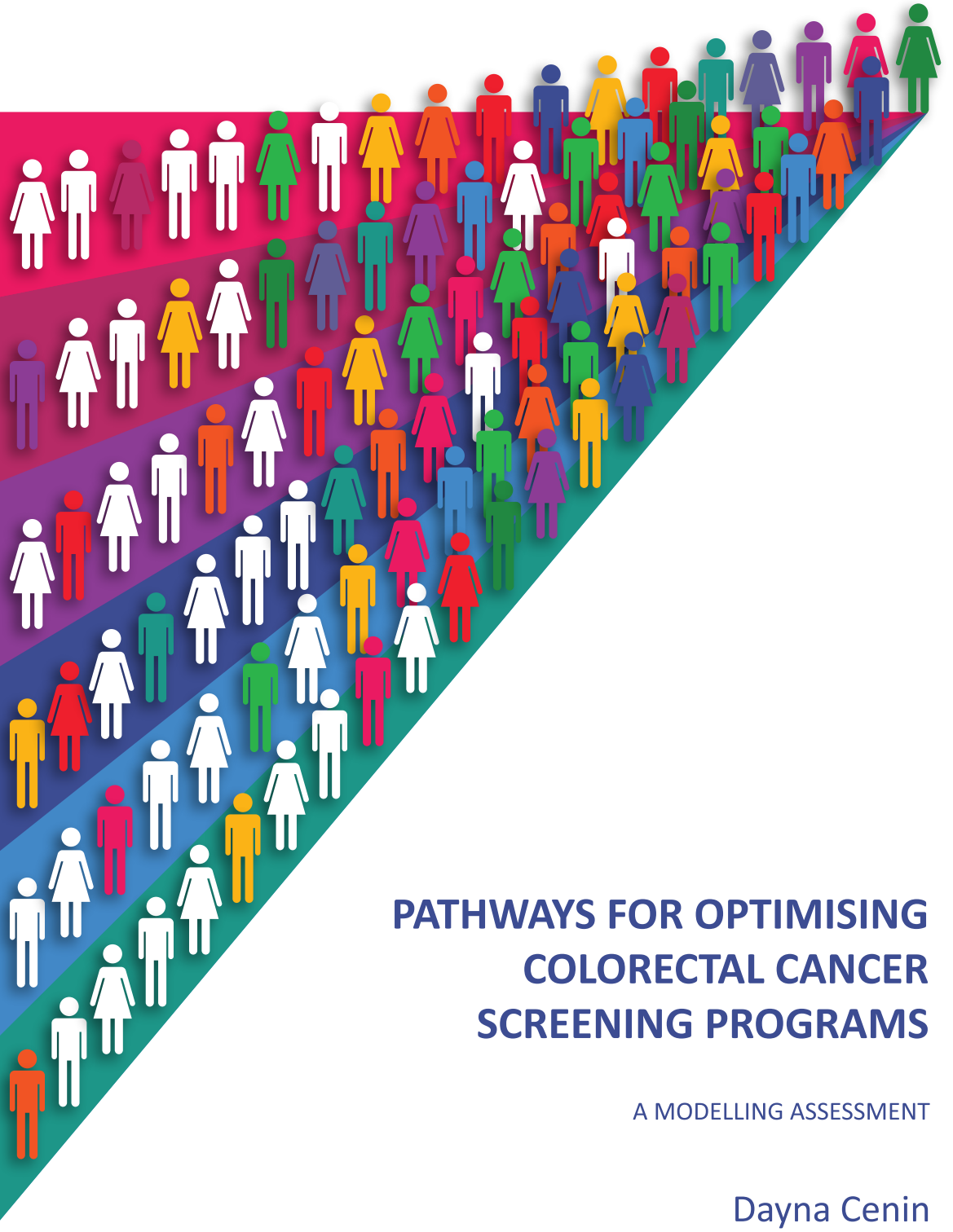

PATHWAYS FOR OPTIMISING COLORECTAL CANCER SCREENING PROGRAMS

A MODELLING ASSESSMENT

Dayna Cenin

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Dayna Rene Cenin

Pathways for Optimising Colorectal Cancer Screening Programs: a modelling assessment
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PATHWAYS FOR OPTIMISING COLORECTAL CANCER SCREENING PROGRAMS

A MODELLING ASSESSMENT

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een model evaluatie

Proefschift

to obtain the degree of Doctor from the
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For Nor Nor

You always believed I could do anything.

I miss you more than words.

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GENERAL INTRODUCTION

COLORECTAL CANCER: A GLOBAL PUBLIC HEALTH PROBLEM

EPIDEMIOLOGY

INCIDENCE

Colorectal cancer is an important global public health issue. With over 1.8 million new diagnoses in 2018, colorectal cancer was the third leading cause of cancer incidence, representing approximately 10% of the global cancer burden (Figure 1a).[1-3] Colorectal cancer incidence increases steeply with age, especially in those aged above 50 year and the median age at diagnosis is 66-70 years in developed countries.[4, 5] At younger ages, colorectal cancer is rare and is generally associated with inherited genetic mutations.[6] Nonetheless, there is a growing body of evidence that colorectal cancer incidence in those under 50 is increasing.[7-10] Incidence is consistently higher in males than in females,[1-3] however globally there is significant variation (Figure 2).[1-3] In 2018, the estimated age-standardised incidence by region ranged from as low as 1.7 cases per 100,000 for males in Africa to 70.6 per 100,000 in Europe, and from 0.5 to 39.3 per 100,000 in the same regions for females.

Traditionally thought of as a disease of the "western world", incidence of colorectal cancer is rising in populations historically considered to be at low risk. This change is largely a result of temporal trends such as population ageing and improved standards of living, which has resulted in the adoption of the Western lifestyle including changes in dietary habits and a rise in modifiable risk factors such as smoking, alcohol consumption, obesity, and lack of physical activity in these populations.[11-14] Conversely, incidence is stabilising or declining in many high income countries, partly due to the implementation of screening programs.[14, 15]

Although individuals in westernised countries generally experience greater risk of colorectal cancer (Figure 2), globally the overall burden of colorectal cancer is unevenly distributed.[1-3] Increased incidence, coupled with large population size means that countries like China are noteworthy contributors to the global burden. In 2018, China accounted for approximately 28.2% of colorectal cancer cases. In comparison, Australia and the Netherlands contribute just 1.0% and 0.8% respectively.

MORTALITY

In 2018, more than 880,000 individuals died from colorectal cancer (Figure 1b), making it the second leading cause of cancer-related deaths.[1-3] This is despite increasing awareness of the disease and its impact among researchers, policymakers and the general public. Although mortality is considerably lower than incidence, like incidence, the burden is unevenly distributed with wide ranges in estimated age-standardised mortality.[1-3] Despite higher individual rates of mortality, Australia and the Netherlands each accounted for just 0.7% of

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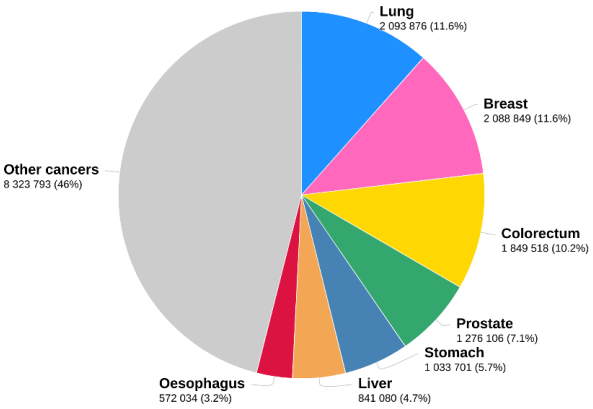

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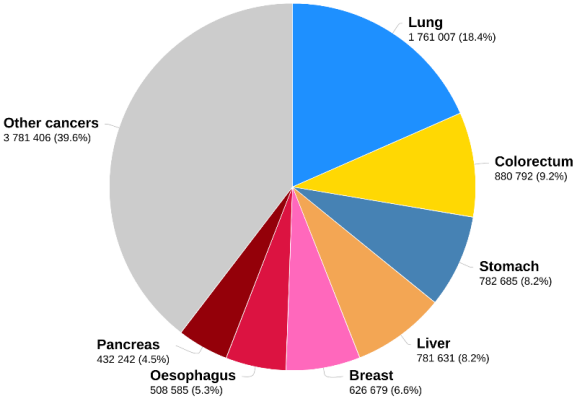

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Data source: Globocan 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

Figure 1: Estimated worldwide cancer a) incidence and b) mortality for males and females of all ages in 2018.[1-3]

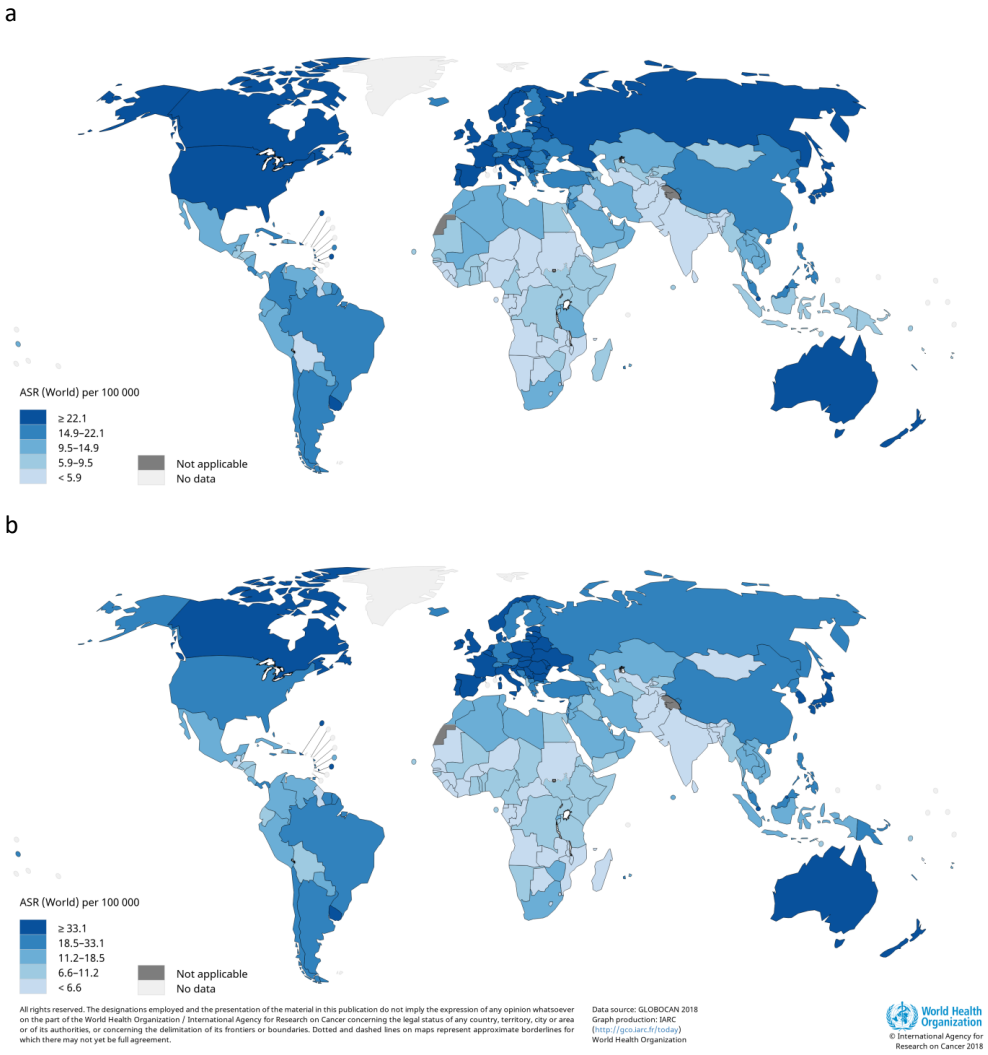

Figure 2: Estimated Age-standardised incidence rates (World) for a) females and b) males of all ages in 2018.[1-3]

deaths in 2018. In the same period, China, due to its large population, contributed a significantly greater proportion accounting for approximately 28.1% of colorectal cancer deaths.

Temporal trends show that mortality is increasing in countries like China, while in more developed countries mortality rates are declining.[14] This decline in mortality in developed countries is multifaceted and can be attributed to improved survival due to earlier diagnosis of colorectal cancer as a result of screening[16, 17] and advances in our understanding of the disease. This has resulted in improved surgical and adjuvant therapy and the adoption of best practice in cancer treatment and management of colorectal cancer.[18-20] Increases in mortality, in countries like China may reflect issues with health infrastructure, disparities in access to cancer care and limited or no access to early detection and appropriate treatment.[21, 22]

Given demographic projections and ongoing societal and economic developments in many low-and middle-income countries the global burden of colorectal cancer is expected to increase dramatically. By 2040, colorectal cancer incidence is projected to increase by 70% to more than 3.1 million new cases, while mortality will increase by more than 80% to an estimated 1.6 million colorectal cancer deaths.[2, 23, 24]

NATURAL HISTORY

Colorectal cancer develops from benign precursor lesions or polyps in the colorectum, the final section of the gastrointestinal tract that performs the vital task of absorbing water and nutrients while converting digested food into faeces. Until recently, it was believed that colorectal cancer only developed from a lesion or polyp known as an adenoma, in what is known as the adenoma-carcinoma sequence. However, it is now recognised that this so-called 'conventional pathway' is only one way in which colorectal cancer develops.[25-27] Serrated polyps are now considered an important premalignant lesion with colorectal cancer developing through the serrated polyp pathway. Although there remains debate about the magnitude of the impact of this pathway, estimates suggest it accounts for between 15-30% of colorectal cancers.[26, 27]

Conventional adenomas and serrated lesions can vary in size and conventional adenoma can also vary in shape (pedunculated (stalked), elevated, flat, oblong or depressed). Serrated lesions can be divided in three subgroups: hyperplastic polyps, sessile serrated polyps and traditional serrated polyps. Hyperplastic polyps are thought to be non-malignant and thus will not develop into colorectal cancer. Sessile serrated polyps and traditional serrated polyps are histologically distinguishable from conventional adenomas by their saw-tooth configuration. Data on the natural history of this pathway is limited and the lesions can be difficult to detect during colonoscopy due to their discrete appearance and frequent covering of mucous.[26, 28]

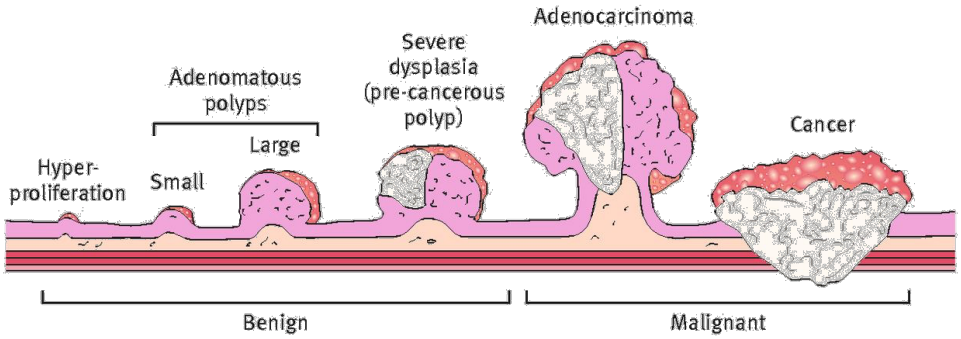

Figure 3: Traditional Adenoma-Carcinoma sequence. (image courtesy of BMJ)[29]

Adenomas are common – approximately 20-50% of the population will develop one or more adenomas during their lifetime.[26] Despite the high risk of developing an adenoma, lifetime risk of developing colorectal cancer is much lower, ranging from 5-8% in westernised countries.[5, 26, 30] Identifying those lesions which are truly at risk of developing into cancer remains a serious and clinically relevant challenge, as it is necessary to avoid both overtreatment and undertreatment.[28] To date, serrated lesions have been over-represented in interval cancers.[31, 32]

High risk characteristics of polyps include size (diameter >1cm), number, proximal location, and the presence of dysplasia.[26, 33] For adenomas, histology (tubular or villous) is also important while for serrated lesions, molecular features, such as methylation, BRAF gene mutations and micro-satellite instability also increase risk.[32]

The transition from a small polyp into colorectal cancer is characterised by a multistep process which involves a series of histological, morphological and genetic changes over time. Although the life history of the sequence is likely to be highly variable, the progression from an asymptomatic polyp or lesion to a symptom detectable colorectal cancer takes on average 10-15 years.[34] Microsimulation models suggest this dwell time to be between 10-25 years.[35] Encouragingly, colorectal cancer is largely preventable if it, or its precursor lesion, is detected and treated in the early stages. The long latent period provides a substantial window of opportunity to achieve this (see Secondary Prevention).

As lesions progress, symptoms may become present but they are often non-specific in nature: abdominal pain, change in bowel habits, rectal blood loss, or weight loss.[36] By the time the signs of colorectal cancer become apparent, the disease has usually progressed to an advanced stage.

SURVIVAL

Survival from colorectal cancer is highly dependent on the stage of tumour development at diagnosis, as well as the treatments that follows. Although survival has steadily improved during the past decades in many countries,[37] overall five year survival estimates vary noticeably around the world; reaching between 60-70% in high-income countries, such as Australia,[5] Canada, the USA,[4, 38] and several European countries,[37, 39, 40] while remaining below 50% in low-income settings, including China.[41] However, it is clear that improved survival is expected with earlier detection and diagnosis of colorectal cancer (Table 1).[5, 38, 39] The detection of colorectal cancer before it develop into its later stages has a profound effect on mortality; significantly fewer patients with late stage colorectal cancer survive five years post diagnosis, compared to those diagnosed at earlier stages.

Table 1: Estimate of five-year survival rate post diagnosis at each stage in the USA, Australia and the Netherlands.

Stage	USA[38]	Australia[5]	Netherlands[39]
I	88	99	94
II	80	89	85
III	66	71	72
IV	13	13	12
Unknown	39	57	29

Early detection and diagnosis also improve treatment outcomes and lessens the need for expensive and invasive therapies. Left in situ in patients who refuse polypectomy, adenomas are more likely to go on and develop colorectal cancer[42] while the removal of adenomatous polyps, coupled with regular and ongoing surveillance, has been shown to reduce the risk of colorectal cancer.[43]

Further improvements in survival will occur as a result of earlier detection through organised screening of asymptomatic individuals and this will have a significant impact on five-year survival rates. In addition, advances in colorectal cancer treatment will continue to make incremental improvements in survival but this will likely be at a considerable financial cost.

AETIOLOGY OF COLORECTAL CANCER

There is no single risk factor or cause that accounts for the majority of cases of colorectal cancer. Rather, there are a range of factors that are known to effect risk. Encouragingly, many of the factors that increase an individual's risk are, in principle, modifiable. These risk factors

are common in nature and therefore account for a larger proportion of the disease burden at the population-level, despite lower relative risks.

MODIFIABLE RISK FACTORS

Modifiable risk factors are things that an individual can change in order to reduce their risk of a given disease. In relation to colorectal cancer these modifiable risk factors include diet, alcohol consumption, smoking, obesity, and physical (in)activity.[44-47]

There is convincing evidence that consumption of red and processed meats increases risk of both adenomas and colorectal cancer.[48-51] In addition, consumption of alcoholic drinks[52] and cigarette smoking[53] are also convincingly associated with an increased risk for colorectal cancer. A clear dose response mechanism has been established for each of these risk factors, highlighting that as consumption of these substances increases, so too does the risk of colorectal cancer. In addition, there is a well-established link between obesity (body and abdominal fatness) and increased colorectal cancer risk,[54] such that those with the largest body mass index or waist circumference are at greatest risk.

In contrast, participation in all types of physical activity has been convincingly shown to reduce the risk of colon cancer, although no conclusion has been drawn for rectal cancer.[55] Like those factors that increase colorectal cancer risk, there is a clear dose response relationship with those participating in the highest level of activity being at significantly lower risk compared with those who are least active. In addition, dietary fibre[56] and intake of calcium (either through supplementation[57] or consumption of milk and other dairy products[58]) are considered to be protective and are associated with probable reduction in colorectal cancer risk.

NON-MODIFIABLE RISK FACTORS

There are a range of non-modifiable factors that increase an individual's colorectal cancer risk. The most well-known non-modifiable risk factors are male sex and advancing age.[1, 59] In addition, several diseases can lead to an increased colorectal cancer risk. These include inflammatory bowel diseases (Crohn's disease[60] and ulcerative colitis[61]) type II diabetes[62, 63] and cystic fibrosis.[64, 65] There is emerging evidence to suggest that infection with *Helicobacter pylori*[66] and *Fusobacterium nucleatum*[67] may also be associated with an increased risk of colorectal cancer.

Aside from the above factors, possibly the most important non-modifiable risk factor for colorectal cancer is family history. Individuals with a positive family history, but without an identified cancer syndrome, are at increased risk for developing the disease. The risk increases with the number of relatives diagnosed with colorectal cancer, the closeness of genetic relationship of the diagnosed relative(s), and the age of diagnosis of the relative(s). For example, for those who have a first-degree relative with colorectal cancer diagnosed at an

early age (below age 55) or two close relatives with colorectal cancer, irrespective of the age at diagnosis, colorectal cancer risk has been found to be three- to six-fold greater than the average population.[68] This risk increases to seven- to ten-fold when there are at least three first- or second-degree relatives with colorectal cancer, with at least one diagnosed under 55 years or at least three first-degree relatives with colorectal cancer diagnosed at 55 years or older.

In addition, there are several familial genes that substantially increase an individual's risk of early-onset colorectal cancer when they are inherited in a mutated form. These genes are associated with Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer), familial adenomatous polyposis (also known as FAP) and MUTYH-associated polyposis. However, together these inherited genetic mutations account for less than 6% of all colorectal cancer cases[69, 70] and do not fully explain why family history is a risk for colorectal cancer.[71, 72] This suggests that other factors associated with heritability may play a role, including dietary, lifestyle and environmental factors,[73] mutations in yet-to-be-discovered colorectal cancer susceptibility genes[74] and common, low risk variants (or single-nucleotide polymorphisms [SNPs]).[75-77] Although in isolation, SNPs are only weakly associated with colorectal cancer risk, individuals with multiple SNPs can have a substantially increased risk. In addition, they explain substantial variation in heritability risk due to their relatively high prevalence in the population.[77-81] Research to date suggests that SNPs explain between 9.6-23.1% of familial risk.[82]

Interventions to Reduce Colorectal Cancer Incidence and Mortality

From a public health perspective, reducing overall risk and thereby preventing disease is extremely desirable. This can be achieved by using proven and acceptable prevention strategies.

Primary prevention

Our comprehensive knowledge about risk and protective factors provides significant opportunity for primary prevention strategies to reduce the incidence of colorectal cancer in our population. As 45-60% of all colorectal cancers can be attributable to unhealthy lifestyle factors,[83-85] encouraging a healthy lifestyle, which encompasses a balanced diet and adequate physical activity, seems pertinent in this quest. As many of these risk factors are shared with other common chronic diseases, including diabetes and cardiovascular diseases, interventions to reduce their impact will provide the additional benefit to both individuals and the population as a whole.

In addition to encouraging a healthy, active lifestyle, there is evidence of effective chemoprevention of colorectal cancer using specific drugs. The best known chemoprevention

medications are non-steroidal anti-inflammatory drugs such as aspirin[86] and hormone replacement therapy in postmenopausal women.[87] Long-term use (greater than five years) of at least 75 mg per day of aspirin has been demonstrated to reduce colorectal cancer risk.[86] Although aspirin has the potential to lower colorectal cancer risk, usage may also result in serious adverse side effects including haemorrhagic strokes and gastrointestinal complications such as peptic ulcers and bleeding.[88] Despite these risks, the balance of benefits to harms is considered favourable for those age 50 to 70 years at average risk of colorectal cancer and aspirin should be considered as a preventative measure in this population.[68, 89] Aspirin should be encouraged for individuals with Lynch syndrome and familial adenomatous polyposis where surgery is inappropriate.[68]

Secondary prevention/Screening

Secondary prevention focuses on the early detection of a disease to reduce disease-specific morbidity and mortality. For colorectal cancer, secondary prevention is predominantly achieved through screening. As the primary focus of this thesis is screening, it will be discussed in greater detail than other forms of prevention.

Screening is a public health intervention where asymptomatic individuals are tested for signs of a disease. The aim of screening is to detect a disease in its early stages, before symptoms develop and the disease spreads, as early detection generally increases the chances of successful treatment and survival. An effective and acceptable screening program should lead to mortality reductions without causing significant harm to the participants.

Colorectal cancer is especially suitable for screening and is one of a handful of cancers where a screening program has been proven to be effective at reducing incidence and mortality. It is an attractive and viable option satisfying most of the World Health Organisation's criteria for a cancer screening program.[90] Early colorectal cancer is often asymptomatic and may be present for several years before signs and symptoms become apparent. During this time, non-visible (occult) bleeding may occur and premalignant lesions can be removed before they become cancerous or colorectal cancers can be detected at earlier stages. This is beneficial for two reasons. Firstly, the identification and removal of premalignant lesions results in reduced colorectal cancer incidence in the longer term,[91] the full effect of which may not been seen for several years.[92] Secondly, detection of colorectal cancer in its early stages means the disease is more curable and therefore chances of survival are better.[93-95] Compared to those who present with symptoms, a higher proportion of early stage cancers are detected in those who are screened.[96-98]

There are a range of acceptable, reliable and safe screening tools available for colorectal cancer screening. The most commonly used screening methods are stool-based tests and endoscopy methods. There are two types of stool-based occult blood tests, the guaiac faecal

occult blood test (gFOBT) and the faecal immunochemical test (FIT). Although the tests are similar in nature in that they both detect small traces of blood in the stool and they can be completed at home, the tests differ significantly. A gFOBT requires sampling over multiple days, individuals are asked to modify their diet, including restriction of red meat intake, and some medications must be stopped during the stool collection phase. These restrictions are not necessary when completing a FIT. This is partly because gFOBT tests for the presence of any blood, whereas the FIT is specific for human blood. In addition, the FIT is a quantitative test which allows the choice of preferred cut-off for a positive test (µg Hb/g faeces). This is an important consideration as it impacts the balance between true and false positive test results and impacts demand for diagnostic follow-up. Several large randomised control trials (RCTs) have shown that annual or biennial screening with gFOBT will reduce colorectal cancer mortality by 11-33%.[93-95, 99-103] As the FIT is considered to be superior to gFOBT, it is expected that the mortality reduction will be larger when this test is used.[104-106] While there are no RCTs to demonstrate this, the finding is supported by several observational studies.[107-109]

Two endoscopy methods are available, sigmoidoscopy and colonoscopy. Both methods inspect the colon using a flexible tube with a fibre optic camera. However, while colonoscopy inspects the entire colon, sigmoidoscopy only inspects the distal part. To date, only the effectiveness of sigmoidoscopy has been established with RCTs, with incidence reductions varying from 18-26% and mortality reductions from 22-31% (intention-to-treat analyses, higher estimate were obtained for per-protocol analyses). [110-115] Because both tests are very similar, and colonoscopy visualizes the same segments as sigmoidoscopy and more, it is expected to be at least as effective as sigmoidoscopy. Randomised controlled trials of colonoscopy screening are currently underway,[116] but this expectation is already supported by evidence from observational studies.[117-120]

In addition to the aforementioned screening tests, there are a range of other test options and emerging technologies for detecting colorectal cancer. These include blood based biomarker tests (Sept9[121]), imaging techniques (computed tomographic colonography[122] and double-contrast barium enema[123]), new endoscopy techniques (capsule endoscopy[124]) and stool based tests incorporating DNA testing (multi-target stool DNA[125]). However, to date, these tests are rarely used in organised screening programs.

Every screening test has its advantages and disadvantages. Stool tests are the least invasive, and cheapest screening option available and can be performed at home. However, the major drawback of screening with stool-based tests (and sigmoidoscopy) is that they have to be followed by a colonoscopy for diagnosis and removal of lesions, plus the lack of sensitivity for stool tests means the tests need to be repeated frequently (annually or biennially). While colonoscopy is able to diagnose and remove lesions, as a screening tool it is not without shortcomings. Compared to stool-based tests, it is expensive and invasive, bowel preparation

is burdensome and the test is associated with rare but serious complications.[126-130] Although the high sensitivity and specificity of the test means that the interval between repeated screening events is substantially longer (generally 10 years),[131] in many regions there is not enough capacity to screen all individuals in the target population with this test.

TERTIARY PREVENTION

Tertiary prevention aims to reduce or prevent further complications and health impact and improve quality of life after a diagnosis with colorectal cancer. For individuals with a colorectal cancer diagnosis, tertiary prevention encompasses available treatment options and encouraging activities post treatment that can help reduce the risk of recurrent cancer.

Significant advances have been made in colorectal cancer treatment over the last decades, which has resulted in improved survivorship.[37] The intensity, cost and effects of treatment depend on the stage and location of the cancer and may include surgery, radiotherapy, chemotherapy or a combination of these. Treatment of rectal cancer varies from that of colon cancer in terms of surgical technique, use of radiation therapy and the method of administration of chemotherapy.[132] Treatment is constantly evolving with new innovations and this, coupled with improvements in diagnostics, will lead to a continuous improvement in the survival of colorectal cancer patients.[37] However, such advancements come at considerable cost.

Several primary prevention factors have also been associated with improved outcomes and decreased risk of colorectal cancer-related death after a diagnosis and treatment of colorectal cancer. Maintaining a healthy bodyweight, being physically active, and eating a healthy diet can increase quality of life during chemotherapy and improve survival by reducing cancer-specific and overall mortality by up to 40%.[133, 134]

GLOBAL STATUS OF COLORECTAL CANCER SCREENING

The status of colorectal cancer screening varies widely around the world. Screening programs have predominantly been introduced in Western countries which generally have higher colorectal cancer incidence and more available resources. However, this is changing, with a growing number of middle income countries introducing screening in recent years.[135]

Screening programs for colorectal cancer can be classified as either opportunistic or organised, or as a combination of the two. In opportunistic screening programs, like the US, Germany and Switzerland, screening occurs on an ad hoc basis, usually through fee-for service reimbursement of physicians. In an organised screening program, like Australia, the Netherlands and some regions of China, there is a systematic process which invites a target population to participate in screening and ensures follow-up of those with a positive screening

test.[135] Although opportunistic and organised screening can yield similar uptake rates, organised programs have a greater potential to reduce cancer incidence and mortality, due to higher levels of population coverage and a centralised commitment to quality and monitoring.[136, 137] Moreover, the focus on quality assurance through each step in the organised screening process provides greater protection against the possible harms of screening, inappropriate use of resources and poor follow-up of those with a positive screen. In this way, organised screening programs are also more likely to be cost-effective.[137]

The different screening programs throughout the world reflect the uncertainty about which strategy is best and differences in decision-making processes. The decision to implement a screening program is a multi-faceted and complex process. The effectiveness of a screening program relies heavily on participation, which is largely determined by population preference.[132] Among other factors, participation in screening is affected by the expected and perceived burden of the test, the risk of complications and other harms and cultural beliefs of the screened individual.[135] Other than population preference, the choice of test needs to take into account several other aspects including: test sensitivity and specificity, resource capacity, costs and the harm-benefit ratio. In addition, screening starting age, stopping age and interval need to be considered.

MODELLING

USING MODELS TO ANSWER POLICY QUESTIONS

While indispensable, traditional methods of gathering empirical evidence of screening effectiveness, such as randomised control trials, case control and cohort studies, are not always feasible and are not without limitations. Although such methods are considered to provide accurate and reliable evidence, they do so under specific conditions that often differ from future daily application and may not be generalisable to other settings. In addition, such methods can only evaluate a limited number of interventions at a time, are expensive and time consuming – requiring several years of follow-up before the effectiveness (colorectal cancer incidence or mortality reduction) of the intervention can be evaluated. Finally, traditional methods usually have a limited follow-up time and as such they are unable to determine lifetime health effects and costs, which is necessary to determine the (cost-) effectiveness of screening. Moreover, as screening strategies can vary in a multitude of ways, with different screening tests, age ranges, screening intervals and referral threshold for follow-up testing, the options are so numerous that it is impossible to compare them all in the traditional way.

Decision models have been developed to allow for the evaluation of many different screening strategies – any number of screening strategies can be simulated and results generated in a

short time frame. Furthermore, models can be adjusted to reflect the setting of interest, taking into account colorectal cancer risk, life expectancy, resource availability and population preferences. These assumptions can also be adjusted to allow comparison of how outcomes of interest might change. Decision models therefore provide a useful tool to extrapolate evidence from traditional methods and address the question of which screening strategy is optimal given local conditions.[138] As such, models have great potential to assist in the development, guidance and decision making process of public health initiatives, including colorectal cancer screening programs.[139, 140]

In this thesis we have used two models to assist in answering policy questions for optimising colorectal cancer screening. The main model used is the MISCAN-Colon model which is described in more detail in the following section and in the **Model Appendix**. To establish the costs and effects of Lynch syndrome screening in the Australia, we developed a second, simplified, decision analysis model (**Chapter 1**).

MISCAN-COLON

Microsimulation Screening Analysis-Colon (MISCAN-Colon) is a well-established microsimulation model for CRC developed at the Department of Public Health, Erasmus University Medical Center.[141] In brief, the model first simulates the life histories of a hypothetical population of individuals from birth to death without screening for colorectal cancer. As the simulated individuals age, adenomas may arise, some may progress in size and some may develop into cancer. During each stage symptoms may present and a colorectal cancer diagnosed. The model then simulates the same population with screening. The introduction of screening potentially alters the simulated life histories through detection and removal of adenomas or through detection of colorectal cancer at earlier stages. By comparing the life histories of a simulated population being screened to the simulated population not screened, MISCAN-Colon quantifies the effectiveness and the costs of screening.

MISCAN-Colon is made of three components which consider demography assumptions, natural history assumptions, and screening assumptions (Figure 3). Where possible these assumptions are derived from literature, however, some natural history and screening assumptions are not readily available or are uncertain. When this is the case, model calibration is required to estimate these parameters or to reduce uncertainty. A more detailed description of the model can be found in the **Model Appendix**.

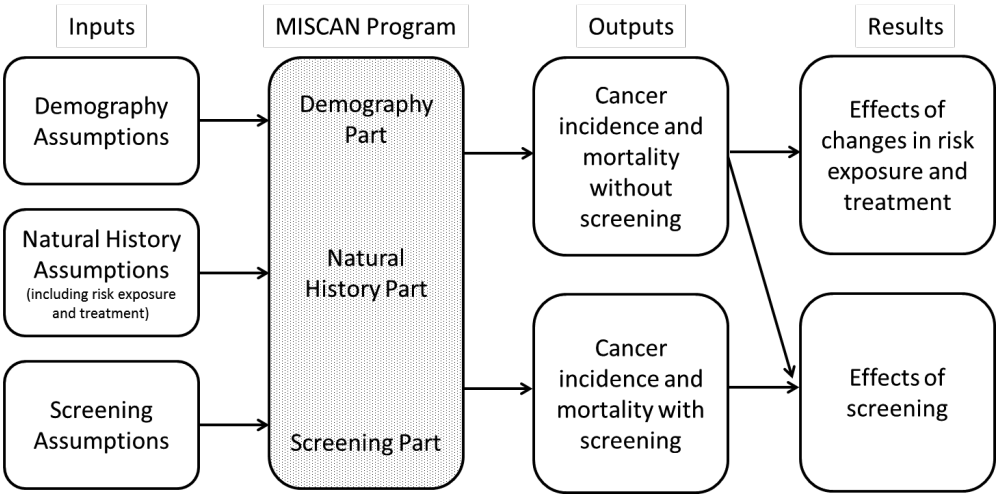

Figure 3: Structure of MISCAN-Colon.

PATHWAYS TO OPTIMISE COLORECTAL CANCER SCREENING PROGRAMS

Although colorectal cancer screening is widely implemented throughout the world, there is opportunity to improve screening programs through optimisation. The term optimisation suggests actions that will result in the best or most effective use of available resources. Screening outcomes can be optimised through various strategies, including the selection of appropriate program characteristics, implementation timeline and personalisation. In this thesis, we investigate several opportunities for optimising colorectal cancer screening addressing these broad topics.

OPTIMISATION OF UNIFORM SCREENING PROGRAMS

Optimising uniform screening programs (where the same strategy is applied to the entire target population) includes answering questions such as: Which screening test should be used? What age should screening start? What age should screening stop? Which screening interval should be used? How should the screening program be implemented? As the selection of inappropriate program characteristics may result in increased economic burden and a poorer balance of benefits to harms, this is an essential step in the decision-making process.

In this thesis, we investigated the optimal screening program to identify Lynch syndrome in those who are diagnosed with colorectal cancer (**Chapter 1**). Although Lynch syndrome is only responsible for a small proportion of colorectal cancers, carriers experience an increased lifetime risk for colorectal cancer and the mutation predisposes them to other cancers.[142] A

diagnosis of Lynch syndrome not only aids clinical decision-making, [70] it allows for cascade testing to identify at-risk family members. However, questions remain about the optimal screening test(s) and screening stop age.

In addition, we investigated opportunities to optimise the recently initiated colorectal cancer program in Shanghai, China.[143] Although implementation of colorectal cancer screening is underway in Shanghai, it appears little research has been done to determine the optimal screening strategy for this population. We therefore assessed the impact of varying program characteristics in terms of test selection, screening start and stop ages and screening interval (**Chapter 2**).

Once the decision to implement a screening program has been made, due consideration must be given to the implementation timeline. The answer to this question will not only be impacted by health system resources, especially colonoscopy capacity, it may also be constrained by political will, as was the case with the National Bowel Cancer Screening program in Australia. Initially slated to take nearly 30 years to achieve biennial screening with FIT for those age 50-74 year,[144] we investigated the impact of this protracted timeline and compared it to alternative implementation timelines to determine the optimal implementation timeline in terms of mortality reduction (**Chapter 3**).

Optimisation through personalisation

Current screening programs operate under a "one size fits all" methodology. However, as in the broader health context, there is increasing demand for a more personalised approach to screening. There is an increasing recognition that every person is unique and the benefits and harms of a given intervention are likely not equally distributed.

Existing guidelines for colorectal cancer screening only take into consideration an individual's age. Although there are separate screening recommendations for those with a positive family history and polyposis syndromes,[68] other known risk factors for colorectal cancer are not considered. Recommendations based solely on age do not consider the heterogeneity of the population, ignoring other factors that play a role in the determination of harms and benefits of screening. Risk of colorectal cancer is affected by several factors including screening history, lifestyle, comorbidity status and polygenic risk (determined by the number of SNPs). Our improved knowledge and understanding of these characteristics provides an opportunity for personalised screening that is tailored to the individual rather than the average population.

A personalised approach to screening would consider these additional risk factors and implies that those at higher risk are offered more intensive screening, while individuals at decreased risk are offered less intensive screening or may avoid screening altogether.[78,138] The subsequent reallocation of resources would likely result in their more efficient use and in theory would result in an improved balance of benefits and harms. Changing screening

programs in this way will increase the complexity of the programs, which could negatively impact participation and diminish any benefits. However, individuals at increased risk of colorectal cancer have been shown to be more compliant to screening guidelines than those at average risk,[145] suggesting that the provision of risk information may also assist in screening uptake.[146, 147]

In this thesis, we will investigate three methods of optimisation through personalisation. In **Chapter 4** addresses the question of which screening modality will result in the best outcomes for individuals based on their background risk of colorectal cancer. We assessed the potential benefits and harms of colorectal cancer screening with annual and biennial FIT, and once only sigmoidoscopy or colonoscopy.

