIT screening with a cut-off for referral to colonoscopy of 275 ng/mL (47 mg/g).

The increased cut-off will be sustained in 2015, but in that same year the MISCAN-Colon model will again be used to compare the increased cut-off with other measures to reduce colonoscopy requirements for the longer term: lengthening the screening interval and narrowing the age range. In addition, when data from repeat screenings become available, the model will be updated to reflect observed positivity and detection rates for repeat screenings and will again be used to predict long-term resource requirements and benefits of the Dutch CRC screening programme. In case of substantial changes in anticipated resource requirements and benefits, the impact of changes to the programme may need to be evaluated anew.

Established programme

In an established programme that has been running for several years and in which a steady state has been reached, the value of modelling may be less apparent than in the decision, planning and implementation phase of a screening programme. However, modelling also has its value in a well-established programme. In the first place, modelling can be used for evaluation of the screening programme. Is the programme working as expected? What are the expected changes in the long-term impact of the programme based on differences in anticipated and observed programme indicators? Model predictions can be used as a benchmark for observed CRC incidence and mortality to determine whether the programme is having the anticipated benefit. An important example of such work has been done using the MISCAN-breast model. Because screening resulted in a substantial increase in the incidence of breast cancer in women in the screen-eligible age range, there was considerable debate about the amount of overdiagnosis from mammography screening. Using the model, we demonstrated that this increase in incidence could be anticipated and that it is almost completely compensated for by a sharp decrease in breast cancer incidence at older age.(41)

Second, in every programme, even the well-conducted programmes, there is room for improvement. There might be regional variation in performance indicators (eg, attendance, delay in diagnostic follow-up) and modelling can be used to estimate the impact of this regional variation on long-term outcomes of the screening programme. This way the impact of reducing regional variation can be determined for each indicator and interventions can be prioritised.

Finally, medicine in general, and CRC screening in particular, is a continuously developing field and therefore a moving target. New technologies for screening may become viable such as computed tomographic colonography, stool DNA testing and serum testing. (42–44) In addition, the call for precision medicine, and in that light risk-stratified screening, is increasing.(45–47) It is important to continuously follow these developments and determine their potential benefits and harms for an existing CRC screening programme. For example, for CRC screening, it is well known that test characteristics of FIT differ by gender and age (48, 49) and using differential cut-offs for men versus women and older versus younger people has therefore been proposed. Modelling can help determine whether these calls are justified and what the potential benefit of gender-specific and age-specific FIT screening is.

DISCUSSION

This overview shows that decision modelling played an important role in the decision, planning and implementation phase of the Dutch CRC screening programme, and we believe it will continue to do so in the coming years as it has done for other programmes. On several occasions, model results have influenced the programme: in the decision phase, FIT screening was chosen over gFOBT screening, a higher age to start screening was chosen than that recommended by the Council of Europe and a lower cut-off for referral to colonoscopy was chosen than that recommended by the test's manufacturer. To remediate the higher-than-anticipated colonoscopy demand during the implementation phase, the cut-off for referral to colonoscopy was temporarily elevated. If modelling would not have been available or used, these choices might not have been made and the benefits and harms of the screening programme could have turned out less favourable than they will now.

Validation of model results

This overview describes how modelling has influenced and changed the Dutch CRC screening programme. However, the use of a model does not necessarily imply that the right decisions are made. Policymakers considering using a model to inform their (CRC) screening programmes should be aware of the considerable variation in quality of available models. An important strength of the MISCAN-Colon model is that it has been extensively validated against available evidence from RCTs and other sources, and, where necessary, adapted to accurately predict the impact of screening on CRC incidence and mortality. The good fit with trial results builds confidence in model extrapolations to the Dutch population and other settings. However, it remains very important to closely monitor the outcomes of the screening programme and compare them with model predictions. Important outcomes to consider include detection rates during repeat

screening rounds, interval cancer rates and CRC mortality. For example, to validate the decision to increase the cut-off for a positive FIT in the programme, it is important to monitor the interval cancer rate after a negative screening in the programme. This rate should not exceed the rate predicted by the model.

An important example of how model-induced changes to a screening programme were validated by subsequent monitoring of the programme comes from the Dutch cervical cancer screening programme. This programme originally offered women 3-yearly Pap smear testing between ages 35 and 53: a total of seven smears. Evaluation using the MISCAN-Cervix model indicated that spreading those seven smears over a wider age range increased the benefits of screening without increasing its costs.(50) Based on this analysis, the cervical cancer screening programme was changed to offer 5-yearly screening between ages 30 and 60. Evaluation of this change several years later showed that the 9-year incidence of cervical cancer after a negative primary smear did not increase.(51) This example clearly illustrates how modelling resulted in the right decision to change an existing screening programme.

Conditions for decision modelling

Decision modelling in the Dutch CRC screening programme could only be applied because several critical conditions were met. First of all, the availability of local data on adherence and yield of FIT screening from the Dutch screening trials was essential to reliably estimate the required capacity and long-term impact of FIT screening in the Netherlands. Second, involvement of monitoring and evaluation experts of the Department of Public Health in the development of quality indicators ensured that all indicators relevant for decision modelling were consistently collected in the screening programme. Third, the IT-system developed for the CRC screening programme allowed real-life tracking, and thus, continuous monitoring of all relevant data from the screening programme. These data timely revealed the higher-than-anticipated adherence to and referral rate of FIT screening and allowed for further diagnosis of the problem followed by the model analysis described above. However, perhaps the most important factor was the good collaboration between the Department of Public Health, the National Institute for Public Health and the Environment, and the Dutch Ministry of Health and the willingness of the decision-makers involved to consider model results.

Other examples of applications of decision modeling in screening

The Dutch CRC screening programme is not the only screening programme that has applied modelling to inform the design, planning and implementation of screening. Modelling has also been used to inform the Irish, Canadian and Australian CRC cancer screening programmes.(52–54) For Ireland, modeling showed that FIT-based screening would be very effective, but that colonoscopy demand could not be met instantly. A staggered age-based roll-out was therefore suggested to gain time to increase colonoscopy capacity to meet the programme demand.(54) In Canada, modelling was used to inform the National Committee on Colorectal Cancer Screening on the mortality reduction, cost-effectiveness and resource requirements of biennial gFOBT screening.(53) The expansion of screening ages in the Australian CRC screening programme has been accelerated to occur in the coming 5 years instead of the previously proposed 17 years after a model analysis showed that this would increase the number of CRC deaths prevented in the upcoming 40 years by almost 30%.(52) Models were also used to inform the US Preventive Services Task Force (USPSTF) recommendations for lung, breast and CRC screening(55–57) and the Centers for Medicare and Medicaid Services coverage decisions for FIT, stool DNA and CT colonography screening.(58, 59) Co-informed by modelling outcomes, the USPSTF no longer recommends routine screening for breast cancer before age 50 and after age 74, nor CRC screening after age 75 in those with an adequate screening history. Interestingly, most examples relate to the use of modelling in the decision phase of screening programmes. The potential of modelling in the planning, implementation and established programme phase is currently underused.

Conclusion

In this overview, we have shown that modelling has been very useful in the decision, planning and implementation phase of the Dutch CRC screening programme. In the absence of a decision model, decisions concerning the programme would have to be made based on expert opinion and implicit assumptions. Decision models synthesise all relevant available data and can be used to extrapolate trial findings and generate information to support optimal resource allocation in CRC screening. When using models to inform health policy, it is important to select a well-validated model for the analysis and closely monitor outcomes of the screening programme in comparison with model predictions. We believe that the MISCAN-Colon microsimulation model has contributed and will continue to contribute to the success of the Dutch CRC screening programme.

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3

Personalising colonoscopy surveillance in adenoma patients

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van Hees F*, van Heijningen EMB*, Steyerberg EW, Kuipers EJ, de Koning HJ, van Ballegooijen M, Lansdorp-Vogelaar I. Personalising colonoscopy surveillance in adenoma patients: a cost-effectiveness analysis.
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ABSTRACT

Objective: Existing guidelines for colonoscopy surveillance in adenoma patients do not consider all important predictors of advanced adenoma recurrence and might therefore be suboptimal. We aimed to determine the appropriate interval for surveillance given a patient's adenoma risk score (i.e., risk according to a previously developed and validated score chart), sex and age.

Design: Microsimulation modelling study.

Setting: The Netherlands (base-case analysis) and various other European countries (scenario analyses).

Populations: Adenoma patients characterised by their adenoma risk score (0-5), sex and age (40-80 years).

Interventions: Colonoscopy surveillance after 1-10 years and referral to biennial faecal immunochemical test (FIT) screening.

Main Outcome Measure: The appropriate interval for colonoscopy surveillance given a threshold for the willingness-to-pay per quality-adjusted life-year gained equal to the incremental cost-effectiveness ratio of biennial FIT screening.

Results: The appropriate interval for colonoscopy surveillance depended heavily on adenoma risk score and to a lesser extent on sex and age. While some patients with risk score 0 should receive a surveillance colonoscopy after 10 years, some patients with risk scores 4 and 5 should receive a surveillance colonoscopy after only 2 years. Surveillance should no longer be recommended in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older and higher risk patients aged 80 years or older. Results were robust to variations in the overall level of health care costs in a country. However, applying higher willingness-to-pay thresholds resulted in substantially more intensive surveillance recommendations, particularly in those with a low adenoma risk score.

Conclusions: The appropriate interval for colonoscopy surveillance depends heavily on a patient's adenoma risk score. Personalising surveillance using this score targets colonoscopies at those patients most likely to benefit and has great potential to increase its efficiency.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers and one of the leading causes of cancer-related death in the Western world today.[1] Screening for CRC is effective and cost-effective in reducing the morbidity and mortality caused by this disease and is therefore widely recommended.[2-6] Individuals in whom precursor lesions for CRC, so-called adenomas, are detected and removed are at increased risk for CRC compared with the general population. They are therefore recommended to undergo more intensive testing by means of colonoscopy surveillance.[7 8]

Recent studies have identified several important predictors of advanced adenoma recurrence in newly diagnosed adenoma patients.[9 10] These predictors include characteristics of the adenomas removed during colonoscopy: the presence of multiple, large (≥10mm), villous and proximal adenomas, as well as patient characteristics: male sex and older age. The identification of these predictors allows for extensive risk stratification of adenoma patients followed by careful tailoring of surveillance recommendations. However, most surveillance guidelines do not consider all relevant predictors and are thus restricted in providing tailored recommendations. The 2002 Dutch guidelines, for example, risk stratified adenoma patients based on adenoma multiplicity only.[11] Other guidelines, that do consider multiple predictors, only consider these predictors in simple combinations. The recently published European guidelines, for example, classify patients as high-risk if either 3 or more adenomas or at least one high-risk adenoma is removed (i.e., a large adenoma or an adenoma with villous histology or high grade dysplasia).[7] However, since the number of adenomas removed, large size and villous histology are independent predictors of advanced adenoma recurrence, a patient with 3 large, villous adenomas is at substantially higher risk for CRC than a patient with 3 small, non-villous adenomas, likely justifying a shorter surveillance interval in the former than in the latter patient.

In prior work, we analysed data from the Dutch Surveillance After Polypectomy (SAP) study to develop a score chart to risk-stratify newly diagnosed adenoma patients. This score chart uses information on all relevant characteristics of adenomas removed during colonoscopy and integrates this information into one measure: the adenoma risk score (range: 0-5).[12] The objective of our current study was to determine the appropriate interval for a first surveillance colonoscopy in adenoma patients given their adenoma risk score, sex and age. We performed analyses for the Netherlands (base-case analysis) and various other European countries (scenario analyses). Through this work we hope to facilitate a more personalised approach to surveillance in adenoma patients, ultimately resulting in more efficient surveillance. Since several European countries recently adopted a population based CRC screening programme,[13] and many of those participating in screening will eventually enter surveillance, a more personalised approach will become increasingly important.

METHODS

SAP Score Chart

In the SAP study, we gathered data on adenoma findings during index colonoscopy (i.e., the first colonoscopy during which adenomas were detected and removed) and at least one surveillance colonoscopy for almost 3,000 Dutch adenoma patients.[10] Based on these data, we developed a score chart that can be used to stratify newly diagnosed adenoma patients by their risk for advanced adenoma recurrence based on all relevant characteristics of adenomas removed during colonoscopy (**Figure 1**).[12] The score resulting from this chart, the 'adenoma risk score', ranges between 0 and 5. Compared with the average age- and sex-specific risks for advanced adenoma recurrence in adenoma patients, the relative risks associated with scores 0 up to 5 were 0.58, 0.95, 1.53, 2.42, 3.69 and 5.35, respectively (**Appendix 1**).

Figure 1 The SAP Score Chart: Calculating the Adenoma Risk Score.

SAP SCORE CHART

Adenoma Characteristic	Values	Points
Number of adenomas	1	0
	2 - 4	1
	≥ 5	2
Presence of at least one large adenoma (≥10mm)	no	0
	yes	1
Presence of at least one villous adenoma*	no	0
	yes	1
Presence of at least one proximal adenoma	no	0
	yes	1
Adenoma risk score†		

*An adenoma with at least 75% villous histology.

†The adenoma risk score ranges between 0 and 5.

Cost-Effectiveness Analyses

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Center (Rotterdam, the Netherlands). The model's structure, underlying assumptions and calibration are described in the **Model Appendix** included at the end of this thesis. In brief, MISCAN-Colon simulates the life histories of a large population of persons from birth to death. As each simulated person ages, one or more adenomas may develop. These adenomas can progress from small (≤5mm in diameter), to medium (6-9mm), to large size (≥10mm). Some adenomas can develop into preclinical cancer, which may progress through stages I to IV. However, during each stage, CRC may also be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage of the cancer at diagnosis, the localization of the cancer and the person's age and is based on CRC survival data observed in the South of the Netherlands, as national data were not available.[14]

Surveillance in adenoma patients will alter some of the simulated life histories. Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favourable survival. However, surveillance can also result in serious complications and overdiagnosis and overtreatment of CRC (i.e., the detection and treatment of cancers that would never have been diagnosed without surveillance). By comparing all life histories with surveillance with the corresponding life histories without surveillance, MISCAN-Colon quantifies the effectiveness of surveillance as well as the associated costs.

MISCAN-Colon was calibrated to the age-, stage- and localization-specific incidence of CRC as observed in the Netherlands before the introduction of screening (i.e., between 1999 and 2003) and the age-specific prevalence and multiplicity distribution of adenomas as observed in autopsy and colonoscopy studies.[15-26] The preclinical duration of CRC and the adenoma dwell-time were calibrated to the rates of screen-detected and interval cancers observed in randomised controlled trials evaluating screening using guaiac faecal occult blood tests and a once-only sigmoidoscopy.[27-31] We validated MISCAN-Colon against the long-term outcomes of the National Polyp Study (i.e., a study on the effectiveness of colonoscopic polypectomy).[32] The model showed good concordance with the mortality outcomes observed (**Model Appendix**).

Populations simulated

We used MISCAN-Colon to simulate the SAP population after index colonoscopy by age (40, 45, (…), 80 years) and assumed that the model correctly predicted the average risk for CRC over time for all ages (**Appendix 2**). We used these populations and the relative risks associated with adenoma risk score (score 0: 0.58, score 1: 0.95, score 2: 1.53, score 3: 2.42, score 4: 3.69 and score 5: 5.35) and sex (males: 1.14, females: 0.85) obtained from the SAP-study to simulate cohorts of 10 million adenoma patients for each combination of adenoma risk score, sex and age. Life-expectancy was based on sex-specific life-tables from 2011 obtained from Statistics Netherlands.[33]

Surveillance strategies

Within each cohort, we simulated colonoscopy surveillance with intervals ranging from every 1 up to 10 years. To increase model flexibility in simulating surveillance strategies, we allowed three stopping ages: 75, 80 and 85 years. As alternative 'surveillance' strategies,

we simulated referral to the Dutch national CRC screening programme from the first subsequent screen eligible age onwards as well as after a minimum of 10 years. Within this recently started programme, individuals are invited for biennial faecal immunochemical test (FIT) screening from age 55 up to age 75 years.[34] In all cohorts, we also simulated a comparator scenario without further testing: the 'no surveillance' scenario.

Test characteristics

The sensitivity of colonoscopy for the detection of adenomas and CRC was obtained from a systematic review on miss-rates observed in tandem colonoscopy studies and was 75% for small adenomas (≤5mm), 85% for medium-sized adenomas (6-9mm) and 95% for large adenomas (≥10mm) and CRC.[35] We assumed that 95% of all colonoscopies reached the cecum; for the remaining 5%, the reach of the procedure was assumed to be distributed uniformly over colon and rectum. We assumed that in 10% of all negative colonoscopies a hyperplastic polyp was detected and removed.

The sensitivity of FIT for the detection of adenomas and CRC was calibrated to positivity and detection rates observed in the Dutch trials on FIT screening and was 0% for small adenomas (≤5mm), 6.5% for medium-sized adenomas (6-9mm), 29.2% for large adenomas (≥10mm), 46.7% for cancers that would not have been clinically detected in their current stage and 80.3% for cancers that would have been clinically detected in their current stage.[30] The specificity of FIT was calibrated to the same data and was 97.0%.

Complications of colonoscopy

Age-specific risks for gastrointestinal and cardiovascular complications of colonoscopy requiring a hospital admission or emergency department visit were derived from a study by Warren and colleagues.[36 37] The overall risk associated with colonoscopies with polypectomy increased exponentially with age: from 2 complications per 1,000 colonoscopies at age 40 to 38 complications per 1,000 colonoscopies at age 85. Colonoscopies without polypectomy were not associated with an increased risk for complications.[36 37] We assumed that one out of every 30,000 colonoscopies involving polypectomy resulted in death.[37 38]

Utility losses

We assumed a utility loss (i.e., a loss of quality of life) equivalent to two full days of life per colonoscopy (0.0055 quality-adjusted life-years [QALYs]) and two weeks of life per complication (0.0384 QALYs). We also assigned a utility loss to each life-year (LY) with CRC care (**Table 1**).[39]

Costs

The cost-effectiveness analyses were conducted from a societal perspective. The costs of FIT include the costs of the test kit, analysis and organization of the screening programme

Table 1 The Utility Losses and Costs Associated with Surveillance in Adenoma Patients.

UTILITY LOSS, QALYs*				
Per FIT	0			
Per colonoscopy				
Without polypectomy/ biopsy	0.005			
With polypectomy/ biopsy	0.005			
Per complication of colonoscopy	0.038			
Per LY with CRC care†‡	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	0.12	0.05	0.70	0.05
Stage II CRC	0.18	0.05	0.70	0.05
Stage III CRC	0.24	0.24	0.70	0.24
Stage IV CRC	0.70	0.70	0.70	0.70
COSTS, 2012 €§				
Per FIT	38			
Per colonoscopy				
Without polypectomy/ biopsy	319			
With polypectomy/ biopsy	456			
Per complication of colonoscopy	1,627			
Per LY with CRC care†	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	17,219	686	23,787	9,353
Stage II CRC	22,177	686	23,787	8,912
Stage III CRC	26,584	686	24,889	10,235
Stage IV CRC	30,992	686	32,051	19,931

QALY = quality-adjusted life-year; FIT = fecal immunochemical test; LY = life-year; CRC = colorectal cancer
*The loss of quality of life associated with a particular event.
†Care for CRC was divided in three clinically relevant phases: the initial, continuing, and terminal care phase. The initial care phase was defined as the first 12 months after diagnosis; the terminal care phase was defined as the final 12 months of life; the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between CRC patients dying from CRC and CRC patients dying from another cause. For patients surviving less than 24 months, the final 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.
‡Utility losses for LYs with initial care were derived from a study by Ness and colleagues.[39] For LYs with continuing care for stage I and II CRC, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV CRC, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for CRC, we assumed the utility loss for LYs with initial care for stage IV CRC. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.
§Costs include patient time costs (i.e. the opportunity costs of spending time on surveillance or being treated for a complication of colonoscopy or CRC), but do not include travel costs, costs of lost productivity, and unrelated health care and non-health care costs in added years of life. We assumed that the value of patient time was equal to the mean wage rate in 2012: €15.93 per hour. We assumed that FITs, colonoscopies, and complications used up 1, 8, and 16 hours of patient time, respectively. Patient times associated with CRC care were derived from a study by Yabroff and colleagues.[43]

(**Table 1**).[40] Colonoscopy costs were obtained from a Dutch trial comparing colonoscopy with CT colonography screening.[24] The costs of complications and initial and continuing care for CRC were based on reimbursement rates obtained from the Dutch Health Care Authority.[41] The costs of terminal care for CRC were based on the average costs of CRC death obtained from a Dutch study on the disease-specific costs of the last year of life and the relationship between these costs and stage as observed in the US.[42 43] As the costs of terminal care for CRC death in the Netherlands were approximately 40% of the corresponding US costs, we assumed that the costs of terminal care for non-CRC death in CRC patients were also 40% of the corresponding US costs.[43] We adjusted all costs to reflect the 2012 level using the Dutch consumer price index and added patient time costs to all cost estimates.

Outcomes

For each cohort, we quantified the lifetime effectiveness of each surveillance strategy (i.e., CRC cases prevented, CRC deaths prevented, LYs gained and QALYs gained) as well as the lifetime costs, applying the internationally conventional 3% annual discount rate to both. We expressed the cost-effectiveness of surveillance in terms of the costs per QALY gained.

Analysis

For each cohort, we ruled out all surveillance strategies that were more costly and less effective than other strategies (i.e., simple dominance) or combinations of other strategies (i.e., extended dominance). For each remaining (i.e., efficient) strategy, we calculated the incremental cost-effectiveness ratio by comparing its costs and QALYs gained with those of the next less costly and less effective efficient strategy. We selected the appropriate surveillance strategies by applying a threshold for the willingness-to-pay per QALY gained equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (i.e., €2,600 per QALY gained given our base case assumptions) (**Appendix 3**). The surveillance intervals applied in the selected surveillance strategies are the appropriate intervals for a first surveillance colonoscopy in adenoma patients. In the results section, we present detailed results for 60-year-old females followed by an overview of the appropriate surveillance intervals for all other patients.

Sensitivity Analyses

To explore the uncertainty in the results of our base-case analysis, we repeated our analysis assuming: 1) a weaker and a stronger association between adenoma risk score and the risk for advanced adenoma recurrence (using the lower and upper boundary of the 95% confidence interval of the relative risk associated with a one point increase in adenoma risk score obtained from the SAP study, respectively (**Appendix 1**)); 2) a lower and higher average risk for advanced adenoma recurrence in adenoma patients (using the lower and upper boundary of the 95% confidence interval of the average risk for advanced adenoma

recurrence in adenoma patients obtained from the SAP study, respectively) (**Appendix 1**); 3) a less favourable average life-expectancy for adenoma patients compared with the general population (78.3 instead of 83.3 years for females and 74.7 instead of 79.7 years for males); 4) twice the base-case colonoscopy miss rates for adenomas and CRC; 5) half and twice the base-case utility losses for colonoscopies and complications; 6) half and twice the base-case costs for colonoscopies; 7) half and twice the base-case costs for CRC care; and 8) differential discounting of costs and effects as recommended by the Dutch National Health Care Institute (using a 4% and 1.5% annual discount rate, respectively). Since the cost-effectiveness of the Dutch national CRC screening programme depends on the assumptions made in the various sensitivity analyses, we adjusted the willingness-to-pay threshold that was applied accordingly (**Appendix 3**).

Scenario Analyses

To explore the generalizability of our results to other European countries, we performed scenario analyses in which we assumed a lower and a higher overall level of health care costs (using half and twice the base case costs for colonoscopies and CRC care, respectively). For all levels of health care costs (i.e., Dutch, low and high) we determined the appropriate surveillance intervals applying cost-effectiveness thresholds of €2,600, €5,000, €10,000, €20,000 and €40,000 per QALY gained.

RESULTS

The Impact of Adenoma Risk Score on the Effects and Costs of Surveillance

Surveillance was substantially more effective in patients with a high rather than a low adenoma risk score. For example, 3-yearly colonoscopy surveillance up to age 80 prevented more CRC cases (140 vs. 20 per 1,000 patients) and CRC deaths (93 vs. 13 per 1,000 patients) in 60-year-old females with risk score 5 than in 60-year-old females with risk score 0 (**Table 2**). It also resulted in more LYs gained (764 vs. 98 per 1,000 patients) and QALYs gained (858 vs. 92 per 1,000 patients). As a result of the larger savings made on CRC care, the net costs of surveillance were substantially lower in patients with a higher adenoma risk score. Among 1,000 60-year-old females, 3-yearly colonoscopy surveillance up to age 80 was associated with a net cost of €823,250 in those with risk score 0 and a net saving of €2,625,092 in those with risk score 5. Hence, each particular surveillance strategy was substantially more cost-effective in patients with a high, rather than a low adenoma risk score.

Appropriate Surveillance Intervals for 60-Year-Old Females

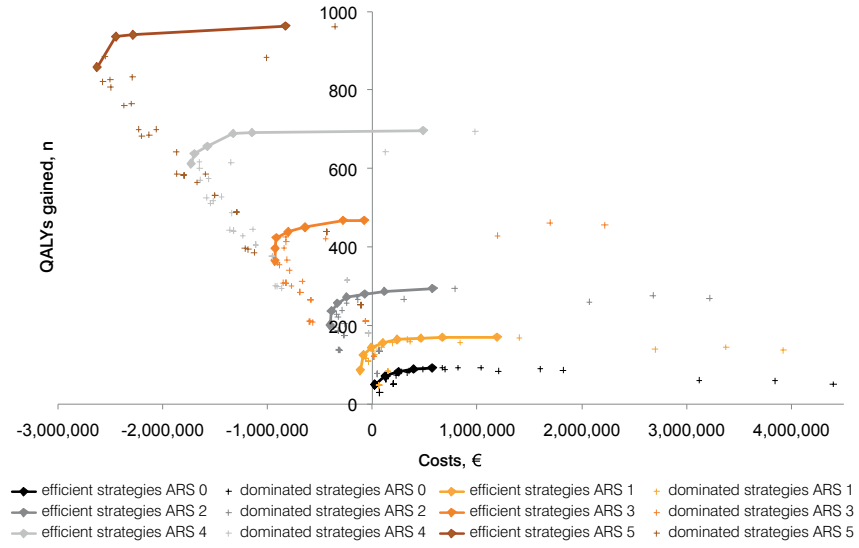
Figure 2 shows the costs and effects of all surveillance strategies in 60-year-old females with risk scores 0 up to 5. Among the efficient surveillance strategies, more intensive

Table 2 The Effectiveness and Costs of 3-Yearly Colonoscopy Surveillance Up To Age 80 in 60-year-old Females with Adenoma Risk Scores 0 up to 5.*

Adenoma Risk Score	EFFECTIVENESS, n					COSTS, €			
	CRC cases prevented	CRC Deaths Prevented	LYs Gained	Impact on Quality of Life (QALYs gained)		QALYs gained	Colonoscopies	Complications	LYs with CRC Care	Total
				Colonoscopies	Complications					
						LYs with CRC Care				
0	20	13	98	-22	-0	16	1,396,215	18,017	-590,982	**823,250**
1	34	21	163	-22	-1	26	1,422,033	23,701	-981,073	**464,661**
2	53	34	261	-22	-1	42	1,455,743	31,561	-1,553,521	**-66,217**
3	79	51	397	-21	-1	63	1,492,334	41,274	-2,332,845	**-799,237**
4	110	72	571	-21	-1	89	1,521,001	51,304	-3,265,673	**-1,693,368**
5	140	93	764	-20	-1	116	1,528,846	59,531	-4,213,468	**-2,625,092**

CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year
*Results are based on a comparison with the 'no surveillance' scenario (ie, no further testing), reported per 1,000 females, and discounted by 3% per year.

Figure 2 The Effectiveness and Costs of All Surveillance Strategies in 60-year-old Females with Adenoma Risk Scores 0 up to 5.*



*Results are based on a comparison with the 'no surveillance' scenario (i.e., no further testing), reported per 1,000 females and discounted by 3% per year.

surveillance resulted in only small increases in the effectiveness of surveillance compared with the increases in costs. In 60-year-old females with risk score 0, for example, the least effective, efficient surveillance strategy (i.e., 10-yearly colonoscopy surveillance up to age 75) resulted in 49 QALYs gained per 1,000 females (**Table 3**). The most effective, efficient surveillance strategy (i.e., 4-yearly colonoscopy surveillance up to age 80), on the other hand, resulted in 92 QALYs gained per 1,000 females: a 2-fold increase. Simultaneously, the costs of surveillance increased from €538 to €46,488 per 1,000 females: a 22-fold increase.

Based on a willingness-to-pay threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme, the appropriate surveillance strategy in 60-year-old females with adenoma risk score 0 was 10-yearly colonoscopy surveillance up to age 75 (**Table 3**). In 60-year-old females with a higher adenoma risk score more intensive surveillance strategies remained cost-effective. As a result, the appropriate interval for colonoscopy surveillance decreased from 10 years in females with risk score 0 to 7 years, 5 years, 4 years, 3 years and 2 years in those with risk scores 1 up to 5.

Table 3 The Incremental Cost-Effectiveness of All Efficient Surveillance Strategies in 60-year-old Females with Adenoma Risk Scores 0 up to 5.*

Adenoma Risk Score	Surveillance Strategy (interval, yrs (stopping age, yrs))	QALYs Gained, n	Costs, €†	Incremental Costs per QALY Gained, €
0	**10 (75)**	**49**	**26,513**	**538‡**
	9 (75)	50	28,231	4,357
	7 (75)	71	131,732	4,739
	6 (80)	82	251,780	11,337
	5 (80)	88	395,541	23,866
	4 (80)	92	573,362	46,488
1	9 (75)	85	-113,302	cost saving
	7 (75)	**123**	**-83,687**	**776‡**
	6 (80)	143	-5,379	3,996
	5 (80)	155	102,341	8,738
	4 (80)	164	242,769	16,099
	3 (80)	167	464,661	77,368
	3 (85)	169	671,107	84,041
	2 (80)	170	1,193,016	492,047
2	6(75)	201	-401,168	cost saving
	5(75)	**237**	**-384,384**	**472‡**
	5(80)	256	-328,588	2,870
	4(80)	272	-240,439	5,451
	3(80)	280	-66,217	22,122
	3(85)	286	122,246	29,822
	2(80)	294	581,276	57,199
3	5(75)	364	-927,511	cost saving
	5(80)	395	-922,363	168
	4(80)	**422**	**-910,897**	**417‡**
	3(80)	437	-799,237	7,378
	3(85)	449	-638,431	13,644
	2(80)	468	-271,927	19,955
	2(85)	468	-75,378	694,588
4	4(80)	612	-1,727,635	cost saving
	3(80)	**638**	**-1,693,368**	**1,341‡**
	3(85)	657	-1,570,667	6,502
	2(80)	689	-1,324,835	7,576

Table 3 Continued.

Adenoma Risk Score	Surveillance Strategy (interval, yrs (stopping age, yrs))	QALYs Gained, n	Costs, €†	Incremental Costs per QALY Gained, €
	2(85)	691	-1,143,723	84,042
	1(80)	697	487,378	281,496
5	3(80)	858	-2,625,092	cost saving
	2(80)	**936**	**-2,443,321**	**2,356‡**
	2(85)	940	-2,280,636	36,843
	1(80)	963	-826,352	62,305

QALY = quality-adjusted life-year

*Results are based on a comparison with the 'no surveillance scenario (ie, no further testing), reported per 1,000 females, and discounted by 3% per year.

†The costs of colonoscopies, complications, and LYs with CRC care with surveillance minus the costs of LYs with CRC care without surveillance.

‡The appropriate strategies are selected using a cost effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (ie, €2,600 per QALY gained) (**Appendix 3**).

Appropriate Surveillance Intervals for Other Adenoma Patients

In general, surveillance was more cost-effective in patients with a high, rather than a low adenoma risk score; in males compared with females; and in older compared with younger patients. As a result, the appropriate surveillance intervals in these groups were shorter (**Table 4**). The appropriate interval ranged from 10 years in some patients with adenoma risk score 0 to 2 years in some patients with adenoma risk scores 4 and 5. Referral to FIT screening was dominated by colonoscopy surveillance in all cohorts.

Surveillance was no longer cost-effective in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older and females with risk score 2 and patients with risk scores 3-5 aged 80 years or older (**Table 4**).

Sensitivity Analyses

The appropriate surveillance intervals were most sensitive to varying the costs of colonoscopies and the costs of CRC care (**Table 5**). Higher colonoscopy costs resulted in longer surveillance intervals (patients with risk score 0 should even be referred to FIT screening). Conversely, higher CRC care costs resulted in shorter surveillance intervals, particularly in those with a low adenoma risk score. The ages at which surveillance was no longer cost-effective were also sensitive to the average risk for advanced adenoma recurrence in adenoma patients, the average life expectancy of adenoma patients and the sensitivity of colonoscopy for the detection of adenomas and CRC (**Table 5**).

Table 4 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex, and Age.*

	FEMALE Age, yrs											
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	5	6	5	5	5	5	4	NS
3	4	5	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS
	MALE Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	8	7	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	2	2	2	NS

NS = no surveillance

*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening program (ie, €2,600 per QALY gained) (**Appendix 3**).

Scenario Analyses

While results were sensitive to varying the costs of either colonoscopies or CRC care, they were relatively robust to varying both costs simultaneously (i.e. the overall level of health care costs in a country) (**Table 6**). Applying higher cost-effectiveness thresholds resulted in substantially more intensive surveillance recommendations, again particularly in those with a low adenoma risk score.

Table 5 Appropriate Surveillance in Females with Adenoma Risk Scores 0 up to 5: Results of Sensitivity Analyses.*

	APPROPRIATE SURVEILLANCE INTERVAL IN 60 YEAR-OLD FEMALES, yrs						AGE AT WHICH SURVEILLANCE SHOULD NO LONGER BE RECOMMENDED, yrs					
	Adenoma Risk Score						Adenoma Risk Score					
Analysis	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Base case	**10**	**7**	**5**	**4**	**3**	**2**	**70**	**75**	**80**	**80**	**80**	**80**
1a. Weaker association adenoma risk score and risk†	9	7	5	4	4	3	70	75	80	80	80	80
1b. Stronger association adenoma risk score and risk†	10	7	5	4	3	2	65	75	80	80	80	>80
2a. Lower average risk for advanced adenoma recurrence†	10	7	6	4	4	3	65	70	80	80	80	80
2b. Higher average risk for advanced adenoma recurrence†	9	7	5	4	3	2	70	75	80	80	80	80
3. Less favourable life-expectancy for adenoma patients (-5 yrs)	9	6	5	4	3	3	65	70	75	80	80	80
4. Colonoscopy miss rates x 2	10	7	5	4	3	2	65	70	75	80	80	80
5a. Utility losses colonoscopies and complications x 0.5	10	7	5	4	3	2	70	75	80	80	80	80
5b. Utility losses colonoscopies and complications x 2	10	7	5	4	3	3	70	75	80	80	80	80
6a. Colonoscopy costs x 0.5	7	5	4	3	2	2	75	80	80	80	>80	>80
6b. Colonoscopy costs x 2	FIT10	10	7	6	4	4	65	70	75	80	80	80
7a. CRC care costs x 0.5	10	7	6	5	4	3	70	70	75	80	80	80
7b. CRC care costs x 2	7	5	4	3	2	2	70	75	80	80	80	80
8Differential discounting of costs and effects	10	6	5	4	3	2	70	75	80	80	80	80

*The appropriate surveillance intervals and ages at which surveillance should no longer be recommended were determined by applying a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening program. For the sensitivity analyses 1a, 1b, 2a, and 2b the cost-effectiveness threshold was identical to that used in the base-case analysis: €2,600 per QALY gained, for sensitivity analyses 3, 4, 5a, 5b, 6a, 6b, 7a, 7b, and 8 the incremental cost-effectiveness ratios were €5,100, €3,400, €2,600, €2,700, €1,800, €4,600, €4,100, €0, and €2,800 per QALY gained, respectively (**Appendix 3**). Red cells indicate a surveillance interval differing more than 1 year from the interval found in the base-case analysis or a stop age differing from the stop age found in the base-case analysis. For all sensitivity analyses, tables similar to **Table 4** are given in **Appendix 4**.

†The calculation of the relative risks associated with adenoma risk score 0 up to 5 in these analyses is given in **Appendix 1**.

Table 6 Appropriate Surveillance in Females with Adenoma Risk Scores 0 up to 5: Generalizability to Other European Countries.*

		APPROPRIATE SURVEILLANCE INTERVAL IN 60 YEAR-OLD FEMALES, yrs						AGE AT WHICH SURVEILLANCE SHOULD NO LONGER BE RECOMMENDED, yrs					
		Adenoma Risk Score						Adenoma Risk Score					
Economic context†	**Cost-Effectiveness Threshold Used**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
1. Country with low health care costs	€2,600 per QALY gained	7	6	5	4	3	2	70	75	80	80	80	>80
	€5,000 per QALY gained	7	5	4	3	2	2	75	80	80	80	>80	>80
	€10,000 per QALY gained	6	4	4	3	2	2	80	80	>80	>80	>80	>80
	€20,000 per QALY gained	5	4	3	2	2	2	80	>80	>80	>80	>80	>80
	€40,000 per QALY gained	4	3	2	2	2	1	80	>80	>80	>80	>80	>80
2. Country with Dutch health care costs	€2,600 per QALY gained	10	7	5	4	3	2	70	75	80	80	80	80
	€5,000 per QALY gained	7	6	5	4	3	2	70	75	80	80	80	>80
	€10,000 per QALY gained	7	5	4	3	2	2	75	80	80	>80	>80	>80
	€20,000 per QALY gained	6	4	4	2	2	2	80	80	>80	>80	>80	>80
	€40,000 per QALY gained	5	4	3	2	2	2	80	>80	>80	>80	>80	>80
3. Country with high health care costs	€2,600 per QALY gained	10	7	5	4	4	3	65	70	75	80	80	80
	€5,000 per QALY gained	10	7	5	4	3	2	70	75	80	80	80	80
	€10,000 per QALY gained	7	6	5	4	3	2	70	75	80	80	80	>80
	€20,000 per QALY gained	7	5	4	3	2	2	75	80	80	>80	>80	>80
	€40,000 per QALY gained	6	4	4	2	2	2	80	80	>80	>80	>80	>80

*For all analyses, tables similar to **Table 4** are given in **Appendix 5**.
†In a countries with low and high health care costs, the costs of colonoscopies and CRC care are assumed to be 0.5 and 2 times the base case costs, respectively.

DISCUSSION

Principal findings

Our study demonstrates that the appropriate interval for a first surveillance colonoscopy in adenoma patients depends heavily on adenoma risk score and to a lesser extent on sex and age. While some patients with risk score 0 (i.e., with 1 small (<10mm), non-villous, distal adenoma) should be recommended a surveillance colonoscopy after 10 years, some patients with risk scores 4 and 5 should be recommended a surveillance colonoscopy after only 2 years. Surveillance should no longer be recommended in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older and patients at higher risk aged 80 years or older. Results were relatively robust to the overall level of health care costs in a country. However, applying less stringent cost-effectiveness thresholds resulted in substantially more intensive surveillance recommendations, particularly in those with a low adenoma risk score.

Strengths and weaknesses

The most important strength of our study is that it provides surveillance recommendations that are carefully tailored to the individual adenoma patient. This ensures that surveillance colonoscopies are targeted at those patients most likely to benefit. The two factors that determine the benefit of surveillance are the patient's risk for CRC and life expectancy. By stratifying patients using the adenoma risk score, we assure that all adenoma findings that predict CRC risk are considered in an appropriate way. Meanwhile, MISCAN-Colon incorporates the impact of sex and age on both CRC risk and life expectancy. Another strength of our study is that we based our recommendations on a formal cost-utility analysis. Within this type of analysis all short and long term costs and health effects (both on quantity and quality of life) of an intervention are explicitly identified, measured, valued and weighed.

A limitation of our study is that it focuses on the appropriate interval for a first surveillance colonoscopy only. Although this is often considered as the most important clinical decision to be made in adenoma patients, most patients will have to undergo multiple surveillance colonoscopies over the course of their lives. To determine the appropriate intervals for subsequent surveillance colonoscopies, studies are required that quantify the risk for advanced adenoma recurrence based on finding during index colonoscopy and at least one surveillance colonoscopy. So far, only few, small studies have been conducted in this area.

Generalizability

The SAP score chart is based on data collected in Dutch adenoma patients. However, since the risk factors for advanced adenoma recurrence observed in the SAP study (as well as the magnitude of risk associated with each risk factor) were very comparable to those

found in an earlier meta-analysis of 8 North American studies,[9] we believe that the SAP score chart is a reliable instrument to risk-stratify adenoma patients in many different settings. The fact that we used a microsimulation model quantified to the Dutch clinical setting is also unlikely to severely hamper the generalizability of our results. Sensitivity analyses show that the appropriate surveillance intervals, as well as the ages to stop surveillance are relatively robust to varying the average risk for advanced adenoma recurrence in adenoma patients, while life-expectancy and CRC survival rates do not differ substantially between Western European countries. Perhaps a more serious threat to the generalizability of our results is the fact that our analysis is based on the Dutch economic setting. In our base case analysis we used Dutch cost estimates and we applied a willingness-to-pay threshold equal to the incremental cost-effectiveness ratio of the Dutch national screening programme to determine appropriate surveillance intervals. We addressed this issue by performing extensive sensitivity analyses on the costs of colonoscopies and CRC care (**Table 5**). Moreover, we performed simple scenario analyses in which we varied the overall level of health care costs (i.e. of both colonoscopies and CRC care) and determined the appropriate surveillance intervals using several higher cost-effectiveness thresholds (**Table 6**). Whereas results were sensitive to varying the costs of either colonoscopies or CRC care, they were relatively robust to varying the overall level of health care costs. Applying higher cost-effectiveness thresholds resulted in more intensive surveillance recommendations.

Comparison with existing surveillance guidelines

Our study demonstrates that existing surveillance guidelines do not consistently target colonoscopies at those patients most likely to benefit. The 2002 Dutch guidelines, for example, risk stratified adenoma patients based on adenoma multiplicity only. This implied that a 60-year-old female with 3 small, non-villous, distal adenomas was recommended colonoscopy surveillance after 3 years, while a 60-year-old female with 2 large, villous, proximal adenomas was recommended colonoscopy surveillance after 6 years.[11] However, according to the SAP score chart, the former patient has an adenoma risk score of 1, whereas the latter patient has an adenoma risk score of 4, corresponding to an almost 4-fold higher risk for CRC. Therefore, according to our study, the former patient should be recommended colonoscopy surveillance after 7 years, while the latter patient should be recommended colonoscopy surveillance after 3 years: almost the exact opposite of surveillance as recommended by the Dutch guidelines. Moreover, our study demonstrates that it is important to treat relevant adenoma characteristics as separate predictors of risk. According to the current European guidelines, for example, both a 60-year-old female with 3 small, non-villous, distal adenomas and a 60-year-old female with 5 large, villous, proximal adenomas are recommended colonoscopy surveillance after 3 years.[44] However, according to the SAP score chart, the former patient has an adenoma risk score of 1, whereas the latter patient has an adenoma risk score of 5, corresponding to an almost

6-fold higher risk for CRC. Therefore, according to our study, the former patient can be recommended a substantially longer surveillance interval (i.e. 7 instead of 3 years), whereas the latter patient should be recommended a shorter surveillance interval (i.e. 2 instead of 3 years).

Implications for clinicians

Our study demonstrates that existing guidelines for colonoscopy surveillance in adenoma patients are suboptimal and that more extensive risk stratification of adenoma patients is indicated. However, we realise that it might not be feasible to stratify adenoma patients to the level we have done in our current study. Since the appropriate surveillance intervals and stop ages are primarily affected by adenoma risk score and to a lesser extent by sex and age, one way to simplify would be to base surveillance recommendations on adenoma risk score only. This approach was chosen by the Dutch Association of Gastro-enterologists when they revisited their guidelines for colonoscopy surveillance based on results of this study in May 2013.[45] Moreover, we believe that our study is the first to demonstrate that colonoscopy surveillance should no longer be recommended in very old patients.

Future research

The benefits of surveillance in elderly adenoma patients depend heavily on a patient's life expectancy. While surveillance may no longer be cost-effective in patients with an average life expectancy, it may still be relevant in patients with a better-than-average life expectancy. Conversely, surveillance that is cost-effective in patients with an average life expectancy may not be cost-effective or even harmful, in patients with a worse-than-average life expectancy. Hence, studies are required that investigate the appropriate age to stop surveillance based on a patient's life expectancy. Moreover, modelling studies estimating the population impact of more targeted surveillance on the costs and health effects of surveillance would be useful. These studies should also assess the potential effects of more targeted surveillance guidelines on adherence to surveillance recommen-dations, which might either increase or decrease.

Conclusions

Our study demonstrates that existing guidelines for colonoscopy surveillance in adenoma patients do not consistently target colonoscopies at those patients most likely to benefit. A more personalised approach to surveillance in adenoma patients, using the adenoma risk score, targets colonoscopies at those patients most likely to benefit and has great potential to increase the efficiency of surveillance. Since several European countries recently adopted a population based CRC screening program and many of those participating in screening will eventually enter colonoscopy surveillance, a more personalised to surveillance approach will become increasingly important.

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Appendix 1 – Relative Risks Associated with Adenoma Risk Scores 0 up to 5

In the SAP study, a one-point increase in adenoma risk score corresponded with an increase in the odds for advanced adenoma recurrence of 1.688 (95% CI: 1.475 - 1.932).[12] Within the SAP study, there were 886 patients with risk score 0, 1,153 patients with risk score 1, 607 patients with risk score 2, 206 patients with risk score 3, 57 patients with risk score 4, and 5 patients with risk score 5. Hence, the average adenoma risk score in the SAP study was 1.111. This score corresponds with an odds ratio (OR) for advanced adenoma recurrence of 1. Hence, in the base case analysis, the OR corresponding with risk score x was 1.688 ^ (x - 1.111), which corresponds to 0.559, 0.943, 1.593, 2.688, 4.538, and 7.660 for risk scores 0 up to 5, respectively. To use these ORs in MISCAN-Colon, we translated them to relative risks (RRs) using the formula: RR = OR / (1 – r + (OR*r)).[46] In this formula r is the average risk for advanced adenoma recurrence observed in the SAP study, which was 0.065 (95% CI: 0.056 – 0.074). The resulting, rounded RRs for risk scores 0 up to 5 were 0.58, 0.95, 1.53, 2.42, 3.69, and 5.35, respectively. For sensitivity analyses 1a ('Weaker association adenoma risk score and risk') and 1b ('Stronger association adenoma risk score and risk'), we repeated the exercise described above using odds ratios for a one-point increase in adenoma risk score of 1.475 and 1.932, respectively. This resulted in RRs for risk scores 0 up to 5 of 0.66, 0.96, 1.38, 1.95, 2.71, and 3.69 and 0.50, 0.93, 1.71, 2.99, 4.89, and 7.30, respectively. For sensitivity analyses 2a ('Lower average risk for advanced adenoma recurrence' and 2b ('Higher average risk for advanced adenoma recurrence') we multiplied the base case RRs with 0.056 / 0.065 = 0.86 and 0.074 / 0.065 = 1.14. This resulted in RRs for risk scores 0 up to 5 of 0.50, 0.82, 1.32, 2.09, 3.18, and 4.61 and 0.66, 1.08, 1.74, 2.75, 4.20, and 6.09, respectively.

Appendix 2 – Simulation of the SAP Population at Baseline

To estimate the average age-specific risks for CRC in adenoma patients, we simulated the SAP population after index colonoscopy by age (40, 45, (…), 80 years). We were able to closely mimic the observed characteristics of the SAP population (**Appendix 2, Table 1**). The 10-year cumulative risk for CRC ranged from 0.37% in patients aged 40 years to 1.41% in patients aged 70 years (**Appendix 2, Figure 1**).

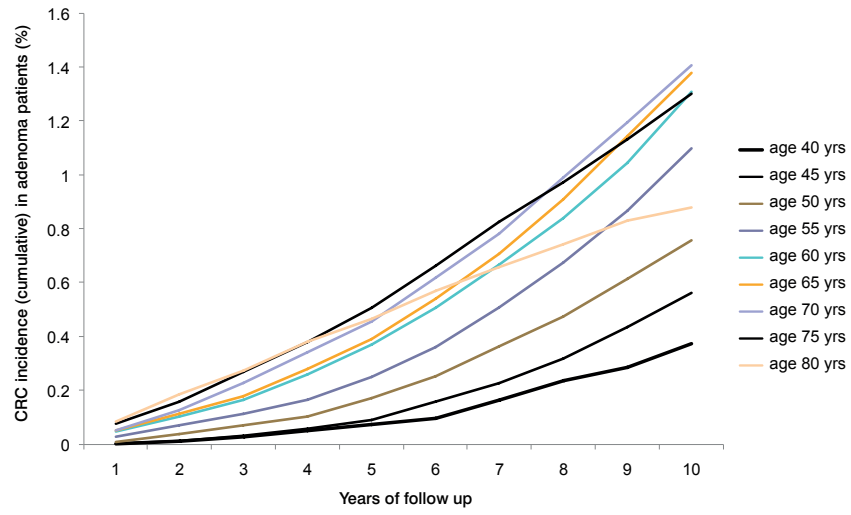
Appendix 2, Table 1 The Observed and Simulated Characteristics of the SAP Population at Baseline by Age.

Age (yrs)	Characteristics		Observed (%)	Simulated (%)	Simulated (%)/ Observed (%)
40	**Number of adenomas**	1	76.6	76.6	1.00
		2	16.2	16.2	1.00
		3	4.5	4.5	1.00
		4	0.6	0.6	1.00
		5+	1.9	1.9	1.00
	Presence of at least one	Yes	35.1	35.7	1.02
	large adenoma (≥10mm)	No	64.9	64.3	0.99
	Presence of at least one	Yes	21.4	21.8	1.02
	proximal adenoma	No	78.6	78.2	1.00
45	**Number of adenomas**	1	76.6	76.6	1.00
		2	16.5	16.5	1.00
		3	4.6	4.6	1.00
		4	0.9	0.9	1.00
		5+	1.4	1.4	1.00
	Presence of at least one	Yes	31.6	33.1	1.05
	large adenoma (≥10mm)	No	68.4	66.9	0.98
	Presence of at least one	Yes	22.7	28.8	1.27
	proximal adenoma	No	77.3	71.2	0.92
50	**Number of adenomas**	1	73.1	73.1	1.00
		2	17.6	17.6	1.00
		3	6.7	6.7	1.00
		4	1.8	1.8	1.00
		5+	0.9	0.9	1.00
	Presence of at least one	Yes	32.4	34.9	1.08
	large adenoma (≥10mm)	No	67.6	65.1	0.96
	Presence of at least one	Yes	25.3	37.5	1.48
	proximal adenoma	No	74.7	62.5	0.84
55	**Number of adenomas**	1	69.3	69.3	1.00
		2	19.8	19.8	1.00
		3	6.9	6.9	1.00
		4	1.9	1.9	1.00
		5+	2.1	2.1	1.00
	Presence of at least one	Yes	36.3	39.8	1.10
	large adenoma (≥10mm)	No	63.7	60.2	0.94
	Presence of at least one	Yes	29.3	41.9	1.43
	proximal adenoma	No	70.7	58.1	0.82
60	**Number of adenomas**	1	66.5	66.5	1.00
		2	19.9	19.9	1.00
		3	8.2	8.2	1.00
		4	2.0	2.0	1.00
		5+	3.3	3.3	1.00
	Presence of at least one	Yes	39.8	43.2	1.08
	large adenoma (≥10mm)	No	60.2	56.8	0.94
	Presence of at least one	Yes	33.0	47.7	1.44
	proximal adenoma	No	67.0	52.3	0.78
65	**Number of adenomas**	1	66.3	66.3	1.00
		2	17.9	17.9	1.00
		3	10.1	10.1	1.00
		4	2.4	2.4	1.00
		5+	3.2	3.2	1.00
	Presence of at least one	Yes	40.4	45.0	1.12
	large adenoma (≥10mm)	No	59.6	55.0	0.92
	Presence of at least one	Yes	34.2	49.5	1.45
	proximal adenoma	No	65.8	50.5	0.77
70	**Number of adenomas**	1	65.9	65.9	1.00
		2	18.3	18.3	1.00
		3	9.3	9.3	1.00
		4	3.1	3.1	1.00
		5+	3.4	3.4	1.00
	Presence of at least one	Yes	41.9	46.9	1.12
	large adenoma (≥10mm)	No	58.1	53.1	0.91
	Presence of at least one	Yes	34.8	51.5	1.48
	proximal adenoma	No	65.2	48.5	0.74
75	**Number of adenomas**	1	64.3	64.3	1.00
		2	19.6	19.6	1.00
		3	9.5	9.5	1.00

Appendix 2, Table 1 Continued.

Age (yrs)	Characteristics		Observed (%)	Simulated (%)	Simulated (%)/ Observed (%)
		4	3.5	3.5	1.00
		5+	3.2	3.2	1.00
	Presence of at least one	Yes	45.9	51.3	1.12
	large adenoma (≥10mm)	No	54.1	48.7	0.90
	Presence of at least one	Yes	36.8	55.0	1.49
	proximal adenoma	No	63.2	45.0	0.71
80	**Number of adenomas**	1	64.1	64.1	1.00
		2	20.0	20.0	1.00
		3	9.8	9.8	1.00
		4	3.1	3.1	1.00
		5+	3.1	3.1	1.00
	Presence of at least one	Yes	47.8	55.3	1.16
	large adenoma (≥10mm)	No	52.2	44.7	0.86
	Presence of at least one	Yes	40.3	56.8	1.41
	proximal adenoma	No	59.7	43.2	0.72

Appendix 2, Figure 1 The Average Cumulative Risk for CRC in Adenoma Patients by Age After Polypectomy According to MISCAN-Colon.*



* The decrease in the 10-year cumulative risk for CRC at the most advanced aged is explained by the increase in the risk for other cause mortality.

Appendix 3 – Cost-Effectiveness of the Dutch National Colorectal Cancer Screening Programme

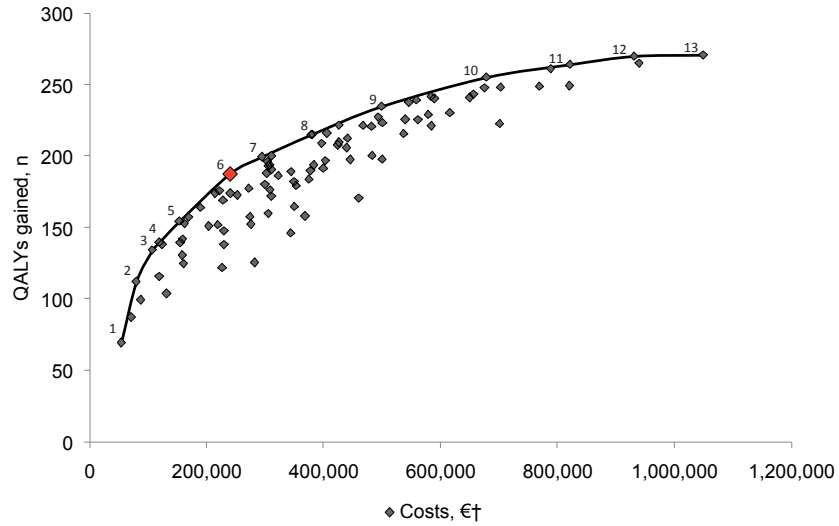
Within the Dutch national CRC screening programme, individuals are invited for biennial faecal immunochemical test (FIT) screening from age 55 up to age 75 years. The test that is used is the FOB-Gold (Sentinel, Italy) with a cut-off for referral to colonoscopy of 275ng Hb/mL buffer (47µg/g faeces). At this cut-off the test characteristics of the FOB-Gold are broadly equivalent to those observed in the Dutch pilot studies executed prior to the implementation of the national screening programme.[47]

To determine the incremental cost-effectiveness ratio of the national screening programme, we determined the costs and the QALYs gained associated with all possible screening strategies with starting ages 40, 45, 50, 55, 60 and 65 years, stopping ages 70, 75, 80 and 85 years and screening intervals 1, 1.5, 2 and 3 years (96 combinations). Test characteristics for the FOB-Gold had to be estimated based on data from the Dutch pilot studies, since data from the national screening programme were still very sparse.

Appendix 3, Figure 1 shows the costs and QALYs gained for all screening strategies given the assumptions used in the base-case analysis of the paper. As can be seen in the figure, the national screening programme is on the efficient frontier. Its incremental cost-effec-

tiveness ratio is €2,600 (**Appendix 3, Table 1**). **Appendix 3, Table 2** shows the incremental cost-effectiveness ratios of the Dutch national screening programme given the assumptions used in the various sensitivity analyses performed (**Table 5** of the paper).

Appendix 3, Figure 1 The Costs and QALYs Gained for All Screening Strategies Given the Assumptions Used in the Base-Case Analysis of the Paper.*



* Results are based on a comparison with no screening, reported per 1,000 individuals aged between 55 and 75 years in 2015 and discounted by 3% per year.
† The costs of FITs, colonoscopies, complications, and LYs with CRC care with screening minus the costs of LYs with CRC care without screening.

Appendix 3, Table 1 The Incremental Cost-Effectiveness of All Efficient Screening Strategies Given the Assumptions Used in the Base-Case Analysis of the Paper (see also **Appendix 3, Figure 1**).*

Number	Screening Strategy (starting age-stopping age (screening interval))	QALYs Gained, n	Costs, €†	Incremental Costs per QALY Gained, €
1	65-70 (3)	69	53,915	Reference
2	60-70 (3)	112	79,644	603
3	60-70 (2)	134	107,200	1,250
4	60-70 (1.5)	140	118,959	2,125
5	55-70 (2)	154	153,505	2,339
6‡	**55-75 (2)**	**188**	**239,606**	**2,593**
7	55-75 (1.5)	199	294,367	4,649
8	50-75 (1.5)	215	378,642	5,431
9	50-80 (1.5)	235	498,777	6,075
10	50-80 (1)	255	677,983	8,816
11	45-80 (1)	264	820,917	15,853
12	45-85 (1)	270	930,802	18,841
13	40-85 (1)	271	1,048,845	138,845

QALY = quality-adjusted life-year
*QALYs gained and costs are based on a comparison with no screening, reported per 1,000 individuals aged between 55 and 75 years in 2015 and discounted by 3% per year.
†The costs of FITs, colonoscopies, complications, and LYs with CRC care with screening minus the costs of LYs with CRC care without screening.
‡The Dutch national CRC screening programme.