In **Chapter 5** we investigate the relevance of general health status (comorbidity) and screening history to determine how these characteristics affected the optimal age to stop screening. We have previously shown that individuals with no comorbidities or those who have not previously participated in screening are likely to benefit from screening past the recommended stop-age, while those experiencing severe comorbid conditions should stop screening earlier than the recommended age.[148-150] However, an investigation considering the complexity and varied nature of screening history was lacking.

Finally, in **Chapter 6**, we investigate the potential benefit of determining an individual's risk of colorectal cancer based on polygenic risk and family history. Colorectal cancer risk was determined by individuals undergoing a polygenic test (used to reveal the presence or absence of single nucleotide polymorphisms (SNPs)) and an assessment for family history of colorectal cancer. Future colorectal cancer screening was determined based on this information. To determine the optimal screening program, we compared the costs and effects of personalised screening based on risk to uniform screening.

RESEARCH QUESTIONS AND THESIS OUTLINE

The aim of this thesis is to investigate opportunities for optimising colorectal cancer screening. The remainder of this thesis is divided into two parts. Part I explores opportunities for optimising the characteristics and implementation schedules of uniform all colorectal cancer screening programs, while Part II investigates opportunities to optimise screening programs through personalisation. The research questions addressed in each part are as follows:

Part I: Optimisation of uniform screening programs

a. What is the optimal screening program to identify Lynch syndrome for those who are diagnosed with colorectal cancer? (**Chapter 1**)
b. How could Shanghai optimise its colorectal cancer screening initiative? (**Chapter 2**)
c. What is the optimal implementation schedule of the National Bowel Cancer Screening Program in Australia? (**Chapter 3**)

Part II: Optimisation through personalisation

a. Which screening modality will offer the best outcomes to individuals based on their background risk of colorectal cancer? (**Chapter 4**)
b. How is age-to-stop screening affected by comorbidity and prior screening history? (**Chapter 5**)
c. Is it cost effective to implement risk stratified screening based on polygenic risk and family history compared to uniform, one size fits all, screening? (**Chapter 6**)

This thesis will conclude with a general discussion which will provide summary answers and further discussion of each of the above research questions – overall conclusions will be drawn and opportunities for future research will be suggested.

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PART I

OPTIMISATION OF UNIFORM SCREENING PROGRAMS

CHAPTER 1

COSTS AND OUTCOMES OF LYNCH SYNDROME SCREENING IN THE AUSTRALIAN COLORECTAL CANCER POPULATION

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ABSTRACT

Background and Aim: Individuals with Lynch syndrome are at increased risk of Lynch syndrome related cancers including colorectal cancer. Colorectal cancer tumour screening for mismatch repair (MMR) deficiency is recommended in Australia to identify Lynch syndrome, although its cost-effectiveness has not been assessed. We aim to determine the cost-effectiveness of screening individuals with colorectal cancer for Lynch syndrome at different age-at-diagnosis thresholds.

Methods: We developed a decision analysis model to estimate yield and costs of Lynch syndrome screening. Age-specific probabilities of Lynch syndrome diagnosis were based on Australian data. Two colorectal cancer tumour screening pathways were assessed (MMR immunohistochemistry followed by *MLH1* methylation (*MLH1*-Pathway) or *BRAF* V600E testing (*BRAF*-Pathway) if *MLH1* expression was lost) for four age-at-diagnosis thresholds – screening <50, screening <60, screening <70 and universal screening.

Results: Per 1,000 CRC cases, screening <50 identified 5.2 Lynch syndrome cases and cost $A7,041 per case detected in the *MLH1*-Pathway. Screening <60 increased detection by 1.5 cases for an incremental cost of $A25,177 per additional case detected. Screening <70 detected 1.6 additional cases at an incremental cost of $A40,278 per additional case detected. Compared to screening <70, universal screening detected no additional Lynch syndrome cases, but cost $A158,724 extra. The *BRAF*-Pathway identified the same number of Lynch syndrome cases for higher costs.

Conclusions: The *MLH1*-Pathway is more cost effective than *BRAF*-Pathway for all age-at-diagnosis thresholds. MMR immunohistochemistry tumour screening in individuals diagnosed with colorectal cancer aged <70 years resulted in higher Lynch syndrome case detection at a reasonable cost. Further research into the yield of Lynch syndrome screening in colorectal cancer patients ≥70 years is needed to determine if universal screening is justified.

INTRODUCTION

Colorectal cancer is a leading cause of cancer incidence and mortality in Australia.[1] While diagnoses are predominantly made in those at older ages, certain groups are at increased risk of early-onset colorectal cancer, largely as a result of inherited genetic mutations.[2] Lynch syndrome, an autosomal dominant condition, is a well-known genetic syndrome that increases risk of early-onset colorectal cancer (average age at diagnosis is 42 years for men and 47 years for women[3]). Caused by a germline mutation in one of the DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, or PMS2), Lynch syndrome is characterised by tumours that develop with high levels of microsatellite instability (MSI) and loss of expression of one or more of the MMR proteins, collectively referred to as tumour MMR deficiency.

Lynch syndrome is estimated to cause 1-3% of all colorectal cancer cases[4] with carriers experiencing accelerated carcinogenesis and an increased lifetime risk for colorectal cancer (10-47% by age 70 years[5-7] compared to 4-5%[8] in the general population) as well as predisposing individuals to other cancers.[9, 10] A diagnosis of Lynch syndrome aids clinical decision-making, including more extensive surgery and highly intensive long-term surveillance, which impacts patient outcomes.[4] Furthermore, a diagnosis permits cascade testing of at-risk family members to determine Lynch syndrome carrier status, thus enabling the commencement of intensive surveillance, which has been shown to lead to a reduction in Lynch syndrome related cancer incidence and mortality.[11-15]

Historically, Lynch syndrome testing has been guided using the Amsterdam or revised Bethesda criteria, both of which rely on obtaining an accurate family history[12] but have limited sensitivity and specificity for Lynch syndrome detection and are poorly implemented in routine clinical practice.[4, 16, 17] More recently, screening for Lynch syndrome has begun with tumour testing for MMR deficiency, prior to proceeding to germline MMR gene testing.[17-19] However, as MMR deficiency can also be caused by sporadic somatic hypermethylation of the *MLH1* gene promoter, tumours showing loss of *MLH1*/PMS2 protein expression require further testing (with either somatic *MLH1* methylation testing or *BRAF* V600E somatic mutation testing). If Lynch syndrome is still suspected after these tumour tests, genetic testing is offered in association with genetic counselling.

Within Australia, there is no national policy for Lynch syndrome screening; however, the National Health and Medical Research Council recently recommenced universal screening,[20] as a means of increasing identification of carriers and their at-risk relatives. While this recommendation is in line with other jurisdictions,[4, 21] no cost-effectiveness analyses have been conducted in the Australian setting and therefore the optimal screening strategy remains unclear.

We aimed to determine the cost-effectiveness of colorectal cancer tumour screening to identify Lynch syndrome at different age-at-diagnosis thresholds for two alternative tumour screening pathways using data from the Australian setting.

METHODS

OVERVIEW

We developed a decision analysis model to simulate Lynch syndrome screening in individuals with colorectal cancer to estimate the annual yield and costs associated with identifying Lynch syndrome in this population. For tumours exhibiting loss of *MLH1*/PMS2 expression by MMR immunohistochemistry (IHC), we tested two alternative pathways based on the follow-up tumour test (*MLH1* methylation test or a *BRAF* V600E mutation test). The primary focus was to determine how yield and cost would vary for each pathway by age-at-diagnosis and compare the incremental differences within and between the pathways.

DATA

Model parameters were based on two Australian research studies, the Australasian Colorectal Cancer Family Registry and the Melbourne Collaborative Cohort Study, which have been systematically characterised for Lynch syndrome. Detailed information about the recruitment strategy and tumour testing for these studies has been previously reported.[18] In brief, the Australasian Colorectal Cancer Family Registry recruited population-based incident colorectal cancer cases of individuals aged 18-59 years (eligible cases n=813) between 1997 and 2007. The Melbourne Collaborative Cohort Study is an Australian cohort study of 41,513 Melbourne residents recruited during 1990-1994 with age range at recruitment of 27-80 years. Data from 826 colorectal cancer cases diagnosed from recruitment until 2010 and aged 41-86 years at diagnosis were used for this analysis.

Colorectal cancer tumour samples from both studies were tested for MMR protein expression using IHC. Tumours showing MMR deficiency underwent germline testing to identify an MMR gene mutation and confirm Lynch syndrome diagnosis. For tumours demonstrating loss of *MLH1*/PMS2 expression by IHC, testing for tumour *MLH1* promoter hypermethylation and *BRAF* V600E somatic mutation were performed, and only those cases with no evidence of somatic *MLH1* methylation or *BRAF* wild-type underwent germline testing of *MLH1* gene.

DECISION ANALYSIS MODEL

Using TreeAge Pro 2016 (Williamstown, Massachusetts) we developed a decision analysis model to simulate Lynch syndrome screening. For tumours exhibiting loss of *MLH1*/PMS2 expression by MMR IHC, we assessed two screening pathways for identifying Lynch syndrome

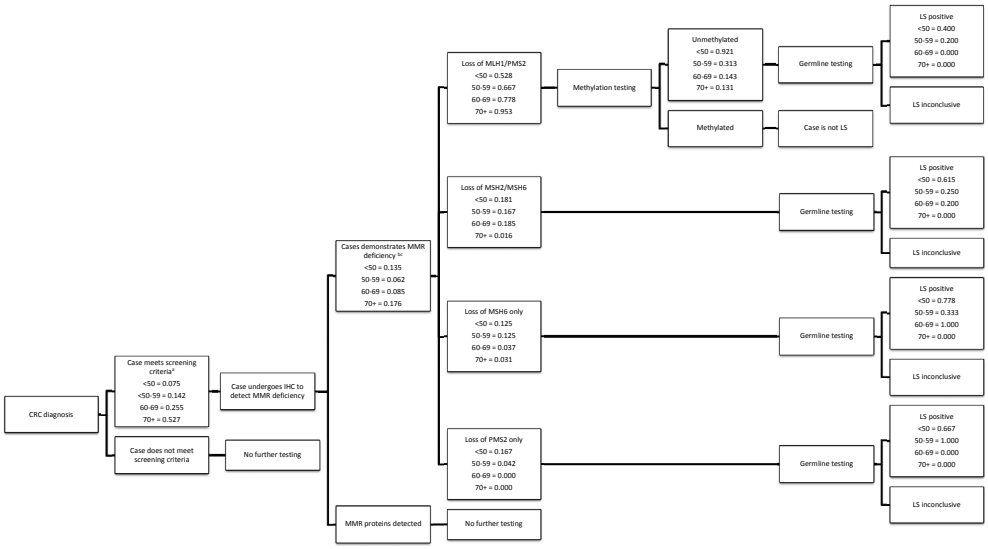

Figure 1.1: *MLH1*-Pathway with age-specific probabilities of progressing through the Lynch syndrome screening pathway.

Abbreviations: CRC, colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair; <60, age specific probabilities for CRC cases aged under 60 years; 60-69, age specific probabilities for CRC cases aged between 60 and 69 years; 70+, age specific probabilities for CRC cases aged over 70 years

a. Probability of meeting inclusion criteria in the age-restricted scenarios is based on the age distribution of CRC incidence data from 2008-2012.[8] Using screening <50 as the example, 7.6% of all CRC cases were eligible for testing with IHC to determine MMR deficiency status.

b. MMR deficiency is determined by testing with immunohistochemistry (IHC) and is defined as loss of MMR expression in one or more of the four MMR genes (MLH1, PMS2, MSH2, MSH6).

c. Progression through the pathway is based on probabilities derived from Buchanan and colleagues.[18] The probabilities differ slightly from those presented in Buchanan and colleagues as we considered LS cases which did not show MMR deficiency with IHC to be missed cases (3 cases in screening <60 and screening <70, 4 cases in universal). In addition, one LS case was excluded from the probabilities in our analysis because although the case showed PMS2 loss, genetic testing identified an MLH1 mutation and this could not be factored into the model.

   Using screening <50 as the example, of the eligible CRC cases who underwent IHC to determine MMR deficiency status, 13.5% were MMR deficient. Of these, 52.8% had loss of MLH1/PMS2, 18.1% had loss of MSH2/MSH6, 12.5% had loss of MSH6 only and 16.7% had loss of PMS2 only. Of the tumours with of MHL1/PMS2, 92.1% were unmethylated and went on for germline testing. LS was confirmed in 66.7% of CRC cases demonstrating MLH1/PMS2 loss (excluding *MLH1* methylated CRCs), 61.5% of the cases demonstrating MSH2/MSH6 loss, 77.8% of the cases demonstrating MSH6 loss and 66.7% of the cases demonstrating PMS2 only.

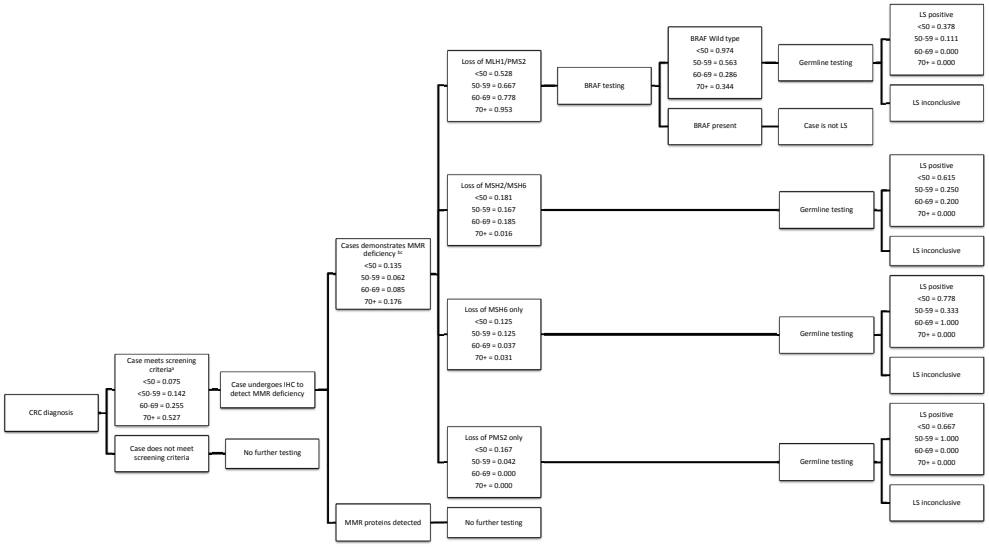

Figure 1.2: *BRAF*-Pathway with age-specific probabilities of progressing through the Lynch syndrome screening pathway.

Abbreviations: CRC, colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair; <60, age specific probabilities for CRC cases aged under 60 years; 60-69, age specific probabilities for CRC cases aged between 60 and 69 years; 70+, age specific probabilities for CRC cases aged over 70 years

a. Probability of meeting inclusion criteria in the age-restricted scenarios is based on the age distribution of CRC incidence data from 2008-2012.8 Using screening <50 as the example, 7.6% of all CRC cases were eligible for testing with IHC to determine MMR deficiency status.

b. MMR deficiency is determined by testing with immunohistochemistry (IHC) and is defined as loss of MMR expression in one or more of the four MMR genes (MLH1, PMS2, MSH2, MSH6).

c. Progression through the pathway is based on probabilities derived from Buchanan and colleagues.18 The probabilities differ slightly from those presented in Buchanan and colleagues as we considered LS cases which did not show MMR deficiency with IHC to be missed cases (3 cases in screening <60 and screening <70, 4 cases in universal). In addition, one LS case was excluded from the probabilities in our analysis because although the case showed PMS2 loss, genetic testing identified an MLH1 mutation and this could not be factored into the model.

   Using screening <50 as the example, of the eligible CRC cases who underwent IHC to determine MMR deficiency status, 13.5% were MMR deficient. Of these, 52.8% had loss of MLH1/PMS2, 18.1% had loss of MSH2/MSH6, 12.5% had loss of MSH6 only and 16.7% had loss of PMS2 only. Of the tumours with of MHL1/PMS2, 97.4% were BRAF wild-type and went on for germline testing. LS was confirmed in 37.8% of CRC cases demonstrating MLH1/PMS2 loss, 61.5% of the cases demonstrating MSH2/MSH6 loss, 77.8% of the cases demonstrating MSH6 loss and 66.7% of the cases demonstrating PMS2 only.

based on follow-up tumour testing. In the first model (*MLH1*-Pathway), IHC was followed by somatic *MLH1* methylation testing (Figure 1.1), while in the second model (*BRAF*-Pathway), IHC was followed by *BRAF* V600E mutation testing (Figure 1.2). For each pathway, we simulated 1,000 colorectal cancer cases and assumed 100% participation in tumour and genetic testing at all stages. Once a diagnosis of colorectal cancer has been made, eligible individuals entered the Lynch syndrome screening pathway and progressed based on age-specific probabilities (Figures 1 and 2). Costs are applied at appropriate time points along the pathway, such as when a test is conducted or when genetic counselling would be initiated.

Screening scenarios

For this analysis, we used empirical data[18] to assess four age-at-diagnosis scenarios: screening <50, screening <60, screening <70 and universal screening. In the reference scenario, screening <50, screening was restricted to colorectal cancer diagnoses occurring before the age of 50 years. Screening <60 expanded tumour screening to include those aged 50-59 years, and screening <70 is a further expansion to include cases aged 60-69 years. The universal scenario included screening of all incident colorectal cancer diagnoses regardless of age. The probability of meeting the Lynch syndrome screening eligibility criteria for the age-restricted scenarios was based on Australian colorectal cancer incidence data from 2008 to 2012.[8]

Costs assumptions

The cost of MMR IHC was provided by the Royal College of Pathologists of Australasia Benchmarking in Pathology Quality Assurance Program (St. Leonards, NSW) (2013) results (personal communication, Dr Tony Badrick). For the *MLH1* methylation testing, cost data were provided by PathWest Laboratory Medicine, Nedlands, the sole government pathology service for Western Australia (personal communication, Dr Benhur Amanuel). The cost of *BRAF* V600E testing was taken from MBS Online[22] (Table 1). Germline testing costs were provided by the Department of Diagnostic Genomics, PathWest Laboratory Medicine, Nedlands, the primary laboratory for genetic testing in Western Australia (personal communication, Dr Karen Carpenter). The costs for genetic counselling were obtained from primary sources at Genetic Services of Western Australia (Subiaco, WA), including the Business Unit and genetic counsellors (personal communication, Anne Hawkins and Cassandra Nichols).

All costs are presented in 2016 Australian dollars, and as they are incurred in a single year, no discounting is required.

Outcomes

For each screening pathway, our decision analysis model estimated the annual yield and costs of identifying Lynch syndrome in the four age-restricted scenarios per 1,000 colorectal cancer cases.

Table 1.1: Cost parameters.[a]

Parameter	Cost (A$)	Source	Range (A$)
Molecular tests			
Mismatch Repair Immunohistochemistry	175	Expert Opinion, Dr Tony Badrick, Royal College of Pathologists of Australasia Quality Assurance Programs (Email)	88-350 [b]
MLH1 Methylation testing	314	Expert Opinion, Dr Benhur Amanuel, PathWest Laboratory Medicine (Email)	157-628 [b]
BRAF V600E testing	231	MBS Online[22]	115-462 [b]
Combined diagnostic genetic test MLH1, MSH2 and MSH6 [c]	1,400	Expert Opinion, Dr Karen Carpenter, PathWest Diagnostic Genomics (Email)	700-2,800 [b]
Diagnostic genetic test PMS2 [d]	1,000		500-2,000 [b]
Genetic counselling [e]			
Initial session	267 [f]	Expert opinion, Anne Hawkins and Cassandra Nichols, Genetic Services of Western Australia (Email)	92-455 [g]
Lynch syndrome diagnosis	251 [f]		78-438 [g]
Lynch syndrome inconclusive	22 [f]		7-36 [g]

a. All costs are presented in 2016 Australian dollars.
b. Extrapolated range based on 50% reduction and a two-fold increase.
c. Based on Illumina TruSight Cancer Massive Parallel Sequencing panel and two Multiple Ligation Dependent Probe Amplification (MLPA) kits (MRC Holland) for MLH1, MSH2 and MSH6.
d. Based on long-range polymerase chain reaction followed by Sanger sequencing and MLPA for PMS2.
e. Costs for genetic counselling vary according to the complexity of the counselling provided. To calculate the cost of the genetic counselling, we first established a range of costs using the shortest and longest duration of genetic counselling and the least to most complex counselling scenarios. The average of these values was used in the analysis. Costs are divided into initial cost for genetic counselling, which includes planning and preparation for individual consultations, and follow-up costs, which vary depending on the outcome of the genetic test.
f. Mean cost of providing each service.
g. Range based on minimum duration and complexity to maximum duration and complexity of counselling service.

SENSITIVITY ANALYSES

To evaluate the robustness of our model outcomes, we conducted a number of univariate analyses. Firstly, we assessed the uncertainty of the diagnostic accuracy by calculating the 95% confidence intervals around the probability of being diagnosed with Lynch syndrome after demonstrating MMR deficiency using the Wilson confidence interval. This provided lower and upper confidence limits of yield and costs of Lynch syndrome screening in the colorectal cancer population.

Furthermore, as no cases of Lynch syndrome were diagnosed in colorectal cancer patients aged ≥70 years in our data set, we performed an analysis of the *MLH1*-Pathway using age-specific probabilities derived from Hampel and colleagues[23] to assess the impact of identifying Lynch syndrome cases in this age group. Unfortunately, similar data was not available from this research to assess the *BRAF*-Pathway.

Finally, we reduced acceptance of genetic counselling to 92.5%[24] and varied the acceptance of germline testing to 81%[17] and 90%[24] to assess the impact of these variables on yield and costs of Lynch syndrome screening.

For all sensitivity analyses, we also explored the effect of varying costs parameters by assuming a 50% reduction and a two-fold increase of all costs (Table 1.1 and Supplementary Results Tables). This provided lower and upper bound cost estimates for each age cohort in the analyses.

RESULTS

MLH1-PATHWAY

By restricting testing to colorectal cancer cases diagnosed <50 years, 76 (7.6%) of the 1,000 colorectal cancer cases would be tested with IHC, leading to the identification of 5.2 Lynch syndrome cases (Table 1.2). Total costs for this pathway were $36,864 per 1,000 colorectal cancer cases, equating to $7,041 per Lynch syndrome case diagnosed.

By expanding screening to include those aged between 50-59 years (screening <60), an extra 142 individuals (totalling 21.8% of total colorectal cancer patient population) would be tested with IHC to identify 1.5 additional Lynch syndrome cases (6.7 Lynch syndrome cases in total). This would cost an additional $36,794 or $25,177 per additional Lynch syndrome case diagnosed. Cost per case detected increased to $10,999.

With further expansion to also screen colorectal cancer cases aged between 60-69 years (screening <70), an additional 255 individuals (totalling 47.3% of total colorectal cancer patient population) would be tested by IHC. This identified 1.6 additional Lynch syndrome

cases (8.3 Lynch syndrome cases in total), annual program cost increased to $138,663 and the cost per additional case detected was $40,278. Cost per case detected increased to $16,685.

Based on our data, universal screening would not identify any additional Lynch syndrome cases: however annual program cost would increase by $158,724 to $297,387 per 1,000 colorectal cancer cases. Cost per Lynch syndrome case detected increased to $35,784.

BRAF-Pathway

The *BRAF*-Pathway identified the same number of Lynch syndrome cases as the *MLH1*-Pathway at higher costs (Table 1.2). For example, screening <50 identified 5.2 Lynch syndrome cases per 1,000 colorectal cancer cases for $36,462 for the *MLH1*-Pathway and $37,177 in the *BRAF*-Pathway. Therefore, Lynch syndrome screening based on IHC followed by *BRAF* V600E is more expensive than the alternative, and the *BRAF*-Pathway is therefore dominated in terms of cost-effectiveness.

Sensitivity analyses

When the probability of a diagnosis of Lynch syndrome was altered, our results changed significantly (Supplementary Results Table 1.1). Although overall costs remained similar to the original analysis, in the lower bound analysis, the number of Lynch syndrome cases diagnosed reduced to between 3.2 and 3.8, while the cost per Lynch syndrome case diagnosed increased ranging from $11,521 to $79,091. The reverse was true for the upper bound analysis where the number of Lynch syndrome cases diagnosed increased to between 7.0 and 23.7 and cost per case detected ranged from $5,350 and $13,731. A similar pattern was seen when the age-specific probabilities derived from Hampel and colleagues[23] were applied to the *MLH1*-Pathway. Using these data, the number of Lynch syndrome cases diagnosed in each age restricted scenario was higher and the cost per Lynch syndrome case diagnosed was lower. However, program costs remained similar to our original analysis (Supplementary Results Table 1.2).

Lowering adherence to genetic counselling and germline testing reduced diagnostic yield by up to 25%. This resulted in a slight reduction in total costs (5-15% for *MLH1*-Pathway and 7-15% for *BRAF*-Pathway), while the cost per Lynch syndrome case detected increased (8-24% for *MLH1*-Pathway and 8-21% for *BRAF*-Pathway) (Supplementary Results Table 1.3). Similar results were found when both costs and acceptance of genetic counselling and germline testing were altered.

Changes to the cost parameters affected the costs proportionally (Table 1.2 and Supplementary Results Tables).

Table 1.2: Yield and costs for each pathway and age restricted scenario per 1,000 individuals diagnosed with colorectal cancer.

	Number of CRC cases undergoing IHC testing [ab]	Number of MMR deficient cases detected by IHC [bc]	Number of MMR deficient cases diagnosed as LS [c]	*MLH1*-Pathway							*BRAF*-Pathway						
				Total cost of LS screening (A$) [d]			Cost per LS diagnosis (A$) [d]				Total cost of LS screening (A$) [d]			Cost per LS diagnosis (A$) [d]			
				Point Estimate	Lower bound	Upper bound	Point Estimate	Lower bound	Upper bound	Per additional LS case diagnosed	Point Estimate	Lower bound	Upper bound	Point Estimate	Lower bound	Upper bound	Per additional LS case diagnosed
Screening<50	76	10	5.2	36,864	17,726	72,441	7,041	3,386	13,837	7,041	37,177	17,869	73,042	7,101	3,413	13,952	7,101
Screening<60	218 (+142)	19 (+9)	6.7 (+1.5)	73,657 (+36,794)	35,823	145,482	10,999	5,349	21,724	25,177	77,414 (+40,237)	37,613	152,834	11,560	5,617	22,822	27,533
Screening<70	473 (+255)	41 (+22)	8.3 (+1.6)	138,663 (+65,006)	67,893	274,703	16,685	8,169	33,054	40,278	147,520 (+70,106)	72,110	292,032	17,751	8,677	35,140	43,438
Universal	1000 (+527)	134 (+93)	8.3 (+0)	297,387 (+158,724)	146,444	590,673	35,784	17,621	71,074	-	349,674 (+202,154)	171,418	693,115	42,076	20,626	83,401	-

Abbreviations: IHC, Immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair

a. Number of cases undergoing IHC testing is determined by age at CRC diagnosis. Probability of meeting inclusion criteria in the age restricted scenarios is based on the age distribution of CRC incidence data from 2008-2012.[8]

b. Number of MMR cases detected is a subset of the number undergoing IHC testing.

c. Figures in parentheses represent increase from previous screening scenario.

d. All costs are presented in 2016 Australian dollars.

DISCUSSION

We developed a decision analysis model and used empirical data[18] to determine the cost and yield of screening for Lynch syndrome per 1,000 colorectal cancer cases. Based on our results, screening for Lynch syndrome using the *MLH1*-Pathway is more cost effective than the *BRAF*-Pathway. Limiting screening to colorectal cancer cases aged under 50 years in the *MLH1*-Pathway would identify 5.2 Lynch syndrome cases per 1,000 colorectal cancer cases for the overall lowest cost, with a cost per Lynch syndrome case detected of $7,041. Expanding this pathway to also screen individuals aged 50-59 years (screening <60) increased diagnostic yield by 28% (1.5 cases). This was associated with a doubling of program costs, an increase in cost per Lynch syndrome case detected (to $10,999) and an incremental cost of $25,177 to detect one additional case. Screening <70 further increased diagnostic yield of screening with program costs increasing by 88%. Cost per case detected in this scenario increased to $16,685, equating to an incremental cost per additional case detected of $40,278. Universal screening more than doubled program costs compared with screening <70 for no additional yield; however, this was because no Lynch syndrome cases were identified in this age group in our dataset. Cost per Lynch syndrome case detected increased to $35,784. The *BRAF*-Pathway identified the same number of Lynch syndrome cases; however, costs were higher for all age-at-diagnosis thresholds.

There remains ongoing discussion about the optimal age to stop screening for Lynch syndrome in the colorectal cancer affected population,[4, 21] and our model, like others,[25-28] demonstrates that applying age restrictions to screening criteria results in fewer Lynch syndrome cases being identified. This impacts patient care and has downstream effects for at-risk relatives who would not be identified, thereby diminishing the opportunity to commence interventions to reduce mortality and morbidity in this cohort. However, concerns have been raised about the feasibility of expanded screening for Lynch syndrome, particularly in relation to the associated costs.[25] While individuals with Lynch syndrome are at higher risk of Lynch syndrome related cancers compared to the general population, the likelihood of developing such a cancer diminishes with age.[14] This suggests that, while expanding screening to include older individuals will identify more cases, the increased detection will likely come at the expense of efficiency. In our model, the proportion of colorectal cancer cases who demonstrate MMR protein loss by IHC and are subsequently found to be Lynch syndrome positive was highest in the screening <50 scenario (52% for both pathways). This congruency reduced in the expanded alternatives (ranging from 0%-16%), demonstrating that although screening older individuals may detect additional Lynch syndrome cases, it does so by conducting disproportionately greater numbers of tests which results in higher program costs. This increase in overall cost could be considerable, with our model demonstrating that universal

screening cost more than twice as much as screening <70 with no additional benefit in Lynch syndrome carrier detection.

Based on our results, there is added benefit in ensuring colorectal cancer cases <70 years are screened and although this requires an increase in total program cost, such an expansion could be considered a reasonable trade-off between costs and yield.[26, 28] While our model suggests there is no additional benefit of universal screening compared to screening <70, this is due to the lack of Lynch syndrome cases identified in this age cohort in our study population. As other investigations have confirmed the existence of colorectal cancer affected Lynch syndrome mutation carriers in this age group,[19, 23] we conducted a sensitivity analysis where we assessed the impact of adjusting the proportion of individuals who were MMR deficient but were not confirmed with Lynch syndrome (Supplementary Results Table 1.1). In the case of universal screening, increasing this proportion of individuals diagnosed with Lynch syndrome dramatically reduced the cost per Lynch syndrome case diagnosed (to between $14,000 and $15,000) and the cost per additional Lynch syndrome diagnosis (approximately $25,000). In a second analysis, we applied the age-specific probabilities of a US study evaluating the *MLH1*-Pathway.[23] Using these probabilities we found similar overall program costs for universal screening with cost per additional Lynch syndrome case detected of approximately $50,000 (Supplementary Results Table 1.2). These results indicate that while there is potential benefit in screening colorectal cancer cases ≥70 years in terms of yield, cost-effectiveness of such an expansion will be significantly impacted by the proportion of Lynch syndrome cases in this age cohort. Further studies with larger samples are needed to enable more precise estimates.

Although screening for Lynch syndrome has shown to be cost effective, consensus of the optimal strategy is yet to be achieved. To our knowledge, few studies have presented results based on age-restricted inclusion criteria for the two pathways we investigated. One analysis investigating the *BRAF*-Pathway to screen for Lynch syndrome found it was cost effective to screen for Lynch syndrome in those aged <70 years.[28] A second study found using MSI, in conjunction with IHC, to be cost effective across different age restrictions.[26] However when we investigated MSI in our preliminary analyses, we found its inclusion was more costly than the alternative strategies for all age cohorts with limited benefit (results not shown). Analyses of universal screening using the *MLH1*-Pathway have indicated that while this strategy is cost effective, it was not as cost effective as possible alternatives, with one study determining it was more cost effective to include both *MLH1* methylation and *BRAF* V600E testing after IHC,[29] and the other finding cost-effectiveness improved when colorectal cancer cases were first triaged with the revised Bethesda guidelines.[30] We have previously noted that implementation of clinical guidelines in routine practice is poor;[4, 16, 17] this would likely impact the effectiveness of this strategy, leading to missed opportunities to diagnose Lynch syndrome and reduced cost-effectiveness. While universal screening using *BRAF*-Pathway has also been shown to be cost effective,[27-29, 31] two studies indicated that this strategy was not as effective

as alternative strategies that included predictive modelling as a first step[27] and the inclusion of both *BRAF* V600E and *MLH1* methylation testing.[29] When we assessed the *BRAF*-Pathway we found it to be as effective but more expensive than the *MLH1*-Pathway at all age thresholds. This was due to the increased number of individuals undergoing germline testing in the *BRAF*-Pathway as *BRAF* V600E only achieves ~75% efficiency as a surrogate marker for *MLH1* methylated sporadic colorectal cancer showing loss of *MLH1*/PMS2.[18] Only one other study has made a direct comparison between the two pathways we investigated and although the authors determined that the *BRAF*-Pathway was more cost effective than the *MLH1*-Pathway, the differences were small.[29]

Benefits of a Lynch syndrome screening program are dependent on ensuring all eligible colorectal cancer cases are screened and that those detected with MMR-deficiency receive genetic counselling and germline testing. In our analysis we assumed all eligible cases would undergo appropriate testing; however, we recognise that this may not occur in practice,[17, 32] as individuals may not wish to participate in genetic testing because of, among other things, possible negative psychological impacts (such as anxiety and depression) and concerns over personal information.[33] Reducing the proportion of MMR-deficient individuals who agree to genetic counselling and subsequently agree to germline testing decreases yield and total cost in all scenarios, while increasing cost per additional Lynch syndrome case detected. Importantly, such reductions lead to more undiagnosed cases of Lynch syndrome and missed opportunities to identify and monitor at-risk relatives. The greatest benefits of Lynch syndrome screening will only be achieved if screening is appropriately implemented and eligible cases have appropriate and informed access to genetic counselling and germline testing.

An important strength of this study is that the model parameters are derived from two large population-based studies for Lynch syndrome testing and our results align with previous estimates of Lynch syndrome in the colorectal cancer population.[19, 34] However, despite this, three limitations are of note. Firstly, this analysis only examined testing incident colorectal cancer cases with IHC. However, while we acknowledge that MSI testing, either with or without IHC, is an alternative pathway for triaging colorectal cancer cases,[16, 24] our preliminary analyses indicated that this pathway was substantially more expensive, and therefore, we excluded it from further investigations.

Secondly, this analysis only considers costs to identify Lynch syndrome in colorectal cancer cases and does not take into account the subsequent costs and cost savings of cascade screening and surveillance of at-risk relatives. While predictive genetic testing of at-risk relatives has been shown to be cost saving in Australia,[35] there is currently no research into the cost-effectiveness of surveillance in Lynch syndrome carriers. Research with similar cost per Lynch syndrome case detected to ours, which has also assessed costs and benefits of

surveillance in this group found screening for Lynch syndrome in those aged <50 gained 43.6 life years ($7,938/LYG).[26] When screening was expanded to include those aged 51-60 years, a further 118 life years were gained ($6,380 per additional LYG). An addition 44.3 life years were gained when those aged 61-70 years were screened ($10,648 per additional LYG). This suggests that with our cost per case detected, cascade screening and surveillance of at-risk individuals will be cost effective at a willingness-to-pay threshold of $50,000. As much of the benefit in identifying Lynch syndrome relates to gains in life expectancy in this group,[36] future research should incorporate analyses of these implications and costs.

Finally, data around the costs of laboratory testing for Lynch syndrome has been difficult to obtain, and our costs may not necessarily reflect the range of costs throughout Australia. To account for this, we conducted sensitivity analyses to provide the lower and upper cost estimates.

CONCLUSIONS

Based on our analysis, *MLH1* methylation testing as a follow-up for colorectal cancers showing loss of *MLH1* protein expression is more cost effective than BRAF V600E somatic mutation testing in identifying Lynch syndrome cases. An expanded screening program that includes screening colorectal cancer cases diagnosed <70 years will identify more Lynch syndrome cases at a reasonable cost. Future research into the yield of Lynch syndrome screening in colorectal cancer patients ≥70 years and the potential to offset additional costs by identifying at-risk relatives is needed to determine if universal screening is justified.

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SUPPLEMENTARY RESULTS

Supplementary Results Table 1.1: Yield and costs for each pathway and age restricted scenario per 1,000 individuals diagnosed with colorectal cancer for the sensitivity analyses with a) the lower bound confidence boundary and b) upper bound confidence boundary.

	MLH1-Pathway								*BRAF*-Pathway							
	Number of MMR deficient cases diagnosed as LS [a]	Total cost of LS screening ($A) [b]			Cost per LS diagnosis ($A) [b]				Number of MMR deficient cases diagnosed as LS [a]	Total cost of LS screening ($A) [b]			Cost per LS diagnosis ($A) [b]			
		Point Estimate [a]	Lower bound	Upper bound	Point Estimate	Lower bound	Upper bound	Per additional LS case diagnosed		Point Estimate [a]	Lower bound	Upper bound	Point Estimate	Lower bound	Upper bound	Per additional LS case diagnosed
a) lower confidence boundary																
Screening<50	3.2	36,388	17,572	71,642	11,521	5,564	22,683	11,521	3.2	36,700	17,714	72,240	11,640	5,618	22,913	11,640
Screening<60	3.4 (+0.3)	72,910 (+36,522)	35,581	144,227	21,232	10,361	41,999	132,492	3.4 (+0.3)	76,666 (+39,965)	37,371	151,577	22,366	10,902	44,221	145,388
Screening<70	3.8 (+0.3)	137,618 (+64,708)	67,554	272,948	36,729	18,029	72,847	206,843	3.7 (+0.3)	146,473 (+69,808)	71,771	290,274	39,158	19,187	77,601	223,145
Universal	3.8 (+0.0)	296,342 (+158,724)	146,105	588,917	79,091	38,994	157,176	0	3.7 (+0.0)	348,628 (+202,154)	171,079	691,357	93,202	45,736	184,827	0
b) upper confidence boundary																
Screening<50	7.0	37,260	17,855	73,106	5,350	2,564	10,497	5,350	7.0	37,579	17,999	73,717	5,375	2,574	10,543	5,375
Screening<60	10.4 +3.4	74,496 +37,237	36,096	146,892	7,190	3,484	14,177	10,963	10.7 +3.7	78,326 +40,747	37,909	154,366	7,335	3,550	14,456	11,054
Screening<70	15.1 +4.7	140,206 +65,709	68,394	277,295	9,318	4,545	18,429	14,023	15.9 +5.2	149,257 +70,931	72,674	294,949	9,390	4,572	18,557	13,597
Universal	21.9 +6.8	300,495 +160,290	147,453	595,895	13,731	6,738	27,230	23,445	23.7 +7.8	353,194 +203,937	172,560	699,027	14,916	7,287	29,521	26,198

Abbreviations: LS, Lynch syndrome; MMR, mismatch repair

a. Figures in parentheses represent increase from previous screening scenario.

b. All costs are presented in 2016 Australian dollars.