Appendix 3, Table 2 The Incremental Cost-Effectiveness of the Dutch National CRC Screening Programme given the assumptions made in the various sensitivity analyses performed.

Analysis	Incremental Costs per QALY Gained, €
Base case	2,600
1a. Weaker association adenoma risk score and risk*	2,600
1b. Stronger association adenoma risk score and risk*	2,600
2a. Lower average risk for advanced adenoma recurrence*	2,600
2b. Average risk for advanced adenoma recurrence*	2,600
3. Less favorable life-expectancy for adenoma patients (-5 yrs)†	5,100
4. Colonoscopy miss rates x 2	3,400
5a. Utility losses colonoscopies and complications x 0.5	2,600
5b. Utility losses colonoscopies and complications x 2	2,700
6a. Colonoscopy costs x 0.5	1,800
6b. Colonoscopy costs x 2	4,600
7a. CRC care costs x 0.5	4,100
7b. CRC care costs x 2†	0
8.Differential discounting of costs and effects†	2,800

*We assumed that the assumptions made in these analyses did not change the incremental cost-effectiveness of the Dutch National CRC screening programme.
†The Dutch national CRC screening programme was dominated by other strategies in these analyses. We used the incremental cost-effectiveness ratio of the most similar strategy (in terms of the life-time number of screens) that was on the efficient frontier instead.

Appendix 4 – Sensitivity Analyses – Detailed Results

Appendix 4, Table 1 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 1a. Weaker Association Adenoma Risk Score and Risk.*

	FEMALE Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	10	10	8	9	7	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	6	6	6	5	6	5	3	NS
3	5	5	5	5	4	4	4	3	NS
4	4	4	4	4	4	4	3	3	NS
5	4	4	3	3	3	3	3	2	NS
	MALE Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	9	9	8	8	6	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	6	5	5	5	5	5	4	NS	NS
3	5	4	4	4	4	4	4	3	NS
4	4	4	4	3	3	3	3	3	NS
5	3	3	3	3	3	3	3	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 2 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 1b. Stronger Association Adenoma Risk Score and Risk.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	10	10	FIT10	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	2	NS
4	3	3	3	3	3	3	2	2	NS
5	3	3	2	2	2	2	2	2	3
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	9	NS	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	4	4	4	4	3	NS
3	4	4	3	3	3	3	3	3	NS
4	3	3	3	3	2	3	2	2	NS
5	2	2	2	2	2	2	2	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 3 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 2a. Lower Average Risk for Advanced Adenoma Recurrence.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	10	10	NS	NS	NS	NS
1	9	10	8	8	7	7	NS	NS	NS
2	6	6	6	6	6	5	5	4	NS
3	5	5	5	4	4	4	4	3	NS
4	4	4	4	4	4	3	3	2	NS
5	3	3	3	3	3	3	3	2	NS
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	9	NS	NS	NS	NS
1	8	7	7	6	6	6	NS	NS	NS
2	6	6	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	3	3	2	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 4 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 2b. Higher Average Risk for Advanced Adenoma Recurrence.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	10	10	9	9	7	NS	NS	NS
1	8	8	7	7	7	6	5	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	8	6	NS	NS	NS
1	7	6	6	6	6	5	5	NS	NS
2	5	5	4	4	4	4	4	3	NS
3	4	4	4	3	3	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	2	2	2	2	2	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 5 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 3. Less Favourable Life-Expectancy for Adenoma Patients (-5yrs)*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	9	NS	NS	NS	NS
1	7	7	7	6	6	6	NS	NS	NS
2	5	5	5	5	5	5	5	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	3	NS
5	3	3	3	3	3	3	3	2	NS
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	8	9	7	8	NS	NS	NS	NS
1	6	7	7	7	6	6	NS	NS	NS
2	5	5	5	5	4	4	4	NS	NS
3	4	4	4	4	3	3	3	NS	NS
4	3	3	3	3	3	3	3	3	NS
5	3	3	3	2	2	2	3	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 6 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 4. Colonoscopy Miss Rates x 2.*

					FEMALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	10	10	NS	NS	NS	NS
1	7	8	7	7	7	7	NS	NS	NS
2	5	5	5	5	5	4	5	NS	NS
3	4	4	4	4	4	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	2	2	2	2	2	2	NS
					MALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	9	NS	NS	NS	NS
1	6	6	6	6	6	7	NS	NS	NS
2	5	4	4	4	4	4	5	NS	NS
3	4	3	3	3	3	3	3	3	NS
4	3	3	3	3	2	3	3	2	NS
5	2	2	2	2	2	2	2	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 7 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 5a. Utility Losses Colonoscopies and Complications x 0.5.*

					FEMALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	7	7	7	7	6	NS	NS
2	6	5	5	5	5	5	5	4	NS
3	4	5	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS
					MALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	8	6	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	4	4	3	NS
3	4	4	4	4	4	4	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	2	2	2	2	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 8 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 5b. Utility Losses Colonoscopies and Complications x 2.*

					FEMALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	6	6	6	5	5	5	4	NS
3	5	5	4	4	4	4	4	3	NS
4	4	4	3	3	3	3	3	2	NS
5	3	3	3	3	3	3	2	2	NS
					MALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	8	7	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	2	2	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 9 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 6a. Colonoscopy Costs x 0.5.*

					FEMALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	7	7	7	7	7	7	5	NS	NS
1	5	5	5	5	5	4	4	3	NS
2	4	4	4	4	4	3	3	3	NS
3	3	3	3	3	3	3	3	2	NS
4	3	3	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	1	2
					MALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	6	6	6	6	6	6	4	NS	NS
1	5	4	4	4	4	4	4	3	NS
2	4	3	3	3	3	3	3	3	NS
3	3	3	3	3	2	3	2	2	NS
4	2	2	2	2	2	2	2	2	NS
5	2	2	2	2	2	2	2	1	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 10 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 6b. Colonoscopy Costs x 2.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	FIT10	FIT10	FIT10	FIT10	FIT10	NS	NS	NS	NS
1	10	10	10	9	10	8	NS	NS	NS
2	9	8	8	7	7	7	6	NS	NS
3	6	7	6	6	6	6	5	4	NS
4	5	5	5	4	4	4	4	4	NS
5	4	4	4	4	4	3	3	2	NS
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	FIT10	FIT10	FIT10	FIT10	NS	NS	NS	NS	NS
1	10	9	10	8	8	7	NS	NS	NS
2	7	7	7	6	6	6	5	NS	NS
3	6	6	5	5	5	5	5	NS	NS
4	5	5	4	4	4	4	4	3	NS
5	4	4	4	3	3	3	3	3	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 11 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 7a. CRC Care Costs x 0.5.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	10	10	FIT10	NS	NS	NS
1	9	10	8	9	7	8	NS	NS	NS
2	7	7	7	6	6	6	6	NS	NS
3	5	5	5	5	5	5	4	4	NS
4	4	4	4	4	4	3	3	4	NS
5	4	4	3	3	3	3	3	2	NS
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	9	9	NS	NS	NS	NS
1	9	8	8	8	7	7	NS	NS	NS
2	6	6	6	5	5	5	5	NS	NS
3	5	5	5	4	4	4	4	3	NS
4	4	4	4	4	4	3	3	3	NS
5	3	3	3	3	3	3	3	2	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 12 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 7b. CRC Care Costs x 2.*

					FEMALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	9	8	8	7	7	NS	NS	NS
1	6	6	6	5	5	5	5	NS	NS
2	4	5	4	4	4	4	4	3	NS
3	4	3	3	3	3	3	3	2	NS
4	3	3	3	3	2	2	2	2	NS
5	2	2	2	2	2	2	2	1	NS
					MALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	7	7	7	6	6	6	NS	NS	NS
1	5	5	5	5	5	4	4	NS	NS
2	4	4	4	4	3	4	3	3	NS
3	3	3	3	3	3	3	3	2	NS
4	2	2	2	2	2	2	2	2	NS
5	2	2	2	2	2	2	2	1	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 4, Table 13 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 8. Differential Discounting of Costs and Effects.*

					FEMALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	8	8	9	7	8	8	NS	NS	NS
1	6	6	6	6	6	6	6	NS	NS
2	5	5	5	5	4	5	5	4	NS
3	4	4	3	4	4	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	2	2	2	3	2	2	3
					MALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	8	8	8	7	7	7	NS	NS	NS
1	5	5	6	5	5	5	5	NS	NS
2	4	4	4	4	4	4	4	3	NS
3	3	3	3	3	3	3	3	3	NS
4	3	3	3	3	2	3	3	2	NS
5	2	2	2	2	2	2	2	1	NS

NS = no surveillance
*The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (**Appendix 3**).

Appendix 5 – Scenario Analyses – Detailed Results

Appendix 5, Table 1 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1a. Low Health Care Costs, Cost-Effectiveness Threshold: €2,600/QALY gained.*

					FEMALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	10	8	9	7	8	NS	NS	NS
1	7	7	7	6	6	6	6	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	2	2	3	2	2	3
					MALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	8	9	8	8	7	6	NS	NS	NS
1	6	6	6	5	5	5	5	NS	NS
2	5	4	4	4	4	4	4	3	NS
3	4	3	3	3	3	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	2	2	2	2	2	2	2	NS

NS = no surveillance

Appendix 5, Table 2 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1b. Low Health Care Costs, Cost-Effectiveness Threshold: €5,000/QALY gained.*

					FEMALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	7	7	7	7	7	7	6	NS	NS
1	5	5	5	5	5	5	5	4	NS
2	4	5	3	4	4	4	4	4	NS
3	4	3	3	3	3	3	3	2	NS
4	3	3	3	3	2	3	2	2	3
5	2	2	2	2	2	2	2	2	2
					MALE Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	7	6	6	6	6	6	6	NS	NS
1	5	5	5	5	5	4	5	4	NS
2	4	4	4	4	4	4	4	3	NS
3	3	3	3	3	3	3	3	2	NS
4	3	3	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	2	3

NS = no surveillance

Appendix 5, Table 3 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1c. Low Health Care Costs, Cost-Effectiveness Threshold: €10,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	6	6	6	6	6	6	6	4	NS
1	5	5	5	4	4	5	3	4	NS
2	4	4	3	3	4	3	3	2	3
3	3	3	3	3	3	3	2	2	3
4	2	2	2	2	2	2	2	2	2
5	2	2	2	2	2	2	2	1	2
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	4	4	4	NS
2	3	3	3	3	3	3	3	2	NS
3	3	3	3	3	2	3	2	2	3
4	2	2	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	1	2

NS = no surveillance

Appendix 5, Table 4 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1d. Low Health Care Costs, Cost-Effectiveness Threshold: €20,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	3	3	4	3
2	3	3	3	3	3	3	3	2	3
3	2	2	2	2	2	2	2	2	2
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	2	2	1	2
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	4	5	4	4	4	4	4	4	NS
1	4	3	3	3	3	3	3	4	NS
2	3	3	3	3	3	3	3	2	3
3	2	2	2	2	2	2	2	2	3
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	1	1	1	2

NS = no surveillance

Appendix 5, Table 5 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1e. Low Health Care Costs, Cost-Effectiveness Threshold: €40,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	4	4	4	4	4	5	5	4	NS
1	3	3	3	3	3	3	3	2	3
2	3	3	3	3	2	3	2	2	3
3	2	2	2	2	2	2	2	1	2
4	2	2	2	2	2	2	2	1	2
5	2	2	2	1	1	1	1	1	1
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	4	4	4	4	4	4	4	4	NS
1	3	3	3	3	3	3	3	2	3
2	2	2	2	2	2	2	2	2	3
3	2	2	2	2	2	2	2	1	2
4	2	2	2	2	2	2	2	1	2
5	1	1	1	1	1	1	1	1	1

NS = no surveillance

Appendix 5, Table 6 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2a. Dutch Health Care Costs, Cost-Effectiveness Threshold: €2,600/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	5	6	5	5	5	5	4	NS
3	4	5	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	8	7	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	2	2	2	NS

NS = no surveillance

Appendix 5, Table 7 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2b. Dutch Health Care Costs, Cost-Effectiveness Threshold: €5,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	10	8	9	7	8	NS	NS	NS
1	7	7	7	6	6	6	6	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	2	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	2	2	3	2	2	3
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	9	8	8	7	6	NS	NS	NS
1	6	6	6	5	5	5	5	NS	NS
2	5	5	4	4	4	4	4	3	NS
3	4	3	3	3	3	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	2	2	2	2	2	2	2	NS

NS = no surveillance

Appendix 5, Table 8 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2c. Dutch Health Care Costs, Cost-Effectiveness Threshold: €10,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	7	7	7	7	7	6	6	NS	NS
1	5	5	5	5	5	5	5	4	NS
2	4	5	4	4	4	4	4	4	NS
3	3	3	3	3	3	3	3	2	3
4	3	3	3	3	2	3	2	2	3
5	2	2	2	2	2	2	2	1	2
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	7	6	6	6	6	6	6	NS	NS
1	5	5	5	5	5	4	4	4	NS
2	4	4	4	4	4	4	4	3	NS
3	3	3	3	3	3	3	3	2	NS
4	3	3	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	1	3

NS = no surveillance

Appendix 5, Table 9 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2d. Dutch Health Care Costs, Cost-Effectiveness Threshold: €20,000/QALY gained.*

	FEMALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	6	6	6	6	6	6	6	4	NS
1	4	5	5	4	4	5	5	4	NS
2	4	3	3	3	4	3	3	2	3
3	3	3	3	3	2	3	2	2	3
4	2	2	2	2	2	2	2	2	2
5	2	2	2	2	2	2	2	1	2
	MALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	4	4	4	NS
2	3	3	3	3	3	3	3	2	NS
3	3	3	3	2	2	3	2	2	3
4	2	2	2	2	2	2	2	2	2
5	2	2	2	2	2	2	2	1	2

NS = no surveillance

Appendix 5, Table 10 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2e. Dutch Health Care Costs, Cost-Effectiveness Threshold: €40,000/QALY gained.*

	FEMALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	3	3	2	3
2	3	3	3	3	3	3	3	2	3
3	2	2	2	2	2	2	2	2	2
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	2	2	1	2
	MALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	4	5	4	4	4	4	4	4	NS
1	4	3	3	3	3	3	3	2	NS
2	3	3	3	3	3	3	2	2	3
3	2	2	2	2	2	2	2	2	3
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	1	1	1	2

NS = no surveillance

Appendix 5, Table 11 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3a. High Health Care Costs, Cost-Effectiveness Threshold: €2,600/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	9	10	FIT10	NS	NS	NS
1	9	9	8	8	7	7	6	NS	NS
2	6	6	6	6	5	5	5	NS	NS
3	5	5	5	4	4	4	4	3	NS
4	4	4	4	3	4	3	3	2	NS
5	3	3	3	3	3	3	3	2	NS
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	8	FIT10	NS	NS	NS
1	8	7	7	6	6	6	6	NS	NS
2	6	6	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS

NS = no surveillance

Appendix 5, Table 12 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3b. High Health Care Costs, Cost-Effectiveness Threshold: €5,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	5	6	5	5	5	5	4	NS
3	4	5	4	4	4	4	4	3	NS
4	4	4	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	8	7	6	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	2	2	2	NS

NS = no surveillance

Appendix 5, Table 13 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3c. High Health Care Costs, Cost-Effectiveness Threshold: €10,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	10	8	9	7	8	NS	NS	NS
1	7	7	7	6	6	6	6	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	2	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	2	2	2	2	2	3
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	9	9	9	8	7	6	6	NS	NS
1	6	6	6	5	5	5	5	NS	NS
2	5	5	4	4	4	4	4	3	NS
3	4	3	3	3	3	3	3	3	NS
4	3	3	3	3	3	3	2	2	NS
5	3	2	2	2	2	2	2	2	NS

NS = no surveillance

Appendix 5, Table 14 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3d. High Health Care Costs, Cost-Effectiveness Threshold: €20,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	8	7	7	7	7	6	6	NS	NS
1	5	5	5	5	5	5	5	4	NS
2	4	5	4	4	4	4	4	4	NS
3	3	3	3	3	3	3	3	2	3
4	3	3	3	3	2	3	2	2	3
5	2	2	2	2	2	2	2	1	2
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	7	6	6	6	6	6	6	NS	NS
1	5	5	5	5	5	4	4	4	NS
2	4	4	4	4	4	3	4	3	NS
3	3	3	3	3	3	3	3	2	NS
4	3	3	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	1	2

NS = no surveillance

Appendix 5, Table 15 The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3e. High Health Care Costs, Cost-Effectiveness Threshold: €40,000/QALY gained.*

					FEMALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	6	6	6	6	6	6	6	4	NS
1	4	5	5	4	4	5	5	4	NS
2	4	3	3	3	4	3	3	2	3
3	3	3	3	3	2	3	2	2	3
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	2	2	1	2
					MALE				
					Age, yrs				
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	4	4	4	NS
2	3	3	3	3	3	3	3	2	NS
3	3	3	3	2	2	3	2	2	3
4	2	2	2	2	2	2	2	2	2
5	2	2	2	2	2	2	2	1	2

NS = no surveillance

4

The Appropriateness of More Intensive Colonoscopy Screening Than Recommended in Medicare Beneficiaries

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ABSTRACT

Importance Many Medicare beneficiaries undergo more intensive colonoscopy screening than recommended. Whether this is favorable for beneficiaries and efficient from a societal perspective is uncertain.

Objective To determine whether more intensive colonoscopy screening than recommended is favorable for Medicare beneficiaries (ie, whether it results in a net health benefit) and whether it is efficient from a societal perspective (ie, whether the net health benefit justifies the additional resources required).

Design, setting, and participants Microsimulation modeling study of 65-year-old Medicare beneficiaries at average risk for colorectal cancer (CRC) and with an average life expectancy who underwent a screening colonoscopy at 55 years with negative results.

Interventions Colonoscopy screening as recommended by guidelines (ie, at 65 and 75 years) vs scenarios with a shorter screening interval (5 or 3 instead of 10 years) or in which screening was continued to 85 or 95 years.

Main outcomes and measures Quality-adjusted life-years (QALYs) gained (measure of net health benefit); additional colonoscopies required per additional QALY gained and additional costs per additional QALY gained (measures of efficiency).

Results Screening previously screened Medicare beneficiaries more intensively than recommended resulted in only small increases in CRC deaths prevented and life-years gained. In comparison, the increases in colonoscopies performed and colonoscopy-related complications experienced were large. As a result, all scenarios of more intensive screening than recommended resulted in a loss of QALYs, rather than a gain (ie, a net harm). The only exception was shortening the screening interval from 10 to 5 years, which resulted in 0.7 QALYs gained per 1000 beneficiaries. However, this scenario was inefficient because it required no less than 909 additional colonoscopies and an additional $711 000 per additional QALY gained. Results in previously unscreened beneficiaries were slightly less unfavorable, but conclusions were identical.

Conclusions and relevance Screening Medicare beneficiaries more intensively than recommended is not only inefficient from a societal perspective; often it is also unfavorable for those being screened. This study provides evidence and a clear rationale for clinicians and policy makers to actively discourage this practice.

INTRODUCTION

All guidelines for colorectal cancer (CRC) screening recommend a screening interval of 10 years for colonoscopy screening in average-risk individuals.(1-4) Moreover, the US Preventive Services Task Force and the American College of Physicians recommend against routine screening in adults older than 75 years with an adequate screening history.(1,3) Whereas CRC screening is well known to be underused by many Medicare beneficiaries,(5,6) recent studies have also demonstrated that many beneficiaries undergo more intensive colonoscopy screening than recommended:(7,8) 1 in 5 beneficiaries with a negative screening colonoscopy result undergoes a repeated screening colonoscopy within 5 years' time instead of after 10 years. Furthermore, 1 in 4 beneficiaries with a negative screening colonoscopy result at 75 years or older receives yet another screening colonoscopy at an even more advanced age. Although the reasons for these practices vary, on some occasions they are likely to result from the beneficiary's or clinician's perception that screening should occur more frequently than recommended. However, whether such practices are actually favorable for Medicare beneficiaries (ie, whether they result in a net health benefit) is uncertain: The low risk for CRC after a negative screening colonoscopy result limits the life-years (LYs) that can be gained by applying a shorter screening interval than recommended,(9-13) whereas the high risk for other-cause mortality at advanced age limits the LYs that can be gained by continuing screening beyond 75 years.(13-15) On the other hand, both practices will substantially increase the number of colonoscopies performed and, hence, the number of colonoscopy-related complications experienced.(16) Moreover, continuing screening beyond 75 years might substantially increase overdiagnosis and overtreatment of CRC (ie, the detection and treatment of cancers that would not have been diagnosed without screening). As a result, more intensive screening than recommended might be associated with a balance among benefits, burden, and harms that is unfavorable for Medicare beneficiaries: it might negatively affect health.

If more intensive screening than recommended is favorable for Medicare beneficiaries, the subsequent question is whether it is efficient from a societal perspective (ie, whether the net health benefit justifies the additional colonoscopies and financial resources required). This is important because both colonoscopy capacity and financial resources are constrained.

The objective of this study was to determine whether more intensive colonoscopy screening than recommended is favorable for Medicare beneficiaries and, if so, whether it is efficient from a societal perspective. In a prior analysis,(13) we already demonstrated that applying a screening interval of 5 instead of 10 years and continuing screening beyond 75 years result in a small increase in LYs gained relative to the increase in colonoscopies performed in those starting screening at 50 years. In this study, we extend this work by determining the net health benefit and cost-effectiveness of screening. Moreover, in our

current analysis, we focus on the Medicare population. Analyses were performed using the microsimulation model MISCAN-Colon (Microsimulation Screening Analysis–Colon).

METHODS

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Center (Rotterdam, the Netherlands). The model's structure, underlying assumptions, and calibration are described in the **Model Appendix** included at the end of this thesis. In brief, MISCAN-Colon simulates the life histories of a large population of persons from birth to death. As each simulated person ages, 1 or more adenomas may develop. These adenomas can progress from small (≤5mmin diameter) to medium (6-9 mm) to large size (≥10 mm). Some adenomas can develop into preclinical cancer, which may progress through stages I to IV. During each stage, CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the localization of the cancer, and the person's age.(17)

Screening will alter some of the simulated life histories: Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favorable chance of survival. However, screening can also result in serious complications and overdiagnosis and overtreatment of CRC. By comparing all life histories with screening with the corresponding life histories without screening, MISCAN-Colon quantifies the effectiveness and efficiency of screening.

MISCAN-Colon was calibrated to the age-specific, stage-specific, and localization-specific incidence of CRC as observed before the introduction of screening and the age-specific prevalence and multiplicity distribution of adenomas as observed in autopsy studies.(18-28) The preclinical duration of CRC and the adenoma dwell-time were calibrated to the rates of interval cancers and surveillance-detected cancers observed in randomized clinical trials evaluating screening using guaiac fecal occult blood tests and a once-only sigmoidoscopy.(29-33)

Model Inputs

Populations Simulated

We simulated 2 cohorts of 10 million 65-year-old Medicare beneficiaries. In the first cohort, all beneficiaries had received a negative screening colonoscopy result at 55 years (ie, were up-to-date with screening recommendations). In the second cohort, all beneficiaries were previously unscreened. For both cohorts, we assumed the average population risk for CRC and an average life expectancy.(34)

Screening Scenarios

In both cohorts we simulated "recommended screening" (ie, colonoscopy screening at 65 and 75 years), as well as 2 scenarios in which a shorter screening interval was applied: (1) screening at a 5-year interval (screening at 65, 70, and 75 years) and (2) screening at a 3-year interval (screening at 65, 68, 71, and 74 years). Furthermore, we simulated 2 scenarios of continued screening beyond 75 years: (1) screening up to 85 years (screening at 65, 75, and 85 years) and (2) screening up to 95 years (screening at 65, 75, 85, and 95 years). Beneficiaries in whom adenomas were removed were assumed to undergo colonoscopy surveillance according to current guidelines.(35) We assumed that surveillance continued until the diagnosis of CRC or death and that adherence to surveillance was 100%.

Test Characteristics

The sensitivity of colonoscopy for the detection of adenomas and CRC was obtained from a systematic review on miss rates observed in tandem colonoscopy studies and was 75% for small adenomas (≤5 mm in diameter), 85% for medium-sized adenomas (6-9 mm), and 95% for large adenomas (≥10 mm) and CRC.(36) We assumed that 95% of all colonoscopies reached the cecum; for the remaining 5%, the reach of the procedure was assumed to be distributed uniformly over colon and rectum.

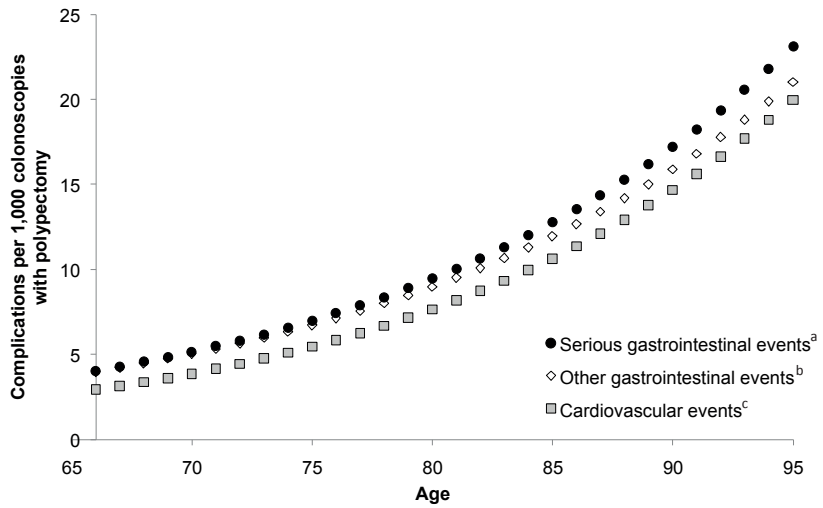
Complications of Colonoscopy

Age-specific risks for gastrointestinal and cardiovascular complications associated with colonoscopy were derived by performing additional statistical analyses on Medicare data used in a study by Warren and colleagues(16) (**Appendix 1**). According to these analyses, colonoscopies with polypectomy were associated with an excess risk for complications, whereas colonoscopies without polypectomy were not. The risks associated with colonoscopies with polypectomy increased exponentially with age (**Figure 1**). Only complications necessitating hospitalization or an emergency department visit were considered. We assumed that 1 of every 30,000 colonoscopies involving a polypectomy resulted in death.(16,37)

Utility Losses Associated With Colonoscopy Screening

We assumed a utility loss (ie, a loss of quality of life) equivalent to 2 days of life per colonoscopy (0.0055 quality-adjusted life-years [QALYs]) and 2 weeks of life per complication (0.0384 QALYs) (**Table 1**). We also assigned a utility loss to each LY with CRC care.(38) Assigning utility losses to LYs with CRC care works 2 ways: On the one hand, screening prevents cancers by the detection and removal of adenomas. This reduces LYs with CRC care and, hence, results in a gain of quality of life. On the other hand, screening results in earlier detection and overdiagnosis and overtreatment of cancers. This adds LYs with CRC care and, hence, results in a loss of quality of life. The resulting net impact on quality of life can be either positive or negative.

Figure 1 Model Inputs: Age-Specific Risks for Complications Associated With Colonoscopies With Polypectomy.



Derived by performing additional statistical analyses on Medicare data used in a study by Warren et al(16) (**Appendix 1**). Only complications necessitating hospitalization or an emergency department visit were considered.

[a] Perforations, gastrointestinal bleeding, or complications necessitating transfusions; risk per colonoscopy = 1/[exp(9.27953 − 0.06105 × Age) + 1] − 1/[exp(10.78719 − 0.06105 × Age) + 1].

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

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

Costs Associated With Colonoscopy Screening

The cost-effectiveness analyses were conducted from a societal perspective. The costs of colonoscopies were based on 2007 Medicare payment rates and copayments (**Table 1**).(41) The costs of complications were obtained from a cost-analysis of cases of unexpected hospital use after endoscopy in 2007.(42) We added patient time costs to both.(39) The costs of LYs with CRC care were obtained from an analysis of Surveillance, Epidemiology, and End Results–Medicare linked data and included patient deductibles, copayments, and patient time costs.(40) We adjusted all costs to reflect the 2013 level using the US Consumer Price Index.(43)

Assigning costs to LYs with CRC care also works 2 ways: On the one hand, screening prevents LYs with CRC care, reducing costs. On the other hand, screening adds LYs with CRC care, increasing costs. The net effect can be either a reduction or an increase in costs.

Table 1 Model Inputs: Utility Losses and Costs Associated with Colonoscopy Screening.

UTILITY LOSS (QALYs)[a]				
Per colonoscopy				
without polypectomy/ biopsy	0.005			
with polypectomy/ biopsy	0.005			
Per complication of colonoscopy	0.038			
Per LY with CRC care[b,c]	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	0.12	0.05	0.70	0.05
Stage II CRC	0.18	0.05	0.70	0.05
Stage III CRC	0.24	0.24	0.70	0.24
Stage IV CRC	0.70	0.70	0.70	0.70
COSTS (2013 US$)				
Per colonoscopy				
without polypectomy/ biopsy	887			
with polypectomy/ biopsy	1,096			
Per complication of colonoscopy	6,045			
Per LY with CRC care	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	36,683	3,050	63,809	19,176
Stage II CRC	49,234	2,870	63,555	17,279
Stage III CRC	59,759	4,021	67,041	21,457
Stage IV CRC	77,790	12,178	88,368	49,866

QALY = quality-adjusted life-year; LY = life-year; CRC = colorectal cancer

[a] The loss of quality of life associated with a particular event.

[b] Care for CRC was divided in three clinically relevant phases: the initial, continuing, and terminal care phase. The initial care phase was defined as the first 12 months after diagnosis; the terminal care phase was defined as the final 12 months of life; the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between CRC patients dying from CRC and CRC patients dying from another cause. For patients surviving less than 24 months, the final 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase. A patient diagnosed with CRC at age 65, who dies from CRC at age 70, will be in the initial care phase from age 65 up to age 66, in the continuing care phase from age 66 up to age 69, and in the terminal care phase associated with death from CRC from age 69 up to age 70. CRC patients who do not die from CRC will be in the continuing care phase from one year after diagnosis until one year before death from another cause.

[c] Utility losses for LYs with initial care were derived from a study by Ness and colleagues.(38) For LYs with continuing care for stage I and II CRC, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV CRC, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for CRC, we assumed the utility loss for LYs with initial care for stage IV CRC. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.

[d] Costs include copayments and patient time costs (i.e. the opportunity costs of spending time on screening or being treated for a complication or CRC), but do not include travel costs, costs of lost productivity, and unrelated health care and non-health care costs in added years of life. We assumed that the value of patient time was equal to the median wage rate in 2012: $16.71 per hour.(39) We assumed that colonoscopies and complications used up 8 and 16 hours of patient time, respectively. Patient time costs were already included in the estimates for the costs of LYs with CRC care obtained from a study by Yabroff and colleagues.(40)

Outcomes and Analysis

For each scenario of more intensive screening than recommended, we determined the associated increase in CRC cases prevented, CRC deaths prevented, LYs gained, LYs with CRC care prevented, colonoscopies performed, and complications experienced. Subsequently, we determined the resulting increases in QALYs gained: the net health benefit of screening. If more intensive screening resulted in a gain of QALYs, it was considered favorable for Medicare beneficiaries; if it resulted in a loss of QALYs, it was considered unfavorable. In a second step, we determined the increase in costs associated with all scenarios simulated. For those scenarios that were favorable for Medicare beneficiaries, we related the increases in colonoscopies performed and costs to the increase in QALYs gained to determine the efficiency of screening.

We present both undiscounted and discounted results (applying the conventional 3% annual discount rate for both effects and resources required). We based our conclusions on the discounted results. Screening strategies associated with an incremental cost per QALY gained exceeding $100 000 (discounted) were considered inefficient.

Sensitivity Analyses

We repeated our analysis assuming (1) half and twice the base case utility losses for colonoscopies and colonoscopy-related complications; (2) no utility loss for LYs with continuing care for CRC and a utility loss of 0.12, 0.18, 0.24, and 0.70 QALYs lost for each LY with continuing care for stage I, II, III, and IV CRC, respectively; (3) twice the base-case costs for LYs with CRC care; (4) twice the base-case miss rates for proximal adenomas and CRC (44-47); and (5) twice the base-case miss rates for all adenomas and CRCs. Furthermore, to determine the extent to which our results were driven by more intensive screening rather than more beneficiaries entering surveillance, we repeated our analysis assuming 0% adherence to surveillance. Finally, we repeated our analysis for beneficiaries at 25% higher and 25% lower risk for CRC and for beneficiaries without comorbidity and with severe comorbidity, using comorbidity status–specific life tables.(48)

RESULTS

Previously Screened Beneficiaries

Benefits, Burden, and Harms

Screening Medicare beneficiaries with a negative screening colonoscopy result at 55 years according to current guideline recommendations (ie, colonoscopy screening at 65 and 75 years) resulted in 14.1 CRC cases prevented, 7.7 CRC deaths prevented, and 63.1 LYs gained per 1,000 beneficiaries, compared with no screening (ie, a mean of 23.0 days per beneficiary) (**Figure 2A-C**). Moreover, recommended screening prevented 37.5 LYs with CRC care per 1,000 beneficiaries (**Figure 2D**). To achieve this effect, 2,131 colonoscopies had to be performed, causing 8.3 complications (**Figure 2E and F**).

Figure 2 Increases in Benefits, Burden, and Harms Associated With More Intensive Colonoscopy Screening Than Recommended in Medicare Beneficiaries With a Negative Screening Colonoscopy Result at 55 Years

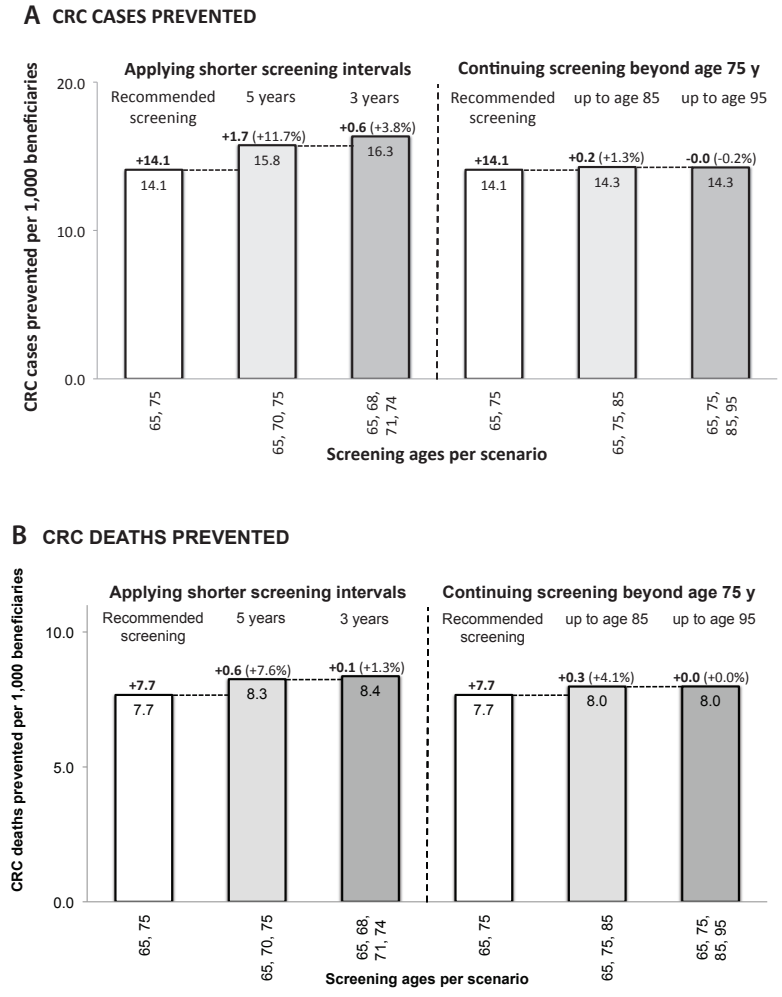
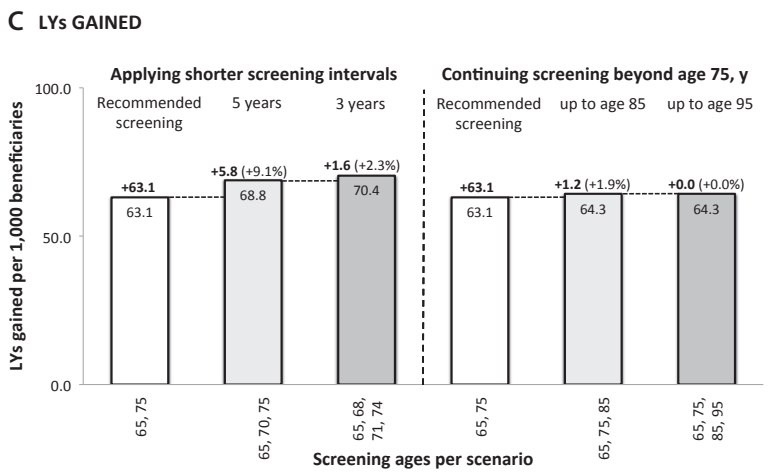


Figure 2 Continued.



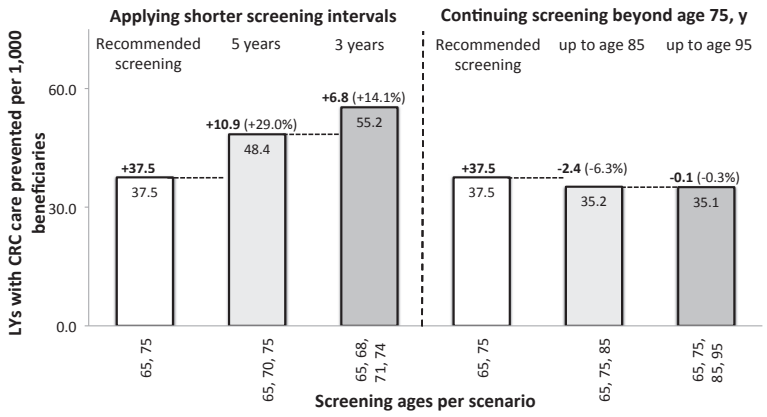
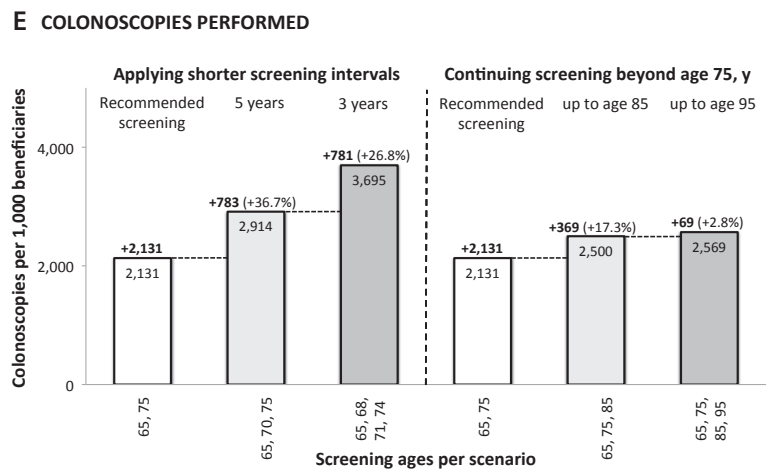
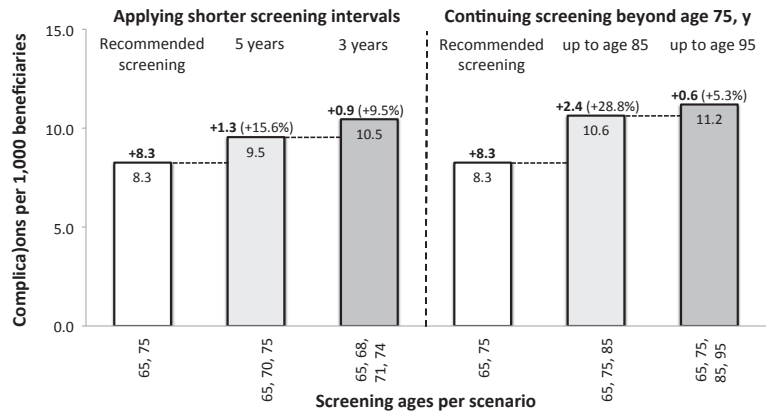


Figure 2 Continued.





Numbers are per 1,000 beneficiaries and undiscounted.
CRC indicates colorectal cancer; LY, life-year.
[a] For each scenario, the distribution of additional LYs with CRC care prevented over the different phases of care and stages of CRC is given in **Appendix 2**.
[b] Only complications necessitating hospitalization or an emergency department visit were considered.

Compared with screening once every 10 years, screening every 5 years resulted in 1.7 additional CRC cases prevented, 0.6 additional CRC deaths prevented, and 5.8 additional LYs gained per 1,000 beneficiaries (ie, a mean of 2.1 additional days of life per beneficiary). Moreover, screening every 5 years prevented 10.9 additional LYs with CRC care per 1,000 beneficiaries. To achieve this relatively small added benefit, 783 additional colonoscopies had to be performed, causing 1.3 additional complications. Continuing screening up to 85 instead of 75 years resulted in even fewer additional CRC cases prevented, CRC deaths prevented, and LYs gained: 0.2, 0.3, and 1.2 per 1,000 beneficiaries (ie, a mean of 0.4 additional days of life per beneficiary), respectively. To achieve this marginal additional benefit, 369 additional colonoscopies had to be performed, causing 2.4 additional complications. Furthermore, instead of preventing additional LYs with CRC care, screening up to 85 instead of 75 years increased the number of LYs with CRC care. Further intensifying screening by reducing the screening interval to 3 years or by continuing screening up to 95 years resulted in even smaller increases in the benefits of screening, also relative to the corresponding increases in burden and harms (**Figure 2**).

Net Health Benefit

In previously screened beneficiaries, recommended screening resulted in 63.1 LYs gained per 1,000 beneficiaries, compared with no screening (**Table 2**). On top of that, screening resulted in 13.4 QALYs gained per 1,000 beneficiaries through preventing LYs with CRC care. However, to achieve these benefits, colonoscopies had to be performed, resulting in a loss of 11.7 QALYs per 1,000 beneficiaries. Furthermore, these colonoscopies caused complications, resulting in a loss of another 0.3 QALYs per 1000 beneficiaries. Hence, recommended screening resulted in a net health benefit of 63.1 + 13.4 – 11.7 – 0.3 = 64.5 QALYs gained per 1,000 beneficiaries.

When a screening interval of 5 instead of 10 years was applied, the gain in quality of life by preventing additional LYs with CRC care was exceeded by the loss of quality of life due to additional colonoscopies and additional complications. As a result, applying a screening interval of 5 instead of 10 years resulted in fewer QALYs than LYs gained: 3.2 vs 5.8 per 1,000 beneficiaries. When screening was continued up to 85 instead of 75 years, the overall loss of quality of life exceeded the associated increase in LYs gained. Hence, continuing screening up to 85 instead of 75 years resulted in a loss of QALYs rather than a gain. Both applying a screening interval of 3 instead of 5 years and continuing screening up to 95 instead of 85 years also negatively affected the number of QALYs gained by screening. Discounting did not change the direction of the effect on QALYs gained for any of the scenarios simulated.

Table 2 The Net Health Benefit of More Intensive Colonoscopy Screening than Recommended in Medicare Beneficiaries with a Negative Screening Colonoscopy at Age 55 (numbers per 1,000 beneficiaries).

Scenario			IMPACT ON QUALITY OF LIFE (QALYs)[b]			NET HEALTH BENEFIT[c]
		LYs gained[a]	**LYs with CRC care**[d]	**Colonoscopies**	**Complications**	**QALYs gained**
		(A)	(B)	(C)	(D)	(A+B+C+D)
UNDISCOUNTED						
Recommended screening[e]		63.1	13.4	-11.7	-0.3	64.5
Applying shorter screening intervals	5 years[f, i]	5.8	1.8	-4.3	-0.0	3.2
	3 years[g]	1.6	0.7	-4.3	-0.0	-2.1
Continuing screening beyond age 75	up to age 85[f]	1.2	0.1	-2.0	-0.1	-0.8
	up to age 95[h]	0.0	-0.0	-0.4	-0.0	-0.4
3% DISCOUNTED						
Recommended screening[e]		36.0	7.7	-9.9	-0.2	33.6
Applying shorter screening intervals	5 years[f]	3.4	1.1	-3.7	-0.0	0.7
	3 years[g]	1.0	0.5	-3.9	-0.0	-2.5
Continuing screening beyond age 75	up to age 85[f]	0.5	0.0	-1.1	-0.1	-0.6
	up to age 95[h]	0.0	-0.0	-0.2	-0.0	-0.2

LY = life-year; CRC = colorectal cancer; QALY = quality-adjusted life-year
[a] The impact of a screening scenario on quantity of life.
[b] The impact of a screening scenario on quality of life.
[c] The impact of a screening scenario on quantity and quality of life incorporated in one measure.
[d] Screening results in a gain of quality of life by preventing LYs with CRC care and a loss of quality of life by adding LYs with CRC care. The net effect can be a gain of quality of life (positive values) or a loss of quality of life (negative values).
[e] Compared with no screening
[f] Compared with recommended screening
[g] Compared with applying shorter screening intervals - 5 years
[h] Compared with continuing screening beyond age 75 - up to age 85
[i] Detailed results for this scenario are given in **Appendix 3**.

Efficiency

Screening previously screened beneficiaries every 5 instead of 10 years was the only scenario of more intensive screening that resulted in QALYs gained: 0.7 per 1,000 beneficiaries (discounted result) (**Table 3**). To gain these QALYs, 675 additional colonoscopies and an additional $528,000 were required; hence, 909 additional colonoscopies and an additional $711,000 were required per additional QALY gained (discounted results).

Previously Unscreened Beneficiaries

In previously unscreened beneficiaries, more intensive screening than recommended was slightly less unfavorable or inefficient; however, screening every 3 instead of 5 years and continuing screening beyond 75 years were still associated with a loss of QALYs rather than a gain and screening every 5 instead of 10 years was still inefficient, necessitating 416 additional colonoscopies and an additional $317,000 per additional QALY gained (discounted results) (**Appendix 4**).

Sensitivity Analyses

When the base-case utility losses for colonoscopies and complications were doubled or when a lower risk for CRC or a worse-than-average life expectancy was assumed, screening previously screened beneficiaries every 5 instead of 10 years resulted in a loss of QALYs rather than a gain (**Table 4**). None of the other sensitivity analyses changed the direction of the effect on QALYs gained for any of the scenarios simulated. Assuming a 25% higher risk for CRC resulted in the least unfavorable efficiency ratios: Screening previously screened beneficiaries every 5 instead of 10 years required 249 additional colonoscopies and an additional $181,000 per additional QALY gained (discounted results) (**Table 4**). Again, results in beneficiaries without prior screening were slightly less unfavorable (**Appendix 4**): In previously unscreened beneficiaries at 25% increased risk for CRC, screening every 5 instead of 10 years was associated with 174 additional colonoscopies and an additional $121,000 per additional QALY gained.

Table 3 The Efficiency of More Intensive Colonoscopy Screening than Recommended in Medicare Beneficiaries with a Negative Screening Colonoscopy at Age 55 (net health benefit and resources required per 1,000 beneficiaries).

Scenario		NET HEALTH BENEFIT	RESOURCES REQUIRED		EFFICIENCY	
		QALYs gained	**Colonoscopies**	**US$ (*1,000)[a]**	**ΔColonoscopies/ ΔQALYs gained**	**ΔUS$/ ΔQALYs gained (*1,000)**
UNDISCOUNTED						
Recommended screening[b]		64.5	2,131	922	33	14
Applying shorter screening intervals	5 years[c, f]	3.2	783	573	245	179
	3 years[d]	-2.1	781	656	unfavorable	unfavorable
Continuing screening beyond age 75	up to age 85[c]	-0.8	369	349	unfavorable	unfavorable
	up to age 95[e]	-0.4	69	68	unfavorable	unfavorable
3% DISCOUNTED						
Recommended screening[b]		33.6	1,815	1,091	54	32
Applying shorter screening intervals	5 years[c]	0.7	675	528	909	711
	3 years[d]	-2.5	711	610	unfavorable	unfavorable
Continuing screening beyond age 75	up to age 85[c]	-0.6	203	196	unfavorable	unfavorable
	up to age 95[e]	-0.2	28	28	unfavorable	unfavorable

QALY = quality-adjusted life-year

[a]Net costs: the costs of additional screening and surveillance colonoscopies, complications and LYs with CRC care minus the savings by preventing additional LYs with CRC care.

[b]Compared with no screening

[c]Compared with recommended screening

[d]Compared with applying shorter screening intervals - 5 years

[e]Compared with continuing screening beyond age 75 - up to age 85

[f]Detailed results for this scenario are given in **Appendix 3**.

Table 4 The Efficiency of More Intensive Colonoscopy Screening than Recommended in Medicare Beneficiaries with a Negative Screening Colonoscopy at Age 55: Results of Sensitivity Analyses (3% discounted).

Scenario		Outcome	ANALYSIS					ANALYSIS							
			Base case	Utility loss colonoscopies and complications*0.5	Utility loss colonoscopies and complications*2	Utility loss LYs with continuing care = 0	Utility loss LYs with continuing care stage I and II CRC = 0.12 and 0.18	Costs LYs with CRC care*2	Miss rates colonoscopy - proximal*2[b]	Miss rates colonoscopy - entire colon and rectum*2[a]	Adherence to surveillance = 0%	CRCrisk*1.25	CRCrisk*0.75	Life-expectancy individuals with no comorbidity[b]	Life-expectancy individuals with severe comorbidity[b]
Applying shorter screening intervals	5 years[c]	ΔColonoscopies/ΔQALYs gained	909	258	unfavorable[f]	11,787	587	909	536	267	1,488	249	unfavorable[f]	655	unfavorable[f]
		ΔUS$/ΔQALYs gained (*1,000)	711	202		9,224	459	582	413	200	1,167	181		505	
	3 years[d]	ΔColonoscopies/ΔQALYs gained	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable
		ΔUS$/ΔQALYs gained (*1,000)													
Continuing screening beyond age 75	up to age 85[c]	ΔColonoscopies/ΔQALYs gained	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable
		ΔUS$/ΔQALYs gained (*1,000)													
	up to age 95[e]	ΔColonoscopies/ΔQALYs gained	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable
		ΔUS$/ΔQALYs gained (*1,000)													

QALY = quality-adjusted life-year

[a] Assuming twice the base case miss-rates implies a sensitivity of 50% for small adenomas (≤5mm), 70% for medium-sized adenomas (6-9mm), and 90% for large adenomas (≥10mm) and CRC.

[b] Individuals are classified as having no comorbidity if none of the following conditions is present: a moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS. Individuals are classified as having severe comorbidity if diagnosed with constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

[c] Compared with recommended screening

[d] Compared with applying shorter screening intervals - 5 years

[e] Compared with continuing screening beyond age 75 - up to age 85

[f] The sensitivity analysis changed the direction of the effect on QALYs gained

DISCUSSION

Recent studies show that many Medicare beneficiaries undergo more intensive colonoscopy screening than recommended.(7,8) Our study shows that the resulting balance among benefits, burden, and harms is often unfavorable. Screening previously screened Medicare beneficiaries up to 85 instead of 75 years, for example, resulted in only 1.2 additional LYs gained per 1,000 beneficiaries, whereas it required 369 additional colonoscopies, causing 2.4 additional complications (undiscounted results). As a result, this practice was associated with a loss of QALYs rather than a gain (ie, a net harm). The only scenario favorable for beneficiaries was screening every 5 instead of 10 years, which required 909 additional colonoscopies and an additional $711,000 per additional QALY gained (discounted results). This well exceeds the conventional thresholds for the willingness to pay per QALY gained of $50,000 and $100,000; and although some researchers regard these thresholds as being too low,(49) even these researchers suggest a threshold well below $711,000. Results in previously unscreened beneficiaries were slightly less unfavorable. However, screening every 3 instead of 5 years and continuing screening beyond 75 years were still associated with a loss of QALYs rather than a gain; and screening every 5 instead of 10 years still required 416 additional colonoscopies and an additional $317,000 per additional QALY gained.

The small increase in LYs gained by applying a shorter screening interval than recommended is explained by a combination of 2 factors: (1) the high sensitivity of colonoscopy for the detection of adenomas and CRC(36) and (2) the low progression rate of adenomas into CRC.(29) As a result of the former, adenomas and CRC are unlikely to be prevalent in individuals who just underwent a screening colonoscopy with negative results. As a result of the latter, adenomas that remain undetected during the first colonoscopy at 65 years or newly developed adenomas after this colonoscopy are unlikely to develop into CRC before 75 years, when the next recommended screening colonoscopy takes place. Hence, an additional screening colonoscopy at 70 years is unlikely to add much benefit. The small increase in LYs gained by continuing screening beyond 75 years is explained by the same 2 factors and by the high risk for other-cause mortality at advanced age, which reduces both the probability that screening will prevent CRC mortality and the number of LYs gained if CRC mortality is prevented. Moreover, the risks for colonoscopy-related complications and overdiagnosis and overtreatment of CRC increase with age, negatively affecting the net health benefit of screening.(16)

In the analysis underlying the US Preventive Services Task Force recommendation statement on CRC screening,(13) we already demonstrated that both applying shorter screening intervals than 10 years and continuing screening beyond 75 years result in a small increase in LYs gained and a large increase in colonoscopies performed in those starting screening at 50 years. However, in that analysis we did not quantify the possible harms of screening (ie, nonlethal colonoscopy-related complications and overdiagnosis and overtreatment of CRC), nor did we explicitly weigh the benefits against the burden and harms. This is one of the strengths of the present study because it allows us to draw conclusions about the net health benefit of screening. Whereas clinicians and patients might be reluctant to apply a relatively long screening interval or to discontinue screening after 75 years on the basis of a certain balance between colonoscopies and LYs gained, they are more likely to respond to evidence demonstrating that more intensive screening than recommended negatively affects health. Furthermore, in our earlier study we did not consider costs, which is necessary to evaluate the appropriateness of screening from a societal perspective.

Our study has 3 main limitations. First, although CRC screening is recommended from 50 years onward, we focused our analysis on the Medicare population; ie, we addressed the appropriateness of more intensive screening than recommended from 65 years onward. We chose to do so because patterns of more intensive screening than recommended have mainly been documented in the Medicare population. Nevertheless, an additional analysis shows that more intensive screening than recommended is also inefficient when started at 50 years (**Appendix 5**). Second, because we aimed to illustrate the impact of more intensive screening than recommended, we assumed 100% adherence to all screening scenarios. However, in reality, a beneficiary with negative results on screening colonoscopies at 65 and 68 years might be unlikely to receive another screening colonoscopy at 71 years. If a lower adherence rate were assumed, the scenarios of more intensive screening than recommended would be more similar to recommended screening. Third, although we did perform a sensitivity analysis on the sensitivity of colonoscopy for adenomas and CRC, we did not perform an analysis assuming low-quality colonoscopies. If a proper colonoscopy cannot be performed because of a bad bowel preparation, for example, an early repeated screening colonoscopy is of course justified.

Our analysis highlights some critical future research directions. First, it shows that continuing screening up to very advanced age can be inefficient or even harmful. This is also likely to be true for surveillance in patients who have had adenomas removed, particularly in those at relatively low risk for CRC. Investigating the appropriateness of surveillance at advanced age is particularly important because a substantial proportion of those being screened eventually enter surveillance. Furthermore, our sensitivity analyses demonstrate that the effectiveness and cost-effectiveness of screening depend on an individual's life expectancy and, more importantly, risk for CRC, which reinforces the need for research on personalizing CRC screening recommendations. Finally, our study demonstrates the importance of considering effects on quality of life when screening is evaluated. However, data regarding the utility losses associated with CRC screening are sparse or even absent. More research is needed in this area.

Conclusions

Screening Medicare beneficiaries more intensively than recommended is not only inefficient from a societal perspective; often it is also unfavorable for those being screened. This study provides strong evidence and a clear rationale for clinicians and policymakers to actively discourage this practice.