Supplementary Results Table 1.2: Yield and costs for the age restricted *MLH1*-Pathway scenarios per 1,000 individuals diagnosed with colorectal cancer for the sensitivity analyses using data from Hampel and colleagues.

	Number of MMR deficient cases diagnosed as LS [a]	Total cost of LS screening ($A) [b]			Cost per LS diagnosis ($A) [b]			
		Point Estimate [a]	Lower bound	Upper bound	Point Estimate	Lower bound	Upper bound	Per additional LS case diagnosed
Screening <50	7.2	38,425	18,427	75,545	5,308	2,545	10,435	5,308
Screening <60	14.5 (+7.2)	94,842 (+56,417)	45,623	186,640	6,562	3,157	12,914	7,822
Screening <70	16.4 (+1.9)	167,504 (+72,661)	81,352	330,862	10,241	4,974	20,229	38,183
Universal	19.3 (+2.9)	313,701 (+146,197)	153,664	621,832	16,289	7,979	32,288	50,359

Abbreviations: LS, Lynch syndrome; MMR, mismatch repair

a. Figures in parentheses represent increase from previous screening scenario.

b. All costs are presented in 2016 Australian dollars.

Supplementary Results Table 1.3: Yield and costs for each pathway and age restricted scenario per 1,000 individuals diagnosed with colorectal cancer for the sensitivity analyses a) when attendance at genetic counselling reduced to 92.5% and acceptance of genetic testing reduced to 81% and b) when attendance at genetic counselling reduced to 92.5% and acceptance of genetic testing reduced to 90%.

	Number of MMR deficient cases diagnosed as LS [a]	*MLH1*-Pathway							*BRAF*-Pathway						
		Total cost of LS screening ($A) [b]			Cost per LS diagnosis ($A) [b]				Total cost of LS screening ($A) [b]			Cost per LS diagnosis ($A) [b]			
		Point Estimate [a]	Lower bound	Upper bound	Point Estimate	Lower bound	Upper bound	Per additional LS case diagnosed	Point Estimate [a]	Lower bound	Upper bound	Point Estimate	Lower bound	Upper bound	Per additional LS case diagnosed
a) attendance at genetic counselling reduced to 92.5% and acceptance of genetic testing reduced to 81%															
Screening<50	3.9	31,425	14,980	61,077	8,011	3,819	15,571	8,011	31,648	15,075	61,478	8,068	3,843	15,673	8,068
Screening<60	5.0 (+1.1)	65,787 (+34,356)	31,837	128,972	13,110	6,345	25,704	31,376	68,484 (+36,836)	33,088	134,101	13,649	6,594	26,727	33,641
Screening<70	6.2 (+1.2)	127,161 (+61,380)	62,056	250,510	20,422	9,966	40,231	50,760	133,355 (+64,872)	64,914	262,236	21,417	10,425	42,115	53,647
Universal	6.2 (+0.0)	276,033 (+148,872)	135,572	545,711	44,330	21,773	87,640	-	312,953 (+179,598)	152,705	615,884	50,259	24,524	98,909	-
b) attendance at genetic counselling reduced to 92.5% and acceptance of genetic testing reduced to 90%															
Screening<50	4.4	33,165	15,903	64,898	7,610	3,649	14,890	7,610	33,417	16,014	65,365	7,667	3,674	14,998	7,667
Screening<60	5.6 (+1.2)	68,299 (+35,134)	33,178	134,518	12,251	5,951	24,129	28,878	71,341 (+37,924)	34,611	140,388	12,796	6,208	25,182	31,171
Screening<70	6.9 (+1.3)	130,835 (+62,536)	64,023	258,630	18,911	9,254	37,382	13,544	137,886 (+66,545)	67,339	272,224	19,930	9,733	39,347	49,528
Universal	6.9 (+0.0)	282,872 (+152,037)	139,238	560,755	40,886	20,125	81,050	-	324,740 (+186,855)	159,014	641,683	46,937	22,984	92,747	-

Abbreviations: LS, Lynch syndrome; MMR, mismatch repair

a. Figures in parentheses represent increase from previous screening scenario.

b. All costs are presented in 2016 Australian dollars.

CHAPTER 2

OPTIMISING COLORECTAL CANCER SCREENING IN SHANGHAI, CHINA: A MODELLING STUDY

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Submitted

ABSTRACT

Background: To reduce the burden of colorectal cancer in Shanghai, China, a CRC screening program was commenced in 2013 inviting those aged 50-74 years to screening with a faecal immunochemical test (FIT) and risk assessment. However, it is unknown whether this is the optimal screening strategy for this population. We aimed to determine the optimal colorectal cancer screening program for Shanghai in terms of benefits, burden, harms and cost-effectiveness.

Methods: Using MISCAN-Colon, we estimated the costs and effects of the current screening program compared to a situation without screening. Subsequently, we estimated the benefits (life years gained (LYG)), burden (number of screening events, colonoscopies and false positive tests), harms (number of colonoscopy complications) and costs (Renminb (¥)) of screening for 323 alternative screening strategies. We compared several different age ranges, screening modalities, intervals, and FIT cut-off levels. We performed an incremental cost-effectiveness analysis to determine the optimal strategy assuming a willingness-to-pay of ¥193,931 per LYG.

Results: Compared to no screening, the current screening program reduced colorectal cancer incidence by 40% (19 cases per 1,000 screened individuals) and colorectal cancer mortality by 67% (7 deaths), and gained an additional 32 LYs and cost an additional ¥199,652. However, the optimal screening strategy was annual testing using a validated one-sample FIT, with a cut-off of 10 µg Hb/g from ages 45-80 years (ICER, ¥62,107). This strategy increased LYG by 0.18% and costs by 28%.

Conclusions: Although the current screening program in Shanghai is effective at reducing colorectal cancer incidence and mortality, the program could be optimised using a validated FIT.

INTRODUCTION

Colorectal cancer is a global health issue with significant incidence and mortality, however, this burden is unevenly distributed. Due to its large population, China is a noteworthy contributor to the global burden of colorectal cancer and is expected to account for approximately 28% of colorectal cancer cases and deaths in 2018.[1, 2] Moreover, colorectal cancer incidence and mortality has been steadily increasing in China: between 2003 to 2011, incidence rose from 12.8 to 16.8 per 100,000, while mortality rose from 5.8 to 7.8.[3] This, coupled with a steadily ageing population[4] suggests the large burden of colorectal cancer is set to remain in the foreseeable future[5] and represents a significant public health challenge for the country.

Although screening has long been established as an effective method to reduce colorectal cancer incidence and mortality, it has not yet been universally implemented. While a diverse range of colorectal cancer screening programs have been established throughout Europe, North America and Australia, to date, very few countries in Asia have implemented such programs.[6] In an effort to reduce the burden of colorectal cancer, there is a growing trend for lower incidence countries to implement organised population colorectal cancer screening,[6] as is the case in China, where region-specific programs are currently being implemented.[7, 8] However, despite the rising colorectal cancer incidence and mortality, the first consensus on organised colorectal cancer screening in China was not available until 2014.[9]

Shanghai, one of the largest and most developed cities in China, experiences some of the highest colorectal cancer incidence and mortality in China.[10] Colorectal cancer incidence rates have increased significantly from 1973 to 2010, with the age-adjusted incidence rates increasing from 13.6 to 28.2 per 100,000 in males and 11.9 to 22.3 per 100,000 in females.[10-12] To address this, the Shanghai Municipal Government implemented a community-based colorectal cancer screening program in 2013.[7] The program invited individuals aged 50-74 to participate in colorectal cancer screening, offering triennial screening with a locally produced faecal immunochemical test (FIT) and a risk questionnaire. This strategy was decided upon after comprehensive evaluation of the capacity of health resources of the region.[7] The initial results of the screening program in Shanghai[7] and the Pudong New Area (the largest district of Shanghai)[13] have recently been published. These results highlight several challenges for the implemented screening program, including poor uptake of initial offer of screening, suboptimal attendance at diagnostic colonoscopy and low rates of cancer detection.

Such results call into question whether the implemented colorectal cancer screening program is optimal for the population. Therefore, the aim of this research is to determine the optimal colorectal cancer screening program for Shanghai in terms of benefits, burden, harms and costs. Using microsimulation modelling, we compared the assessed the performance of the

current screening strategy against standardised and validated FITs considering varying program characteristics including screening interval and screening start- and stop-age.

METHODS

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model to simulate a cohort of citizens of Shanghai aged 45 years in 2013. We assessed 324 different screening strategies to determine the benefits, burden, harms and costs of screening compared to the same population without screening. Subsequently, we performed incremental cost-effectiveness analysis to identify strategies that provide good value for money and determine the optimal strategy from a cost-effectiveness perspective.

MISCAN-COLON

MISCAN-Colon is a well-established microsimulation model for colorectal cancer developed at the Department of Public Health, Erasmus University Medical Center.[14] The model has been extensively described previously and is described in Appendix 1.[15, 16] In brief, the model simulates the life-histories of a large population of individuals from birth to death, first without and then with screening for colorectal cancer. As each simulated person ages, one or more adenomas may arise and some can progress in size from small (<5 mm) to medium (6- 9 mm) to large (>10 mm). Some adenomas develop into preclinical cancer and subsequently progress through cancer stages I to IV. At any time during the development of the disease, symptoms may present and colorectal cancer may be diagnosed. The introduction of screening may alter the simulated life-histories through detection and removal of adenomas or through detection of colorectal cancer at an earlier stage with a more favourable survival. By comparing the life-histories of a simulated population being screened to the corresponding life-histories in a simulated population not screened, MISCAN-Colon quantifies the effectiveness and the costs of screening.

MISCAN-Colon was adjusted to match age-specific incidence of colorectal cancer in China before the introduction of screening in 2013.[17] Stage distribution,[18] localisation of cancers in the colorectum[19] and five-year relative survival[18] after clinical diagnosis of a cancer were based on Chinese literature. Additional assumptions of the MISCAN-Colon model are presented in the **Model Appendix**.

SCREENING STRATEGIES

In this analysis, we will assess four screening modalities: the FIT as currently offered in the Shanghai screening program (Shanghai FIT), the Shanghai FIT coupled with the risk assessment (Shanghai FIT+RA) and a standardised and validated FIT taking either one-sample (FIT 1) or two-samples (FIT 2, at least one-sample positive). For the validated tests, we considered five

different cut-off values – 10, 15, 20, 30 and 40 micrograms of haemoglobin per gram faeces (µg Hb/g, Table 2.1).

For each modality and cut-off value, we assessed multiple start ages (45, 50 or 55 years), stop ages (70, 75 or 80 years) and intervals (annual, biennial and triennial). Individuals with a positive screening test were invited to a diagnostic colonoscopy. Surveillance was based on findings at diagnostic colonoscopy in accordance with the European Society of Gastrointestinal Endoscopy Guidelines.[20] We elected to simulated surveillance consistent with these guidelines because there is conflicting advice in China about the post diagnostic colonoscopy pathway (including when to return to screening and the surveillance pathway),[13, 21-24] and the Asia Pacific Consensus Group did not provide precise guidelines on interval of surveillance, other than to suggest that such intervals should be tailored to the risk level.[25] In a sensitivity analysis, we assessed a surveillance pathway, derived from Chinese literature.[21, 22]

We assumed 100% adherence to all screening, diagnostic and surveillance tests because this allows for the determination of the optimal benefit of colorectal cancer screening. All strategies were compared to a situation without screening.

In total, 324 unique screening strategies were evaluated. For each strategy, we simulated a population of 10 million 45-year-olds, with life expectancy as observed in China in 2010.[26] It was assumed that no screening occurred before or after the screening start and stop ages. Individuals were followed for life, until a maximum age of 100 years, commencing in 2015.

Test Characteristics

Although the Shanghai screening program reports that it is using a qualitative FIT with a pre-set cut-off of 100 nanograms of haemoglobin per millilitre of faeces (equivalent to 20µg Hb/g faeces),[7] laboratory tests have shown that the quantity of faeces in samples and diluents of the test were not standardised, with the actual cut-off being lower than the pre-set cut-off.[27] Consequently, the characteristics and actual cut-off of the Shanghai FIT remain unknown. Therefore, the test characteristics of the Shanghai FIT and the Shanghai FIT+RA (Table 2.1) were fitted to the positivity and detection rates observed in the first three years of screening in Pudong New Area, the largest district of Shanghai (Supplementary Methods Table 2.1). Data was provided by the Pudong Centre for Disease Control (Pudong CDC).

The test characteristics of the validated FIT 1 and FIT 2 were fitted to the positivity and detection rates of advanced neoplasia observed in the first screening round of two Dutch randomised trials, which utilised the OC-Sensor micro (Eiken Chemical, Tokyo, Japan, Table 2.1).[28-31] To estimate the two-sample FIT test characteristics, we followed the approach described in Goede and colleagues.[32] The characteristics differ to those previously presented as the natural history of the MISCAN-Colon model has been updated since this publication.[33]

Table 2.1: Test characteristics of the faecal immunochemical tests and colonoscopy

Test	Sensitivity (%)					Specificity (%)
	Adenoma ≤5mm	Adenoma 6-9mm	Adenoma ≥10mm	CRC early preclinical [a]	CRC late preclinical [a]	
Shanghai FIT [b]	0.0	8.7	20.3	44.6	78.9	87.4
Shanghai FIT + RA [b]	0.0	9.4	33.0	74.2	93.1	79.3
One-sample FIT10 [c]	0.0	11.0	39.4	65.5	90.0	96.1
One-sample FIT15 [c]	0.0	6.5	33.3	58.5	87.0	97.3
One-sample FIT20 [c]	0.0	5.0	29.3	52.0	83.5	97.9
One-sample FIT30 [c]	0.0	3.3	26.6	50.5	83.0	98.4
One-sample FIT40 [c]	0.0	2.6	22.1	50.0	82.5	98.7
Two-sample FIT10 [c,d]	0.0	16.2	63.3	75.0	93.5	94.1
Two-sample FIT15 [c,d]	0.0	8.9	52.7	71.0	92.0	95.7
Two-sample FIT20 [c,d]	0.0	7.1	46.9	66.0	90.0	96.7
Two-sample FIT30 [c,d]	0.0	4.6	42.5	66.5	90.5	97.4
Two-sample FIT40 [c,d]	0.0	4.9	12.5	66.0	90.0	97.7
Colonoscopy [e,f]	75.0	85.0	95.0	95.0	95.0	86.0

Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; RA, risk assessment; FIT10, faecal immunochemical test, 10 µg Hb/g faeces cut-off value; FIT15, faecal immunochemical test, 15 µg Hb/g cut-off value; FIT20, faecal immunochemical test, 20 µg Hb/g faeces cut-off value; FIT30, faecal immunochemical test, 30 µg Hb/g cut-off value; FIT40, faecal immunochemical test, 40 µg Hb/g cut-off value; µg Hb/g, micrograms of haemoglobin per gram faeces

a. It was assumed that the probability a colorectal cancer bleeds and thus the sensitivity of a FIT for colorectal cancer depends on the time until clinical diagnosis.[34]
b. Specificity and sensitivity based on the positivity rates and detection rates of advanced neoplasia observed in the first screening round in Pudong, Shanghai. This data for this was provided by Pudong Centre for Disease Control. Sensitivity for adenomas smaller than 5 mm was assumed to be 0% for all tests.
c. Specificity and sensitivity based on the positivity rates and detection rates of advanced neoplasia observed in the first screening round of two Dutch randomised trials.[28-31] Sensitivity for adenomas smaller than 5 mm was assumed to be 0% for all tests, at any cut-off level.
d. A two-sample FIT is considered positive when at least one-sample contains detectable blood at the specified cut-off value.
e. Specificity for colonoscopy is based on Schroy et al, 2013.[35] The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, which, in the case of colonoscopy, leads to unnecessary polypectomy, which is associated with an increased risk complications.
f. Sensitivity of colonoscopy for the detection of adenomas and colorectal cancer within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies.[36]

In all instances, the sensitivity and specificity of the test characteristics were estimated so that simulated positivity rates and detection rates for (non-) advanced adenomas and cancer matched the observed rates to within 1%.The test characteristics were adjusted to take into account the effect of systematic false-positive and false-negative results (individuals who always test positive but do not have adenomas or how test negative because of adenomas which do not bleed).[37]

For colonoscopy, test characteristics were based on a systematic review of polyp miss rates in tandem colonoscopy studies.[36] The lack of specificity of colonoscopy reflects the detection of benign hyperplastic polyps, which are not cancer precursors.[35] Complications of colonoscopy were measured as the number of perforations arising from colonoscopy.[38]

Costs of screening, surveillance and colorectal cancer care

Costs associated with colonoscopy, polypectomy, complications from colonoscopy and costs of cancer treatment were obtained from Chinese literature (Table 2.2).[19, 39-41] The costs of the Shanghai FIT, FIT 1, FIT 2 and the risk assessment were provided by Pudong CDC. The costs of all of the FITs were based on the current reimbursement funding arrangement. These costs include the test kits, their distribution, return, and analysis and expenses in marketing. We also included costs associated with colonoscopy, such as costs for following up individuals with a positive screening test to encourage them to attend diagnostic colonoscopy and general outpatient costs.[19] All costs are presented in Chinese Renminbi (RMB, ¥) and where necessary are standardised to 2019 prices using the consumer price index.[42]

Outcomes

For all strategies, the model estimated colorectal cancer incidence, the number of colorectal cancer deaths and the number of screening, diagnostic and surveillance tests required between ages 45 and 80 years per 1,000 individuals. The benefits of screening were measured as the reduction in colorectal cancer incidence and mortality and the number of life years gained (LYG) per 1,000 individuals. The number of screening events and colonoscopies were taken as measures of the burden of screening and for colonoscopy, both diagnostic and surveillance colonoscopies were included. Harms of screening were measured as the number of perforations arising from colonoscopy and the number of false positive tests (which is defined as a positive screening test followed by a colonoscopy with no clinical findings).

Cost-effectiveness analysis

We conducted a cost-effectiveness analysis from the health care sector perspective, and discounted both future costs and life-years using a standard annual rate of 3%.[43] Undiscounted results and results discounted to 5% are presented in the Supplementary Results Table 2.2 and Figure 2.1). We plotted all of the screening strategies in a cost-effectiveness plane and performed an incremental cost-effectiveness analysis to see which strategies were efficient. The efficient strategy with the highest incremental cost effectiveness ratio (ICER) below the willingness-to-pay (WTP) threshold was considered optimal. The WTP threshold was set at three times the Chinese gross domestic product per capita in 2018 (¥193,931 RMB which is equal to $29,313 US)[44] for one LYG.

Table 2.2: Costs associated with colorectal cancer screening and treatment.[a]

Cost parameter	¥
Per quantitative FIT – one-sample [b,c]	15.00
Per quantitative FIT – two-sample [b,c]	25.00
Per qualitative FIT – two-sample [b,c]	13.00
Per risk assessment [b]	3.48
Per positive screening test [b,d]	15.00
Per colonoscopy [e]	375.30
Per polypectomy [f]	654.83
Per perforation of colonoscopy [g]	19761.04
Treatment by stage and location [h]	
Stage I CRC	35227.92
Stage II CRC	37342.58
Stage III CRC	37481.16
Stage IV CRC	38472.04
General outpatient cost [i]	23.30

Abbreviations: CRC, Colorectal Cancer; FIT, faecal immunochemical test

a. Costs are from a health system perspective and do not include patient time costs. All costs are presented in Chinese Renminbi (¥) and are indexed to 2019 prices.[42]
b. Costs provided by Pudong Centre for Disease Control and are based on the current reimbursement funding arrangement.
c. Costs for the FITs include the test kits, their distribution, return, and analysis and expenses in marketing.
d. These costs are provided to encourage those with positive screening test to attend diagnostic colonoscopy, as well as support other activities related to colonoscopy.
e. Costs for colonoscopy are based on sources from China[39] and includes cost of bowel preparation.[41]
f. Costs polypectomy is based on sources from China[39] and includes costs of biochemical and pathological testing.[41] This cost is in addition to the cost for colonoscopy.
g. Costs for perforation during colonoscopy is based on sources from China.[39]
h. Costs of cancer treatment are taken from the Chinese setting.[19, 40]
i. Co-payment made by patients when seeing a doctor and undergoing a colonoscopy.[19]

SENSITIVITY ANALYSES

We conducted a series of sensitivity analyses to assess the robustness of our assumptions. First, due to uncertainty about the performance of the validated FIT in the Chinese population, we conducted an analysis where we adjusted the characteristics such that the sensitivity and specificity were halfway between calibrated Shanghai FIT and validated FITs (Supplementary Methods Table 2.2). Second, due to uncertainty about the actual cost of the validated FITs, we explored the impact of varying its cost by assuming a 50% reduction and a two-fold increase in its cost. All other costs were held constant. Third, quality-adjusted life years were excluded from the main analysis because at present there is no available information on these measures in the Chinese setting. Therefore, we assessed the impact of utilising international quality of life measurements in a sensitivity analysis (Supplementary Methods Table 2.3).[45] Fourth, we assessed the impact of an alternative surveillance pathway, derived from Chinese literature

(Supplementary Methods Figure 2.1).[21, 22] Finally, we assessed the impact of reducing the WTP threshold to the Chinese gross domestic product per capita in 2018 (¥64,644 RMB which is equal to $9,7701US) for one LYG.

RESULTS

BENEFITS OF SCREENING

MISCAN-Colon predicted that, compared to no screening, all screening strategies reduced colorectal cancer incidence and mortality (Supplementary Results Table 2.1). In a situation without screening, colorectal cancer incidence was 49 per 1,000 individuals with colorectal cancer mortality at 11 per 1,000 individuals. Screening reduced colorectal cancer incidence by 16 to 53% (8 to 26 cases) and colorectal cancer mortality by 41 to79% (4 to 9 deaths), depending on intensity of screening (Supplementary Results Table 2.1). In addition, screening gained an additional 20 to 39 LYs. The current screening program (triennial screening with Shanghai FIT+RA from ages 50-75 years) reduced colorectal cancer incidence by 19 cases (40%) and mortality by 7 deaths (67%) and gained an additional 32 LY.

Annual screening with the Shanghai FIT+RA, from ages 45-80 years was the most effective strategy at reducing colorectal cancer incidence, while annual screening with the FIT 2 with a cut-off of 10 µg Hb/g from ages 45-80 years was the most effective at reducing colorectal cancer mortality.

SCREENING BURDEN

In general, screening strategies with a shorter screening interval and a greater number of years of screening required more screening tests than strategies with longer screening interval for fewer years. For example, annual screening with FIT 1, with a cut-off of 40 µg Hb/g, from 45-80 years required the greatest number of screening tests (29,329 tests), while triennial screening with the Shanghai FIT+RA, from ages 55-70 years required the least number of screening tests (3,706 tests). The current screening program required 5,346 tests.

This pattern however, did not hold for the number of required colonoscopies. Although triennial screening with FIT 1, with a cut-off of 40 µg Hb/g, from ages 55-70 years required the least number of colonoscopies (265 colonoscopies) and annual screening with the Shanghai FIT+RA, from 45-80 years required the greatest number of colonoscopies (2,609 colonoscopies), the order of strategies between this varied greatly. The current screening program required 1,434 colonoscopies. In general, the screening strategies that utilised the Shanghai FIT had a substantially greater colonoscopy requirement than those utilising the validated tests.

Table 2.3: Costs and effects (discounted at 3%) per 1,000 simulated 45-year-olds for a situation without screening, the current screening program in Shanghai and screening strategies on the efficient frontier.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval									
No Screening			0	49	0	0.01	49	11	21,482	869,648	
Current screening program in Shanghai											
Shanghai FIT+RA	50-75	3	5,346	1,434	890	0.07	30	4	21,514	1,022,213	Dominated
Cost-effective screening strategies											
FIT-1-10	50-70	3	5,901	514	151	0.03	36	5	21,509	874,095	164
FIT-2-10	50-70	3	5,645	652	239	0.04	33	5	21,511	884,484	4,027
FIT-2-10	50-75	3	6,884	744	294	0.04	31	4	21,514	904,162	7,778
FIT-2-10	50-80	3	7,768	795	327	0.05	30	3	21,515	917,846	14,254
FIT-1-10	45-80	2	13,519	801	334	0.05	31	3	21,517	989,444	31,130
FIT-1-10	50-80	1	20,134	986	476	0.05	28	3	21,518	1,007,490	31,660
FIT-1-15	45-80	1	26,112	846	359	0.05	29	3	21,520	1,071,462	32,309
FIT-1-10	45-80	1	24,054	1,104	572	0.06	27	2	21,520	1,101,071	59,218
FIT-2-15	45-80	1	23,434	1,186	635	0.06	26	2	21,521	1,225,260	302,900
FIT-2-10	45-80	1	21,214	1,456	867	0.07	24	2	21,521	1,254,847	739,677

Note: Screening strategies: screening test – screening interval – test cut-off. Grey shading highlights optimal screening strategy at the willingness-to-pay threshold.
Abbreviations: CRC, colorectal cancer, FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio.

a. Results are discounted at an annual rate of 3%.

b. Costs are presented in Chinese Renminbi (¥).

Table 2.4: Cost-effective strategies (discounted at 3%) for the sensitivity analyses. Outcomes are per 1,000 45-year-olds.

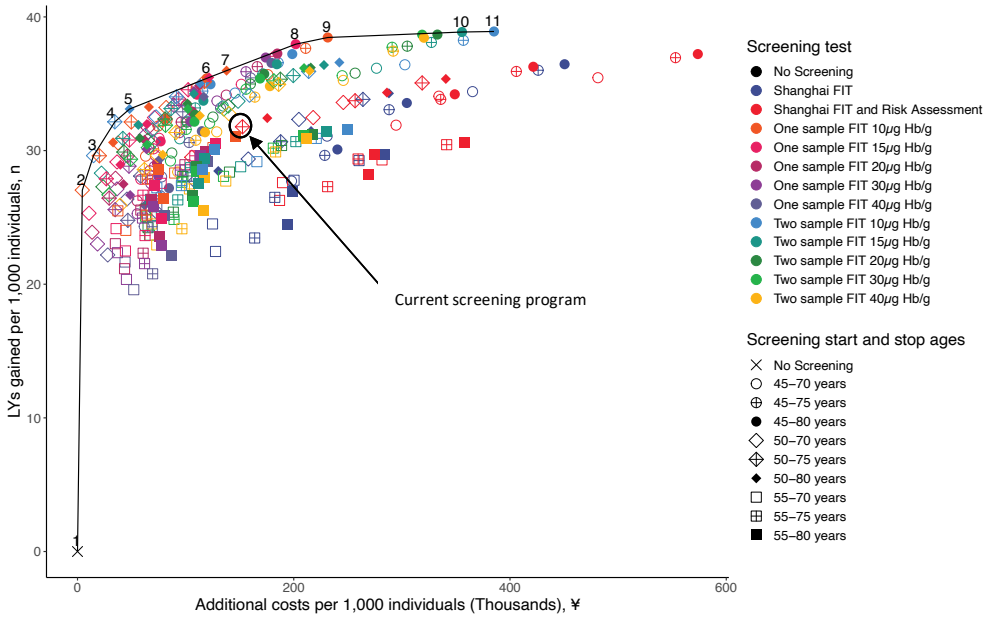
Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval										
a. Assuming adjusted FIT characteristics.												
FIT-1-10	45-80	1	18,630	1,758	1,144	0.08	26	3	21,519	-	1,242,210	60,319
b. Assuming a 50% reduction in the costs of the validated FITs.												
FIT-2-30	45-80	1	26,476	807	320	0.05	29	2	21,520	-	1,018,114	66,922
c. Assuming a 200% increase in the costs of the validated FITs.												
FIT-1-10	45-80	1	24,054	1,104	572	0.06	27	2	21,520	-	1,288,058	62,198
d. Assuming Chinese surveillance guidelines.												
FIT-2-10	45-80	1	29,675	2,123	1,499	0.08	22	2	21,524		1,487,932	164,958
e. Assuming international quality of life estimates.												
FIT-2-10	45-80	1	867	1,456	867	0.07	24	2	21,521	20,277	1,254,847	3,374

Note: Screening strategies: screening test – screening interval – test cut-off.

Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

a. Results are discounted at an annual rate of 3%.

b. Costs are presented in Chinese Renminbi (¥).



	1	2	3	4	5	6	7	8	9	10	11
Screen test	NoScr	FIT–1–10	FIT–2–10	FIT–2–10	FIT–2–10	FIT–1–10	FIT–1–10	FIT–1–15	FIT–1–10	FIT–2–15	FIT–2–10
Screen ages	–	50–70	50–70	50–75	50–80	45–80	50–80	45–80	45–80	45–80	45–80
Screen frequency	–	3	3	3	3	2	1	1	1	1	1
ICER (¥)	–	164	4027	7778	14254	31130	31660	32309	59218	302900	739677

Figure 2.1: Costs and life years (discounted at 3%) per 1,000 45 year-olds of all 324 colorectal cancer screening strategies and a strategy without screening, with the efficient frontier connecting the economically efficient strategies.[a]

Abbreviations: FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio, LY, life years; μg Hb/g, micrograms of haemoglobin per gram faeces

Note: black circle highlights current screening program in Shanghai.

a. Discounted costs and life years gained reflect total costs and life years gained of a screening program, accounting for time preference for present over future outcomes. Life years gained are plotted on the y-axis, and total costs are plotted on the x-axis. Each possible screening strategy is represented by a point. Strategies that form the solid line connecting the points lying left and upward are the economically rational subset of choices. This line is called the efficient frontier. The inverse slope of the line represents the incremental cost-effectiveness ratio of the connected strategies. Points lying to the right and beneath the line represent the dominated strategies.

Screening harms

Overall, the risk of screening related perforations was very low – ranging between 0.01-0.09 per 1,000 individuals. Complications were proportional to the number of colonoscopies, such that those strategies with fewer colonoscopies had fewer complications. The number of false-positive tests ranged from 21 to 1917 and was generally highest for the Shanghai FITs, particularly with risk assessment.

Costs and cost-effectiveness

Without screening the cost of diagnosing and treating colorectal cancer was ¥869,648 per 1,000 individuals. Screening increased costs by 1 to 66% (¥884,095 to ¥1,443,352). The current screening program cost an additional ¥152,565, an increase of 18% (¥1,022,213).

Of the 324 screening strategies, 10 were on the efficient frontier (i.e. considered to provide good value for money, Table 2.3, Figure 2.1). The efficient strategies all had a low cut-off (10-15 µg Hb/g), and were an even mix of one- and two-sample tests. Screening start age varied from a relatively short time period (50-70) years to the longest assessed period (45-80 years), and the screening interval ranged from 1 to 3 years. All screening strategies using the Shanghai FIT, either with or without the risk assessment, were dominated.

Using a WTP threshold of ¥193,931 per LYG, the optimal screening strategy was annual testing with FIT 1, using a cut-off of 10 µg Hb/g from ages 45-80 years (ICER, ¥59,218). Annual screening with FIT 2, using a cut-off of 10 µg Hb/g from ages 45-80 years was also on the efficient frontier, but with an ICER, ¥739,677 per LYG, it would not be considered as cost effective.

Sensitivity analyses

Our results were robust to changes in the validated FIT characteristics, costs, the use of international quality of life measurements and the adoption of a Chinese surveillance pathway. For all of these analyses, the validated FITs outperformed the Shanghai FIT, both with and without the risk assessment (Supplementary Results Table 2.2a-e and Figure 2.2a-e). At the WTP threshold, the cost-effective strategies varied in terms of the test (FIT 1 and FIT 2) and cut-off, however all strategies required annual testing from ages 45 to 80 years (Table 2.4). The Shanghai FIT+RA was on the efficient frontier when the Chinese surveillance pathway was assessed, however, with an ICER of ¥750,686, it would not be considered cost effective. When assessed against a lower WTP threshold, the optimal screening strategy remained the same (annual testing with FIT 1, using a cut-off of 10 µg Hb/g from ages 45-80 years).

DISCUSSION

This microsimulation analysis assessed the performance of the Shanghai FIT, with and without the use of a risk assessment, compared to the use of validated one- and two-sample FITs. Our results suggest that the screening tests currently used in the Shanghai screening program are not the most cost effective as in all instances, they were outperformed by validated screening tests. Although the Shanghai tests performed similarly terms of reductions in incidence and mortality and gains in LYs, they were generally more expensive. In addition, they required substantially more colonoscopies. Based on our results, the Shanghai screening program could be optimised by utilising a validated, one-sample FIT, with a cut-off of 10 µg Hb/g, with screening occurring annually from ages 45-80 years (Table 2.3). Although this strategy increases the number of screening tests and costs compared to the screening program currently implemented in Shanghai, these increases are outweighed by the reductions in colonoscopy demand and associated harms, colorectal cancer incidence and mortality and increase in the number of LYG.

Shanghai is one of the only regions in the world to implement a triennial screening program.[6] This strategy was chosen after the completion of a comprehensive evaluation of the capacity of health resources of the region.[7] This suggests that an alternative program could be implemented if it did not exceed the demand of health services such as colonoscopy. According to our analysis, the current program requires a colonoscopy capacity of 1,434 per 1,000 individuals, while our proposed cost-effective strategy reduces colonoscopy demand by approximately 30% (to 1,104 colonoscopies). If colonoscopy demand was a key driver of the selection of a triennial screening program, there are several cost-effective alternatives that could be implemented. For example, whilst not considered to be cost effective (ICER: ¥739,677), annual screening of individuals from 45-80 years with a validated, two-sample FIT, with a cut-off of 10 µg Hb/g results in a similar colonoscopy demand (1,456 colonoscopies). Alternatively, to achieve the same number of LYG (21,514 per 1,000), a program of triennial screening from 50-75 years with a validated, two-sample FIT, with a cut-off of 10 µg Hb/g could be implemented. This strategy would half the colonoscopy demand (to 744 colonoscopies) at an ICER of ¥7,778. Other strategies could also be selected depending on desired outcomes, however, all of these alternatives utilise a validated FIT.

The sub-optimal performance of the Shanghai screening tests is not surprising given their characteristics (Table 2.2). Although the sensitivity of the Shanghai screening tests is comparable to the validated screening tests, the specificity is considerably lower, especially when the risk assessment is included. Low specificity increases the rate of false-positive tests[46] and consequently, greater numbers of individuals are unnecessarily sent for colonoscopy. This impacts the cost-effectiveness of the screening program by increasing the burdens, harms and costs of screening. Shifting to a validated, quantitative FIT could help alleviate these issues

while also providing an opportunity to assess stool haemoglobin concentrations which has been demonstrated to be a strong predictor for future cancer risk.[47]

The high rate of false positivity of the screening tests used in the Shanghai screening program has been suggested as an explanation for the low uptake of diagnostic colonoscopy.[7, 13] Although failure to complete an appropriate follow-up test after a positive result further undermines the benefits of screening, the situation is not unique to the Shanghai screening program as sub-optimal compliance to diagnostic colonoscopy after a positive FIT has been noted in several screening programs.[48] Compliance to diagnostic colonoscopy is complex and multidimensional.[49-51] In China, the results of primary screening test, perceived severity of the disease, personal or others experiences with colonoscopy and health care provider recommendation have also been shown to influence compliance.[50] Cultural beliefs may also play a significant role.[52] This suggests that health literacy related to colorectal cancer screening could be improved.

With compliance to diagnostic colonoscopy, and participation in screening in general, already demonstrated to be low in Shanghai and other locations in China,[8] the optimal screening strategy suggested by this investigation may not be optimal in practice. Screening programs have to consider their "real world" application and as the effectiveness of a FIT screening program relies heavily on participation, the implementation of an annual screening program over an extended 35-year period may further diminish this already low participation rate. Participation may be further diminished as a result of 'screening fatigue' – where motivation to participate is reduced due to a false perception of decreased colorectal cancer risk after several negative screening test results.[53, 54] As colorectal cancer risk increases with age[1, 2, 55] participation of older individuals is important. It has also been suggested that offering screening to those aged 75-80 in Shanghai is potentially warranted as Shanghai is one of the most ageing cities in China.[56] Therefore, it may be pertinent to consider an alternative cost-effective strategy such as annual screening from 50-80 years, utilising a validated, one-sample FIT, with a cut-off of 10 µg Hb/g (ICER: ¥31,660) or triennial screening from 50-80 years, utilising a validated, two-sample FIT, with a cut-off of 10 µg Hb/g (ICER: ¥ 14,254). Choosing either of these strategies would substantially reduce the screening burden and costs and would still result in comparable benefits.

There are three noteworthy limitations to our research. Firstly, there remains some uncertainty about the accuracy of test characteristics and therefore the performance of the validated FITs in the Chinese population. We therefore conducted a sensitivity analysis where we reduced the performance of validated FITs. Our results were robust to this change in test characteristics, although there was less difference in effectiveness, the analysis produced similar results as base case. Secondly, we simulated surveillance in our main analysis consistent with European Society of Gastrointestinal Endoscopy Guidelines,[20] because there

is conflicting advice in China about the post diagnostic colonoscopy pathway, (including when to return to screening and the surveillance pathway).[13, 21-24] When we assumed surveillance guidelines derived from Chinese literature, our results did not change significantly. Although annual screening from 45 to 80 years with the Shanghai FIT and risk assessment was on the efficient frontier, it was still not cost effective. Finally, there is limited information on complications arising from colonoscopy in China which likely means our results provide an underestimate of complications and their associated costs. However, given that the Shanghai FIT, both with and without the risk assessment, had higher numbers of colonoscopy, we do not feel that this would significantly alter our results. Fortunately, there is research underway to address this gap in knowledge.[57]

Despite these limitations, our research has important implications. Firstly, our results suggest that the colorectal cancer screening program in Shanghai could achieve better outcomes and costs could be reduced if the program was to switch to using a validated screening test. Based on our results the most cost-effective strategy is annual testing with the validated one-sample FIT, using a cut-off of 10 µg Hb/g and screening from ages 45-80 years. Secondly, although the current screening program is not considered optimal based on our results, our findings support the implementation of screening in Shanghai; even the use of sub-optimal screening tests result in a reduction of colorectal cancer incidence and mortality in a cost-effective way compared to no screening (CER, ¥4,801). Given the recent trend of rising colorectal cancer incidence and mortality,[10-12] coupled with the expectation that the burden is set to increase as the Chinese economy grows,[5, 58] efforts to reduce the impact of colorectal cancer are important. Moreover, despite the use of these tests, the program already appears to be having an impact on survival – individuals diagnosed with colorectal cancer who participated in the screening program and were compliant with the screening policy experienced better survival outcomes compared to those who did not participate.[59] While this finding should be interpreted with caution given the short follow-up time and the potential for lead-time and length bias,[46] it adds support to the benefits of screening in this population. Finally, our results demonstrate that screening for colorectal cancer is a highly cost-effective method of reducing the burden of colorectal cancer in Shanghai. This is particularly salient in China where out-of-pocket expenses for treating cancer have been described as 'catastrophic' (defined as out-of-pocket expenditure in access of 40% of annual household income) in China for both newly diagnosed and end stage cancer.[60, 61] This finding may be relevant to other jurisdictions with limited health resources who are considering implementing colorectal cancer screening.