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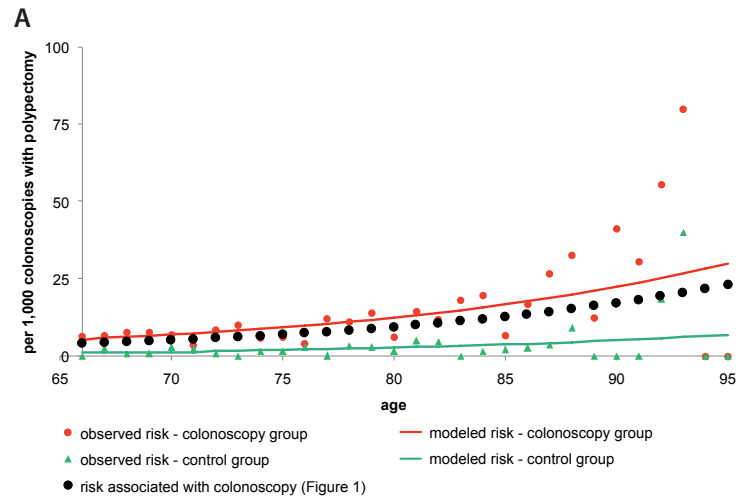
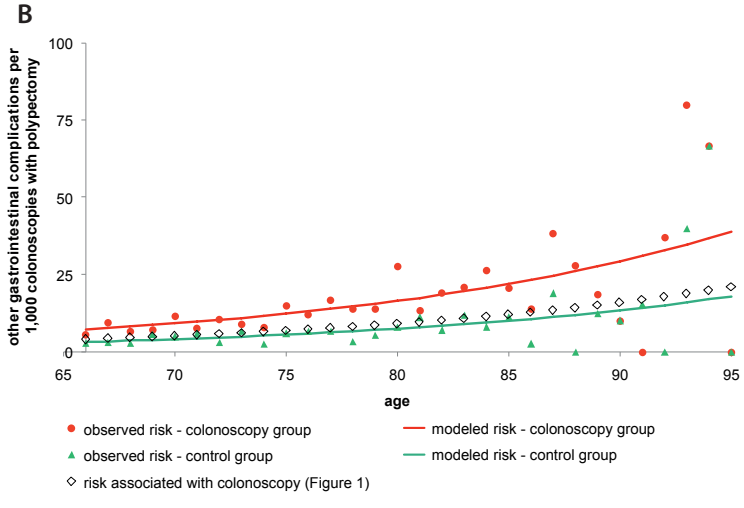
Appendix 1. Complications of Colonoscopy

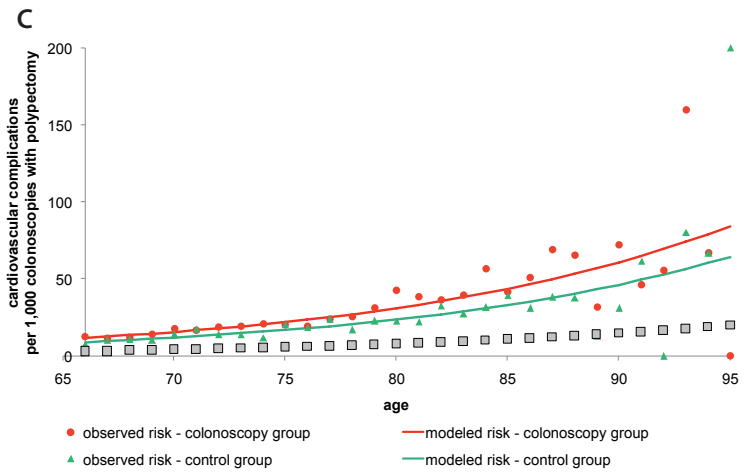
A study by Warren and colleagues reported risks for complications of colonoscopy by age and by polypectomy status, however, not by both factors simultaneously.(16) We performed additional statistical analyses on the data used in this study to derive these risks. In Warren's study, Medicare claims data were used to determine the risks for serious gastrointestinal events (i.e. perforations, gastrointestinal bleeding or transfusions), other gastrointestinal events (i.e. paralytic ileus, nausea and vomiting, dehydration, abdominal pain), and cardiovascular events (i.e. myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock) in groups of Medicare beneficiaries undergoing either a screening colonoscopy without polypectomy, or a colonoscopy with polypectomy. These risks were compared to the risks observed in equally sized, matched control groups (i.e. groups of Medicare beneficiaries who did not undergo a colonoscopy). For both types of colonoscopy we used generalized linear modeling to predict the risk for each type of complication based on colonoscopy status (yes/ no) and age. By subtracting the predicted age specific risks without colonoscopy from the predicted risks with colonoscopy, we determined the age specific risks associated with both types of colonoscopy. The risks for complications associated with colonoscopies with polypectomy increased exponentially with age (**Appendix 1, Figure)**. Screening colonoscopies without polypectomy were not associated with an excess risk for complications. In our study, we used the estimated age specific risks associated with colonoscopies with polypectomy for all modeled colonoscopies with polypectomy.

Appendix 1, Figure 1 Age-specific Risks for Serious Gastrointestinal Complications (A), Other Gastrointestinal Complications (B), and Cardiovascular Complications (C) Associated with Colonoscopies with Polypectomy.





Appendix 1, Figure 1 Continued.



Appendix 2. The Additional Numbers of LYs With CRC Care Prevented by More Intensive Colonoscopy Screening Than Recommended in Medicare Beneficiaries With a Negative Screening Colonoscopy at Age 55

Appendix 2, Table 1 The Additional Number of LYs with CRC Care Prevented by More Intensive Colonoscopy Screening than Recommended in Medicare Beneficiaries with a Negative Screening Colonoscopy at Age 55 (numbers per 1,000 beneficiaries; undiscounted).[a]

		Initial care				Continuing care[b]				Terminal care - death CRC				Total (Figure 2D)
		Stage I CRC	Stage II CRC	Stage III CRC	Stage IV CRC	Stage I CRC	Stage II CRC	Stage III CRC	Stage IV CRC	Stage I CRC`	Stage II CRC	Stage III CRC	Stage IV CRC	
Recommended screening[c]		-0.92	4.40	2.85	1.41	-25.64	28.70	17.04	4.07	0.20	1.16	1.39	2.88	**37.5**
Applying shorter screening intervals	5 years[d]	0.28	0.57	0.32	0.10	1.07	5.19	2.55	0.35	0.04	0.13	0.12	0.18	**10.9**
	3 years[e]	0.28	0.17	0.09	0.01	3.00	2.18	0.94	0.06	0.00	0.04	0.03	0.03	**6.8**
Continuing screening beyond age 75	up to age 85[d]	-0.32	0.07	0.03	0.05	-2.29	-0.17	-0.05	0.09	0.01	0.04	0.04	0.12	**-2.4**
	up to age 95[f]	-0.02	-0.01	-0.00	0.00	-0.06	-0.01	-0.01	0.00	0.00	0.00	0.00	0.00	**-0.1**

LY = life-year; CRC = colorectal cancer

[a] Positve values indicate that LYs with CRC care are prevented by screening; negative values indicate that LYs with CRC care are induced by screening.

[b] As LYs with continuing care for CRC and with terminal care before death from another cause are assigned the same utility loss in our analysis, they are summed up in this table.

[c] Compared with no screening.

[d] Compared with recommended screening.

[e] Compared with applying shorter screening intervals - 5 years.

[f] Compared with continuing screening beyond age 75 - up to age 85.

Appendix 3. Detailed Results for 5-Yearly Instead of 10-Yearly Colonoscopy Screening in Medicare Beneficiaries With a Negative Screening Colonoscopy at Age 55

Appendix 3, Table 1 The Effects of Applying a Screening Interval of 5 instead of 10 Years for Colonoscopy Screening in Medicaire Beneficiaries with a Negative Screening Colonoscopy at Age 55 (results per 1,000 individuals; undiscounted)

	5-yearly colonoscopy screening	10-yearly colonoscopy screening	Difference
EFFECTS ON HEALTH CARE USE			
Colonoscopies			
Screening - polypectomy	456	367	89
Screening - no polypectomy	1,976	1,326	649
Surveillance - polypectomy	142	132	10
Surveillance - no polypectomy	340	307	34
Complications of colonoscopy	9.5	8.3	1.3
LYs with initial CRC care			
Stage I	11.4	11.6	-0.3
Stage II	6.1	6.7	-0.6
Stage III	2.7	3.1	-0.3
Stage IV	0.6	0.7	-0.1
LYs with continuing CRC care			
Stage I	206.6	207.4	-0.8
Stage II	100.0	104.7	-4.7
Stage III	45.1	47.4	-2.3
Stage IV	2.8	3.1	-0.3
LYs with terminal care - CRC			
Stage I	0.9	0.9	-0.0
Stage II	1.5	1.6	-0.1
Stage III	1.2	1.3	-0.1
Stage IV	1.2	1.4	-0.2
LYs with terminal care - other cause			
Stage I	15.8	16.1	-0.3
Stage II	7.8	8.3	-0.5
Stage III	3.4	3.6	-0.2
Stage IV	0.3	0.3	-0.0

Appendix 3, Table 1 Continued.

	5-yearly colonoscopy screening	10-yearly colonoscopy screening	Difference
EFFECTS ON HEALTH			
CRC cases	24.0	25.6	-1.7
CRC deaths	5.7	6.3	-0.6
LYs lost due to CRC	90.4	96.2	-5.8
Utility loss (QALYs lost)			
Screening colonoscopies	13.3	9.3	4.0
Surveillance colonoscopies	2.6	2.4	0.2
Complications of colonoscopy	0.4	0.3	0.0
LYs with CRC care	37.2	38.9	-1.8
Total	53.5	50.9	2.6
QALYs lost	143.9	147.1	-3.2
EFFECTS ON COSTS (*$1,000)			
Screening colonoscopies	2,252	1,578	674
Surveillance colonoscopies	457	416	41
Complications of colonoscopy	58	50	8
LYs with CRC care	2,922	3,071	-149
Total	5,689	5,115	573

LY = life-year; CRC = colorectal cancer; QALY = quality-adjusted life-year

Appendix 4, Table 1 The Net Health Benefit of More Intensive Colonoscopy Screening than Recommended in Medicare Beneficiaries without Prior Screening (numbers per 1,000 beneficiaries).

Scenario		IMPACT ON QUALITY OF LIFE (QALYs)[b]				NET HEALTH BENEFIT[c]
		LYs gained[a]	**LYs with CRC care[d]**	**Colonoscopies**	**Complications**	**QALYs gained**
		(A)	(B)	(C)	(D)	(A+B+C+D)
UNDISCOUNTED						
Recommended screening[e]		163.8	31.1	-14.1	-0.6	180.3
Applying shorter screening intervals	5 years[f]	5.3	1.6	-3.3	-0.0	3.6
	3 years[g]	1.5	0.6	-3.2	-0.0	-1.1
Continuing screening beyond age 75	up to age 85[f]	0.9	0.1	-1.5	-0.1	-0.6
	up to age 95[h]	0.0	-0.0	-0.3	-0.0	-0.3
3% DISCOUNTED						
Recommended screening[e]		95.1	17.7	-11.7	-0.5	100.8
Applying shorter screening intervals	5 years[f]	3.1	1.0	-2.8	-0.0	1.2
	3 years[g]	0.9	0.4	-2.9	-0.0	-1.6
Continuing screening beyond age 75	up to age 85[f]	0.4	0.0	-0.8	-0.0	-0.4
	up to age 95[h]	0.0	-0.0	-0.1	-0.0	-0.1

LY = life-year; CRC = colorectal cancer; QALY = quality-adjusted life-year
[a] The impact of a screening scenario on quantity of life.
[b] The impact of a screening scenario on quality of life.
[c] The impact of a screening scenario on quantity and quality of life incorporated in one measure.
[d] Screening results in a gain of quality of life by preventing LYs with CRC care and a loss of quality of life by adding LYs with CRC care. The net effect can be a gain of quality of life (positive values) or a loss of quality of life (negative values).
[e] Compared with no screening
[f] Compared with recommended screening
[g] Compared with applying shorter screening intervals - 5 years
[h] Compared with continuing screening beyond age 75 - up to age 85

Appendix 4, Table 2 The Efficiency of More Intensive Colonoscopy Screening than Recommended in Medicare Beneficiaries without Prior Screening (net health benefit and resources required per 1,000 beneficiaries),

Scenario		NET HEALTH BENEFIT	RESOURCES REQUIRED		EFFICIENCY	
		QALYs gained	**Colonoscopies**	**US$ (*1,000)[a]**	**ΔColonoscopies/ ΔQALYs gained**	**ΔUS$/ ΔQALYs gained (*1,000)**
UNDISCOUNTED						
Recommended screening[b]		180,3	2,570	-61	14	cost saving
Applying shorter screening intervals	5 years[c]	3,6	596	420	168	118
	3 years[d]	-1,1	584	484	unfavorable	unfavorable
Continuing screening beyond age 75	up to age 85[c]	-0,6	274	259	unfavorable	unfavorable
	up to age 95[e]	-0,3	51	50	unfavorable	unfavorable
3% DISCOUNTED						
Recommended screening[b]		100,8	2,127	615	21	6
Applying shorter screening intervals	5 years[c]	1,2	514	392	416	317
	3 years[d]	-1,6	532	452	unfavorable	unfavorable
Continuing screening beyond age 75	up to age 85[c]	-0,4	150	145	unfavorable	unfavorable
	up to age 95[e]	-0,1	21	21	unfavorable	unfavorable

QALY = quality-adjusted life-year
[a] Net costs: the costs of additional screening and surveillance colonoscopies, complications and LYs with CRC care minus the savings by preventing additional LYs with CRC care,
[b] Compared with no screening
[c] Compared with recommended screening
[d] Compared with applying shorter screening intervals - 5 years
[e] Compared with continuing screening beyond age 75 - up to age 85

Appendix 4, Table 3 The Efficiency of More Intensive Colonoscopy Screening than Recommended in Medicare Beneficiaries without Prior Screening: Results of Sensitivity Analyses (3% discounted).

Scenario		Outcome	ANALYSIS				ANALYSIS								
			Base case	Utility loss colonoscopies and complications*0.5	Utility loss colonoscopies and complications*2	Utility loss LYs with continuing care = 0	Utility loss LYs with continuing care stage I and II CRC = 0.12 and 0.18	Costs LYs with CRC care*2	Miss rates colonoscopy - proximal*2[a]	Miss rates colonoscopy - entire colon and rectum*2[a]	Adherence to surveillance = 0%	CRCrisk*1.25	CRCrisk*0.75	Life-expectancy individuals with no comorbidity[b]	Life-expectancy individuals with severe comorbidity[b]
Applying shorter screening intervals	5 years[c]	ΔColonoscopies/ ΔQALYs gained	416	193	unfavorable[f]	791	327	416	297	174	563	174	unfavorable[f]	338	13,821
		ΔUS$/ΔQALYs gained (*1,000)	317	147		604	249	249	223	125	432	121		252	11,272
	3 years[d]	ΔColonoscopies/ ΔQALYs gained	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable
		ΔUS$/ΔQALYs gained (*1,000)													
Continuing screening beyond age 75	up to age 85[c]	ΔColonoscopies/ ΔQALYs gained	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable
		ΔUS$/ΔQALYs gained (*1,000)													
	up to age 95[e]	ΔColonoscopies/ ΔQALYs gained	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable
		ΔUS$/ΔQALYs gained (*1,000)													

QALY = quality-adjusted life-year

[a] Assuming twice the base case miss-rates implies a sensitivity of 50% for small adenomas (≤5mm), 70% for medium-sized adenomas (6-9mm), and 90% for large adenomas (≥10mm) and CRC.

[b] Individuals are classified as having no comorbidity if none of the following conditions is present: an ulcer, a history of acute myocardial infarction, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS. Individuals are classified as having severe comorbidity if diagnosed with constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

[c] Compared with recommended screening

[d] Compared with applying shorter screening intervals - 5 years

[e] Compared with continuing screening beyond age 75 - up to age 85

[f] The sensitivity analysis changed the direction of the effect on QALYs gained

Appendix 5. Results for More Intensive Colonoscopy Screening Than Recommended From Age 50 Onwards

Appendix 5, Table 1 The Net Health Benefit of More Intensive Colonoscopy Screening than Recommended from Age 50 Onwards (numbers per 1,000 beneficiaries).

Scenario		IMPACT ON QUALITY OF LIFE (QALYs)[b]				NET HEALTH BENEFIT[c]
		LYs gained[a]	**LYs with CRC care[d]**	**Colonoscopies**	**Complications**	**QALYs gained**
		(A)	(B)	(C)	(D)	(A+B+C+D)
UNDISCOUNTED						
Recommended screening[e]		235.4	48.8	-20.4	-0.5	263.3
Applying shorter screening intervals	5 years[f]	15.3	4.8	-9.6	-0.1	10.4
	3 years[g]	4.3	1.5	-9.9	-0.1	-4.1
Continuing screening beyond age 75	up to age 85[f]	3.1	0.6	-2.1	-0.1	1.5
	up to age 95[h]	0.1	-0.0	-0.7	-0.0	-0.6
3% DISCOUNTED						
Recommended screening[e]		99.8	21.6	-14.6	-0.3	106.4
Applying shorter screening intervals	5 years[f]	6.7	2.3	-6.7	-0.1	2.3
	3 years[g]	2.1	0.8	-7.4	-0.0	-4.6
Continuing screening beyond age 75	up to age 85[f]	0.9	0.2	-0.8	-0.0	0.2
	up to age 95[h]	0.0	-0.0	-0.2	-0.0	-0.2

LY = life-year; CRC = colorectal cancer; QALY = quality-adjusted life-year
[a] The impact of a screening scenario on quantity of life.
[b] The impact of a screening scenario on quality of life.
[c] The impact of a screening scenario on quantity and quality of life incorporated in on measure.
[d] Screening results in a gain of quality of life by preventing LYs with CRC care and a loss of quality of life by adding LYs with CRC care. The net effect can be a gain of quality of life (positive values) or a loss of quality of life (negative values).
[e] Compared with no screening
[f] Compared with recommended screening
[g] Compared with applying shorter screening intervals - 5 years
[h] Compared with continuing screening beyond age 75 - up to age 85

Appendix 5, Table 2 The Efficiency of More Intensive Colonoscopy Screening than Recommended from Age 50 Onwards (net health benefit and resources required per 1,000 beneficiaries),

Scenario		NET HEALTH BENEFIT	RESOURCES REQUIRED		EFFICIENCY	
		QALYs gained	**Colonoscopies**	**US$ (*1,000)[a]**	**ΔColonoscopies/ ΔQALYs gained**	**ΔUS$/ ΔQALYs gained (*1,000)**
UNDISCOUNTED						
Recommended screening[b]		263,3	3,732	96	14	0
Applying shorter screening intervals	5 years[c]	10,4	1,757	1,276	170	123
	3 years[d]	-4,1	1,799	1,527	unfavorable	unfavorable
Continuing screening beyond age 75	up to age 85[c]	1,5	375	303	unfavorable	unfavorable
	up to age 95[e]	-0,6	120	117	unfavorable	unfavorable
3% DISCOUNTED						
Recommended screening[b]		106,4	2,671	1,017	25	10
Applying shorter screening intervals	5 years[c]	2,3	1,217	954	529	415
	3 years[d]	-4,6	1,356	1,173	unfavorable	unfavorable
Continuing screening beyond age 75	up to age 85[c]	0,2	152	131	unfavorable	unfavorable
	up to age 95[e]	-0,2	37	36	unfavorable	unfavorable

QALY = quality-adjusted life-year
[a] Net costs: the costs of additional screening and surveillance colonoscopies, complications and LYs with CRC care minus the savings by preventing additional LYs with CRC care,
[b] Compared with no screening
[c] Compared with recommended screening
[d] Compared with applying shorter screening intervals - 5 years
[e] Compared with continuing screening beyond age 75 - up to age 85

Appendix 5, Table 3 The Efficiency of More Intensive Colonoscopy Screening than Recommended from Age 50 onwards: Results of Sensitivity Analyses (3% discounted).

Scenario		Outcome	ANALYSIS					ANALYSIS							
			Base case	Utility loss colonoscopies and complications*0.5	Utility loss colonoscopies and complications*2	Utility loss LYs with continuing care = 0	Utility loss LYs with continuing care stage I and II CRC = 0.12 and 0.18	Costs LYs with CRC care*2	Miss rates colonoscopy - proximal*2[a]	Miss rates colonoscopy - entire colon and rectum*2[a]	Adherence to surveillance = 0%	CRCrisk*1.25	CRCrisk*0.75	Life-expectancy individuals with no comorbidity[b]	Life-expectancy individuals with severe comorbidity[b]
Applying shorter screening intervals	5 years[c]	ΔColonoscopies/ ΔQALYs gained	529	215	unfavorable[f]	1,844	371	529	382	263	unfavorable	202	unfavorable[f]	429	2,832
		ΔUS$/ΔQALYs gained (*1,000)	415	168		1,445	291	341	298	201		148		334	2,274
	3 years[d]	ΔColonoscopies/ ΔQALYs gained	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable
		ΔUS$/ΔQALYs gained (*1,000)													
Continuing screening beyond age 75	up to age 85[c]	ΔColonoscopies/ ΔQALYs gained	616	224	unfavorable[f]	694	769	616	484	333	504	218	unfavorable[f]	917	847
		ΔUS$/ΔQALYs gained (*1,000)	529	192		597	661	466	421	291	430	183		798	740
	up to age 95[e]	ΔColonoscopies/ ΔQALYs gained	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable	unfavorable
		ΔUS$/ΔQALYs gained (*1,000)													

QALY = quality-adjusted life-year

[a] Assuming twice the base case miss-rates implies a sensitivity of 50% for small adenomas (≤5mm), 70% for medium-sized adenomas (6-9mm), and 90% for large adenomas (≥10mm) and CRC.

[b] Individuals are classified as having no comorbidity if none of the following conditions is present: an ulcer, a history of acute myocardial infarction, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS. Individuals are classified as having severe comorbidity if diagnosed with constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

[c] Compared with recommended screening

[d] Compared with applying shorter screening intervals - 5 years

[e] Compared with continuing screening beyond age 75 - up to age 85

[f] The sensitivity analysis changed the direction of the effect on QALYs gained

5

Should Colorectal Cancer Screening Be Considered in Elderly Persons Without Previous Screening?

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ABSTRACT

Background: The US Preventive Services Task Force recommends against routine screening for colorectal cancer (CRC) in adequately screened persons older than 75 years but does not address the appropriateness of screening in elderly persons without previous screening.
Objective: To determine at what ages CRC screening should be considered in unscreened elderly persons and to determine which test is indicated at each age.
Design: Microsimulation modeling study.
Data Sources: Observational and experimental studies.
Target Population: Unscreened persons aged 76 to 90 years with no, moderate, and severe comorbid conditions.
Time Horizon: Lifetime.
Perspective: Societal.
Intervention: One-time colonoscopy, sigmoidoscopy, or fecal immunochemical test (FIT) screening.
Outcome Measures: Quality-adjusted life-years gained, costs, and costs per quality-adjusted life-year gained.
Results of Base-Case Analysis: In unscreened elderly persons with no comorbid conditions, CRC screening was cost-effective up to age 86 years. Screening with colonoscopy was indicated up to age 83 years, sigmoidoscopy was indicated at age 84 years, and FIT was indicated at ages 85 and 86 years. In unscreened persons with moderate comorbid conditions, screening was cost-effective up to age 83 years (colonoscopy indicated up to age 80 years, sigmoidoscopy at age 81 years, and FIT at ages 82 and 83 years). In unscreened persons with severe comorbid conditions, screening was cost-effective up to age 80 years (colonoscopy indicated up to age 77 years, sigmoidoscopy at age 78 years, and FIT at ages 79 and 80 years).
Results of Sensitivity Analyses: Results were most sensitive to assuming a lower willingness to pay per quality-adjusted life-year gained.
Limitation: Only persons at average risk for CRC were considered.
Conclusion: In unscreened elderly persons CRC screening should be considered well beyond age 75 years. A colonoscopy is indicated at most ages.
Primary Funding Source: National Cancer Institute.

INTRODUCTION

In its most recent recommendation statement on colorectal cancer (CRC) screening, the US Preventive Services Task Force (USPSTF) recommends screening using fecal occult blood testing, sigmoidoscopy, or colonoscopy, starting at age 50 years and continuing up to age 75 years (1). The USPSTF recommends against routine screening in persons older than 75 years with an adequate screening history (1). This latter recommendation is warranted by an analysis showing that the benefits of continuing screening from age 50 to 85 years instead of 75 years do not justify the additional colonoscopies required (2). Although the USPSTF did not address the appropriateness of screening in inadequately screened elderly persons, this recommendation has led many members of the medical community to believe that no one older than 75 years should be screened for CRC (3, 4). However, because unscreened elderly persons are at greater risk for CRC than adequately screened elderly persons, screening them is likely to be effective and cost-effective up to a more advanced age. If so, the lack of more specific recommendations on the age to stop screening may result in an unfounded denial of access to screening in elderly persons who were never screened for CRC—a group representing 23% of all US persons older than 75 years (5).

Many other elderly persons continue to be screened up to their late 80s or early 90s (6). However, at these ages, screening is not likely to be cost-effective, even in those without previous screening. First, the high risk for death of competing disease at advanced age tends to offset the benefits of screening (7, 8). Second, the risks for screening-induced harms (colonoscopy-related complications and overdiagnosis and overtreatment of CRC) increase with increasing age (9).

The objective of this study was to determine up to what age CRC screening should be considered in elderly persons without previous screening and to determine which screening test— colonoscopy, sigmoidoscopy, or fecal immunochemical test (FIT)—is indicated at what age. We performed separate analyses for elderly persons with no, moderate, and severe comorbid conditions because the effectiveness and cost-effectiveness of screening depend heavily on a person's life expectancy.

METHODS

We used the Microsimulation Screening Analysis–Colon (MISCAN-Colon) model (Erasmus University Medical Center, Rotterdam, the Netherlands) to quantify the effectiveness and costs of screening.

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Center. The model's

structure, underlying assumptions, and calibration are described in the **Model Appendix** included at the end of this thesis. In brief, MISCAN-Colon simulates the life histories of a large population from birth to death. As each simulated person ages, 1 or more adenomas may develop. These adenomas can progress from small (≤5 mm) to medium (6 to 9 mm) to large (≥10 mm) size. Some adenomas can develop into preclinical cancer, which may progress through stages I to IV. During each stage, CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the localization of the cancer, and the person's age (10).

Screening will alter some of the simulated life histories: Some cancer cases will be prevented by the detection and removal of adenomas; other cancer cases will be detected in an earlier stage with a more favorable survival. However, screening can also result in serious complications and overdiagnosis and overtreatment of CRC (that is, the detection and treatment of cancer that would not have been diagnosed without screening). By comparing all life histories with screening with the corresponding life histories without screening, MISCAN-Colon quantifies the effectiveness of screening as well as the associated costs.

MISCAN-Colon was calibrated to the age-, stage-, and localization-specific incidence of CRC as seen in the SEER (Surveillance, Epidemiology, and End Results) Program before the introduction of screening (that is, between 1975 and 1979) and the age-specific prevalence and multiplicity distribution of adenomas seen in autopsy studies (11–21). The preclinical duration of CRC and the adenoma dwell-time were calibrated to the rates of interval and surveillance-detected cancer seen in randomized, controlled trials evaluating screening using guaiac fecal occult blood tests and a 1-time sigmoidoscopy (22–26).

Model Inputs

Populations Simulated

For each age between 76 and 90 years, we simulated a cohort of 10 million elderly persons without previous screening with no, moderate, and severe comorbid conditions (a total of 45 cohorts). Compared with cohorts of adequately screened elderly persons, the risk for CRC in these cohorts was substantially greater: CRC and adenomas were prevalent in 0.3% and 14.1%, respectively, of simulated patients aged 80 years with negative screening colonoscopies at ages 50, 60, and 70 years and in 2.6% and 44.9%, respectively, of simulated patients aged 80 years without previous screening.

We used comorbid condition level–specific life tables to simulate elderly persons with no, moderate, and severe comorbid conditions (27). Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions are present.

Screening Strategies

We simulated 1-time colonoscopy, 1-time sigmoidoscopy, and 1-time FIT screening within each cohort. Test characteristics and complication rates for each screening test are given in **Appendix Table 1**. Patients with an adenoma or CRC detected during sigmoidoscopy or with a positive FIT result were referred for a diagnostic colonoscopy. Persons with adenomas detected and removed during a screening or diagnostic colonoscopy were assumed to have colonoscopy surveillance according to the current guidelines (28). We assumed that surveillance continued until the diagnosis of CRC or death. Adherence to screening and diagnostic and surveillance colonoscopies was assumed to be 100%.

We restricted ourselves to 1-time colonoscopy and 1-time sigmoidoscopy screening because performing more screening colonoscopies or sigmoidoscopies is unlikely to be cost-effective at older age. We explored the effect of FIT screening during 2 consecutive years in a sensitivity analysis.

Utility Losses Associated With CRC Screening

We assumed a utility loss (that is, a loss of quality of life) equal to 2 full days of life per colonoscopy (0.0055 quality-adjusted life-years [QALYs]), 1 day of life per sigmoidoscopy (0.0027 QALYs), and 2 weeks of life per complication (0.0384 QALYs) (**Table 1**). We also assigned a utility loss to each LY with CRC care (29).

The assignment of utility losses to LYs with CRC care works 2 ways: On the one hand, screening prevents cancer by the detection and removal of adenomas, thereby reducing LYs with CRC care and hence resulting in a gain of quality of life. On the other hand, screening results in overdiagnosis and overtreatment of cancer, resulting in LYs with CRC care in persons who would never have been diagnosed with CRC without screening and hence a loss of quality of life. The net effect on quality of life depends on the balance between cancer cases prevented and cancer cases overdiagnosed and can be either positive or negative.

Costs Associated With CRC Screening

The cost-effectiveness analyses were conducted from a societal perspective. The costs of colonoscopy, sigmoidoscopy, and FIT were based on 2007 Medicare payment rates and copayments (**Table 1**) (32). The costs of complications were obtained from a cost analysis of cases of unexpected hospital use after endoscopy in 2007 (33). We added patient time costs to both (30). The costs of LYs with CRC care were obtained from an analysis of SEER–Medicare linked data and included copayments and patient time costs (31). We adjusted all costs to reflect the 2013 level using the US Consumer Price Index (34).

The assignment of costs to LYs with CRC care also works 2 ways: On the one hand, screening prevents cancer, reducing the costs of CRC care. On the other hand, screening results in overtreatment of cancer, increasing these costs. The net effect can be either a reduction or an increase in costs.

Table 1 Model Inputs: Utility Losses and Costs Associated with Colorectal Cancer Screening.

	UTILITY LOSS (QALYs)*			
Per FIT	0			
Per sigmoidoscopy				
without biopsy	0.003			
with biopsy	0.003			
Per colonoscopy				
without polypectomy/ biopsy	0.005			
with polypectomy/ biopsy	0.005			
Per complication of colonoscopy	0.038			
Per LY with CRC care†‡	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	0.12	0.05	0.70	0.05
Stage II CRC	0.18	0.05	0.70	0.05
Stage III CRC	0.24	0.24	0.70	0.24
Stage IV CRC	0.70	0.70	0.70	0.70
	COSTS (2013 US$)§			
Per FIT	42			
Per sigmoidoscopy				
without biopsy	299			
with biopsy	557			
Per colonoscopy				
without polypectomy/ biopsy	887			
with polypectomy/ biopsy	1,096			
Per complication of colonoscopy	6,045			
Per LY with CRC care†	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	36,683	3,050	63,809	19,176
Stage II CRC	49,234	2,870	63,555	17,279
Stage III CRC	59,759	4,021	67,041	21,457
Stage IV CRC	77,790	12,178	88,368	49,866

QALY = quality-adjusted life-year; FIT = fecal immunochemical test; LY = life-year; CRC = colorectal cancer
*The loss of quality of life associated with a particular event.
†Care for CRC was divided in three clinically relevant phases: the initial, continuing, and terminal care phase. The initial care phase was defined as the first 12 months after diagnosis; the terminal care phase was defined as the final 12 months of life; the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between CRC patients dying from CRC and CRC patients dying from another cause. For patients surviving less than 24 months, the final 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.
‡Utility losses for LYs with initial care were derived from a study by Ness and colleagues(29). For LYs with continuing care for stage I and II CRC, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV CRC, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for CRC, we assumed the utility loss for LYs with initial care for stage IV CRC. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.
§Costs include copayments and patient time costs (i.e. the opportunity costs of spending time on screening or being treated for a complication or CRC), but do not include travel costs, costs of lost productivity, and unrelated health care and non-health care costs in added years of life. We assumed that the value of patient time was equal to the median wage rate in 2012: $16.71 per hour(30). We assumed that FITs, sigmoidoscopies, colonoscopies, and complications used up 1, 4, 8 and 16 hours of patient time, respectively. Patient time costs were already included in the estimates for the costs of LYs with CRC care obtained from a study by Yabroff and colleagues(31).

Outcomes

For each cohort, we quantified the effectiveness (that is, the number of CRC cases prevented, CRC deaths prevented, LYs gained, and QALYs gained) and costs of 1-time colonoscopy, sigmoidoscopy, and FIT screening, applying the conventional 3% annual discount rate for both.

Analyses

We first determined the cost-effectiveness of each screening strategy compared with no screening for all cohorts. For each comorbid condition level, we determined the upper age at which each screening strategy was cost-effective compared with no screening, assuming a willingness to pay per QALY gained of $100 000.

We subsequently performed an analysis to determine the optimal screening strategy for each cohort (that is, the most effective, still cost-effective screening strategy). To do so, we first excluded all dominated screening strategies (that is, those that were more costly and less effective than other strategies or combinations of other strategies). We determined the incremental cost-effectiveness ratio for all remaining strategies ("efficient strategies"): the additional costs per additional QALY gained compared with the next less effective and costly efficient strategy. From the efficient strategies, we selected the optimal strategy, again assuming a willingness to pay per QALY gained of $100 000.

Sensitivity Analyses

We repeated our analyses assuming half and twice the base-case utility losses for colonoscopy, sigmoidoscopy, and complications; a utility loss of 0.12, 0.18, 0.24, and 0.70 QALYs for each LY with continuing care for stage I, II, III, and IV CRC, respectively; 25% higher and 25% lower costs for colonoscopy, sigmoidoscopy, and FIT; 25% higher and 25% lower costs for CRC care; twice the base-case miss rates for adenomas and CRC for both sigmoidoscopy and colonoscopy; no surveillance in patients with adenomas; 25% higher and 25% lower risk for CRC in all cohorts; and a willingness to pay per QALY gained of $50 000. Further, we explored the effect of FIT screening during 2 consecutive years.

Role of the Funding Source

The study was supported by the National Cancer Institute. The funding source had no role in the study's design, conduct, and reporting.

This study did not include patient-specific information and was exempt from institutional review board review.

RESULTS

Effectiveness

The effectiveness of CRC screening in unscreened elderly persons declined with increasing age (**Table 2**). For example, 1-time colonoscopy screening prevented fewer CRC deaths (4.5 vs. 11.9 per 1000 persons) and resulted in fewer LYs gained (12.3 vs. 68.5 per 1000 persons) in healthy persons aged 90 years than in healthy persons aged 76 years. Moreover, whereas colonoscopy screening prevented 15.4 CRC cases per 1000 healthy persons aged 76 years, it resulted in overdiagnosis and hence overtreatment of 7.7 CRC cases per 1000 healthy persons aged 90 years. As a result, colonoscopy screening resulted in a positive overall effect on length and quality of life (that is, a net health benefit) in healthy persons aged 76 years (67.2 QALYs gained per 1000 persons) but in a net harm in healthy persons aged 90 years (1.7 QALYs lost per 1000 persons).

One-time sigmoidoscopy and, particularly, 1-time FIT screening were generally less effective than 1-time colonoscopy screening (**Table 2**). For example, in healthy persons aged 76 years, colonoscopy screening resulted in 67.2 QALYs gained per 1000 persons,

Table 2 Effectiveness of 1-Time Colonoscopy, Sigmoidoscopy, and FIT Screening in Elderly Persons Without Previous Screening With No Comorbid Conditions (compared with no screening; results per 1,000 individuals; 3% discounted).*

		CRC cases prevented†	**CRC deaths prevented**	**LYs gained‡**	**Impact on quality of life (QALYs)§**					**QALYs gained¶**
					Screening test	*Diagnostic colonoscopies*	*Surveillance colonoscopies*	*Complications*	*LYs with CRC care‖*	
Screening strategy	**Age**			(A)	(B)	(C)	(D)	(E)	(F)	(A+B+C+D+E+F)
1-time colonoscopy screening	**76****	15.4	11.9	68.5	*-5.5*	*0*	*-3.2*	*-0.6*	*8.1*	67.2
	80	10.4	10.7	52.9	*-5.5*	*0*	*-2.8*	*-0.7*	*3.0*	46.9
	85	0.8	7.4	28.3	*-5.5*	*0*	*-2.0*	*-0.9*	*-2.9*	17.1
	90	-7.7	4.5	12.3	*-5.5*	*0*	*-1.4*	*-1.1*	*-6.1*	-1.7
1-time sigmoidoscopy screening	**76**	12.0	9.4	54.6	*-2.7*	*-1.6*	*-2.2*	*-0.4*	*6.2*	53.9
	80	8.2	8.7	43.1	*-2.7*	*-1.7*	*-2.0*	*-0.5*	*2.3*	38.6
	85	0.6	6.0	23.1	*-2.7*	*-1.7*	*-1.4*	*-0.6*	*-2.3*	14.3
	90	-6.2	3.7	9.9	*-2.7*	*-1.6*	*-1.0*	*-0.7*	*-4.9*	-1.0
1-time FIT screening	**76**	1.7	4.1	25.9	*0*	*-0.4*	*-0.5*	*-0.1*	*-0.6*	24.2
	80	0.2	4.2	22.5	*0*	*-0.4*	*-0.4*	*-0.1*	*-2.2*	19.2
	85	-2.8	3.4	13.8	*0*	*-0.5*	*-0.4*	*-0.1*	*-3.8*	9.0
	90	-6.2	2.3	6.6	*0*	*-0.5*	*-0.3*	*-0.2*	*-4.7*	0.9

FIT = fecal immunochemical test; CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year

*Persons are classified as having no comorbid conditions if none of the following conditions is present: an ulcer, a history of acute myocardial infarction, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

†Negative values occur when the number of CRC cases prevented by screening is exceeded by the number of CRC cases over-diagnosed by screening.

‡The impact of screening on quantity of life.

§The impact of the screening test, diagnostic colonoscopies, surveillance colonoscopies, complications, and LYs with CRC care on quality of life. Values are derived by multiplying number(s) of events with the corresponding utility loss(es) per event stated in Table 1. An example: When applying the once-only colonoscopy screening strategy, in each cohort, 1,000 individuals undergo a screening colonoscopy. As the utility loss per screening colonoscopy is 0.0055 QALYs, the total utility loss due to screening colonoscopies is 5.5 QALYs in each cohort.

‖ Screening results in a gain of quality of life by preventing LYs with CRC care and a loss of quality of life by adding LYs with CRC care. The net effect can be a gain of quality of life (positive values) or a loss of quality of life (negative values). As a result of the shift from preventing to over-diagnosing CRC with increasing age, the net effect on quality of life becomes less favorable with age. Whereas once-only colonoscopy screening in unscreened elderly without comorbidity reduced the total number of LYs with CRC care for stage III or IV CRC at age 76 (-14 LYs per 1,000 individuals), it increased this number of LYs at age 90 (+16 LYs per 1,000 individuals).

¶ The impact of screening on quantity and quality of life incorporated in one measure, i.e. the net health benefit of screening.

Discrepancies between the columns might occur due to rounding.

More detailed results for this cohort are given in **Appendix Table 2.

whereas sigmoidoscopy and FIT screening resulted in 53.9 and 24.2 QALYs gained per 1000 persons, respectively. The only exceptions were seen at the most advanced ages, at which FIT screening was most effective—a result primarily explained by the 0 utility loss associated with this test. In persons with moderate and, particularly, severe comorbid conditions, screening was less effective than in persons without comorbid conditions (**Appendix Table 3**).

Costs

Whereas the effectiveness of screening in unscreened elderly persons declined with increasing age, the net costs of screening increased substantially (**Table 3**). While colonoscopy screening was associated with a lifetime cost of $725 000 per 1000 healthy persons aged 76 years, it was associated with a lifetime cost of $2 130 000 per 1000 healthy persons aged 90 years. This increase was again explained by the shift from preventing to overtreating CRC with age.

Besides being the most effective strategy, colonoscopy screening was also the most expensive (**Table 3**). For example, in healthy persons aged 76 years, the costs of colonoscopy screening were $725 000 per 1000 persons compared with $439 000 and $218 000 for sigmoidoscopy and FIT screening, respectively. In persons with moderate and, particularly, severe comorbid conditions, screening was not only less effective but also more costly (**Appendix Table 4**).

Cost-Effectiveness Compared With No Screening

As the effectiveness of screening declined with increasing age and the costs increased substantially, the cost-effectiveness of screening deteriorated rapidly with age (**Figure 1**). In unscreened elderly persons without comorbid conditions, colonoscopy and sigmoidoscopy screening were cost-effective up to age 85 years, whereas FIT screening was cost-effective up to age 86 years. In elderly persons with moderate comorbid conditions, colonoscopy and sigmoidoscopy screening were cost-effective up to age 82 years, whereas FIT screening was cost-effective up to age 83 years. In persons with severe comorbid conditions, colonoscopy and sigmoidoscopy screening were cost-effective up to age 79 years, whereas FIT screening was cost-effective up to age 80 years.

Incremental Cost-Effectiveness

We determined the optimal screening strategy for each cohort on the basis of the incremental cost-effectiveness ratios of the efficient screening strategies. In unscreened elderly persons with no comorbid conditions, colonoscopy screening was most effective and still cost-effective up to age 83 years (**Appendix Table 5** and **Figure 2**), sigmoidoscopy screening was the optimal strategy at age 84 years, and FIT screening was the optimal strategy at ages 85 and 86 years. In elderly persons with moderate comorbid conditions, colonoscopy screening was the optimal strategy up to age 80 years, sigmoidoscopy

Table 3 Costs of 1-Time Colonoscopy, Sigmoidoscopy, and FIT Screening in Elderly Persons Without Previous Screening With No Comorbid Conditions (compared with no screening; results per 1,000 individuals; 3% discounted).*

Screening strategy	Age	Costs (*$1,000)					
		Screening test†	*Diagnostic colonoscopies*	*Surveillance colonoscopies*	*Complications*	*LYs with CRC care‡*	Total§
1-time colonoscopy screening	**76**‖	*983*	*0*	*569*	*98*	*-925*	725
	80	*987*	*0*	*484*	*114*	*-483*	1,102
	85	*987*	*0*	*350*	*137*	*230*	1,705
	90	*986*	*0*	*239*	*168*	*737*	2,130
1-time sigmoidoscopy screening	**76**	*387*	*309*	*397*	*64*	*-718*	439
	80	*392*	*331*	*345*	*75*	*-380*	764
	85	*392*	*330*	*251*	*89*	*189*	1251
	90	*390*	*323*	*169*	*106*	*592*	1580
1-time FIT screening	**76**	*42*	*80*	*88*	*14*	*-7*	218
	80	*42*	*87*	*78*	*17*	*130*	355
	85	*42*	*93*	*62*	*23*	*356*	577
	90	*42*	*98*	*46*	*29*	*541*	756

FIT = fecal immunochemical test; LY = life-year; CRC = colorectal cancer

* Individuals are classified as having no comorbidity if none of the following conditions is present: an ulcer, a history of acute myocardial infarction, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

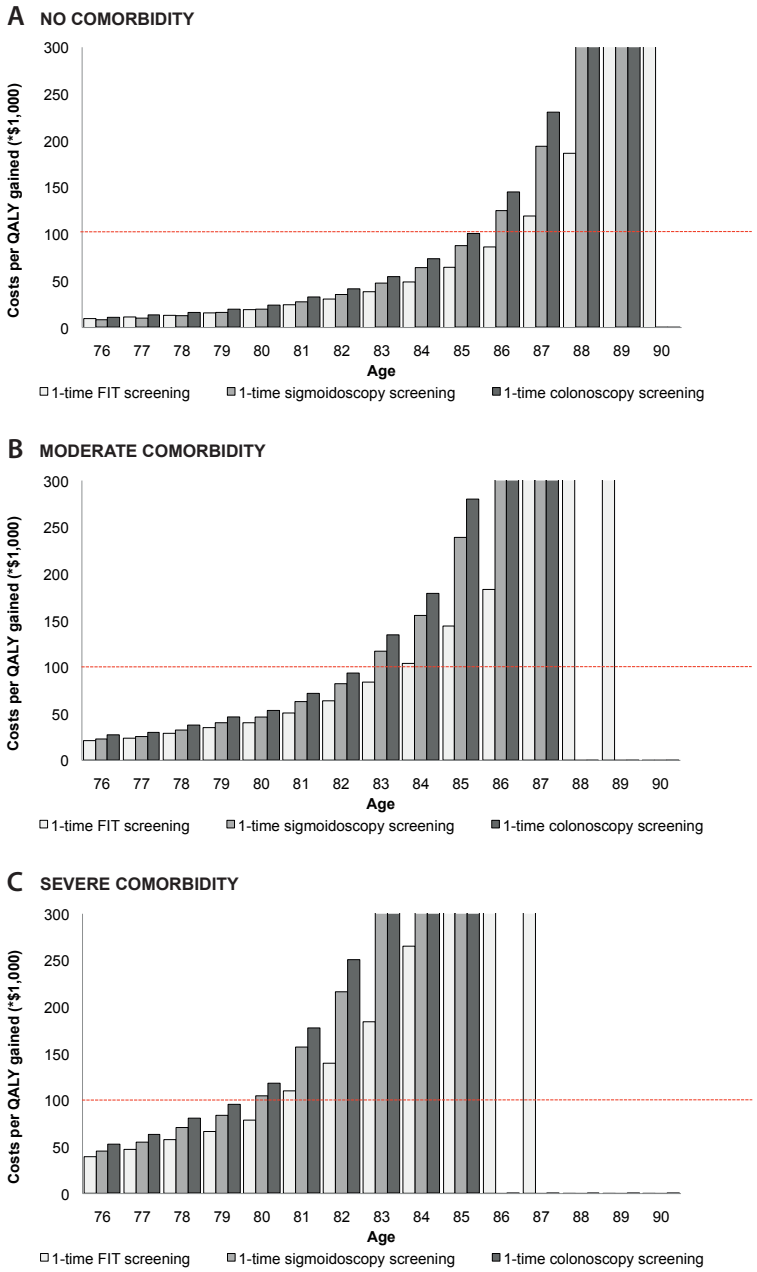
† At very advanced age, the costs of screening colonoscopies and sigmoidoscopies show a slight decline. This is explained by the small observed decrease in the prevalence of adenomas at very advanced age(11-18, 20, 21).

‡ Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be an increase in costs (positive values) or a decrease in costs (negative values).

§ Discrepancies between the columns might occur due to rounding.

‖ More detailed results for this cohort are given in **Appendix Table 2**.

Figure 1 Cost-effectiveness of 1-time colonoscopy, sigmoidoscopy, and FIT screening compared with no screening in elderly persons without previous screening with no, moderate, and severe comorbid conditions.



Results are presented per 1000 persons and discounted by 3% per year. Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions are present. The dashed line indicates a willingness to pay per QALY gained of $100 000. Screening strategies costing less than $100 000 per QALY gained are considered cost-effective. Asterisks for missing screening strategies indicate that they were associated with a net health loss rather than a benefit (**Appendix Table 3** and **Table 2**). FIT = fecal immunochemical test; QALY = quality-adjusted life-year.

screening was the optimal strategy at age 81 years, and FIT screening was the optimal strategy at ages 82 and 83 years. In persons with severe comorbid conditions, colonoscopy screening was the optimal strategy up to age 77 years, followed by sigmoidoscopy screening at age 78 years and FIT screening at ages 79 and 80 years.

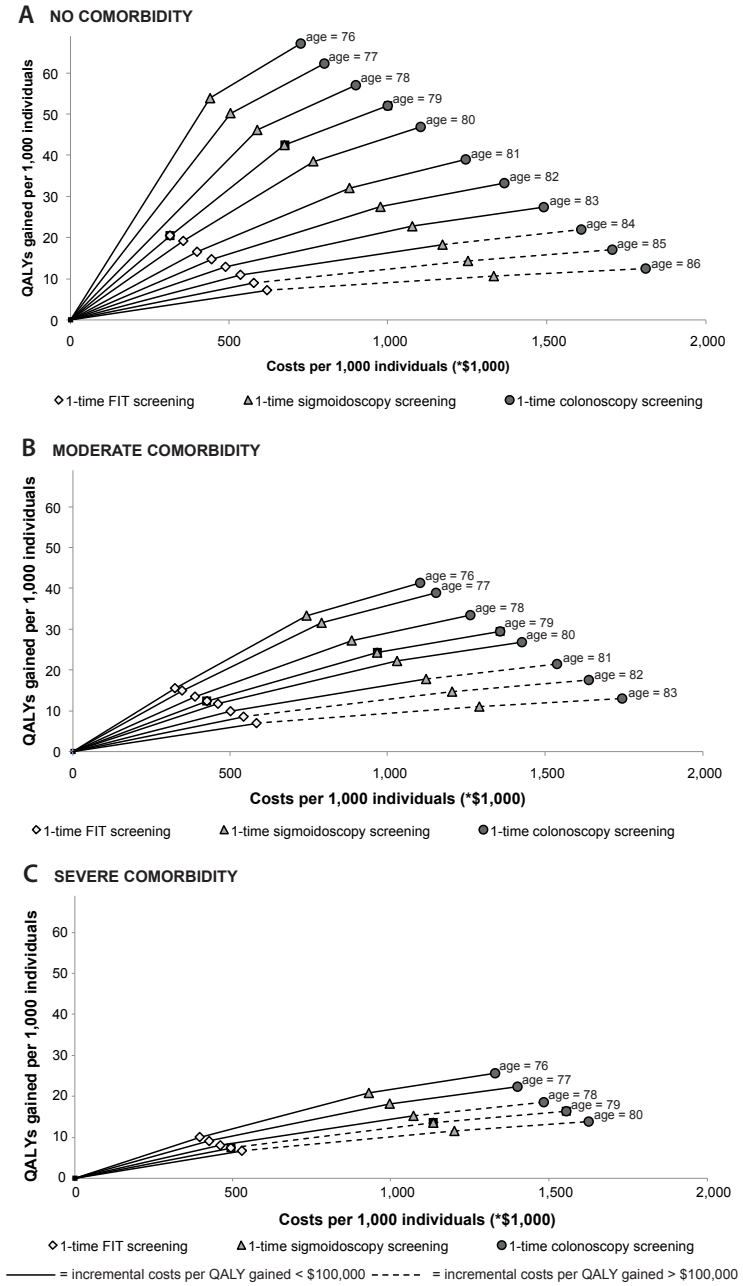
Sensitivity Analyses

Besides comorbid condition level, the upper age at which screening was cost-effective was most sensitive to lowering the willingness-to-pay threshold to $50 000 per QALY gained (**Appendix Table 6**). Based on this threshold, screening unscreened elderly persons with no, moderate, and severe comorbid conditions should be considered up to age 84, 80, and 77 years, respectively. The upper ages at which screening should be considered were robust to all other sensitivity analyses.

The tests that were indicated at specific ages differed substantially between analyses (**Appendix Table 6**). Besides the threshold for the willingness to pay per QALY gained, the level of CRC risk and utility losses associated with colonoscopy, sigmoidoscopy, and complications were the most important factors in this respect.

In persons aged 84 years without comorbid conditions and persons aged 78 years with severe comorbid conditions, sigmoidoscopy screening was not cost-effective compared with FIT screening during 2 consecutive years (**Appendix Table 6**). In persons aged 85 years without comorbid conditions, persons aged 82 years with moderate comorbid conditions, and persons aged 79 and 80 years with severe comorbid conditions, FIT screening during 2 consecutive years was cost-effective compared with 1-time FIT screening.

Figure 2 The incremental cost-effectiveness of the efficient screening strategies in elderly persons without previous screening with no, moderate, and severe comorbid conditions.



Results are presented per 1000 persons and discounted by 3% per year. Persons are classified as having moderate comorbid conditions if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions are present. In elderly persons without previous screening with no, moderate, or severe comorbid conditions, none of the screening strategies are cost-effective from age 87, 84, and 81 years onward, respectively (**Figure 1**). For each age, the efficient screening strategies are connected by an efficiency frontier. A solid line indicates that the ICER of a screening strategy is <$100 000 per QALY gained, implying that the strategy is considered cost-effective. A dashed line indicates that the ICER of a screening strategy exceeds $100 000 per QALY gained, implying that the strategy is not considered cost-effective. FIT = fecal immunochemical test; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

DISCUSSION

Our study shows that in elderly persons without previous screening for CRC, screening remains cost-effective well beyond age 75 years, which is the recommended age to discontinue screening in adequately screened persons (**Table 4**). In unscreened elderly persons with no comorbid conditions, screening was cost-effective up to age 86 years. Screening with colonoscopy was most effective and still cost-effective up to 83 years, sigmoidoscopy was indicated at age 84 years, and FIT was indicated at ages 85 and 86 years. In unscreened elderly persons with moderate comorbid conditions, screening was cost-effective up to age 83 years (colonoscopy indicated up to age 80 years, sigmoidoscopy at age 81 years, and FIT at ages 82 and 83 years). In persons with severe comorbid conditions, screening was cost-effective up to age 80 years (colonoscopy indicated up to age 77 years, sigmoidoscopy at age 78 years, and FIT at ages 79 and 80 years).

In a situation when an elderly person is willing to have only 1 type of screening test, the cost-effectiveness of that test compared with no screening becomes relevant. In such a person without comorbid conditions, colonoscopy and sigmoidoscopy screening can be considered up to age 85 years and FIT screening can be considered up to age 86 years. The ages for similar persons with moderate comorbid conditions are 82 years for colonoscopy and sigmoidoscopy and 83 years for FIT; for persons with severe comorbid conditions, the ages are 79 years for colonoscopy and sigmoidoscopy and 80 years for FIT. Although the incidence of CRC increases up to very advanced ages (19), the effectiveness of screening declines with increasing age. This decline is primarily explained by the increasing risk for other-cause death with age, which reduces both the probability that screening will prevent CRC death and the number of LYs gained if death is prevented. Moreover, the risks for screening-induced harms (colonoscopy-related complications and, more importantly, overdiagnosis and overtreatment of CRC) increase with age (9). At the same time, the shift from preventing to overtreating CRC causes the net costs of screening to increase with age. Together, these phenomena explain the rapid deterioration of the cost-effectiveness of screening with increasing age.

Table 4 Results Summary of CRC Screening Indicated in Elderly Persons Without Previous Screening.

Comorbidity status*	Up to what age should CRC screening be considered?	Which screening strategy is indicated at what age?											
		Age											
		76	77	78	79	80	81	82	83	84	85	86	
No comorbidity	86	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT	
Moderate comorbidity	83	COL	COL	COL	COL	COL	SIG	FIT	FIT				
Severe comorbidity	80	COL	COL	SIG	FIT	FIT							

CRC = colorectal cancer; COL = 1-time colonoscopy screening; SIG = 1-time sigmoidoscopy screening; FIT = 1-time fecal immunochemical test screening

*Individuals are classified as having moderate comorbidity if diagnosed with an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, or cerebrovascular disease and in case of a history of acute myocardial infarction; as having severe comorbidity if diagnosed with constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and as having no comorbidity if none of these conditions is present.

Although colonoscopy every 10 years, sigmoidoscopy every 5 years, and FIT every year are almost equally effective when applied from age 50 to 75 years (1, 2), colonoscopy is more effective than sigmoidoscopy and FIT when only 1 screening examination is performed because of its greater overall sensitivity for adenomas and CRC. However, because colonoscopy is also more expensive than sigmoidoscopy and FIT and because the effectiveness of all screening tests is marginal at very advanced ages, screening with colonoscopy is not cost-effective compared with sigmoidoscopy and FIT at the most advanced ages at which screening should be considered.

Screening remains cost-effective up to a more advanced age in persons without comorbid conditions than in those with comorbid conditions because their more favorable life expectancy increases the probability that screening will prevent CRC, thus increasing the effectiveness of screening while simultaneously reducing the costs of CRC care.

To our knowledge, our study is the first to investigate the net health benefit and the cost-effectiveness of CRC screening in persons older than 75 years without previous screening. An earlier study by Ko and Sonnenberg (7) demonstrated that the effectiveness of screening for preventing CRC death declines with increasing age, whereas the probability of screening-related complications increases with age. Further, a study by Lin and colleagues (8) demonstrated that the number of LYs gained by screening declines with age, resulting in an increase in the number of colonoscopies required per LY gained. However, neither study considered costs or measured the overdiagnosis and overtreatment of cancer, which is the most important adverse effect of screening in elderly persons. As a result, these studies cannot easily be used to determine whether unscreened elderly persons should be screened. Some other, more recent studies have suggested that screening should be continued after age 75 years (3, 4). However, these studies did not distinguish between adequately screened elderly persons and elderly persons without previous screening. Further, these studies based their conclusions only on CRC incidence data.

The USPSTF selected its recommended screening strategies on the basis of the number of colonoscopies required per LY gained (undiscounted) (1, 2), but we based our conclusions on the costs per QALY gained (discounted at 3% per year). We did so for 2 reasons. First, policymakers should be able to compare the efficiency of a wide range of health interventions; the USPSTF outcome measure does not allow for this. Second, we believe that effects on both length and quality of life should be considered. However, the 2 approaches led to screening recommendations associated with similar numbers of colonoscopies per LY gained: Screening with colonoscopy as recommended by the USPSTF (that is, at ages 50, 60, and 70 years) required 30 to 35 colonoscopies per LY gained (2). Also, screening with colonoscopy in unscreened persons aged 83 years with no comorbid conditions, for example, required 32 colonoscopies per LY gained.

Our study has 2 main limitations. First, we did not perform separate analyses by sex and race. However, we do not expect that results from such analyses would have differed

much from those reported here because a substantial part of the difference in life expectancy between men and women and between black and white persons is explained by differences in the prevalence of moderate and severe comorbid conditions. Also, persons with the most favorable life expectancy (that is, white females) are at lowest risk for CRC and vice versa. Hence, the effect of life expectancy on the cost-effectiveness of screening is counterbalanced by the effect of CRC risk (at least partially) (35). Second, we did not perform separate analyses for identifiable high-risk subgroups, such as elderly persons with a family history of CRC (36). In some of these subgroups, screening may be cost-effective up to a more advanced age.

Our analysis highlights some future research directions. First, future research should determine the optimal number of FIT screenings in elderly persons who are relatively young and not willing to have a screening colonoscopy or sigmoidoscopy. Second, other research should study how the benefits, burden, and harms of screening affect patient decisions about CRC screening. Third, studies evaluating the appropriate age to stop screening by comorbid condition level are also required for adequately screened persons.

In conclusion, our study demonstrates that in the 23% of US elderly persons without previous screening, CRC screening should be considered well beyond age 75 years. In unscreened elderly persons with no comorbid conditions, CRC screening should be considered up to age 86 years (up to age 83 years for those with moderate comorbid conditions and up to age 80 years for those with severe comorbid conditions). Screening with colonoscopy is indicated at most ages.

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Appendix, Table 1 Test Characteristics of Colonoscopy, Sigmoidoscopy, and FIT.

Test Characteristic	Test		
	Colonoscopy	Sigmoidoscopy	FIT
Specificity	90%*	92%*	97.7%
Sensitivity			
Small adenomas (≤5mm)	75%†	75%†	0%‡
Medium-sized adenomas (6-9mm)	85%†	85%†	5.2%‡
Large adenomas (≥10mm)	95%†	95%†	26%‡
CRCs that would not have been clinically detected in their current stage	95%†	95%†	41%‡
CRCs that would have been clinically detected in their current stage	95%†	95%†	77%‡
Reach	95% reaches the cecum; the reach of the remaining 5% is distributed uniformly over colon and rectum	100% reaches the recto-sigmoid junction, 88% reaches the sigmoid-descending junction, 6% reaches the splenic flexure§	whole colon and rectum
Complication rate			
Positive test	increases exponentially with age; from 20 per 1,000 colonoscopies at age 76 to 48 per 1,000 colonoscopies at age 90‖	0	0
Negative test	0	0	0
Mortality rate			
Positive test	0.033 per 1,000¶	0	0
Negative test	0	0	0

*We assumed that in 10% of all negative colonoscopies and in 8% of all negative sigmoidoscopies a non-adenomatous lesion was detected, resulting in a polypectomy or a biopsy, respectively.
†The sensitivity of colonoscopy and sigmoidoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies (39).
‡The test characteristics of FIT were fitted to the positivity rates and detection rates as observed in the first screening round of the Dutch screening trial. We assumed that the probability that a CRC bleeds and thus the sensitivity of FIT for CRC depends on the time until clinical diagnosis, in concordance with our findings for gFOBT (25).
§The reach of sigmoidoscopy was obtained from a study by Painter and colleagues (38).
‖ Age-specific risks for complications of colonoscopy requiring a hospital admission or emergency department visit were obtained from a study by Warren and colleagues (9).
¶ The mortality rate associated with colonoscopies with a polypectomy was derived by multiplying the risk for a perforation obtained from a study by Warren and colleagues by the risk of mortality after a perforation obtained from a study by Gatto and colleagues (9, 37).

Appendix, Table 2 The Effects of 1-time Colonoscopy Screening in 76-Year-Olds Without Prior Screening Without Comorbid Conditions (results per 1,000 individuals; 3% discounted).*

	Screening	No screening	Screening - No screening†
EFFECTS ON HEALTH CARE USE			
Colonoscopies			
Screening - polypectomy	461	0	461
Screening - no polypectomy	539	0	539
Surveillance - polypectomy	219	0	219
Surveillance - no polypectomy	370	0	370
Complications of colonoscopy	16.2	0	16.2
LYs with initial CRC care‡			
Stage I	11.5	6.4	5.1
Stage II	8.0	12.4	-4.4
Stage III	5.1	7.3	-2.2
Stage IV	0.7	2.9	-2.2
LYs with continuing CRC care			
Stage I	92.8	34.9	57.9
Stage II	60.0	61.6	-1.6
Stage III	33.9	30.7	3.2§
Stage IV	1.5	5.2	-3.7
LYs with terminal care - CRC			
Stage I	0.5	0.7	-0.2
Stage II	1.0	2.6	-1.6
Stage III	1.5	3.2	-1.8
Stage IV	1.1	5.8	-4.7
LYs with terminal care - other cause			
Stage I	8.3	5.1	3.2
Stage II	5.4	9.3	-4.0
Stage III	2.9	4.6	-1.8
Stage IV	0.2	1.0	-0.8
EFFECTS ON HEALTH			
CRC cases	27.9	43.4	-15.4
CRC deaths	4.5	16.4	-11.9
LYs lost due to CRC (A)	32.5	100.9	-68.5‖
Utility losses (QALYs)			
Screening colonoscopies	5.5	0	5.5
Surveillance colonoscopies	3.2	0	3.2
Complications of colonoscopy	0.6	0	0.6
LYs with CRC care	25.7	33.8	-8.1
Total (B)	35.1	33.8	1.3
QALYs lost (A+B)	67.5	134.7	-67.2¶

Appendix, Table 2 Continued.

	Screening	No screening	Screening - No screening†
EFFECTS ON COSTS (*$1,000)			
Screening colonoscopies	983	0	983
Surveillance colonoscopies	569	0	569
Complications of colonoscopy	98	0	98
LYs with CRC care	2,404	3,329	-925
Total	4,054	3,329	725**

LY = life-year; CRC = colorectal cancer; QALY = quality-adjusted life-year

*Individuals are classified as having no comorbidity if none of the following conditions is present: an ulcer, a history of acute myocardial infarction, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

† Discrepancies between columns might occur due to rounding.

‡ As screening results in the prevention and earlier detection of CRC, it reduces the total numbers of LYs with initial care for CRC, terminal care for CRC, and terminal care for other causes in CRC patients; however, as screening improves the average survival of CRC patients, it increases the total number of LYs with continuing care for CRC.

§ The increase in LYs with continuing care for stage III CRC is explained by the more favorable average survival that we model for screen-detected versus clinically detected cancers as described in the Model Appendix included at the end of this thesis.

‖ number of LYs gained by screening **(Table 2)**.

¶ The number of QALYs gained by screening **(Table 2)**.

The costs of screening **(Table 3).

Appendix, Table 3 The Effectiveness of 1-Time Colonoscopy, Sigmoidoscopy, and FIT Screening in Elderly Persons Without Prior Screening With Moderate and Severe Comorbid Conditions (compared with no screening; results per 1,000 individuals; 3% discounted).*

MODERATE COMORBIDITY					**Impact on quality of life (QALYs)§**					**QALYs gained¶**
		CRC cases prevented†	**CRC deaths prevented**	**LYs gained‡**	*Screening test*	*Diagnostic colonoscopies*	*Surveillance colonoscopies*	*Complications*	*LYs with CRC care‖*	
Screening strategy	**Age**			(A)	(B)	(C)	(D)	(E)	(F)	(A+B+C+D+E+F)
1-time colonoscopy screening	**76**	8.8	9.0	46.3	*-5.5*	*0*	*-2.6*	*-0.6*	*3.8*	41.4
	80	4.0	8.1	35.2	*-5.5*	*0*	*-2.2*	*-0.7*	*-0.0*	26.8
	85	-4.3	5.6	18.9	*-5.5*	*0*	*-1.6*	*-0.8*	*-4.2*	6.8
	90	-11.0	3.5	8.8	*-5.5*	*0*	*-1.1*	*-1.0*	*-6.1*	-4.8
1-time sigmoidoscopy screening	**76**	6.8	7.2	36.9	*-2.7*	*-1.6*	*-1.8*	*-0.4*	*2.9*	33.4
	80	3.1	6.6	28.7	*-2.7*	*-1.7*	*-1.6*	*-0.4*	*-0.1*	22.2
	85	-3.5	4.6	15.4	*-2.7*	*-1.7*	*-1.1*	*-0.5*	*-3.4*	5.9
	90	-8.8	2.9	7.1	*-2.7*	*-1.6*	*-0.7*	*-0.6*	*-4.9*	-3.5
1-time FIT screening	**76**	-0.1	3.3	17.9	*0*	*-0.4*	*-0.4*	*-0.1*	*-1.5*	15.6
	80	-1.9	3.4	15.4	*0*	*-0.4*	*-0.4*	*-0.1*	*-2.8*	11.7
	85	-4.8	2.7	9.4	*0*	*-0.5*	*-0.3*	*-0.1*	*-4.0*	4.6
	90	-7.7	1.9	4.8	*0*	*-0.5*	*-0.2*	*-0.2*	*-4.4*	-0.5
SEVERE COMORBIDITY										
		CRC cases prevented†	**CRC deaths prevented**	**LYs gained‡**	**Impact on quality of life (QALYs)§**					**QALYs gained¶**
					Screening test	*Diagnostic colonoscopies*	*Surveillance colonoscopies*	*Complications*	*LYs with CRC care‖*	
Screening strategy	**Age**			(A)	(B)	(C)	(D)	(E)	(F)	(A+B+C+D+E+F)
1-time colonoscopy screening	**76**	2.6	6.7	32.3	*-5.5*	*0*	*-2.0*	*-0.5*	*1.4*	25.7
	80	-2.2	5.9	23.3	*-5.5*	*0*	*-1.6*	*-0.6*	*-1.7*	13.9
	85	-9.4	4.0	12.2	*-5.5*	*0*	*-1.1*	*-0.8*	*-4.5*	0.4
	90	-14.6	2.6	5.8	*-5.5*	*0*	*-0.7*	*-1.0*	*-5.7*	-7.1
1-time sigmoidoscopy screening	**76**	2.0	5.3	25.8	*-2.7*	*-1.6*	*-1.4*	*-0.3*	*1.1*	20.8
	80	-1.9	4.8	19.0	*-2.7*	*-1.7*	*-1.2*	*-0.4*	*-1.4*	11.6
	85	-7.6	3.3	10.0	*-2.7*	*-1.7*	*-0.8*	*-0.5*	*-3.6*	0.6
	90	-11.7	2.1	4.6	*-2.7*	*-1.6*	*-0.5*	*-0.6*	*-4.5*	-5.4
1-time FIT screening	**76**	-2.2	2.5	12.7	*0*	*-0.4*	*-0.3*	*-0.1*	*-1.8*	10.1
	80	-4.2	2.5	10.4	*0*	*-0.4*	*-0.3*	*-0.1*	*-2.9*	6.7
	85	-7.1	2.0	6.2	*0*	*-0.5*	*-0.2*	*-0.1*	*-3.7*	1.7
	90	-9.5	1.4	3.2	*0*	*-0.5*	*-0.1*	*-0.2*	*-4.0*	-1.7

FIT = fecal immunochemical test; CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year

* Individuals are classified as having moderate comorbidity if diagnosed with an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, or cerebrovascular disease and in case of a history of acute myocardial infarction and as having severe comorbidity if diagnosed with constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

† Negative values occur when the number of CRC cases prevented by screening is exceeded by the number of CRC cases over-diagnosed by screening.

‡ The impact of screening on quantity of life.

§ The impact of the screening test, diagnostic colonoscopies, surveillance colonoscopies, complications, and LYs with CRC care on quality of life. Values are derived by multiplying number(s) of events with the corresponding utility loss(es) per event stated in Table 1. An example: When applying the once-only colonoscopy screening strategy, in each cohort, 1,000 individuals undergo a screening colonoscopy. As the utility loss per screening colonoscopy is 0.0055 QALYs, the total utility loss due to screening colonoscopies is 5.5 QALYs in each cohort.

‖ Screening results in a gain of quality of life by preventing LYs with CRC care and a loss of quality of life by adding LYs with CRC care. The net effect can be a gain of quality of life (positive values) or a loss of quality of life (negative values). As a result of the shift from preventing to over-diagnosing CRC with increasing age, the net effect on quality of life becomes less favorable with age.

¶ The impact of screening on quantity and quality of life incorporated in one measure, i.e. the net health benefit of screening. Discrepancies between the columns might occur due to rounding.

Appendix, Table 4 The Costs of 1-Time Colonoscopy, Sigmoidoscopy, and FIT Screening in Elderly Persons Without Prior Screening With Moderate and Severe Comorbid Conditions (compared with no screening; results per 1,000 individuals; 3% discounted).*

MODERATE COMORBIDITY							
		Costs (*$1,000)					
Screening strategy	**Age**	*Screening test†*	*Diagnostic colonoscopies*	*Surveillance colonoscopies*	*Complications*	*LYs with CRC care‡*	Total§
Once-only colonoscopy screening	**76**	*983*	*0*	*462*	*90*	*-434*	1,102
	80	*987*	*0*	*388*	*106*	*-57*	1,425
	85	*987*	*0*	*278*	*131*	*502*	1,898
	90	*986*	*0*	*185*	*161*	*838*	2,170
Once-only sigmoidoscopy screening	**76**	*387*	*309*	*323*	*58*	*-336*	742
	80	*392*	*331*	*278*	*69*	*-41*	1029
	85	*392*	*330*	*199*	*84*	*409*	1414
	90	*390*	*323*	*132*	*100*	*673*	1618
Once-only FIT screening	**76**	*42*	*80*	*72*	*13*	*116*	324
	80	*42*	*87*	*63*	*16*	*252*	460
	85	*42*	*93*	*50*	*22*	*448*	655
	90	*42*	*98*	*36*	*28*	*578*	782
SEVERE COMORBIDITY							
		Costs (*$1,000)					
Screening strategy	**Age**	*Screening test†*	*Diagnostic colonoscopies*	*Surveillance colonoscopies*	*Complications*	*LYs with CRC care‡*	Total§
Once-only colonoscopy screening	**76**	*983*	*0*	*354*	*83*	*-91*	1,329
	80	*987*	*0*	*288*	*99*	*250*	1,625
	85	*987*	*0*	*199*	*123*	*658*	1,967
	90	*986*	*0*	*131*	*154*	*868*	2,139
Once-only sigmoidoscopy screening	**76**	*387*	*309*	*248*	*52*	*-67*	930
	80	*392*	*331*	*206*	*63*	*207*	1200
	85	*392*	*330*	*143*	*77*	*534*	1477
	90	*390*	*323*	*94*	*95*	*698*	1600
Once-only FIT screening	**76**	*42*	*80*	*56*	*12*	*204*	395
	80	*42*	*87*	*47*	*15*	*337*	528
	85	*42*	*93*	*36*	*20*	*493*	685
	90	*42*	*98*	*26*	*27*	*576*	769

FIT = fecal immunochemical test; LY = life-year; CRC = colorectal cancer

*Individuals are classified as having moderate comorbidity if diagnosed with an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, or cerebrovascular disease and in case of a history of acute myocardial infarction and as having severe comorbidity if diagnosed with constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS.

†At very advanced age, the costs of screening colonoscopies and sigmoidoscopies show a slight decline. This is explained by the small observed decrease in the prevalence of adenomas at very advanced age (11-18, 20, 21).

‡Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be an increase in costs (positive values) or a decrease in costs (negative values).

§Discrepancies between the columns might occur due to rounding.

Appendix, Table 5 The Incremental Cost-Effectiveness Ratios (ICERs) of the Efficient Screening Strategies in Elderly Persons Without Prior Screening by Comorbidity Status (QALYs gained, incremental QALYs gained, costs, and incremental costs per 1,000 individuals; 3% discounted; visually displayed in Figure 2).*†

				NO COMORBIDITY			
	Screening strategy‡	**QALYs gained§**	**Incremental QALYs gained‖**	**Costs (*$1,000)**	**Incremental costs (*$1,000)**	**ICER (*$1,000)**	**Optimal screening strategy¶**
Age			(A)		(B)	(B/A)	
76**	Sigmoidoscopy	53.9	53.9	439	439	8	
	Colonoscopy	67.2	13.3	725	285	21	***X***
77**	Sigmoidoscopy	50.3	50.3	503	503	10	
	Colonoscopy	62.3	12.1	799	296	25	***X***
78**	Sigmoidoscopy	46.2	46.2	588	588	13	
	Colonoscopy	57.1	10.9	898	310	29	***X***
79	FIT	20.5	20.5	313	313	15	
	Sigmoidoscopy	42.5	22.0	673	360	16	
	Colonoscopy	52.1	9.6	998	325	34	***X***
80	FIT	19.2	19.2	355	355	18	
	Sigmoidoscopy	38.6	19.4	764	409	21	
	Colonoscopy	46.9	8.4	1102	338	40	***X***
81	FIT	16.6	16.6	398	398	24	
	Sigmoidoscopy	32.1	15.5	878	480	31	
	Colonoscopy	39.0	7.0	1244	366	53	***X***
82	FIT	14.8	14.8	444	444	30	
	Sigmoidoscopy	27.5	12.7	976	532	42	
	Colonoscopy	33.3	5.8	1365	390	68	***X***
83	FIT	12.9	12.9	488	488	38	
	Sigmoidoscopy	22.8	9.9	1076	588	60	
	Colonoscopy	27.4	4.7	1490	414	89	***X***
84	FIT	11.0	11.0	535	535	49	
	Sigmoidoscopy	18.3	7.3	1171	636	87	***X***
	Colonoscopy	22.0	3.7	1608	437	119	
85	FIT	9.0	9.0	577	577	64	***X***
	Sigmoidoscopy	14.3	5.3	1251	674	126	
	Colonoscopy	17.1	2.7	1705	454	166	
86	FIT	7.2	7.2	619	619	86	***X***
	Sigmoidoscopy	10.7	3.4	1332	714	208	
	Colonoscopy	12.5	1.8	1810	478	261	
				MODERATE COMORBIDITY			
	Screening strategy‡	**QALYs gained§**	**Incremental QALYs gained‖**	**Costs (*$1,000)**	**Incremental costs (*$1,000)**	**ICER (*$1,000)**	**Optimal screening strategy¶**
Age			(A)		(B)	(B/A)	
76	FIT	15.6	15.6	324	324	21	
	Sigmoidoscopy	33.4	17.8	742	418	23	
	Colonoscopy	41.4	8.0	1,102	361	45	***X***
77	FIT	15.0	15.0	347	347	23	
	Sigmoidoscopy	31.6	16.6	789	443	27	
	Colonoscopy	38.9	7.4	1,153	363	49	***X***
78	FIT	13.5	13.5	387	387	29	
	Sigmoidoscopy	27.3	13.8	885	497	36	
	Colonoscopy	33.5	6.2	1,262	377	61	***X***
79	FIT	12.4	12.4	426	426	34	
	Sigmoidoscopy	24.3	11.9	966	540	45	
	Colonoscopy	29.5	5.2	1,356	390	75	***X***

Appendix, Table 5 Continued

Age	Screening strategy‡	QALYs gained§	Incremental QALYs gained‖ (A)	Costs (*$1,000)	Incremental costs (*$1,000) (B)	ICER (*$1,000) (B/A)	Optimal screening strategy¶
			MODERATE COMORBIDITY				
80	FIT	11.7	11.7	460	460	39	
	Sigmoidoscopy	22.2	10.5	1,029	569	54	
	Colonoscopy	26.8	4.6	1,425	396	86	***X***
81	FIT	9.9	9.9	500	500	51	
	Sigmoidoscopy	17.8	7.9	1,121	621	79	***X***
	Colonoscopy	21.5	3.7	1,537	416	113	
82	FIT	8.6	8.6	542	542	63	***X***
	Sigmoidoscopy	14.7	6.1	1,204	662	108	
	Colonoscopy	17.6	2.8	1,638	434	152	
83	FIT	7.0	7.0	583	583	83	***X***
	Sigmoidoscopy	11.0	4.1	1,290	707	174	
	Colonoscopy	13.0	2.0	1,744	453	230	
			SEVERE COMORBIDITY				
Age	**Screening strategy‡**	**QALYs gained§**	**Incremental QALYs gained‖ (A)**	**Costs (*$1,000)**	**Incremental costs (*$1,000) (B)**	**ICER (*$1,000) (B/A)**	**Optimal screening strategy¶**
76	FIT	10.1	10.1	395	395	39	
	Sigmoidoscopy	20.8	10.8	930	535	50	
	Colonoscopy	25.7	4.8	1,329	399	83	***X***
77	FIT	9.1	9.1	425	425	47	
	Sigmoidoscopy	18.2	9.1	995	571	62	
	Colonoscopy	22.4	4.1	1,400	404	98	***X***
78	FIT	8.1	8.1	460	460	57	
	Sigmoidoscopy	15.3	7.2	1,071	611	85	***X***
	Colonoscopy	18.6	3.3	1,483	412	124	
79	FIT	7.4	7.4	493	493	66	***X***
	Sigmoidoscopy	13.6	6.1	1,134	640	104	
	Colonoscopy	16.4	2.8	1,554	420	150	
80	FIT	6.7	6.7	528	528	78	***X***
	Sigmoidoscopy	11.6	4.8	1,200	672	139	
	Colonoscopy	13.9	2.3	1,625	424	185	

QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; FIT = fecal immunochemical test

* Individuals are classified as having moderate comorbidity if diagnosed with an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, or cerebrovascular disease and in case of a history of acute myocardial infarction; as having severe comorbidity if diagnosed with constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and as having no comorbidity if none of these conditions is present.

† In elderly persons without prior screening with no, moderate, and severe comorbidity, none of the screening strategies is cost-effective from age 87, 84, and 81 onwards, respectively (**Figure 1**).

‡ All screening strategies consist of a one-time screening examination followed by diagnostic and surveillance colonoscopies if indicated.

§ Compared with no screening.

‖ Compared with the next less effective, efficient strategy, which is no screening for the first screening strategy mentioned at each age.

¶ The most effective, still cost-effective screening strategy based on a threshold for the willingness to pay per QALY gained of $100,000.

In elderly without prior screening with no comorbidity aged 76 up to 78, FIT screening is dominated by a combination of sigmoidoscopy and no screening (Figure 2**).

Appendix, Table 6 CRC Screening in Elderly Without Prior Screening: Results of Sensitivity Analyses.

NO COMORBIDITY

Analysis	Up to what age should CRC screening be considered?	Which screening strategy is indicated at what age?														
		Age														
		76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
Base Case	**86**	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT				
Utility loss colonoscopy, sigmoidoscopy, complication*0.5	86	COL	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT				
Utility loss colonoscopy, sigmoidoscopy, complication*2	86	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT	FIT	FIT				
Utility loss LYs with continuing care stage I, II CRC = 0.12, 0.18	84	COL	COL	COL	COL	COL	COL	COL	SIG	SIG						
Costs of colonoscopy, sigmoidoscopy, FIT*1.25	86	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT	FIT				
Costs of colonoscopy, sigmoidoscopy, FIT*0.75	86	COL	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT				
Costs of CRC care*1.25	86	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT				
Costs of CRC care*0.75	87	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT	FIT			
Miss rates colonoscopy, sigmoidoscopy*2	86	COL	COL	COL	COL	COL	COL	COL	COL	FIT	FIT	FIT				
No surveillance in adenoma patients	86	COL	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT				
CRC risk*1.25	86	COL	COL	COL	COL	COL	COL	COL	COL	COL	COL	FIT				
CRC risk*0.75	86	COL	COL	COL	COL	COL	SIG	SIG	SIG	FIT	FIT	FIT				
2 annual FITs as an additional screening strategy	86	COL	COL	COL	COL	COL	COL	COL	COL	2FITs	2FITs	FIT				
Threshold willingness to pay per QALY gained = $50,000	84	COL	COL	COL	COL	COL	SIG	SIG	FIT	FIT						

MODERATE COMORBIDITY

Analysis	Up to what age should CRC screening be considered?	Which screening strategy is indicated at what age?														
		Age														
		76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
Base Case	**83**	COL	COL	COL	COL	COL	SIG	FIT	FIT							
Utility loss colonoscopy, sigmoidoscopy, complication*0.5	84	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT						
Utility loss colonoscopy, sigmoidoscopy, complication*2	83	COL	COL	COL	SIG	FIT	FIT	FIT	FIT							
Utility loss LYs with continuing care stage I, II CRC = 0.12, 0.18	81	COL	COL	COL	COL	SIG	SIG									
Costs of colonoscopy, sigmoidoscopy, FIT*1.25	83	COL	COL	COL	COL	SIG	FIT	FIT	FIT							
Costs of colonoscopy, sigmoidoscopy, FIT*0.75	84	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT						
Costs of CRC care*1.25	83	COL	COL	COL	COL	COL	SIG	FIT	FIT							
Costs of CRC care*0.75	84	COL	COL	COL	COL	COL	SIG	FIT	FIT	FIT						
Miss rates colonoscopy, sigmoidoscopy*2	83	COL	COL	COL	COL	COL	SIG	FIT	FIT							
No surveillance in adenoma patients	84	COL	COL	COL	COL	COL	COL	COL	FIT	FIT						
CRC risk*1.25	83	COL	COL	COL	COL	COL	COL	COL	FIT							
CRC risk*0.75	83	COL	COL	SIG	SIG	SIG	FIT	FIT	FIT							
2 annual FITs as an additional screening strategy	83	COL	COL	COL	COL	COL	SIG	2FITs	FIT							
Threshold willingness to pay per QALY gained = $50,000	80	COL	COL	SIG	SIG	FIT										

Appendix, Table 6 Continued.

SEVERE COMORBIDITY

Analysis	Up to what age should CRC screening be considered?	Which screening strategy is indicated at what age?														
		Age														
		76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
Base Case	**80**	**COL**	**COL**	**SIG**	**FIT**	**FIT**										
Utility loss colonoscopy, sigmoidoscopy, complication*0.5	80	**COL**	**COL**	**COL**	**SIG**	**SIG**										
Utility loss colonoscopy, sigmoidoscopy, complication*2	80	**SIG**	**FIT**	**FIT**	**FIT**	**FIT**										
Utility loss LYs with continuing care stage I, II CRC = 0.12, 0.18	78	**COL**	**SIG**	**SIG**												
Costs of colonoscopy, sigmoidoscopy, FIT*1.25	80	**SIG**	**SIG**	**FIT**	**FIT**	**FIT**										
Costs of colonoscopy, sigmoidoscopy, FIT*0.75	80	**COL**	**COL**	**COL**	**SIG**	**SIG**										
Costs of CRC care*1.25	80	**COL**	**COL**	**SIG**	**SIG**	**FIT**										
Costs of CRC care*0.75	81	**COL**	**COL**	**SIG**	**FIT**	**FIT**	**FIT**									
Miss rates colonoscopy, sigmoidoscopy*2	80	**COL**	**COL**	**FIT**	**FIT**	**FIT**										
No surveillance in adenoma patients	81	**COL**	**COL**	**COL**	**SIG**	**FIT**	**FIT**									
CRC risk*1.25	80	**COL**	**COL**	**COL**	**COL**	**FIT**										
CRC risk*0.75	80	**SIG**	**SIG**	**FIT**	**FIT**	**FIT**										
2 annual FITs as an additional screening strategy	80	**COL**	**COL**	**2FITs**	**2FITs**	**2FITs**										
Threshold willingness to pay per QALY gained = $50,000	77	**SIG**	**FIT**													

CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year; COL = one-time colonoscopy screening; SIG = one-time sigmoidoscopy screening; FIT = one-time fecal immunochemical test screening; 2FITs = fecal immunochemical test screening during two consecutive years

*Individuals are classified as having moderate comorbidity if diagnosed with an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, or cerebrovascular disease, and in case of a history of acute myocardial infarction; as having severe comorbidity if diagnosed with constructive obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis or AIDS; and as having no comorbidity if none of these conditions is present.

6

Smarter Screening for Cancer: Possibilities and Challenges of Personalization

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An important emerging model for screening and many preventive strategies is personalization. This approach uses individual patient characteristics to project the benefit of screening for a given patient and has the potential to improve cancer outcomes while reducing the probability of harm and preserving scarce health care resources. Yet all too often, the existing health care system fails to personalize screening in even the most rudimentary way. A recent study found that 75-year-old patients with severe comorbidities were nearly 2 times more likely to be screened for colorectal cancer than 76-year-old patients with no comorbidities, even though healthy 76-year-old patients tend to live longer and gain greater benefit from screening.(1) In another study, 48% of primary care physicians reported that they would recommend breast cancer screening for women diagnosed with terminal lung cancer, a group of patients for whom screening cannot provide any benefit, may cause harm, and is a waste of resources.(2) Although most clinicians would agree that cancer screening should focus on patients most likely to benefit, the US health care system is failing to achieve this type of personalized care.

If most clinicians agree that cancer screening should be personalized, why is such an approach not implemented in practice? Numerous studies have demonstrated how the benefits of preventive services such as cancer screening change over the life span. Others have shown how the benefits vary by factors such as screening history and comorbidity status. Yet these data alone are clearly not enough. Indeed, a more systematic approach to synthesizing these data for clinical use and developing systems of care that support their implementation is needed. In this Viewpoint, we provide an overview of how personalized recommendations for cancer screening can be developed and discuss challenges to implementation that must be overcome if clinicians are to provide the best possible care for their patients.

The benefit of a given screening test for a given patient is a function of 2 key variables: cancer risk and life expectancy. However, unaided clinical judgment is not reliable for estimating these variables and integrating them into an appropriate screening recommendation for an individual patient. Although clinicians have at their disposal multiple prediction tools for both of these variables,(3,4) these tools are rarely used. One reason they are not used more frequently is that these tools do not provide clinically meaningful information needed for personalization. For instance, if prediction tools indicate that an individual has a 4-fold increased risk of developing lung cancer within the next 5 years and a life expectancy of 8 years, how should this information be used to arrive at a screening decision? For risk models to be useful in practice, a way is needed to translate simple risk estimates into clinically meaningful estimates of benefit, which can then be used to guide individual clinical decisions.

Clinical trials, which are often used to study screening tests, are not aimed at individual decision making, instead establishing overall causality and average efficacy. Thus, alternative methods are needed to personalize estimates of screening benefit. One alternative approach involves disease simulation modeling.(5,6) Simulation models have

the ability to simultaneously incorporate cancer risk, life expectancy, and screening efficacy, and, although less familiar to many clinicians than clinical trials, have been used to inform US Preventive Services Task Force (USPSTF) screening recommendations. Even though validated simulation models are available for a variety of screen-detectable cancers,(5) the capability of these models to provide personalized recommendations for screening has not been fully exploited.

MISCAN-Colon, a widely cited simulation model of colorectal cancer screening, can be used to illustrate how the benefit of screening can vary according to characteristics such as age, sex, race, screening history, comorbidity status, and exposure to risk factors for colorectal cancer ("background risk")(**Figure**). For example, all other factors being equal, a recently screened, average-risk, 75-year-old white woman with no comorbidities is nearly twice as likely to benefit from screening as one who has severe comorbidities (3.7 vs 2.2 cancer deaths prevented per 1000 individuals screened). Yet health status is not explicitly incorporated into current guidelines for colorectal cancer screening. Moreover, patients at low risk for colorectal cancer (either because of a prior negative screening colonoscopy or a low background risk for colorectal cancer) are substantially less likely to benefit from screening, but guidelines do not distinguish between individuals based on these factors.

These simple examples do not consider interactions between cancer risk and life expectancy, but models can quantitatively weigh such complexities. For instance, smoking and obesity are risk factors for colorectal cancer, but also are risk factors for early mortality. When these factors are weighed together, MISCAN-Colon suggests that an obese smoker should not be screened for colorectal cancer more aggressively than a nonobese nonsmoker.

Even with personalized screening recommendations available, this approach is unlikely to be accepted unless the context in which it will be implemented is considered. Patients and physicians may be unreceptive to personalized screening. For instance, personalized screening approaches would recommend against screening for low-benefit individuals. However, many patients are reluctant to stop screening even if the expected benefit is low.(8) For some patients, the necessary degree of benefit is likely to be substantially greater than physicians presume, such that these patients might elect less aggressive approaches than are currently suggested. Moreover, physicians might find personalization time consuming and cumbersome or might simply disagree with personalized recommendations, ultimately failing to incorporate them into their practice. In addition, systems of care may have existing approaches to screening that directly conflict with personalized recommendations. For example, current quality measures for colorectal cancer screening encourage screening individuals up to age 75 years.(1) A physician who appropriately discourages screening in a 74-year-old with limited life expectancy could be penalized under such age-based quality measures. As a result, physicians in such systems of care may be less likely to embrace a personalized approach.

Efforts at multiple levels are needed to overcome these challenges. At the patient level, personalized information about the benefits and harms of screening needs to be

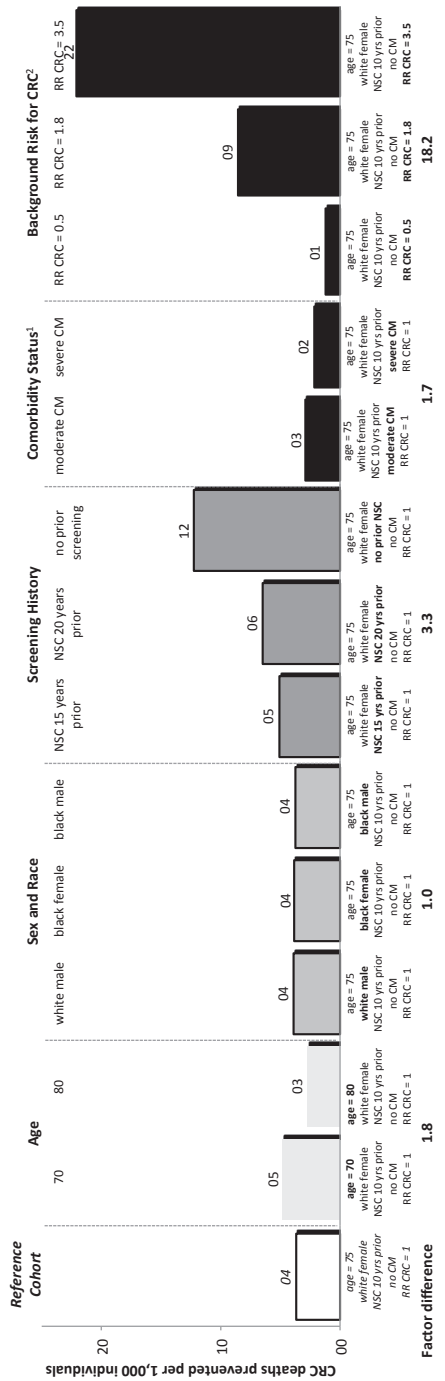

Figure Example of Relationship of Risk Factors With Lifetime Benefit of Colorectal Cancer Screening With Colonoscopy.

CRC = colorectal cancer; RR = relative risk.

The "reference cohort" consists of 75 year-old white females with no comorbidities, average colorectal cancer risk, and a negative screening colonoscopy 10 years prior.

[a] Individuals are classified as having moderate comorbidity if diagnosed with an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, or cerebrovascular disease and in case of a history of acutemyocardial infarction; as having severe comorbidity if diagnosed with chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and as having no comorbidity if none of these conditions is present.

[b] The range of the background risk for CRC is based on the National Cancer Institute's Colorectal Cancer Risk Assessment Tool.(7) In white women, the minimum background risk for CRC is 0.5, the maximum background risk in the absence of a family history of CRC is 1.8, and the maximum risk in the presence of a family history of CRC is 3.5.

incorporated into educational materials. We also need a better understanding of how to communicate such information so that it can be used to aid decision making. Similarly, physicians need easily accessible, personalized estimates of benefit (ideally embedded into electronic health record systems) to inform patient-physician discussions. Because many of these discussions will include estimates of life expectancy, they will be difficult. In addition, health care systems need to be willing to implement personalized approaches to screening and establish clinically sensitive, personalized measures of quality. For instance, colorectal cancer screening quality measures, which are currently based primarily on age, could be modified to use both age and health status. Better yet, these measures could consider whether an active discussion about the benefits and harms of screening took place, with an informed decision used as the marker of quality.

Current decisions about cancer screening are often based primarily on patient age. As a result, some patients who are likely to benefit from screening are not being screened, and others who are not likely to benefit are being screened unnecessarily. Simulation models, integrated with point-of-care decision aids and decision support tools, could help bridge the gap between prediction models and clinical decision making. Implementing personalized screening recommendations in clinical practice presents many challenges. However, these challenges must be met to provide optimal cancer screening for patients.

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7

Personalizing Colonoscopy Screening for Elderly Individuals Based on Screening History, Cancer Risk, and Comorbidity Status Could Increase Cost Effectiveness

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ABSTRACT

Background & Aims: Colorectal cancer (CRC) screening decisions for elderly individuals are often made based primarily on age—other factors that affect the effectiveness and cost effectiveness of screening are often not considered. We investigated the relative importance of factors that could be used to identify those elderly individuals most likely to benefit from CRC screening and determined the maximum ages at which screening remains cost effective based on these factors.

Methods: We used a microsimulation model (Microsimulation Screening Analysis-Colon) that was calibrated to the incidence of CRC in the US and the prevalence of adenomas reported in autopsy studies to determine the appropriate age to stop colonoscopy screening in 19,200 cohorts of individuals defined by sex, race, screening history, background risk for CRC, and comorbidity status. We applied a willingness-to-pay threshold of $100,000 per quality-adjusted life-year (QALY) gained.

Results: A less-intensive screening history, a higher background risk for CRC, and fewer comorbidities were associated with cost-effective screening at older ages. Sex and race had only a small effect on the appropriate age to stop screening. For some individuals likely to be screened in current practice (for example, 74-year-old white women with moderate comorbidities, half the average background risk for CRC, and negative findings from a screening colonoscopy 10 y prior), screening resulted in a loss of QALYs, rather than a gain. For some individuals unlikely to be screened in current practice (for example, 81-year-old black men with no comorbidities, an average background risk for CRC, and no prior screening), screening was highly cost effective. While screening some previously screened, low-risk individuals was not even cost effective at age 66 years, screening some healthy, high-risk individuals remained cost effective up to age 88 years.

Conclusion: The current approach to CRC screening in elderly individuals, in which decisions are often based primarily on age, is inefficient, resulting in underuse of screening for some and overuse of screening for others. CRC screening could be more effective and cost effective if individual factors for each patient were considered.

Keywords: colon cancer screening; individualized care; MISCAN; tumor

INTRODUCTION

Screening for colorectal cancer (CRC) has been shown to be effective and cost effective in reducing CRC mortality and is therefore widely recommended.(1-4) The US Preventive Services Task Force (USPSTF), for example, calls for routine screening for average risk individuals starting at age 50 years and continuing up to age 75 years.(1) Although clinicians are generally aware that factors other than age affect the effectiveness and cost effectiveness of CRC screening,(5) many make their decisions on screening for elderly individuals primarily based on age: individuals aged 75 years or younger are offered screening, whereas individuals aged over 75 years are not. This practice is in concordance with existing age-based guidelines and performance measures.(6) On the other hand, a substantial minority of clinicians still offer CRC screening to elderly individuals with a life-expectancy less than 5 years.(5, 7-9) Hence, screening is not always targeted at those elderly individuals most likely to benefit.

The effectiveness and cost effectiveness of screening for a particular elderly individual depend on two key variables: CRC risk and life-expectancy. Both of these variables are affected by age. With increasing age, the average risk for CRC increases, but simultaneously the average life-expectancy declines. This results in a deterioration of the effectiveness and cost effectiveness of screening with age. An individual's risk for CRC, however, is also affected by the individual's sex, race, screening history, and level of exposure to other risk factors for CRC, such as a family history of CRC and smoking (i.e., the individual's "background risk for CRC"). Similarly, an individual's life-expectancy is affected by the individual's sex, race, and comorbidity status. Therefore, ideally all these factors should be considered when making decisions about offering CRC screening.

The objective of this study was to determine the appropriate age to stop colonoscopy screening (i.e., the maximum age at which screening is cost effective) given an individual's sex, race, screening history, background risk for CRC, and comorbidity status. We focused on colonoscopy screening, because it is the most commonly used screening modality in the United States today.(10) Through this work, we hope to facilitate a more personalized approach to CRC screening for elderly individuals, which would ultimately result in more efficient screening. As the population ages, and clinicians are faced with increasing numbers of both healthy and unhealthy elderly individuals, such an approach will become increasingly relevant to clinical practice.

METHODS

To quantify the effectiveness and cost effectiveness of screening we used Microsimulation Screening Analysis-Colon (MISCAN-Colon).

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Center (Rotterdam, the Netherlands). The model's structure, underlying assumptions, and calibration are described in the **Model Appendix** at the end of this thesis. In brief, MISCAN-Colon simulates the life histories of a large population of persons from birth to death. As each simulated person ages, one or more adenomas may develop. These adenomas can progress from small (≤5mm in diameter), to medium (6-9mm), to large size (≥10mm). Some adenomas can develop into preclinical cancer, which may progress through stages I to IV. However, during each stage, CRC may also be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the localization of the cancer, and the person's age.

Screening will alter some of the simulated life histories. Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favorable survival. However, screening can also result in serious complications and overdiagnosis and overtreatment of CRC. By comparing all life histories with screening with the corresponding life histories without screening, MISCAN-Colon quantifies the effectiveness of screening as well as the associated costs.

For our current study, we calibrated four distinct versions of MISCAN-Colon: a version for white men, white women, black men, and black women (**Model Appendix**). To do so, we used sex- and race-specific data on the age-, stage-, and localization-specific incidence of CRC as observed in the US before the introduction of mass endoscopic screening (i.e. between 1990 and 1994) and data on the age-specific prevalence and multiplicity distribution of adenomas as observed in autopsy studies.(11-21) Moreover, we used US sex- and race-specific CRC survival data.(22) We assumed that the average preclinical duration of CRC and adenoma dwell-time were independent of sex and race. These durations were calibrated to the rates of interval and surveillance-detected cancers observed in randomized controlled trials evaluating screening using guaiac fecal occult blood tests and a once-only sigmoidoscopy.(23-27)

Model Inputs

Populations Simulated

We simulated a cohort of 10 million individuals for each combination of:

I. Age (66/ 67/ (…)/ 90 years);
II. Sex (men/ women);
III. Race (black/ white);
IV. Screening history (negative finding from a screening colonoscopy 10 years prior/ 15 years prior/ 20 years prior/ no prior screening);
V. Background risk for CRC (white men: 17 levels, white women: 14 levels, black men: 18 levels, black women: 15 levels (see below)); and

VI. Comorbidity status (no/ moderate/ severe comorbidities (see below)).

This amounted to a total of 19,200 cohorts. Our analysis does not address individuals previously diagnosed with an adenoma or CRC.

Background Risk for CRC

To determine plausible sex- and race-specific ranges for the background risk for CRC, we used the National Cancer Institute's Colorectal Cancer Risk Assessment Tool (**Appendix 1**).(28, 29) This tool allowed us to determine an individual's background risk for CRC based on the following risk factors: the number of first-degree relatives with CRC, current leisure-time vigorous activity, aspirin/ NSAID use, vegetable intake, body mass index, current and past smoking (men only), and estrogen status within the last two years (women only). Based on these risk factors, the background risk for CRC in white women ranged from 0.5 times up to 3.5 times the average background risk in white women. The corresponding ranges in white men, black women, and black men were 0.5-4.9, 0.4-3.5, and 0.5-5.3, respectively. For each combination of sex and race, we modeled cohorts with the minimum risk, the maximum risk, all risks between the minimum risk and average risk using an increment of 0.1, all risks between the average risk and twice the average risk using an increment of 0.2, and all risks between twice the average risk and the maximum risk using an increment of 0.5. We modeled different risk levels by multiplying the age-specific onset rates of adenomas. We did not exclude individuals with a family history of CRC from our analyses.

Comorbidity Status

To simulate individuals with no, moderate, and severe comorbidities, we used US sex-, race-, and comorbidity status specific life-tables.(30) Individuals are classified as having moderate comorbidities if diagnosed with an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, or cerebrovascular disease and in case of a history of acute myocardial infarction; as having severe comorbidities if diagnosed with chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and as having no comorbidities if none of these conditions is present.

Screening Strategy

Within each cohort, we simulated a screening colonoscopy for all individuals simulated. Individuals in whom adenomas were removed were assumed to undergo colonoscopy surveillance according to the current guidelines.(31) We assumed that surveillance continued until the diagnosis of CRC or death. Adherence to surveillance was assumed to be 100%.

Test Characteristics of Colonoscopy

The sensitivity of colonoscopy for the detection of adenomas and CRC was obtained from a systematic review on miss rates observed in tandem colonoscopy studies and was 75%

for small adenomas (≤5mm in diameter), 85% for medium-sized adenomas (6-9mm), and 95% for large adenomas (≥10mm) and CRC.(32) We assumed that 95% of all colonoscopies reached the cecum; for the remaining 5% the reach of the procedure was assumed to be distributed uniformly over colon and rectum. Age-specific risks for nonlethal complications of colonoscopy were derived from a study by Warren and colleagues.(33, 34) We assumed that one of every 30,000 colonoscopies involving a polypectomy resulted in death.(34, 35)

Utility Losses Associated with Colonoscopy Screening

We assumed a utility loss (i.e., a loss of quality of life) equivalent to two full days of life per colonoscopy (0.0055 quality-adjusted life-years [QALYs]) and two weeks of life per complication (0.0384 QALYs). Utility losses for life-years (LYs) with CRC care were derived from a study by Ness and colleagues (**Table 1**).(36)

Costs Associated with Colonoscopy Screening

The cost effectiveness analyses were conducted from a societal perspective. The costs of colonoscopies were based on 2007 Medicare payment rates and copayments (**Table 1**).(37) The costs of complications were obtained from a cost analysis of cases of unexpected hospital use after endoscopy in 2007.(38) We added patient time costs to both.(39) The costs of LYs with CRC care were obtained from an analysis of Surveillance, Epidemiology, and End Results-Medicare linked data and included patient deductibles, copayments, and patient time costs.(40) We adjusted all costs to reflect the 2013 level using the US Consumer Price Index.(41)

Outcomes

For each cohort, we quantified the effectiveness of screening (i.e., the number of CRC cases prevented, CRC deaths prevented, LYs gained, and QALYs gained by screening) as well as the associated costs, applying the conventional 3% annual discount rate to both.(42) We expressed the cost effectiveness of screening in terms of the costs per QALY gained.

Analyses

For all demographic groups, we first quantified the effect of age on the effectiveness and cost effectiveness of screening. To demonstrate the (relative) importance of also considering factors other than age, we subsequently quantified the effect of screening history, background risk for CRC, and comorbidity status on the effectiveness and cost effectiveness of screening. Finally, we determined the appropriate age to stop screening given an individual's sex and race, screening history, background risk for CRC, and comorbidity status, applying the currently recommended willingness-to-pay threshold of $100,000 per QALY gained.(43)

Table 1 Model Inputs: Utility Losses and Costs Associated with Colonoscopy Screening.

	UTILITY LOSS (QALYs)[1]			
Per colonoscopy				
without polypectomy/ biopsy	0.005			
with polypectomy/ biopsy	0.005			
Per complication of colonoscopy	0.038			
Per LY with CRC care[2, 3]	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	0.12	0.05	0.70	0.05
Stage II CRC	0.18	0.05	0.70	0.05
Stage III CRC	0.24	0.24	0.70	0.24
Stage IV CRC	0.70	0.70	0.70	0.70
	COSTS (2013 US$)[4]			
Per colonoscopy				
without polypectomy/ biopsy	887			
with polypectomy/ biopsy	1,096			
Per complication of colonoscopy	6,045			
Per life-year with CRC care[2]	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	36,683	3,050	63,809	19,176
Stage II CRC	49,234	2,870	63,555	17,279
Stage III CRC	59,759	4,021	67,041	21,457
Stage IV CRC	77,790	12,178	88,368	49,866

QALY = quality-adjusted life-year; LY = life-year; CRC = colorectal cancer

[1] The loss of quality of life associated with a particular event.

[2] Care for CRC was divided in three clinically relevant phases: the initial, continuing, and terminal care phase. The initial care phase was defined as the first 12 months after diagnosis; the terminal care phase was defined as the final 12 months of life; the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between CRC patients dying from CRC and CRC patients dying from another cause. For patients surviving less than 24 months, the final 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.

[3] Utility losses for LYs with initial care were derived from a study by Ness and colleagues.(36) For LYs with continuing care for stage I and II CRC, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV CRC, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for CRC, we assumed the utility loss for LYs with initial care for stage IV CRC. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.

[4] Costs include copayments and patient time costs (i.e. the opportunity costs of spending time on screening or being treated for a complication or CRC), but do not include travel costs, costs of lost productivity, and unrelated health care and non-health care costs in added years of life. We assumed that the value of patient time was equal to the median wage rate in 2012: $16.71 per hour.(39) We assumed that colonoscopies and complications used up 8 and 16 hours of patient time, respectively. Patient time costs were already included in the estimates for the costs of LYs with CRC care obtained from a study by Yabroff and colleagues.(40)

Sensitivity Analyses

We repeated our analyses assuming 1) 50% higher and 50% lower utility losses for colonoscopies and complications; 2) 25% higher and 25% lower costs for colonoscopies; 3) 25% higher and 25% lower costs for CRC care; and 4) a cost effectiveness threshold of $50,000 per QALY gained. Moreover, we performed a multivariate probabilistic sensitivity analysis on the above-mentioned utility losses and costs for one representative case (details on this analysis are given in **Appendix 5**).

RESULTS

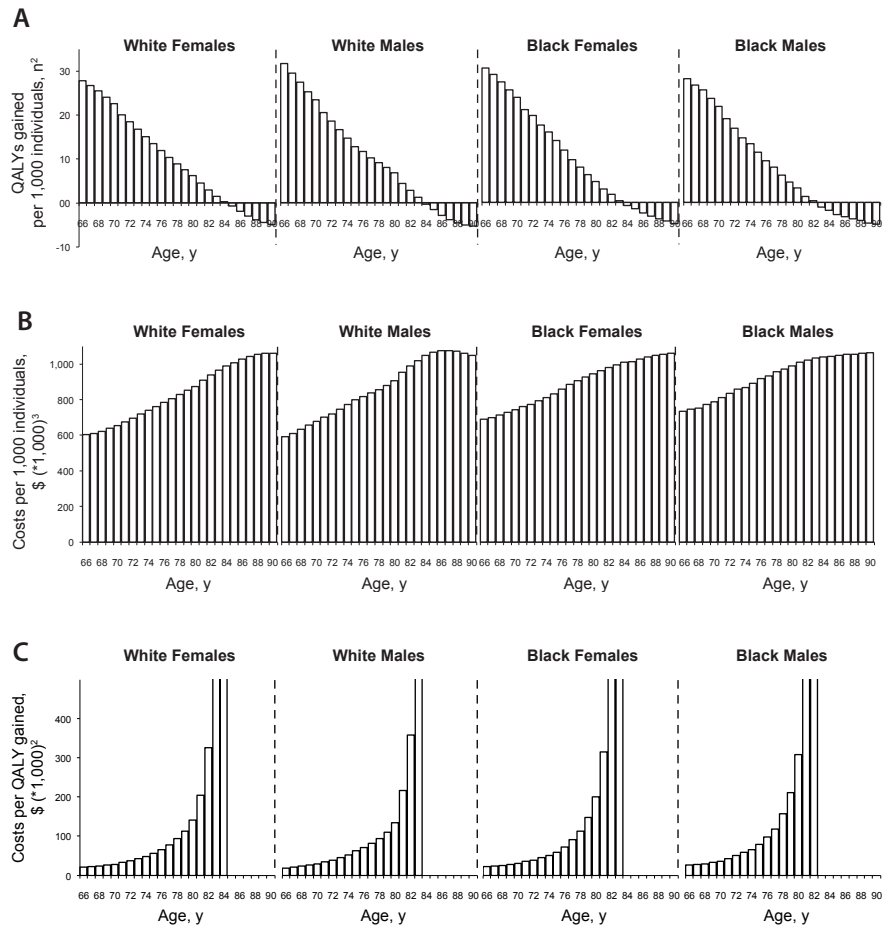
The Effect of Age on the Effectiveness and Cost Effectiveness of Screening

The effectiveness of colonoscopy screening declined with increasing age. While screening healthy, average risk, white women with a negative screening colonoscopy 10 years prior resulted in 27.8 QALYs gained per 1,000 women aged 66 years, it resulted in a loss of QALYs, rather than a gain in women aged 85 years and older (**Figure 1A**). On the other hand, the costs of screening increased with age: from $602,000 per 1,000 women aged 66 years to $1,061,000 per 1,000 women aged 90 years (**Figure 1B**). As a result, the cost effectiveness of screening deteriorated with age. While screening was associated with a cost of $22,000 per QALY gained for women aged 66 years, it was associated with a cost of nearly $4M per QALY gained for women aged 84 years (**Figure 1C**). Sex and race had relatively little effect on the effectiveness and cost effectiveness of screening (**Figure 1**).

The Effect of Factors Other than Age on the Effectiveness and Cost Effectiveness of Screening

Screening history and comorbidity status had a large effect on the effectiveness of colonoscopy screening. While screening healthy, average risk, 75-year-old, white women with a negative screening colonoscopy 10 years prior (our "reference cohort" for this comparison) resulted in 13.4 QALYs gained per 1,000 women, screening women with identical characteristics, but without prior screening, resulted in 55.2 QALYs gained per 1,000 women (factor difference = 55.2 QALYs gained/ 13.4 QALYs gained = 4.1) (**Figure 2A**). Similarly, screening women with severe, rather than no comorbidities resulted in 4.3 QALYs gained per 1,000 women (factor difference = 3.1). These relative differences in effectiveness were comparable to the difference in effectiveness between screening 70-year-old and 80-year-old women. Nevertheless, the most important factor influencing the effectiveness of screening was the individual's background risk for CRC. While screening women with the lowest possible background risk resulted in 0.8 QALYs gained per 1,000 women, screening women with the highest possible background risk resulted in 106.5 QALYs gained per 1,000 women (factor difference = 137.7). The relative effect of all factors on the cost effectiveness of screening was slightly larger than the corresponding effect on the

Figure 1 The Effect of Age on the Effectiveness (A), Costs (B), and Cost Effectiveness (C) of Colonoscopy Screening: Results for Average Risk Individuals with a Negative Screening Colonoscopy 10 Years Prior and No Comorbidities (QALYs gained and costs per 1,000 individuals; 3% discounted).



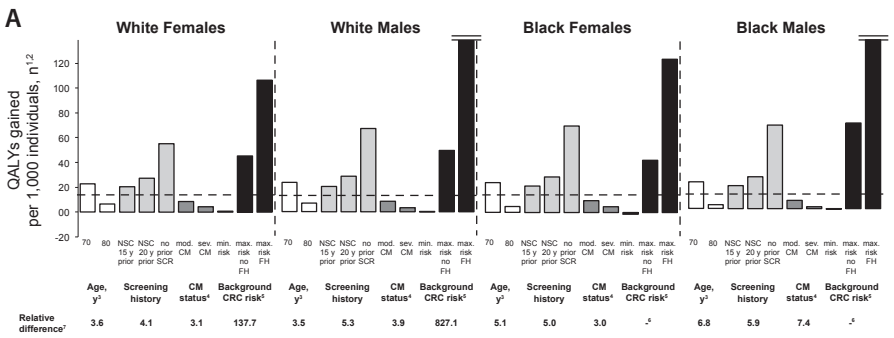
QALY = quality-adjusted life-year

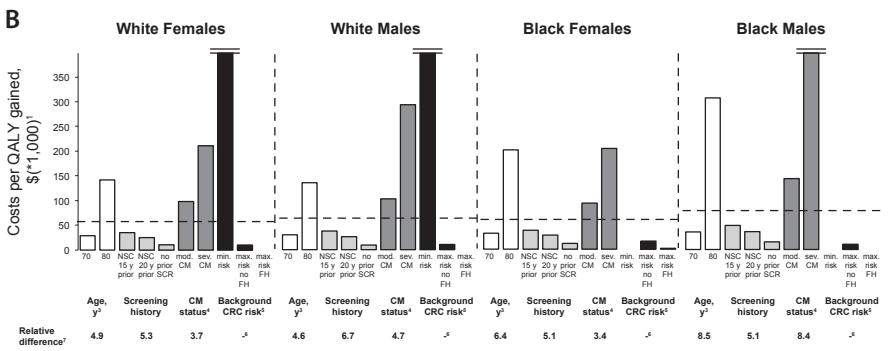
[1] Detailed results on the effectiveness and costs of screening can be found in **Appendix 2**.

[2] The effect of screening on quantity and quality of life incorporated in one measure (i.e. the net health benefit of screening). A negative value indicates that screening is associated with a net harm, rather than a net health benefit.

[3] The costs of screening and surveillance colonoscopies, complications of colonoscopy, and overtreatment of CRC minus the savings associated with preventing CRC treatment.

Figure 2 The Relative Effect of Age, Screening History, Comorbidity Status, and Background Risk for CRC on the Effectiveness (A) and Cost Effectiveness (B) of Colonoscopy Screening (QALYs gained per 1,000 individuals; 3% discounted).





CRC = colorectal cancer; QALY = quality-adjusted life-year; NSC = negative screening colonoscopy; SCR = screening; RR CRC = background risk for CRC; CM = comorbidities; FH = family history; CS = cost saving; NE = negative effect

[1] The dashed lines indicate results for healthy, average risk, 75-year-old individuals with a negative screening colonoscopy 10 years prior.

[2] The effect of screening on quantity and quality of life incorporated in one measure (i.e. the net health benefit of screening). A negative value indicates that screening is associated with a net harm, rather than a net health benefit.

[3] See also **Figure 1**.

[4] Individuals are classified as having moderate comorbidities if diagnosed with an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, or cerebrovascular disease and in case of a history of acute myocardial infarction; as having severe comorbidities if diagnosed with chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS; and as having no comorbidities if none of these conditions is present. 'Moderate comorbidities' corresponds with 'low/medium comorbidity' and 'severe comorbidities' corresponds with 'high comorbidity' as used in the study by Cho and colleagues.(30)

[5] The range of the background risk for CRC is based on the National Cancer Institute's Colorectal Cancer Risk Assessment Tool.(28) This tool incorporates the following risk factors: the number of first-degree relatives with CRC, current leisure-time vigorous activity, aspirin/ NSAID use, vegetable intake, body mass index, current and past smoking (men only), and estrogen status within the last two years (women only). In white women, the minimum background risk for CRC is 0.5, the maximum background risk in the absence of a family history of CRC is 2.0, and the maximum background risk in the presence of a family history of CRC is 3.5. In white men, black women, and black men, the corresponding risks are 0.5, 2.0, and 4.9; 0.4, 1.8, and 3.5; and 0.5, 2.5, and 5.3, respectively.

[6] Cannot be calculated.

effectiveness of screening (**Figure 2B**). The relative importance of considering factors other than age did not differ substantially by sex and race (**Figure 2**).

The Appropriate Ages to Stop Screening

As expected, screening was cost effective up to a more advanced age for individuals without prior screening compared with individuals with prior screening; for individuals without comorbidities compared with individuals with comorbidities; and for individuals with a high background risk for CRC compared with individuals with a low background risk for CRC (**Table 2**).

Table 3 shows the appropriate ages to stop screening for all individuals. Although screening some previously screened, low risk individuals was not even cost effective at age 66 years, screening some healthy, high risk individuals was cost effective up to age 88 years. Results were comparable across the demographic groups.

Sensitivity Analyses

Results were robust to varying the utility losses associated with colonoscopies and complications and to varying the costs of colonoscopies and CRC care (**Appendix 4** [univariate deterministic sensitivity analyses] and **Appendix 5** [multivariate probabilistic sensitivity analysis]). Applying a willingness-to-pay threshold of $50,000 instead of $100,000 per QALY gained reduced the maximum age at which screening was cost effective by an average of 3 years.