CONCLUSION

Screening for colorectal cancer in Shanghai is an attractive and cost-effective option for reducing the burden of colorectal cancer. Although the current screening program reduces

incidence and mortality of colorectal cancer, a program utilising a standardised, validated FIT could save more lives at a lower cost. In addition, addressing barriers to screening, such as poor health literacy and financial concerns, may increase participation and therefore improve the effectiveness of the screening program.

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SUPPLEMENTARY METHODS

DATA AND ASSUMPTIONS FOR OCCULT BLOOD SCREENING

We estimated the test characteristics of the Shanghai FIT and the Shanghai FIT+RA so that the model predicted positivity and detection rates for advanced neoplasia are similar to those observed in the first three years of screening in Pudong (2013-2015). These observed rates were provided by the Pudong Centre for Disease Control (Supplementary Methods Table 2.1). The algorithm used for this estimation is the Nelder-Mead Simplex method.[62] This iterative parameter search method constructs a simplex consisting of a number of sets of potential test characteristics equal to the number of test characteristics plus one. For each set, the goodness-of-fit (GOF) is computed and a better set (in terms of GOF) replaces the worst set.[63] Since the data consists of rates, the Poisson likelihood was used as the GOF during the calibration.

PARAMETERS FOR THE SENSITIVITY ANALYSES

CHANGES TO TEST CHARACTERISTICS

We conducted a series of sensitivity analyses to assess the robustness of our assumptions. Due to uncertainty about the performance of the validated FIT in the Chinese population, we conducted an analysis where we adjusted the characteristics such that the sensitivity and specificity were halfway between calibrated Shanghai FIT and validated FITs (Supplementary Methods Table 2.2).

QUALITY-ADJUSTED LIFE YEARS

As information on quality-adjusted life years is scarce in the Chinese setting, they were excluded from the main analysis. Therefore, we assessed the impact of utilising international quality of life measurements in a sensitivity analysis (Supplementary Methods Table 2.3).[45]

CHINESE SURVEILLANCE PATHWAY

Although there is conflicting advice in China about the post diagnostic colonoscopy pathway (including when to return to screening and the surveillance pathway), we assessed the impact of following a surveillance pathway derived from Chinese literature (Supplementary Methods Figure 2.1).[21, 22]

Supplementary Methods Table 2.1: Positive and detection rate per 1,000 obtained by estimation and provided by Pudong CDC for the first three years of screening.

	Positivity rate		Detection rate for non-advanced adenomas		Detection rate for advanced adenomas		Detection rate for CRC	
	Observed [a] (95% CI)	Estimated [b]	Observed [c] (95% CI)	Estimated [b]	Observed [c] (95% CI)	Estimated [b]	Observed [c] (95% CI)	Estimated [b]
Shanghai FIT	145.26 (144.06–146.47)	145.32	25.05 (24.15–25.98)	25.07	17.51 (16.76–18.29)	17.52	3.63 (3.29–4.00)	3.63
Shanghai FIT+RA	231.37 (229.94–232.82)	231.37	38.32 (37.06–39.61)	38.32	25.82 (24.79–26.88)	25.82	4.80 (4.36–5.27)	4.79

Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; RA, risk assessment; CI, confidence interval

a. The observed positivity rate is determined as the total number of positive tests divided by the total number of participants using the specific screening test. In case of the Shanghai FIT+RA, this screening test was considered positive when both Shanghai FIT and the risk assessment were positive. The total number of participants consists of only participants for the Shanghai FIT or only participants for both the Shanghai FIT and the risk assessment.

b. The estimated positivity and detection rates are obtained by the Nelder-Mead Simplex method [62] as explained in the methods section.

c. The observed detection rates were determined by multiplying the observed positivity rate with the positive predictive value to correct for the assumed 100% adherence in the model estimation.

Supplementary Methods Table 2.2: Test characteristics of the validated faecal immunochemical tests used in the sensitivity analysis.

Test	Sensitivity (%)					Specificity (%)
	Adenoma ≤5mm	Adenoma 6-9mm	Adenoma ≥10mm	CRC early preclinical [a]	CRC late preclinical [a]	
One sample FIT10 [b]	12.4	9.9	29.9	54.8	84.5	91.7
One sample FIT15 [b]	8.8	7.6	26.8	51.6	83.0	92.3
One sample FIT20 [b]	7.9	6.8	24.8	48.3	81.2	92.7
One sample FIT30 [b]	6.6	6.0	23.4	47.6	81.0	92.9
One sample FIT40 [b]	6.1	5.6	9.9	47.3	80.7	93.1
Two sample FIT10 [b,c]	12.4	12.4	41.8	59.8	86.2	90.8
Two sample FIT15 [b,c]	8.8	8.8	36.5	57.8	85.5	91.6
Two sample FIT20 [b,c]	7.9	7.9	33.6	55.3	84.5	92.0
Two sample FIT30 [b,c]	6.6	6.6	31.4	55.6	84.7	92.4
Two sample FIT40 [b,c]	6.1	6.1	12.4	55.3	84.5	92.6

Abbreviations: CRC, colorectal cancer; FIT10, faecal immunochemical test, 10 µg Hb/g faeces cut-off value; FIT15, faecal immunochemical test, 15 µg Hb/g cut-off value; FIT20, faecal immunochemical test, 20 µg Hb/g faeces cut-off value; FIT30, faecal immunochemical test, 30 µg Hb/g cut-off value; FIT40, faecal immunochemical test, 40 µg Hb/g cut-off value; µg Hb/g, micrograms of haemoglobin per gram faeces

a. It was assumed that the probability a CRC bleeds and thus the sensitivity of a FIT for CRC depends on the time until clinical diagnosis.[34]
b. Original specificity and sensitivity based on the positivity rates and detection rates of advanced neoplasia observed in the first screening round of two Dutch randomised trials.[28-31] This was then adjusted so that it was halfway between this and the specificity and sensitivity of the Shanghai FIT. Sensitivity for adenomas smaller than 5 mm was assumed to be 0% for all tests, at any cut-off level.
c. A two sample FIT is considered positive when at least one sample contains detectable blood at the specified cut-off value.

Supplementary Methods Table 2.3: International utility losses associated with colorectal cancer screening and treatment.

Utility Losses				
Per FIT				0
Per colonoscopy [b]				0.00274
Per perforation during colonoscopy [c]				0.00548
Per LY with CRC Care [d,e]	Initial Care	Continuing Care	Terminal care (Death CRC)	Terminal care (Death OC)
Stage I	0.12	0.05	0.70	0.05
Stage II	0.18	0.05	0.70	0.05
Stage III	0.24	0.24	0.70	0.24
Stage IV	0.70	0.70	0.70	0.70

Abbreviations: CRC, Colorectal Cancer; FIT, faecal immunochemical test; OC, Other Cause; LY, Life Year

a. The loss of quality of life associated with a particular event.
b. Equal to 2 days per colonoscopy at a utility of 0.5.
c. Perforations associated with colonoscopy were assumed to be equal to 4 days at a utility of 0.5.
d. 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.
e. Utility losses for LYs with initial care were derived from a study by Ness and colleagues.[45] 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.

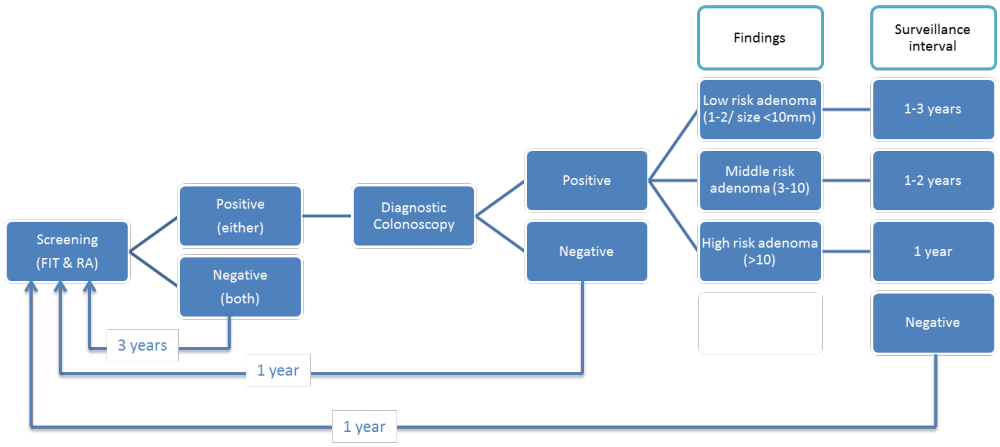


Figure 2.1: Screening pathway as reported by Gong[21] and surveillance pathway as reported in Chinese clinical practice guidelines.[22]

Note: In the sensitivity analysis, the surveillance interval after finding a low risk adenoma is 3 years and after finding a middle risk adenoma is 2 years.

SUPPLEMENTARY RESULTS

Supplementary Results Table 2.1: Costs and effects (discounted at 3%) of 324 screening scenarios and a scenario without screening, per 1,000 simulated 45-year-olds, assuming perfect adherence.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval									
No Screening			0	49	0	0.01	49	11	21,482	869,648	
FIT-1-10	50-70	3	5,901	514	151	0.03	36	5	21,509	874,095	164
FIT-1-15	50-70	3	6,065	425	96	0.03	38	6	21,507	880,303	Dominated
FIT-1-20	50-70	3	6,163	369	64	0.03	39	6	21,506	883,159	Dominated
FIT-2-10	50-70	3	5,645	652	239	0.04	33	5	21,511	884,484	4,027
FIT-1-30	50-70	3	6,246	321	37	0.02	40	6	21,505	888,156	Dominated
FIT-1-10	50-75	3	7,208	583	188	0.04	34	4	21,511	889,841	Dominated
FIT-2-15	50-70	3	5,844	551	169	0.04	35	5	21,510	891,807	Dominated
FIT-2-20	50-70	3	5,973	484	123	0.03	36	5	21,509	893,295	Dominated
FIT-1-15	50-75	3	7,419	480	121	0.03	36	5	21,510	896,283	Dominated
FIT-1-40	50-70	3	6,301	282	22	0.02	42	6	21,504	897,592	Dominated
FIT-2-30	50-70	3	6,081	426	87	0.03	38	6	21,508	898,845	Dominated
FIT-1-20	50-75	3	7,547	415	82	0.03	38	5	21,508	898,949	Dominated
FIT-1-10	50-80	3	8,171	620	209	0.04	34	4	21,512	902,544	Dominated
FIT-2-10	50-75	3	6,884	744	294	0.04	31	4	21,514	904,162	7,778
FIT-1-30	50-75	3	7,656	359	49	0.03	39	5	21,507	904,505	Dominated
FIT-1-20	55-70	2	6,778	379	66	0.03	38	6	21,505	904,663	Dominated
FIT-1-20	50-70	2	9,424	445	95	0.03	37	5	21,510	904,771	Dominated
FIT-1-15	55-70	2	6,642	436	101	0.03	37	5	21,506	905,330	Dominated
FIT-1-30	50-70	2	9,599	381	54	0.03	38	5	21,509	906,163	Dominated
FIT-1-15	50-70	2	9,221	519	144	0.03	36	5	21,511	906,225	Dominated
FIT-1-30	55-70	2	6,895	328	37	0.03	39	6	21,504	906,607	Dominated
FIT-1-10	55-70	2	6,415	527	160	0.03	35	5	21,507	906,973	Dominated
FIT-1-10	50-70	2	8,887	636	226	0.04	34	5	21,512	907,172	Dominated

FIT-2-40	50-70	3	6,147	385	67	0.03	39	6	21,508	908,998	Dominated
FIT-1-15	50-80	3	8,434	507	133	0.04	36	4	21,511	909,297	Dominated
FIT-2-15	50-75	3	7,136	625	209	0.04	33	4	21,513	911,585	Dominated
FIT-1-20	50-80	3	8,595	436	89	0.03	37	4	21,509	912,196	Dominated
FIT-2-20	50-75	3	7,301	546	154	0.04	34	4	21,512	912,631	Dominated
FIT-1-20	55-70	3	5,111	343	55	0.03	39	6	21,503	913,143	Dominated
FIT-1-40	55-70	2	6,971	289	21	0.02	41	6	21,503	913,621	Dominated
FIT-1-15	55-70	3	5,033	392	81	0.03	38	6	21,504	913,967	Dominated
FIT-1-10	55-70	3	4,900	469	126	0.03	36	5	21,506	914,303	Dominated
FIT-1-30	55-70	3	5,178	300	33	0.02	41	6	21,502	914,926	Dominated
FIT-1-40	50-70	2	9,709	334	31	0.03	39	5	21,508	915,395	Dominated
FIT-1-20	50-75	2	10,756	472	104	0.03	36	4	21,511	915,809	Dominated
FIT-1-40	50-75	3	7,728	316	31	0.03	41	5	21,507	916,198	Dominated
FIT-1-30	50-75	2	10,962	401	57	0.03	37	5	21,511	917,261	Dominated
FIT-1-15	50-75	2	10,517	554	160	0.04	34	4	21,513	917,634	Dominated
FIT-2-10	50-80	3	7,768	795	327	0.05	30	3	21,515	917,846	14,254
FIT-1-30	50-80	3	8,732	374	52	0.03	39	4	21,508	918,336	Dominated
FIT-2-30	50-75	3	7,440	479	109	0.03	36	4	21,511	918,748	Dominated
FIT-1-10	50-75	2	10,125	684	253	0.04	32	4	21,514	919,398	Dominated
FIT-1-40	55-70	3	5,224	265	21	0.02	42	6	21,501	921,673	Dominated
FIT-1-20	45-70	3	7,994	419	88	0.03	38	6	21,508	924,811	Dominated
FIT-1-30	45-70	3	8,107	361	52	0.03	40	6	21,507	924,853	Dominated
FIT-2-15	50-80	3	8,081	665	233	0.04	32	3	21,514	925,920	Dominated
FIT-2-20	50-80	3	8,288	578	170	0.04	34	4	21,513	927,248	Dominated
FIT-1-40	50-75	2	11,092	350	32	0.03	39	5	21,510	928,092	Dominated
FIT-1-20	55-75	2	8,765	419	80	0.03	36	5	21,507	928,213	Dominated
FIT-1-15	45-70	3	7,861	486	130	0.03	37	5	21,510	928,227	Dominated
FIT-1-30	55-75	2	8,934	358	42	0.03	38	5	21,507	929,735	Dominated
FIT-1-15	55-75	2	8,570	489	125	0.03	35	4	21,508	930,189	Dominated
FIT-1-20	55-75	3	5,788	359	59	0.03	39	5	21,504	930,341	Dominated
FIT-1-40	45-70	3	8,179	317	33	0.02	41	6	21,506	931,352	Dominated
FIT-2-40	50-75	3	7,526	432	85	0.03	37	5	21,510	931,470	Dominated

FIT-1-30	55-75	3	5,869	313	35	0.03	40	6	21,503	931,647	Dominated
FIT-1-20	50-80	2	12,342	497	115	0.04	35	4	21,513	931,654	Dominated
FIT-1-40	50-80	3	8,823	328	32	0.03	41	5	21,508	931,772	Dominated
FIT-1-15	55-75	3	5,695	412	89	0.03	38	5	21,505	932,115	Dominated
FIT-2-20	55-70	2	6,518	492	130	0.03	35	5	21,507	932,277	Dominated
FIT-1-30	50-70	1	17,946	442	75	0.03	35	5	21,513	932,365	Dominated
FIT-2-30	55-70	2	6,668	432	91	0.03	36	5	21,507	932,524	Dominated
FIT-1-10	45-70	3	7,640	593	203	0.04	35	5	21,511	932,621	Dominated
FIT-1-30	50-80	2	12,603	417	61	0.03	37	4	21,512	933,459	Dominated
FIT-1-10	55-75	3	5,538	497	140	0.03	36	5	21,507	933,723	Dominated
FIT-1-15	50-80	2	12,040	588	178	0.04	34	3	21,514	933,801	Dominated
FIT-2-30	50-80	3	8,462	504	120	0.04	35	4	21,512	933,956	Dominated
FIT-1-10	55-75	2	8,250	599	200	0.04	33	4	21,510	934,249	Dominated
FIT-2-20	50-70	2	9,043	588	184	0.04	34	5	21,513	934,461	Dominated
FIT-1-20	50-70	1	17,295	544	150	0.04	34	4	21,513	934,892	Dominated
FIT-2-20	55-70	3	4,956	445	103	0.03	36	5	21,506	934,914	Dominated
FIT-2-30	50-70	2	9,265	511	129	0.03	35	5	21,512	935,176	Dominated
FIT-1-10	50-80	2	11,549	733	284	0.04	31	3	21,515	935,694	Dominated
FIT-2-30	55-70	3	5,042	394	73	0.03	38	5	21,505	936,274	Dominated
FIT-1-20	45-75	3	9,323	453	97	0.03	37	5	21,510	936,538	Dominated
FIT-2-15	55-70	2	6,341	562	178	0.04	34	5	21,508	937,236	Dominated
FIT-1-30	45-75	3	9,460	388	56	0.03	39	5	21,509	937,374	Dominated
FIT-1-30	55-70	1	13,375	387	53	0.03	36	5	21,508	937,778	Dominated
FIT-2-15	55-70	3	4,853	503	141	0.03	35	5	21,507	937,878	Dominated
FIT-1-20	55-80	2	9,817	436	87	0.03	36	4	21,508	938,268	Dominated
FIT-2-40	55-70	2	6,759	391	69	0.03	38	5	21,506	938,290	Dominated
FIT-1-40	55-75	2	9,043	314	22	0.03	39	5	21,506	938,743	Dominated
FIT-2-15	50-70	2	8,778	680	252	0.04	32	4	21,513	938,906	Dominated
FIT-1-40	55-75	3	5,923	275	21	0.02	41	6	21,503	939,136	Dominated
FIT-1-40	50-70	1	18,335	377	32	0.03	37	5	21,512	939,709	Dominated
FIT-2-10	55-70	3	4,692	592	198	0.04	33	5	21,508	939,920	Dominated
FIT-1-15	45-75	3	9,162	529	146	0.04	36	4	21,512	939,969	Dominated

FIT-1-30	55-80	2	10,026	370	45	0.03	38	4	21,508	940,088	Dominated
FIT-1-20	55-70	1	12,923	467	109	0.03	35	5	21,509	940,333	Dominated
FIT-1-15	55-80	2	9,576	512	137	0.04	35	4	21,509	940,475	Dominated
FIT-1-30	45-70	2	11,616	402	61	0.03	38	5	21,511	940,633	Dominated
FIT-1-15	50-70	1	16,557	659	236	0.04	33	4	21,514	940,866	Dominated
FIT-1-20	45-70	2	11,401	477	112	0.03	37	5	21,511	941,639	Dominated
FIT-2-10	50-70	2	8,380	814	354	0.05	31	4	21,514	942,307	Dominated
SH-FIT	50-70	3	5,054	906	491	0.05	35	5	21,507	942,515	Dominated
FIT-2-40	55-70	3	5,097	357	57	0.03	39	6	21,505	942,926	Dominated
FIT-1-40	55-70	1	13,648	335	22	0.03	38	5	21,508	942,965	Dominated
FIT-2-10	55-70	2	6,070	665	251	0.04	32	5	21,509	943,029	Dominated
FIT-1-20	45-80	3	9,867	462	101	0.03	37	4	21,511	943,151	Dominated
FIT-2-40	50-70	2	9,398	460	99	0.03	36	5	21,511	943,650	Dominated
FIT-1-10	45-75	3	8,897	649	230	0.04	34	4	21,514	944,174	Dominated
FIT-1-30	45-80	3	10,017	394	57	0.03	39	5	21,510	944,223	Dominated
FIT-1-10	55-80	2	9,183	631	220	0.04	33	4	21,510	944,505	Dominated
FIT-1-15	45-70	2	11,150	562	172	0.04	35	5	21,513	945,081	Dominated
FIT-1-20	55-80	3	6,905	382	67	0.03	38	5	21,505	945,763	Dominated
FIT-1-40	50-80	2	12,766	362	32	0.03	38	4	21,511	946,182	Dominated
FIT-1-40	45-75	3	9,549	339	34	0.03	40	5	21,508	946,385	Dominated
FIT-1-15	45-80	3	9,691	541	153	0.04	36	4	21,512	946,541	Dominated
FIT-1-15	55-70	1	12,409	557	173	0.04	34	5	21,509	947,045	Dominated
FIT-1-40	45-70	2	11,749	350	33	0.03	39	6	21,510	947,433	Dominated
FIT-1-30	55-80	3	7,009	329	38	0.03	40	5	21,505	947,443	Dominated
FIT-1-15	55-80	3	6,783	442	102	0.03	37	4	21,507	947,731	Dominated
FIT-2-40	50-80	3	8,569	453	93	0.03	37	4	21,511	948,558	Dominated
FIT-1-10	55-80	3	6,582	538	163	0.04	35	4	21,508	949,512	Dominated
FIT-1-40	55-80	2	10,159	322	22	0.03	39	4	21,507	950,435	Dominated
FIT-1-10	45-80	3	9,402	667	241	0.04	33	4	21,514	950,599	Dominated
FIT-2-20	50-75	2	10,308	631	206	0.04	32	4	21,514	950,649	Dominated
FIT-2-30	50-75	2	10,569	544	143	0.04	34	4	21,514	951,052	Dominated
FIT-1-10	50-70	1	15,401	834	372	0.05	31	4	21,515	951,596	Dominated

FIT-1-10	45-70	2	10,739	697	273	0.04	34	5	21,514	952,510	Dominated
FIT-1-40	45-80	3	10,115	343	34	0.03	40	5	21,509	954,258	Dominated
FIT-2-30	45-70	3	7,886	485	118	0.03	37	5	21,511	955,616	Dominated
FIT-2-15	50-75	2	9,997	733	283	0.04	31	4	21,515	956,251	Dominated
FIT-1-40	55-80	3	7,080	289	21	0.02	41	5	21,504	956,745	Dominated
FIT-2-20	45-70	3	7,740	555	166	0.04	35	5	21,512	956,870	Dominated
FIT-2-20	55-75	3	5,605	469	114	0.03	36	5	21,507	958,261	Dominated
FIT-2-30	55-75	3	5,707	414	80	0.03	37	5	21,507	958,887	Dominated
FIT-1-30	50-75	1	21,270	473	83	0.03	34	4	21,515	958,984	Dominated
FIT-1-10	55-70	1	11,590	694	275	0.04	32	4	21,510	959,511	Dominated
FIT-2-40	50-75	2	10,724	488	109	0.03	35	4	21,513	960,696	Dominated
FIT-2-10	50-75	2	9,533	882	398	0.05	29	3	21,516	961,132	Dominated
FIT-2-40	45-70	3	7,973	437	92	0.03	38	5	21,510	962,292	Dominated
FIT-2-15	55-75	3	5,483	533	156	0.04	34	5	21,508	962,404	Dominated
FIT-1-20	50-75	1	20,462	591	171	0.04	32	3	21,516	963,312	Dominated
FIT-1-30	45-75	2	13,657	431	66	0.03	37	4	21,513	963,951	Dominated
FIT-2-15	45-70	3	7,566	637	226	0.04	34	5	21,513	964,178	Dominated
FIT-1-30	55-75	1	16,694	418	61	0.03	35	4	21,510	964,751	Dominated
FIT-1-20	45-75	2	13,392	516	125	0.04	35	4	21,514	965,533	Dominated
FIT-2-10	55-75	3	5,295	630	221	0.04	32	4	21,509	965,721	Dominated
FIT-2-40	55-75	3	5,771	374	62	0.03	38	5	21,506	966,173	Dominated
FIT-2-30	55-75	2	8,610	481	111	0.03	35	4	21,509	966,183	Dominated
FIT-1-40	50-75	1	21,753	397	33	0.03	35	4	21,515	966,993	Dominated
FIT-2-20	55-75	2	8,397	554	162	0.04	33	4	21,510	967,096	Dominated
FIT-1-20	55-75	1	16,084	514	130	0.04	33	4	21,511	968,995	Dominated
FIT-2-30	45-75	3	9,192	525	132	0.04	35	4	21,513	970,158	Dominated
FIT-1-15	45-75	2	13,084	613	196	0.04	34	4	21,515	970,183	Dominated
FIT-1-40	55-75	1	17,061	356	22	0.03	36	4	21,510	970,593	Dominated
FIT-2-20	45-75	3	9,016	604	187	0.04	34	4	21,514	970,860	Dominated
FIT-2-10	45-70	3	7,300	760	317	0.04	32	5	21,514	970,985	Dominated
FIT-2-20	50-80	2	11,779	672	230	0.04	31	3	21,515	971,329	Dominated
FIT-2-30	50-80	2	12,108	575	160	0.04	33	3	21,515	971,717	Dominated

FIT-1-15	50-75	1	19,552	723	273	0.04	31	3	21,516	971,999	Dominated
FIT-1-40	45-75	2	13,822	373	34	0.03	38	4	21,512	972,848	Dominated
FIT-2-40	55-75	2	8,738	433	84	0.03	36	4	21,509	973,204	Dominated
FIT-2-15	55-75	2	8,145	640	223	0.04	32	4	21,510	974,277	Dominated
FIT-1-30	45-80	2	14,751	443	69	0.03	36	4	21,514	974,330	Dominated
SH-FIT-RA	50-70	3	4,411	1,225	731	0.06	32	5	21,511	975,375	Dominated
FIT-1-20	45-80	2	14,447	533	133	0.04	35	4	21,515	975,498	Dominated
FIT-2-20	55-80	3	6,669	504	132	0.04	35	4	21,508	976,455	Dominated
FIT-2-30	55-80	3	6,801	441	92	0.03	36	4	21,508	977,201	Dominated
FIT-2-15	50-80	2	11,388	785	317	0.05	30	3	21,516	977,265	Dominated
FIT-1-30	50-80	1	23,928	491	89	0.04	33	3	21,516	977,281	Dominated
FIT-2-30	45-80	3	9,724	536	137	0.04	35	4	21,514	977,790	Dominated
FIT-1-15	55-75	1	15,396	621	209	0.04	32	4	21,511	978,146	Dominated
FIT-2-20	45-80	3	9,532	619	196	0.04	33	4	21,514	978,320	Dominated
SH-FIT	50-75	3	6,134	1,058	599	0.05	33	4	21,509	978,459	Dominated
FIT-2-15	45-75	3	8,807	698	257	0.04	32	4	21,515	978,553	Dominated
FIT-2-40	45-75	3	9,298	471	101	0.03	37	4	21,513	979,085	Dominated
FIT-2-30	55-80	2	9,627	502	122	0.04	34	4	21,510	979,247	Dominated
FIT-1-10	45-75	2	12,581	769	313	0.05	32	4	21,516	979,418	Dominated
FIT-2-20	55-80	2	9,365	582	178	0.04	33	4	21,511	979,997	Dominated
FIT-1-15	45-80	2	14,094	636	208	0.04	33	3	21,516	980,248	Dominated
FIT-2-15	55-80	3	6,512	577	182	0.04	33	4	21,509	981,127	Dominated
FIT-1-20	50-80	1	22,945	621	188	0.04	31	3	21,517	982,049	Dominated
FIT-2-40	50-80	2	12,303	513	120	0.04	34	3	21,514	982,797	Dominated
FIT-2-10	50-80	2	10,808	950	446	0.05	28	3	21,517	982,901	Dominated
FIT-1-30	55-80	1	19,346	436	68	0.03	34	3	21,511	983,237	Dominated
FIT-2-10	55-75	2	7,766	765	316	0.05	30	4	21,511	983,251	Dominated
FIT-1-40	45-80	2	14,939	382	34	0.03	38	4	21,513	984,636	Dominated
FIT-2-10	55-80	3	6,272	688	258	0.04	31	4	21,510	984,859	Dominated
FIT-2-10	45-75	3	8,490	838	362	0.05	30	3	21,516	985,512	Dominated
FIT-2-15	45-80	3	9,303	717	269	0.04	32	3	21,515	986,059	Dominated
FIT-2-40	55-80	3	6,883	397	70	0.03	38	4	21,507	986,287	Dominated

FIT-1-40	50-80	1	24,514	408	33	0.03	35	3	21,516	986,462	Dominated
FIT-1-10	50-75	1	18,132	925	433	0.05	29	3	21,517	987,112	Dominated
FIT-2-40	55-80	2	9,785	450	91	0.03	35	4	21,510	987,262	Dominated
FIT-2-15	55-80	2	9,055	675	246	0.04	31	3	21,511	987,391	Dominated
FIT-2-40	45-80	3	9,840	481	105	0.03	36	4	21,513	987,618	Dominated
FIT-1-20	55-80	1	18,561	544	147	0.04	33	3	21,512	987,882	Dominated
FIT-1-10	45-80	2	13,519	801	334	0.05	31	3	21,517	989,444	31,130
FIT-1-40	55-80	1	19,818	367	23	0.03	36	3	21,511	990,233	Dominated
FIT-1-15	50-80	1	21,842	766	301	0.05	30	3	21,517	991,409	Dominated
FIT-2-30	45-70	2	11,208	551	154	0.04	35	5	21,514	991,845	Dominated
FIT-2-10	45-80	3	8,958	863	380	0.05	30	3	21,517	992,642	Dominated
SH-FIT	55-70	2	5,267	939	504	0.05	33	5	21,506	994,525	Dominated
FIT-2-20	45-70	2	10,934	641	222	0.04	34	5	21,514	994,905	Dominated
FIT-1-10	55-75	1	14,316	786	334	0.05	30	4	21,512	994,922	Dominated
FIT-2-10	55-80	2	8,592	810	347	0.05	29	3	21,512	996,526	Dominated
SH-FIT	55-70	3	4,238	795	405	0.04	35	5	21,504	997,304	Dominated
FIT-1-15	55-80	1	17,680	664	237	0.04	31	3	21,512	997,705	Dominated
FIT-2-40	45-70	2	11,370	493	117	0.03	36	5	21,513	998,393	Dominated
FIT-1-30	45-70	1	22,637	476	89	0.03	35	4	21,515	998,625	Dominated
SH-FIT	50-80	3	6,824	1,144	663	0.06	32	4	21,510	999,827	Dominated
FIT-1-40	45-70	1	23,144	398	34	0.03	36	5	21,515	1,001,944	Dominated
FIT-2-15	45-70	2	10,605	748	305	0.04	33	4	21,515	1,004,414	Dominated
FIT-2-30	55-70	1	12,547	538	154	0.04	34	5	21,510	1,004,668	Dominated
FIT-2-30	50-70	1	16,758	634	211	0.04	32	4	21,515	1,004,976	Dominated
FIT-2-40	55-70	1	12,875	479	114	0.03	35	5	21,509	1,006,756	Dominated
FIT-1-20	45-70	1	21,782	600	185	0.04	33	4	21,516	1,007,233	Dominated
FIT-1-10	50-80	1	20,134	986	476	0.05	28	3	21,518	1,007,490	31,660
FIT-2-20	50-70	1	15,965	754	304	0.04	31	4	21,515	1,009,036	Dominated
FIT-2-40	50-70	1	17,224	560	157	0.04	33	4	21,515	1,009,612	Dominated
FIT-2-20	55-70	1	11,988	632	224	0.04	32	4	21,510	1,010,209	Dominated
FIT-2-10	45-70	2	10,114	904	429	0.05	31	4	21,516	1,015,357	Dominated
FIT-1-10	55-80	1	16,312	846	378	0.05	29	3	21,513	1,015,619	Dominated

FIT-2-15	50-70	1	15,051	891	413	0.05	30	4	21,515	1,018,164	Dominated
FIT-2-15	55-70	1	11,340	739	305	0.04	31	4	21,511	1,020,540	Dominated
FIT-1-15	45-70	1	20,815	739	295	0.04	32	4	21,517	1,021,111	Dominated
SH-FIT-RA	50-75	3	5,346	1,434	890	0.07	30	4	21,514	1,022,213	Dominated
FIT-2-30	45-75	2	13,155	599	175	0.04	33	4	21,516	1,025,466	Dominated
FIT-1-30	45-75	1	25,966	506	97	0.04	33	3	21,518	1,025,486	Dominated
SH-FIT	50-70	2	7,163	1,196	702	0.06	31	4	21,511	1,027,590	Dominated
FIT-2-10	50-70	1	13,775	1,078	566	0.06	28	4	21,516	1,028,721	Dominated
FIT-2-20	45-75	2	12,819	703	253	0.04	32	3	21,517	1,029,542	Dominated
FIT-1-40	45-75	1	26,566	418	35	0.03	35	4	21,517	1,029,716	Dominated
SH-FIT	55-75	3	4,762	863	454	0.05	34	5	21,505	1,033,501	Dominated
FIT-2-40	45-75	2	13,354	534	132	0.04	35	4	21,516	1,033,662	Dominated
FIT-2-10	55-70	1	10,419	887	420	0.05	30	4	21,511	1,035,548	Dominated
FIT-1-20	45-75	1	24,955	646	206	0.04	32	3	21,518	1,035,902	Dominated
FIT-2-30	45-80	2	14,176	621	186	0.04	32	3	21,517	1,038,484	Dominated
FIT-2-15	45-75	2	12,417	826	350	0.05	30	3	21,517	1,041,086	Dominated
FIT-2-20	45-80	2	13,792	730	270	0.04	31	3	21,517	1,042,339	Dominated
FIT-1-30	45-80	1	28,627	524	103	0.04	32	3	21,519	1,043,702	Dominated
SH-FIT-RA	50-80	3	5,860	1,539	973	0.07	29	3	21,514	1,045,156	Dominated
FIT-1-10	45-70	1	19,306	952	468	0.05	30	4	21,517	1,045,692	Dominated
FIT-2-40	45-80	2	14,403	551	139	0.04	34	3	21,517	1,047,603	Dominated
FIT-1-40	45-80	1	29,329	429	35	0.03	34	3	21,518	1,049,078	Dominated
FIT-2-30	55-75	1	15,580	598	186	0.04	32	4	21,512	1,050,769	Dominated
FIT-2-30	50-75	1	19,799	693	243	0.04	30	3	21,517	1,051,216	Dominated
SH-FIT	55-75	2	6,636	1,113	633	0.06	31	4	21,508	1,052,112	Dominated
FIT-1-15	45-75	1	23,816	803	331	0.05	30	3	21,519	1,052,274	Dominated
FIT-2-40	55-75	1	16,018	528	137	0.04	33	4	21,512	1,052,886	Dominated
FIT-2-15	45-80	2	13,331	861	373	0.05	29	3	21,518	1,053,960	Dominated
FIT-1-20	45-80	1	27,443	677	223	0.04	31	3	21,519	1,054,448	Dominated
FIT-2-10	45-75	2	11,820	1,004	494	0.05	28	3	21,518	1,055,227	Dominated
FIT-2-40	50-75	1	20,373	608	180	0.04	32	3	21,517	1,055,675	Dominated
SH-FIT-RA	55-70	3	3,706	1,071	603	0.05	32	5	21,508	1,056,505	Dominated

FIT-2-20	50-75	1	18,824	831	353	0.05	29	3	21,517	1,057,255	Dominated
SH-FIT	50-75	2	8,105	1,314	792	0.06	30	4	21,512	1,057,526	Dominated
FIT-2-20	55-75	1	14,840	710	272	0.04	30	4	21,512	1,058,372	Dominated
SH-FIT-RA	55-70	2	4,457	1,239	729	0.06	30	4	21,509	1,059,262	Dominated
SH-FIT	55-80	3	5,576	965	529	0.05	34	4	21,506	1,064,117	Dominated
SH-FIT	45-70	3	6,481	1,098	647	0.05	34	5	21,509	1,067,597	Dominated
FIT-2-10	45-80	2	12,651	1,049	526	0.06	27	3	21,519	1,068,267	Dominated
SH-FIT	55-80	2	7,201	1,182	686	0.06	31	4	21,509	1,068,421	Dominated
FIT-2-15	50-75	1	17,703	990	480	0.05	28	3	21,517	1,069,207	Dominated
SH-FIT	55-70	1	7,868	1,275	755	0.06	30	4	21,510	1,069,910	Dominated
FIT-1-15	45-80	1	26,112	846	359	0.05	29	3	21,520	1,071,462	32,309
FIT-2-15	55-75	1	13,989	839	372	0.05	29	3	21,512	1,071,578	Dominated
SH-FIT	50-70	1	10,250	1,577	1,008	0.07	28	4	21,514	1,074,395	Dominated
FIT-2-30	55-80	1	17,917	637	211	0.04	31	3	21,513	1,078,966	Dominated
FIT-2-30	50-80	1	22,142	732	268	0.05	29	3	21,518	1,079,189	Dominated
FIT-1-10	45-75	1	22,046	1,043	528	0.06	28	3	21,519	1,080,650	Dominated
FIT-2-40	55-80	1	18,475	560	155	0.04	32	3	21,513	1,081,598	Dominated
FIT-2-10	50-75	1	16,149	1,205	658	0.06	26	3	21,518	1,083,434	Dominated
FIT-2-40	50-80	1	22,837	640	198	0.04	31	3	21,518	1,084,351	Dominated
FIT-2-20	50-80	1	20,966	884	389	0.05	28	3	21,518	1,085,373	Dominated
SH-FIT	50-80	2	9,016	1,423	877	0.07	29	3	21,513	1,085,652	Dominated
FIT-2-20	55-80	1	16,976	763	308	0.05	29	3	21,513	1,086,709	Dominated
SH-FIT-RA	50-70	2	6,002	1,574	1,006	0.07	28	4	21,514	1,087,581	Dominated
FIT-2-10	55-75	1	12,800	1,014	512	0.05	28	3	21,513	1,090,473	Dominated
FIT-2-15	50-80	1	19,618	1,055	528	0.06	27	3	21,518	1,097,581	Dominated
SH-FIT	45-75	3	7,513	1,233	743	0.06	32	4	21,511	1,098,318	Dominated
FIT-2-15	55-80	1	15,900	904	420	0.05	28	3	21,513	1,100,195	Dominated
SH-FIT	45-70	2	8,575	1,366	854	0.06	31	5	21,513	1,100,494	Dominated
SH-FIT-RA	55-75	3	4,158	1,167	676	0.06	31	4	21,509	1,100,988	Dominated
FIT-1-10	45-80	1	24,054	1,104	572	0.06	27	2	21,520	1,101,071	59,218
SH-FIT	45-80	3	7,888	1,278	777	0.06	32	4	21,512	1,110,020	Dominated
FIT-2-10	50-80	1	17,765	1,286	720	0.06	25	2	21,518	1,111,829	Dominated

FIT-2-30	45-70	1	21,081	708	263	0.04	32	4	21,517	1,114,413	Dominated
SH-FIT-RA	50-70	1	7,715	1,920	1,303	0.08	26	4	21,515	1,115,459	Dominated
FIT-2-40	45-70	1	21,688	619	195	0.04	33	4	21,517	1,115,466	Dominated
FIT-2-10	55-80	1	14,414	1,095	574	0.06	27	3	21,513	1,119,186	Dominated
SH-FIT-RA	50-75	2	6,768	1,733	1,134	0.08	27	3	21,515	1,126,386	Dominated
FIT-2-20	45-70	1	20,045	854	381	0.05	30	4	21,518	1,126,396	Dominated
SH-FIT-RA	55-75	2	5,534	1,463	907	0.07	28	3	21,511	1,129,147	Dominated
SH-FIT	55-75	1	9,542	1,478	918	0.07	28	3	21,511	1,130,051	Dominated
SH-FIT	50-75	1	11,862	1,771	1,164	0.08	26	3	21,516	1,133,633	Dominated
SH-FIT-RA	55-80	3	4,810	1,301	782	0.06	30	3	21,510	1,138,803	Dominated
SH-FIT-RA	55-80	2	5,890	1,535	965	0.07	28	3	21,511	1,144,689	Dominated
FIT-2-15	45-70	1	18,851	1,021	520	0.05	29	4	21,518	1,146,170	Dominated
SH-FIT-RA	55-70	1	6,074	1,577	1,003	0.07	27	4	21,511	1,151,265	Dominated
SH-FIT	55-80	1	10,381	1,576	998	0.07	27	3	21,511	1,153,884	Dominated
SH-FIT-RA	50-80	2	7,394	1,858	1,237	0.08	26	3	21,516	1,155,841	Dominated
SH-FIT	50-80	1	12,721	1,872	1,247	0.08	26	3	21,516	1,157,678	Dominated
SH-FIT	45-75	2	9,946	1,537	984	0.07	29	4	21,515	1,157,820	Dominated
FIT-2-30	45-75	1	24,128	767	295	0.05	30	3	21,519	1,160,623	Dominated
FIT-2-40	45-75	1	24,842	667	218	0.04	31	3	21,519	1,161,608	Dominated
SH-FIT-RA	45-70	3	5,648	1,490	959	0.07	31	4	21,514	1,164,269	Dominated
FIT-2-10	45-70	1	17,201	1,248	712	0.06	28	4	21,518	1,172,422	Dominated
SH-FIT	45-80	2	10,516	1,606	1,037	0.07	29	3	21,515	1,174,222	Dominated
FIT-2-20	45-75	1	22,910	932	430	0.05	28	3	21,520	1,174,611	Dominated
FIT-2-30	45-80	1	26,476	807	320	0.05	29	2	21,520	1,188,375	Dominated
SH-FIT-RA	50-75	1	8,898	2,159	1,504	0.09	24	3	21,517	1,188,421	Dominated
FIT-2-40	45-80	1	27,310	699	235	0.04	30	3	21,520	1,190,044	Dominated
FIT-2-15	45-75	1	21,512	1,120	587	0.06	27	3	21,520	1,196,983	Dominated
FIT-2-20	45-80	1	25,058	984	466	0.05	27	2	21,520	1,202,507	Dominated
SH-FIT-RA	45-70	2	7,160	1,804	1,220	0.08	28	4	21,516	1,203,877	Dominated
SH-FIT-RA	45-75	3	6,527	1,677	1,102	0.07	29	3	21,516	1,205,562	Dominated
SH-FIT-RA	50-80	1	9,379	2,255	1,585	0.09	24	3	21,517	1,210,308	Dominated
SH-FIT-RA	55-75	1	7,174	1,800	1,189	0.08	26	3	21,512	1,211,069	Dominated

SH-FIT-RA	45-80	3	6,816	1,734	1,149	0.08	29	3	21,516	1,218,569	Dominated
FIT-2-15	45-80	1	23,434	1,186	635	0.06	26	2	21,521	1,225,260	302,900
FIT-2-10	45-75	1	19,588	1,375	804	0.07	25	3	21,520	1,226,525	Dominated
SH-FIT-RA	55-80	1	7,529	1,871	1,248	0.08	25	3	21,512	1,227,673	Dominated
SH-FIT	45-70	1	12,622	1,852	1,259	0.08	28	4	21,516	1,235,011	Dominated
FIT-2-10	45-80	1	21,214	1,456	867	0.07	24	2	21,521	1,254,847	739,677
SH-FIT-RA	45-75	2	8,256	2,030	1,402	0.08	26	3	21,518	1,275,517	Dominated
SH-FIT-RA	45-80	2	8,626	2,104	1,463	0.09	26	3	21,518	1,291,208	Dominated
SH-FIT	45-75	1	14,305	2,054	1,423	0.09	26	3	21,518	1,295,685	Dominated
SH-FIT	45-80	1	15,186	2,157	1,508	0.09	25	3	21,518	1,320,127	Dominated
SH-FIT-RA	45-70	1	9,490	2,265	1,629	0.09	26	4	21,517	1,350,956	Dominated
SH-FIT-RA	45-75	1	10,746	2,519	1,841	0.10	24	3	21,519	1,422,729	Dominated
SH-FIT-RA	45-80	1	11,197	2,609	1,917	0.10	23	3	21,519	1,443,352	Dominated

Note: Screening strategies: screening test - screening interval – test cut-off. Grey shading highlights screening scenarios on the efficient frontier.
Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio

a. Results are discounted at an annual rate of 3%.

b. Costs are presented in Chinese Renminbi Yuan (¥).