Table 2 The Costs per QALY Gained (*$1,000) of Colonoscopy Screening for White Females by Screening History, Comorbidity Status, Background Risk for CRC, and Age (3% discounted).[1]

NEGATIVE SCREENING COLONOSCOPY 10 YEARS PRIOR

NO COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5[4]	3.0[4]	3.5[4]
66	124	73	51	37	28	22	14	9	5	3	1	CS	CS	CS
68	152	86	59	42	31	24	16	10	6	4	2	CS	CS	CS
70	202	108	70	50	38	29	19	12	8	5	3	CS	CS	CS
72	324	153	93	67	48	38	24	17	12	8	5	1	CS	CS
74	>500	232	130	88	64	49	32	22	16	12	8	3	CS	CS
76	>500	417	193	123	86	66	43	30	22	17	13	6	2	CS
78	NE	>500	343	186	126	94	59	41	31	24	19	10	6	3
80	NE	NE	>500	323	201	141	86	59	45	36	28	17	11	7
82	NE	NE	NE	>500	>500	325	168	107	80	64	51	34	24	18
84	NE	NE	NE	NE	NE	>500	468	237	164	125	98	65	48	36
86	NE	NE	NE	NE	NE	NE	NE	>500	>500	349	245	142	99	79
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	322	234
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

MODERATE COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5[4]	3.0[4]	3.5[4]
66	180	100	68	50	38	30	19	13	9	6	4	0	CS	CS
68	238	123	82	58	44	34	23	16	11	8	5	1	CS	CS
70	367	168	103	73	55	42	28	20	14	10	7	3	CS	CS
72	>500	260	144	100	71	55	37	26	19	14	11	5	2	CS
74	NE	>500	244	154	105	79	52	37	28	22	17	10	5	2
76	NE	NE	>500	277	172	127	79	55	42	34	27	17	11	7
78	NE	NE	>500	>500	300	200	116	79	61	48	39	25	18	13
80	NE	NE	NE	>500	>500	378	191	120	92	73	58	38	28	22
82	NE	NE	NE	NE	NE	>500	>500	259	180	138	107	70	53	42
84	NE	NE	NE	NE	NE	NE	NE	>500	>500	383	259	150	106	81
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	389	232	177
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

NO PRIOR SCREENING

NO COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5[4]	3.0[4]	3.5[4]
66	16	11	9	6	5	3	1	CS	CS	CS	CS	CS	CS	CS
68	17	12	9	7	5	4	2	0	CS	CS	CS	CS	CS	CS
70	19	14	10	8	6	5	2	1	CS	CS	CS	CS	CS	CS
72	24	17	13	10	8	7	4	2	1	CS	CS	CS	CS	CS
74	29	21	17	13	11	9	6	4	2	1	0	CS	CS	CS
76	36	27	22	18	15	12	9	7	5	4	2	0	CS	CS
78	49	36	30	24	21	18	14	11	9	7	6	3	1	CS
80	67	51	41	35	30	26	21	17	15	13	11	8	5	3
82	115	85	69	58	50	45	37	31	27	24	21	17	14	11
84	235	161	126	105	90	79	65	56	49	45	40	33	28	25
86	>500	441	299	229	189	163	129	110	98	87	79	66	57	51
88	NE	NE	NE	>500	>500	>500	405	312	263	222	199	160	134	120
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	453

MODERATE COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5[4]	3.0[4]	3.5[4]
66	22	17	13	10	8	7	4	2	1	CS	CS	CS	CS	CS
68	25	18	14	11	9	8	5	3	2	1	CS	CS	CS	CS
70	29	21	17	14	11	9	7	5	3	2	1	CS	CS	CS
72	35	26	21	17	14	12	9	7	5	4	2	0	CS	CS
74	47	36	29	24	20	18	14	11	9	7	6	3	1	CS
76	67	51	41	35	30	26	21	17	15	13	11	8	5	3
78	93	70	57	47	41	36	30	25	22	19	17	13	10	8
80	139	103	82	69	60	53	44	38	33	30	27	22	18	15
82	289	193	149	122	104	92	76	66	57	52	47	39	34	30
84	>500	>500	373	284	225	192	151	128	111	101	91	76	66	58
86	NE	NE	>500	>500	>500	>500	343	268	227	197	176	142	122	108
88	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	391	328
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Table 2 Continued.

NEGATIVE SCREENING COLONOSCOPY 10 YEARS PRIOR

SEVERE COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5[4]	3.0[4]	3.5[4]
66	335	160	104	74	56	45	30	21	16	12	9	4	1	CS
68	>500	210	129	89	66	52	35	25	18	14	11	5	2	CS
70	>500	373	187	125	92	70	47	34	25	20	15	9	5	2
72	NE	>500	348	208	139	104	67	49	36	29	23	14	9	6
74	NE	NE	>500	407	229	160	98	69	53	42	34	22	15	11
76	NE	NE	NE	>500	427	272	148	100	75	60	49	32	23	18
78	NE	NE	NE	NE	>500	>500	298	177	128	99	79	53	39	31
80	NE	NE	NE	NE	NE	NE	>500	334	220	164	127	81	60	48
82	NE	NE	NE	NE	NE	NE	NE	>500	>500	461	311	170	122	96
84	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	472	267	196
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

NO PRIOR SCREENING

SEVERE COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5[4]	3.0[4]	3.5[4]
66	34	26	21	17	14	12	9	7	5	3	2	CS	CS	CS
68	38	29	23	19	16	14	10	8	6	4	3	1	CS	CS
70	47	36	29	24	21	18	14	11	9	7	6	3	1	CS
72	65	48	39	33	29	25	20	17	14	12	10	7	4	3
74	88	66	54	46	39	35	28	24	20	18	16	11	9	7
76	124	91	73	61	53	47	38	33	28	25	23	18	14	12
78	216	149	118	96	83	73	61	52	45	41	37	31	26	22
80	425	256	190	154	131	113	93	80	70	63	58	48	41	36
82	NE	>500	>500	388	296	244	190	157	133	120	109	91	78	70
84	NE	NE	NE	>500	>500	>500	491	363	295	253	223	177	149	131
86	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	437	364
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

QALY = quality-adjusted life-year; CRC = colorectal cancer; CS = cost saving; NE = negative effect

[1] The black lines indicate a willingness-to-pay threshold of $100,000 per QALY gained. Green cells indicate that screening is cost-effective given this threshold. Red cells indicate that screening is not cost-effective given this threshold. Similar tables for white males, black females, and black males are given in **Appendix 3.**

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

Table 3 The Appropriate Ages to Stop Colonoscopy Screening: Results by Sex, Race, Screening History, Comorbidity Status, and Background Risk for CRC.[1]

WHITE FEMALES SCREENING HISTORY								WHITE FEMALES SCREENING HISTORY							
	Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
	COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	**No comorbidity**	**Moderate comorbidity**	**Severe comorbidity**	**RR CRC[3]**	**No comorbidity**	**Moderate comorbidity**	**Severe comorbidity**	**RR CRC[3]**	**No comorbidity**	**Moderate comorbidity**	**Severe comorbidity**	**RR CRC[3]**	**No comorbidity**	**Moderate comorbidity**	**Severe comorbidity**
0.5	<66[5]	<66[5]	<66[5]	**0.5**	70	67	<66[5]	**0.5**	73	70	67	**0.5**	81	78	74
0.6	69	66	<66[5]	**0.6**	73	70	67	**0.6**	76	73	70	**0.6**	82	79	76
0.7	72	69	<66[5]	**0.7**	76	72	70	**0.7**	78	75	72	**0.7**	83	80	77
0.8	74	71	68	**0.8**	78	74	71	**0.8**	80	76	73	**0.8**	83	81	78
0.9	76	73	70	**0.9**	79	76	73	**0.9**	80	78	74	**0.9**	84	81	78
1.0	*78*	*75*	*71*	**1.0**	*80*	*77*	*74*	**1.0**	*81*	*79*	*76*	**1.0**	*84*	*82*	*79*
1.2	80	77	74	**1.2**	81	79	76	**1.2**	82	80	77	**1.2**	85	82	80
1.4	81	79	75	**1.4**	83	80	77	**1.4**	83	81	78	**1.4**	85	83	80
1.6	82	80	77	**1.6**	83	81	78	**1.6**	84	82	79	**1.6**	86	83	81
1.8	83	81	78	**1.8**	84	82	79	**1.8**	85	82	80	**1.8**	86	83	81
2.0	84	81	78	**2.0**	85	82	80	**2.0**	85	83	80	**2.0**	86	84	81
2.5[4]	85	82	80	**2.5[4]**	85	83	81	**2.5[4]**	86	84	81	**2.5[4]**	87	84	82
3.0[4]	86	83	81	**3.0[4]**	86	84	82	**3.0[4]**	86	84	82	**3.0[4]**	87	85	82
3.5[4]	86	84	82	**3.5[4]**	87	85	82	**3.5[4]**	87	85	82	**3.5[4]**	87	85	83

Table 3 Continued.

WHITE MALES								WHITE MALES							
SCREENING HISTORY								SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	70	68	<66[5]	**0.5**	73	71	67	**0.5**	81	79	74
0.6	69	66	<66[5]	**0.6**	73	70	67	**0.6**	76	73	69	**0.6**	82	80	76
0.7	71	69	<66[5]	**0.7**	75	73	69	**0.7**	78	75	71	**0.7**	83	80	77
0.8	74	71	67	**0.8**	78	74	70	**0.8**	80	77	72	**0.8**	83	81	77
0.9	76	73	69	**0.9**	79	76	72	**0.9**	80	77	73	**0.9**	83	81	78
1.0	*78*	*74*	*70*	**1.0**	*80*	*77*	*73*	**1.0**	*81*	*78*	*75*	**1.0**	*84*	*81*	*78*
1.2	80	77	73	**1.2**	81	79	75	**1.2**	82	80	76	**1.2**	84	82	79
1.4	81	79	75	**1.4**	82	80	76	**1.4**	83	80	77	**1.4**	85	82	79
1.6	82	80	76	**1.6**	83	81	77	**1.6**	83	81	78	**1.6**	85	83	80
1.8	83	80	77	**1.8**	83	81	78	**1.8**	84	82	79	**1.8**	85	83	80
2.0	83	81	78	**2.0**	84	82	79	**2.0**	84	82	79	**2.0**	85	83	80
2.5[4]	84	82	80	**2.5[4]**	85	83	80	**2.5[4]**	85	83	80	**2.5[4]**	86	83	81
3.0[4]	85	83	80	**3.0[4]**	85	83	81	**3.0[4]**	86	83	81	**3.0[4]**	86	84	81
3.5[4]	85	83	81	**3.5[4]**	86	84	81	**3.5[4]**	86	84	81	**3.5[4]**	86	84	81
4.0[4]	86	84	81	**4.0[4]**	86	84	81	**4.0[4]**	86	84	81	**4.0[4]**	86	84	82
4.5[4]	86	84	82	**4.5[4]**	86	84	82	**4.5[4]**	87	84	82	**4.5[4]**	87	84	82
4.9[4]	86	84	82	**4.9[4]**	87	84	82	**4.9[4]**	87	84	82	**4.9[4]**	87	84	82

Table 3 Continued.

BLACK FEMALES								BLACK FEMALES							
SCREENING HISTORY								SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.4	<66[5]	<66[5]	<66[5]	**0.4**	<66[5]	<66[5]	<66[5]	**0.4**	68	<66[5]	<66[5]	**0.4**	80	78	73
0.5	<66[5]	<66[5]	<66[5]	**0.5**	69	67	<66[5]	**0.5**	72	70	<66[5]	**0.5**	81	79	75
0.6	68	<66[5]	<66[5]	**0.6**	73	70	<66[5]	**0.6**	75	73	69	**0.6**	82	80	77
0.7	72	70	<66[5]	**0.7**	75	73	68	**0.7**	77	75	71	**0.7**	83	81	77
0.8	74	72	67	**0.8**	77	75	70	**0.8**	79	77	72	**0.8**	84	81	78
0.9	76	74	69	**0.9**	78	76	72	**0.9**	80	78	74	**0.9**	84	82	79
1.0	*77*	*75*	*71*	**1.0**	*79*	*78*	*73*	**1.0**	*81*	*79*	*75*	**1.0**	*85*	*82*	*80*
1.2	79	77	73	**1.2**	81	79	76	**1.2**	82	80	77	**1.2**	85	83	80
1.4	80	79	75	**1.4**	82	80	77	**1.4**	83	81	78	**1.4**	85	83	81
1.6	81	80	77	**1.6**	83	81	78	**1.6**	84	82	79	**1.6**	86	84	81
1.8	82	80	77	**1.8**	83	81	79	**1.8**	84	82	80	**1.8**	86	84	82
2.0[4]	83	81	78	**2.0[4]**	84	82	80	**2.0[4]**	85	83	80	**2.0[4]**	86	84	82
2.5[4]	84	82	80	**2.5[4]**	85	83	81	**2.5[4]**	86	84	82	**2.5[4]**	87	85	82
3.0[4]	85	83	81	**3.0[4]**	86	84	82	**3.0[4]**	86	84	82	**3.0[4]**	87	86	83
3.5[4]	86	84	82	**3.5[4]**	87	85	83	**3.5[4]**	87	86	83	**3.5[4]**	88	86	83

Table 3 Continued.

BLACK MALES								BLACK MALES							
SCREENING HISTORY								SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	68	<66[5]	<66[5]	**0.5**	71	69	<66[5]	**0.5**	80	78	72
0.6	66	<66[5]	<66[5]	**0.6**	71	69	<66[5]	**0.6**	74	71	67	**0.6**	81	79	73
0.7	70	68	<66[5]	**0.7**	74	71	67	**0.7**	76	73	68	**0.7**	82	80	75
0.8	72	70	<66[5]	**0.8**	76	72	67	**0.8**	77	74	70	**0.8**	82	80	75
0.9	74	71	67	**0.9**	77	74	70	**0.9**	79	76	71	**0.9**	83	81	76
1.0	*76*	*73*	*68*	**1.0**	*78*	*76*	*70*	**1.0**	*80*	*78*	*72*	**1.0**	*84*	*81*	*76*
1.2	78	75	70	**1.2**	80	78	72	**1.2**	81	79	73	**1.2**	84	81	76
1.4	79	78	72	**1.4**	81	79	73	**1.4**	82	80	75	**1.4**	84	81	77
1.6	80	78	73	**1.6**	82	80	75	**1.6**	82	81	76	**1.6**	85	82	79
1.8	81	79	75	**1.8**	82	81	76	**1.8**	83	81	76	**1.8**	85	82	79
2.0	82	80	75	**2.0**	83	81	76	**2.0**	84	81	77	**2.0**	86	82	80
2.5	83	81	77	**2.5**	84	82	79	**2.5**	85	82	79	**2.5**	86	83	80
3.0[4]	84	82	79	**3.0[4]**	85	82	80	**3.0[4]**	86	83	80	**3.0[4]**	87	83	80
3.5[4]	85	82	80	**3.5[4]**	86	83	80	**3.5[4]**	86	83	80	**3.5[4]**	87	84	80
4.0[4]	86	83	80	**4.0[4]**	86	84	80	**4.0[4]**	87	84	80	**4.0[4]**	87	84	80
4.5[4]	87	83	80	**4.5[4]**	87	84	81	**4.5[4]**	87	84	81	**4.5[4]**	88	84	81
5.0[4]	87	84	81	**5.0[4]**	87	84	82	**5.0[4]**	87	84	82	**5.0[4]**	88	84	82
5.3[4]	87	84	81	**5.3[4]**	88	84	82	**5.3[4]**	88	84	82	**5.3[4]**	88	84	82

CRC = colorectal cancer; RR CRC = background risk for CRC
[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.
[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.
[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.
[4] Background risk for CRC only possible in case of a family history of CRC.
[5] In these cohorts screening was not cost-effective at age 66 years. We did not perform analyses for individuals aged 65 years or younger.

DISCUSSION

In current practice, decisions on CRC screening for elderly individuals are often based primarily on age.(6) Our study shows that this approach is inefficient, resulting in underuse of screening for some and overuse of screening for others. An 81-year-old black man with no comorbidities, an average background risk for CRC, and no prior screening, for example, might currently be denied screening, while our study shows that screening these individuals is highly cost effective (costs per QALY gained: $50,000). A 74-year-old white woman with moderate comorbidities (e.g. diabetes), half the average background risk for CRC, and a negative screening colonoscopy 10 years prior, on the other hand, might currently be offered screening, while our study shows that screening these individuals is harmful. While screening some previously screened, low risk individuals is not even cost effective at age 66 years, screening healthy, high risk individuals can remain cost effective up to age 88 years. To facilitate the use of our results in clinical practice, we developed a web tool that can be used to quantify the cost effectiveness of colonoscopy screening for individual elderly patients. This tool can be accessed at: http://www.frankly.yetes.nl/.

Although our study shows that the appropriate age to stop screening varies widely among individuals, our results are in line with the USPSTF recommendation to discontinue routine screening for CRC in adequately screened individuals aged over 75 years.(1) Based on our analyses, the appropriate age to stop screening for average risk, white women with a negative screening colonoscopy 10 years prior is 78 years for those with no comorbidities, 75 years for those with moderate comorbidities, and 71 years for those with severe comorbidities. Results for the other demographic groups were comparable. Our results are also in agreement with the results of an earlier study on the cost effectiveness of screening in elderly individuals without prior screening.(44) In that study, in which we did not consider previously screened individuals, nor stratify results by sex and race or background risk for CRC, we found colonoscopy screening to be cost effective up to age 85, 82, and 79 years for average risk individuals with no, moderate, and severe comorbidities, respectively. For white women, the corresponding ages found in our current study were 84, 82, and 79 years. Finally, our results are in line with the results of an earlier study on FIT screening in elderly individuals with an adequate screening history.(45) In that study, in which we did not consider previously unscreened individuals, nor stratify results by sex and race or background risk for CRC, we found FIT screening to have a favorable balance between benefits and harms up to age 76, 74, and 71 years for average risk individuals with no, moderate, and severe comorbidities, respectively. For white women, the corresponding ages to stop colonoscopy screening found in our current study were 78, 75, and 71 years.

The idea of personalizing screening decisions for elderly patients is not new. Walter and Covinsky described a theoretical framework for personalization in elderly individuals in 2001.(46) This framework, which focused primarily on the effect of life-expectancy on the effectiveness of screening, was followed by many studies that examined the univariate relationships between sex and race, screening history, comorbidity status, and cancer risk on the one hand, and the effectiveness and cost effectiveness of CRC screening on the other.(47-49) However, none of these studies considered all relevant factors simultaneously, using a multivariate approach. This complicates the use of the results of these studies in clinical practice. For example, how should one approach an individual with a high risk for CRC, but a poor life-expectancy, or vice versa? We believe that our study is more applicable to the complex situations commonly encountered in clinical practice. Additionally, our work may prove useful to policy makers aiming at improving the efficiency of cancer prevention.

Our study has several important limitations. First, in our analyses we did not consider individuals with a negative screening colonoscopy less than 10 years prior. Because some screening guidelines recommend a screening interval of 5 years for individuals with a family history of CRC, we provided results for high-risk individuals with a negative screening colonoscopy 5 years prior in an Appendix (**Appendix 6**). Second, we only considered screening by colonoscopy. Since the costs of a screening sigmoidoscopy and, particularly, a fecal occult blood test are considerably lower than those of a colonoscopy, these screening modalities might remain cost effective up to a more advanced age.

However, in an earlier study, age differences between tests were found to be small.(44) Third, we did not consider individuals with multiple prior negative screening colonoscopies. However, since the interval since the last negative screening colonoscopy is likely to be the most important screening-related predictor of CRC risk, having had multiple prior negative screening colonoscopies is unlikely to substantially lower the appropriate age to stop screening. Finally, the National Cancer Institute's CRC Risk Assessment Tool only provides risk estimates for average risk adenoma patients. Since recommendations for surveillance in adenoma patients should be tailored according to the characteristics of adenomas removed during colonoscopy, we could not use our current approach to provide guidance for elderly individuals with adenomas removed during a prior colonoscopy. Given that the majority of colonoscopies in elderly patients are performed for post-polypectomy surveillance,(50) this is an important area for future research.

Although we believe that effectiveness and cost effectiveness should be important criteria when making decisions about offering medical interventions, we recognize that decisions on CRC screening should also be based on patient preferences. This requires reliable, personalized information on the benefits, burden, and harms of screening. Hence, additional studies focusing on those outcomes most meaningful to patients are required.

Another important future research direction is the development of new prediction models for both CRC risk and life-expectancy. Research in this area should not only focus on developing more sophisticated and accurate models, but also on developing simpler models that are less time consuming to use than the currently available models. Along these lines, it is important to realize that implementing personalized screening in clinical practice will be challenging: many patients are reluctant to discontinue screening even if the expected benefit is low,(51) physicians might find personalization cumbersome, and system-level incentives, which currently encourage "one size fits all" age-based screening, need to be aligned with benefit.

In conclusion: The current approach to CRC screening in elderly individuals, in which the decision to offer screening is often based primarily on age, is inefficient, resulting in underuse of screening for some and overuse of screening for others. A more personalized approach to screening has great potential to increase the efficiency of screening. As the population ages, this will become increasingly important.

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Appendix 1. Background Risk for CRC

To determine plausible sex- and race-specific ranges for the background risk for CRC (i.e. the relative level of exposure to risk factors for CRC other than sex, race, and screening history, which are already incorporated in MISCAN-Colon), we used the National Cancer Institute's Colorectal Cancer Risk Assessment Tool.(28,29) Using this tool, we determined the absolute risk of developing CRC between ages 50 and 85 (not corrected for other cause mortality) for previously unscreened white women, white men, black women, and black men for all combinations of the following risk factors:

- the number of first-degree relatives with a history of CRC (0/ 1/ ≥2);
- current leisure-time vigorous activity (0/ >0 and ≤2/ >2 and ≤4/ >4 hours per week);
- use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) (nonuser/ regular user);
- vegetable intake (<5/ ≥5 servings per day);
- body mass index (≤24.9/ 25.0 to ≤30/ >30 kg/m2);
- years of smoking (in current and former smokers) (0/ >0 and <15/ ≥15 and <35/ ≥35 years; men only);
- usual number of cigarettes smoked per day (in current and former smokers) (never smoker/ >0 and <11/ ≥11 and ≤20/ >20 cigarettes per day; men only); and
- estrogen status within the last two years (negative (postmenopausal and not on hormone replacement therapy/ positive (premenopausal or on hormone-replacement therapy); women only).

For white women this risk ranged from 2.7% (for women with the following characteristics: 0 first-degree relatives with a history of CRC, >4 hours of leisure-time vigorous activity per week, a regular user of aspirin or NSAIDs, ≥5 servings of vegetables per day, a body mass index ≤24.9 kg/m2, and a positive estrogen status during the last two years) to 21.3% (for women with the following characteristics: ≥2 first-degree relatives with a history of CRC, 0 hours of leisure-time vigorous activity per week, a nonuser of aspirin or NSAIDs, <5 servings of vegetables per day, a body mass index >30 kg/m2, and a negative estrogen status during the last two years). For white men, black women, and black men, the risk ranged from 4.4% to 43.5%, from 3.0% to 23.3%, and from 4.3% to 47.1%.

To incorporate these risk levels in MISCAN-Colon, we transformed these absolute risks into relative risks. To do this, we first used the sex- and race-specific versions of MISCAN-Colon (which are calibrated on CRC incidence data observed in SEER between 1990 and 1994) to determine average risks of developing CRC between ages 50 and 85 (uncorrected for other cause mortality). The resulting average risks for white women, white men, black women, and black men were 6.0%, 8.8%, 6.7%, and 9.0%, respectively. We then calculated the ranges of the relative background risk for CRC in white women, white men, black women, and black men 0.5 - 3.5, 0.5 - 4.9, 0.4 - 3.5, and 0.5 - 5.3, respectively.

For each combination of sex and race, we modeled cohorts with the minimum risk, the maximum risk, all risks between the minimum risk and average risk using an increment

of 0.1, all risks between the average risk and twice the average risk using an increment of 0.2, and all risks between twice the average risk and the maximum risk using an increment of 0.5. Hence, for white women we modeled cohorts with a background risk for CRC of 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.5, 3.0, and 3.5 (14 levels); for black women we modeled cohorts with a background risk of 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.5, 3.0, and 3.5 (15 levels); for white men we modeled cohorts with a background risk of 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 4.9 (17 levels); and for black men we modeled cohorts with a background risk of 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.3 (18 levels).

Appendix 2: The Impact of Age on the Effectiveness, Costs, and Cost-Effectiveness of Colonoscopy Screening – Detailed Results

Appendix 2, Table 1 The Impact of Age on the Effectiveness, Costs, and Cost-Effectiveness of Colonoscopy Screening: Results for Healthy, Average Risk, White Women with a Negative Screening Colonoscopy 10 Years Prior (effectiveness and costs per 1,000 females; 3% discounted).

	EFFECTIVENESS				COSTS (*$1,000)*					COST-EFFECTIVENESS
Age	**CRC cases prevented**[1]	**CRC deaths prevented**	**LYs gained**	**QALYs gained**[2]	**Screening colonoscopies**	**Surveillance colonoscopies**	**Complications**	**CRC care**[3]	**Total**	**Costs/ QALY gained (*$1,000)**
66	7.4	3.5	28.0	27.8	932	224	25	-578	602	22
67	7.3	3.5	27.0	26.7	932	218	26	-565	610	23
68	7.1	3.4	26.1	25.4	932	211	27	-549	621	24
69	6.9	3.4	25.0	24.0	932	204	27	-526	638	27
70	6.8	3.3	23.8	22.5	932	197	29	-506	652	29
71	6.5	3.2	21.7	20.0	932	191	30	-479	674	34
72	6.2	3.1	20.4	18.4	932	185	31	-452	696	38
73	6.0	2.9	19.0	16.7	932	178	32	-425	718	43
74	5.7	2.8	17.7	15.1	932	172	33	-399	739	49
75	5.4	2.7	16.4	13.4	933	164	35	-370	761	57
76	5.1	2.6	15.1	11.8	933	159	36	-346	783	66
77	4.9	2.5	13.9	10.3	933	154	38	-320	806	78
78	4.6	2.4	12.7	8.8	934	148	40	-294	829	94
79	4.2	2.2	11.6	7.5	934	143	42	-267	852	114
80	4.0	2.1	10.6	6.2	935	136	44	-241	874	141
81	3.4	1.9	9.2	4.4	934	127	46	-200	907	205
82	2.9	1.7	7.9	2.9	934	117	47	-160	937	325
83	2.4	1.6	6.8	1.5	933	108	49	-125	965	652
84	2.0	1.4	5.8	0.2	933	100	51	-95	989	3,973
85	1.5	1.3	5.0	-0.8	933	87	52	-66	1,006	negative effect
86	1.0	1.1	4.0	-2.0	931	77	53	-35	1,026	negative effect
87	0.6	0.9	3.1	-3.0	930	67	54	-9	1,041	negative effect
88	0.3	0.7	2.4	-3.9	928	58	54	13	1,053	negative effect
89	-0.0	0.6	1.8	-4.5	926	50	55	28	1,059	negative effect
90	-0.2	0.5	1.3	-5.1	925	43	56	37	1,061	negative effect

CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year

[1] A negative value indicates that the number of CRC cases prevented by screening is exceeded by the number of CRC cases over-diagnosed by screening.

[2] The effect of screening on quantity and quality of life incorporated in one measure (i.e. the net health benefit of screening). A negative value indicates that screening is associated with a net harm, rather than a net health benefit.

[3] Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be a reduction in costs (negative values) or an increase in costs (positive values).

Appendix 2. Table 2 The Impact of Age on the Effectiveness. Costs. and Cost-Effectiveness of Colonoscopy Screening: Results for Healthy. Average Risk. White Men with a Negative creening Colonoscopy 10 Years Prior (effectiveness and costs per 1.000 females; 3% discounted).

	EFFECTIVENESS				COSTS (*$1.000)*					COST-EFFECTIVENESS
Age	**CRC cases prevented**[1]	**CRC deaths prevented**	**LYs gained**	**QALYs gained**[2]	**Screening colonoscopies**	**Surveillance colonoscopies**	**Complications**	**CRC care**[3]	**Total**	**Costs/ QALY gained (*$1.000)**
66	8.3	4.3	31.4	31.6	938	255	28	-631	590	19
67	8.0	4.1	29.6	29.4	937	244	29	-600	610	21
68	7.6	4.0	28.1	27.4	937	233	30	-569	631	23
69	7.3	3.9	26.3	25.3	937	223	31	-535	655	26
70	6.9	3.8	24.7	23.4	937	212	31	-503	677	29
71	6.7	3.5	22.3	20.5	937	205	33	-474	700	34
72	6.4	3.4	20.7	18.5	937	197	34	-447	720	39
73	6.0	3.3	19.1	16.6	936	189	35	-414	746	45
74	5.7	3.1	17.6	14.7	936	182	36	-382	773	53
75	5.3	2.9	16.0	12.8	936	172	38	-348	798	63
76	5.1	2.9	15.1	11.6	937	169	40	-329	817	70
77	4.8	2.8	14.0	10.2	938	164	42	-307	837	82
78	4.6	2.7	13.1	9.1	940	159	44	-289	854	94
79	4.3	2.6	12.2	8.0	940	154	46	-262	878	110
80	3.9	2.5	11.3	6.7	941	147	49	-231	906	135
81	3.1	2.2	9.4	4.4	940	132	50	-167	954	217
82	2.4	2.0	8.1	2.8	939	118	50	-119	988	358
83	1.8	1.7	6.8	1.2	937	106	52	-76	1,019	870
84	1.1	1.5	5.6	-0.3	936	95	53	-36	1,048	negative effect
85	0.7	1.3	4.5	-1.6	934	81	54	-3	1,066	negative effect
86	0.2	1.0	3.4	-2.9	932	68	53	21	1,073	negative effect
87	-0.1	0.8	2.5	-3.9	929	56	53	38	1,076	negative effect
88	-0.3	0.6	1.8	-4.6	927	46	52	48	1,073	negative effect
89	-0.4	0.4	1.2	-5.1	924	38	52	47	1,061	negative effect
90	-0.4	0.3	0.8	-5.4	922	30	51	45	1,048	negative effect

CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year

[1] A negative value indicates that the number of CRC cases prevented by screening is exceeded by the number of CRC cases over-diagnosed by screening.

[2] The effect of screening on quantity and quality of life incorporated in one measure (i.e. the net health benefit of screening). A negative value indicates that screening is associated with a net harm. rather than a net health benefit.

[3] Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be a reduction in costs (negative values) or an increase in costs (positive values).

Appendix 2, Table 3 The Impact of Age on the Effectiveness, Costs, and Cost-Effectiveness of Colonoscopy Screening: Results for Healthy, Average Risk, Black Women with a Negative Screening Colonoscopy 10 Years Prior (effectiveness and costs per 1,000 females; 3% discounted).

	EFFECTIVENESS				COSTS (*$1,000)*					COST-EFFECTIVENESS
Age	**CRC cases prevented**[1]	**CRC deaths prevented**	**LYs gained**	**QALYs gained**[2]	**Screening colonoscopies**	**Surveillance colonoscopies**	**Complications**	**CRC care**[3]	**Total**	**Costs/ QALY gained (*$1,000)**
66	6.4	4.0	31.7	30.6	933	218	23	-486	688	23
67	6.3	3.9	30.5	29.1	933	210	24	-470	696	24
68	6.1	3.8	29.0	27.4	933	203	25	-449	711	26
69	5.8	3.7	27.5	25.5	933	195	26	-425	728	28
70	5.6	3.6	26.1	23.9	932	188	26	-404	743	31
71	5.4	3.4	23.5	21.1	932	181	27	-382	759	36
72	5.2	3.3	22.5	19.8	932	175	29	-365	771	39
73	4.9	3.1	20.6	17.5	932	167	30	-334	794	45
74	4.6	3.0	19.3	16.0	932	161	31	-314	810	51
75	4.3	2.9	17.6	14.0	932	151	32	-284	830	59
76	3.9	2.7	15.9	11.9	931	143	33	-250	857	72
77	3.4	2.5	14.1	9.7	931	134	34	-216	884	91
78	3.1	2.3	12.6	8.0	930	127	35	-188	904	113
79	2.7	2.1	11.2	6.3	930	119	37	-159	927	148
80	2.4	1.9	9.9	4.7	930	111	38	-134	945	200
81	2.1	1.7	8.4	3.1	929	103	39	-109	963	315
82	1.8	1.6	7.4	1.8	929	95	41	-86	979	544
83	1.4	1.4	6.1	0.3	928	87	42	-62	996	2,916
84	1.1	1.2	5.1	-0.8	928	81	44	-43	1,009	negative effect
85	0.9	1.1	4.4	-1.5	927	70	45	-30	1,012	negative effect
86	0.6	1.0	3.6	-2.4	927	64	47	-9	1,028	negative effect
87	0.3	0.9	3.0	-3.2	926	58	49	7	1,040	negative effect
88	0.2	0.7	2.5	-3.8	925	54	50	17	1,047	negative effect
89	-0.0	0.6	2.0	-4.3	924	50	52	29	1,055	negative effect
90	-0.2	0.5	1.5	-4.8	924	45	54	38	1,060	negative effect

CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year

[1] A negative value indicates that the number of CRC cases prevented by screening is exceeded by the number of CRC cases over-diagnosed by screening.

[2] The effect of screening on quantity and quality of life incorporated in one measure (i.e. the net health benefit of screening). A negative value indicates that screening is associated with a net harm, rather than a net health benefit.

[3] Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be a reduction in costs (negative values) or an increase in costs (positive values).

Appendix 2, Table 4 The Impact of Age on the Effectiveness, Costs, and Cost-Effectiveness of Colonoscopy Screening: Results for Healthy, Average Risk, Black Men with a Negative Screening Colonoscopy 10 Years Prior (effectiveness and costs per 1,000 females; 3% discounted).

	EFFECTIVENESS				COSTS (*$1,000)*					COST-EFFECTIVENESS
Age	**CRC cases prevented**[1]	**CRC deaths prevented**	**LYs gained**	**QALYs gained**[2]	**Screening colonoscopies**	**Surveillance colonoscopies**	**Complications**	**CRC care**[3]	**Total**	**Costs/ QALY gained (*$1,000)**
66	6.3	4.2	29.8	28.1	938	222	25	-451	733	26
67	6.1	4.1	28.6	26.7	937	214	26	-433	744	28
68	6.0	4.1	27.7	25.6	937	208	27	-421	751	29
69	5.7	3.9	26.1	23.6	937	199	28	-393	771	33
70	5.4	3.8	24.6	21.8	937	190	29	-369	787	36
71	5.1	3.6	22.1	19.0	937	182	30	-338	811	43
72	4.7	3.4	20.3	16.8	936	172	31	-304	835	50
73	4.3	3.2	18.4	14.7	936	163	32	-274	858	58
74	4.1	3.0	17.2	13.3	936	158	33	-259	868	65
75	3.7	2.9	15.6	11.4	936	147	34	-227	890	78
76	3.3	2.6	14.0	9.4	935	138	35	-192	916	97
77	3.0	2.5	12.8	8.0	934	130	36	-168	933	117
78	2.6	2.3	11.2	6.1	934	121	37	-136	956	156
79	2.2	2.1	10.0	4.6	933	113	39	-113	972	210
80	1.8	1.9	8.8	3.2	932	105	40	-87	989	307
81	1.4	1.6	7.1	1.3	931	94	41	-56	1,010	754
82	1.1	1.5	6.2	0.3	930	86	42	-37	1,020	3,557
83	0.7	1.2	4.9	-1.1	929	76	43	-13	1,034	negative effect
84	0.6	1.1	4.2	-1.9	928	71	44	-4	1,038	negative effect
85	0.3	0.9	3.3	-2.8	927	60	45	12	1,042	negative effect
86	0.2	0.8	2.9	-3.3	926	56	47	19	1,048	negative effect
87	0.0	0.8	2.5	-3.8	926	52	48	27	1,054	negative effect
88	-0.0	0.7	2.2	-4.2	925	49	51	29	1,055	negative effect
89	-0.2	0.6	1.6	-4.7	925	44	53	40	1,061	negative effect
90	-0.3	0.5	1.3	-5.0	924	39	55	43	1,062	negative effect

CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year

[1] A negative value indicates that the number of CRC cases prevented by screening is exceeded by the number of CRC cases over-diagnosed by screening.

[2] The effect of screening on quantity and quality of life incorporated in one measure (i.e. the net health benefit of screening). A negative value indicates that screening is associated with a net harm, rather than a net health benefit.

[3] Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be a reduction in costs (negative values) or an increase in costs (positive values).

Appendix 3: The Costs per QALY Gained of Colonoscopy Screening by Screening History, Comorbidity Status, Background Risk for CRC, and Age – Results for White Men, Black Women, and Black Men

Appendix 3, Table 1 The Costs per QALY Gained (*$1,000) of Colonoscopy Screening for White Men by Screening History, Comorbidity Status, Background Risk for CRC, and Age (3% discounted).[1]

NEGATIVE SCREENING COLONOSCOPY 10 YEARS PRIOR

NO COMORBIDITY[2]

	Background risk for CRC[3]																
Age	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0**	**2.5[4]**	**3.0[4]**	**3.5[4]**	**4.0[4]**	**4.5[4]**	**4.9[4]**
66	116	68	47	33	24	19	11	7	3	1	CS	CS	CS	CS	CS	CS	CS
68	152	86	57	40	30	23	14	9	5	3	1	CS	CS	CS	CS	CS	CS
70	214	113	71	51	38	29	18	12	8	5	3	CS	CS	CS	CS	CS	CS
72	388	169	101	70	51	39	25	17	11	8	5	0	CS	CS	CS	CS	CS
74	>500	265	141	95	69	53	33	23	16	11	8	3	CS	CS	CS	CS	CS
76	NE	493	211	131	93	70	45	30	22	16	12	6	2	CS	CS	CS	CS
78	NE	>500	342	187	129	94	57	40	30	23	18	10	5	2	CS	CS	CS
80	NE	NE	>500	295	196	135	80	56	41	33	26	16	10	7	4	1	1
82	NE	NE	NE	>500	>500	358	177	114	82	66	53	36	26	21	16	12	12
84	NE	NE	NE	NE	NE	NE	>500	305	196	145	113	78	57	45	37	32	32
86	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	413	219	141	111	88	78	67
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	406	245	207	161
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500

MODERATE COMORBIDITY[2]

	Background risk for CRC[3]																
Age	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0**	**2.5[4]**	**3.0[4]**	**3.5[4]**	**4.0[4]**	**4.5[4]**	**4.9[4]**
66	163	91	62	44	32	25	16	11	7	4	2	CS	CS	CS	CS	CS	CS
68	227	118	76	54	40	31	20	14	9	6	4	CS	CS	CS	CS	CS	CS
70	405	176	105	73	54	42	28	19	13	10	7	2	CS	CS	CS	CS	CS
72	>500	325	167	110	79	60	39	27	20	15	11	5	2	CS	CS	CS	CS
74	NE	>500	270	164	113	85	53	38	28	21	17	10	5	2	1	CS	CS
76	NE	NE	>500	282	177	128	78	54	41	32	25	16	10	7	4	2	1
78	NE	NE	>500	>500	305	196	109	75	57	44	36	24	17	12	9	6	5
80	NE	NE	NE	>500	>500	354	169	113	83	65	52	36	26	20	16	12	11
82	NE	NE	NE	NE	NE	NE	>500	354	218	163	126	84	65	53	43	38	35
84	NE	NE	NE	NE	NE	NE	NE	NE	>500	491	313	191	135	102	85	75	76
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	399	261	203	162	151
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	472
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

NO PRIOR SCREENING

NO COMORBIDITY[2]

	Background risk for CRC[3]																
Age	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0**	**2.5[4]**	**3.0[4]**	**3.5[4]**	**4.0[4]**	**4.5[4]**	**4.9[4]**
66	11	8	5	3	2	1	CS	CS	CS	CS	CS	CS	CS	CS	CS	CS	CS
68	13	9	6	4	3	2	0	CS	CS	CS	CS	CS	CS	CS	CS	CS	CS
70	15	11	8	6	4	3	1	CS	CS	CS	CS	CS	CS	CS	CS	CS	CS
72	19	14	11	8	6	5	3	1	CS	CS	CS	CS	CS	CS	CS	CS	CS
74	24	18	14	11	9	8	5	3	2	1	CS	CS	CS	CS	CS	CS	CS
76	32	24	19	15	13	11	8	6	4	3	2	0	CS	CS	CS	CS	CS
78	41	32	26	21	18	16	12	10	8	7	5	3	1	CS	CS	CS	CS
80	59	46	38	32	28	25	20	17	14	13	11	8	6	5	3	2	2
82	110	84	69	58	52	46	39	34	30	27	25	21	18	16	14	12	11
84	246	174	136	114	100	90	75	66	59	55	50	43	38	34	31	29	28
86	>500	>500	402	302	243	211	172	147	129	119	108	93	82	74	68	64	61
88	NE	NE	NE	>500	>500	>500	>500	469	386	321	285	232	197	173	157	145	139
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	493	449

MODERATE COMORBIDITY[2]

	Background risk for CRC[3]																
Age	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0**	**2.5[4]**	**3.0[4]**	**3.5[4]**	**4.0[4]**	**4.5[4]**	**4.9[4]**
66	16	12	9	7	5	4	2	0	CS	CS	CS	CS	CS	CS	CS	CS	CS
68	18	13	10	8	6	5	3	1	0	CS	CS	CS	CS	CS	CS	CS	CS
70	23	17	14	11	9	7	5	3	2	1	CS	CS	CS	CS	CS	CS	CS
72	31	24	19	16	13	11	8	6	5	3	2	0	CS	CS	CS	CS	CS
74	40	31	25	21	18	16	12	10	8	6	5	3	1	CS	CS	CS	CS
76	56	43	35	30	26	23	19	16	13	12	10	7	5	4	2	1	1
78	78	61	50	42	37	34	28	24	21	19	17	13	11	9	7	6	6
80	120	92	75	63	56	50	42	37	33	30	27	23	19	17	15	14	13
82	331	227	175	143	125	111	93	80	73	66	62	53	47	43	39	36	34
84	>500	>500	443	336	275	235	187	159	141	128	118	101	90	81	74	70	67
86	NE	NE	NE	>500	>500	>500	>500	428	346	306	269	218	188	166	150	141	133
88	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	497	421	371	346
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Appendix 3, Table 1 Continued.

NEGATIVE SCREENING COLONOSCOPY 10 YEARS PRIOR

SEVERE COMORBIDITY[2]

	Background risk for CRC[3]																
Age	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0**	**2.5**[4]	**3.0**[4]	**3.5**[4]	**4.0**[4]	**4.5**[4]	**4.9**[4]
66	433	184	116	80	59	47	31	22	16	12	9	4	1	CS	CS	CS	CS
68	>500	282	162	105	77	61	40	29	22	16	13	7	4	1	CS	CS	CS
70	NE	>500	256	157	111	85	55	39	30	23	19	11	7	4	2	1	CS
72	NE	NE	>500	276	178	127	80	56	42	33	27	17	12	8	5	4	2
74	NE	NE	>500	>500	333	219	121	83	62	48	40	26	19	14	11	8	7
76	NE	NE	NE	NE	>500	448	202	128	94	73	58	40	29	23	19	15	13
78	NE	NE	NE	NE	NE	>500	377	218	151	111	88	61	46	37	31	25	22
80	NE	NE	NE	NE	NE	NE	>500	>500	282	199	149	100	75	61	51	44	41
82	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	447	219	169	135	107	92	87
84	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	333	262	208	214
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

NO PRIOR SCREENING

SEVERE COMORBIDITY[2]

	Background risk for CRC[3]																
Age	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0**	**2.5**[4]	**3.0**[4]	**3.5**[4]	**4.0**[4]	**4.5**[4]	**4.9**[4]
66	31	24	19	16	13	11	8	6	5	3	2	0	CS	CS	CS	CS	CS
68	37	28	23	19	16	14	11	8	7	5	4	2	0	CS	CS	CS	CS
70	46	36	30	25	22	19	15	12	10	9	7	5	3	2	1	CS	CS
72	62	48	40	34	30	26	21	18	15	13	12	9	7	5	4	3	2
74	88	67	55	47	42	37	31	26	23	20	18	15	12	10	8	7	7
76	134	98	80	68	60	54	45	39	35	31	28	23	20	17	15	14	13
78	223	158	125	106	93	83	69	60	54	49	45	38	33	29	27	25	24
80	>500	319	232	188	162	141	115	100	90	81	75	64	57	52	47	44	42
82	NE	>500	>500	>500	427	347	264	214	188	166	154	129	114	103	95	89	85
84	NE	NE	NE	NE	NE	>500	>500	>500	>500	489	425	318	272	234	208	195	184
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	>500
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

QALY = quality-adjusted life-year; CRC = colorectal cancer; CS = cost saving; NE = negative effect

[1] The black line indicates a willingness-to-pay threshold of $100,000 per QALY gained. Green cells indicate that screening is cost-effective given this threshold. Red cells indicate that screening is not cost-effective given this threshold.

[2] Detailed information on comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

Appendix 3, Table 2 The Costs per QALY Gained (*$1,000) of Colonoscopy Screening for Black Women by Screening History, Comorbidity Status, Background Risk for CRC, and Age (3% discounted).[1]

NEGATIVE SCREENING COLONOSCOPY 10 YEARS PRIOR

NO COMORBIDITY[2]

	Background risk for CRC[3]														
Age	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0[4]**	**2.5[4]**	**3.0[4]**	**3.5[4]**
66	308	125	75	51	37	28	23	15	10	7	4	3	CS	CS	CS
68	444	151	89	60	43	32	26	17	11	8	6	4	1	CS	CS
70	>500	196	111	72	52	39	31	20	14	10	7	5	2	CS	CS
72	>500	313	154	96	66	50	39	26	18	13	10	7	3	1	CS
74	NE	>500	230	132	88	66	51	34	24	18	14	11	6	3	1
76	NE	>500	426	209	130	95	72	47	34	25	20	16	10	6	3
78	NE	NE	>500	454	229	154	113	71	50	38	30	25	16	11	8
80	NE	NE	NE	>500	>500	300	200	112	77	57	46	38	25	18	14
82	NE	NE	NE	NE	NE	>500	>500	227	142	103	80	62	42	31	24
84	NE	NE	NE	NE	NE	NE	NE	>500	380	226	164	122	79	59	45
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	455	274	153	110	82
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	432	258	175
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500

MODERATE COMORBIDITY[2]

	Background risk for CRC[3]														
Age	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0[4]**	**2.5[4]**	**3.0[4]**	**3.5[4]**
66	>500	178	102	67	49	37	30	20	14	10	7	5	2	CS	CS
68	>500	210	116	77	54	41	33	22	16	11	8	6	3	0	CS
70	>500	309	156	98	69	52	41	27	19	15	11	9	4	2	0
72	NE	>500	245	142	93	70	54	36	26	20	15	12	7	4	2
74	NE	>500	419	204	128	94	71	47	34	26	21	17	10	6	4
76	NE	NE	>500	481	239	164	119	75	54	40	33	27	18	13	9
78	NE	NE	NE	>500	430	255	174	102	72	54	43	36	24	17	13
80	NE	NE	NE	NE	NE	>500	484	208	133	94	75	62	42	31	25
82	NE	NE	NE	NE	NE	NE	NE	>500	360	223	160	120	80	58	47
84	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	371	238	143	100	75
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	309	199	136
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	428
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500

NO PRIOR SCREENING

NO COMORBIDITY[2]

	Background risk for CRC[3]														
Age	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0[4]**	**2.5[4]**	**3.0[4]**	**3.5[4]**
66	19	14	10	8	6	5	4	2	1	0	CS	CS	CS	CS	CS
68	21	15	11	9	7	5	4	3	2	1	CS	CS	CS	CS	CS
70	24	17	13	10	8	7	6	4	3	2	1	0	CS	CS	CS
72	29	21	16	13	10	9	7	5	4	3	2	1	CS	CS	CS
74	36	26	20	16	13	11	10	8	6	5	4	3	1	CS	CS
76	47	33	26	22	18	16	14	11	9	8	6	5	3	2	1
78	63	45	35	30	25	22	20	16	14	12	10	9	7	5	4
80	90	63	50	42	36	32	29	24	21	18	16	15	12	10	8
82	154	102	79	66	56	50	45	38	34	30	27	25	21	18	16
84	379	203	146	118	100	88	78	66	59	53	49	45	39	34	30
86	>500	>500	336	240	191	165	142	118	103	92	84	78	67	60	54
88	NE	NE	>500	>500	>500	420	333	252	212	183	163	148	125	111	99
90	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	399	323	275

MODERATE COMORBIDITY[2]

	Background risk for CRC[3]														
Age	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0[4]**	**2.5[4]**	**3.0[4]**	**3.5[4]**
66	26	18	14	11	9	8	7	5	3	2	1	1	CS	CS	CS
68	27	20	15	12	10	8	7	5	4	3	2	1	CS	CS	CS
70	33	23	18	15	12	10	9	7	5	4	3	2	1	CS	CS
72	41	29	23	19	16	14	12	9	8	6	5	4	2	1	CS
74	50	36	28	24	20	17	16	13	10	9	7	6	4	3	2
76	74	53	42	35	30	26	24	20	17	15	13	12	9	7	6
78	91	64	50	42	36	32	29	24	21	19	17	15	12	10	8
80	159	106	82	68	59	52	47	40	35	32	29	27	22	19	17
82	418	223	159	128	106	95	84	72	63	57	52	48	41	36	33
84	>500	>500	312	236	188	163	141	117	102	92	84	78	66	58	53
86	NE	NE	>500	>500	417	339	274	214	181	159	143	132	111	98	89
88	NE	NE	NE	NE	NE	>500	>500	>500	>500	462	380	329	263	225	197
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	423

Appendix 3, Table 2 Continued.

NEGATIVE SCREENING COLONOSCOPY 10 YEARS PRIOR

SEVERE COMORBIDITY[2]

	Background risk for CRC[3]														
Age	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0[4]**	**2.5[4]**	**3.0[4]**	**3.5[4]**
66	NE	474	204	122	87	64	52	35	26	19	15	12	7	4	2
68	NE	>500	290	165	109	80	64	43	32	24	19	16	10	6	4
70	NE	>500	497	234	147	103	82	53	39	30	24	20	13	9	6
72	NE	NE	>500	443	217	149	111	73	51	40	32	27	18	13	10
74	NE	NE	NE	>500	482	281	188	114	78	60	49	41	28	21	16
76	NE	NE	NE	NE	>500	469	278	151	101	76	62	51	35	27	21
78	NE	NE	NE	NE	NE	NE	>500	373	205	143	110	91	60	46	37
80	NE	NE	NE	NE	NE	NE	NE	>500	384	224	168	131	84	62	51
82	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	432	270	158	108	86
84	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	449	252	171
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	465
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

NO PRIOR SCREENING

SEVERE COMORBIDITY[2]

	Background risk for CRC[3]														
Age	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**	**1.2**	**1.4**	**1.6**	**1.8**	**2.0[4]**	**2.5[4]**	**3.0[4]**	**3.5[4]**
66	45	33	26	21	18	16	14	11	9	7	6	5	3	1	0
68	53	38	30	25	21	18	17	13	11	9	8	7	5	3	2
70	64	46	36	30	26	22	20	17	14	12	11	9	7	5	4
72	83	57	45	38	32	29	26	21	18	16	14	13	10	8	6
74	123	84	65	55	47	42	37	32	27	24	22	20	16	14	12
76	150	101	78	65	56	49	44	37	33	29	27	24	20	18	15
78	302	180	131	108	91	80	72	60	53	48	44	40	34	30	27
80	>500	268	186	147	121	107	96	79	70	63	57	54	46	41	37
82	NE	>500	415	296	228	193	168	139	119	106	96	89	76	67	61
84	NE	NE	NE	>500	>500	>500	429	315	255	218	194	176	146	127	114
86	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	461	343	282	245
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

QALY = quality-adjusted life-year; CRC = colorectal cancer; CS = cost saving; NE = negative effect

[1] The black line indicates a willingness-to-pay threshold of $100,000 per QALY gained. Green cells indicate that screening is cost-effective given this threshold. Red cells indicate that screening is not cost-effective given this threshold.

[2] Detailed information on comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

Appendix 3, Table 3 The Costs per QALY Gained (*$1,000) of Colonoscopy Screening for Black Men by Screening History, Comorbidity Status, Background Risk for CRC, and Age (3% discounted).[1]

NEGATIVE SCREENING COLONOSCOPY 10 YEARS PRIOR

NO COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5	3.0[4]	3.5[4]	4.0[4]	4.5[4]	5.0[4]	5.3[4]
66	155	90	60	44	34	26	17	12	8	6	4	1	CS	CS	CS	CS	CS	CS
68	191	108	68	50	38	29	20	14	9	7	4	1	CS	CS	CS	CS	CS	CS
70	276	136	85	60	46	36	24	17	12	9	6	3	0	CS	CS	CS	CS	CS
72	>500	216	123	85	65	50	33	23	17	13	10	5	3	1	CS	CS	CS	CS
74	>500	357	180	117	86	65	42	30	23	18	14	8	5	3	1	CS	CS	CS
76	NE	>500	340	190	131	97	61	44	33	26	21	14	10	7	4	3	2	2
78	NE	NE	>500	385	229	156	91	64	49	40	32	22	15	12	9	7	6	6
80	NE	NE	NE	>500	>500	307	154	102	77	60	50	34	25	19	16	13	12	12
82	NE	NE	NE	NE	NE	>500	387	217	147	112	89	60	42	34	29	26	21	22
84	NE	NE	NE	NE	NE	NE	NE	>500	404	248	175	107	78	61	49	45	40	38
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	467	223	145	107	87	77	69	62
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	301	205	141	130	125	102
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	484	463	383	308

NO PRIOR SCREENING

NO COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5	3.0[4]	3.5[4]	4.0[4]	4.5[4]	5.0[4]	5.3[4]
66	15	11	9	7	6	5	3	2	1	0	CS	CS	CS	CS	CS	CS	CS	CS
68	16	12	10	8	6	5	3	2	1	0	CS	CS	CS	CS	CS	CS	CS	CS
70	19	15	12	9	8	7	5	4	3	2	1	CS	CS	CS	CS	CS	CS	CS
72	25	19	16	13	11	10	7	6	5	4	3	1	CS	CS	CS	CS	CS	CS
74	30	24	20	17	15	13	10	9	7	6	5	3	2	1	0	CS	CS	CS
76	41	33	27	23	21	18	15	13	11	10	9	7	5	4	3	3	2	2
78	55	44	37	32	28	26	22	19	17	15	14	11	9	8	7	6	5	5
80	79	63	52	45	40	37	32	28	25	23	22	18	16	14	13	12	11	10
82	135	102	84	72	65	59	51	45	42	38	36	31	27	25	23	21	20	20
84	257	185	145	123	108	98	83	74	68	63	59	51	46	42	39	36	35	34
86	>500	426	296	239	197	175	145	128	115	106	99	86	76	70	65	61	58	57
88	NE	>500	>500	>500	451	373	283	240	209	189	171	146	128	116	106	100	95	91
90	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	416	347	309	278	258	245

MODERATE COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5	3.0[4]	3.5[4]	4.0[4]	4.5[4]	5.0[4]	5.3[4]
66	224	121	78	57	43	34	23	16	12	9	6	3	1	CS	CS	CS	CS	CS
68	339	163	98	71	53	42	28	20	15	11	9	4	2	0	CS	CS	CS	CS
70	>500	224	126	88	67	52	35	25	19	15	11	7	4	2	0	CS	CS	CS
72	NE	>500	239	151	110	83	54	39	30	24	19	13	8	6	4	3	1	1
74	NE	>500	372	208	145	105	67	48	37	29	24	16	11	8	6	4	3	3
76	NE	NE	>500	436	258	174	103	72	55	44	36	25	19	15	12	9	8	7
78	NE	NE	NE	>500	446	259	139	93	71	57	46	32	24	19	15	13	12	11
80	NE	NE	NE	NE	NE	>500	356	201	140	106	87	59	44	36	29	27	25	23
82	NE	NE	NE	NE	NE	NE	NE	>500	>500	304	223	135	93	75	66	58	51	53
84	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	309	185	143	111	104	96	86
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	311	206	161	142	128	111
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

MODERATE COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5	3.0[4]	3.5[4]	4.0[4]	4.5[4]	5.0[4]	5.3[4]
66	20	16	13	10	9	7	5	4	3	2	1	CS	CS	CS	CS	CS	CS	CS
68	24	19	15	13	11	9	7	6	4	3	3	1	CS	CS	CS	CS	CS	CS
70	28	22	18	15	13	12	9	8	6	5	4	3	1	0	CS	CS	CS	CS
72	41	33	27	23	21	19	15	13	11	10	9	7	5	4	3	2	2	1
74	48	39	32	28	25	22	19	16	14	13	11	9	7	6	5	4	3	3
76	67	54	45	39	35	31	27	24	21	19	18	15	13	11	10	9	8	8
78	80	64	54	46	41	38	33	29	26	24	22	19	16	14	13	12	11	11
80	145	112	92	79	71	64	56	49	45	42	39	34	30	27	25	24	23	22
82	447	282	212	174	151	135	115	101	92	85	79	69	62	57	53	50	48	46
84	>500	>500	500	371	298	253	206	176	158	144	133	115	101	93	87	82	78	76
86	NE	>500	>500	>500	>500	433	319	265	228	208	191	160	140	128	118	110	105	102
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	>500	493	456
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Appendix 3, Table 3 Continued.

NEGATIVE SCREENING COLONOSCOPY 10 YEARS PRIOR

SEVERE COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5	3.0[4]	3.5[4]	4.0[4]	4.5[4]	5.0[4]	5.3[4]
66	>500	364	186	125	93	71	48	35	28	22	18	11	8	5	3	2	1	0
68	NE	>500	306	190	133	100	66	48	37	29	24	16	12	9	7	5	4	3
70	NE	>500	419	238	162	120	77	55	43	34	28	19	14	11	9	7	6	5
72	NE	NE	>500	>500	359	231	133	92	71	55	45	32	24	19	17	14	12	11
74	NE	NE	NE	NE	>500	>500	269	171	122	93	75	52	41	35	29	26	22	22
76	NE	NE	NE	NE	NE	>500	>500	257	175	132	103	70	54	47	39	33	31	30
78	NE	NE	NE	NE	NE	NE	NE	>500	403	266	187	114	89	76	61	54	52	50
80	NE	NE	NE	NE	NE	NE	NE	>500	>500	398	277	158	117	93	76	70	65	62
82	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	363	223	174	139	120	107	106
84	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	463	524	380	307
86	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	438	378	295
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

NO PRIOR SCREENING

SEVERE COMORBIDITY[2]

Background risk for CRC[3]

Age	0.5	0.6	0.7	0.8	0.9	1.0	1.2	1.4	1.6	1.8	2.0	2.5	3.0[4]	3.5[4]	4.0[4]	4.5[4]	5.0[4]	5.3[4]
66	42	34	28	24	21	19	16	13	11	10	8	6	4	3	2	2	1	1
68	55	44	37	32	28	25	21	18	16	14	12	10	8	6	5	5	4	4
70	61	48	40	35	31	28	24	21	18	16	15	12	10	8	7	6	6	5
72	97	75	62	54	48	44	37	33	30	27	24	21	18	16	14	13	12	12
74	168	126	101	87	77	69	60	53	48	43	40	35	31	28	26	24	23	22
76	230	166	132	112	99	88	76	67	60	55	52	45	40	37	34	32	30	30
78	>500	317	232	189	163	142	120	105	95	87	81	70	63	58	54	51	49	47
80	>500	451	306	241	205	180	149	128	116	106	99	85	77	70	66	62	60	58
82	NE	>500	>500	>500	462	376	289	239	210	189	172	145	129	118	109	103	98	96
84	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	444	381	340	308	285	275
86	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500	>500	410	354	316	283	272	259
88	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	>500	>500	>500	>500
90	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

QALY = quality-adjusted life-year; CRC = colorectal cancer; CS = cost saving; NE = negative effect

[1] The black line indicates a willingness-to-pay threshold of $100,000 per QALY gained. Green cells indicate that screening is cost-effective given this threshold. Red cells indicate that screening is not cost-effective given this threshold.

[2] Detailed information on comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

Appendix 4: The Appropriate Ages to Stop Screening – Results of Univariate Deterministic Sensitivity Analyses

Appendix 4, Table 1 The Appropriate Ages to Stop Colonoscopy Screening Assuming 50% Lower Utility Losses for Colonoscopies and Complications.[1]

WHITE FEMALES SCREENING HISTORY																
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening				
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	68	<66[5]	<66[5]	**0.5**	72	70	67	**0.5**	75	72	70	**0.5**	82	80	76
0.6	72	69	<66[5]	**0.6**	76	73	70	**0.6**	78	75	72	**0.6**	83	81	77
0.7	75	72	69	**0.7**	78	75	71	**0.7**	80	77	73	**0.7**	84	81	78
0.8	77	74	70	**0.8**	80	76	73	**0.8**	81	78	75	**0.8**	84	82	79
0.9	79	75	72	**0.9**	81	78	74	**0.9**	82	79	76	**0.9**	85	82	80
1.0	***80***	***77***	***73***	***1.0***	***81***	***79***	***76***	***1.0***	***82***	***80***	***77***	***1.0***	***85***	***82***	***80***
1.2	81	79	76	**1.2**	83	80	77	**1.2**	84	81	78	**1.2**	86	83	80
1.4	82	80	77	**1.4**	84	81	79	**1.4**	85	82	80	**1.4**	86	84	81
1.6	83	81	78	**1.6**	84	82	80	**1.6**	85	83	80	**1.6**	86	84	81
1.8	84	82	79	**1.8**	85	82	80	**1.8**	85	83	81	**1.8**	86	84	82
2.0	85	82	80	**2.0**	85	83	81	**2.0**	86	84	81	**2.0**	87	84	82
2.5[4]	86	83	81	**2.5**[4]	86	84	82	**2.5**[4]	86	84	82	**2.5**[4]	87	85	83
3.0[4]	86	84	82	**3.0**[4]	87	85	82	**3.0**[4]	87	85	83	**3.0**[4]	87	85	83
3.5[4]	87	85	83	**3.5**[4]	87	85	83	**3.5**[4]	87	86	83	**3.5**[4]	88	86	83

Appendix 4, Table 1 Continued.

WHITE MALES SCREENING HISTORY								WHITE MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	68	<66[5]	<66[5]	**0.5**	72	70	66	**0.5**	75	73	69	**0.5**	82	80	76
0.6	71	69	<66[5]	**0.6**	75	73	69	**0.6**	78	75	71	**0.6**	83	80	77
0.7	74	71	67	**0.7**	78	75	71	**0.7**	80	77	73	**0.7**	83	81	78
0.8	77	73	69	**0.8**	80	76	72	**0.8**	81	78	74	**0.8**	84	81	79
0.9	79	75	71	**0.9**	80	78	73	**0.9**	81	79	75	**0.9**	84	82	79
1.0	***80***	***77***	***72***	***1.0***	***81***	***79***	***75***	***1.0***	***82***	***80***	***76***	***1.0***	***84***	***82***	***79***
1.2	81	79	75	**1.2**	82	80	77	**1.2**	83	81	77	**1.2**	85	83	80
1.4	82	80	76	**1.4**	83	81	78	**1.4**	84	81	79	**1.4**	85	83	80
1.6	83	81	77	**1.6**	84	81	79	**1.6**	84	82	79	**1.6**	85	83	80
1.8	83	81	79	**1.8**	84	82	79	**1.8**	85	82	80	**1.8**	86	83	81
2.0	84	82	79	**2.0**	85	83	80	**2.0**	85	83	80	**2.0**	86	84	81
2.5[4]	85	83	80	**2.5**[4]	85	83	81	**2.5**[4]	86	83	81	**2.5**[4]	86	84	81
3.0[4]	85	83	81	**3.0**[4]	86	84	81	**3.0**[4]	86	84	81	**3.0**[4]	86	84	82
3.5[4]	86	84	81	**3.5**[4]	86	84	82	**3.5**[4]	86	84	82	**3.5**[4]	87	84	82
4.0[4]	86	84	82	**4.0**[4]	87	84	82	**4.0**[4]	87	84	82	**4.0**[4]	87	84	82
4.5[4]	87	84	82	**4.5**[4]	87	85	82	**4.5**[4]	87	85	82	**4.5**[4]	87	84	82
4.9[4]	87	84	82	**4.9**[4]	87	85	82	**4.9**[4]	87	85	82	**4.9**[4]	87	85	82

Appendix 4, Table 1 Continued.

BLACK FEMALES SCREENING HISTORY								BLACK FEMALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.4	<66[5]	<66[5]	<66[5]	**0.4**	67	<66[5]	<66[5]	**0.4**	71	69	<66[5]	**0.4**	81	79	75
0.5	68	<66[5]	<66[5]	**0.5**	72	70	<66[5]	**0.5**	75	73	68	**0.5**	82	80	77
0.6	72	69	<66[5]	**0.6**	75	73	68	**0.6**	77	75	71	**0.6**	83	81	78
0.7	74	72	67	**0.7**	77	75	71	**0.7**	79	77	73	**0.7**	84	82	79
0.8	76	74	70	**0.8**	79	77	73	**0.8**	80	78	75	**0.8**	85	82	80
0.9	77	75	72	**0.9**	80	78	74	**0.9**	81	79	76	**0.9**	85	83	80
1.0	***79***	***77***	***73***	***1.0***	***81***	***79***	***76***	***1.0***	***82***	***80***	***77***	***1.0***	***85***	***83***	***80***
1.2	80	79	75	**1.2**	82	80	77	**1.2**	83	81	78	**1.2**	86	84	81
1.4	82	80	77	**1.4**	83	81	78	**1.4**	84	82	80	**1.4**	86	84	82
1.6	82	81	78	**1.6**	84	82	80	**1.6**	85	83	80	**1.6**	86	84	82
1.8	83	81	79	**1.8**	85	83	80	**1.8**	85	83	81	**1.8**	87	85	82
2.0[4]	84	82	80	**2.0**[4]	85	83	81	**2.0**[4]	86	84	81	**2.0**[4]	87	85	83
2.5[4]	85	83	81	**2.5**[4]	86	84	82	**2.5**[4]	87	85	82	**2.5**[4]	87	86	83
3.0[4]	86	84	82	**3.0**[4]	87	85	83	**3.0**[4]	87	86	83	**3.0**[4]	88	86	83
3.5[4]	87	85	83	**3.5**[4]	87	86	83	**3.5**[4]	88	86	83	**3.5**[4]	88	87	84

Appendix 4, Table 1 Continued.

BLACK MALES SCREENING HISTORY								BLACK MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	70	69	<66[5]	**0.5**	73	71	67	**0.5**	82	79	73
0.6	70	67	<66[5]	**0.6**	74	71	<66[5]	**0.6**	76	73	68	**0.6**	82	80	75
0.7	73	70	<66[5]	**0.7**	76	73	68	**0.7**	78	75	70	**0.7**	83	81	76
0.8	75	72	67	**0.8**	77	74	70	**0.8**	79	77	71	**0.8**	84	81	76
0.9	76	74	69	**0.9**	79	76	71	**0.9**	80	78	72	**0.9**	84	81	76
1.0	***77***	***75***	***70***	***1.0***	***80***	***78***	***72***	***1.0***	***81***	***79***	***73***	***1.0***	***84***	***81***	***77***
1.2	79	78	72	**1.2**	81	79	73	**1.2**	82	80	75	**1.2**	85	82	78
1.4	80	78	73	**1.4**	82	80	75	**1.4**	83	81	76	**1.4**	85	82	79
1.6	81	80	75	**1.6**	82	81	76	**1.6**	84	81	76	**1.6**	86	83	80
1.8	82	80	76	**1.8**	84	81	76	**1.8**	84	81	77	**1.8**	86	83	80
2.0	83	81	76	**2.0**	84	81	78	**2.0**	85	82	79	**2.0**	86	83	80
2.5	84	81	79	**2.5**	85	82	80	**2.5**	86	83	80	**2.5**	87	84	80
3.0[4]	85	83	80	**3.0**[4]	86	83	80	**3.0**[4]	86	83	80	**3.0**[4]	87	84	80
3.5[4]	86	83	80	**3.5**[4]	87	84	80	**3.5**[4]	87	84	80	**3.5**[4]	87	84	81
4.0[4]	87	84	81	**4.0**[4]	87	84	81	**4.0**[4]	88	84	82	**4.0**[4]	88	84	82
4.5[4]	87	84	81	**4.5**[4]	87	84	82	**4.5**[4]	88	84	82	**4.5**[4]	88	84	82
5.0[4]	87	84	82	**5.0**[4]	88	84	82	**5.0**[4]	88	84	82	**5.0**[4]	88	84	82
5.3[4]	88	84	82	**5.3**[4]	88	84	82	**5.3**[4]	88	84	82	**5.3**[4]	88	84	82

CRC = colorectal cancer; RR CRC = background risk for CRC

[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

[5] In these cohorts screening was not cost-effective at age 66 years. We did not perform analyses for individuals aged 65 years or younger.

Appendix 4, Table 2 The Appropriate Ages to Stop Colonoscopy Screening Assuming 50% Higher Utility Losses for Colonoscopies and Complications.[1]

WHITE FEMALES SCREENING HISTORY																
	Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
	COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	67	<66[5]	<66[5]	**0.5**	71	68	<66[5]	**0.5**	80	76	72
0.6	<66[5]	<66[5]	<66[5]	**0.6**	71	68	<66[5]	**0.6**	74	71	68	**0.6**	81	78	74
0.7	70	66	<66[5]	**0.7**	74	71	67	**0.7**	76	73	70	**0.7**	82	79	76
0.8	72	69	<66[5]	**0.8**	76	73	70	**0.8**	78	75	71	**0.8**	82	80	76
0.9	74	71	68	**0.9**	77	74	71	**0.9**	79	76	73	**0.9**	83	80	77
1.0	***76***	***73***	***70***	***1.0***	***79***	***75***	***72***	***1.0***	***80***	***77***	***74***	***1.0***	***83***	***81***	***78***
1.2	79	75	72	**1.2**	80	78	74	**1.2**	81	79	76	**1.2**	84	82	79
1.4	80	77	74	**1.4**	82	79	76	**1.4**	82	80	77	**1.4**	85	82	79
1.6	81	78	75	**1.6**	82	80	77	**1.6**	83	81	78	**1.6**	85	82	80
1.8	82	79	76	**1.8**	83	81	78	**1.8**	84	81	79	**1.8**	85	83	80
2.0	83	80	77	**2.0**	84	81	79	**2.0**	84	82	79	**2.0**	86	83	80
2.5[4]	84	82	79	**2.5**[4]	85	82	80	**2.5**[4]	85	83	80	**2.5**[4]	86	84	81
3.0[4]	85	82	80	**3.0**[4]	86	83	81	**3.0**[4]	86	84	81	**3.0**[4]	86	84	82
3.5[4]	85	83	81	**3.5**[4]	86	84	81	**3.5**[4]	86	84	82	**3.5**[4]	87	85	82

Appendix 4, Table 2 Continued.

WHITE MALES SCREENING HISTORY																
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	67	<66[5]	<66[5]	**0.5**	71	69	<66[5]	**0.5**	80	77	73
0.6	66	<66[5]	<66[5]	**0.6**	71	68	<66[5]	**0.6**	74	71	68	**0.6**	81	78	74
0.7	69	67	<66[5]	**0.7**	73	71	67	**0.7**	76	73	70	**0.7**	82	80	75
0.8	72	69	<66[5]	**0.8**	75	73	69	**0.8**	78	75	71	**0.8**	82	80	76
0.9	74	71	67	**0.9**	77	74	70	**0.9**	79	76	72	**0.9**	83	80	77
1.0	***76***	***73***	***69***	***1.0***	***79***	***75***	***71***	***1.0***	***80***	***77***	***73***	***1.0***	***83***	***81***	***77***
1.2	79	75	71	**1.2**	80	78	73	**1.2**	81	79	75	**1.2**	84	81	78
1.4	80	77	73	**1.4**	81	79	75	**1.4**	82	80	76	**1.4**	84	82	79
1.6	81	79	74	**1.6**	82	80	76	**1.6**	83	80	77	**1.6**	84	82	79
1.8	82	80	76	**1.8**	83	80	77	**1.8**	83	81	78	**1.8**	85	82	80
2.0	82	80	77	**2.0**	83	81	78	**2.0**	84	81	79	**2.0**	85	83	80
2.5[4]	83	81	79	**2.5**[4]	84	82	79	**2.5**[4]	84	82	80	**2.5**[4]	85	83	80
3.0[4]	84	82	80	**3.0**[4]	85	83	80	**3.0**[4]	85	83	80	**3.0**[4]	86	83	81
3.5[4]	85	83	80	**3.5**[4]	85	83	81	**3.5**[4]	85	83	81	**3.5**[4]	86	84	81
4.0[4]	85	83	81	**4.0**[4]	86	84	81	**4.0**[4]	86	84	81	**4.0**[4]	86	84	81
4.5[4]	86	84	81	**4.5**[4]	86	84	81	**4.5**[4]	86	84	81	**4.5**[4]	86	84	82
4.9[4]	86	84	81	**4.9**[4]	86	84	82	**4.9**[4]	86	84	82	**4.9**[4]	87	84	82

Appendix 4, Table 2 Continued.

BLACK FEMALES SCREENING HISTORY																
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.4	<66[5]	<66[5]	<66[5]	**0.4**	<66[5]	<66[5]	<66[5]	**0.4**	<66[5]	<66[5]	<66[5]	**0.4**	79	76	71
0.5	<66[5]	<66[5]	<66[5]	**0.5**	66	<66[5]	<66[5]	**0.5**	70	68	<66[5]	**0.5**	80	78	73
0.6	<66[5]	<66[5]	<66[5]	**0.6**	70	68	<66[5]	**0.6**	73	71	66	**0.6**	81	79	75
0.7	69	67	<66[5]	**0.7**	73	71	66	**0.7**	76	74	69	**0.7**	82	80	76
0.8	72	70	<66[5]	**0.8**	75	73	69	**0.8**	77	75	71	**0.8**	83	80	77
0.9	74	72	67	**0.9**	77	74	70	**0.9**	79	76	72	**0.9**	83	81	77
1.0	***76***	***74***	***69***	***1.0***	***78***	***76***	***72***	***1.0***	***80***	***78***	***73***	***1.0***	***84***	***81***	***78***
1.2	78	75	72	**1.2**	80	78	73	**1.2**	81	79	76	**1.2**	84	82	80
1.4	79	78	73	**1.4**	81	79	76	**1.4**	82	80	77	**1.4**	85	83	80
1.6	80	79	75	**1.6**	82	80	77	**1.6**	83	81	78	**1.6**	85	83	80
1.8	81	79	76	**1.8**	83	81	78	**1.8**	83	81	79	**1.8**	85	83	81
2.0[4]	82	80	77	**2.0**[4]	83	81	78	**2.0**[4]	84	82	80	**2.0**[4]	86	84	81
2.5[4]	83	81	79	**2.5**[4]	85	83	80	**2.5**[4]	85	83	81	**2.5**[4]	86	84	82
3.0[4]	85	83	80	**3.0**[4]	85	84	81	**3.0**[4]	86	84	82	**3.0**[4]	87	85	82
3.5[4]	85	84	81	**3.5**[4]	86	84	82	**3.5**[4]	86	84	82	**3.5**[4]	87	85	83

Appendix 4, Table 2 Continued.

BLACK MALES SCREENING HISTORY								BLACK MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	<66[5]	<66[5]	<66[5]	**0.5**	69	67	<66[5]	**0.5**	79	77	70
0.6	<66[5]	<66[5]	<66[5]	**0.6**	69	67	<66[5]	**0.6**	72	70	<66[5]	**0.6**	80	78	72
0.7	68	<66[5]	<66[5]	**0.7**	72	70	<66[5]	**0.7**	74	71	67	**0.7**	81	79	73
0.8	70	68	<66[5]	**0.8**	74	71	67	**0.8**	76	73	68	**0.8**	82	80	73
0.9	72	70	<66[5]	**0.9**	75	72	67	**0.9**	77	74	70	**0.9**	82	80	75
1.0	***74***	***71***	***67***	***1.0***	***77***	***74***	***69***	***1.0***	***79***	***76***	***70***	***1.0***	***82***	***80***	***75***
1.2	77	74	69	**1.2**	79	77	71	**1.2**	80	78	72	**1.2**	83	81	76
1.4	78	76	70	**1.4**	80	78	72	**1.4**	81	79	73	**1.4**	84	81	76
1.6	79	78	72	**1.6**	81	79	73	**1.6**	82	80	75	**1.6**	84	81	77
1.8	80	78	73	**1.8**	82	80	75	**1.8**	82	80	76	**1.8**	84	82	77
2.0	81	79	75	**2.0**	82	80	76	**2.0**	83	81	76	**2.0**	85	82	79
2.5	82	80	76	**2.5**	84	81	77	**2.5**	84	81	77	**2.5**	86	83	80
3.0[4]	84	81	77	**3.0**[4]	84	82	78	**3.0**[4]	85	82	79	**3.0**[4]	86	83	80
3.5[4]	84	82	78	**3.5**[4]	85	82	80	**3.5**[4]	86	83	80	**3.5**[4]	86	83	80
4.0[4]	85	82	80	**4.0**[4]	86	83	80	**4.0**[4]	86	83	80	**4.0**[4]	87	84	80
4.5[4]	86	83	80	**4.5**[4]	86	83	80	**4.5**[4]	87	84	80	**4.5**[4]	87	84	80
5.0[4]	86	83	80	**5.0**[4]	87	84	80	**5.0**[4]	87	84	81	**5.0**[4]	87	84	81
5.3[4]	87	84	80	**5.3**[4]	87	84	80	**5.3**[4]	87	84	81	**5.3**[4]	88	84	81

CRC = colorectal cancer; RR CRC = background risk for CRC

[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

[5] In these cohorts screening was not cost-effective at age 66 years. We did not perform analyses for individuals aged 65 years or younger.

Appendix 4, Table 3 The Appropriate Ages to Stop Colonoscopy Screening Assuming 25% Higher Colonoscopy Costs.[1]

WHITE FEMALES SCREENING HISTORY															
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	67	<66[5]	<66[5]	**0.5**	71	68	<66[5]	**0.5**	80	77	73
0.6	66	<66[5]	<66[5]	**0.6**	71	68	<66[5]	**0.6**	74	71	68	**0.6**	81	78	74
0.7	70	66	<66[5]	**0.7**	74	71	68	**0.7**	76	73	70	**0.7**	82	79	76
0.8	72	70	66	**0.8**	76	73	70	**0.8**	78	75	72	**0.8**	83	80	77
0.9	75	72	68	**0.9**	78	74	71	**0.9**	80	76	73	**0.9**	83	81	77
1.0	***76***	***73***	***70***	***1.0***	***79***	***76***	***73***	***1.0***	***80***	***77***	***74***	***1.0***	***84***	***81***	***78***
1.2	79	75	72	**1.2**	81	78	74	**1.2**	82	79	76	**1.2**	84	82	79
1.4	80	77	74	**1.4**	82	79	76	**1.4**	83	80	77	**1.4**	85	82	80
1.6	81	79	76	**1.6**	83	80	77	**1.6**	83	81	78	**1.6**	85	82	80
1.8	82	80	76	**1.8**	83	81	78	**1.8**	84	82	79	**1.8**	85	83	80
2.0	83	80	77	**2.0**	84	82	79	**2.0**	85	82	80	**2.0**	86	83	81
2.5[4]	84	82	79	**2.5**[4]	85	82	80	**2.5**[4]	85	83	80	**2.5**[4]	86	84	81
3.0[4]	85	82	80	**3.0**[4]	86	83	81	**3.0**[4]	86	84	81	**3.0**[4]	87	84	82
3.5[4]	86	83	81	**3.5**[4]	86	84	82	**3.5**[4]	86	84	82	**3.5**[4]	87	85	82

Appendix 4, Table 3 Continued.

WHITE MALES SCREENING HISTORY																
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	68	66	<66[5]	**0.5**	71	69	<66[5]	**0.5**	80	78	73
0.6	66	<66[5]	<66[5]	**0.6**	71	69	<66[5]	**0.6**	74	71	68	**0.6**	81	79	75
0.7	70	67	<66[5]	**0.7**	74	71	67	**0.7**	76	73	70	**0.7**	82	80	76
0.8	72	70	<66[5]	**0.8**	76	73	69	**0.8**	78	75	71	**0.8**	83	80	77
0.9	74	71	67	**0.9**	78	74	70	**0.9**	80	77	72	**0.9**	83	80	77
1.0	***76***	***73***	***69***	***1.0***	***79***	***76***	***72***	***1.0***	***80***	***77***	***73***	***1.0***	***83***	***81***	***77***
1.2	79	75	71	**1.2**	80	78	74	**1.2**	81	79	75	**1.2**	84	81	78
1.4	80	78	73	**1.4**	82	79	75	**1.4**	82	80	76	**1.4**	84	82	79
1.6	81	79	75	**1.6**	82	80	76	**1.6**	83	81	77	**1.6**	85	82	79
1.8	82	80	76	**1.8**	83	81	77	**1.8**	83	81	78	**1.8**	85	82	80
2.0	83	80	77	**2.0**	83	81	78	**2.0**	84	81	79	**2.0**	85	83	80
2.5[4]	84	81	79	**2.5**[4]	84	82	79	**2.5**[4]	85	82	80	**2.5**[4]	85	83	80
3.0[4]	84	82	80	**3.0**[4]	85	83	80	**3.0**[4]	85	83	80	**3.0**[4]	86	83	81
3.5[4]	85	83	80	**3.5**[4]	85	83	81	**3.5**[4]	86	83	81	**3.5**[4]	86	84	81
4.0[4]	85	84	81	**4.0**[4]	86	84	81	**4.0**[4]	86	84	81	**4.0**[4]	86	84	81
4.5[4]	86	84	81	**4.5**[4]	86	84	81	**4.5**[4]	86	84	81	**4.5**[4]	86	84	82
4.9[4]	86	84	82	**4.9**[4]	86	84	82	**4.9**[4]	86	84	82	**4.9**[4]	87	84	82

Appendix 4, Table 3 Continued.

BLACK FEMALES SCREENING HISTORY																
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.4	<66[5]	<66[5]	<66[5]	**0.4**	<66[5]	<66[5]	<66[5]	**0.4**	66	<66[5]	<66[5]	**0.4**	79	76	71
0.5	<66[5]	<66[5]	<66[5]	**0.5**	67	<66[5]	<66[5]	**0.5**	70	69	<66[5]	**0.5**	80	78	73
0.6	66	<66[5]	<66[5]	**0.6**	71	69	<66[5]	**0.6**	74	71	67	**0.6**	82	79	76
0.7	70	67	<66[5]	**0.7**	74	71	66	**0.7**	76	74	69	**0.7**	82	80	77
0.8	72	70	<66[5]	**0.8**	76	74	69	**0.8**	78	75	71	**0.8**	83	81	77
0.9	74	72	67	**0.9**	77	75	71	**0.9**	79	77	73	**0.9**	83	81	78
1.0	***76***	***74***	***69***	***1.0***	***78***	***76***	***72***	***1.0***	***80***	***78***	***73***	***1.0***	***84***	***81***	***79***
1.2	78	76	72	**1.2**	80	78	75	**1.2**	81	79	76	**1.2**	85	82	80
1.4	80	78	73	**1.4**	81	79	76	**1.4**	82	80	77	**1.4**	85	83	80
1.6	81	79	76	**1.6**	82	80	77	**1.6**	83	81	78	**1.6**	85	83	80
1.8	81	80	77	**1.8**	83	81	78	**1.8**	84	82	79	**1.8**	86	84	81
2.0[4]	82	80	77	**2.0**[4]	83	81	79	**2.0**[4]	84	82	80	**2.0**[4]	86	84	81
2.5[4]	83	82	79	**2.5**[4]	85	83	80	**2.5**[4]	85	83	81	**2.5**[4]	86	84	82
3.0[4]	85	83	80	**3.0**[4]	85	84	81	**3.0**[4]	86	84	82	**3.0**[4]	87	85	82
3.5[4]	86	84	81	**3.5**[4]	86	84	82	**3.5**[4]	87	85	82	**3.5**[4]	87	86	83

Appendix 4, Table 3 Continued.

BLACK MALES SCREENING HISTORY																
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	<66[5]	<66[5]	<66[5]	**0.5**	70	67	<66[5]	**0.5**	80	78	70
0.6	<66[5]	<66[5]	<66[5]	**0.6**	70	67	<66[5]	**0.6**	72	70	<66[5]	**0.6**	80	78	72
0.7	69	<66[5]	<66[5]	**0.7**	72	70	<66[5]	**0.7**	75	71	67	**0.7**	81	79	73
0.8	71	69	<66[5]	**0.8**	74	71	67	**0.8**	76	74	69	**0.8**	82	80	73
0.9	72	70	<66[5]	**0.9**	76	73	67	**0.9**	78	75	70	**0.9**	82	80	75
1.0	***74***	***71***	***67***	***1.0***	***77***	***74***	***70***	***1.0***	***79***	***76***	***71***	***1.0***	***83***	***81***	***75***
1.2	77	74	70	**1.2**	79	77	71	**1.2**	80	78	72	**1.2**	84	81	76
1.4	78	76	71	**1.4**	80	78	72	**1.4**	81	79	73	**1.4**	84	81	76
1.6	80	78	72	**1.6**	81	79	73	**1.6**	82	80	75	**1.6**	84	81	77
1.8	80	78	73	**1.8**	82	80	75	**1.8**	82	81	76	**1.8**	85	82	78
2.0	81	79	75	**2.0**	82	81	76	**2.0**	83	81	76	**2.0**	85	82	79
2.5	82	81	76	**2.5**	84	81	77	**2.5**	84	81	78	**2.5**	86	83	80
3.0[4]	84	81	77	**3.0**[4]	84	82	79	**3.0**[4]	85	82	79	**3.0**[4]	86	83	80
3.5[4]	84	82	79	**3.5**[4]	85	82	80	**3.5**[4]	86	83	80	**3.5**[4]	87	83	80
4.0[4]	85	83	80	**4.0**[4]	86	83	80	**4.0**[4]	86	83	80	**4.0**[4]	87	84	80
4.5[4]	86	83	80	**4.5**[4]	86	83	80	**4.5**[4]	87	84	80	**4.5**[4]	87	84	80
5.0[4]	87	83	80	**5.0**[4]	87	84	80	**5.0**[4]	87	84	81	**5.0**[4]	87	84	81
5.3[4]	87	84	80	**5.3**[4]	87	84	80	**5.3**[4]	87	84	81	**5.3**[4]	88	84	81

CRC = colorectal cancer; RR CRC = background risk for CRC

[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

[5] In these cohorts screening was not cost-effective at age 66 years. We did not perform analyses for individuals aged 65 years or younger.

Appendix 4, Table 4 The Appropriate Ages to Stop Colonoscopy Screening Assuming 25% Lower Colonoscopy Costs.[1]

WHITE FEMALES SCREENING HISTORY								WHITE FEMALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	67	<66[5]	<66[5]	**0.5**	72	69	66	**0.5**	75	72	69	**0.5**	82	79	76
0.6	71	68	<66[5]	**0.6**	75	72	69	**0.6**	78	74	71	**0.6**	83	80	77
0.7	74	71	68	**0.7**	77	74	71	**0.7**	79	76	73	**0.7**	84	81	78
0.8	76	73	70	**0.8**	79	76	73	**0.8**	81	78	74	**0.8**	84	82	79
0.9	78	75	72	**0.9**	80	77	74	**0.9**	81	79	76	**0.9**	85	82	79
1.0	***80***	***76***	***73***	***1.0***	***81***	***79***	***76***	***1.0***	***82***	***80***	***77***	***1.0***	***85***	***82***	***80***
1.2	81	78	75	**1.2**	82	80	77	**1.2**	83	81	78	**1.2**	85	83	80
1.4	82	80	77	**1.4**	84	81	78	**1.4**	84	82	79	**1.4**	86	83	81
1.6	83	81	78	**1.6**	84	82	79	**1.6**	85	82	80	**1.6**	86	84	81
1.8	84	82	79	**1.8**	85	82	80	**1.8**	85	83	80	**1.8**	86	84	82
2.0	84	82	80	**2.0**	85	83	80	**2.0**	86	83	81	**2.0**	87	84	82
2.5[4]	85	83	81	**2.5**[4]	86	84	81	**2.5**[4]	86	84	82	**2.5**[4]	87	85	82
3.0[4]	86	84	82	**3.0**[4]	87	85	82	**3.0**[4]	87	85	83	**3.0**[4]	87	85	83
3.5[4]	87	85	82	**3.5**[4]	87	85	83	**3.5**[4]	87	85	83	**3.5**[4]	87	86	83

Appendix 4, Table 4 Continued.

WHITE MALES SCREENING HISTORY								WHITE MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	67	<66[5]	<66[5]	**0.5**	72	69	<66[5]	**0.5**	75	72	69	**0.5**	82	80	75
0.6	71	68	<66[5]	**0.6**	74	72	68	**0.6**	77	74	71	**0.6**	83	80	77
0.7	74	71	67	**0.7**	77	74	70	**0.7**	79	77	72	**0.7**	83	81	78
0.8	76	73	69	**0.8**	79	76	72	**0.8**	80	78	74	**0.8**	84	81	78
0.9	78	75	71	**0.9**	80	77	73	**0.9**	81	79	75	**0.9**	84	81	79
1.0	***80***	***76***	***72***	***1.0***	***81***	***78***	***74***	***1.0***	***82***	***80***	***76***	***1.0***	***84***	***82***	***79***
1.2	81	79	74	**1.2**	82	80	76	**1.2**	83	80	77	**1.2**	85	82	80
1.4	82	80	76	**1.4**	83	81	77	**1.4**	84	81	78	**1.4**	85	83	80
1.6	83	81	77	**1.6**	84	81	79	**1.6**	84	82	79	**1.6**	85	83	80
1.8	83	81	78	**1.8**	84	82	79	**1.8**	84	82	80	**1.8**	85	83	81
2.0	84	82	79	**2.0**	85	82	80	**2.0**	85	83	80	**2.0**	86	83	81
2.5[4]	85	83	80	**2.5**[4]	85	83	81	**2.5**[4]	85	83	81	**2.5**[4]	86	84	81
3.0[4]	85	83	81	**3.0**[4]	86	84	81	**3.0**[4]	86	84	81	**3.0**[4]	86	84	81
3.5[4]	86	84	81	**3.5**[4]	86	84	81	**3.5**[4]	86	84	82	**3.5**[4]	87	84	82
4.0[4]	86	84	82	**4.0**[4]	86	84	82	**4.0**[4]	87	84	82	**4.0**[4]	87	84	82
4.5[4]	86	84	82	**4.5**[4]	87	84	82	**4.5**[4]	87	84	82	**4.5**[4]	87	84	82
4.9[4]	87	84	82	**4.9**[4]	87	84	82	**4.9**[4]	87	84	82	**4.9**[4]	87	85	82

Appendix 4, Table 4 Continued.

BLACK FEMALES SCREENING HISTORY								BLACK FEMALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.4	<66[5]	<66[5]	<66[5]	**0.4**	66	<66[5]	<66[5]	**0.4**	70	68	<66[5]	**0.4**	81	79	75
0.5	67	<66[5]	<66[5]	**0.5**	72	69	<66[5]	**0.5**	74	72	68	**0.5**	82	80	77
0.6	71	69	<66[5]	**0.6**	75	73	68	**0.6**	77	74	70	**0.6**	83	81	77
0.7	74	71	66	**0.7**	77	74	70	**0.7**	79	77	72	**0.7**	84	81	79
0.8	76	74	69	**0.8**	78	76	72	**0.8**	80	78	74	**0.8**	84	82	80
0.9	77	75	71	**0.9**	80	78	73	**0.9**	81	79	76	**0.9**	85	83	80
1.0	***78***	***76***	***72***	***1.0***	***80***	***79***	***75***	***1.0***	***82***	***80***	***77***	***1.0***	***85***	***83***	***80***
1.2	80	78	75	**1.2**	82	80	77	**1.2**	83	81	78	**1.2**	86	84	81
1.4	81	80	77	**1.4**	83	81	78	**1.4**	84	82	79	**1.4**	86	84	82
1.6	82	80	77	**1.6**	84	82	79	**1.6**	85	83	80	**1.6**	86	84	82
1.8	83	81	79	**1.8**	84	82	80	**1.8**	85	83	81	**1.8**	87	84	82
2.0[4]	84	82	80	**2.0**[4]	85	83	80	**2.0**[4]	85	84	81	**2.0**[4]	87	85	82
2.5[4]	85	83	81	**2.5**[4]	86	84	82	**2.5**[4]	86	84	82	**2.5**[4]	87	86	83
3.0[4]	86	84	82	**3.0**[4]	87	85	83	**3.0**[4]	87	85	83	**3.0**[4]	88	86	83
3.5[4]	87	85	83	**3.5**[4]	87	86	83	**3.5**[4]	87	86	83	**3.5**[4]	88	86	83

Appendix 4, Table 4 Continued.

BLACK MALES SCREENING HISTORY								BLACK MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	70	67	<66[5]	**0.5**	73	71	<66[5]	**0.5**	81	79	73
0.6	70	67	<66[5]	**0.6**	73	71	<66[5]	**0.6**	75	72	67	**0.6**	82	80	75
0.7	72	70	<66[5]	**0.7**	75	72	67	**0.7**	77	74	70	**0.7**	83	81	75
0.8	74	71	67	**0.8**	77	74	70	**0.8**	79	77	71	**0.8**	83	81	76
0.9	76	73	68	**0.9**	78	76	70	**0.9**	80	78	72	**0.9**	84	81	76
1.0	***77***	***74***	***70***	***1.0***	***79***	***78***	***72***	***1.0***	***80***	***78***	***73***	***1.0***	***84***	***81***	***77***
1.2	79	77	72	**1.2**	81	79	73	**1.2**	82	80	75	**1.2**	85	82	77
1.4	80	78	73	**1.4**	82	80	75	**1.4**	82	81	76	**1.4**	85	82	79
1.6	81	79	75	**1.6**	82	81	76	**1.6**	83	81	76	**1.6**	86	82	80
1.8	82	80	75	**1.8**	83	81	76	**1.8**	84	81	77	**1.8**	86	83	80
2.0	82	81	76	**2.0**	84	81	77	**2.0**	84	82	79	**2.0**	86	83	80
2.5	84	81	78	**2.5**	85	82	80	**2.5**	85	83	80	**2.5**	87	83	80
3.0[4]	85	82	80	**3.0**[4]	86	83	80	**3.0**[4]	86	83	80	**3.0**[4]	87	84	80
3.5[4]	86	83	80	**3.5**[4]	86	84	80	**3.5**[4]	87	84	80	**3.5**[4]	87	84	81
4.0[4]	87	84	80	**4.0**[4]	87	84	81	**4.0**[4]	87	84	81	**4.0**[4]	88	84	82
4.5[4]	87	84	81	**4.5**[4]	87	84	82	**4.5**[4]	87	84	82	**4.5**[4]	88	84	82
5.0[4]	87	84	82	**5.0**[4]	87	84	82	**5.0**[4]	88	84	82	**5.0**[4]	88	84	82
5.3[4]	88	84	82	**5.3**[4]	88	84	82	**5.3**[4]	88	84	82	**5.3**[4]	88	84	82

CRC = colorectal cancer; RR CRC = background risk for CRC

[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

[5] In these cohorts screening was not cost-effective at age 66 years. We did not perform analyses for individuals aged 65 years or younger.

Appendix 4, Table 5 The Appropriate Ages to Stop Colonoscopy Screening Assuming 25% Higher CRC Care Costs.[1]

WHITE FEMALES SCREENING HISTORY																
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening				
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	70	67	<66[5]	**0.5**	73	71	68	**0.5**	81	78	74
0.6	69	66	<66[5]	**0.6**	73	71	68	**0.6**	76	73	70	**0.6**	82	80	76
0.7	72	70	66	**0.7**	76	73	70	**0.7**	78	75	72	**0.7**	83	80	77
0.8	75	72	69	**0.8**	78	75	71	**0.8**	80	77	73	**0.8**	83	81	78
0.9	77	74	70	**0.9**	80	76	73	**0.9**	81	78	74	**0.9**	84	81	78
1.0	***78***	***75***	***72***	***1.0***	***80***	***77***	***74***	***1.0***	***81***	***79***	***76***	***1.0***	***84***	***82***	***79***
1.2	80	77	74	**1.2**	82	79	76	**1.2**	83	80	77	**1.2**	85	82	80
1.4	82	79	76	**1.4**	83	80	77	**1.4**	84	81	78	**1.4**	85	83	80
1.6	82	80	77	**1.6**	84	81	78	**1.6**	84	82	79	**1.6**	85	83	80
1.8	83	81	78	**1.8**	84	82	79	**1.8**	85	82	80	**1.8**	86	83	81
2.0	84	81	79	**2.0**	85	82	80	**2.0**	85	83	80	**2.0**	86	84	81
2.5[4]	85	82	80	**2.5**[4]	85	83	81	**2.5**[4]	86	84	81	**2.5**[4]	86	84	82
3.0[4]	86	83	81	**3.0**[4]	86	84	81	**3.0**[4]	86	84	82	**3.0**[4]	87	85	82
3.5[4]	86	84	82	**3.5**[4]	86	84	82	**3.5**[4]	87	85	82	**3.5**[4]	87	85	82

Appendix 4, Table 5 Continued.

WHITE MALES SCREENING HISTORY								WHITE MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	70	68	<66[5]	**0.5**	73	71	67	**0.5**	81	79	74
0.6	69	67	<66[5]	**0.6**	73	71	67	**0.6**	76	73	70	**0.6**	82	80	76
0.7	72	70	<66[5]	**0.7**	76	73	69	**0.7**	78	75	71	**0.7**	83	80	77
0.8	74	71	68	**0.8**	78	75	71	**0.8**	80	77	73	**0.8**	83	80	77
0.9	76	73	69	**0.9**	79	76	72	**0.9**	80	78	74	**0.9**	83	81	78
1.0	***78***	***75***	***71***	***1.0***	***80***	***77***	***73***	***1.0***	***81***	***79***	***75***	***1.0***	***84***	***81***	***78***
1.2	80	77	73	**1.2**	81	79	75	**1.2**	82	80	76	**1.2**	84	82	79
1.4	81	79	75	**1.4**	82	80	77	**1.4**	83	80	77	**1.4**	84	82	79
1.6	82	80	76	**1.6**	83	81	77	**1.6**	83	81	78	**1.6**	85	82	80
1.8	83	80	77	**1.8**	83	81	78	**1.8**	84	81	79	**1.8**	85	83	80
2.0	83	81	78	**2.0**	84	82	79	**2.0**	84	82	79	**2.0**	85	83	80
2.5[4]	84	82	80	**2.5**[4]	85	83	80	**2.5**[4]	85	83	80	**2.5**[4]	85	83	81
3.0[4]	85	83	80	**3.0**[4]	85	83	81	**3.0**[4]	85	83	81	**3.0**[4]	86	83	81
3.5[4]	85	83	81	**3.5**[4]	86	84	81	**3.5**[4]	86	84	81	**3.5**[4]	86	84	81
4.0[4]	86	84	81	**4.0**[4]	86	84	81	**4.0**[4]	86	84	81	**4.0**[4]	86	84	81
4.5[4]	86	84	82	**4.5**[4]	86	84	82	**4.5**[4]	86	84	81	**4.5**[4]	86	84	81
4.9[4]	86	84	82	**4.9**[4]	86	84	82	**4.9**[4]	86	84	82	**4.9**[4]	86	84	82

Appendix 4, Table 5 Continued.

BLACK FEMALES SCREENING HISTORY								BLACK FEMALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.4	<66[5]	<66[5]	<66[5]	**0.4**	<66[5]	<66[5]	<66[5]	**0.4**	68	67	<66[5]	**0.4**	80	78	73
0.5	<66[5]	<66[5]	<66[5]	**0.5**	70	68	<66[5]	**0.5**	73	70	66	**0.5**	81	79	75
0.6	69	67	<66[5]	**0.6**	73	71	<66[5]	**0.6**	76	73	69	**0.6**	82	80	77
0.7	72	70	<66[5]	**0.7**	75	73	69	**0.7**	77	75	71	**0.7**	83	81	77
0.8	75	73	67	**0.8**	77	75	71	**0.8**	79	77	73	**0.8**	83	81	78
0.9	76	74	70	**0.9**	78	76	72	**0.9**	80	78	74	**0.9**	84	82	79
1.0	***77***	***75***	***71***	***1.0***	***80***	***78***	***73***	***1.0***	***81***	***79***	***76***	***1.0***	***84***	***82***	***80***
1.2	79	78	73	**1.2**	81	79	76	**1.2**	82	80	77	**1.2**	85	83	80
1.4	80	79	76	**1.4**	82	80	77	**1.4**	83	81	78	**1.4**	85	83	80
1.6	82	80	77	**1.6**	83	81	78	**1.6**	84	82	79	**1.6**	86	84	81
1.8	82	80	77	**1.8**	84	81	79	**1.8**	84	82	80	**1.8**	86	84	81
2.0[4]	83	81	78	**2.0**[4]	84	82	80	**2.0**[4]	85	83	80	**2.0**[4]	86	84	82
2.5[4]	84	83	80	**2.5**[4]	85	83	81	**2.5**[4]	86	84	81	**2.5**[4]	87	84	82
3.0[4]	85	83	81	**3.0**[4]	86	84	82	**3.0**[4]	86	84	82	**3.0**[4]	87	85	83
3.5[4]	86	84	82	**3.5**[4]	87	85	82	**3.5**[4]	87	85	83	**3.5**[4]	87	86	83

Appendix 4, Table 5 Continued.

BLACK MALES SCREENING HISTORY								BLACK MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	68	<66[5]	<66[5]	**0.5**	71	69	<66[5]	**0.5**	80	78	72
0.6	67	<66[5]	<66[5]	**0.6**	71	69	<66[5]	**0.6**	74	71	67	**0.6**	81	79	73
0.7	71	69	<66[5]	**0.7**	74	71	67	**0.7**	76	74	68	**0.7**	82	80	73
0.8	73	71	<66[5]	**0.8**	76	73	68	**0.8**	78	75	70	**0.8**	82	80	75
0.9	75	71	67	**0.9**	77	74	70	**0.9**	79	77	71	**0.9**	83	81	75
1.0	***76***	***74***	***68***	***1.0***	***78***	***76***	***70***	***1.0***	***80***	***78***	***72***	***1.0***	***83***	***81***	***76***
1.2	78	76	70	**1.2**	80	78	72	**1.2**	81	79	73	**1.2**	84	81	76
1.4	80	78	72	**1.4**	81	79	73	**1.4**	82	80	75	**1.4**	84	81	77
1.6	80	78	73	**1.6**	82	80	75	**1.6**	82	81	76	**1.6**	84	82	77
1.8	81	79	75	**1.8**	82	81	76	**1.8**	83	81	76	**1.8**	85	82	78
2.0	82	80	75	**2.0**	83	81	76	**2.0**	84	81	77	**2.0**	85	82	79
2.5	83	81	77	**2.5**	84	81	78	**2.5**	84	82	79	**2.5**	86	83	80
3.0[4]	84	82	79	**3.0**[4]	85	82	79	**3.0**[4]	85	83	80	**3.0**[4]	86	83	80
3.5[4]	85	82	80	**3.5**[4]	86	83	80	**3.5**[4]	86	83	80	**3.5**[4]	86	83	80
4.0[4]	86	83	80	**4.0**[4]	86	83	80	**4.0**[4]	86	83	80	**4.0**[4]	87	84	80
4.5[4]	86	83	80	**4.5**[4]	86	83	80	**4.5**[4]	87	84	80	**4.5**[4]	87	84	80
5.0[4]	87	83	80	**5.0**[4]	87	84	80	**5.0**[4]	87	84	81	**5.0**[4]	87	84	80
5.3[4]	87	84	80	**5.3**[4]	87	84	80	**5.3**[4]	87	84	81	**5.3**[4]	87	84	80

CRC = colorectal cancer; RR CRC = background risk for CRC

[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

[5] In these cohorts screening was not cost-effective at age 66 years. We did not perform analyses for individuals aged 65 years or younger.

Appendix 4, Table 6 The Appropriate Ages to Stop Colonoscopy Screening Assuming 25% Lower CRC Care Costs.[1]

WHITE FEMALES SCREENING HISTORY															
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	69	66	<66[5]	**0.5**	72	70	67	**0.5**	81	78	74
0.6	68	<66[5]	<66[5]	**0.6**	73	70	67	**0.6**	75	72	70	**0.6**	82	79	76
0.7	71	69	<66[5]	**0.7**	75	72	69	**0.7**	77	74	71	**0.7**	83	80	77
0.8	74	71	68	**0.8**	77	74	71	**0.8**	79	76	73	**0.8**	83	81	78
0.9	76	73	70	**0.9**	79	75	72	**0.9**	80	77	74	**0.9**	84	81	78
1.0	***77***	***74***	***71***	***1.0***	***80***	***77***	***74***	***1.0***	***81***	***78***	***75***	***1.0***	***84***	***82***	***79***
1.2	80	77	73	**1.2**	81	79	76	**1.2**	82	80	77	**1.2**	85	82	80
1.4	81	78	75	**1.4**	82	80	77	**1.4**	83	81	78	**1.4**	85	83	80
1.6	82	80	76	**1.6**	83	81	78	**1.6**	84	82	79	**1.6**	86	83	81
1.8	83	80	77	**1.8**	84	82	79	**1.8**	85	82	80	**1.8**	86	84	81
2.0	83	81	78	**2.0**	85	82	80	**2.0**	85	83	80	**2.0**	86	84	81
2.5[4]	85	82	80	**2.5**[4]	85	83	81	**2.5**[4]	86	84	81	**2.5**[4]	87	85	82
3.0[4]	85	83	81	**3.0**[4]	86	84	82	**3.0**[4]	87	84	82	**3.0**[4]	87	85	83
3.5[4]	86	84	82	**3.5**[4]	87	85	82	**3.5**[4]	87	85	83	**3.5**[4]	87	86	83

Appendix 4, Table 6 Continued

WHITE MALES SCREENING HISTORY								WHITE MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	69	67	<66[5]	**0.5**	73	70	67	**0.5**	81	78	74
0.6	68	66	<66[5]	**0.6**	72	70	66	**0.6**	75	73	69	**0.6**	82	80	76
0.7	71	69	<66[5]	**0.7**	75	72	68	**0.7**	78	75	71	**0.7**	83	80	77
0.8	73	71	67	**0.8**	77	74	70	**0.8**	79	76	72	**0.8**	83	81	77
0.9	75	73	69	**0.9**	79	75	71	**0.9**	80	77	73	**0.9**	84	81	78
1.0	***77***	***74***	***70***	***1.0***	***80***	***77***	***73***	***1.0***	***81***	***78***	***74***	***1.0***	***84***	***81***	***79***
1.2	80	77	72	**1.2**	81	79	75	**1.2**	82	80	76	**1.2**	84	82	79
1.4	81	78	74	**1.4**	82	80	76	**1.4**	83	80	77	**1.4**	85	83	80
1.6	82	80	76	**1.6**	83	81	77	**1.6**	83	81	78	**1.6**	85	83	80
1.8	83	80	77	**1.8**	83	81	78	**1.8**	84	82	79	**1.8**	85	83	80
2.0	83	81	78	**2.0**	84	82	79	**2.0**	84	82	80	**2.0**	86	83	81
2.5[4]	84	82	79	**2.5**[4]	85	83	80	**2.5**[4]	85	83	80	**2.5**[4]	86	84	81
3.0[4]	85	83	80	**3.0**[4]	85	83	81	**3.0**[4]	86	84	81	**3.0**[4]	86	84	81
3.5[4]	85	84	81	**3.5**[4]	86	84	81	**3.5**[4]	86	84	81	**3.5**[4]	87	84	82
4.0[4]	86	84	82	**4.0**[4]	86	84	82	**4.0**[4]	86	84	82	**4.0**[4]	87	84	82
4.5[4]	86	84	82	**4.5**[4]	87	84	82	**4.5**[4]	87	84	82	**4.5**[4]	87	85	82
4.9[4]	87	84	82	**4.9**[4]	87	84	82	**4.9**[4]	87	85	82	**4.9**[4]	87	85	82

Appendix 4, Table 6 Continued

BLACK FEMALES SCREENING HISTORY								BLACK FEMALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.4	<66[5]	<66[5]	<66[5]	**0.4**	<66[5]	<66[5]	<66[5]	**0.4**	68	<66[5]	<66[5]	**0.4**	80	78	72
0.5	<66[5]	<66[5]	<66[5]	**0.5**	69	67	<66[5]	**0.5**	72	70	<66[5]	**0.5**	81	79	75
0.6	68	<66[5]	<66[5]	**0.6**	72	70	<66[5]	**0.6**	75	73	68	**0.6**	82	80	77
0.7	71	69	<66[5]	**0.7**	75	73	68	**0.7**	77	75	70	**0.7**	83	81	77
0.8	74	72	66	**0.8**	77	74	70	**0.8**	79	77	72	**0.8**	84	81	78
0.9	75	74	69	**0.9**	78	76	72	**0.9**	80	78	73	**0.9**	84	82	79
1.0	***77***	***75***	***70***	***1.0***	***79***	***78***	***73***	***1.0***	***81***	***79***	***75***	***1.0***	***85***	***83***	***80***
1.2	79	77	73	**1.2**	81	79	76	**1.2**	82	80	77	**1.2**	85	83	80
1.4	80	78	75	**1.4**	82	80	77	**1.4**	83	81	78	**1.4**	86	84	81
1.6	81	80	77	**1.6**	83	81	78	**1.6**	84	82	79	**1.6**	86	84	82
1.8	82	80	77	**1.8**	83	81	79	**1.8**	84	82	80	**1.8**	86	84	82
2.0[4]	83	81	78	**2.0**[4]	84	82	80	**2.0**[4]	85	83	80	**2.0**[4]	87	84	82
2.5[4]	84	82	80	**2.5**[4]	85	83	81	**2.5**[4]	86	84	82	**2.5**[4]	87	85	83
3.0[4]	85	83	81	**3.0**[4]	86	84	82	**3.0**[4]	87	85	82	**3.0**[4]	88	86	83
3.5[4]	86	84	82	**3.5**[4]	87	85	83	**3.5**[4]	87	86	83	**3.5**[4]	88	86	84

Appendix 4, Table 6 Continued

BLACK MALES SCREENING HISTORY								BLACK MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	68	<66[5]	<66[5]	**0.5**	71	69	<66[5]	**0.5**	80	78	72
0.6	66	<66[5]	<66[5]	**0.6**	71	69	<66[5]	**0.6**	74	71	67	**0.6**	82	79	73
0.7	70	67	<66[5]	**0.7**	74	71	<66[5]	**0.7**	76	73	68	**0.7**	82	80	75
0.8	72	70	<66[5]	**0.8**	75	72	67	**0.8**	77	74	70	**0.8**	83	81	75
0.9	74	71	67	**0.9**	77	74	70	**0.9**	79	76	71	**0.9**	83	81	76
1.0	***75***	***72***	***67***	***1.0***	***78***	***75***	***70***	***1.0***	***80***	***78***	***72***	***1.0***	***84***	***81***	***76***
1.2	78	75	70	**1.2**	80	78	72	**1.2**	81	79	73	**1.2**	84	81	77
1.4	79	78	72	**1.4**	81	79	73	**1.4**	82	80	75	**1.4**	85	82	78
1.6	80	78	73	**1.6**	82	80	75	**1.6**	82	81	76	**1.6**	85	82	79
1.8	81	79	75	**1.8**	82	81	76	**1.8**	84	81	76	**1.8**	86	83	80
2.0	82	80	75	**2.0**	83	81	76	**2.0**	84	81	77	**2.0**	86	83	80
2.5	83	81	77	**2.5**	84	82	79	**2.5**	85	82	80	**2.5**	87	83	80
3.0[4]	84	82	79	**3.0**[4]	85	83	80	**3.0**[4]	86	83	80	**3.0**[4]	87	84	80
3.5[4]	85	83	80	**3.5**[4]	86	83	80	**3.5**[4]	86	84	80	**3.5**[4]	88	84	81
4.0[4]	86	83	80	**4.0**[4]	87	84	80	**4.0**[4]	87	84	81	**4.0**[4]	88	84	82
4.5[4]	87	84	81	**4.5**[4]	87	84	82	**4.5**[4]	87	84	82	**4.5**[4]	88	84	82
5.0[4]	87	84	82	**5.0**[4]	87	84	82	**5.0**[4]	88	84	82	**5.0**[4]	88	86	82
5.3[4]	88	84	82	**5.3**[4]	88	84	82	**5.3**[4]	88	84	82	**5.3**[4]	88	86	82

CRC = colorectal cancer; RR CRC = background risk for CRC

[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

[5] In these cohorts screening was not cost-effective at age 66 years. We did not perform analyses for individuals aged 65 years or younger.

Appendix 4, Table 7 The Appropriate Ages to Stop Colonoscopy Screening Assuming a Cost-Effectiveness Threshold of $50,000.[1]

WHITE FEMALES SCREENING HISTORY															
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	<66[5]	<66[5]	<66[5]	**0.5**	68	<66[5]	<66[5]	**0.5**	78	74	70
0.6	<66[5]	<66[5]	<66[5]	**0.6**	68	<66[5]	<66[5]	**0.6**	71	69	<66[5]	**0.6**	79	75	72
0.7	<66[5]	<66[5]	<66[5]	**0.7**	71	68	<66[5]	**0.7**	74	71	68	**0.7**	80	77	73
0.8	70	66	<66[5]	**0.8**	73	70	67	**0.8**	76	73	69	**0.8**	81	78	74
0.9	72	69	<66[5]	**0.9**	75	72	69	**0.9**	77	74	71	**0.9**	81	78	75
1.0	***74***	***71***	***67***	***1.0***	***77***	***74***	***70***	***1.0***	***79***	***75***	***72***	***1.0***	***82***	***79***	***76***
1.2	77	73	70	**1.2**	79	75	72	**1.2**	80	77	74	**1.2**	83	80	77
1.4	79	75	72	**1.4**	80	77	74	**1.4**	81	78	75	**1.4**	83	81	77
1.6	80	77	73	**1.6**	81	78	75	**1.6**	82	79	76	**1.6**	84	81	78
1.8	81	78	74	**1.8**	82	79	76	**1.8**	83	80	77	**1.8**	84	81	78
2.0	81	79	76	**2.0**	82	80	77	**2.0**	83	81	78	**2.0**	84	82	79
2.5[4]	83	80	77	**2.5**[4]	84	81	78	**2.5**[4]	84	82	79	**2.5**[4]	85	82	80
3.0[4]	84	81	79	**3.0**[4]	84	82	80	**3.0**[4]	85	82	80	**3.0**[4]	85	82	80
3.5[4]	84	82	80	**3.5**[4]	85	82	80	**3.5**[4]	85	83	80	**3.5**[4]	85	83	80

Appendix 4, Table 7 Continued.