Supplementary Results Table 2.2: Costs and effects per 1,000 simulated 45-year-olds for screening scenarios on the efficient frontier.

a. Results are undiscounted.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years	Total Costs[a]	ICER[a]
Test	Start-Stop Age	Interval									
No Screening			0	49	0	0.01	49	11	35,247	1,860,008	
FIT-1-10	55-75	3	5,538	497	140	0.03	36	5	35,316	1,763,905	Dominates
FIT-1-10	55-75	2	8,250	599	200	0.04	33	4	35,323	1,780,895	2,241
FIT-1-10	50-80	2	11,549	733	284	0.04	31	3	35,335	1,850,981	5,680
FIT-1-10	45-80	2	13,519	801	334	0.05	31	3	35,339	1,907,838	15,002
FIT-1-15	45-80	1	26,112	846	359	0.05	29	3	35,346	2,061,889	24,414
FIT-1-10	45-80	1	24,054	1,104	572	0.06	27	2	35,347	2,112,382	40,395
FIT-2-15	45-80	1	23,434	1,186	635	0.06	26	2	35,348	2,349,866	237,483
FIT-2-10	45-80	1	21,214	1,456	867	0.07	24	2	35,348	2,397,793	532,520

b. Results are discounted at 5%.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval									
No Screening			0	49	0	0.01	49	11	16,550	561,215	
FIT-1-10	50-70	3	5,901	514	151	0.03	36	5	16,565	588,830	1,820
FIT-2-10	50-70	3	5,645	652	239	0.04	33	5	16,567	595,424	4,516
FIT-2-10	50-75	3	6,884	744	294	0.04	31	4	16,568	617,411	18,476
FIT-2-10	50-80	3	7,768	795	327	0.05	30	3	16,568	626,582	22,368
FIT-1-15	45-80	1	26,112	846	359	0.05	29	3	16,572	760,572	43,223
FIT-1-10	45-80	1	24,054	1,104	572	0.06	27	2	16,572	784,885	81,043
FIT-2-15	45-80	1	23,434	1,186	635	0.06	26	2	16,572	876,114	380,124
FIT-2-10	45-80	1	21,214	1,456	867	0.07	24	2	16,572	900,603	1,224,423

Note: Screening strategies: screening test - screening interval – test cut-off. Grey shading highlights optimal screening scenario at the willingness-to-pay threshold.
Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio

a. Costs are presented in Chinese Renminbi (¥).

b. Results are discounted at an annual rate of 5%.

Supplementary Results Table 2.3: Costs and effects (discounted at 3%) per 1,000 simulated 45-year-olds for screening scenarios on the efficient frontier.

a. Assuming adjusted FIT characteristics.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval									
No Screening			0	49	0	0.01	49	11	21,482	869,648	
FIT-1-10	50-70	3	5,443	729	335	0.04	35	5	21,508	914,230	1,700
FIT-2-10	50-70	3	5,324	797	373	0.04	34	5	21,509	928,340	9,344
FIT-2-10	50-75	3	6,473	920	456	0.05	32	4	21,512	959,707	13,124
FIT-2-10	50-80	3	7,250	991	506	0.05	31	3	21,513	978,968	22,397
FIT-1-10	50-70	1	12,302	1,286	753	0.06	29	4	21,515	1,031,672	27,739
FIT-1-10	50-75	1	14,348	1,444	874	0.07	27	3	21,516	1,083,250	31,071
FIT-1-10	50-80	1	15,621	1,538	949	0.07	26	3	21,517	1,107,699	42,153
FIT-1-10	45-80	1	18,630	1,758	1,144	0.08	26	3	21,519	1,242,210	60,319
FIT-2-10	45-80	1	17,690	1,873	1,240	0.08	24	3	21,520	1,344,893	256,708

b. Assuming a 50% reduction in the costs of the validated FITs.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval									
No Screening			0	49	0	0.01	49	11	21,482	869,648	Dominated
FIT-2-10	50-70	3	5,645	652	239	0.04	33	5	21,511	852,337	Dominates
FIT-2-10	50-75	3	6,884	744	294	0.04	31	4	21,514	864,063	4,635
FIT-2-10	50-80	3	7,768	795	327	0.05	30	3	21,515	873,441	9,769
FIT-1-30	50-80	1	23,928	491	89	0.04	33	3	21,516	892,706	14,376
FIT-1-30	45-80	1	28,627	524	103	0.04	32	3	21,519	933,826	16,383
FIT-1-15	45-80	1	26,112	846	359	0.05	29	3	21,520	970,599	36,773
FIT-2-30	45-80	1	26,476	807	320	0.05	29	2	21,520	1,018,114	66,922
FIT-2-15	45-80	1	23,434	1,186	635	0.06	26	2	21,521	1,073,151	275,187
FIT-2-10	45-80	1	21,214	1,456	867	0.07	24	2	21,521	1,115,972	1,070,518

c. Assuming a 200% increase in the costs of the validated FITs.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval									
No Screening			0	49	0	0.01	49	11	21,482	869,648	
FIT-1-10	50-70	3	5,901	514	151	0.03	36	5	21,509	914,585	1,662
FIT-1-10	50-75	3	7,208	583	188	0.04	34	4	21,511	940,484	10,078
FIT-2-10	50-75	3	6,884	744	294	0.04	31	4	21,514	984,361	17,274
FIT-2-10	50-80	3	7,768	795	327	0.05	30	3	21,515	1,006,655	23,223
FIT-1-10	45-80	2	13,519	801	334	0.05	31	3	21,517	1,098,355	39,869
FIT-1-10	45-80	1	24,054	1,104	572	0.06	27	2	21,520	1,288,058	62,198
FIT-2-10	45-80	1	21,214	1,456	867	0.07	24	2	21,521	1,532,598	543,423

d. Assuming Chinese surveillance guidelines.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval									
No Screening			0	49	0	0.01	49	11	21,482	869,648	
FIT-1-10	50-70	3	6,572	638	343	0.03	39	6	21,509	932,920	2,357
FIT-2-10	50-70	3	6,563	801	449	0.04	35	5	21,512	946,907	4,632
FIT-2-10	50-75	3	8,108	949	561	0.04	32	4	21,515	980,771	10,924
FIT-2-10	50-80	3	9,185	1,008	601	0.05	31	3	21,516	995,748	11,432
FIT-1-15	50-80	1	25,386	967	570	0.05	31	3	21,519	1,073,331	27,808
FIT-1-10	50-80	1	25,130	1,291	815	0.06	28	2	21,520	1,112,751	34,579
FIT-1-15	45-80	1	30,333	1,113	695	0.05	30	2	21,522	1,173,484	35,516
FIT-1-10	45-80	1	30,063	1,499	993	0.06	27	2	21,523	1,232,248	46,638
FIT-2-10	45-80	1	29,675	2,123	1,499	0.08	22	2	21,524	1,487,932	164,958
SH-FIT-RA	45-80	1	27,798	6,290	5,290	0.18	16	1	21,526	2,433,797	750,686

e. Assuming international quality of life estimates.

Screening Strategy			FITs	Colonoscopies	False Positives	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start-Stop Age	Interval										
No Screening			0	49	0	0.01	49	11	21,482	19,035	869,648	
FIT-1-10	50-70	3	5,901	514	151	0.03	36	5	21,509	19,768	874,095	6
FIT-2-10	50-70	3	5,645	652	239	0.04	33	5	21,511	19,892	884,484	84
FIT-2-10	50-75	3	6,884	744	294	0.04	31	4	21,514	19,959	904,162	298
FIT-2-10	45-75	3	8,490	838	362	0.05	30	3	21,516	20,085	985,512	642
FIT-2-10	45-80	3	8,958	863	380	0.05	30	3	21,517	20,096	992,642	652
FIT-1-10	45-75	1	22,046	1,043	528	0.06	28	3	21,519	20,213	1,080,650	754
FIT-1-10	45-80	1	24,054	1,104	572	0.06	27	2	21,520	20,232	1,101,071	1,092
FIT-2-10	45-80	1	21,214	1,456	867	0.07	24	2	21,521	20,277	1,254,847	3,374

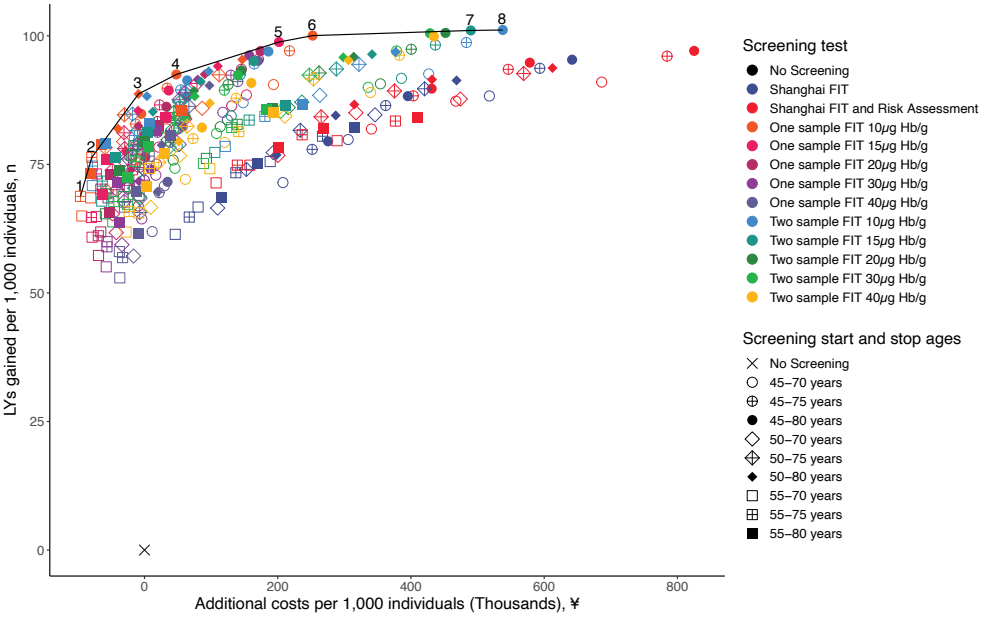
Note: Screening strategies: screening test - screening interval – test cut-off. Grey shading highlights optimal screening scenario at the willingness-to-pay threshold.
Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years

a. Results are discounted at an annual rate of 3%.

b. Costs are presented in Chinese Renminbi (¥).

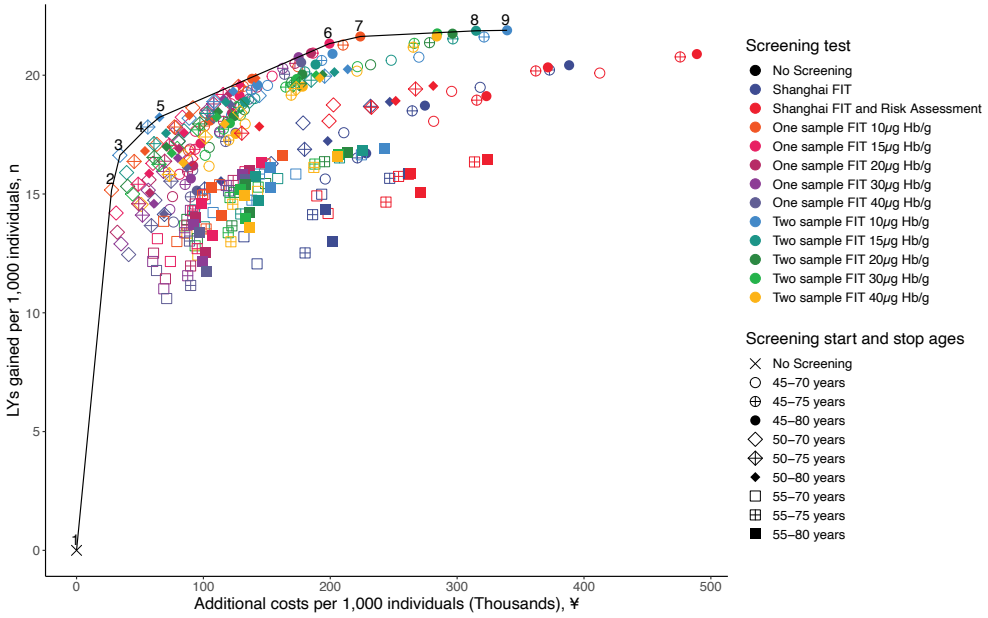
Supplementary Results Figure 2.1: Costs and life years gained (per 1,000 45-year-olds for all 324 colorectal cancer screening scenarios and a scenario without screening, assuming perfect adherence. The efficient frontier connects the economically efficient strategies.[a]

a. Results are undiscounted.



	1	2	3	4	5	6	7	8
Screen test	FIT–1–10	FIT–1–10	FIT–1–10	FIT–1–10	FIT–1–15	FIT–1–10	FIT–2–15	FIT–2–10
Screen ages	55–75	55–75	50–80	45–80	45–80	45–80	45–80	45–80
Screen frequency	3	2	2	2	1	1	1	1
ICER (¥)	dominates	2241	5680	15002	24414	40395	237483	532520

b. Results are discounted at 5%.



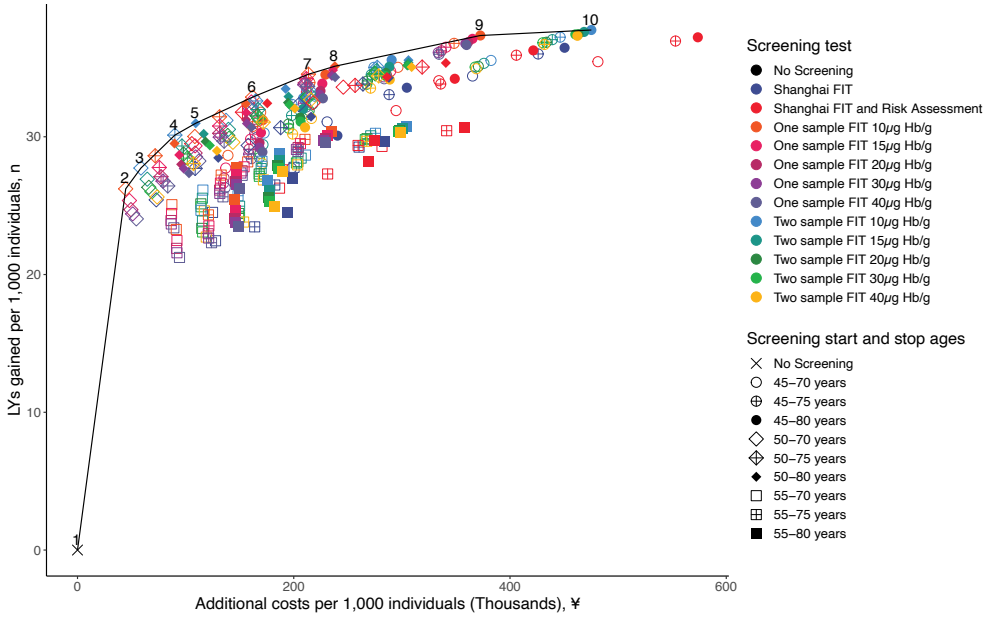
	1	2	3	4	5	6	7	8	9
Screen test	NoScr	FIT–1–10	FIT–2–10	FIT–2–10	FIT–2–10	FIT–1–15	FIT–1–10	FIT–2–15	FIT–2–10
Screen ages	–	50–70	50–70	50–75	50–80	45–80	45–80	45–80	45–80
Screen frequency	–	3	3	3	3	1	1	1	1
ICER (¥)	–	1820	4516	18476	22368	43223	81043	380124	1224423

Abbreviations: FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio, LYs, life years; μg Hb/g, micrograms of haemoglobin per gram faeces

a. Discounted costs and life years gained reflect total costs and life years gained of a screening program, accounting for time preference for present over future outcomes. Life years gained are plotted on the y-axis, and total costs are plotted on the x-axis. Each possible screening strategy is represented by a point. Strategies that form the solid line connecting the points lying left and upward are the economically rational subset of choices. This line is called the efficient frontier. The inverse slope of the line represents the incremental cost-effectiveness ratio of the connected strategies. Points lying to the right and beneath the line represent the dominated strategies.

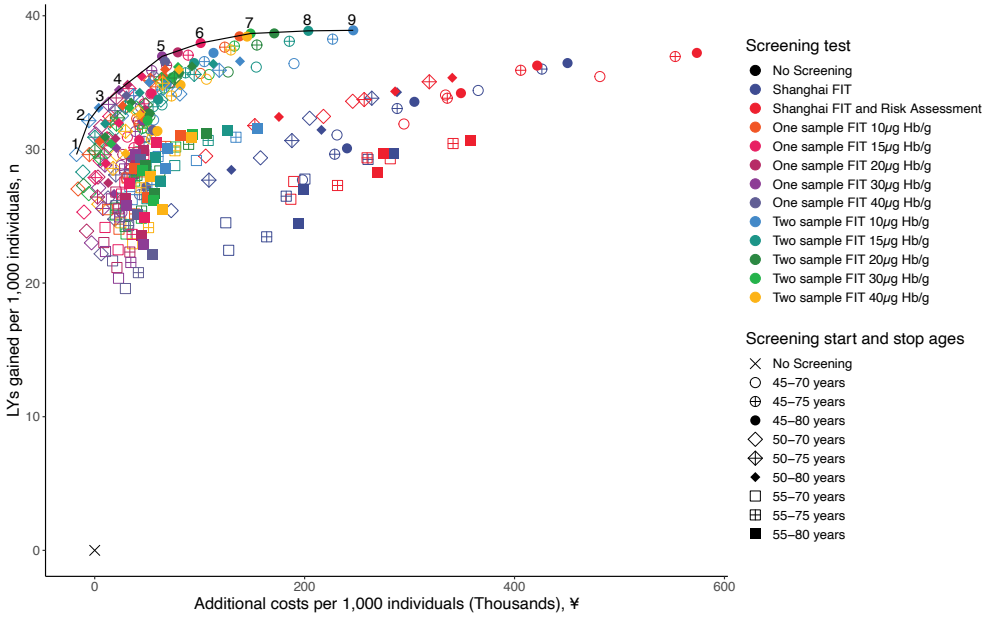
Supplementary Results Figure 2.2: Costs and life years gained (discounted at 3%) per 1,000 45-year-olds for all 324 colorectal cancer screening scenarios and a scenario without screening. The efficient frontier connects the economically efficient strategies.[a]

a. Assuming perfect adherence and adjusted FIT characteristics.



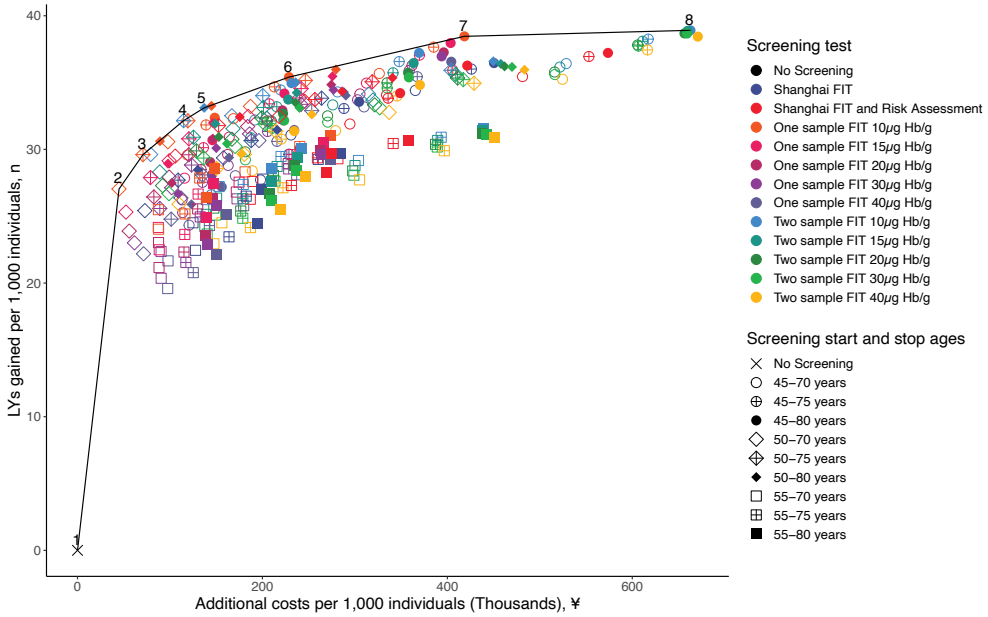
	1	2	3	4	5	6	7	8	9	10
Screen test	NoScr	FIT–1–10	FIT–2–10	FIT–2–10	FIT–2–10	FIT–1–10	FIT–1–10	FIT–1–10	FIT–1–10	FIT–2–10
Screen ages	–	50–70	50–70	50–75	50–80	50–70	50–75	50–80	45–80	45–80
Screen frequency	–	3	3	3	3	1	1	1	1	1
ICER (¥)	–	1700	9344	13124	22397	27739	31071	42153	60319	256708

b. Assuming perfect adherence and a 50% decrease in the costs of the validated FITs.



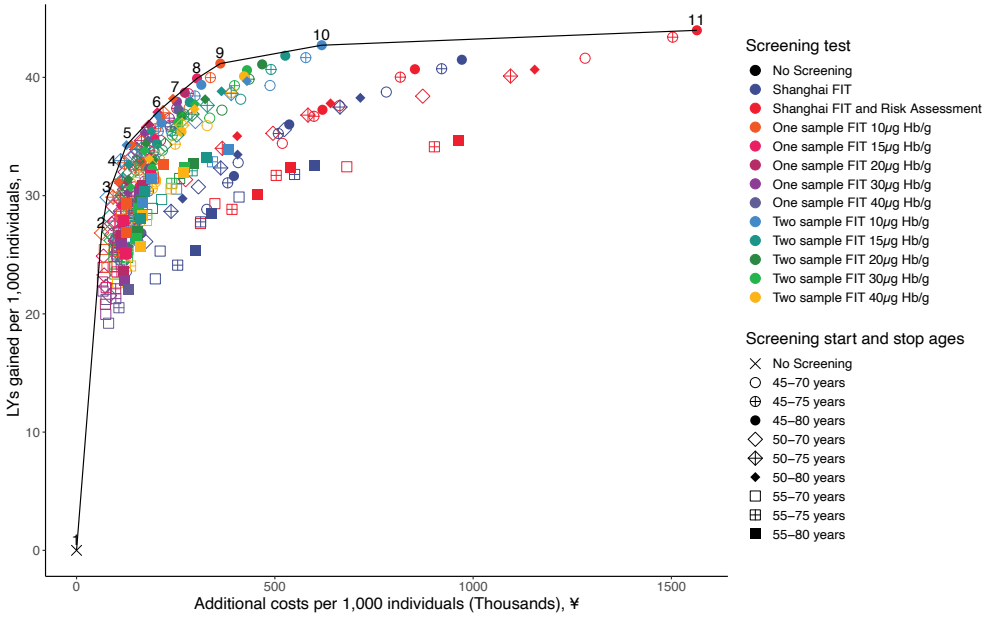
	1	2	3	4	5	6	7	8	9
Screen test	FIT–2–10	FIT–2–10	FIT–2–10	FIT–1–30	FIT–1–30	FIT–1–15	FIT–2–30	FIT–2–15	FIT–2–10
Screen ages	50–70	50–75	50–80	50–80	45–80	45–80	45–80	45–80	45–80
Screen frequency	3	3	3	1	1	1	1	1	1
ICER (¥)	dominates	4635	9769	14376	16383	36773	66922	275187	1070518

c. Assuming perfect adherence and a 200% increase in the costs of the validated FITs.



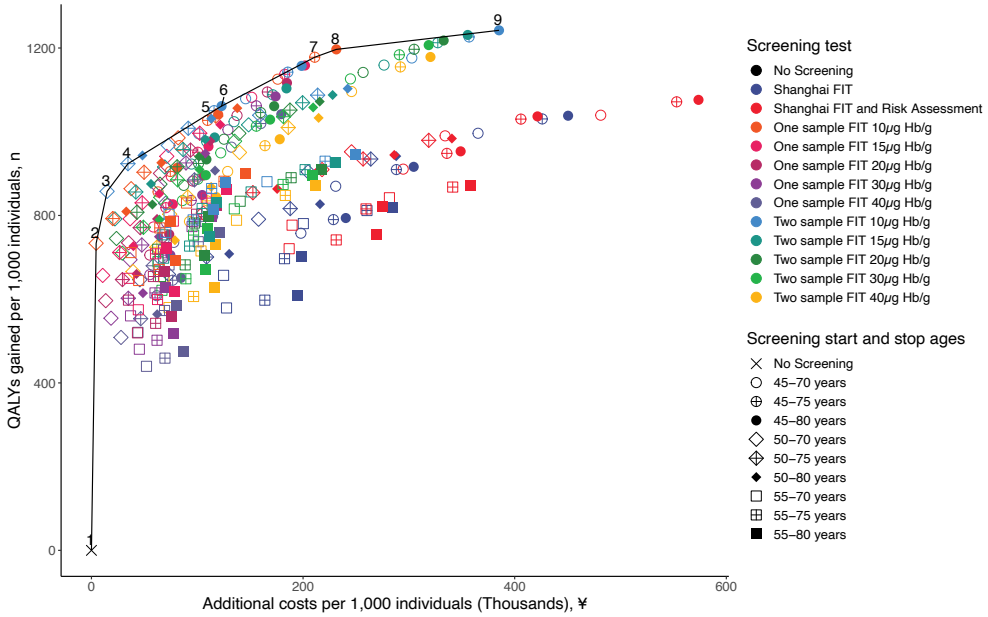
	1	2	3	4	5	6	7	8
Screen test	NoScr	FIT–1–10	FIT–1–10	FIT–2–10	FIT–2–10	FIT–1–10	FIT–1–10	FIT–2–10
Screen ages	–	50–70	50–75	50–75	50–80	45–80	45–80	45–80
Screen frequency	–	3	3	3	3	2	1	1
ICER (¥)	–	1662	10078	17274	23223	39869	62198	543423

d. Assuming perfect adherence and Chinese surveillance guidelines.



	1	2	3	4	5	6	7	8	9	10	11
Screen test	NoScr	FIT–1–10	FIT–2–10	FIT–2–10	FIT–2–10	FIT–1–15	FIT–1–10	FIT–1–15	FIT–1–10	FIT–2–10	SH–FIT–RA
Screen ages	–	50–70	50–70	50–75	50–80	50–80	50–80	45–80	45–80	45–80	45–80
Screen frequency	–	3	3	3	3	1	1	1	1	1	1
ICER (¥)	–	2357	4632	10924	11432	27808	34579	35516	46638	164958	750686

e. Assuming perfect adherence and international quality of life estimates.



	1	2	3	4	5	6	7	8	9
Screen test	NoScr	FIT–1–10	FIT–2–10	FIT–2–10	FIT–2–10	FIT–2–10	FIT–1–10	FIT–1–10	FIT–2–10
Screen ages	–	50–70	50–70	50–75	45–75	45–80	45–75	45–80	45–80
Screen frequency	–	3	3	3	3	3	1	1	1
ICER (¥)	–	6	84	298	642	652	754	1092	3374

Abbreviations: FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio, LY, life years; QALY, quality adjusted life years; μg Hb/g, micrograms of haemoglobin per gram faeces

a. Discounted costs and life years gained reflect total costs and life years gained of a screening program, accounting for time preference for present over future outcomes. Life years gained are plotted on the y-axis, and total costs are plotted on the x-axis. Each possible screening strategy is represented by a point. Strategies that form the solid line connecting the points lying left and upward are the economically rational subset of choices. This line is called the efficient frontier. The inverse slope of the line represents the incremental cost-effectiveness ratio of the connected strategies. Points lying to the right and beneath the line represent the dominated strategies.

CHAPTER 3

OPTIMISING THE EXPANSION OF THE NATIONAL BOWEL CANCER SCREENING PROGRAM

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ABSTRACT

Objectives: To estimate the impact of various expansion scenarios of the National Bowel Cancer Screening Program (NBCSP) on the number of bowel cancer deaths prevented and to investigate the impact of the expansion scenarios on colonoscopy demand.

Design: MISCAN-Colon, a well-established, validated computer simulation model for bowel cancer screening, was adjusted to reflect the Australian situation. In July 2013, we simulated the effects of screening over a 50-year period, starting in 2006. The model parameters included rates of participation in screening and follow up, rates of identification of cancerous and pre-cancerous lesions, bowel cancer incidence, mortality and the outcomes of the NBCSP. Five implementation scenarios, based on biennial screening using an immunochemical faecal occult blood test, were developed and modelled. A sensitivity analysis that increased screening participation to 60% was also conducted.

Participants: Australian residents aged 50 to 74 years.

Main outcome measures: Comparison of the impact of five implementation scenarios on the number of bowel cancer deaths prevented and demand for colonoscopy.

Results: MISCAN-Colon calculated that in its current state, the NBCSP should prevent 35,169 bowel cancer deaths in the coming 40 years. Accelerating the expansion of the program to achieve biennial screening by 2020 would prevent more than 70,000 deaths. If complete implementation of biennial screening results in a corresponding increase in participation to 60%, the number of deaths prevented will increase across all scenarios.

Conclusion(s): The findings strongly support the need for rapid implementation of the NBCSP Compared to the current situation, achieving biennial screening by 2020 could result in 100% more bowel cancer deaths (approximately 35,000) being prevented in the coming 40 years.

INTRODUCTION

With more than 14,000 newly diagnosed cases and approximately 4000 deaths each year, bowel cancer, or colorectal cancer, is the second most commonly reported cancer and the second most common cause of cancer related death in Australia.[1] Estimates show that one in 12 Australians are likely to develop bowel cancer before the age of 85 years,[2] making Australia highly ranked in bowel cancer incidence by international comparisons.[3]

Screening for bowel cancer is an attractive and viable option based on the World Health Organization's criteria for a cancer screening program.[4] Screening using the faecal occult blood test (FOBT) is well established as an effective way to reduce incidence and mortality of bowel cancer in the general population.[5-8] In 1999, the Australian National Health and Medical Research Council (NHMRC) recommended biennial screening with the FOBT for those aged over 50 years.[9] The National Bowel Cancer Screening Program (NBCSP), using the immunochemical FOBT (FIT), commenced in 2006 but was limited in scope, only offering screening to specific age cohorts (ages 55 and 65 years from 2006 and age 50 years from 2008).[10]

In the 2012-13 Budget, the Australian Government announced an on-going commitment to the NBCSP and additional funding to expand the eligibility criteria.[11] The funding was used to add 60-year-olds in 2013 and will enable 70-year-olds to be included from 2015. The announcement also indicated the Government's intention to further expand the NBCSP to meet NHMRC guidelines, stating that biennial screening would be progressively phased in and achieved by 2034.[11] In August 2013, the then Shadow Health Minister announced that under a Coalition government, biennial screening for 50 to 74-year olds would be achieved by 2020. In August 2013, the then shadow health minister, quoting the preliminary findings of this research, announced that under a Collation government, biennial screening for 50-74-year-olds would be achieved by 2020. The Coalition won the federal election in September 2013 and was expected to act on this commitment. In the 2014-15 Budget, the federal government made an announcement committing to the full implementation of biennial screening for the NBCSP by 2020.

We used micro-simulation modelling to estimate the impact and outcome of various expansion scenarios in order to establish the best possible implementation of the NBCSP.

METHODS

MISCAN-COLON MODEL

The MISCAN (Microsimulation Screening Analysis)-Colon model and the data sources that inform the quantification of the model are described in the **Model Appendix**. In brief, the

model simulates a large population of individuals from birth to death, first without and then with screening for bowel cancer. The simulation of life history modelled several factors including adenoma prevalence, size and multiplicity; progression of adenoma to cancer; stage at diagnosis; and life expectancy after diagnosis.

Table 3.1: Modelled implementation scenarios showing the age cohorts added to the National Bowel Cancer Screening Program in each year.

	Implementation scenario				
Year	**Current**	**Slow**	**Annual**	**Multiple**	**5-year**
2006	55/65	55/65	55/65	55/65	55/65
2007					
2008	50	50	50	50	50
2009					
2010					
2011					
2012					
2013	60	60	60	60	60
2014					
2015	70	70	70	70	70/72/74
2016					64/68#
2017		72/74	72/74	72/74	54/58*
2018			68	64/68#	62/66
2019		68	64#	62/58/54	52/56^
2020			62/58	52/66	
2021		68#	66	56^	
2022			54*		
2023		66	52		
2024			56^		
2025		64			
2026					
2027		62			
2028					
2029		58*	# final year of screening for 65-year-olds		
2030			* final year of screening for 55-year-olds		
2031		56	^ biennial screening achieved		
2032					
2033		54			
2034					
2035		52^			

The model simulated the Australian population age distribution as at June 2011[12] and life expectancy observed in 2009.[13] The model was calibrated to match age-specific incidence of bowel cancer as observed in Australia before the introduction of the NBCSP in 2006.[10] Stage distribution, localisation of cancers in the bowel and five-year relative survival after clinical diagnosis of a cancer were based on Australian literature.[14, 15]

The validity of the MISCAN-Colon model has been successfully tested on the results of several large screening and surveillance studies.[5-7, 16-18] The model has also been shown to explain observed incidence and mortality trends in the United States, accounting for risk factor trends, screening practice, and chemotherapy.[19]

Modelling Parameters

Scenarios

Screening in the Australian population was simulated over 50 years starting in 2006 (the year the NBCSP commenced), using five scenarios (Table 3.1). The "Current" scenario modelled the existing screening program including the addition of 70-year-olds in 2015. The base scenario ("Slow") was based on a proposed implementation plan, as set out in the 2012-13 Budget.[11] In this scenario, one age cohort was added every two years, starting with 70-year-olds in 2015. Subsequent age cohorts, from oldest to youngest, were added every other year. Full implementation was achieved by 2035.

The other scenarios were accelerations of Slow, adding one age cohort ("Annual" scenario) or two age cohorts ("Multiple" scenario) every year. In the fifth scenario ("5-year") implementation was completed within five years, commencing in 2015. Full implementation of all scenarios was defined as being achieved when all those aged 50 to 74-years were invited to screen on a biennial basis. Additional details about the criteria used can be found in Supplementary Methods Table 3.1.

Follow-up and surveillance

For all scenarios, it was assumed that after a positive FIT result, a diagnostic colonoscopy was offered. If no adenomas were found during the colonoscopy, the individual was invited to re-screen with FIT after five years.[20] Adenomas identified at colonoscopy were removed and the individual entered surveillance according to the NHMRC-approved guidelines.[21] It was assumed that surveillance stopped at 75 years of age.