WHITE MALES SCREENING HISTORY								WHITE MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	<66[5]	<66[5]	<66[5]	**0.5**	69	67	<66[5]	**0.5**	79	75	70
0.6	<66[5]	<66[5]	<66[5]	**0.6**	68	66	<66[5]	**0.6**	72	69	<66[5]	**0.6**	80	77	72
0.7	66	<66[5]	<66[5]	**0.7**	71	68	<66[5]	**0.7**	74	71	67	**0.7**	80	78	73
0.8	69	67	<66[5]	**0.8**	73	71	66	**0.8**	76	73	69	**0.8**	81	78	74
0.9	71	69	<66[5]	**0.9**	75	72	68	**0.9**	77	74	70	**0.9**	81	79	75
1.0	***73***	***71***	***66***	***1.0***	***77***	***73***	***69***	***1.0***	***79***	***75***	***71***	***1.0***	***82***	***79***	***75***
1.2	76	73	69	**1.2**	79	75	71	**1.2**	80	77	73	**1.2**	82	80	76
1.4	79	75	71	**1.4**	80	77	73	**1.4**	81	78	74	**1.4**	83	80	77
1.6	80	77	72	**1.6**	81	78	74	**1.6**	81	79	75	**1.6**	83	80	77
1.8	81	78	74	**1.8**	82	79	75	**1.8**	82	80	76	**1.8**	83	81	78
2.0	81	79	75	**2.0**	82	80	76	**2.0**	82	80	77	**2.0**	83	81	78
2.5[4]	82	80	77	**2.5**[4]	83	81	77	**2.5**[4]	83	81	78	**2.5**[4]	84	81	79
3.0[4]	83	81	78	**3.0**[4]	84	81	79	**3.0**[4]	84	81	79	**3.0**[4]	84	82	79
3.5[4]	84	81	79	**3.5**[4]	84	82	79	**3.5**[4]	84	82	79	**3.5**[4]	85	82	79
4.0[4]	84	82	79	**4.0**[4]	84	82	80	**4.0**[4]	85	82	80	**4.0**[4]	85	82	80
4.5[4]	85	82	80	**4.5**[4]	85	83	80	**4.5**[4]	85	83	80	**4.5**[4]	85	83	80
4.9[4]	85	82	80	**4.9**[4]	85	83	80	**4.9**[4]	85	83	80	**4.9**[4]	85	83	80

Appendix 4, Table 7 Continued.

BLACK FEMALES SCREENING HISTORY								BLACK FEMALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.4	<66[5]	<66[5]	<66[5]	**0.4**	<66[5]	<66[5]	<66[5]	**0.4**	<66[5]	<66[5]	<66[5]	**0.4**	76	73	67
0.5	<66[5]	<66[5]	<66[5]	**0.5**	<66[5]	<66[5]	<66[5]	**0.5**	67	<66[5]	<66[5]	**0.5**	78	75	70
0.6	<66[5]	<66[5]	<66[5]	**0.6**	67	<66[5]	<66[5]	**0.6**	71	69	<66[5]	**0.6**	80	77	72
0.7	<66[5]	<66[5]	<66[5]	**0.7**	70	68	<66[5]	**0.7**	73	71	66	**0.7**	80	78	73
0.8	69	67	<66[5]	**0.8**	73	70	<66[5]	**0.8**	75	73	68	**0.8**	81	79	75
0.9	72	69	<66[5]	**0.9**	75	73	67	**0.9**	77	74	70	**0.9**	82	79	76
1.0	***73***	***71***	**<66[5]**	***1.0***	***76***	***74***	***69***	***1.0***	***78***	***75***	***71***	***1.0***	***82***	***80***	***76***
1.2	76	74	69	**1.2**	78	76	72	**1.2**	80	78	73	**1.2**	82	80	77
1.4	77	75	71	**1.4**	79	78	73	**1.4**	80	79	75	**1.4**	83	81	77
1.6	79	77	73	**1.6**	80	79	75	**1.6**	81	79	76	**1.6**	83	81	78
1.8	80	78	74	**1.8**	81	79	76	**1.8**	82	80	77	**1.8**	84	81	79
2.0[4]	81	79	75	**2.0**[4]	82	80	77	**2.0**[4]	82	80	77	**2.0**[4]	84	82	79
2.5[4]	82	80	77	**2.5**[4]	83	81	78	**2.5**[4]	83	81	79	**2.5**[4]	85	82	80
3.0[4]	83	81	78	**3.0**[4]	84	82	79	**3.0**[4]	84	82	80	**3.0**[4]	85	83	80
3.5[4]	84	82	79	**3.5**[4]	85	83	80	**3.5**[4]	85	83	80	**3.5**[4]	85	83	81

Appendix 4, Table 7 Continued.

BLACK MALES SCREENING HISTORY								BLACK MALES SCREENING HISTORY							
Negative screening colonoscopy 10 years prior				Negative screening colonoscopy 15 years prior				Negative screening colonoscopy 20 years prior				No prior screening			
COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]			
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
0.5	<66[5]	<66[5]	<66[5]	**0.5**	<66[5]	<66[5]	<66[5]	**0.5**	66	<66[5]	<66[5]	**0.5**	77	74	67
0.6	<66[5]	<66[5]	<66[5]	**0.6**	<66[5]	<66[5]	<66[5]	**0.6**	70	67	<66[5]	**0.6**	78	75	70
0.7	<66[5]	<66[5]	<66[5]	**0.7**	69	66	<66[5]	**0.7**	72	69	<66[5]	**0.7**	79	77	70
0.8	68	<66[5]	<66[5]	**0.8**	71	69	<66[5]	**0.8**	74	71	<66[5]	**0.8**	80	78	71
0.9	70	67	<66[5]	**0.9**	73	71	<66[5]	**0.9**	75	72	67	**0.9**	80	78	72
1.0	***72***	***69***	**<66[5]**	**1.0**	***75***	***71***	***67***	**1.0**	***76***	***74***	***68***	**1.0**	***81***	***78***	***72***
1.2	74	71	67	**1.2**	77	74	69	**1.2**	78	75	70	**1.2**	81	79	73
1.4	76	74	68	**1.4**	78	76	70	**1.4**	79	78	71	**1.4**	82	80	73
1.6	78	75	70	**1.6**	79	77	71	**1.6**	80	78	72	**1.6**	82	80	75
1.8	79	76	71	**1.8**	80	78	72	**1.8**	81	78	73	**1.8**	82	80	75
2.0	80	78	72	**2.0**	80	78	73	**2.0**	81	79	73	**2.0**	82	81	75
2.5	81	79	73	**2.5**	82	80	75	**2.5**	82	80	75	**2.5**	83	81	76
3.0[4]	82	80	75	**3.0[4]**	82	81	76	**3.0[4]**	83	81	76	**3.0[4]**	84	81	76
3.5[4]	82	81	76	**3.5[4]**	83	81	76	**3.5[4]**	84	81	76	**3.5[4]**	84	81	76
4.0[4]	84	81	76	**4.0[4]**	84	81	77	**4.0[4]**	84	81	77	**4.0[4]**	84	81	77
4.5[4]	84	81	77	**4.5[4]**	84	81	77	**4.5[4]**	84	81	77	**4.5[4]**	84	82	77
5.0[4]	84	81	77	**5.0[4]**	84	82	78	**5.0[4]**	84	82	78	**5.0[4]**	85	82	78
5.3[4]	84	81	77	**5.3[4]**	85	82	79	**5.3[4]**	85	82	79	**5.3[4]**	85	82	78

CRC = colorectal cancer; RR CRC = background risk for CRC

[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

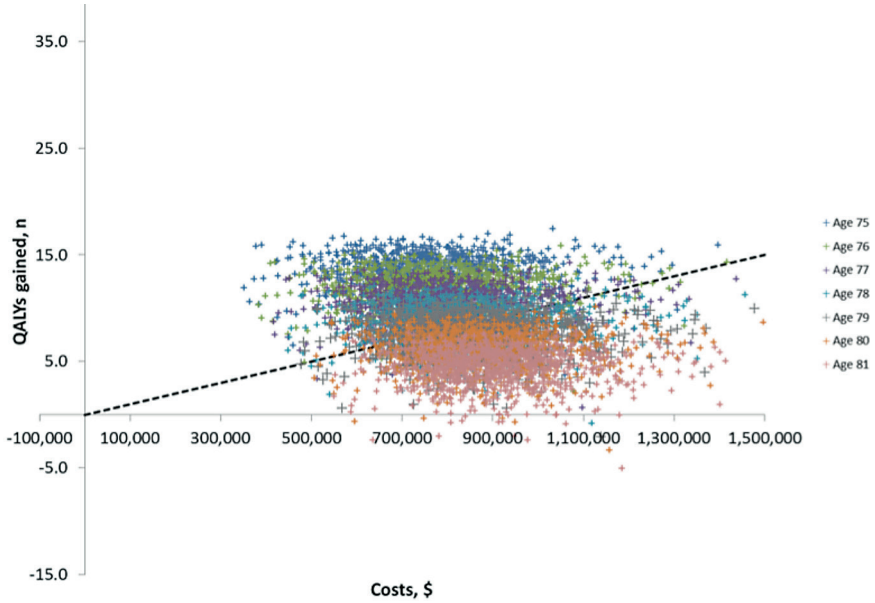
[4] Background risk for CRC only possible in case of a family history of CRC.

[5] In these cohorts screening was not cost-effective at age 66 years. We did not perform analyses for individuals aged 65 years or younger.

Appendix 5: The Appropriate Ages to Stop Screening – Results of a Multivariate Probabilistic Sensitivity Analysis

To assess the overall impact of uncertainty in model inputs on the appropriate age to stop colonoscopy screening, we performed a multivariate probabilistic sensitivity analysis for one representative case: healthy, average risk, white women with a negative screening colonoscopy 10 years prior. The inputs that were varied were identical to those varied in the univariate deterministic sensitivity analyses: the utility losses for colonoscopies and complications, the costs for colonoscopies, and the costs for CRC care. For the utility losses for colonoscopies and complications, we assumed a lognormal distribution with a mean corresponding to the base case utility loss and a standard deviation corresponding to 25% of the base case utility loss. For the costs of colonoscopies and CRC care, we assumed a lognormal distribution with a mean corresponding to the base case costs and a standard deviation corresponding to 12.5% of the base case costs. We assumed perfect correlation between the disutilities associated with colonoscopies and complications, between the costs of colonoscopies with and without a polypectomy/ biopsy, and between the costs

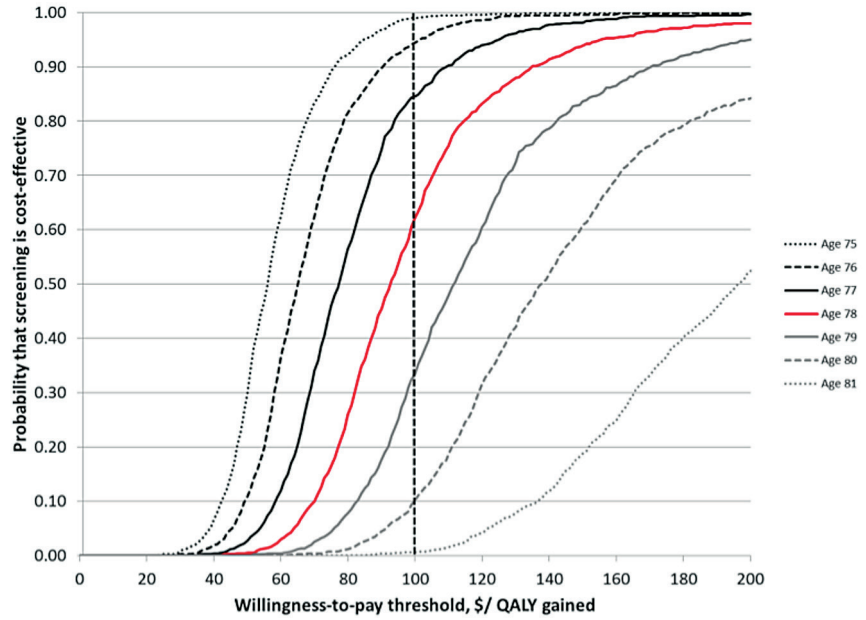
Appendix 5, Figure 1 The Costs and QALYs Gained of Colonoscopy Screening for Healthy, Average Risk, White Women, with a Negative Screening Colonoscopy 10 Years Prior: Results of a Multivariate Probabilistic Sensitivity Analysis.[1]



[1]The dashed line indicates a willingness-to-pay threshold of $100,000 per QALY gained.

for the different phases/ stages of CRC care, but no correlation across these groups of parameters. From these distributions we drew 1,000 random parameter sets, and for each set we determined the costs and QALYs gained associated with colonoscopy screening at age 78 years (i.e. the appropriate age to stop colonoscopy screening according to our base case analysis); at younger ages: 75, 76, and 77 years; and at older ages 79, 80, and 81 years. **Appendix 5, Figure 1** shows that the number of QALYs gained by screening decreases with age and that the costs of screening increase with age. The proportion of parameter sets for which screening is cost-effective given a willingness-to-pay threshold of $100,000 per QALY gained (i.e., the proportion of symbols above the dashed line) decreases with age. **Appendix 5, Figure 2** shows that the probability that screening is cost-effective at age 78 years (i.e. the appropriate age to stop screening according to our base case analysis) is 62%. The probabilities that screening is cost-effective at ages 75, 76, and 77 years are 99%, 94%, and 85%, respectively. The probabilities that screening is cost-effective at ages 79, 80, and 81 years are 34%, 10%, and 1%, respectively. Hence, the probability that our estimates of the appropriate ages to stop screening are more than one year off, is small.

Appendix 5, Figure 2 The Probability that Screening Healthy, Average Risk, White Women, with a Negative Screening Colonoscopy 10 Years Prior is Cost-Effective as a Function of the Willingness-To-Pay per QALY Gained: Results of a Multivariate Probabilistic Sensitivity Analysis.[1]



[1]The dashed line indicates a willingness-to-pay threshold of $100,000 per QALY gained.

Appendix 6: The Appropriate Ages to Stop Screening – Results for High Risk Individuals with a Negative Screening Colonoscopy 5 Years Prior

Appendix 6, Table 1 The Appropriate Ages to Stop Colonoscopy Screening: Results for High Risk Individuals with a Negative Screening Colonoscopy 5 Years Prior.[1]

WHITE FEMALES				WHITE MALES				BLACK FEMALES				BLACK MALES			
	COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]				COMORBIDITY STATUS[2]		
RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity	RR CRC[3]	No comorbidity	Moderate comorbidity	Severe comorbidity
2.0	81	79	76	**2.0**	81	80	75	**2.0**[4]	81	79	76	**2.0**	80	78	73
2.5[4]	83	81	78	**2.5**[4]	82	81	78	**2.5**[4]	83	80	77	**2.5**	82	80	75
3.0[4]	84	82	80	**3.0**[4]	83	82	79	**3.0**[4]	84	82	80	**3.0**[4]	83	81	76
3.5[4]	85	83	80	**3.5**[4]	84	82	80	**3.5**[4]	85	83	81	**3.5**[4]	84	81	77
				4.0[4]	85	83	81					**4.0**[4]	85	82	80
				4.5[4]	86	84	81					**4.5**[4]	86	83	80
				4.9[4]	86	84	81					**5.0**[4]	87	83	80
												5.3[4]	87	84	81

CRC = colorectal cancer; RR CRC = background risk for CRC

[1] Given a willingness-to-pay threshold of $100,000 per QALY gained.

[2] Detailed information on the assessment of comorbidity status is given in **Figure 2**, footnote 4.

[3] Detailed information on the assessment of background risk for CRC is given in **Figure 2**, footnote 5.

[4] Background risk for CRC only possible in case of a family history of CRC.

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The Potential Effects of Personalizing the Age to Stop Colonoscopy Screening on Population Health and Medicare Spending

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INTRODUCTION

Recent studies have demonstrated that colorectal cancer (CRC) screening in elderly individuals could be more cost-effective if individual patient characteristics, such as sex, race, screening history, and comorbidity status, were considered.[1 2] The objective of our current study was to quantify the potential clinical and economic effects of personalized versus uniform age-based colonoscopy screening in the 2013 US Medicare population, thereby illustrating the impact that personalizing cancer screening could have on health and health care budgets.

METHODS

In a prior study, we used the micro-simulation model MISCAN-Colon to determine the costs and effects of colonoscopy screening in cohorts of individuals characterized by their age (66-90 years), sex (male/ female), race (black/ white), screening history (a negative screening colonoscopy 10 years prior/ 15 years prior/ 20 years prior/ no prior screening), and comorbidity status (no/ moderate/ severe comorbidity).[2] In this study, we used these data to determine the appropriate age to stop colonoscopy screening according to sex, race, screening history, and comorbidity status using four distinct thresholds for the willingness-to-pay per quality-adjusted life-year (QALY) gained ($25,000, $50,000, $75,000, and $100,000). By applying these thresholds, we constructed four scenarios of personalized screening varying in screening intensity (**Table**).

We then modeled the 2013 US Medicare population (39.6M individuals). Data on the number of individuals by age, sex, and race were obtained from the US Census Bureau.[3] Data on the age-specific, sex-specific, and race-specific proportions of individuals up-to-date with screening, not up-to-date but previously screened, and never screened were obtained from the 2013 National Health Interview Survey.[4] Finally, data on the age-specific, sex-specific, and race-specific proportions of individuals with no, moderate, and severe comorbidity were obtained from a publication by Cho and colleagues.[5] In our analysis, we assumed that individuals who were not black or white (e.g. Hispanic or Asian) had an identical risk for CRC, screening history distribution, and comorbidity status distribution as whites. Moreover, we assumed that being up-to-date with CRC screening tests other than colonoscopy (e.g. fecal immunochemical testing) conferred identical protection from CRC as being up-to-date with colonoscopy screening. In addition, we assumed that those not up-to-date but previously screened were protected as if they had had a negative screening colonoscopy 15 years prior. Finally, we assumed no correlations between screening history and comorbidity status, screening history and CRC risk, and comorbidity status and CRC risk. Since we aimed to quantify the *potential* impact of personalized colonoscopy screening, we assumed that everyone would be willing to have colonoscopy screening in the future, also those without prior screening.

Table The appropriate ages to stop colonoscopy screening in one scenario of age-based screening and four scenarios of personalized screening, years.

	SCREENING HISTORY					
	Negative screening colonoscopy 10 years prior			Negative screening colonoscopy 15 years prior		
	COMORBIDITY STATUS			COMORBIDITY STATUS		
	No comorbidity	Moderate comorbidity	Severe comorbidity	No comorbidity	Moderate comorbidity	Severe comorbidity
AGE BASED SCREENING						
All demographic groups	75	75	75	75	75	75
PERSONALIZED SCREENING[a]						
Scenario a (WTP = $25,000/QALY gained)						
White females	68	≤66	≤66	72	69	≤66
White males	68	≤66	≤66	72	69	≤66
Black females	67	≤66	≤66	71	69	≤66
Black males	≤66	≤66	≤66	70	67	≤66
Scenario b (WTP = $50,000/QALY gained)						
White females	74	71	67	77	74	70
White males	73	71	66	77	73	69
Black females	73	71	≤66	76	74	69
Black males	72	69	≤66	75	71	67
Scenario c (WTP = $75,000/QALY gained)						
White females	76	73	70	79	76	72
White males	76	73	69	79	75	72
Black females	76	74	69	78	76	72
Black males	74	71	67	77	74	69
Scenario d (WTP = $100,000/QALY gained)						
White females	78	75	71	80	77	74
White males	78	74	70	80	77	73
Black females	77	75	71	79	78	73
Black males	76	73	68	78	76	70

	SCREENING HISTORY					
	Negative screening colonoscopy 20 years prior			No prior screening		
	COMORBIDITY STATUS			COMORBIDITY STATUS		
	No comorbidity	Moderate comorbidity	Severe comorbidity	No comorbidity	Moderate comorbidity	Severe comorbidity
AGE BASED SCREENING						
All demographic groups	75	75	75	75	75	75
PERSONALIZED SCREENING[a]						
Scenario a (WTP = $25,000/QALY gained)						
White females	74	71	68	79	75	71
White males	74	71	67	80	76	71
Black females	74	71	≤66	79	76	71
Black males	72	69	≤66	77	74	67
Scenario b (WTP = $50,000/QALY gained)						
White females	79	75	72	82	79	76
White males	79	75	71	82	79	75
Black females	78	75	71	82	80	76
Black males	76	74	68	81	78	72
Scenario c (WTP = $75,000/QALY gained)						
White females	80	77	74	83	81	78
White males	80	77	73	83	80	77
Black females	80	78	73	83	81	78
Black males	78	76	70	82	80	75
Scenario d (WTP = $100,000/QALY gained)						
White females	81	79	76	84	82	79
White males	81	78	75	84	81	78
Black females	81	79	75	85	82	80
Black males	80	78	72	84	81	76

To determine the impact of personalized screening, we compared the undiscounted lifetime Medicare costs and CRC deaths prevented under the four scenarios of personalized screening to the costs and CRC deaths prevented by uniform colonoscopy screening up to age 75 years.

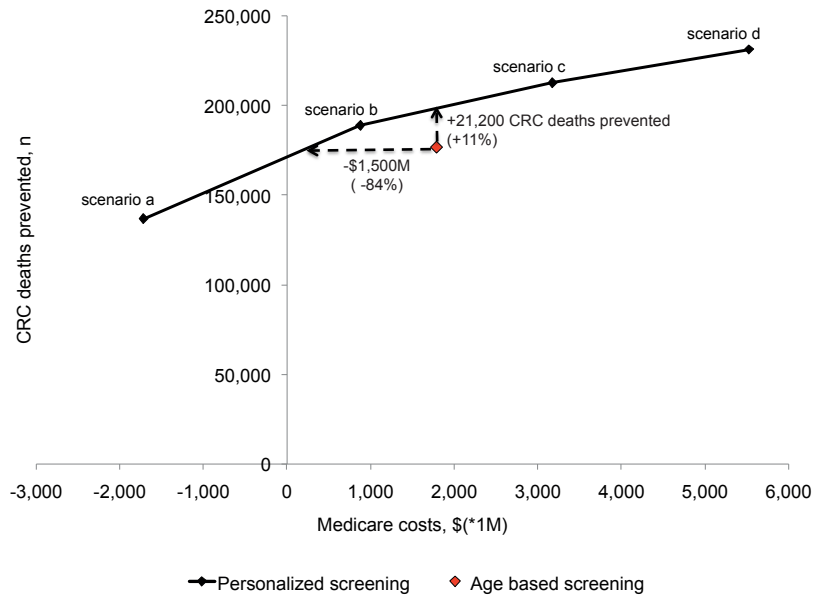
RESULTS

Across the full projected lifespan of the 2013 Medicare population, uniform colonoscopy screening up to age 75 years would prevent 177,000 CRC deaths at a cost of $1,787M (**Figure**). Personalized screening would be more efficient: while the least intensive personalized screening scenario (scenario a) would still be less effective (and substantially less costly!) than uniform screening, personalized screening scenario b would be both more effective and less costly. At the uniform screening cost level ($1,787M), personalized screening would prevent approximately 21,200 additional CRC deaths (+11%). Alternatively, the same number of CRC deaths (177,000) could be prevented at substantially lower costs ($1,500M lower costs or -84%). The benefits of personalized screening were most sensitive to the proportion of never screened individuals willing to have future colonoscopy screening (*data not shown*).

DISCUSSION

The potential impact of personalizing decisions on colonoscopy screening in the Medicare population is large: compared with uniform age-based screening either tens of thousands of additional CRC deaths can be prevented or billions of dollars can be saved. Dedicated efforts to personalize cancer screening decisions are needed. Particular emphasis should be put on screening those without prior screening.

Figure The lifetime number of CRC deaths prevented and the lifetime costs from a Medicare perspective associated with four scenarios of personalized screening versus age-based screening up to age 75 years.*



CRC = colorectal cancer; QALY = quality-adjusted life-year.
Scenario a = personalized screening, WTP = $25,000/ QALY gained; scenario b = personalized screening, WTP = $50,000/ QALY gained; scenario c = personalized screening, WTP = $75,000/ QALY gained, scenario d = personalized screening, WTP = $100,000/ QALY gained.
*Undiscounted results.

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Discussion

In this chapter, we will first answer the research questions formulated in **Chapter 1**. Subsequently, we will explain how trials can be used to inform models, how models can also be used to inform trials and, hence, why modelers and trialists should cooperate. After that, we will discuss some important areas for future research. Finally, we will briefly summarize the conclusions that can be derived from our work and postulate our recommendations.

ANSWERS TO THE RESEARCH QUESTIONS

How can models be used to inform policy decisions regarding screening programs?

Models can be used to extrapolate evidence from RCTs and answer questions that might arise during the whole cycle of a screening program: during the decision phase the optimal screening strategy can be determined; during the planning phase the resource requirements, costs, and effects of the program can be estimated; during the implementation phase observed data can be compared to model estimates to see whether the program functions as expected; and during the established program phase modeling can be used to further optimize the program based on emerging data.

Although RCTs are the gold standard for determining the effectiveness of screening, they also have their limitations. First, RCTs are expensive and time consuming. As a result, the number of RCTs that have evaluated CRC screening is limited. Second, RCTs usually have a limited follow-up time. Hence, they cannot be used to determine lifetime health effects and costs, which is necessary to determine the cost-effectiveness of screening. Third, the effectiveness of screening in a certain country might differ from that observed in an RCT, for example because attendance rates to screening are substantially lower or higher. Finally, country-level resource demands for a certain screening program cannot easily be inferred from an RCT. To summarize: RCTs alone do not answer the question of which screening strategy is optimal for a certain country.

We demonstrated that decision models provide a useful tool to extrapolate evidence from RCTs during the whole cycle of a screening program, using the role MISCAN-Colon played in the Dutch CRC screening program as an example.[1] In the decision phase of the Dutch screening program, modeling analyses informed the decision to choose FIT screening over gFOBT screening, to choose a higher age to start screening than recommended by the Council of Europe and to choose a lower cut-off for referral to colonoscopy than recommended by the test's manufacturer. A modeling analysis also informed the decision to temporarily elevate the cut-off for referral to colonoscopy when a shortage of colonoscopy capacity was imminent during the first year of the program. If

modeling would not have been used at these instances, other choices could have been made, and the balance between the benefits and harms of the screening program could have turned out less favorable than it will now.

What is the appropriate interval for a first surveillance colonoscopy in adenoma patients given the characteristics of the adenomas that were removed and the sex and age of the patient?

The appropriate surveillance interval depends heavily on a patient's adenoma risk score (i.e., risk according to all relevant characteristics of adenomas removed during colonoscopy) and to a lesser extent on sex and age. While some patients with risk score 0 should receive a surveillance colonoscopy after 10 years, some patients with risk scores 4 and 5 should receive a surveillance colonoscopy after only 2 years. Surveillance should no longer be recommended in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older, and higher-risk patients aged 80 years or older.

Several important predictors of advanced adenoma recurrence in newly diagnosed adenoma patients have been identified.[2 3] These predictors include characteristics of adenomas removed during colonoscopy: the presence of multiple, large (≥10mm), villous, and proximal adenomas, as well as patient characteristics: male sex and older age. The identification of these predictors allows for extensive risk stratification of adenoma patients followed by careful tailoring of surveillance recommendations. However, most surveillance guidelines do not consider all relevant predictors and are thus restricted in providing tailored recommendations.

In prior work, we analyzed data from a cohort of Dutch adenoma patients to develop a score chart that can be used to risk-stratify adenoma patients according to all relevant characteristics of adenomas removed during colonoscopy.[4] This chart results in an "adenoma risk score" for each patient (range: 0-5). In the study described in this thesis, we modeled a cohort of adenoma patients for each combination of adenoma risk score (0-5), sex (men/ women), and age (40/ 45/ (…)/ 80 years).[5] Within each cohort, we simulated colonoscopy surveillance every 1 up to 10 years as well as referral to the Dutch national CRC screening program from the first subsequent screen eligible age onwards and after a minimum of 10 years. For each cohort, we selected the optimal surveillance strategy using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch National CRC Screening program. The appropriate interval for a first surveillance colonoscopy was the surveillance interval corresponding with the strategy selected. This analysis showed that the appropriate interval for colonoscopy surveillance depends heavily on a patient's adenoma risk score and to a lesser extent on sex and age. While some patients with risk score 0 should receive a surveillance colonoscopy after 10 years, some patients with risk scores 4 and 5 should receive a surveillance colonoscopy after only 2 years. The analysis also showed that existing surveillance guidelines do not consistently target colonoscopies at those patients most likely to benefit. According to the 2002 Dutch guidelines, which were based on adenoma multiplicity only, for example, a 60 year-old female with 3 small, non-villous, distal adenomas was recommended colonoscopy surveillance after 3 years, while a 60 year-old female with 2 large, villous, proximal adenomas was recommended colonoscopy surveillance after 6 years. [6] However, according to our analysis, the former patient (who has an adenoma risk score of 1) should be recommended colonoscopy surveillance after 7 years, while the latter patient (who has an adenoma risk score of 4) should be recommended colonoscopy surveillance after 3 years: almost the exact opposite. Results were robust to variations in the overall level of health care costs in a country. However, applying higher cost-effectiveness thresholds resulted in substantially more intensive surveillance recommendations, particularly in those with a low adenoma risk score. The Dutch guidelines for surveillance in adenoma patients were revisited based on the results of our study in May 2013.[7]

Is more intensive colonoscopy screening than recommended favorable for Medicare beneficiaries and, if so, is it efficient from a societal perspective?

Screening average-risk Medicare beneficiaries more intensively than recommended is often associated with a net harm and is always inefficient from a societal perspective.

In current practice, many US Medicare beneficiaries (i.e., US individuals aged 65 years and older) receive more intensive colonoscopy screening than recommended: 20% of beneficiaries with a negative screening colonoscopy result receive a repeated screening colonoscopy within 5 year's time instead of after the recommended 10 years.[8 9] Moreover, 25% of beneficiaries with a negative screening colonoscopy result at age 75 years or older receive yet another screening colonoscopy at an even more advanced age. Although the reasons for these practices might vary, sometimes they are likely to result from the beneficiary's or clinician's perception that screening should occur more frequently than recommended.

We modeled a cohort of 65 year-old, average-risk Medicare beneficiaries with a negative screening colonoscopy at age 55 years and compared colonoscopy screening as recommended by guidelines (i.e., at ages 65 and 75 years) with scenarios of more intensive screening in which either a shorter screening interval was applied or in which screening was continued after age 75 years.[10] This comparison showed that more intensive screening than recommended generally results in only small increases in the benefits of screening (i.e., CRC cases prevented, CRC deaths prevented, and LYs gained) compared with the increases in the burden and harms associated with screening (i.e., colonoscopies performed and complications experienced). As a result, most scenarios of more intensive

screening than recommended were associated with a net harm (i.e., QALYs lost), rather than a net health benefit (i.e., QALYs gained). The only scenario that resulted in a net health benefit (i.e., colonoscopy screening every 5 instead of 10 years) was very inefficient from a societal perspective, requiring 909 additional colonoscopies and an additional $711,000 per additional QALY gained. Results in beneficiaries without prior screening were only slightly less unfavorable. Results in individuals at high risk for CRC, however, were substantially more favorable; indicating that more intensive colonoscopy screening than recommended might be justified in those at high risk.

Should CRC screening be considered in elderly individuals without previous screening? If so, up to what age and which screening test should be used at what age?

Screening elderly individuals without previous screening should be considered well beyond age 75 years. Screening remains cost-effective up to age 86 years in individuals with no comorbidity, up to age 83 years in individuals with moderate comorbidity, and up to age 80 years in individuals with severe comorbidity. At most ages, a screening colonoscopy is indicated.

In its most recent recommendation statement on CRC screening, the US Preventive Services Task Force (USPSTF) recommends against routine screening in individuals aged older than 75 years with an adequate screening history.[11] Although the USPSTF did not address screening in inadequately screened individuals, this recommendation has led many members of the medical community to believe that no one aged older than 75 years should be screened for CRC. However, since unscreened elderly individuals (a group representing 23% of all US elderly individuals) are at substantially higher risk for CRC than those who are adequately screened, screening them is likely to be cost-effective up to a more advanced age.

We modeled a cohort of elderly individuals without previous screening for each combination of age (76-90 years) and comorbidity status (no/ moderate/ severe comorbidity).[12] In these cohorts, we modeled one-time colonoscopy, one-time sigmoidoscopy, and one-time FIT screening. This showed that screening previously unscreened individuals remains cost- effective well beyond age 75 years. The maximum age at which screening was cost- effective was 86 years for individuals with no comorbidity, 83 years for individuals with moderate comorbidity, and 80 years for individuals with severe comorbidity. In unscreened individuals with no comorbidity, a screening colonoscopy was most effective and still cost-effective up to age 83 years, a screening sigmoidoscopy was indicated at age 84 years, and FIT screening was indicated at ages 85 and 86 years. In those with moderate comorbidity, a screening colonoscopy was indicated up to age 80 years, a screening sigmoidoscopy was indicated at age 81 years, and FIT screening was indicated at ages 82 and 83 years. Finally, in those with severe comorbidity, a screening colonoscopy

was indicated up to age 77 years, a screening sigmoidoscopy was indicated at age 78 years, and FIT screening was indicated at ages 79 and 80 years. Results were most sensitive to the cost-effectiveness threshold applied. Applying a threshold of $50,000 instead of $100,000 per QALY gained resulted in upper ages for screening that were 2 to 3 years lower than those stated above.

Why should decisions on cancer screening be personalized and how can personalized screening recommendations be derived?

Screening history, comorbidity status, and background risk for CRC are important determinants of the effectiveness of CRC screening. Disease simulation models can be used to integrate estimates of cancer risk, life expectancy, and screening efficacy into clinically meaningful estimates of the benefits of screening.

An important emerging model for screening is personalization. In this approach, individual patient characteristics are used to project the benefits, burden, harms, and sometimes also the costs of screening. This information is subsequently used to guide clinical decision-making. Personalization has the potential to improve cancer outcomes while reducing the harms of screening and preserving scarce health care resources. Yet, all to often, the US health care system fails to personalize screening in even the most rudimentary way. For example, a recent study found that 75 year-old individuals with severe comorbidity were nearly twice as likely to be screened for CRC than 76 year-old individuals with no comorbidity, even though healthy 76 year-olds tend to live longer and, hence, gain greater benefit from screening.[13] In another study, 48% of primary care physicians reported that they would recommend breast cancer screening for women diagnosed with terminal lung cancer:[14] a group of patients for whom screening cannot provide any benefit, may cause harm, and is a waste of resources.

We modeled one-time colonoscopy screening in a cohort of 75 year-old, white women with a negative screening colonoscopy 10 years prior, no comorbidity, and an average background risk for CRC.[15] Subsequently, we varied all patient characteristics (i.e., age, sex, race, screening history, comorbidity status, and background risk for CRC) in a one-by-one fashion. This showed that screening history, comorbidity status, and background risk for CRC are equally or more important determinants of the effectiveness of screening than age. The effects of sex and race were less pronounced. The analysis also demonstrated how disease simulation models can be used integrate estimates of cancer risk, life expectancy, and screening efficacy into clinically meaningful estimates of the effectiveness of screening and, hence, to derive personalized screening recommendations.

What is the appropriate age to stop colonoscopy screening given an individual's sex, race, screening history, background risk for CRC, and comorbidity status?

The appropriate age to stop colonoscopy screening depends heavily on an individual's screening history, background risk for CRC, and comorbidity status. While screening some previously screened, low-risk individuals was not even cost-effective at age 66 years, screening some, healthy, high-risk individuals remained cost-effective up to age 88 years.

In concordance with existing age-based guidelines and performance measures for CRC screening, many US clinicians make their decisions on CRC screening for elderly individuals primarily on the basis of age.[13] Other factors that influence the effectiveness of screening, such as sex, race, screening history, background risk for CRC, and comorbidity status are often ignored. As a result, CRC screening might not always be targeted at those individuals most likely to benefit.

We modeled a cohort of individuals for each combination of age (66-90 years), sex (men/ women), race (black/ white), screening history (a negative screening colonoscopy 10 years prior/ 15 years prior/ 20 years prior/ no prior screening), background risk for CRC (white men: 17 levels, white women: 14 levels, black men: 18 levels, black women: 15 levels), and comorbidity status (no/ moderate/ severe comorbidity) (a total of 19,200 cohorts).[16] Within these cohorts we modeled one-time colonoscopy screening. This showed that screening remains cost-effective up to a substantially older age in individuals without prior screening compared with individuals with prior screening, in individuals with a high background risk for CRC compared with individuals with a low background risk for CRC, and in individuals without comorbidity compared with individuals with comorbidity. In contrast, the effects of sex and race on the appropriate age to stop screening were small. Our analysis also demonstrated that the current age-based approach to screening results in overuse of screening in some and underuse of screening in others. For example, we found screening 81 year-old black men with no comorbidity, an average background risk for CRC, and no previous screening (a group unlikely to be screened in current practice) to be highly cost-effective (ICER: $50,000/ QALY gained). In contrast, we found screening 74 year-old white women with moderate comorbidity, half the average background risk for CRC, and a negative screening colonoscopy 10 years prior (a group likely to be screened in current practice) to be harmful. While screening some previously screened, low-risk individuals was not even cost-effective at age 66 years, screening some, healthy, high-risk individuals remained cost-effective up to age 88 years. Results were most sensitive to the cost-effectiveness threshold that was applied: applying a threshold of $50,000 instead of $100,000 per QALY gained reduced the maximum age at which screening was cost-effective by an average of 3 years.

What would be the effect of personalizing colonoscopy screening in the Medicare population on population health and Medicare spending?

The potential effect of personalizing colonoscopy screening in the Medicare population is large: compared with uniform age-based screening either tens of thousands of additional CRC deaths can be prevented or billions of dollars can be saved.

In current practice, decisions on CRC screening are often based solely on age: individuals aged 75 years or younger are offered screening, whereas individuals aged older than 75 years are not.[13] Studies have shown that screening could be more cost-effective if individual patient characteristics, such as sex, race, screening history, and comorbidity status, were considered.[16] However, the order of magnitude of the benefit that could be achieved by personalizing screening decisions is unclear.

We used data on the cost-effectiveness of colonoscopy screening by age, sex, race, screening history, and comorbidity status (see the previous paragraph) to construct four scenarios of personalized screening with increasing screening intensity.[17] To do so, we determined the appropriate ages to stop colonoscopy screening according to sex, race, screening history, and comorbidity status using four distinct cost-effectiveness thresholds: $25,000, $50,000, $75,000, and $100,000 per QALY gained. We then modeled the 2013 US Medicare population by age, sex, race, screening history, and comorbidity status and compared the undiscounted life-time Medicare costs and CRC deaths prevented under the four scenarios of personalized colonoscopy screening with the costs and CRC deaths prevented by uniform age-based colonoscopy screening up to age 75 years. This showed that personalized colonoscopy screening is substantially more efficient than uniform age-based screening. In the current Medicare population, personalizing colonoscopy screening could potentially prevent 21,200 additional CRC deaths (+11%) or save $1,500M (-84%). This is assuming that everyone in whom screening is cost-effective would be willing to have future colonoscopy screening, also those without prior screening.

THE SYNERGY BETWEEN TRIALS AND MODELS

How trials are used to inform models

The process of building a disease model can be subdivided into three steps. The first step is to identify all disease stages that should be modeled. The second step is to inform the transitions between disease stages using all relevant data that is available. The third step is to consult experts in order to make assumptions for those characteristics of the disease process that are unknown and sometimes even unobservable.

After a disease model has been build, it should be properly maintained. This implies that every time new data becomes available, the assumptions made in the model should be

tested against that data. If the outcomes of the model correspond with the data, the model is "validated" against the data. If the outcomes of the model do not correspond with the data, at least one assumption made in the model must be wrong. In this case, the assumption most likely to be wrong should be identified and the model parameters corresponding to this assumption should be changed. Usually new parameter values are determined by "calibrating" the model against the new data. During this process different sets of parameter values are explored and the parameter set for which the model outcomes show the best fit with the observed data is selected. We will illustrate the process of validating and calibrating a model using an example.

In 2010, the long-term outcomes of the U.K. Flexible Sigmoidoscopy Screening (UKFSS) trial were published.[18] Within this RCT, one-time sigmoidoscopy screening in average-risk individuals was compared with no screening. Among the outcomes reported in the paper was the cumulative incidence of distal CRC. We figured that this incidence could give us important information about the time it takes a progressive adenoma to develop into CRC (i.e., the adenoma dwell-time).

During sigmoidoscopy screening, most adenomas and preclinical cancers prevalent in the distal colon are detected and removed or treated. As a result, during follow-up, the incidence of distal CRC in the intervention group of a sigmoidoscopy screening trial is lower than that in the control group. Exactly how low the distal CRC incidence in the intervention group is, depends on the adenoma dwell-time. The longer the adenoma dwell-time, the lower the incidence of distal CRC. However, the incidence of distal CRC in the intervention group also depends on other factors, such as the attendance to screening and diagnostic and surveillance colonoscopies, the sensitivity of sigmoidoscopy and colonoscopy for the detection of adenomas and CRC, the reach of sigmoidoscopy and colonoscopy, the age-distribution of the population screened, etcetera. By exactly mimicking the UKFSS trial in MISCAN-Colon and comparing the simulated incidence of distal CRC with that observed in the trial, we could determine whether the mean adenoma dwell-time in our model of 7.6 years, which was based on expert opinion, was either correct, too short, or too long.

After simulating the UKFSS, we observed that the distal CRC incidence simulated by the model was substantially higher than that seen in the trial, indicating that the adenoma dwell-time in MISCAN-Colon was too short. Therefore, we decided to calibrate the adenoma dwell-time in our model to the distal CRC incidence observed in the trial. This resulted in an estimate for the mean adenoma dwell-time of 12.5 years (+4.9 years [+64%] compared with the old mean adenoma dwell-time). When we simulated the UKFSS trial using the new adenoma dwell-time, the simulated distal CRC incidence nicely matched that observed in the trial (**Model Appendix, Figure 4**). In all papers described in this thesis, the MISCAN-Colon model with the newly calibrated, longer adenoma dwell-time was used.

How models can also be used to inform trials

The adenoma dwell-time is an important determinant of the effectiveness of CRC screening, particularly of screening using colonoscopy, which is the screening modality relying most on the detection and removal of adenomas versus the early detection of CRC. The adenoma dwell-time is also an important determinant of the optimal distribution of screening examinations over an individual's lifespan, again particularly for colonoscopy screening. Based on the results of an analysis performed with 2 micro-simulation models, one of which was the MISCAN-Colon model with the old, short adenoma dwell-time, the USPSTF has been recommending 10-yearly colonoscopy screening starting at age 50 years and continuing up to age 75 years (i.e., screening at ages 50, 60, and 70 years) since 2008.[11 19] However, a longer adenoma dwell-time implies that more cancers that develop later in life are already present in the form of an adenoma at a relatively young age. Hence, a screening colonoscopy at a relative young age is likely to prevent more future cancers than we expected based on our old model and a younger age to start screening than 50 years could be indicated.

A recent analysis (again performed for the USPSTF) using the new MISCAN-Colon model, confirms this hypothesis: in most of the colonoscopy screening strategies found to be efficient, the first screening examination takes place at age 45 years instead of age 50 years.[20] However, this finding was insufficient for the USPSTF to recommend an earlier age to start colonoscopy screening. The task force states that: "there continues to be insufficient empiric data to support lowering the recommended age to begin colorectal cancer screening from 50 to 45".[21] Hence, studies should be conducted to evaluate the effectiveness of starting colonoscopy screening at age 45 years instead of age 50 years.

Why modelers and trialists should cooperate

The example described above shows that modelers need trials to inform their models and that trialists can benefit from modeling work to inform their trials. Hence, modelers and trialists should cooperate. At the Department of Public Health of the Erasmus University Medical Center we try to lead by example in that respect. First, we have got a long-lasting, intensive collaboration with the Department of Gastroenterology and Hepatology of the Erasmus University Medical Center. Second, whenever the results of modeling work for external clinical parties prompts a trial to be conducted, we will work together with those external parties to try and obtain funding for such a trial. Finally, we obtained funding from the Dutch National Institute for Public Health and the Environment to monitor and evaluate the Dutch national CRC screening program. This allows us to test the assumptions made in MISCAN-Colon using data from the program. The other way around, the Dutch National Institute for Public Health and the Environment can ask us to perform modeling analyses whenever important decisions about the screening program have to be made, as they did when a shortage of colonoscopy capacity was imminent in 2014 (see **Chapter 2**). We feel that it is important for trialists, modelers, as well as funders of health care research to

know that cooperation between trialists and modelers offers many advantages. Without the use of trial data, it is impossible to make a good model. Without the use of models, on the other hand, trial data cannot be extrapolated and trials will not have their maximum effect on health.

FUTURE RESEARCH DIRECTIONS

Cancer screening in general, and CRC screening in particular, is a rapidly developing field. Many countries are in the process of implementing CRC screening programs and personalized medicine is a topic of growing interest. Some topics we expect to be working on in the near future are mentioned below.

Identify optimal screening programs given local conditions in different countries

Remarkable differences are observed when comparing the CRC screening programs that are implemented across the world.[22] For example, in Europe alone, the Netherlands invites individuals for FIT screening, whereas regions of Belgium, regions of Italy, and Poland offer gFOBT, sigmoidoscopy, and colonoscopy screening, respectively. Another source of discrepancy is the target population invited for screening. For example, in some countries, such as Finland and Sweden, screening is confined to individuals aged between 60 and 69 years, whereas in other countries, such as Denmark and Estonia, a clearly larger range of at risk individuals is covered by screening (i.e., everyone age between 50 and 74 years). Finally, even in countries offering the same screening test, different screening intervals are applied: while most countries that offer gFOBT screening invite individuals every 2 years, Latvia offers yearly gFOBT screening.

Given the different background risk for CRC, the different life expectancy, the different costs of screening tests and CRC care, and the different amounts of resources available in different countries, implementing the same screening program in all countries is neither optimal nor feasible. In many of the examples above, however, there is no plausible reason for the differences in CRC screening programs that are observed. Models such as MISCAN-Colon could be used to determine optimal CRC screening programs given the local conditions in different countries. Similar research might be conducted for other forms of cancer screening.

Determine the appropriate interval for subsequent surveillance colonoscopies in adenoma patients and personalize the age to stop surveillance

In **Chapter 3** of this thesis, we determined the appropriate interval for a first surveillance colonoscopy in adenoma patients given their adenoma risk score, sex, and age.[5] Although this is often considered to be the most important clinical decision to be made in adenoma patients, most patients will have to undergo multiple surveillance

colonoscopies over the course of their lives. To determine the appropriate intervals for subsequent surveillance colonoscopies, a study is required that quantifies the risk for advanced adenoma recurrence based on findings during index colonoscopy and at least one surveillance colonoscopy. To obtain sufficient power to perform such a study, data from several existing cohorts of adenoma patients have to be pooled.[2 3] If such a study shows that only adenoma findings at index colonoscopy are important, the new surveillance interval can be read from **Table 4** in **Chapter 3** using the adenoma risk score at index colonoscopy and the sex and actual age of the patient. If the study shows that only adenoma findings during the last surveillance colonoscopy are important, the new surveillance interval can be read from the table using the adenoma risk score corresponding with the most recent surveillance colonoscopy and the sex and actual age of the patient. If findings during both colonoscopies are important, the new surveillance interval will lie somewhere in between these surveillance intervals. In this case, a new modeling study could be performed to determine the appropriate interval for a surveillance colonoscopy given the adenoma risk scores on two or more previous colonoscopies.

Another way to improve surveillance recommendations would be to personalize the age to stop surveillance according to a patient's comorbidity status. The ages resulting from the analysis described in **Chapter 3** of this thesis might be slightly too low for adenoma patients with no or mild comorbidity and slightly too high for patients with moderate or severe comorbidity.

Further personalize CRC screening recommendations

In **Chapter 7** of this thesis, we described a study in which we personalized the age to stop colonoscopy screening in US elderly individuals according to their sex, race, screening history, comorbidity status, and background risk for CRC.[16] This study could be extended in several directions. First, for each group of patients, one could determine the costs and effects of other screening modalities than colonoscopy and determine which screening test is optimal given an individual's characteristics (as we did for previously unscreened elderly individuals in **Chapter 5** of this thesis).[12] Second, screening recommendations could also be personalized based on an individual's preferences (for one screening test over another, for example). Finally, analyses could be performed that not only aim to personalize the age to stop screening, but also the age to start screening and the screening interval.

In the United States an opportunistic approach to screening is used. That is, the system relies on the patient and the health care provider to remember that screening should take place. Hence, patients and providers generally meet before screening is offered. This would be the obvious moment for personalization. The Netherlands, on the other hand, has an organized CRC screening program. That is, all individuals with a certain age in a certain year are automatically offered screening. This organized approach offers several advantages compared with an opportunistic approach to screening: participation is

generally higher and everyone has an equal chance to participate in screening, which many regard as being equitable. However, because screening is offered automatically, implementing personalized screening might be harder. Nonetheless, the National Institute for Public Health and the Environment might consider offering elderly individuals the opportunity to fill out an online questionnaire that helps them to determine whether screening is still worthwhile in their situation. Another possibility for personalization in the Dutch national screening program that could be explored, is to relate the interval for a next FIT to the hemoglobin concentration measured during FIT screening.

Continue to improve MISCAN-Colon

As described above and in the Model Appendix, MISCAN-Colon has been validated and, if needed, calibrated to the results of several large trials on the effectiveness of CRC screening and surveillance in adenoma patients. For example, data from the Nottingham, Minnesota, and Funen trials on the effectiveness of gFOBT screening have been used to estimate the average preclinical duration of CRC. Similarly, data from the UKFSS trial on the effectiveness of 1-time sigmoidoscopy screening have been used to estimate the average adenoma dwell-time. It is of the utmost importance to keep testing the assumptions made in MISCAN-Colon against the new evidence that becomes available.

In the near future, we expect to be able to test our assumptions regarding the risks for two consecutive false positive or false negative FIT screening results. Currently, we assume that individuals with a false positive or false negative test result are not at increased risk for another false positive or false negative test result. However, based on data from multiple rounds of the Dutch FIT screening trials, it appears that those with a false positive test result are at increased risk of having another false positive test result (probably because they suffer from another condition which causes bleeding, such as hemorrhoids) and that those with a false negative test result are at increased risk of having another false negative test result (probably because they have a type of adenoma that is less likely to bleed).

We also expect to be able to test our assumptions regarding the adenoma dwell-time in the proximal colon. Currently, we assume that this dwell-time is equal to the adenoma dwell-time in the distal colon. However, this assumption should be tested against the outcomes of the colonoscopy screening studies that are underway. If the adenoma dwell-time in the proximal colon differs from the adenoma dwell-time in the distal colon, we would need to model distal and proximal adenomas using different transition probabilities and durations in states. We should grasp this opportunity to also simulate the distribution of adenomas over the colorectum correctly. Currently, we use the simple assumption that this distribution of adenomas over the colorectum is equal to the distribution of CRC.

Furthermore, in the near future, we expect to be able to add a separate pathway for sessile serrated lesions to our model. This pathway is estimated to account for one-third of all CRC cases (two-third is accounted for by the adenoma-carcinoma pathway). Sessile serrated lesions are often flat or depressed, making them more difficult to detect with endoscopy. If they also differ from adenomas in other respects, such as the survival associated with the cancers that they cause, this might affect the cost-effectiveness of CRC screening in general and the specific CRC screening programs that should be recommended in certain settings. We also expect to be able to add the adenoma characteristics dysplasia and villous aspect to our model.

Finally, we should continue to update the input parameters used in MISCAN-Colon. Priority should be given to the costs of CRC care for both the US and the Netherlands, the CRC survival probabilities for the Netherlands, and all utility losses, since the data that are currently used are dated and some utility losses are still based on expert opinion.

CONCLUSIONS AND RECOMMENDATIONS

Based on the results of the studies described in this thesis, we derived the following conclusions:

- Decision models provide a useful tool to extrapolate evidence from RCTs and inform decisions about CRC screening programs. (**Chapter 2**)
- The appropriate interval for a first surveillance colonoscopy in adenoma patients depends heavily on a patient's adenoma risk score (i.e., risk according to all relevant characteristics of adenomas removed during colonoscopy) and to a lesser extent on sex and race. While some patients with risk score 0 should receive a surveillance colonoscopy after 10 years, some patients with risk scores 4 and 5 should receive a surveillance colonoscopy after only 2 years. Personalizing surveillance using the adenoma risk score targets colonoscopies at those patients most likely to benefit. (**Chapter 3**)
- Screening can have negative effects on quality-of-life. As a result, more intensive screening is not always better. More intensive colonoscopy screening than recommended in average-risk US Medicare beneficiaries, for example, is often harmful and always inefficient. (**Chapter 4**)
- An individual's screening history is an important determinant of the effectiveness and cost-effectiveness of CRC screening. In contrast with adequately screened individuals, screening previously unscreened individuals remains cost-effective well beyond age 75 years: up to age 86 years in those with no comorbidity, 83 years in those with moderate comorbidity, and 80 years in those with severe comorbidity. A screening colonoscopy is indicated at most ages. (**Chapter 5**)
- Disease simulation models can be used to integrate estimates of cancer risk, life expectancy, and screening efficacy into clinically meaningful estimates of the effectiveness of screening and, hence, to derive personalized screening recommendations. (**Chapter 6**)

- Besides screening history, an individual's comorbidity status and background risk for CRC are also important determinants of the effectiveness and cost-effectiveness of CRC screening. While colonoscopy screening is not even cost-effective at age 66 years in some, low-risk individuals, it remains cost-effective up to age 88 years in some previously unscreened, healthy, high-risk individuals. (**Chapter 7**)
- The potential effects of personalizing screening are large. On the Medicare population-level, personalizing colonoscopy screening could potentially prevent tens of thousands of additional CRC deaths or save billions of dollars. (**Chapter 8**)

Based on these conclusions, we formulated the following recommendations:

- Decision models should be used more frequently to inform decisions about screening.
- When making decisions about surveillance in newly diagnosed adenoma patients all relevant characteristics of adenomas removed during colonoscopy should be considered. This can be achieved by using the adenoma risk score.
- When evaluating screening, effects on quality of life must be considered. Not considering effects on quality of life can lead to wrong decisions.
- More intensive screening than recommended can be harmful. The current practice of more intensive colonoscopy screening than recommended in Medicare beneficiaries should be actively discouraged.
- When making decisions about stopping CRC screening, an individual's screening history, comorbidity status, and background risk for CRC should be considered. CRC screening guidelines should provide guidance on the appropriate age to stop screening according to these factors.
- Efforts should be made to overcome barriers to the implementation of personalized CRC screening in clinical practice, also in the Netherlands.

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Model Appendix

MISCAN-COLON

General Model Structure

In all chapters of this thesis, the MISCAN-Colon model was used. MISCAN-Colon is a stochastic microsimulation model for colorectal cancer (CRC) programmed in Delphi (Borland Software Corporation, Scotts Valley, California, United States). It can be used to explain and predict trends in CRC incidence and mortality and to quantify the effects and costs of primary prevention of CRC, screening for CRC, and surveillance after polypectomy. The term 'microsimulation' implies that individuals are moved through the model one at a time, rather than as proportions of a cohort. This allows future state transitions to depend on past transitions, giving the model a 'memory'. Furthermore, unlike most traditional Markov models, MISCAN-Colon does not use yearly transition probabilities. Instead it generates durations in states, thereby increasing model flexibility and computational performance. The term 'stochastic' implies that the model simulates sequences of events by drawing from distributions of probabilities/ durations, rather than using fixed values. Hence, the results of the model are subject to random variation.
MISCAN-Colon consists of 3 modules: a demography module, a natural history module, and a screening and surveillance module.

The Demography Module

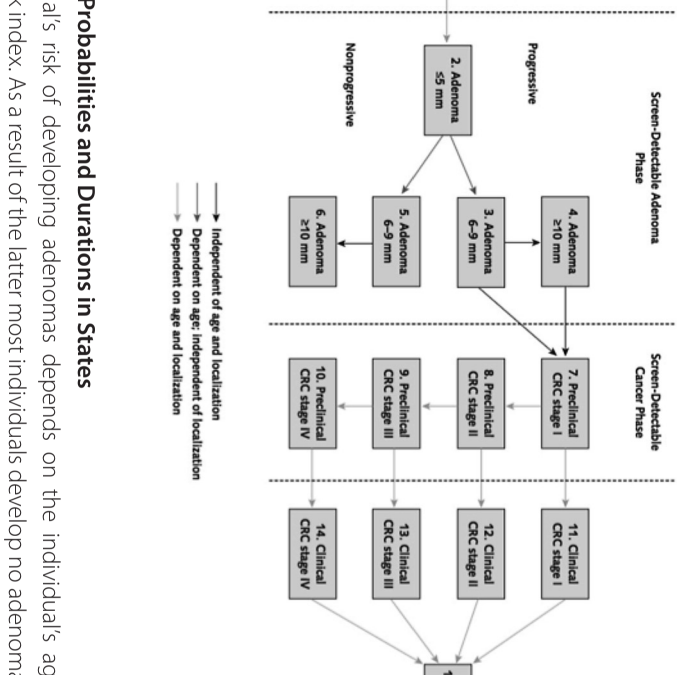
Using birth- and life-tables representative for the population under consideration, MISCAN-Colon draws a date of birth and a date of non-CRC death for each individual simulated (see **Table 1** for an overview of the data used in the different chapters). In MISCAN-Colon the maximum age an individual can achieve is exactly 100 years.

The Natural History Module

Transitions

As each simulated person ages, one or more adenomas may develop (**Figure 1**). These adenomas can be progressive or non-progressive. Both progressive and non-progressive adenomas can grow in size from small (≤5mm), to medium (6-9mm), to large (≥10mm). However, only progressive adenomas can develop into preclinical cancer. A preclinical cancer may progress through stages I to IV. However, during each stage CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage of the cancer at diagnosis, the localization of the cancer, and the patient's age and is based on CRC survival data observed in the population under consideration (**Table 1**). For individuals with synchronous CRCs at time of diagnosis, the survival of the most advanced cancer is used. The date of death for individuals with CRC is set to the earliest simulated death (either due to CRC or due to another cause (see: 'The demography module').

Figure 1 The general model structure of MISCAN-Colon.



Transition Probabilities and Durations in States

An individual's risk of developing adenomas depends on the individual's age and a personal risk index. As a result of the latter most individuals develop no adenomas, whilst some develop many. We assumed that the distribution of adenomas over the colorectum equaled the distribution of cancers as observed in the population under consideration before the introduction of screening (**Table 1**). The age-specific onset of adenomas and the dispersion of the personal risk index were calibrated to data on the age-specific prevalence and multiplicity distribution of adenomas as observed in autopsy/colonoscopy studies (see **Table 1** for an overview of the data used in the different chapters and **Figure 2** for calibration results). The age-specific probability of adenoma-progressivity and the age- and localization-specific transition probabilities between preclinical cancer stages and between preclinical and clinical cancer stages were simultaneously calibrated to the age-, stage-, and localization-specific incidence of CRC as observed in the population under consideration, again before the introduction of screening (**Table 1** and **Figure 3**).

The average durations of the preclinical cancer stages were calibrated to the rates of screen-detected and interval cancers observed in randomized controlled trials evaluating screening using gFOBT[1-4]. The average total preclinical duration of the preclinical cancer stages was found to be 4.7 years. The average duration from the emergence of an adenoma (state 2) until progression into preclinical cancer (state 7) (i.e. the adenoma dwell-time) was calibrated to the interval cancer rates observed in a randomized controlled trial evaluating once-only sigmoidoscopy screening and was found to be 12.5 years

Table 1 Overview of the data used to model the populations in the different chapters of this thesis.

Chapter[a]	Life expectancy	Adenoma prevalence[b]	CRC incidence	Localization distribution of CRC	CRC survival
Chapter 3[c]	Life expectancy by age and sex in the Netherlands in 2011[9]	Adenoma prevalence in autopsy and colonoscopy studies[6 10-19]	CRC incidence by age, stage, localization in the Netherlands between 1999 and 2003[20]	Localization distribution in the Netherlands between 1999 and 2003[20]	CRC survival by stage, localization, and age in the South of the Netherlands between 1985 and 2004[21]
Chapter 4	Life expectancy by age in the US in 2007[22]	Adenoma prevalence in autopsy studies[10-19]	CRC incidence by age, stage, and localization in the US between 1975 and 1979[23]	Localization distribution in the US between 1975 and 1979[23]	CRC survival by stage, localization, and age in the US in 2003[24]
Chapter 5	Life expectancy by age and comorbidity status in the US between 1992 and 2005[25]	Adenoma prevalence in autopsy studies[10-19]	CRC incidence by age, stage, and localization in the US between 1975 and 1979[23]	Localization distribution in the US between 1975 and 1979[23]	CRC survival by stage, localization, and age in the US in 2003[24]
Chapters 6 and 7	Life expectancy by age, sex, race, and comorbidity status in the US between 1992 and 2005[25]	Adenoma prevalence in autopsy studies[10-19]	CRC incidence by age, stage, localization, sex, and race in the US between 1990 and 1994[23]	Localization distribution by sex and race in the US between 1990 and 1994[23]	CRC survival by stage, localization, age, sex, and race in the US in 2003[24]

CRC = colorectal cancer, US = United States

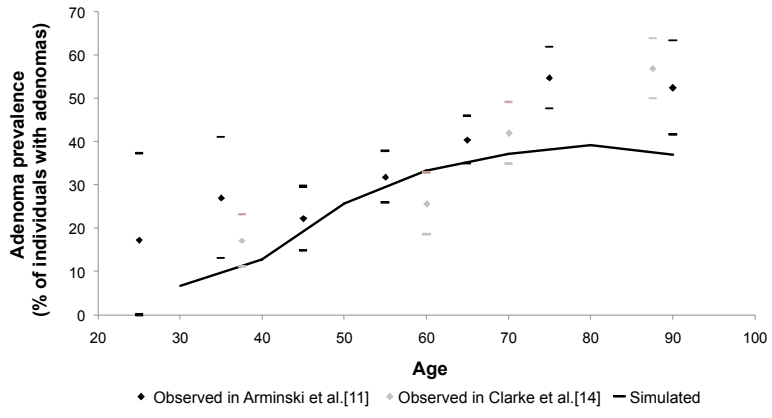
[a] In **Chapters 2 and 8** of this thesis, no new analyses were conducted using MISCAN-Colon.

[b] The adenoma prevalence in the different autopsy studies was corrected for the difference in CRC risk between the population modeled and the population in which the autopsy study was conducted.

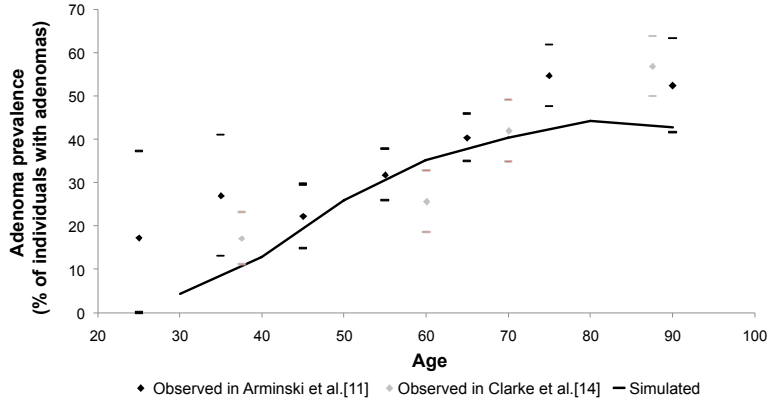
[c] In **Chapter 3** we did not calibrate separate disease models for men and women. Instead, we used our Dutch general population model and applied sex-specific correction factors for CRC risk to model men and women.

Figure 2 Calibration results: adenoma prevalence observed in selected autopsy studies versus simulated by MISCAN-Colon in **Chapter 3** (A), **Chapters 4 and 5** (B), and **Chapters 6 and 7** (C) of this thesis.*

A



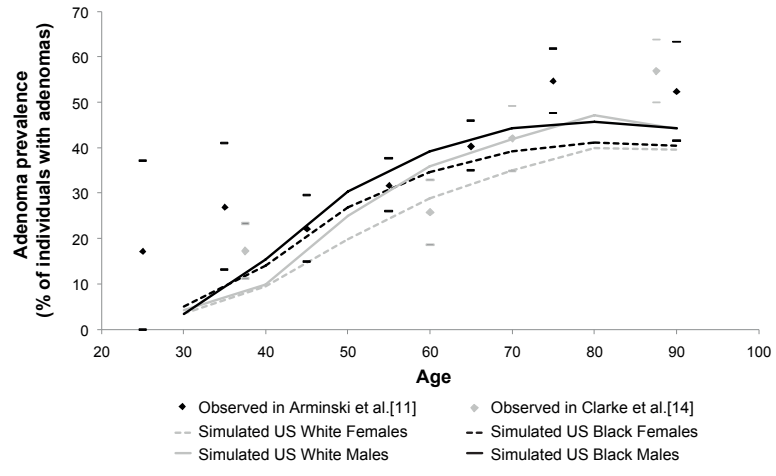
B



*Stage- and localization-specific model outcomes also showed good concordance with observed data.

Figure 2 Continued.

C

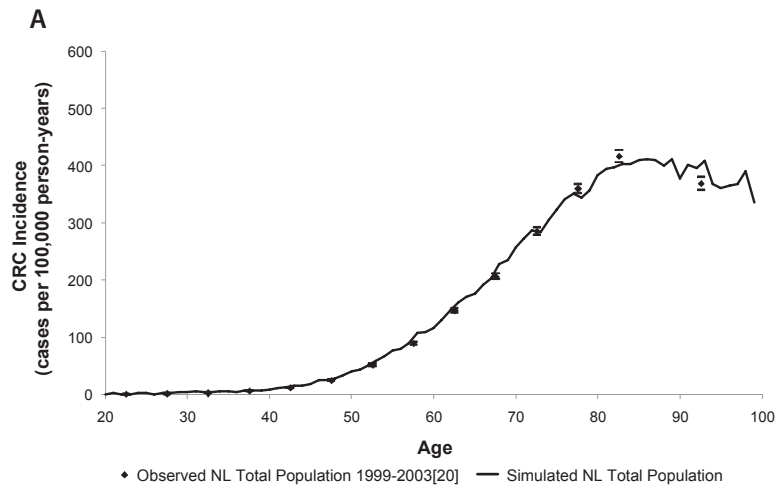


(**Figure 4**, see also **Chapter 9**).[5] We assumed an equal overall dwell-time for adenomas developing into CRC from a medium size (30% of all CRCs) and from a large size (70% of all CRCs). The durations of the preclinical cancer stages as well as the adenoma dwell-time were assumed to be equal in all populations modeled in this thesis.

All durations in the adenoma and preclinical cancer phase are drawn from exponential distributions. Durations within the adenoma phase and within the preclinical cancer phase are assumed to be perfectly correlated (i.e. if a small adenoma grows into a medium-sized adenoma rapidly, it will also grow into a large adenoma or develop into CRC rapidly); however, durations in the adenoma phase are assumed to be uncorrelated with durations in the preclinical cancer phase (i.e. a rapidly growing adenoma does not necessarily develop into a rapidly progressing cancer). The proportion of medium sized, non-progressive adenomas growing large and the average duration in the medium size, non-progressive adenoma state (state 5) were calibrated to size-specific adenoma detection rates observed in a Dutch randomized controlled trial on colonoscopy screening (data not shown).[6]

We validated MISCAN-Colon against the long-term mortality outcomes of the National Polyp Study: a study assessing the effectiveness of colonoscopic polypectomy. The model showed good concordance with the mortality rates observed (**Figure 5**).[7]

Figure 3 Calibration results: CRC incidence observed in the populations under consideration versus simulated by MISCAN-Colon in **Chapter 3** (A), **Chapters 4 and 5** (B), and **Chapters 6 and 7** (C) of this thesis.*



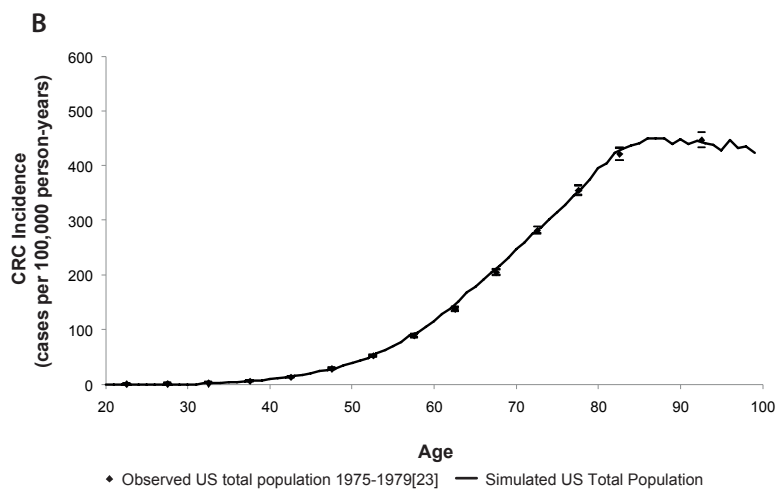
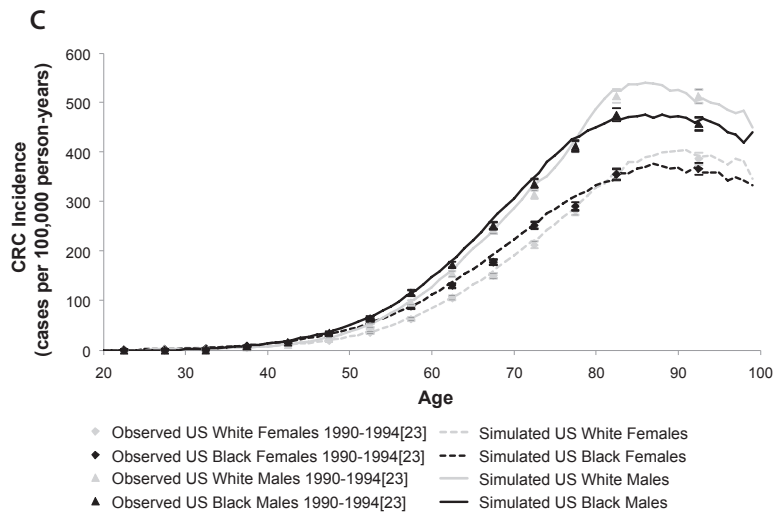


Figure 3 Continued.

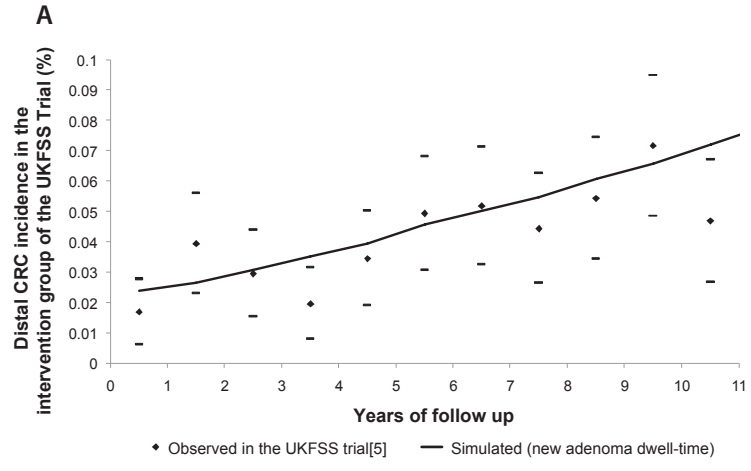


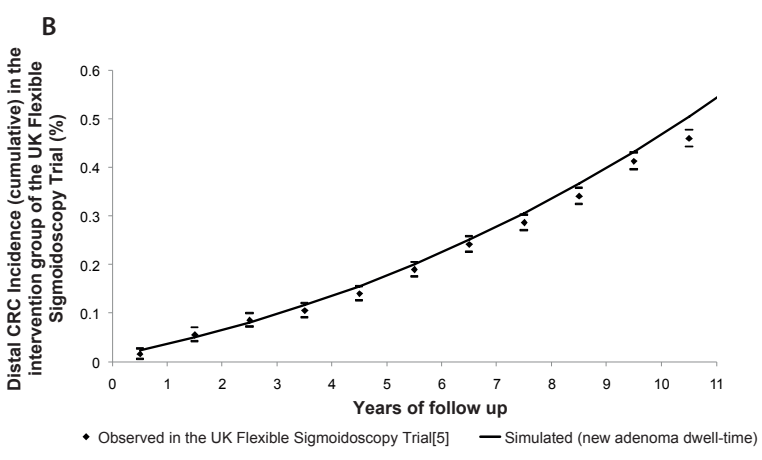
The Screening and Surveillance Module

Screening and surveillance will alter some of the simulated life histories: Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favorable survival. Because the stage-specific survival of screen-detected CRC as observed in randomized controlled trials on guaiac fecal occult blood testing was substantially more favorable than that of clinically detected CRC, even after correcting for lead-time bias,[4] we assigned those screen-detected and surveillance-detected cancers that would have been clinically detected in the same stage a survival corresponding to a one stage less progressive cancer. Hence, a cancer detected in stage II, that would also have been clinically diagnosed in stage II, is assigned the survival of a clinically diagnosed stage I cancer. The only exceptions are stage IV cancers. These cancers are always assigned the survival of a clinically diagnosed stage IV cancer.

Besides modeling positive health effects of screening and surveillance, we also model colonoscopy-related complications and over-diagnosis and over-treatment of CRC (i.e. the detection and treatment of cancers that would not have been diagnosed without screening/ surveillance).[8]

Figure 4 Distal CRC Incidence Observed in the Intervention Group of the UK Flexible Sigmoidoscopy Trial Versus Simulated by MISCAN-Colon (per year of follow-up (A), cumulative (B)).

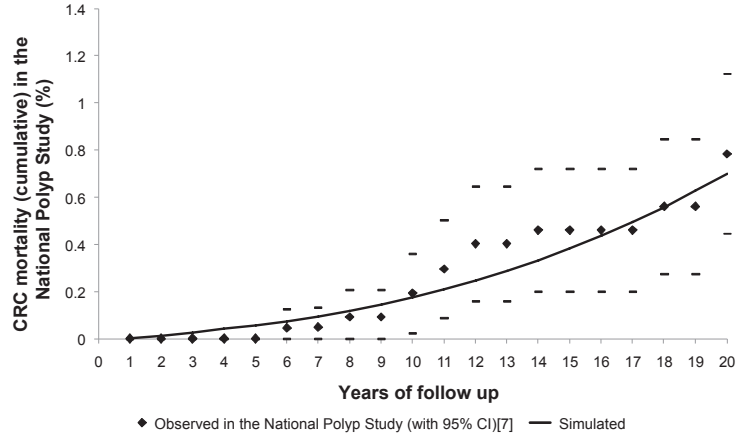




Integrating Modules

Within MISCAN-Colon the results of the demography module, the natural history module, and the screening and surveillance module are integrated. In the demography module dates of birth and a dates of non-CRC death are generated. In the natural history module adenomas and CRCs are added to some of the generated life histories. In the screening

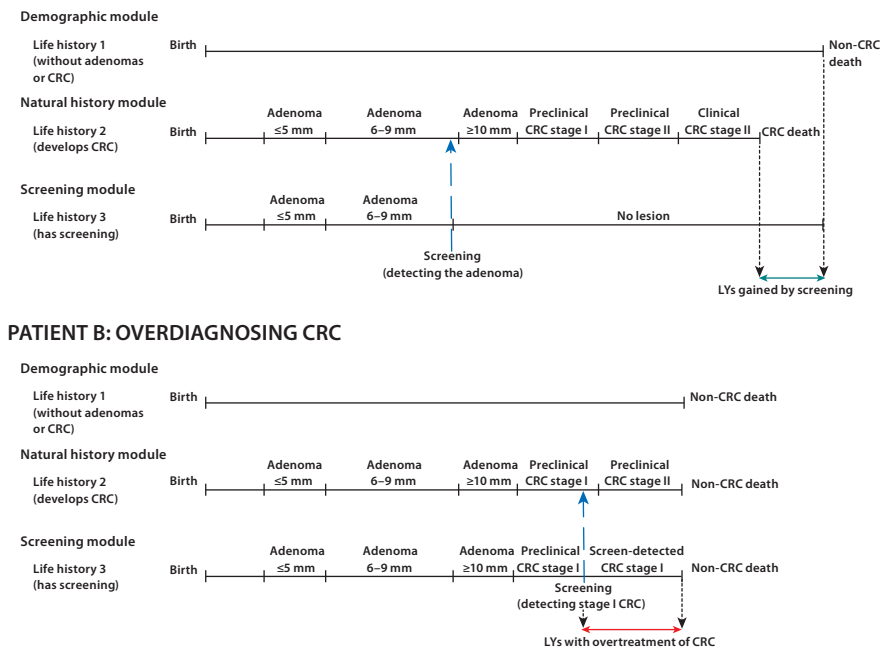
Figure 5 Cumulative CRC Mortality Observed in the National Polyp Study Versus Simulated by MISCAN-Colon.



and surveillance module screening and surveillance are superimposed to the life histories with adenomas and CRC. By comparing the life histories without screening and surveillance with the life histories with screening and surveillance, MISCAN-Colon quantifies the effects and costs of screening.

In Patient A in **Figure 6**, the natural history module generates an adenoma. This adenoma progresses into cancer, is diagnosed in stage II, and results in CRC death before non-CRC death would have occurred. In the screening module a screening examination is simulated, indicated by the vertical arrow. During this examination the adenoma is detected, and as a result both CRC and CRC death are prevented. Hence, in Patient A, screening prolongs life by the amount indicated by the horizontal arrow. Patient B in **Figure 6** also develops an adenoma. This adenoma has the potential to progress into preclinical cancer. However, patient B would never have been diagnosed with CRC in a scenario without screening, because he would have died from another cause before the cancer would have been diagnosed (see life history 2). During the screening examination simulated in the screening module, again indicated by the vertical arrow, CRC is screen-detected in stage I. Hence, in patient B, screening results in over-diagnosis of CRC: it detects a cancer that would never have been diagnosed in a scenario without screening. Hence, screening does not prolong life, but it does result in additional LYs with CRC care (over-treatment) as indicated by the horizontal arrow.

Figure 6 Integrating Modules: Two example Patients.



CRC = colorectalcancer; LY = life-year.

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Summary

In most developed countries, colorectal cancer (CRC) is an important public health problem. In the Netherlands alone, 13,370 individuals were diagnosed with CRC in 2013. In the same year, 4,940 individuals died of the disease. This makes CRC the second most common cancer and the second most common cause of cancer-related death in the Netherlands today. The lifetime risk of developing CRC in the Netherlands is 4.4%. The lifetime risk of dying of the disease is 1.8%. In the US, the relative burden of CRC is comparable to that in the Netherlands.

One way to reduce CRC mortality is CRC screening. During screening individuals without signs or symptoms are offered a test aimed at detecting unrecognized disease in an early stage. CRC is particularly well suited for screening because it has a long pre-clinical screen-detectable phase. During this phase, screening can prevent CRC by detecting and removing its precursor lesion (i.e., the adenoma) or it might detect CRC in an earlier stage, resulting in an improved prognosis. However, screening can also result in serious complications and overdiagnosis and overtreatment of cancer (i.e., the detection and treatment of cancers that would never have been diagnosed without screening). Multiple tests are available for screening. First, there are stool tests: the guaiac fecal occult blood test (gFOBT) aimed at detecting any blood in stool, the fecal immunochemical test (FIT) aimed at detecting human blood only, and the fecal DNA test aimed at detecting human blood as well as mutated DNA from neoplastic cells. Second, there are endoscopic tests: sigmoidoscopy, during which the distal end of the colorectum is inspected, and colonoscopy, during which the entire colorectum is visualized. Finally, there is an imaging test: CT colonography, during which images of the colorectum are inspected for anomalies. All screening tests differ from one another in important respects. They differ in their acceptability to the population being screened, their ability to detect adenomas and CRC, the burden that they cause, the risks they are associated with, and their costs. All tests other than colonoscopy require referral to colonoscopy if positive.
A second way to reduce CRC mortality is surveillance in adenoma patients. Adenoma patients are individuals in whom adenomas were detected and removed, either as a result of screening or during a colonoscopy indicated because of symptoms. Because adenoma patients are at increased risk for CRC compared with the general population, they are recommended to undergo more intensive testing using colonoscopy: the test most sensitive for detecting adenomas and CRC.

The Netherlands started rolling out a national CRC screening program in January 2014. Within this program, ultimately, all individuals aged 55 up to 75 years will be invited for biennial FIT screening. In the US, CRC screening was already introduced in the late 1980s. In contrast with the Netherlands, screening in the US is not nationally organized. Instead, most screening is carried out 'opportunistically': that is, the system relies on the patient and health care provider to remember that screening should take place. Another important difference is that in

the US, individuals are free to choose between the different screening tests available.
In this thesis, we used a microsimulation model to inform both clinical and policy decisions regarding CRC screening and surveillance in adenoma patients. In **Chapter 2**, we showed how models were used to inform decisions about the Dutch national CRC screening program. In **Chapter 3**, we described an analysis that formed the basis of the new Dutch guidelines for surveillance in adenoma patients. In **Chapter 4**, we quantified the effects of observed patterns of more intensive colonoscopy screening than recommended in US Medicare beneficiaries on the effectiveness and cost-effectiveness of screening. In **Chapter 5**, we studied the cost-effectiveness of CRC screening in US elderly without previous screening. In **Chapter 6,** we showed why the age to stop colonoscopy screening should be different for individuals with different characteristics. In **Chapter 7**, we constructed personalized recommendations for colonoscopy screening in US elderly individuals. Finally, in **Chapter 8** we quantified the effects that personalizing CRC in elderly individuals could have on US population health and health care expenditures.

How models can be used to inform decisions regarding screening programs

RCTs are the gold standard for determining the effectiveness of screening, but they also have their limitations. First, RCTs are expensive and time consuming. As a result, the number of RCTs that have evaluated CRC screening is limited. Second, RCTs usually have a limited follow-up time. Hence, they cannot be used to determine lifetime health effects and costs, which is necessary to determine the cost-effectiveness of screening. Third, the effectiveness of screening in a certain country might differ from that observed in an RCT, for example because attendance rates to screening are substantially lower or higher. Finally, country-level resource demands for a certain screening program cannot easily be inferred from an RCT. To summarize: RCTs alone do not answer the question of which screening strategy is optimal for a certain country.
In **Chapter 2** of this thesis, we demonstrated that decision models provide a useful tool to extrapolate evidence from RCTs during the whole cycle of a screening program, using the role MISCAN-Colon played in the Dutch CRC screening program as an example.[1] In the decision phase of the Dutch screening program, modeling analyses were used to inform the decisions to 1) choose FIT screening over gFOBT screening, 2) choose a higher age to start screening than recommended by the Council of Europe, and 3) choose a lower cut-off for referral to colonoscopy than recommended by the test's manufacturer. A modeling analysis also informed the decision to temporarily elevate the cut-off for referral to colonoscopy when a shortage of colonoscopy capacity was imminent during the first year of the program. If modeling would not have been used at these instances, other choices could have been made, and the balance between the benefits and harms of the screening program could have turned out less favorable than it will now.

Personalizing surveillance in Dutch adenoma patients

Several important predictors of advanced adenoma recurrence in newly diagnosed adenoma patients have been identified. These predictors include characteristics of adenomas removed during colonoscopy: the presence of multiple, large (≥10mm), villous, and proximal adenomas, as well as patient characteristics: male sex and older age. The identification of these predictors allows for extensive risk stratification of adenoma patients followed by careful tailoring of surveillance recommendations. However, existing surveillance guidelines do not consider all relevant predictors and are thus restricted in providing tailored recommendations. In prior work, we analyzed data from a cohort of Dutch adenoma patients to develop a score chart that can be used to risk-stratify adenoma patients according to all relevant characteristics of adenomas removed during colonoscopy. This chart results in a so-called 'adenoma risk score' for each adenoma patient (range: 0-5).
In **Chapter 3** of this thesis, we determined the appropriate interval for colonoscopy surveillance in newly diagnosed adenoma patients given their adenoma risk score, sex, and age. This analysis showed that the appropriate interval for colonoscopy surveillance depends heavily on a patient's adenoma risk score and to a lesser extent on sex and age. While some patients with risk score 0 could receive a surveillance colonoscopy after 10 years, some patients with risk scores 4 and 5 should receive a surveillance colonoscopy after only 2 years. The analysis also showed that existing surveillance guidelines do not consistently target colonoscopies at those patients most likely to benefit. According to the 2002 Dutch guidelines, which are based on adenoma multiplicity only, for example, a 60 year-old female with 3 small, non-villous, distal adenomas was recommended colonoscopy surveillance after 3 years, while a 60 year-old female with 2 large, villous, proximal adenomas was recommended colonoscopy surveillance after 6 years. However, according to our analysis, the former patient (who has an adenoma risk score of 1) should be recommended colonoscopy surveillance after 7 years, while the latter patient (who has an adenoma risk score of 4 [corresponding to an almost 4-fold higher risk for CRC]) should be recommended colonoscopy surveillance after 3 years: almost the exact opposite. The Dutch guidelines for surveillance in adenoma patients were revisited based on the results of our study in May 2013.

More intensive colonoscopy screening than recommended in the Medicare population

All US guidelines for CRC screening recommend a screening interval of 10 years for colonoscopy screening in average-risk individuals. Moreover, the US Preventive Services Task Force and the American College of Physicians recommend against routine screening in adults older that 75 years with an adequate screening history. Still, many US Medicare beneficiaries (i.e., US individuals aged 65 years and older) undergo more intensive colonoscopy screening than recommended: 20% of beneficiaries with a negative screening colonoscopy result receive a repeated screening colonoscopy within 5 year's

time instead of after the recommended 10 years. Moreover, 25% of beneficiaries with a negative screening colonoscopy result at age 75 years or older receive yet another screening colonoscopy at an even more advanced age.

In **Chapter 4** of this thesis, we showed that more intensive colonoscopy screening than recommended in average-risk Medicare beneficiaries results in only small increases in the benefits of screening (i.e., CRC cases prevented, CRC deaths prevented, and LYs gained) compared with the increases in the burden and harms associated with screening (i.e., colonoscopies performed and complications experienced). As a result, more intensive screening than recommended is often associated with a net harm (i.e., QALYs lost), rather than a net health benefit. The only scenario that resulted in a net health benefit (i.e., colonoscopy screening every 5 instead of 10 years) was very inefficient from a societal perspective, requiring 909 additional colonoscopies and an additional $711,000 per additional QALY gained.

CRC screening in US elderly individuals without previous screening

In its most recent recommendation statement on colorectal cancer (CRC) screening, the US Preventive Services Task Force (USPSTF) recommends against routine screening in persons older than 75 years with an adequate screening history. This recommendation has led many members of the medical community to believe that no one older than 75 years should be screened for CRC. However, because unscreened elderly persons are at greater risk for CRC than adequately screened elderly persons, screening them is likely to be effective and cost-effective up to a more advanced age. If so, the lack of more specific recommendations on the age to stop screening may result in an unfounded denial of access to screening in elderly persons who were never screened for CRC—a group representing 23% of all US persons older than 75 years.

In **Chapter 5**, we demonstrated the importance of considering an individual's screening history when making decisions about screening. We showed that CRC screening remains cost-effective well beyond age 75 years in elderly individuals without previous screening. The maximum age at which screening was cost-effective was 86 years for individuals with no comorbidity, 83 years for individuals with moderate comorbidity, and 80 years for individuals with severe comorbidity. In unscreened individuals with no comorbidity, a screening colonoscopy was most effective and still cost-effective up to age 83 years, a screening sigmoidoscopy was indicated at age 84 years, and FIT screening was indicated at ages 85 and 86 years. In those with moderate comorbidity, a screening colonoscopy was indicated up to age 80 years, a screening sigmoidoscopy was indicated at age 81 years, and FIT screening was indicated at ages 82 and 83 years. Finally, in those with severe comorbidity, a screening colonoscopy was indicated up to age 77 years, a screening sigmoidoscopy was indicated at age 78 years, and FIT screening was indicated at ages 79 and 80 years.

Personalizing colonoscopy screening for US elderly individuals

The effectiveness of CRC screening does not only depend on the screening strategy that is used. It also depends on the characteristics of the individuals being screened. Screening is more effective in individuals at high risk for CRC, than in individuals at low risk for CRC. Moreover, screening is more effective in individuals with a favorable life expectancy, than in individuals with an unfavorable life expectancy. Although clinicians are generally aware that factors other than age affect the effectiveness and, thus, the cost-effectiveness of screening, many still make their decisions on screening for elderly individuals primarily on the basis of age: individuals aged 75 years or younger are offered screening, whereas individuals aged older than 75 years are not.

In **Chapter 6** of this thesis, we explained why recommendations for screening should be personalized and how models can be used to derive personalized screening recommendations. Next, in **Chapter 7**, we constructed personalized recommendations for colonoscopy screening in US elderly. To do so, we determined the cost-effectiveness of colonoscopy screening for 19,200 cohorts of individuals characterized by age, sex, race, screening history, background risk for CRC (i.e., level of exposure to risk factors for CRC), and comorbidity status. This analysis showed that while screening some previously screened, low-risk individuals is not even cost-effective at age 66 years, screening some, healthy, high-risk individuals remains cost-effective up to age 88 years. It also showed that the current uniform, age-based approach to screening is inefficient: resulting in harmful screening in some, and the denial of cost-effective screening in others. Finally, in **Chapter 8**, we estimated the effects that personalizing CRC screening in elderly individuals could have on US population health and health care expenditures. To do so, we modeled the 2013 Medicare population (39.6M individuals) and compared the lifetime health effects and costs of uniform age-based screening up to age 75 years with four scenarios of personalized screening with increasing screening intensity. This analysis showed that personalized screening is more efficient than uniform age-based screening up to age 75 years. At the uniform age-based screening cost-level personalized screening could potentially prevent 21,200 additional CRC deaths (+11%). Alternatively, personalized screening could result in the same number of CRC deaths prevented at $1,500M lower costs (-84%).

Based on the results of the studies described in this thesis, we derived the following conclusions:

- Decision models provide a useful tool to extrapolate evidence from RCTs and inform decisions about screening. (**Chapter 2**)
- The appropriate interval for a first surveillance colonoscopy in adenoma patients depends heavily on a patient's adenoma risk score (i.e., risk for CRC according to all relevant characteristics of adenomas removed during colonoscopy). Personalizing surveillance using the adenoma risk score targets colonoscopies at those patients most likely to benefit. (**Chapter 3**)

- Screening also has negative effects on health. As a result, more intensive screening is not always better. More intensive colonoscopy screening than recommended in average-risk US Medicare beneficiaries, for example, is often harmful and always inefficient. (**Chapter 4**)
- An individual's screening history is an important determinant of the effectiveness and cost-effectiveness of CRC screening. In contrast with adequately screened individuals, screening previously unscreened individuals remains cost-effective well beyond age 75 years. (**Chapter 5**)
- Disease simulation models can be used to integrate estimates of cancer risk, life expectancy, and screening efficacy into clinically meaningful estimates of the effectiveness of screening and, hence, to derive personalized screening recommendations. (**Chapter 6**)
- Besides screening history, comorbidity status and background risk for CRC are also important determinants of the effectiveness and cost-effectiveness of CRC screening. (**Chapter 7**)
- The potential effects of personalizing screening decisions in elderly individuals are large. On the Medicare population-level, personalizing colonoscopy screening could prevent tens of thousands of additional CRC deaths or save billions of dollars. (**Chapter 8**)

Based on these conclusions, we formulated the following recommendations:

- Decision models should be used more frequently to inform decisions about screening.
- When making decisions about surveillance in newly diagnosed adenoma patients all relevant characteristics of adenomas removed during colonoscopy should be considered. This can be achieved by using the adenoma risk score.
- When evaluating screening, effects on quality of life must be considered. Not considering effects on quality of life can lead to wrong decisions.
- More intensive screening than recommended can be harmful. The current practice of more intensive colonoscopy screening than recommended in Medicare beneficiaries should be actively discouraged.
- When making decisions about stopping CRC screening, an individual's screening history, comorbidity status, and background risk for CRC should be considered.
- Efforts should be made to overcome barriers to the implementation of personalized CRC screening and surveillance in adenoma patients in clinical practice.

Samenvatting

In de meeste ontwikkelde landen is dikkedarmkanker (DDK) een belangrijk gezondheidsprobleem. In 2013 werden alleen al in Nederland 13,370 mensen gediagnosticeerd met DDK. In hetzelfde jaar overleden 4,940 mensen aan de ziekte. Hiermee is DDK op dit moment de op één na meest voorkomende kanker en de op één na meest voorkomende oorzaak van sterfte aan kanker in Nederland. Het risico om gedurende het leven met DDK gediagnosticeerd te worden is 4.4%. Het risico om aan de ziekte te overlijden is 1.8%. In de Verenigde Staten (VS) is de relatieve ziektelast ten gevolge van DDK vergelijkbaar met die in Nederland.

Eén van de manieren waarop DDK-sterfte verminderd kan worden is DDK-screening. Screening wil zeggen dat mensen zonder symptomen een test aangeboden krijgen waarmee ziekte in een vroeg stadium gedetecteerd kan worden. DDK is bij uitstek geschikt voor screening omdat het een lange periode kent waarin de ziekte nog geen symptomen veroorzaakt, maar al wel te detecteren is. Gedurende deze periode kan screening DDK voorkómen door het detecteren en verwijderen van het voorstadium ervan (het adenoom) of de prognose van DDK verbeteren door de ziekte in een vroeger stadium te detecteren. Screening kan echter ook ernstige complicaties en overdiagnose en overbehandeling van kanker veroorzaken (het kan ervoor zorgen dat kankers gediagnosticeerd en behandeld worden die zonder screening nooit gediagnosticeerd zouden zijn). Er zijn verschillende tests beschikbaar voor DDK-screening. Ten eerste zijn er de ontlastingstests: de guajak *'fecal occult blood tests'* (gFOBTs) gericht op het detecteren van elke vorm van bloed, de immunologische *'fecal occult blood tests'* (iFOBTs) gericht op het detecteren van menselijk bloed en de fecaal DNA tests gericht op het detecteren van menselijk bloed en gemuteerd DNA. Ten tweede zijn er endoscopische tests: sigmoïdoscopie, waarbij de distale (linker) zijde van de dikke darm wordt geïnspecteerd, en colonoscopie, waarbij de gehele dikke darm wordt gevisualiseerd. Ten slotte is er een test waarbij gebruik wordt gemaakt van een beeldvormende techniek: de CT-colografie, waarbij beelden van de dikke darm worden beoordeeld op afwijkingen. Alle screeningtests verschillen op belangrijke punten van elkaar. Ze verschillen in de mate waarin ze geaccepteerd worden door de populatie die screening moet ondergaan, in hun vermogen om adenomen en dikke darm te detecteren, in de belasting die het ondergaan van de test met zich meebrengt, in hun risico's op complicaties en in hun kosten. Alle tests, behalve colonoscopie, vereisen dat een colonoscopie wordt verricht wanneer de uitslag van de test afwijkend is.

Een tweede manier waarop DDK-sterfte verminderd kan worden, is surveillance in adenoompatiënten. Adenoompatiënten zijn mensen bij wie naar aanleiding van deelname aan screening (of een colonoscopie naar aanleiding van symptomen) adenomen zijn gedetecteerd en verwijderd. Omdat adenoompatiënten een verhoogd risico op DDK hebben ten opzichte van de algemene populatie, wordt hen meer intensieve follow-up aanbevolen in de vorm van periodiek onderzoek door middel van colonoscopie: de test met de hoogste gevoeligheid voor het detecteren van adenomen en DDK.

In Nederland werd in 2014 begonnen met het uitrollen van een nationaal bevolkingsonderzoek DDK. Binnen dit bevolkingsonderzoek, zal uiteindelijk iedereen tussen de 55 en 75 jaar uitgenodigd worden voor tweejaarlijkse iFOBT screening. In de VS werd DDK-screening al geïntroduceerd in de jaren '80. In tegenstelling tot Nederland, is er in de VS geen sprake van een nationaal georganiseerd screeningsprogramma. In plaats daarvan vindt 'opportunistische screening' plaats. Dat wil zeggen dat de patiënt of de zorgverlener eraan moet denken dat screening plaats moet vinden. Een ander belangrijk verschil met Nederland is dat mensen in de VS vrij zijn om te kiezen welke screeningtest ze willen ondergaan.

In dit proefschrift gebruikten we een micro-simulatie model om beslissingen over DDK-screening en surveillance in adenoompatiënten te informeren. In **Hoofdstuk 2** lieten we zien hoe modellen zijn gebruikt om beslissingen over het Nederlandse bevolkingsonderzoek DDK te informeren. In **Hoofdstuk 3** beschreven we de analyse die ten grondslag ligt aan de nieuwe Nederlandse richtlijnen voor surveillance in adenoompatiënten. In **Hoofdstuk 4** bepaalden we de gevolgen van meer intensieve colonoscopiescreening dan aanbevolen in Amerikaanse 65-plussers. In **Hoofdstuk 5** bepaalden we de kosteneffectiviteit van DDK-screening in Amerikaanse ouderen die nooit eerder op DDK gescreend waren. In **Hoofdstuk 6** lieten we zien waarom de stopleeftijd voor colonoscopiescreening afhankelijk zou moeten zijn van eigenschappen van de patiënt in kwestie. In **Hoofdstuk 7** genereerden we gepersonaliseerde aanbevelingen voor colonoscopiescreening in Amerikaanse ouderen. Ten slotte kwantificeerden we in **Hoofdstuk 8** de voordelen die gepersonaliseerde colonoscopiescreening in ouderen zou kunnen hebben voor de Amerikaanse maatschappij.

Hoe modellen gebruikt kunnen worden om beslissingen over screeningsprogramma's te informeren

Gerandomiseerde gecontroleerde trials (zogenaamde 'randomized controlled trials' [RCTs]) worden beschouwd als de gouden standaard voor het bepalen van de effectiviteit van screening, maar ze kennen ook hun beperkingen. Ten eerste zijn RCTs erg duur en tijdrovend. Hierdoor is het aantal RCTs waarin de effectiviteit van DDK-screening is geëvalueerd zeer beperkt. Ten tweede is de follow-up tijd die gehanteerd wordt binnen RCTs doorgaans niet lang genoeg om het volledige effect en de volledige kosten van screening te bepalen. Ten derde kan de effectiviteit van screening in een specifieke setting sterk afwijken van de effectiviteit geobserveerd in een RCT, bijvoorbeeld doordat de opkomst bij screening sterk afwijkt. Ten slotte is het moeilijk om de benodigde zorgcapaciteit voor een specifiek screeningsprogramma te bepalen aan de hand van de resultaten van een RCT. Al met al is het onmogelijk om enkel aan de hand van RCTs te bepalen welke screeningsstrategie optimaal is in een specifieke setting.

In **Hoofdstuk 2** van dit proefschrift, demonstreerden we dat modellen een belangrijke rol kunnen spelen bij het beantwoorden van vragen over screeningsprogramma's. Dit deden we aan de hand van de modelanalyses die ten grondslag liggen aan de huidige vormgeving van het Nederlandse bevolkingsonderzoek DDK. In de beslissingsfase van het bevolkingsonderzoek, werd op basis van modelanalyses gekozen voor 1) iFOBT screening in plaats van gFOBT screening, 2) een hogere startleeftijd dan aanbevolen door de Raad van Europa en 3) een lagere afkapwaarde voor doorverwijzing naar colonoscopie dan aanbevolen door de producent van de iFOBT. Toen tijdens de implementatiefase van het bevolkingsonderzoek een groot tekort aan colonoscopiecapaciteit dreigde werd op basis van een modelanalyse besloten om de afkapwaarde voor doorverwijzing naar colonoscopie tijdelijk te verhogen. Als deze modelanalyses niet verricht zouden zijn, zouden andere, minder gunstige keuzes gemaakt kunnen zijn.

Het personaliseren van surveillance voor Nederlandse adenoompatiënten

Patiënten bij wie ooit een adenoom verwijderd is, lopen een verhoogd risico op het ontwikkelen van nieuwe adenomen. Recent zijn verschillende factoren geïdentificeerd aan de hand waarvan het risico op een nieuw adenoom bij deze patiënten bepaald kan worden. Voorbeelden van deze factoren zijn karakteristieken van eerder verwijderde adenomen, zoals de aanwezigheid van meerdere adenomen, grote adenomen (≥10mm), zogenaamde villeuze adenomen (dit is een weefselkenmerk) en proximaal (rechts) gelokaliseerde adenomen, maar ook patiëntkarakteristieken, zoals geslacht en leeftijd. Het feit dat al deze voorspellende factoren bekend zijn, betekent dat het mogelijk is om adenoompatienten in een groot aantal risicogroepen te verdelen. Vervolgens kunnen de surveillance-aanbevelingen zorgvuldig op het risico van de patiënt worden afgestemd. De meeste surveillancerichtlijnen houden echter maar rekening met één of enkele factoren en stemmen hun aanbevelingen dus maar beperkt af op het risico van de patiënt. In een eerdere studie, hebben we een score ontwikkeld aan de hand waarvan adenoompatienten - op basis van alle relevante karakteristieken van adenomen verwijderd tijdens een eerste colonoscopie - in risicogroepen verdeeld kunnen worden: de 'adenoom risico score' (ARS). De ARS die kan worden behaald loopt van 0 (laag risico) tot 5 (hoog risico).
In **Hoofdstuk 3** van dit proefschrift, hebben we voor elke combinatie van ARS, geslacht en leeftijd het juiste interval voor een eerste surveillance colonoscopie bepaald. Deze analyse toonde aan dat het juiste surveillance interval sterk afhankelijk is van de ARS van een patiënt en minder van geslacht en leeftijd. Waar sommige patiënten met ARS 0 pas na 10 jaar een colonoscopie hoeven te ondergaan, moeten sommige patiënten met risico score 4 of 5 al na 2 jaar een colonoscopie ondergaan. De analyse liet ook zien dat bestaande surveillancerichtlijnen er niet altijd in slagen colonoscopiën te richten op patiënten met het hoogste risico. Zo zou een vrouw van 60 jaar met 3 kleine, niet villeuze, distale adenomen op basis van de oude Nederlandse richtlijnen voor surveillance (die alleen gebaseerd zijn op het aantal adenomen dat is verwijderd) na 3 jaar een colonoscopie

moeten ondergaan, terwijl een even oude vrouw met 2 grote, villeuze proximale adenomen na 6 jaar een colonoscopie zou moeten ondergaan. Volgens onze analyse, zou de eerste vrouw (met een ARS van 1) echter na 7 jaar een colonoscopie moeten ondergaan, terwijl de tweede vrouw (met een ARS van 4 [corresponderend met een bijna 4 maal zo hoog risico]) na 3 jaar een colonoscopie zou moeten ondergaan: bijna exact het tegenovergestelde. De Nederlandse richtlijnen voor surveillance in adenoompatienten zijn in mei 2013 herzien op basis van de resultaten van deze analyse.

Intensievere colonoscopiescreening dan aanbevolen in Amerikaanse 65-plussers

Alle Amerikaanse richtlijnen voor DDK-screening bevelen een screeninginterval van 10 jaar aan voor screening door middel van colonoscopie. De 'US Preventive Service Task Force' en het 'American College of Physicians' bevelen daarnaast aan om mensen ouder dan 75 jaar, met een adequate screeningsgeschiedenis, niet langer te screenen. Ondanks deze aanbevelingen worden veel Amerikaanse 65-plussers vaker gescreend dan aanbevolen: 20% van alle 65-plussers met een negatieve screeningscolonoscopie, ondergaan binnen 5 jaar (in plaats van ná 10 jaar) een nieuwe screeningscolonoscopie en 25% van alle mensen met een negatieve screeningscolonoscopie na leeftijd 75 jaar ondergaan op latere leeftijd nog een screeningscolonoscopie.

In **Hoofdstuk 4** van dit proefschrift lieten we zien dat intensievere colonoscopiescreening dan aanbevolen in Amerikaanse 65-plussers slechts tot een kleine toename van de positieve gezondheidseffecten van screening leidt, vergeleken met de toename in de belasting en het aantal complicaties ten gevolge van screening. Wanneer de positieve gezondheidseffecten worden afgewogen tegen de negatieve gezondheidseffecten, blijkt dat intensievere screening dan aanbevolen vaak gepaard gaat met een netto verlies aan gezondheid in plaats van een netto winst. Het enige scenario dat leidt tot een netto winst aan gezondheid (5-jaarlijkse in plaats van 10-jaarlijkse colonoscopiescreening) was niet kosteneffectief: elk gewonnen levensjaar ging ten koste van 909 colonoscopiën en $711.000.

DDK-screening in niet eerder gescreende Amerikaanse ouderen

Sinds 2008 raadt de 'US Preventive Services Task Force' screening naar DDK af voor mensen ouder dan 75 jaar met een adequate screeningsgeschiedenis. Deze aanbeveling heeft ertoe geleid dat veel Amerikaanse artsen denken dat niemand ouder dan 75 jaar gescreend hoeft te worden. Omdat ouderen die nooit eerder gescreend zijn een hoger risico op DDK hebben dan ouderen met een adequate screeningsgeschiedenis, is het echter waarschijnlijk dat screening in deze groep langer effectief en kosteneffectief blijft. Mocht dit het geval zijn, dan kan het gebrek aan meer specifieke aanbevelingen voor de juiste stopleeftijd voor screening ertoe leiden dat niet eerder gescreende ouderen toegang tot screening wordt ontzegd zonder duidelijke reden.

In **Hoofdstuk 5** van dit proefschrift, toonden we aan hoe belangrijk het is om de screeningsgeschiedenis van een persoon in acht te nemen bij het maken van de beslissingen omtrent het stoppen van screening naar DDK. We lieten zien dat DDK-screening in niet eerder gescreende ouderen kosteneffectief blijft tot ver boven een leeftijd van 75 jaar. In niet eerder gescreende ouderen zonder comorbiditeit bleek screening kosteneffectief te blijven tot en met leeftijd 86 jaar, in ouderen met matig-ernstige en ernstige comorbiditeit bleek screening kosteneffectief te blijven tot en met respectievelijk 83 en 80 jaar. In niet eerder gescreende ouderen zonder comorbiditeit was colonoscopiescreening het meest effectief en nog steeds kosteneffectief tot en met leeftijd 83 jaar, terwijl op leeftijd 84 jaar sigmoïdoscopie- en op leeftijden 85 en 86 jaar iFOBT-screening aanbevolen zou moeten worden. In ouderen met matig-ernstige comorbiditeit zou tot en met leeftijd 80 jaar colonoscopiescreening aanbevolen moeten worden, terwijl op leeftijd 81 jaar sigmoïdoscopie- en op leeftijden 82 en 83 jaar iFOBT-screening aanbevolen zou moeten worden. In ouderen met ernstige comorbiditeit zou tot en met leeftijd 77 jaar colonoscopiescreening aanbevolen moeten worden, terwijl op leeftijd 78 jaar sigmoïdoscopie- en op leeftijden 79 en 80 jaar iFOBT-screening aanbevolen zou moeten worden.

Het personaliseren van colonoscopiescreening voor Amerikaanse ouderen

De effectiviteit van screening naar DDK hangt niet alleen af van de screeningstrategie die wordt gekozen, maar ook van de karakteristieken van de personen die gescreend worden. Screening is effectiever in personen met een hoog risico op DDK, dan in personen met een laag risico op DDK en in personen met een gunstige levensverwachting, dan in personen met een ongunstige levensverwachting. Hoewel artsen zich er doorgaans van bewust zijn dat andere factoren dan leeftijd de effectiviteit en kosteneffectiviteit van screening beïnvloeden, baseren veel van hen de beslissing om een persoon te screenen primair op zijn of haar leeftijd: personen van 75 jaar of jonger worden doorgaans gescreend, personen ouder dan 75 jaar doorgaans niet.

In **Hoofdstuk 6** van dit proefschrift, legden we uit waarom aanbevelingen voor screening in ouderen gepersonaliseerd moeten worden en hoe modellen gebruikt kunnen worden om tot gepersonaliseerde screeningsaanbevelingen te komen. In **Hoofdstuk 7** ontwikkelden we gepersonaliseerde aanbevelingen voor colonoscopiescreening in Amerikaanse ouderen. Om tot deze aanbevelingen te komen, bepaalden we de kosteneffectiviteit van colonoscopiescreening naar leeftijd, geslacht, etniciteit, screeningsgeschiedenis, achtergrondrisico op DDK (dat wil zeggen: het niveau van blootstelling aan risicofactoren voor DDK) en comorbiditeitsstatus. Uit deze analyse bleek dat colonoscopiescreening in sommige eerder gescreende personen met een laag achtergrondrisico niet meer kosteneffectief is op leeftijd 66 jaar, terwijl screening in andere, niet eerder gescreende, gezonde personen met een hoog achtergrondrisico kosteneffectief blijft tot en met

leeftijd 88 jaar. In **Hoofdstuk 8** kwantificeerden we de impact die het personaliseren van colonoscopiescreening onder ouderen zou kunnen hebben op het niveau van de Amerikaanse populatie. Hiertoe modelleerden we de Amerikaanse populatie 65-plussers in 2013 (39,6 miljoen mensen) en vergeleken we de gezondheidseffecten en kosten van uniforme, op leeftijd gebaseerde, screening tot en met leeftijd 75 jaar met 4 scenario's van gepersonaliseerde screening met een toenemende intensiteit van screening. Deze analyse toonde aan dat gepersonaliseerde screening efficienter is dan uniforme, op leeftijd gebaseerde, screening. Wanneer uitgegaan wordt van de kosten van uniforme, op leeftijd gebaseerde screening, kan gepersonaliseerde screening 21.200 extra sterfgevallen aan DDK voorkomen (+11%). Andersom kan het aantal DDK sterfgevallen dat voorkomen wordt door middel van uniforme, op leeftijd gebaseerde, screening behaald worden tegen substantieel lagere kosten (-$1.500M [-84%]).

Op basis van de resultaten van de studies beschreven in dit proefschrift, trekken we de volgende conclusies:

- Modellen kunnen gebruikt worden om de resultaten van gerandomiseerde gecontroleerde trials te extrapoleren en een belangrijke rol spelen bij het informeren van beslissingen over screening. (**Hoofdstuk 2**)
- Het juiste interval voor een eerste surveillance colonoscopie bij adenoompatiënten hangt in belangrijke mate af van de 'adenoom risico score' van een patiënt (het risico op DDK gegeven alle relevante karakteristieken van adenomen verwijderd tijdens een eerder colonoscopie). Waar sommige patiënten met risico score 0 pas na 10 jaar een colonoscopie hoeven te ondergaan, moeten sommige patiënten met risico score 4 of 5 al na 2 jaar een colonoscopie ondergaan. Het personaliseren van surveillance op basis van de 'adenoom risico score' zorgt voor een efficiënter gebruik van surveillance colonoscopiën. (**Hoofdstuk 3**)
- Screening heeft behalve positieve effecten ook negatieve effecten op de gezondheid. Meer screening is hierdoor niet altijd beter. Intensievere colonoscopiescreening dan aanbevolen in Amerikaanse 65-plussers met een gemiddeld risico op DDK, bijvoorbeeld, heeft vaak een negatief netto effect op de gezondheid en is nooit kosteneffectief. (**Hoofdstuk 4**)
- De effectiviteit en kosteneffectiviteit van screening hangen in belangrijke mate af van de screeningsgeschiedenis van een persoon. In tegenstelling tot screening van personen met een adequate screeningsgeschiedenis, blijft screening van niet eerder gescreende personen kosteneffectief tot ver boven leeftijd 75 jaar. (**Hoofdstuk 5**)
- Modellen kunnen gebruikt worden om schattingen van het risico op kanker, de levensverwachting en de werkzaamheid van screening te integreren en te vertalen in schattingen van de effectiviteit en kosteneffectiviteit van screening in een bepaald individu. Op die manier kunnen aanbevelingen voor screening gepersonaliseerd worden. (**Hoofdstuk 6**)

- De effectiviteit en kosteneffectiviteit van screening hangen niet alleen sterk af van de screeningsgeschiedenis van een persoon, maar ook van zijn comorbiditeitsstatus en achtergrondrisico op DDK. (**Hoofdstuk 7**)
- De potentiële effecten van het personaliseren van screening voor ouderen zijn groot. Op het niveau van de Amerikaanse populatie kan het personaliseren van screening leiden tot tienduizenden extra voorkomen sterfgevallen aan DDK of een besparing van ongeveer $1.500M. (**Hoofdstuk 8**)

Op basis van deze conclusies komen we tot de volgende aanbevelingen:

- Modellen zouden vaker gebruikt moeten worden om beslissingen over screening te informeren.
- Bij het aanbevelen van intervallen voor colonoscopie surveillance moeten alle relevante karakteristieken van eerder verwijderde adenomen in acht genomen worden. Dit kan gerealiseerd worden door het gebruik van de 'adenoom risico score'.
- Bij het evalueren van screening moeten effecten op de kwaliteit van leven meegenomen worden. Het negeren van deze effecten kan leiden tot verkeerde beslissingen.
- Intensievere screening dan aanbevolen kan negatieve gevolgen hebben voor de gezondheid. De huidige praktijk van intensievere colonoscopiescreening dan aanbevolen in Amerikaanse 65-plussers moet ontmoedigd worden.
- Beslissingen over het stoppen van DDK-screening moeten niet alleen gemaakt worden op basis van de leeftijd van een persoon. De screeningsgeschiedenis, het achtergrondrisico op DDK en de comorbiditeitsstatus van de persoon moeten ook meegewogen worden.
- Barrières voor het implementeren van gepersonaliseerde DDK-screening en surveillance in adenoompatiënten moeten weggenomen worden.

About the author

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CURRICULUM VITAE

Frank van Hees was born on August 26th 1983, in Nijmegen, the Netherlands. In 2001, he completed his secondary school education (Atheneum; cum laude) at the Hendrik Pierson College in Zetten. That same year, he started studying Molecular Life Sciences at the Radboud University in Nijmegen. After one year, he switched to the study Biomedical Sciences, also at the Radboud University in Nijmegen. During the final year of this study: 2007, he started working at the Department of Public Health of the Erasmus Medical Center in Rotterdam, where he evaluated the cost-effectiveness of cervical cancer screening using a microsimulation model. During that year, he obtained his Master of Science degree with specializations in Epidemiology and Health Technology Assessment. In 2009, he started working a the Centre for Prevention and Health Services Research of the Dutch National Institute for Public Health and the Environment in Bilthoven, where he wrote policy reports on promising developments in screening for diabetes and cancer. In 2010, he returned to the Department of Public Health of the Erasmus Medical Center to evaluate the cost-effectiveness of colorectal cancer screening using a microsimulation model. Meanwhile he obtained a Postgraduate Certificate in Health Economic for Health Care Professional from the University of York. The results of his research during his second period at the Department of Public Health of the Erasmus Medical Center are described in this thesis.

Currently, Frank works at BresMed (http://www.bresmed.co.uk): an independent health economic and outcomes research consultancy. At BresMed, he designs, conducts, and reports economic evaluations for a wide range of clients, including top pharmaceutical companies, medical device manufacturers and small biopharma at the global, European and affiliate level.

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PHD PORTFOLIO

Name PhD student:	Frank van Hees
Erasmus MC Department:	Public Health
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PhD period:	2010–2016
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PhD training	Year	Workload
General academic skills		
Postgraduate Certificate in Health Economics for Health Care Professionals. Department of Economics and Related Studies, University of York, York, the United Kingdom	2012-2014	60 ECTS*
Internal writing course. Department of Public Health, Erasmus MC, Rotterdam, Netherlands	2011	40 hours
Planning and Evaluation of screening. Netherlands Institute for Health Sciences, Erasmus MC, Rotterdam, the Netherlands	2007	40 hours
Presentations		
International Cancer Screening Network Meeting, Rotterdam, the Netherlands	2015	40 hours
Cancer Intervention and Surveillance Modeling Network Meetings, various locations in the United States	2010-2013	180 hours
South Carolina Screening Program Initiative Meeting, Columbia, SC, the United States.	2012	20 hours
International Cancer Screening Network Meeting, Sydney, Australia	2012	20 hours
Working group memberships		
Junior researcher representative; section Early Detection 2	2013	48 hours
Substitute member of the working group: Monitoring and Evaluation of the Dutch National Colorectal Cancer Screening Program	2010-2011	48 hours
Attendance to international conferences		
International Cancer Screening Network Meeting, Rotterdam, the Netherlands	2015	24 hours
International Cancer Screening Network Meeting, Sydney, Australia	2015	24 hours
Seminars and workshops attended		
[Symposium nieuwe richtlijn economische evaluaties; verduidelijking en verdieping], Amsterdam, the Netherlands	2016	8 hours
Seminars at the Department of Public Health, Erasmus MC, Rotterdam, the Netherlands	2010-2015	100 hours
Symposium on the Economics of Cancer Research, Galway, Ireland	2013	8 hours
[Nationaal symposium: colorectaal carcinoom en de toegevoegde waarde van colonscreening], Oestgeest, the Netherlands	2011	8 hours
Teaching		
Supervising other researchers	2014-2015	100 hours
Marking essays by medical students	2015	20 hours

*1 ECTS = 28 hours