Test Characteristics

The test characteristics were adjusted to simulate FIT positivity and cancer detection rates observed in the Queensland Bowel Cancer Screening Program between August 2006 and December 2010.[22, 23] This data set was chosen because of the unique and comprehensive nature of data collected by the Queensland program. Sensitivity and specificity were chosen

so that simulated FIT positivity rates and positive predictive values for cancer matched the observed rates to within 0.1%. The sensitivity of FIT for cancer was split to account for the variance in test sensitivity at different time points before clinical diagnosis (shortly before and longer before). Additional assumptions of the MISCAN-Colon model can be found in Table 3.2.

Table 3.2: MISCAN-Colon Model Assumptions.

Parameter	%
Sensitivity and specificity of FIT [a]	
Specificity (per person)	95.0
Sensitivity diminutive adenomas (1-5mm)	0.0
Sensitivity small adenomas (6-9mm)	9.0
Sensitivity large adenomas (≥10mm)	32.0
Sensitivity cancer long before clinical diagnosis	36.5
Sensitivity cancer shortly before clinical diagnosis	72.8
Simulated positivity rates [b] and positive predictive values of FIT (observed values)	
Overall FIT positivity rate [b]	7.7 (7.7)
Positives without histopathologically confirmed adenomas or cancer [c]	47.4 (47.7)
Positives with adenomas [c]	48.2 (48.0)
Positives with advanced adenomas [c]	25.6 (26.0)
Positives with confirmed cancer [c]	4.4 (4.3)
Sensitivity of colonoscopy	
Diminutive adenoma (1-5mm)	75.0
Small adenoma (6-9mm)	85.0
Large adenoma (≥10mm)	95.0
Preclinical cancer	95.0
Uptake of rescreening	
Previously attended	80.0
Previously not attended	15.0
Participation rates for follow-up colonoscopy and surveillance	
Colonoscopy follow-up after positive FIT	74.0
Surveillance	80.0

Abbreviations: FIT, immunochemical faecal occult blood test; MISCAN, Microsimulation Screening Analysis

a. Sensitivity in the table constitutes the probability of an individual lesion to bleed and be detected. The overall probability of a positive FIT result in a person depends on the person's number and type of lesions and probability of bleeding from other causes than adenomas and cancer. This latter probability is equal to the lack of specificity.

b. Simulated positivity rate is the percentage of FIT results that were positive (ie, blood was detected in the sample).

c. Positive predictive value is the percentage of positive FIT results that have a clinically significant finding (eg, adenoma, advanced adenoma or cancer).

PARTICIPATION

In each of the modelled implementation scenarios, those eligible were invited to participate in screening. For all scenarios, age specific participation rates for uptake of FIT screening for the first time and diagnostic colonoscopy following a positive FIT result were simulated based on participation rates for July 2008-June 2011, as reported in the *NBCSP Monitoring Report: Phase 2*[10] (Supplementary Methods Table 3.2). Participation rates for ages between those reported were linearly extrapolated. As rescreening within the NBSCP did not commence until mid-2013, there are no data available on adherence with rescreening in the Australian setting. Therefore, we used data from the United Kingdom on follow-up screening rounds, which suggested that 80% of those who participated in the previous screening round would do so again,[24] and 15% of non-participants would take up the next offer to screen. Similarly, attendance at surveillance colonoscopy was assumed to be 80%, based on data from US clinical practice.[25]

OUTCOMES

For each scenario, the model estimated the number of bowel cancer deaths prevented and colonoscopies required from 2006 to 2055. We then compared these results with the Current and Slow scenarios. The number of colonoscopies required each year per scenario includes colonoscopies that were a result of both a positive FIT result and surveillance colonoscopy. Overall estimates, as well as estimates by calendar year and birth cohort, were calculated. Due to space limitations, we will only present here the results of three scenarios – Current, Slow and 5-year. The results for the other scenarios are available in Supplementary Results Table 3.1.

SENSITIVITY ANALYSES

As there is no target participation rate for the NBCSP, we used the sensitivity analysis to explore the effect of a potential increase in screening participation rates to 60% once full implementation was achieved. This participation rate was chosen because, on balance, it appears to be achievable; both BreastScreen and the National Cervical Screening Program have previously achieved similar rates of participation,[1] and bowel cancer screening has the potential to achieve higher rates of participation as FIT is a convenient test that can be easily performed in private.

RESULTS

BOWEL CANCER DEATHS PREVENTED

Without expansion, the current NBCSP would prevent 35,169 bowel cancer deaths between 2015 and 2055. Completing implementation by 2035, as per the Slow scenario, would prevent 25,702 extra deaths between 2015 (the first year the scenarios diverge) and 2055 (Table 3.3, see Supplementary Results Table 3.1 for results of all scenarios). Accelerating the implementation, as per the 5-year scenario, with full implementation by 2020, prevented up to 9,167 additional bowel cancer deaths (34,869 more deaths prevented compared with Current scenario), clearly demonstrating that speed of implementation affects the number of deaths prevented.

The annual distribution of deaths prevented when compared to the Slow showed that the difference in bowel cancer deaths between the scenarios reached its peak between 2026 and 2031, with almost 400 more deaths prevented in 2026 in the 5-year scenario (Figure 3.1). Although all scenarios simulate biennial screening (age 50-74 years) from 2035 onwards, the number of deaths prevented differs between scenarios until after 2055, with the 5-year scenario preventing the most deaths each year.

To ensure that no birth cohort was disadvantaged by the different scenarios, we conducted a comparison of deaths prevented by year of birth. In all cases, additional deaths were prevented in each birth cohort compared to Current. This was most notable in the 5-year scenario.

COLONOSCOPY REQUIREMENT

The scenarios with a faster implementation also required more colonoscopies (Supplementary Results Table 3.1). To prevent the additional 25,702 deaths between the Current and Slow scenarios, 1,943,395 additional colonoscopies (85%) would be required. However, only a further 701,117 colonoscopies (17% more than Slow) would be needed to prevent the additional 9,167 deaths in the 5-year scenario. The overall number of colonoscopies required per death prevented is 65 in the Current scenario, 69 in the Slow scenario and 70 in the 5-year scenario, representing a good balance between burden and benefit.

Colonoscopy requirement over time (2015-2055) showed a distinct pattern related to the speed of implementation – the faster the implementation, the greater the increase in requirement. The greatest increase in colonoscopy requirement occurred during the implementation of each scenario. From 2014 to 2015, the absolute increase in colonoscopy requirement was largest, ranging from 6,887 for the Current scenario to 16,739 for the 5-year scenario. Over time, the absolute increase in colonoscopy requirement reduced for all scenarios, and at many time points, requirement was less than the previous year. There was

a noticeable dip in the Slow scenario in 2022 and 2030, when the 55- and 65-year-old cohorts were removed from the screening program.

Table 3.3: Summary of projected major outcomes by modelled implementation scenario, 2015-2055.

	Implementation scenario		
Outcome	**Current**	**Slow**	**5-year**
Total number of deaths prevented	35,169	60,871	70,038
Mean number of deaths prevented per year	879	1,522	1,750
Total number of colonoscopies per scenario	2,275,054	4,218,449	4,919,555
Number of colonoscopies per death prevented	65	69	70
Compared with *Current*			
Additional deaths prevented	-	25,702	34,869
Mean additional deaths prevented per year	-	643	872
Additional colonoscopies (% increase)	-	1,943,395 (85%)	2,644,512 (116%)
Compared with *Slow*			
Additional deaths prevented	-	-	9,167
Mean additional deaths prevented per year	-	-	229
Additional colonoscopies (% increase)	-	-	701,117 (17%)

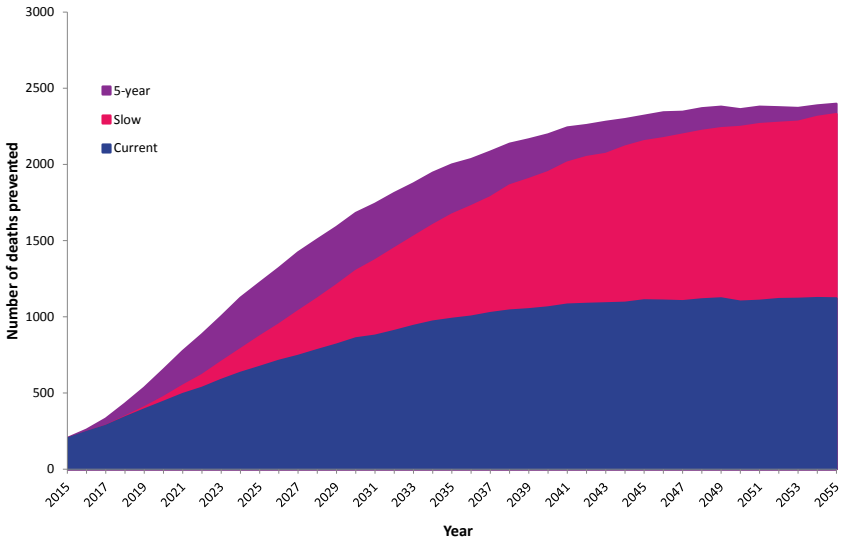

Figure 3.1: Deaths prevented over time by selected screening scenarios compared with Slow, 2015-2055.

SENSITIVITY ANALYSES

Once full biennial screening was achieved and participation increased to 60%, a substantial increase in deaths prevented was seen in all scenarios. This was most notable for the 5-year scenario, where over 54,000 additional deaths were prevented between 2015 and 2055 compared with Current scenario (Figure 3.2). The number of required colonoscopies also increased for all scenarios: the most notable increase was in the 5-year scenario, where approximately 4.35 million additional colonoscopies were required over the 40-year modelled period. Results for all scenarios can be found in Supplementary Results Table 3.2.

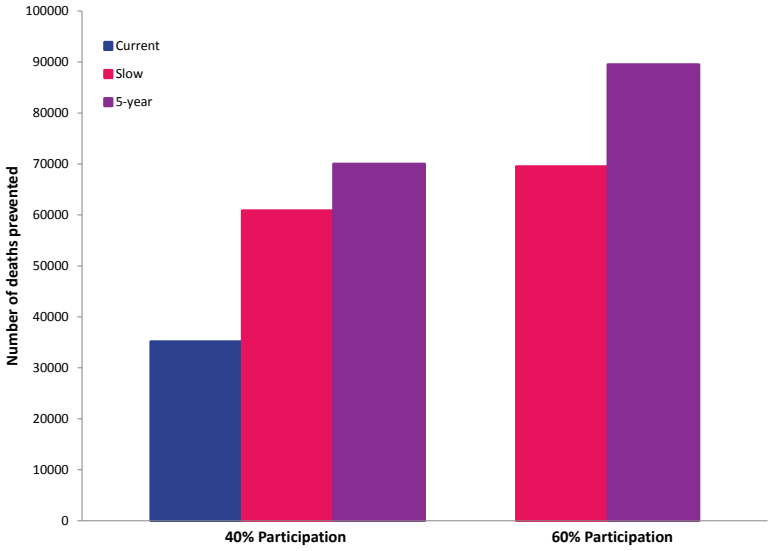

Figure 3.2: Total deaths prevented by selected screening scenario at 40% and 60% participation, 2015-2055.

DISCUSSION

Our research clearly shows that the choice of implementation scenario for the NBCSP affects the number of deaths prevented. Based on current participation rates in the NBCSP, the Slow scenario prevents more than 25,000 additional bowel cancer deaths compared with the Current scenario. Accelerating the implementation, as per the 5-year scenario, increases this number by about 40% to 34,869, with close to 100% more bowel cancer deaths prevented than in the Current situation. This equates to a mean of 872 deaths prevented per year over 40 years (2015 to 2055), 229 per year more than the Slow scenario.

The sensitivity analysis highlighted that if, once fully implemented, participation reached 60%, there is potential to prevent an additional 20,000 deaths in the 5-year scenario compared with Slow, equating to about 500 additional deaths prevented per year over the 40-year period.

It is unsurprising that a faster implementation will result in greater numbers of deaths prevented. A strength of our research is that it quantified the impact of different implementation scenarios to establish their effect on deaths prevented. These results are conservative estimates, as they are based on current rates of participation in the NBCSP which, while varying across age cohorts, remain collectively low. While acceptability of FIT has been reported to be as high as 83%,[26] low participation may, in part, be due to the lack of communication about the program and the difficulty in communicating a clear message about participation when eligibility is limited.[27] The assumed 60% participation in the sensitivity analysis appears optimistic compared to the current rates of participation in bowel cancer screening, but it is an unrealistic target participation rate.[28] The convenience of the FIT coupled with the reported high levels of acceptability suggest that the FIT has the potential to reach more people, including those in regional and remote Australia. Given the current low participation rates, a well-planned, comprehensive and long-term social marketing campaign with support strategies including community and health professional education will be required for the screening program to achieve an optimal level of participation – the importance of which cannot be underestimated.

Colonoscopy requirement also increased with all expansion scenarios (Supplementary Results Table 3.1). The calculations underpinning the modelled colonoscopy utilisation rely on national guidelines for screening and colonoscopy utilisation.[9, 21] However, as these assumptions do not necessarily reflect current practice, it was important to compare the increase in requirement resulting from a fully implemented screening program with current utilisation. Data from the Department of Human Services and Medicare Australia indicate that current colonoscopy utilisation (which is recognised as an underestimate of colonoscopy utilisation[29, 30]) is markedly higher than the modelled required utilisation, even for a program that is fully implemented within five years and achieves a participation rate of 60%.[29] The

NBCSP Quality Working Group reported that some colonoscopy utilisation in Australia is due to its overuse as a primary screening and surveillance tool.[30] While this may have some impact on the mortality gains of the program, yield has been shown to be limited.[31] A well-functioning program should encourage better compliance with NHMRC guidelines for screening and colonoscopic surveillance and, coupled with other appropriate strategies, should free up capacity for an increased number of NBCSP-related procedures, a notion supported by the NBCSP Quality Working Group.[30] Recommendations for workforce, service capacity and program quality assurance were beyond the scope of this project but were investigated by the NBCSP Quality Working Group, and several of these recommendations have been or are in the process of being implemented.[30]

Our research considered the number of deaths prevented by bowel cancer screening and did not take into account disability- or quality-adjusted life years gained. It is not expected that this would greatly influence the results with respect to the speed of implementation.

While we did not investigate the cost-effectiveness of an expedited implementation, there is a strong body of evidence to show that bowel cancer screening is highly cost effective, and in light of the increasing treatment costs, there is some suggestion that screening might even be cost-saving.[14, 32, 33] This indicates that a faster rollout may actually be desirable from a cost-effectiveness perspective.

Implementing the NBCSP within a five year time frame from 2015 is not unrealistic, as both the national breast and cervical cancer screening programs became fully operational within five years.[34] Moreover, while there is a substantial increase in colonoscopy requirement, within the context of current utilisation, the demand for colonoscopy due to over-use as a primary screening tool will likely decease.

Our analysis focused on the impact of accelerating the implementation of the NBCSP, comparing the Current situation with the Slow scenario with full implementation by 2035 and with the 5-year scenario with full implementation by 2020. The findings strongly support an expedited implementation of the NBCSP, using the 5-year scenario as the benchmark, to prevent maximum loss of life from bowel cancer.

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SUPPLEMENTARY METHODS

Supplementary Methods Table 3.1: Scenario Criteria.

The scenarios adhered to the following criteria:

- the 72-year-old cohort and the 74-year-old cohorts were invited at the same time because of the smaller population size of these two groups;
- age cohorts were added in the following order given the higher incidence of bowel cancer in the older cohorts: 70's, followed by the 60's, concluding with the 50's;
- cohort substitution was permitted when the 55- and 65-year-old cohorts were removed, with screening being offered to an extra cohort; and
- screening interval was at least two years and no more than five years apart (as is the current screening interval). This was achieved for all scenarios except *slow*, where there was a six-year screening interval associated with the removal of the 55- and 65-year-old cohorts.

Supplementary Methods Table 3.2: Modelled participation rates for FIT, follow-up colonoscopy, surveillance colonoscopy and uptake of rescreening if previously attended or not attended screening.

Age	50	52	54	55	56	58	60	62	64	65	66	68	70	72	74	Avg
Participation rate FIT (%)	34.0	35.9	37.8	38.8	39.6	41.3	42.9	44.5	46.1	46.9	46.9	46.9	46.9	46.9	46.9	38.4
Colonoscopy follow-up after positive FIT (%)	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0	74.0
Surveillance (%)	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0
Uptake of rescreening if previously attended (%)	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0	80.0
Uptake of rescreening if previously not attended (%)	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0

Abbreviations: FIT, faecal immunochemical test

SUPPLEMENTARY RESULTS

Supplementary Results Table 3.1: Summary of projected major outcomes by modelled implementation scenarios, 2015-2055.

Outcome	Implementation scenario				
	Current	**Slow**	**Annual**	**Multiple**	**5year**
Total number of deaths prevented	35,169	60,871	66,930	67,961	70,038
Mean number of deaths prevented per year	879	1522	1673	1699	1750
Total number of colonoscopies per scenario	2,275,054	4,218,449	4,713,117	4,803,501	4,919,566
Number of colonoscopies per death prevented	65	69	70	71	70
Additional deaths prevented compared to *Current*	-	25,702	31,761	32,792	34,869
Compared to *Current*					
Mean additional deaths prevented per year	-	643	794	820	872
Additional colonoscopies (%increase)	-	1,943,363 (85%)	2,438,180 (107%)	2,528,560 (111%)	2,644,779 (116%)
Compared to *Slow*					
Additional deaths prevented	-	-	6059	7091	9167
Average additional deaths prevented per year	-	-	151	177	229
Additional colonoscopies (%increase)	-	-	494,817 (12%)	585,197 (14%)	701,416 (17%)

Supplementary Results Table 3.2: Summary of projected major outcomes by modelled implementation scenario sensitivity analysis, 2015-2055.

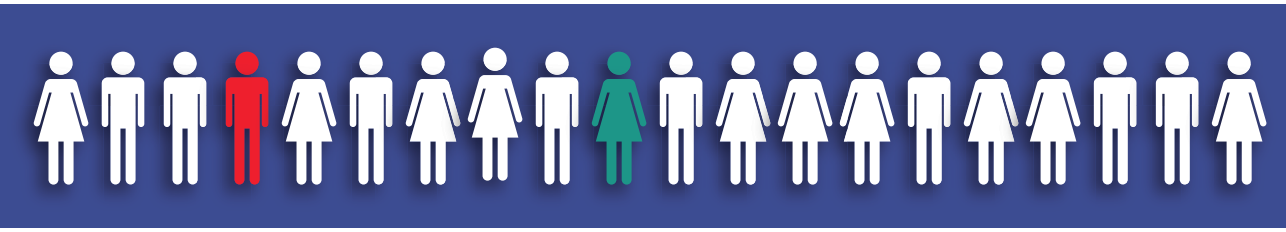
Outcome	Implementation scenario				
	Current	**Slow**	**Annual**	**Multiple**	**5year**
Total number of deaths prevented	35,169	69,520	83,002	86,137	89,519
Mean number of deaths prevented per year	879	1738	2075	2153	2238
Total number of colonoscopies per scenario	2,275,054	5,178.748	6,184,886	6,417,749	6,625,881
Number of colonoscopies per death prevented	65	74	75	75	74
Compared to *Current*					
Additional deaths prevented	-	34,351	47,833	50,968	54,350
Mean additional deaths prevented per year	-	859	1196	1275	1359
Additional colonoscopies (%increase)	-	2,903,694 (128%)	3,909,833 (172%)	4,142,695 (182%)	4,350,827 (191%)
Compared to *Slow (60%)*					
Additional deaths prevented	-	-	13,482	16,617	20,000
Average additional deaths prevented per year	-	-	337	415	500
Additional colonoscopies (%increase)	-	-	1,006,13 (35%)	1,239,001 (43%)	1,447,134 (50%)

PART II

OPTIMISATION THROUGH PERSONALISATION

CHAPTER 4

COLORECTAL CANCER SCREENING WITH FAECAL IMMUNOCHEMICAL TESTING, SIGMOIDOSCOPY OR COLONOSCOPY: A MICROSIMULATION MODELLING STUDY



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ABSTRACT

Objective: To estimate benefits and harms of different colorectal cancer screening strategies, stratified by (baseline) 15-year colorectal cancer risk.

Design: Microsimulation modelling study using MIcrosimulation SCreening ANalysis-Colon (MISCAN-Colon).

Setting: A parallel guideline committee (*BMJ* Rapid Recommendations) defined the time frame and screening interventions, including selection of outcome measures.

Population: Norwegian men and women aged 50-79 with varying 15-year colorectal cancer risk (1%-7%).

Comparisons: Four screening strategies were compared with no screening: biennial or annual faecal immunochemical test (FIT), or single sigmoidoscopy or colonoscopy at 100% adherence.

Main outcome measures: Colorectal cancer mortality and incidence, burdens, and harms over 15 years of follow-up. The certainty of the evidence was assessed using the GRADE approach.

Results: Over 15 years of follow-up, screening individuals aged 50-79 at 3% risk of colorectal cancer with annual FIT or single colonoscopy reduced colorectal cancer mortality by 6 per 1,000 individuals. Single sigmoidoscopy and biennial FIT reduced it by 5 per 1,000 individuals. Colonoscopy, sigmoidoscopy, and annual FIT reduced colorectal cancer incidence by 10, 8, and 4 per 1,000 individuals, respectively. The estimated incidence reduction for biennial FIT was 1 per 1,000 individuals. Serious harms were estimated to be between 3 per 1,000 (biennial FIT) and 5 per 1,000 individuals (colonoscopy); harms increased with older age. The absolute benefits of screening increased with increasing colorectal cancer risk, while harms were less affected by baseline risk.

Results were sensitive to the setting defined by the guideline panel. Because to uncertainty associated with modelling assumptions, we applied a GRADE rating of low certainty evidence to all estimates.

Conclusions: Over a 15 year period, all screening strategies may reduce colorectal cancer mortality to a similar extent. Colonoscopy and sigmoidoscopy may also reduce colorectal cancer incidence, while FIT shows a smaller incidence reduction. Harms are rare and of similar magnitude for all screening strategies.

INTRODUCTION

Colorectal cancer is a public health issue, with an estimated 1.4 million new cases and 700,000 deaths worldwide in 2018.[1] Screening is intended to reduce colorectal cancer incidence and mortality, and its effectiveness has been demonstrated in randomised controlled trials of guaiac faecal occult blood testing (gFOBT) and sigmoidoscopy.[2-11] Colonoscopy is likely to be at least as effective as sigmoidoscopy since it reaches the whole large bowel, whereas sigmoidoscopy reaches only the distal part of the large bowel. Faecal immunochemical testing (FIT) is likely to be at least as effective as gFOBT, since both tests detect blood in stools, and FIT demonstrates higher sensitivity and specificity.[12] However, because of the lack of published evidence from randomised trials for colonoscopy and FIT screening, it is not known if they are more effective, compared to gFOBT and sigmoidoscopy.[13]

Despite its benefits, colorectal cancer screening can be burdensome, and colonoscopy is associated with rare but serious complications. In addition, screening performance depends on the baseline risk of cancer for individuals. Few studies and guidelines have incorporated how baseline risk affects the balance between benefits, burden, and harms of screening in the past.

To elucidate these issues, we undertook microsimulation modelling as part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation programme (www.magicproject.org) and the *BMJ*. The aim of the Rapid Recommendations is to respond to new, potentially practice changing, evidence and provide trustworthy practice guidelines in a timely manner. The *BMJ* Rapid Recommendations project for colorectal cancer screening was triggered by recent updates from three large randomised trials on sigmoidoscopy screening with follow-up data of 15 years or longer.[3, 5, 14] In light of this new evidence, we addressed the potential benefits and harms of colorectal cancer screening with annual or biennial FIT or a single sigmoidoscopy or colonoscopy in the time frame of 15 years. This work informed the parallel guideline published in a multi-layered electronic format on bmj.com and MAGICapp.

METHODS

At the request of the guideline panel (Helsingen et al.[15]), we applied the MIcrosimulation SCreening ANalysis-Colon (MISCAN-Colon) model to simulate 15 years follow-up of population cohorts aged 50-79 years. We estimated the benefits, burden, and harms of the following four screening strategies: annual FIT, biennial FIT, a single sigmoidoscopy, and a single colonoscopy. We compared the four screening strategies with each other, and with no screening. We performed the analyses stratified by different levels of baseline colorectal

cancer risk. Additionally, we determined screening benefits for men and women separately, and screening harms for different age groups, as requested by the panel.

MISCAN-COLON MODEL

MISCAN-Colon is a well-established microsimulation model for colorectal cancer.[16, 17] In brief, MISCAN-Colon simulates life histories of a large group of individuals from birth to death. In addition, the model simulates the development of colorectal cancer through the adenoma carcinoma sequence. As each simulated person ages, one or more adenomas may develop. These adenomas can progress in size increasing from small (≤5 mm) to medium (6–9 mm) to large (≥10 mm). Some adenomas can develop into preclinical cancer, which may progress through cancer stages I to IV. At any time during the development of the disease, the process may be interrupted because a person dies of other causes. With screening, colorectal cancer may either be prevented (by the detection and removal of adenomas) or detected at an earlier stage with a more favourable prognosis. In this way, colorectal cancer incidence and/or colorectal cancer mortality may be reduced. The model also estimates harms associated with screening.

The quantification and model assumptions are described in detail in the **Model Appendix**. In brief, the age-specific prevalence and multiplicity distribution of adenomas (the distribution of the individual number of adenomas across the population) were calibrated using autopsy studies.[18-28] The duration of preclinical colorectal cancer (sojourn time) and the adenoma dwell-time (the duration of progression of adenomas) were calibrated using rates of interval cancers (cancers that are diagnosed between screening tests) and surveillance detected cancers (cancers found during surveillance) in randomised gFOBT and sigmoidoscopy trials.[6, 8, 29-33]

For this study, we developed a MISCAN-Colon model version calibrated to the sex-, age-, stage-, and localisation-specific colorectal cancer incidence and survival as observed in Norway during the timeframe of the Norwegian Colorectal Cancer Prevention (NORCCAP) trial (1999-2011) (Supplementary Methods, Part 1), using data provided by the Norwegian Cancer Registry.[34] Life expectancy was based on sex-specific lifetables for 2007, the middle of the NORCCAP trial period, from Statistics Norway.[35] We validated this model using the results of one of the trigger publications: 15-year follow-up data from the NORCCAP trial.[5] The validation methods and results are described in Supplementary Methods Part 2.

SIMULATED COHORTS

We simulated seven population cohorts consisting of men and women aged 50-79 years with a 15-year colorectal cancer risk varying from 1% to 7%, using the same Norwegian sex-specific MISCAN-Colon versions as we used for the validation. The age-specific onset of adenomas in MISCAN-Colon for all ages was adjusted to match the 15-year colorectal cancer risk in the

seven cohorts. The modelled risk levels were chosen to cover the majority of individuals under consideration for this study (healthy people aged 50 to 79 years), but still with a manageable number of risk levels. We used the range of risk levels found when applying the QCancer® risk prediction model to the UK Biobank cohort as guidance.[36] The simulated risk levels from 1% to 7% cover approximately 90% of the colorectal cancer risk levels found in the UK Biobank cohort (personal communication UK Biobank researcher Juliet Usher-Smith). We confirmed that the chosen risk levels also cover the range of risk levels observed in the general population, by comparing the risk levels with the 15 year colorectal cancer risk ranges found in two large population-based cancer databases.[37, 38] Data from the UK Biobank were also used to validate the QCancer® prediction model for colorectal cancer. The QCancer® Calculator is an open-access online tool that aims to predict individual colorectal cancer risk based on risk factors such as medical history, lifestyle factors, and ethnicity.[39] Individuals may predict their 15-year colorectal cancer risk with this calculator (https://qcancer.org/15yr/colorectal/index.php). Subsequently, they may use this predicted colorectal cancer risk to look up the best risk-matching MISCAN-Colon predictions of screening outcomes, to get a personal estimate of the magnitude of benefits and harms of colorectal cancer screening. The clinical practice guideline presents relevant details.[15]

SCREENING STRATEGIES

For each cohort, we assessed four colorectal cancer screening strategies during a 15-year period: biennial FIT, annual FIT, a single sigmoidoscopy, and colonoscopy. All strategies were compared with no screening. For FIT, we chose a cut-off of 20 µg Hb/g faeces since this is used in many screening programmes.[40] We assumed that individuals with a positive FIT result and those with at least one adenoma (of any size) diagnosed at sigmoidoscopy screening were referred for colonoscopy.

Sensitivity and specificity of the screening tests were based on diagnostic test accuracy studies (Table 4.1).[41, 42] Age-specific risks for complications associated with colonoscopy were derived from SEER-Medicare data (Table 4.1).[43-45] Only complications requiring hospital admission within 30 days after the colonoscopy were taken into account. Only colonoscopies with polypectomies were considered to cause adverse effects. We included colorectal perforations and bleedings, other gastrointestinal adverse events, cardiovascular adverse events, and mortality related to screening procedure. The number of complications was calculated by multiplying the number of colonoscopies with polypectomies by each complication risk. The simulated cohorts were assumed to have no prior screening.

Table 4.1. Key modelling assumptions used in the study.

Input parameter	Base-case assumption	References
Demography		
All-cause mortality	Norwegian lifetables 2007	Statistics Norway[35]
Natural history [f]		
Adenoma onset	Age-dependent (non-homogeneous Poisson) [f]	
Adenoma progression		
State transitions	Age-dependent	
State duration, years (total)	Exp(λ=130)	
Cancer progression (preclinical)		
Stage transitions	Age-dependent	
Stage durations, years	Exp(λ=2.5)	
Colorectal cancer incidence (without exposure to screening)	Age-, stage- and location-dependent	Norwegian Cancer Registry[34]
Colorectal cancer stage distribution	Age- and location-dependent	Norwegian Cancer Registry[34]
Colorectal cancer survival	Age-, stage- and location-dependent	Norwegian Cancer Registry[34]
Colonoscopy quality		
Sensitivity (%) [a, f]		
adenomas 0-5mm	75%	
adenomas 6-9mm	85%	van Rijn et al[41]
adenomas ≥10mm	95%	van Rijn et al[41]
malignant neoplasia	95%	
Specificity (%)	100%	
Complete colonoscopy examination (%) [c]	Men 93.5% / Women: 85.2%	Holme et al[46]
Complication rates (%) [d]		
with polypectomy	Age-dependent (50-79 years)	van Hees et al[44]
Perforations and bleeding	0.2-0.9	
Other GI adverse events	0.2-0.8	
Cardiovascular events	0.1-0.7	
Screening procedure related mortality	0.008-0.04	
without polypectomy [d]	-	
Sigmoidoscopy quality		
Sensitivity (%) [a, f]		
adenomas 0-5mm	75%	
adenomas 6-9mm	85%	van Rijn et al[41]
adenomas ≥10mm	95%	van Rijn et al[41]
malignant neoplasia	95%	
Specificity (%) [b]	98.2%	Buskermolen at al[47]
Complete examination (%) [e]	Men: 93.2% / Women: 83.8%	Holme et al[46]
Faecal immunochemical test (FIT) quality		
Sensitivity (%) [a]		Imperiale et al[42]
adenomas 0-5mm	0	
adenomas 6-9mm	11.4	
adenomas ≥10mm	15.9	
malignant neoplasia		
short before clinical detection	88.6	
long before clinical detection	62.6	
Specificity (%) [b]	97.6	

Abbreviations: Poisson, Poisson distribution; Exp, exponential distribution

a. Sensitivity was defined as the probability of detecting an adenoma that was present at the time of test.

b. The lack of specificity indicates how many of the tests that did not detect adenomatous lesions resulted in a referral for follow-up colonoscopy. The MISCAN-Colon model is a natural history microsimulation model simulating onset of adenomas in some individuals, that may progress to colorectal cancer in some cases. The model does not explicitly simulate the presence of blood in stool. To simulate FIT screening, we rather use estimates of per-person sensitivity and

specificity by disease status based on a study by Imperiale et al. with a cut-off of 20 µg of haemoglobin per g of faeces.[42] We fitted per-lesion sensitivity and per-person specificity of the model to the per-person sensitivity and specificity estimates found in the study. In the model, the probability for a person to test positive depends on the lack of specificity and the per-lesion sensitivity for the lesions present in that individual.

c. Colonoscopy was considered complete if the cecum was reached. In the incomplete examinations, the endpoint was assumed to be distributed uniformly over the colon/rectum.
d. We assumed that colonoscopy without polypectomy was not associated with a higher risk of complications. The risk of complications for polypectomy was assumed to increase exponentially with age. Perforation and bleeding concerned adverse events requiring blood transfusions; other GI adverse events included paralytic ileus, nausea, vomiting and dehydration, abdominal pain; and cardiovascular adverse events included myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, or syncope, hypotension, or shock. The screening procedure related mortality was derived from estimates of the incidence of perforation and case-fatality for perforation.[43-45]
e. Flexible sigmoidoscopy was considered complete if the junction of the sigmoid/colon descendens was reached. In the incomplete examinations, the endpoint was assumed to be distributed uniformly over the rectosigmoid.
f. More details regarding the calibrated natural history parameters and other model elements are provided in the **Model Appendix**.

We simulated surveillance consistent with European Society of Gastrointestinal Endoscopy Guidelines.[48] Individuals with low risk findings (fewer than 3 low risk adenomas (<10mm diameter) at primary screening) did not receive any surveillance, whereas individuals with high risk findings were offered surveillance with colonoscopy after three years, and thereafter colonoscopies repeated at intervals of three to five years depending on the findings.

As our aim is to provide individuals who are considering screening with estimates of the possible benefits and harms of participation, we assumed 100% adherence to screening, follow-up and surveillance for all analyses.

Outcomes

We distinguished the three screening-related outcome groups for the 15-year follow-up time frame chosen by the *BMJ* Rapid Recommendation guideline panel: benefits of screening, screening harms, and screening burden. For benefits of screening, we present model-predicted colorectal cancer incidence and mortality, and all-cause mortality reduction. For screening burden, we present the number of screening tests, number of individuals with at least one colonoscopy (including screening colonoscopies), and number of individuals with at least two colonoscopies (for example, individuals with at least one surveillance colonoscopy). For screening harms, we present risk of screening related colorectal perforations and bleedings, other gastrointestinal adverse events, cardiovascular adverse events, and mortality related to screening procedure.

Sensitivity analyses

As a one-way sensitivity analysis, we assessed results stratified by age and sex; and we assessed outcomes with lifetime follow-up instead of 15-year follow-up.

CERTAINTY OF EVIDENCE

We used the GRADE approach to address the certainty of the evidence.[49] GRADE has not yet produced detailed guidance for assessing certainty of evidence in modelling studies. To make our assessment, we considered uncertainty associated with key inputs into the model.

GUIDELINE PANEL AND PATIENT INVOLVEMENT

According to the *BMJ* Rapid Recommendations process, a multiprofessional guideline panel that included three patients who have experienced colorectal cancer screening provided oversight to the study and identified the population and outcomes of interest.

RESULTS

The Rapid Recommendation panel suggests against screening if the risk is below a 15-year colorectal cancer risk of 3% and suggests screening if the risk is above 3%.[15] For simplification, we only describe the estimates for individuals with the 3% risk level. Estimates for all other risk levels are provided in the Table 4.2 and Figure 4.1.

BENEFITS OF SCREENING

MISCAN-Colon predicted that all screening strategies reduced colorectal cancer incidence and mortality across all colorectal cancer risk groups (Figure 4.1a and b, Table 4.2). Colonoscopy showed the largest reduction in colorectal cancer mortality, but the differences between the screening strategies were small and the reduction may be similar for all strategies. For instance, the model-predicted that, at 3% risk without screening, colorectal cancer mortality was nine deaths per 1,000 individuals. There were six per 1,000 fewer colorectal cancer deaths with colonoscopy and annual FIT (approximately 60% reduction) and five fewer deaths per 1,000 with sigmoidoscopy and biennial FIT screening (approximately 50% reduction).

Colonoscopy may be the most effective strategy in reducing colorectal cancer incidence, followed by sigmoidoscopy (Figure 4.1b, Table 4.2). Colonoscopy was estimated to reduce colorectal cancer incidence by 10 colorectal cancer cases and sigmoidoscopy by eight per 1,000 individuals (approximately 30% reduction); annual FIT had four fewer and biennial FIT had one fewer incident cancer per 1,000 screened (approximately 10% and 5% reduction).

The estimated relative effects were similar across the different levels of baseline risk (1% to 7% over 15 years) for both colorectal cancer incidence and mortality, resulting in larger absolute effects for colorectal cancer incidence and mortality for individuals with higher risk. The model assumes that prevented colorectal cancer deaths lead to a corresponding reduction in all-cause mortality. At 3% risk, the estimated relative reduction in all-cause mortality was around 1.5% (Table 4.2), corresponding to a reduction of five per 1,000 individuals (all-cause mortality reduced from 328 to 323).

SCREENING BURDEN

The two FIT strategies required the most screening tests (Figure 4.1c, Table 4.2). The number of FIT rounds for the simulated cohort depended on the age of the individual at the first screening and the screening interval. Individuals ≤65 years old at cohort entry received seven rounds with biennial FIT and 15 rounds with annual FIT. However, many individuals received fewer screening rounds: individuals >65 years at cohort entry because they stopped screening after age 79; individuals that died within 15 years of follow-up; individuals that tested FIT positive and were referred for a colonoscopy and therefore received screening according to the surveillance guidelines. For individuals with a 3% colorectal cancer risk, we predicted that approximately 8,700 tests were required with annual FIT screening, and 5,100 with biennial FIT screening. Colonoscopy screening resulted in the highest number of individuals receiving at least one colonoscopy, since all individuals received colonoscopy as a screening test (Figure 4.1d, Table 4.2). The number of individuals with at least two colonoscopies (that is, individuals with at least one surveillance colonoscopy) was highest for colonoscopy regardless of colorectal cancer risk (Table 4.2).

SCREENING HARMS

The risk of screening related mortality, colorectal perforations and bleedings, other serious gastrointestinal adverse events, or cardiovascular adverse events was proportional to the number of required colonoscopies (Figure 4.1e-g). In the 3% colorectal cancer risk group, the predicted overall complication risk was lowest with biennial FIT screening (2.9 per 1,000) and highest with colonoscopy screening (4.6 per 1,000) (Table 4.2).

SENSITIVITY ANALYSES

The model predicted similar reductions in cancer incidence and mortality for the screening tests for men and women for all levels of 15-year baseline risk of colorectal cancer, except for sigmoidoscopy, for which the model predicted that women may benefit slightly less than men (Supplementary Results Part 1: Figure 4.1 and Part 2: Tables 4.1-12).

When results were stratified by age, annual FIT was more effective in reducing colorectal cancer mortality than a single colonoscopy in younger individuals (50-59 years old). In older individuals (aged 75-79 years), colonoscopy and sigmoidoscopy were more effective. In addition, the estimated risk of complications increased more with age for the colonoscopy and sigmoidoscopy screening strategies than for the FIT strategies, although the increase in risk in absolute numbers was small (Supplementary Results Part 1: Figure 4.2 and Part 2: Tables 4.1-12). For example, at 3% colorectal cancer risk, a single colonoscopy strategy resulted in colorectal perforations and bleedings of 1.6 per 1,000 in men aged 50-54 years and of 3.4 per 1,000 in men aged 75-79 years.

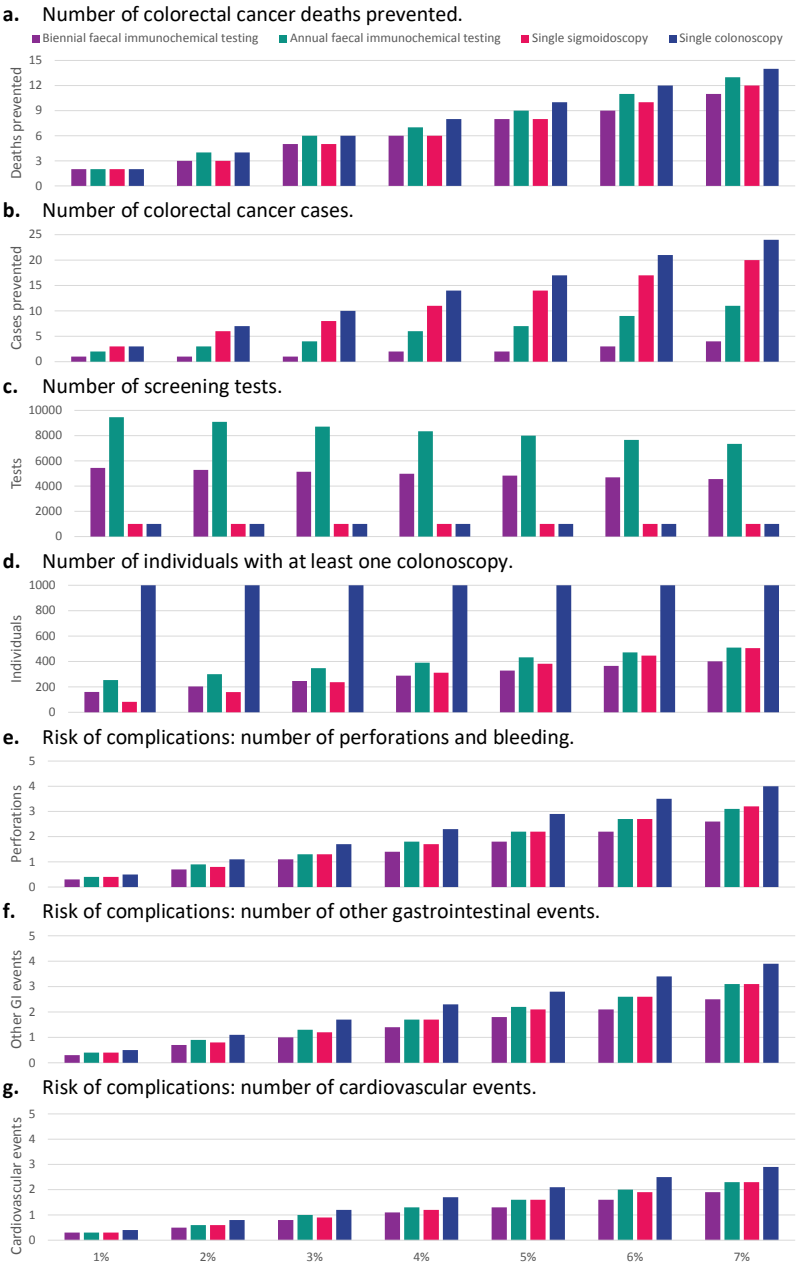

Figure 4.1: MISCAN-Colon predictions of colorectal cancer mortality and incidence reduction, screen tests, colonoscopies and complications per 1000 individuals, using FIT, flexible sigmoidoscopy or colonoscopy. Results are stratified by colorectal cancer risk. Individuals were followed-up during 15 years.

When we considered lifetime follow-up, the model predicted larger absolute reductions in colorectal cancer incidence and mortality for all screening strategies (Supplementary Results, Figures 4.3 and 4.4), and less differences between annual FIT and colonoscopy. At younger ages (50-64 years) the model predicted that annual FIT was more effective at reducing colorectal cancer incidence and mortality than a single colonoscopy, although the difference was small. For example, annual FIT screening prevented 43 lifetime colorectal cancer cases in those aged 50-54 compared to 37 prevented cases with a single colonoscopy.

CERTAINTY OF EVIDENCE

We noted appreciable uncertainty associated with the following model inputs: a) all colorectal cancers develop through adenomas; b) differences in colorectal cancer risk are caused by differences in adenoma incidence; and c) adenoma dwell time. There is no high certainty data to inform the model regarding these model inputs. Therefore, despite the predictive and external validity of the model against the NORCCAP study (Supplementary Methods Part 2), the panel considered all model estimates as low certainty evidence.

DISCUSSION

Our microsimulation model analysis suggests that all screening strategies reduce colorectal cancer mortality during 15-years of follow-up, and colonoscopy, sigmoidoscopy, and annual FIT may also reduce colorectal cancer incidence. The extent of absolute risk reduction varies with baseline colorectal cancer risk. Few differences were observed when results were stratified by sex. When outcomes were stratified by age, we observed that FIT screening strategies were estimated to be more effective in younger individuals, while colonoscopy and sigmoidoscopy were more effective in older individuals. FIT screening strategies required the highest overall number of screening tests, and colonoscopy screening resulted in the highest number of colonoscopies, regardless of colorectal cancer risk. Consequently, we observed the highest probability of experiencing a complication in individuals who underwent screening with a single colonoscopy, with increasing risk at older age groups.

Table 4.2: Predictions of benefits and harms of screening for individuals aged 50-79 years at varying levels of colorectal cancer risk. All outcomes are given per 1000 screened individuals over 15 years and compared to a scenario with no screening.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	8	1	53	2	0.4	5441	160	26	0.3	0.3	0.3	0.02
Annual FIT	18	2	62	2	0.5	9464	254	31	0.4	0.4	0.3	0.02
Single sigmoidoscopy	29	3	57	2	0.4	1000	82	28	0.4	0.4	0.3	0.02
Single colonoscopy	35	3	66	2	0.5	1000	1000	33	0.5	0.5	0.4	0.03
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	6	1	51	3	0.8	5288	203	54	0.7	0.7	0.5	0.04
Annual FIT	16	3	60	4	0.9	9091	300	66	0.9	0.9	0.6	0.05
Single sigmoidoscopy	28	6	54	3	0.8	1000	159	57	0.8	0.8	0.6	0.05
Single colonoscopy	34	7	64	4	0.9	1000	1000	68	1.1	1.1	0.8	0.07
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	5	1	50	5	1.1	5134	246	83	1.1	1.0	0.8	0.06
Annual FIT	15	4	59	6	1.3	8715	347	101	1.3	1.3	1.0	0.08
Single sigmoidoscopy	27	8	52	5	1.1	1000	237	86	1.3	1.2	0.9	0.07
Single colonoscopy	34	10	63	6	1.4	1000	1000	105	1.7	1.7	1.2	0.10

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	4	2	49	6	1.5	4980	288	112	1.4	1.4	1.1	0.09
Annual FIT	15	6	59	7	1.8	8346	391	138	1.8	1.7	1.3	0.11
Single sigmoidoscopy	27	11	52	6	1.5	1000	312	119	1.7	1.7	1.2	0.10
Single colonoscopy	34	14	63	8	1.8	1000	1000	144	2.3	2.3	1.7	0.14
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	4	2	49	8	1.8	4834	328	142	1.8	1.8	1.3	0.11
Annual FIT	15	7	59	9	2.2	7996	433	175	2.2	2.2	1.6	0.13
Single sigmoidoscopy	27	14	52	8	1.8	1000	382	153	2.2	2.1	1.6	0.13
Single colonoscopy	34	17	63	10	2.4	1000	1000	184	2.9	2.8	2.1	0.17
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	5	3	50	9	2.2	4694	365	171	2.2	2.1	1.6	0.13
Annual FIT	15	9	59	11	2.6	7664	472	211	2.7	2.6	2.0	0.16
Single sigmoidoscopy	28	17	53	10	2.2	1000	446	189	2.7	2.6	1.9	0.16
Single colonoscopy	34	21	64	12	2.8	1000	1000	226	3.5	3.4	2.5	0.20
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	5	4	50	11	2.6	4558	401	201	2.6	2.5	1.9	0.15
Annual FIT	16	11	59	13	3.0	7346	509	247	3.1	3.1	2.3	0.18
Single sigmoidoscopy	29	20	54	12	2.6	1000	505	228	3.2	3.1	2.3	0.19
Single colonoscopy	35	24	64	14	3.2	1000	1000	268	4.0	3.9	2.9	0.24

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Colonoscopy may result in the largest reduction in colorectal cancer incidence, followed by sigmoidoscopy and annual FIT. However, this finding was sensitive to the follow-up setting defined by the guideline panel. The panel chose a 15-year follow-up period because this allowed model predictions to be validated against trial data. With lifetime follow-up, the model predicted that relative incidence and mortality reductions from screening would persist for some more years, resulting in larger absolute numbers of prevented colorectal cancer cases and deaths. This was especially true for FIT, where lifetime follow-up resulted in higher estimates for colorectal cancer incidence reductions, making the test comparable to colonoscopy. However, because longer term follow-up data from trials is lacking, lifetime estimates are more uncertain and were thus not taken into account by the panel.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Model predictions for colorectal cancer mortality and incidence reduction in this study are considerably higher than those observed in randomised screening trials. These seemingly discrepant results can be explained by our assumption of 100% adherence to screening tests, work-up, and surveillance colonoscopies, whereas trial outcomes are the result of real-world adherence patterns, which are considerably lower. When we replicated the NORCCAP trial population including observed adherence patterns, MISCAN-Colon predictions for colorectal cancer incidence and mortality reduction were in line with the trial results (Supplementary Methods Part 2). Moreover, when we replicated the design of an Italian cohort study, the model predicted reductions in colorectal cancer incidence and mortality resulting from FIT screening that aligned well with those observed in that study (data not shown).[50] We acknowledge that 100% adherence gives estimates that are higher than what would be expected in a population screening program, when adherence is never 100%. However, our intention was to inform individuals about expected effectiveness when they (fully) participate in screening rather than considering the impact of a screening program from a public health perspective and assessing results at the population level. The aim of this study was to support the *BMJ* Rapid Recommendation panel by comparing different screening strategies, stratified by baseline 15-year colorectal cancer risk, using microsimulation modelling. A strength of this work is that we validated our model using the recently published 15-year follow-up results of the NORCCAP trial.[5] To our knowledge, this is the first modelling study to enable individuals to directly link their individual colorectal cancer risk to their predicted benefits and harms of colorectal cancer screening. Individuals can do this through determining their colorectal cancer risk using a calculator, such as the QCancer® Calculator,[39] incorporating information on age, sex, ethnicity, and other colorectal cancer risk factors. The QCancer® (10yr) Calculator performed better than other prediction tools when externally validated against the UK Biobank cohort. However, like the other colorectal cancer risk prediction tools, it is far from perfect, and with an area under the curve of 0.67 in men and 0.65 in women, it poorly

discriminates between those at a lower and those at a higher risk, which may lead to misclassification of individual baseline colorectal cancer risk.[51, 52]

Our study has several limitations. First, MISCAN-Colon could not replicate the sex-specific differences in colorectal cancer incidence and mortality reduction as observed in the NORCCAP sigmoidoscopy screening trials[52] (Supplementary Methods Part 2: Table 4.1), despite the sex-specific adjustments to the model.[5] On the one hand, it may be that the dwell time of adenomas differs between men and women, potentially because the proportion of cancers in the proximal colon is higher in women. In MISCAN-Colon we did not assume sex-specific or location-specific differences in duration because of insufficient information from clinical studies or autopsy studies. On the other hand, the observed difference in screening effectiveness of sigmoidoscopy between men and women is higher in the NORCCAP trial than what was observed in the other sigmoidoscopy studies.[52]

Second, at the request of the panel, we only modelled four screening strategies, and, for FIT, applied only one cut-off value (20 µg Hb/g faeces). Applying lower or higher FIT cut-off values may result in higher or lower colorectal cancer screening effectiveness. In view of the results of diagnostic studies, there are also uncertainties regarding the additional benefit of using FIT annually instead of biennially.[53]

Third, it remains unknown whether differences in colorectal cancer risk among the population are caused by variations in the number of adenomas, a faster adenoma progression to malignancy, or a combination of the two. These variations may exist between men and women, different ethnicities, different levels of genetic predisposition or different environments. For this analysis, we assumed that differences in adenoma incidence cause differences in colorectal cancer risk.

Fourth, in MISCAN-Colon we assumed that all cancers developed from precursors via a common pathway. In the model description we refer to this as the adenoma carcinoma pathway with adenoma being the precursor lesions. However, recent evidence suggested that three distinct cancer pathways are relevant: about 60% to 70% of the cancers develop via the conventional adenoma carcinoma sequence, 20% to 30% via the serrated polyp pathway, and 3% via the Lynch pathway.[54] In the model, we calibrated the average time it takes for a precursor to develop into colorectal cancer. Therefore, all precursor types are included in the modelled mix of slow and rapid progressing lesions. Modelling one common pathway may have consequences for the modelled results. For instance, we may overestimate the effectiveness of FIT and sigmoidoscopy compared with colonoscopy. Evidence is accumulating that FIT might be less sensitive for serrated polyps, and these polyps are usually located in the right side of the colon.[37, 38, 42, 55] These polyps may have higher malignant potential than conventional adenomas. However, evidence for the malignant potential of the precursors from the distinct pathways is not yet decisive.

Fifth, this project focuses on the individual's perspective rather than on the perspective of public health professionals deciding on population-based screening programmes, which was the reason for assuming 100% adherence to screening and follow-up for all screening options. In population-based screening programs, adherence rates of the various screening options can differ widely across countries.[56-58] When public health professionals make decisions about population-based screening programmes, they should also include evidence on the country-specific adherence rate to determine which screening option is most suitable. In addition, cost-effectiveness analyses should be performed. For public health professionals, a message from this study still may lie in the finding that benefits of screening do not differ much between the screening options.

Sixth, the estimated reduction in all-cause mortality is not observed in large randomised trials of gFOBT and sigmoidoscopy screening, which have not shown a significant reduction of all-cause mortality with screening. The *BMJ* Rapid Recommendations panel did not regard all-cause mortality estimates from the model as clinically relevant when making their recommendations.

Finally, we did not model probability bands. An important strength of this study is the large number of simulations we have performed, with different screening strategies, background colorectal cancer risks, age groups, and sex. The drawback is that to obtain probability bands for all simulations in this article, would require 840,000 simulations, which is too computationally expensive.

POLICY IMPLICATIONS AND CONCLUSIONS

Notwithstanding the limitations, this modelling study addresses an important gap in current knowledge on colorectal cancer screening. There is insufficient evidence from clinical studies to determine which screen modality is most effective.[13] Currently, three large randomised trials are under way to assess the comparative effectiveness of colonoscopy and FIT,[59] and one on sigmoidoscopy versus FIT.[51] Our results indicate that the difference in colorectal cancer mortality reduction between screening modalities is substantially smaller than the differences in colorectal cancer mortality between screening and no screening. To achieve sufficient power to demonstrate these differences, the current colorectal cancer screening trials would require very large sample sizes. It is therefore unlikely that a comparison of all evaluated strategies will ever become available from randomised trials. Comparing screening modalities stratified by baseline colorectal cancer risk, age, and sex is even more complicated. In these cases, clinicians and patients must make choices on the basis of the best available evidence, even if it is of low certainty.

Our belief is that our modelling results are generalisable to individuals across the Western world. Although there may be some differences in life expectancy, age-specific colorectal

cancer incidence, colorectal cancer stage distribution, and colorectal cancer survival compared to Norway, we expect that these differences do not significantly affect relative differences between screening modalities.

This study, together with the other publications in this *BMJ* Rapid Recommendations cluster, supports patients and physicians in the process of shared decision making by quantifying screening benefits, harms, and burdens on an individual level. For example, based on a certain colorectal cancer risk threshold, some low risk individuals may conclude that the undesirable consequences of screening outweigh the desirable consequences. Evaluating the modelling results, we predicted that lifetime follow-up of screened individuals resulted in different estimates of screening effectiveness compared to 15-year follow-up. This additional finding encourages researchers to continue the follow-up in their randomised cohorts to evaluate longer-term benefits of screening.

In conclusion, MISCAN-Colon predicted that all screening modalities reduce colorectal cancer mortality during a 15-year follow-up period, regardless of colorectal cancer risk, age, and sex. A single colonoscopy may be the most effective screening modality in preventing colorectal cancer incidence during 15 years follow-up. Colonoscopy screening is also associated with the highest risk for complications, but overall complication risks are low for colorectal screening. These results will contribute to risk-based colorectal cancer screening recommendations in this *BMJ* Rapid Recommendation project.[15]

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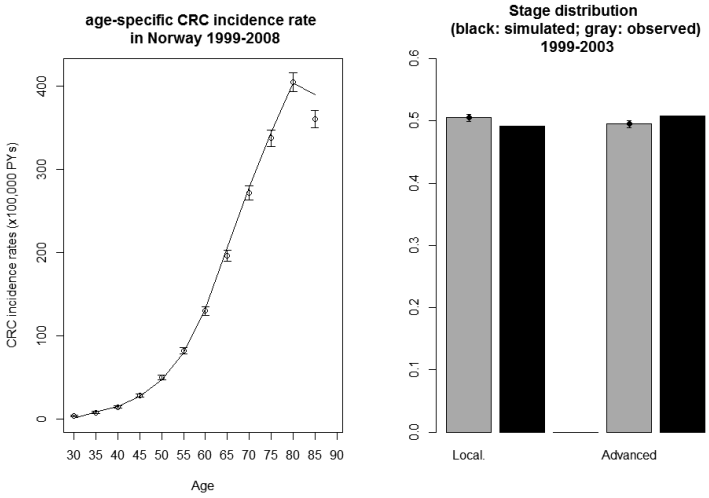
SUPPLEMENTARY METHODS

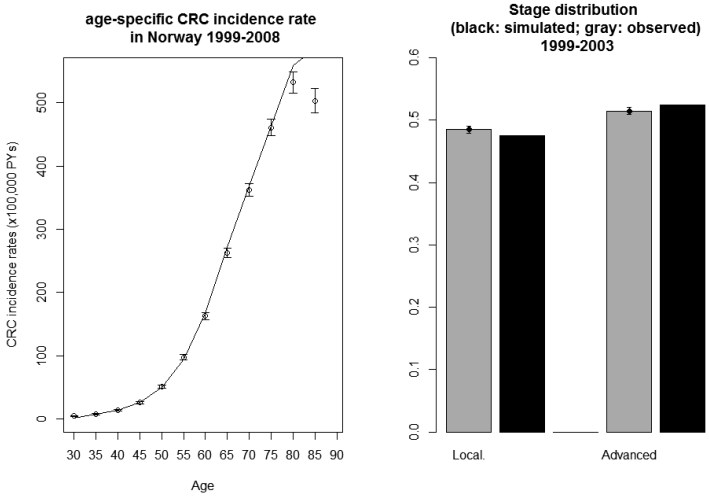
PART 1: CALIBRATION RESULTS OF THE MISCAN-COLON MICROSIMULATION MODEL TO THE NORWEGIAN SETTING

Supplementary Methods Figure 4.1: Calibration results: Observed and model-predicted colorectal cancer incidence rates by age and stage distribution for Norway.

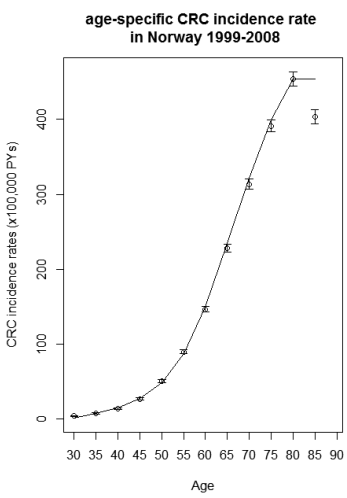
a. Calibration results MISCAN-Colon female model.

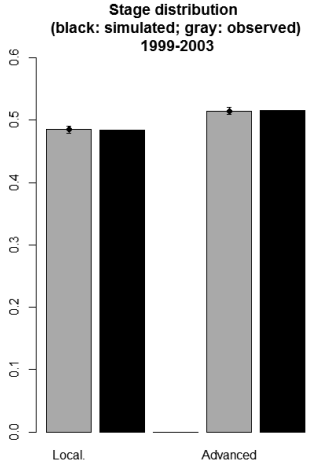


b. Calibration results MISCAN-Colon male model.



c. Calibration results MISCAN-Colon combined model.





PART 2: VALIDATION OF THE MISCAN-COLON MICROSIMULATION MODEL AGAINST THE NORCCAP SIGMOIDOSCOPY STUDY

METHODS

We used MISCAN-Colon to simulate Norwegian Colorectal Cancer Prevention (NORCCAP) trial outcomes and compared predictions with those observed according to the same methodology as previously described.[1] Primary validation targets were relative overall and distal colorectal cancer incidence reduction and mortality reduction observed by Holme et al.,[2] who described the 15-year follow-up results of the NORCCAP trial. To simulate the NORCCAP trial, we adjusted MISCAN-Colon to the demography and screening behaviour of the NORCCAP trial population.

NORCCAP TRIAL

In the NORCCAP trial, individuals between the ages of 50 and 65 years from two Norwegian regions were randomly assigned to either a control group (n = 78,220) or an intervention group that consisted of two arms (n = 10,283 and n = 10,289). Since there was no screening program in place in Norway during the study period, the control group did not receive routine colorectal cancer screening.[3] In the intervention arm, individuals were offered a once-only sigmoidoscopy (arm 1, n = 10,283) or sigmoidoscopy with a qualitative faecal occult blood test (FOBT) (arm 2, n = 10,289).[4]

The trial was carried out in two phases; individuals born from 1935 to 1945 were selected and randomized to undergo screening in 1999 and 2000 (i.e., 53–65 years old at time of screening), and individuals born from 1946 to 1950 were selected and randomized to undergo screening in 2001 (i.e., 49–54 years old at the time of screening). Individuals were followed until colorectal cancer diagnosis, death, emigration, or 31 December 2015, whichever occurred first.[2] The latest paper on long-term effects of the study made no distinction between the 2 different intervention arms. Therefore, we compared model outcomes with the overall results of the intervention arms and will use the term intervention group when referring to both intervention arms.

ADJUSTMENT OF MISCAN-COLON TO THE NORCCAP TRIAL

We used MISCAN-Colon to simulate a population with an age distribution comparable to the NORCCAP trial (personal communication with research leader G. Hoff, 2016). colorectal cancer incidence in the NORCCAP control group was 11% lower than incidence in the whole of Norway. We therefore adjusted the model accordingly by lowering the age-specific onset of adenomas by 11% for all ages. Comparing incidence rates observed in the NORCCAP trial, we assumed that non-adherers had a slightly higher age-specific onset of adenomas for all ages than individuals in the control group (relative risk of 1.05). In addition, age-specific onset in

adherers was lowered for all ages to ensure that the overall colorectal cancer risk in the intervention group did not differ from the colorectal cancer risk in the control group, taking participation rate into account (relative risk of 0.97).

Control group and intervention group were simulated for 16 years according to trial design. For the intervention group, we assumed age-specific participation rates for sigmoidoscopy, FOBT and diagnostic colonoscopy as observed in the NORCCAP trial. Adherence for surveillance colonoscopies was not reported in trial publications and was assumed to be 80%. Test sensitivity of flexible sigmoidoscopy and follow-up colonoscopy and specificity of follow-up colonoscopy were based on literature.[5] Test specificity of flexible sigmoidoscopy, faecal occult blood test characteristics and reach of sigmoidoscopy and colonoscopy were based on observations in the NORCCAP study.

VALIDATION TARGETS

Our primary validation targets were the overall and distal colorectal cancer incidence and mortality rate and HRs of overall and distal colorectal cancer incidence and mortality at 14- to 16-year follow-up (depending on the year of trial inclusion) in the intervention group relative to the control group. Model outcomes were considered consistent when predicted within 95% confidence intervals (CIs) of the corresponding NORCCAP trial targets.

VALIDATION RESULTS

Overall, the MISCAN-Colon predictions for 15-year incidence and mortality reduction from a once-only sigmoidoscopy in the NORCCAP trial were consistent with the trial results. The simulated hazard ratio (HR) for incidence was 0.84 compared to an observed HR of 0.78 (95% CI: 0.70-0.87) (Table 4.1), while simulated and observed HR for mortality reduction were 0.72 and 0.79 (95% CI: 0.65-0.96), respectively.

For males, MISCAN-Colon underestimated the impact of screening on colorectal cancer incidence compared to the NORCCAP trial results (observed HR: 0.66, 95% CI: 0.57-0.78; simulated HR: 0.81), but MISCAN-Colon predictions of colorectal cancer mortality reduction were consistent (observed HR: 0.63, 95% CI: 0.47-0.83; simulated HR: 0.70). For females, MISCAN-Colon predictions for colorectal cancer incidence reduction were in line with the trial results (observed HR: 0.92, 95% CI: 0.79-1.07; simulated HR: 0.85), but colorectal cancer mortality reduction was overestimated (observed HR: 1.01, 95% CI: 0.77-1.33; simulated HR: 0.76).

Supplementary Methods Table 4.1: Hazard ratios: 14-16 years follow-up interventions effects of the NORCCAP trial including 95% confidence intervals for these effects and MISCAN- Colon predictions of these effects. [a] NORCCAP trial results were derived from Holme et al, 2018.[2]

Gender	Outcome	CRC location	Observed HR	Confidence interval	Simulated HR	Cases per 100,000 person-years					
						Observed (control)[b]	Confidence Interval	Simulated (control)[c]	Observed (intervention group)	Confidence Interval	Simulated (intervention group)[d]
Both[e]	Incidence	Overall	0.78	(0.70-0.87)	0.84	174.5	(166.9-182.1)	174.5	135.9	(122.5-149.3)	146.5
Both[e]	Mortality	Overall	0.79	(0.65-0.96)	0.72	52.9	(48.8-57)	51.2	41.9	(34.5-49.3)	36.7
Male	Incidence	Overall	0.66	(0.57-0.78)	0.81	196.9	(185.4-208.4)	195.4	131.4	(112.5-150.3)	158.9
Male	Mortality	Overall	0.63	(0.47-0.83)	0.70	63.3	(57-69.6)	61.6	40.0	(29.6-50.4)	43.0
Female	Incidence	Overall	0.92	(0.79-1.07)	0.85	153.1	(143.2-163)	152.7	140.1	(121.0-159.2)	130.4
Female	Mortality	Overall	1.01	(0.77-1.33)	0.76	43.3	(38.2-48.4)	39.0	43.7	(33.1-54.3)	29.5
Both[e]	Incidence	Distal	0.68	(0.58-0.79)	0.80	98.5	(92.8-104.2)	96.2	67.1	(57.7-76.5)	77.3
Both[e]	Mortality	Distal	0.83	(0.64-0.87)	0.65	27.8	(24.8-30.8)	28.5	23.4	(17.8-29.0)	19.0
Male	Incidence	Distal	0.59	(0.48-0.73)	0.80	124.3	(115.1-133.5)	119.7	74.3	(60.1-88.5)	95.4
Male	Mortality	Distal	0.65	(0.45-0.93)	0.66	37.3	(32.4-42.2)	35.6	24.6	(16.5-32.7)	23.5
Female	Incidence	Distal	0.81	(0.64-1.02)	0.81	74.3	(67.4-81.2)	74.8	60.1	(47.6-72.6)	60.8
Female	Mortality	Distal	1.17	(0.79-1.73)	0.69	18.8	(15.4-22.2)	18.0	22.2	(14.6-29.8)	12.4
Both[e]	Incidence	Proximal	0.92	(0.78-1.08)	0.88	72.0	(67.2-76.8)	78.3	66.1	(56.7-75.5)	69.2
Both[e]	Mortality	Proximal	0.71	(0.52-0.98)	0.78	22.7	(20-25.4)	22.7	16.2	(11.6-20.8)	17.7
Male	Incidence	Proximal	0.81	(0.63-1.04)	0.84	67.6	(60.9-74.3)	76.3	55.1	(42.9-67.3)	63.8
Male	Mortality	Proximal	0.60	(0.37-0.96)	0.75	23.3	(19.5-27.1)	26.2	14.1	(7.9-20.3)	19.7
Female	Incidence	Proximal	1.01	(0.82-1.25)	0.89	76.1	(69.2-83)	77.9	76.5	(62.4-90.6)	69.6
Female	Mortality	Proximal	0.83	(0.54-1.26)	0.81	22.2	(18.6-25.8)	21.0	18.2	(11.4-25.0)	17.1

Shading indicates model predictions outside confidence intervals of the trial. Blue shading indicates underestimation by the model, while red shading indicates overestimation.

Abbreviations: HR, hazard ratio; CRC, colorectal cancer.; NORCCAP trial, Norwegian Colorectal CAncer Prevention trial

a. NORCCAP is screening trial comparing effectiveness reducing CRC mortality of once-only flexible sigmoidoscopy to no screening. Validation has been performed as described previously.[1]

b. For observed values, the number of distal and proximal CRC cases and deaths are less than the total number of overall CRC cases and deaths. This is due to some unclassified cancers in the NORCCAP trial. For simulated values, the number of distal and proximal CRC cases are equal to the total number of overall CRC cases and deaths, since there is no correction for unclassified cancers. MISCAN-Colon is therefore more likely to overestimate proximal and distal CRC cases and deaths compared to the NORCCAP trial results.

c. Adenoma onset for all ages was adjusted to match overall CRC incidence in control group.

d. Adenoma onset for all ages was adjusted to match the risk difference between CRC incidence in the control group versus non-adherers.

e. For the results of both genders, aggregated data was used.

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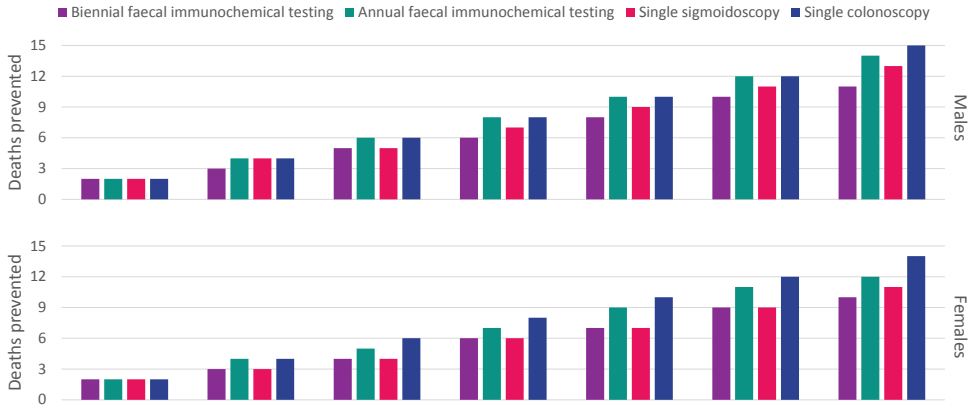
Supplementary Results

For consistency and completeness, we present outcomes for all combinations of colorectal cancer risk, age and gender. However, with the current discriminatory performance of risk calculators, many of these combinations will be obsolete or very rare. For example, according to the QCancer risk calculator, the 15-year colorectal cancer risk in women aged 50 years varies between 0.9% (9 per 1,000) without risk factors and 2.2% (22 per 1,000) with all risk factors. Similarly, 15-year colorectal cancer risk in men aged 75 years varies between 6.4% (64 per 1,000) without any risk factors and 18.6% (186 per 1,000) with all risk factors. Thus, results presented for 50-54y old women with a 7% colorectal cancer risk and 75-79y old men with 3% colorectal cancer risk (and many other combinations) are currently not applicable.

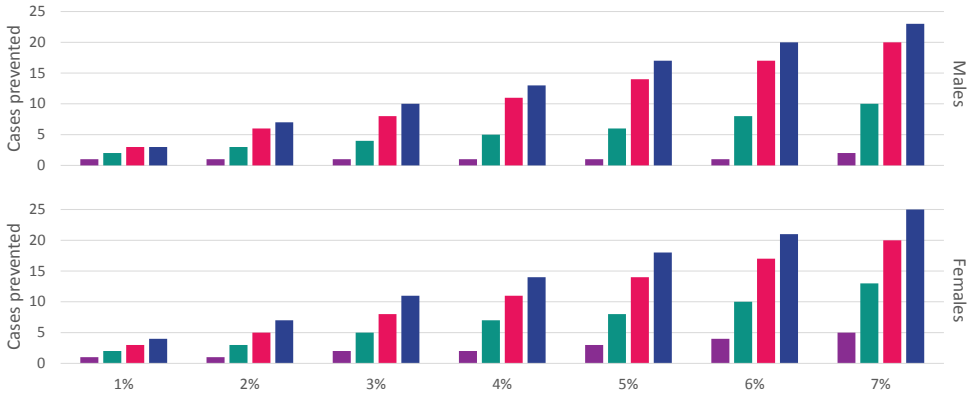
Part 1: MISCAN-Colon predictions stratified for colorectal cancer risk and sex. Individuals were followed-up during 15 years

Supplementary Results Figure 4.1: MISCAN-Colon predictions of colorectal cancer mortality and incidence reduction per 1000 individuals, using FIT, flexible sigmoidoscopy or colonoscopy. Results are stratified by CRC risk and sex. Individuals were followed-up during 15 years.

a. Colorectal cancer deaths prevented.



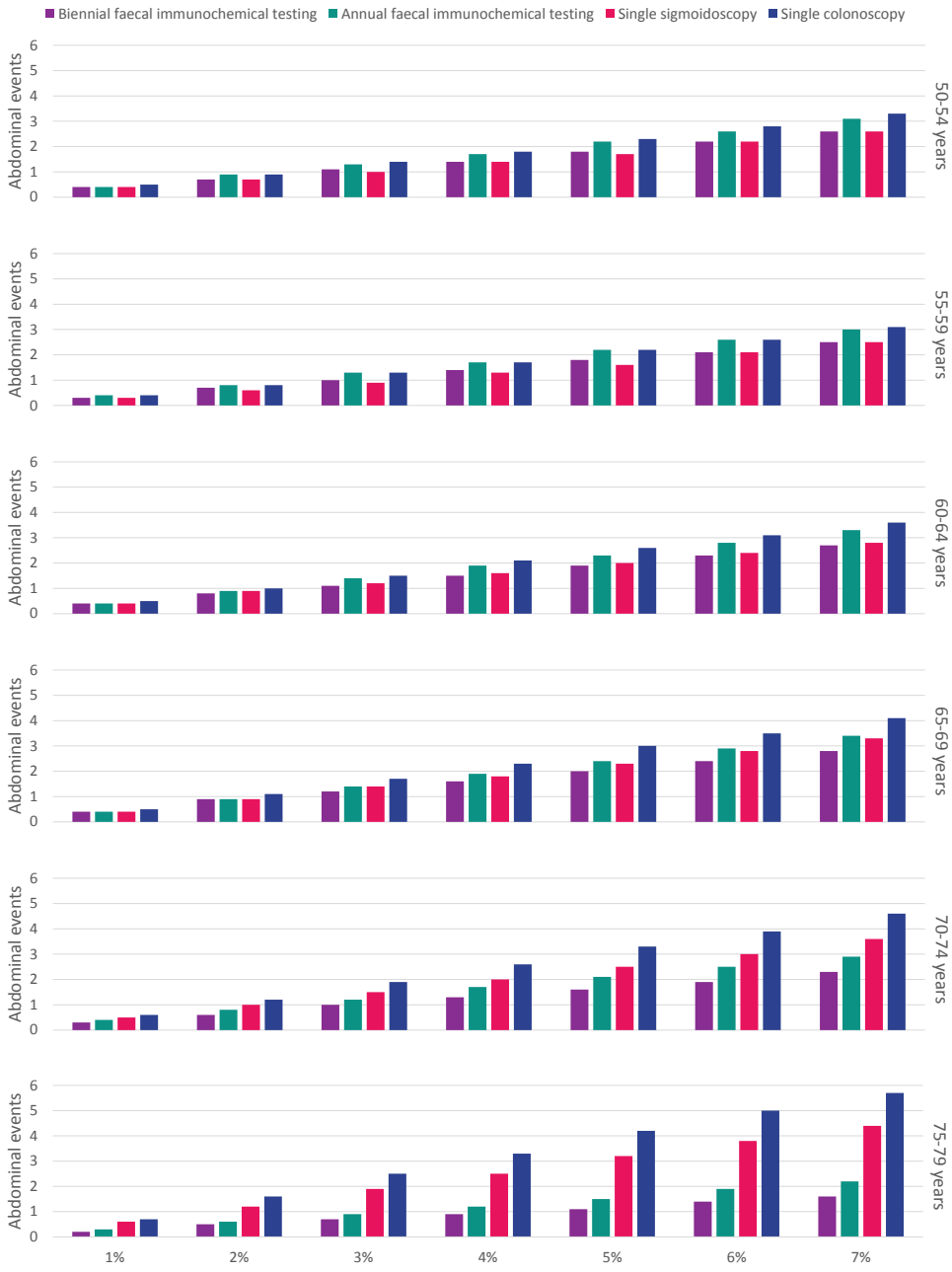
b. Colorectal cancer cases prevented.



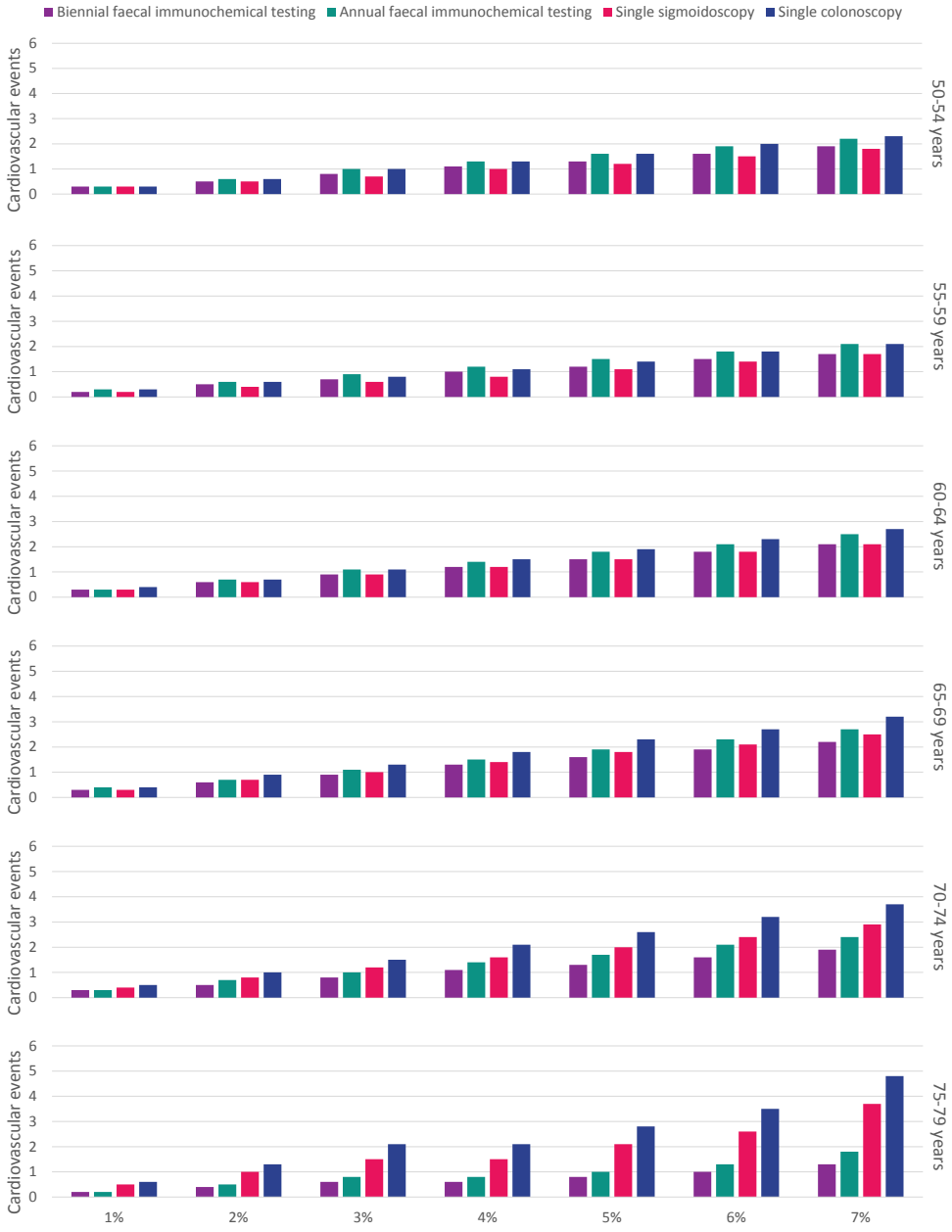
Supplementary Results Figure 4.2: MISCAN-Colon predictions of complications per 1000 individuals, using FIT, flexible sigmoidoscopy or colonoscopy. Results are stratified by CRC risk and age. Individuals were followed-up during 15 years.

a. Number of perforation complications.

b. Number of abdominal complications.



c. Number of cardiovascular complications.



PART 2: MISCAN-COLON PREDICTIONS STRATIFIED FOR COLORECTAL CANCER RISK, AGE AND SEX. INDIVIDUALS WERE FOLLOWED-UP DURING 15 YEARS.

Supplementary Results Table 4.1: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for men, aged 50-54, stratified by risk

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	-5	-1	53	2	1.4	6893	211	39	0.4	0.6	0.9	0.03
Annual FIT	9	1	63	2	1.6	11882	329	48	0.5	0.7	1.1	0.03
Single sigmoidoscopy	25	3	47	1	1.2	1000	113	36	0.4	0.6	0.9	0.02
Single colonoscopy	32	3	58	2	1.5	1000	1000	42	0.5	0.8	1.1	0.03
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	-7	-1	51	3	2.5	6641	274	80	0.9	1.2	1.8	0.05
Annual FIT	7	1	62	4	3.0	11276	395	98	1.1	1.5	2.3	0.06
Single sigmoidoscopy	24	5	44	3	2.1	1000	226	68	0.8	1.1	1.6	0.05
Single colonoscopy	30	6	55	3	2.7	1000	1000	82	1.1	1.5	2.2	0.06
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	-7	-2	52	5	3.7	6405	332	121	1.3	1.8	2.8	0.08
Annual FIT	7	2	62	6	4.5	10716	456	149	1.6	2.2	3.4	0.09
Single sigmoidoscopy	23	7	44	4	3.1	1000	328	103	1.2	1.7	2.4	0.07
Single colonoscopy	30	9	55	5	3.9	1000	1000	124	1.6	2.2	3.2	0.09

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	-7	-3	52	6	4.8	6160	390	165	1.8	2.5	3.7	0.10
Annual FIT	8	3	63	7	5.8	10133	515	205	2.2	3.0	4.6	0.13
Single sigmoidoscopy	24	10	46	5	4.2	1000	426	147	1.6	2.3	3.4	0.10
Single colonoscopy	31	12	57	7	5.2	1000	1000	174	2.1	3.0	4.4	0.13
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	-6	-3	52	8	5.9	5930	443	209	2.2	3.1	4.7	0.13
Annual FIT	9	5	64	9	7.3	9608	567	260	2.7	3.8	5.7	0.16
Single sigmoidoscopy	25	12	47	7	5.3	1000	508	195	2.1	3	4.4	0.13
Single colonoscopy	30	15	57	8	6.5	1000	1000	226	2.7	3.8	5.5	0.16
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	-4	-2	53	9	7.1	5727	488	252	2.6	3.7	5.6	0.16
Annual FIT	10	6	64	11	8.5	9146	611	312	3.2	4.5	6.8	0.19
Single sigmoidoscopy	26	16	49	9	6.6	1000	576	245	2.7	3.8	5.5	0.16
Single colonoscopy	31	19	58	10	7.8	1000	1000	280	3.3	4.6	6.7	0.19
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	-2	-2	55	11	8.4	5525	530	294	3.1	4.3	6.6	0.18
Annual FIT	12	8	65	13	9.9	8693	652	365	3.7	5.3	8.0	0.22
Single sigmoidoscopy	27	19	52	11	8.0	1000	636	298	3.3	4.6	6.8	0.19
Single colonoscopy	32	22	60	12	9.2	1000	1000	336	3.9	5.5	8.0	0.23

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in men aged 52 years varies between 1.2% without risk factors and 4.3% with all risk factors.

Supplementary Results Table 4.2: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for men, aged 55-59, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
h. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	5	1	56	2	0.9	6757	192	30	0.4	0.6	1.0	0.03
Annual FIT	17	2	66	2	1.1	11703	307	36	0.5	0.7	1.2	0.03
Single sigmoidoscopy	31	3	58	2	0.9	1000	86	31	0.5	0.7	1.0	0.03
Single colonoscopy	35	3	65	2	1.1	1000	1000	35	0.6	0.8	1.2	0.03
i. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	0	0	52	3	1.7	6561	239	62	0.9	1.2	2.0	0.05
Annual FIT	13	3	63	4	2.0	11236	356	76	1.1	1.5	2.4	0.06
Single sigmoidoscopy	29	6	52	3	1.6	1000	174	63	0.9	1.3	2.0	0.06
Single colonoscopy	35	7	62	4	2.0	1000	1000	72	1.2	1.6	2.5	0.07
j. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	-1	0	51	5	2.4	6360	287	95	1.3	1.9	3.0	0.08
Annual FIT	12	4	61	6	2.9	10764	405	116	1.6	2.3	3.7	0.10
Single sigmoidoscopy	28	8	50	5	2.3	1000	262	94	1.4	1.9	3.0	0.08
Single colonoscopy	34	10	60	6	2.8	1000	1000	109	1.8	2.5	3.8	0.10

k. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	-1	-1	52	6	3.1	6163	333	128	1.8	2.5	4.0	0.11
Annual FIT	12	5	62	7	3.7	10305	453	158	2.2	3.1	4.9	0.13
Single sigmoidoscopy	27	11	49	6	2.9	1000	346	127	1.9	2.6	4.0	0.11
Single colonoscopy	34	13	59	7	3.5	1000	1000	148	2.3	3.3	5.0	0.14
l. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	-2	-1	52	8	3.9	5973	377	161	2.3	3.2	5.0	0.13
Annual FIT	12	6	62	10	4.7	9858	498	198	2.8	3.9	6.1	0.16
Single sigmoidoscopy	28	14	51	8	3.8	1000	421	163	2.3	3.3	5.1	0.14
Single colonoscopy	34	17	61	9	4.6	1000	1000	188	2.9	4.1	6.3	0.17
m. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	-1	-1	53	10	4.7	5781	421	197	2.8	3.8	6.1	0.16
Annual FIT	12	7	63	12	5.6	9418	542	243	3.3	4.7	7.4	0.2
Single sigmoidoscopy	28	17	51	9	4.6	1000	494	204	2.9	4.1	6.3	0.17
Single colonoscopy	34	20	61	11	5.4	1000	1000	233	3.6	5.0	7.7	0.21
n. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	-1	0	53	11	5.4	5601	461	231	3.2	4.5	7.2	0.19
Annual FIT	13	9	63	14	6.5	9008	581	285	3.9	5.4	8.7	0.23
Single sigmoidoscopy	29	20	53	11	5.4	1000	556	246	3.5	4.9	7.5	0.21
Single colonoscopy	34	24	62	13	6.3	1000	1000	278	4.2	5.9	9.0	0.25

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in men aged 57 years varies between 2.0% without risk factors and 6.1% with all risk factors.

Supplementary Results Table 4.3: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for men, aged 60-64, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	11	1	60	2	0.6	6500	177	23	0.5	0.6	1.1	0.03
Annual FIT	21	2	67	2	0.7	11303	287	28	0.5	0.7	1.2	0.03
Single sigmoidoscopy	33	3	62	2	0.6	1000	72	27	0.5	0.7	1.2	0.03
Single colonoscopy	38	4	69	2	0.7	1000	1000	29	0.6	0.8	1.4	0.04
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	6	1	56	4	1.1	6341	213	49	0.9	1.3	2.2	0.06
Annual FIT	18	4	65	4	1.3	10934	325	60	1.1	1.5	2.6	0.07
Single sigmoidoscopy	32	6	59	4	1.2	1000	140	55	1.1	1.5	2.4	0.06
Single colonoscopy	37	7	68	4	1.4	1000	1000	62	1.3	1.8	2.8	0.07
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	5	1	53	5	1.6	6170	254	77	1.4	2.0	3.3	0.08
Annual FIT	17	5	63	6	1.9	10531	367	94	1.7	2.4	4.0	0.10
Single sigmoidoscopy	31	9	55	5	1.6	1000	215	85	1.6	2.2	3.6	0.09
Single colonoscopy	37	11	65	6	1.9	1000	1000	96	2.0	2.7	4.4	0.12

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	4	1	52	7	2.0	6000	293	104	1.9	2.7	4.5	0.11
Annual FIT	16	6	63	8	2.4	10137	407	128	2.3	3.2	5.4	0.14
Single sigmoidoscopy	31	12	56	7	2.1	1000	289	114	2.1	3	4.8	0.13
Single colonoscopy	37	15	65	8	2.5	1000	1000	131	2.6	3.7	5.9	0.16
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	3	1	53	8	2.5	5838	331	132	2.4	3.3	5.6	0.14
Annual FIT	16	8	63	10	3.0	9757	446	162	2.9	4.1	6.8	0.17
Single sigmoidoscopy	30	15	55	9	2.6	1000	359	145	2.7	3.7	6.0	0.16
Single colonoscopy	36	18	65	10	3.1	1000	1000	165	3.3	4.6	7.4	0.2
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	3	2	52	10	3.0	5676	367	159	2.9	4.0	6.8	0.17
Annual FIT	16	9	63	12	3.6	9389	484	196	3.5	4.9	8.2	0.21
Single sigmoidoscopy	31	18	56	11	3.1	1000	425	177	3.3	4.5	7.3	0.19
Single colonoscopy	36	22	64	12	3.6	1000	1000	202	4.0	5.5	8.9	0.23
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	4	3	52	12	3.5	5517	404	187	3.4	4.7	7.9	0.2
Annual FIT	16	12	63	14	4.2	9018	520	231	4.1	5.7	9.6	0.24
Single sigmoidoscopy	31	22	55	12	3.6	1000	485	212	3.9	5.4	8.7	0.23
Single colonoscopy	37	26	64	15	4.3	1000	1000	239	4.7	6.5	10.5	0.27

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in men aged 62 years varies between 3.0% without risk factors and 8.6% with all risk factors.

Supplementary Results Table 4.4: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for men, aged 65-69, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	13	1	58	2	0.3	5488	149	19	0.5	0.6	1.1	0.03
Annual FIT	22	2	66	2	0.4	9751	247	23	0.6	0.8	1.3	0.03
Single sigmoidoscopy	33	3	65	2	0.4	1000	66	24	0.6	0.8	1.4	0.04
Single colonoscopy	37	4	70	2	0.4	1000	1000	26	0.7	0.9	1.6	0.04
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	12	2	54	4	0.7	5377	180	42	1	1.3	2.3	0.06
Annual FIT	21	4	63	4	0.8	9479	280	51	1.2	1.6	2.8	0.07
Single sigmoidoscopy	34	7	61	4	0.7	1000	127	51	1.2	1.7	2.9	0.07
Single colonoscopy	38	8	68	5	0.8	1000	1000	57	1.5	2.0	3.4	0.09
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	10	3	52	5	0.9	5260	212	66	1.5	2.0	3.5	0.09
Annual FIT	20	6	61	6	1.1	9191	315	80	1.8	2.5	4.3	0.11
Single sigmoidoscopy	33	10	59	6	1.0	1000	194	79	1.9	2.6	4.4	0.11
Single colonoscopy	38	11	66	7	1.1	1000	1000	89	2.3	3.1	5.3	0.13

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	9	3	52	7	1.2	5140	246	90	2	2.7	4.8	0.12
Annual FIT	19	7	61	8	1.4	8893	352	110	2.5	3.4	5.9	0.15
Single sigmoidoscopy	32	13	58	8	1.3	1000	262	108	2.5	3.5	5.9	0.15
Single colonoscopy	37	15	66	9	1.5	1000	1000	121	3.1	4.2	7.1	0.18
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	8	4	51	8	1.5	5024	278	114	2.5	3.5	6.0	0.15
Annual FIT	18	9	60	10	1.7	8607	386	139	3.1	4.3	7.4	0.18
Single sigmoidoscopy	32	16	57	9	1.6	1000	328	138	3.2	4.4	7.5	0.19
Single colonoscopy	38	19	65	11	1.8	1000	1000	155	3.9	5.3	9.0	0.23
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	8	5	51	10	1.7	4910	310	137	3	4.1	7.3	0.18
Annual FIT	18	11	60	12	2.0	8326	420	168	3.7	5.1	8.9	0.22
Single sigmoidoscopy	32	19	57	11	1.9	1000	390	167	3.8	5.3	9.0	0.23
Single colonoscopy	37	22	65	13	2.2	1000	1000	188	4.6	6.4	10.8	0.27
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	8	6	51	12	2.0	4797	341	162	3.6	4.9	8.5	0.21
Annual FIT	19	13	60	14	2.4	8051	453	199	4.4	6	10.5	0.26
Single sigmoidoscopy	33	23	57	13	2.2	1000	450	199	4.5	6.3	10.6	0.27
Single colonoscopy	37	26	65	15	2.5	1000	1000	223	5.5	7.5	12.7	0.32

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in men aged 67 years varies between 4.2% without risk factors and 11.8% with all risk factors.

Supplementary Results Table 4.5: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for men, aged 70-74, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	12	1	56	2	0.2	3617	104	16	0.4	0.5	1.0	0.02
Annual FIT	18	2	62	2	0.2	6509	173	20	0.5	0.7	1.2	0.03
Single sigmoidoscopy	29	3	64	2	0.2	1000	69	24	0.6	0.9	1.5	0.04
Single colonoscopy	33	3	69	2	0.2	1000	1000	26	0.7	1.0	1.8	0.04
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	10	2	53	4	0.3	3564	130	35	0.8	1.1	2.0	0.05
Annual FIT	17	3	61	4	0.4	6362	204	44	1	1.4	2.5	0.06
Single sigmoidoscopy	29	6	62	4	0.4	1000	132	52	1.3	1.8	3.2	0.08
Single colonoscopy	34	7	69	5	0.4	1000	1000	57	1.6	2.2	3.9	0.10
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	10	3	51	5	0.5	3509	158	54	1.2	1.7	3.0	0.07
Annual FIT	17	5	59	6	0.6	6208	236	68	1.6	2.2	3.9	0.09
Single sigmoidoscopy	30	9	60	6	0.6	1000	199	80	2.1	2.8	5.0	0.12
Single colonoscopy	35	10	68	7	0.7	1000	1000	89	2.5	3.5	6.1	0.15

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	9	4	50	7	0.6	3452	186	74	1.7	2.3	4.1	0.1
Annual FIT	16	6	59	8	0.7	6049	270	94	2.2	2.9	5.3	0.13
Single sigmoidoscopy	30	12	60	8	0.8	1000	268	110	2.8	3.9	6.8	0.17
Single colonoscopy	34	14	67	9	0.8	1000	1000	123	3.5	4.8	8.4	0.21
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	9	4	50	9	0.8	3398	214	93	2.1	2.9	5.1	0.12
Annual FIT	16	8	59	10	0.9	5898	302	119	2.7	3.7	6.6	0.16
Single sigmoidoscopy	30	15	60	10	0.9	1000	333	140	3.6	4.9	8.6	0.21
Single colonoscopy	34	17	67	12	1.1	1000	1000	157	4.4	6.0	10.5	0.26
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	9	5	49	10	0.9	3345	241	113	2.5	3.4	6.1	0.15
Annual FIT	16	10	59	12	1.1	5748	334	144	3.3	4.5	8.0	0.19
Single sigmoidoscopy	31	18	60	12	1.1	1000	397	171	4.3	5.9	10.4	0.26
Single colonoscopy	35	21	67	14	1.2	1000	1000	191	5.3	7.2	12.7	0.31
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	9	6	49	12	1.1	3291	267	132	2.9	4.0	7.2	0.17
Annual FIT	16	11	59	14	1.3	5599	365	169	3.8	5.2	9.3	0.23
Single sigmoidoscopy	31	21	60	14	1.3	1000	457	203	5.1	6.9	12.2	0.30
Single colonoscopy	35	24	67	16	1.5	1000	1000	226	6.1	8.4	14.8	0.36

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in men aged 72 years varies between 5.6% without risk factors and 16.1% with all risk factors.

Supplementary Results Table 4.6: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for men, aged 75-79, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	3	0	43	2	0.1	1723	58	12	0.3	0.4	0.7	0.02
Annual FIT	6	1	51	2	0.1	2792	86	16	0.4	0.5	1.0	0.02
Single sigmoidoscopy	21	2	65	2	0.1	1000	81	27	0.8	1.1	2.0	0.05
Single colonoscopy	23	2	69	3	0.1	1000	1000	30	1.0	1.3	2.5	0.06
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	1	0	40	3	0.1	1712	78	25	0.6	0.8	1.5	0.04
Annual FIT	4	1	48	4	0.2	2754	112	32	0.8	1.1	2.0	0.05
Single sigmoidoscopy	19	4	61	5	0.2	1000	155	57	1.7	2.3	4.2	0.10
Single colonoscopy	23	5	68	5	0.2	1000	1000	63	2.1	2.9	5.3	0.13
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	1	0	39	4	0.2	1699	100	38	0.9	1.2	2.3	0.05
Annual FIT	4	1	47	5	0.2	2713	140	50	1.2	1.7	3.1	0.07
Single sigmoidoscopy	20	6	61	7	0.3	1000	234	90	2.7	3.6	6.7	0.16
Single colonoscopy	23	7	68	7	0.3	1000	1000	100	3.4	4.6	8.4	0.20

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	1	0	40	6	0.3	1687	120	50	1.2	1.6	3.0	0.07
Annual FIT	4	2	48	7	0.3	2674	165	66	1.6	2.2	4.0	0.10
Single sigmoidoscopy	21	8	62	9	0.4	1000	305	120	3.6	4.8	8.9	0.21
Single colonoscopy	24	10	69	10	0.5	1000	1000	133	4.5	6.1	11.1	0.27
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	0	0	38	7	0.3	1676	141	64	1.5	2.1	3.8	0.09
Annual FIT	3	2	47	9	0.4	2635	192	85	2	2.8	5.1	0.12
Single sigmoidoscopy	21	10	61	11	0.5	1000	381	154	4.5	6.2	11.3	0.27
Single colonoscopy	24	12	68	12	0.6	1000	1000	171	5.7	7.7	14.1	0.34
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	1	1	38	8	0.4	1664	162	77	1.8	2.5	4.5	0.11
Annual FIT	4	2	47	10	0.5	2596	217	102	2.5	3.3	6.1	0.15
Single sigmoidoscopy	21	13	61	13	0.6	1000	450	188	5.5	7.4	13.5	0.32
Single colonoscopy	24	14	68	15	0.7	1000	1000	208	6.7	9.2	16.7	0.40
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	1	1	39	10	0.4	1652	182	90	2.1	2.9	5.3	0.13
Annual FIT	4	3	47	12	0.5	2557	244	120	2.9	3.9	7.1	0.17
Single sigmoidoscopy	21	15	62	16	0.7	1000	516	223	6.4	8.6	15.8	0.38
Single colonoscopy	24	17	69	18	0.8	1000	1000	246	7.8	10.5	19.3	0.46

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in men aged 77 years varies between 6.7% without risk factors and 21.4% with all risk factors.

Supplementary Results Table 4.7: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for women, aged 50-54, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	0	0	50	1	1.8	6929	224	44	0.5	0.6	1.0	0.03
Annual FIT	12	1	60	2	2.2	11898	345	52	0.6	0.8	1.2	0.03
Single sigmoidoscopy	24	2	42	1	1.5	1000	113	35	0.4	0.5	0.8	0.02
Single colonoscopy	33	3	55	2	2.0	1000	1000	46	0.6	0.8	1.1	0.03
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	-3	-1	50	3	3.4	6613	299	89	0.9	1.3	2.0	0.06
Annual FIT	11	2	60	3	4.1	11143	422	108	1.1	1.6	2.4	0.07
Single sigmoidoscopy	21	4	39	2	2.7	1000	221	67	0.7	1.0	1.5	0.04
Single colonoscopy	32	6	56	3	3.8	1000	1000	91	1.1	1.6	2.3	0.07
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	-3	-1	50	4	5.0	6311	368	136	1.4	2.0	3.0	0.08
Annual FIT	10	3	59	5	5.9	10431	493	164	1.7	2.4	3.6	0.10
Single sigmoidoscopy	21	6	40	3	4.0	1000	319	104	1.1	1.6	2.3	0.07
Single colonoscopy	31	9	55	4	5.5	1000	1000	140	1.7	2.4	3.4	0.1

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	-2	-1	51	5	6.6	6017	434	185	1.9	2.7	4.1	0.11
Annual FIT	11	4	61	6	7.8	9751	558	224	2.3	3.2	4.8	0.13
Single sigmoidoscopy	23	9	42	4	5.3	1000	410	149	1.6	2.2	3.3	0.09
Single colonoscopy	31	13	57	6	7.3	1000	1000	196	2.3	3.2	4.7	0.13
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	0	0	51	7	8.0	5756	490	233	2.4	3.4	5.1	0.14
Annual FIT	12	6	60	8	9.5	9159	612	282	2.8	4.0	6	0.17
Single sigmoidoscopy	24	12	43	6	6.8	1000	487	197	2.1	2.9	4.3	0.12
Single colonoscopy	32	16	58	8	9.1	1000	1000	253	2.9	4.1	5.9	0.17
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	1	1	53	8	9.5	5507	540	280	2.9	4.0	6.1	0.17
Annual FIT	14	9	62	10	11.2	8604	660	340	3.4	4.8	7.2	0.2
Single sigmoidoscopy	25	15	46	7	8.4	1000	554	251	2.6	3.7	5.5	0.16
Single colonoscopy	32	19	59	9	10.7	1000	1000	313	3.5	4.9	7.2	0.21
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	3	2	54	10	11.1	5271	586	326	3.3	4.7	7.1	0.20
Annual FIT	16	11	63	12	13.0	8094	703	396	4.0	5.6	8.4	0.23
Single sigmoidoscopy	27	19	50	9	10.2	1000	612	307	3.2	4.6	6.7	0.19
Single colonoscopy	33	23	61	11	12.4	1000	1000	374	4.1	5.8	8.5	0.24

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in women aged 52 years varies between 1.0% without risk factors and 2.6% with all risk factors.

Supplementary Results Table 4.8: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for women, aged 55-59, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	6	1	56	2	1.4	6884	205	35	0.5	0.7	1.1	0.03
Annual FIT	19	2	66	2	1.6	11878	323	41	0.6	0.8	1.3	0.03
Single sigmoidoscopy	28	3	52	1	1.2	1000	89	31	0.4	0.6	1	0.03
Single colonoscopy	36	4	65	2	1.6	1000	1000	39	0.6	0.8	1.3	0.04
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	3	1	51	3	2.4	6626	264	72	1.0	1.4	2.2	0.06
Annual FIT	15	3	61	3	2.8	11271	383	86	1.2	1.6	2.6	0.07
Single sigmoidoscopy	25	5	46	3	2.1	1000	174	60	0.9	1.2	1.8	0.05
Single colonoscopy	34	7	60	3	2.8	1000	1000	79	1.2	1.7	2.6	0.07
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	1	0	52	4	3.5	6373	321	110	1.5	2.1	3.3	0.09
Annual FIT	15	4	61	5	4.1	10670	442	132	1.8	2.5	3.9	0.11
Single sigmoidoscopy	25	7	44	4	3.0	1000	259	91	1.3	1.8	2.7	0.07
Single colonoscopy	34	10	60	5	4.0	1000	1000	120	1.8	2.6	3.9	0.11

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	2	1	51	6	4.6	6132	375	147	2.0	2.7	4.4	0.12
Annual FIT	15	6	61	7	5.4	10112	496	176	2.4	3.3	5.2	0.14
Single sigmoidoscopy	25	10	44	5	3.9	1000	335	124	1.7	2.4	3.6	0.10
Single colonoscopy	34	14	59	7	5.3	1000	1000	161	2.4	3.4	5.2	0.14
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	2	1	52	7	5.7	5893	427	185	2.5	3.5	5.5	0.15
Annual FIT	15	7	61	8	6.7	9565	547	223	3.0	4.1	6.6	0.17
Single sigmoidoscopy	25	13	45	6	5.0	1000	407	161	2.2	3.1	4.7	0.13
Single colonoscopy	34	17	60	8	6.5	1000	1000	208	3.1	4.3	6.6	0.18
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	3	2	52	9	6.8	5670	473	223	3.0	4.2	6.6	0.18
Annual FIT	16	10	62	10	8.0	9063	593	269	3.5	4.9	7.8	0.21
Single sigmoidoscopy	26	16	47	8	6.0	1000	472	200	2.7	3.8	5.8	0.16
Single colonoscopy	35	21	61	10	7.9	1000	1000	255	3.7	5.2	7.9	0.22
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	4	3	53	10	7.8	5462	515	261	3.5	4.9	7.7	0.21
Annual FIT	17	12	62	12	9.1	8600	633	315	4.1	5.7	9.1	0.24
Single sigmoidoscopy	27	19	49	9	7.2	1000	529	243	3.3	4.6	7.0	0.19
Single colonoscopy	35	24	62	12	9.0	1000	1000	303	4.3	6.0	9.3	0.25

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in women aged 57 years varies between 1.6% without risk factors and 3.6% with all risk factors.

Supplementary Results Table 4.9: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for women, aged 60-64, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	11	1	57	2	0.9	6760	28	62	0.5	0.7	1.2	0.03
Annual FIT	21	2	66	2	1.0	11710	33	77	0.6	0.8	1.4	0.04
Single sigmoidoscopy	31	3	56	2	0.9	1000	28	81	0.5	0.7	1.2	0.03
Single colonoscopy	38	4	68	2	1.0	1000	33	98	0.7	0.9	1.5	0.04
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	8	2	54	3	1.6	6551	238	59	1.1	1.5	2.5	0.06
Annual FIT	20	4	63	4	1.9	11220	354	70	1.3	1.7	2.9	0.07
Single sigmoidoscopy	30	6	51	3	1.5	1000	143	55	1.0	1.4	2.2	0.06
Single colonoscopy	37	7	64	4	1.9	1000	1000	69	1.3	1.9	3.0	0.08
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	6	2	52	4	2.3	6335	286	90	1.6	2.2	3.7	0.09
Annual FIT	18	5	62	5	2.7	10713	403	108	1.9	2.6	4.4	0.11
Single sigmoidoscopy	28	8	49	4	2.1	1000	215	83	1.5	2.0	3.3	0.09
Single colonoscopy	37	11	64	5	2.7	1000	1000	106	2.0	2.9	4.6	0.12

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	5	2	52	6	3.0	6123	332	122	2.1	3.0	5.0	0.13
Annual FIT	18	7	62	7	3.6	10230	449	146	2.6	3.5	5.9	0.15
Single sigmoidoscopy	28	11	48	6	2.8	1000	283	111	2.0	2.7	4.4	0.12
Single colonoscopy	37	15	64	7	3.7	1000	1000	143	2.7	3.8	6.1	0.16
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	5	3	52	7	3.7	5918	377	153	2.7	3.7	6.3	0.16
Annual FIT	18	9	62	9	4.4	9750	495	184	3.2	4.4	7.4	0.19
Single sigmoidoscopy	27	14	48	7	3.4	1000	349	142	2.5	3.4	5.6	0.15
Single colonoscopy	37	18	63	9	4.4	1000	1000	182	3.4	4.8	7.7	0.20
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	7	4	52	9	4.4	5722	419	184	3.2	4.4	7.5	0.19
Annual FIT	19	11	62	11	5.2	9307	537	221	3.8	5.3	8.8	0.23
Single sigmoidoscopy	28	17	49	9	4.1	1000	407	174	3.0	4.2	6.7	0.18
Single colonoscopy	37	22	63	11	5.3	1000	1000	220	4.1	5.7	9.2	0.24
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	7	5	52	11	5.1	5528	459	216	3.8	5.2	8.7	0.22
Annual FIT	19	13	62	12	6.0	8866	577	260	4.5	6.2	10.3	0.26
Single sigmoidoscopy	29	20	50	10	4.9	1000	464	209	3.6	5.0	8.1	0.21
Single colonoscopy	37	26	64	13	6.2	1000	1000	260	4.8	6.7	10.7	0.28

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in women aged 62 years varies between 2.2% without risk factors and 4.8% with all risk factors.

Supplementary Results Table 4.10: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for women, aged 65-69, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	17	2	56	2	0.5	5769	161	23	0.5	0.7	1.3	0.03
Annual FIT	26	3	62	2	0.6	10241	264	27	0.6	0.8	1.5	0.04
Single sigmoidoscopy	33	3	58	2	0.5	1000	66	24	0.6	0.8	1.3	0.03
Single colonoscopy	39	4	66	2	0.6	1000	1000	29	0.7	1.0	1.7	0.04
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	14	3	52	3	0.9	5628	198	49	1.1	1.5	2.6	0.06
Annual FIT	23	5	60	4	1.1	9895	304	58	1.3	1.8	3.1	0.08
Single sigmoidoscopy	31	6	53	3	1.0	1000	125	50	1.1	1.6	2.7	0.07
Single colonoscopy	38	8	64	4	1.2	1000	1000	62	1.5	2.1	3.5	0.09
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	13	4	51	5	1.3	5480	238	77	1.6	2.2	3.9	0.10
Annual FIT	22	7	59	5	1.6	9527	347	91	2.0	2.7	4.7	0.12
Single sigmoidoscopy	30	9	51	5	1.4	1000	189	77	1.7	2.4	4.0	0.10
Single colonoscopy	39	12	63	6	1.7	1000	1000	96	2.3	3.2	5.4	0.14

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	12	5	51	6	1.8	5332	278	104	2.2	3.0	5.3	0.13
Annual FIT	22	9	60	7	2.1	9159	389	125	2.7	3.6	6.3	0.16
Single sigmoidoscopy	30	12	50	6	1.8	1000	253	104	2.3	3.1	5.3	0.13
Single colonoscopy	39	15	64	8	2.2	1000	1000	131	3.1	4.3	7.3	0.18
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	11	6	51	8	2.2	5186	317	132	2.8	3.8	6.6	0.16
Annual FIT	22	11	59	9	2.6	8800	429	158	3.3	4.6	8.0	0.20
Single sigmoidoscopy	30	15	50	8	2.2	1000	315	132	2.9	4.0	6.7	0.17
Single colonoscopy	39	19	64	10	2.8	1000	1000	166	3.9	5.4	9.2	0.23
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	12	7	50	9	2.6	5043	353	159	3.3	4.6	8.0	0.20
Annual FIT	22	13	58	11	3.0	8452	468	191	4.0	5.5	9.6	0.24
Single sigmoidoscopy	31	18	50	9	2.6	1000	372	161	3.5	4.8	8.2	0.21
Single colonoscopy	39	23	63	11	3.3	1000	1000	202	4.7	6.5	11	0.28
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	12	8	50	11	3.0	4905	389	186	3.9	5.3	9.4	0.23
Annual FIT	22	16	59	13	3.6	8112	506	224	4.7	6.5	11.3	0.28
Single sigmoidoscopy	30	21	50	11	3.0	1000	426	192	4.1	5.7	9.6	0.24
Single colonoscopy	39	27	63	13	3.8	1000	1000	238	5.5	7.6	12.8	0.33

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in women aged 67 years varies between 3.0% without risk factors and 6.2% with all risk factors.

Supplementary Results Table 4.11: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for women, aged 70-74, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	0.18	2	0.53	2	1.0	3754	111	19	0.4	0.6	1.1	0.03
Annual FIT	0.24	2	0.61	2	1.0	6771	183	23	0.5	0.7	1.3	0.03
Single sigmoidoscopy	0.33	3	0.58	2	1.0	1000	67	24	0.6	0.8	1.4	0.04
Single colonoscopy	0.38	4	0.67	2	1.0	1000	1000	29	0.8	1.1	1.9	0.05
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	16	3	52	3	0.5	3691	141	39	0.9	1.2	2.1	0.05
Annual FIT	22	4	60	4	0.6	6596	218	49	1.1	1.5	2.7	0.07
Single sigmoidoscopy	31	6	56	4	0.6	1000	124	50	1.2	1.7	2.9	0.07
Single colonoscopy	38	8	67	4	0.7	1000	1000	61	1.7	2.3	4.0	0.1
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	15	4	51	5	0.8	3626	173	61	1.3	1.8	3.3	0.08
Annual FIT	22	7	59	6	0.9	6409	257	76	1.7	2.3	4.2	0.1
Single sigmoidoscopy	31	9	54	5	0.8	1000	187	77	1.9	2.6	4.5	0.11
Single colonoscopy	39	12	67	7	1.0	1000	1000	96	2.6	3.6	6.2	0.15

d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	14	6	50	7	1.0	3561	205	160	1.8	2.4	4.4	0.11
Annual FIT	21	8	59	8	1.2	6225	295	204	2.3	3.2	5.6	0.14
Single sigmoidoscopy	30	12	53	7	1.1	1000	249	231	2.5	3.5	6.1	0.15
Single colonoscopy	38	15	66	9	1.3	1000	1000	287	3.5	4.8	8.4	0.21
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	14	7	49	8	1.2	3496	236	82	2.3	3.1	5.5	0.13
Annual FIT	21	10	58	10	1.4	6043	332	103	2.9	4.0	7.1	0.17
Single sigmoidoscopy	30	15	53	9	1.3	1000	310	104	3.2	4.4	7.7	0.19
Single colonoscopy	38	19	66	11	1.6	1000	1000	129	4.4	6.0.	10.6	0.26
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	14	8	49	10	1.5	3432	267	103	2.7	3.7	6.6	0.16
Annual FIT	21	13	59	12	1.7	5865	367	130	3.5	4.7	8.5	0.21
Single sigmoidoscopy	30	18	53	11	1.6	1000	366	132	3.8	5.3	9.2	0.23
Single colonoscopy	38	23	66	13	1.9	1000	1000	164	5.3	7.2	12.6	0.31
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	14	10	49	11	1.7	3370	297	124	3.2	4.3	7.7	0.19
Annual FIT	22	15	58	14	2.0	5690	402	157	4.1	5.5	9.9	0.24
Single sigmoidoscopy	31	22	54	13	1.9	1000	419	161	4.5	6.2	10.8	0.27
Single colonoscopy	39	27	66	15	2.3	1000	1000	199	6.1	8.3	14.6	0.36

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

Note: According to the QCancer risk calculator, the 15-year colorectal cancer risk in women aged 72 years varies between 3.8% without risk factors and 7.7% with all risk factors.

Supplementary Results Table 4.12: MISCAN-Colon predictions of benefits and harms of various screening strategies during a follow-up period of 15 years for women, aged 75-79, stratified by risk.

Screening strategy	Colorectal cancer				All-cause mortality reduction (%)	Number of screening tests	Number of individuals with ≥1 colonoscopy	Number of individuals with ≥2 colonoscopies	Risk of complications			
	Incidence reduction (%)	Number of cases prevented	Mortality reduction (%)	Number of deaths prevented					Perforation and bleeding	Other GI events	Cardio-vascular events	Screen procedure related mortality
a. 1% colorectal cancer risk (10 cases per 1000, with a risk of dying of colorectal cancer of 0.3% (3 per 1000)).												
Biennial FIT	10	1	42	2	0.1	1741	60	10	0.3	0.4	0.8	0.02
Annual FIT	14	1	49	2	0.1	2825	89	13	0.4	0.5	1.0	0.02
Single sigmoidoscopy	27	3	58	2	0.2	1000	74	22	0.7	1.0	1.8	0.04
Single colonoscopy	33	3	69	3	0.2	1000	1000	26	1.0	1.3	2.4	0.06
b. 2% colorectal cancer risk (20 cases per 1000 with a risk of dying of colorectal cancer of 0.6% (6 per 1000)).												
Biennial FIT	8	2	40	3	0.2	1728	81	21	0.6	0.8	1.5	0.04
Annual FIT	12	2	48	4	0.3	2782	117	27	0.8	1.1	2.1	0.05
Single sigmoidoscopy	26	5	57	4	0.3	1000	139	45	1.5	2.1	3.8	0.09
Single colonoscopy	32	6	68	5	0.4	1000	1000	55	2.1	2.9	5.3	0.13
c. 3% colorectal cancer risk (30 cases per 1000 with a risk of dying of colorectal cancer of 0.9% (9 per 1000)).												
Biennial FIT	8	2	39	4	0.3	1715	104	31	0.9	1.3	2.3	0.06
Annual FIT	11	3	48	5	0.4	2738	146	42	1.3	1.7	3.1	0.07
Single sigmoidoscopy	26	8	56	6	0.4	1000	209	69	2.3	3.2	5.8	0.14
Single colonoscopy	33	10	69	7	0.5	1000	1000	85	3.3	4.5	8.3	0.20

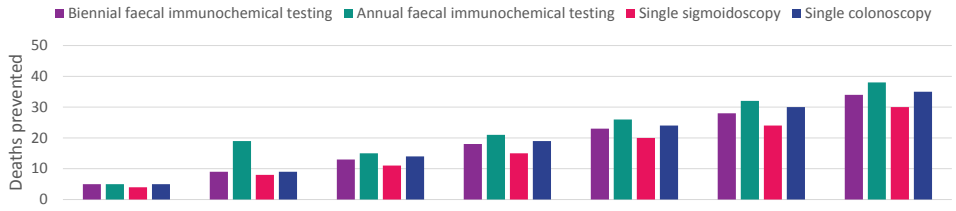
d. 4% colorectal cancer risk (40 cases per 1000 with a risk of dying of colorectal cancer of 1.2% (12 per 1000)).												
Biennial FIT	7	3	38	6	0.4	1701	127	42	1.3	1.7	3.1	0.07
Annual FIT	11	4	46	7	0.5	2694	175	56	1.7	2.3	4.2	0.10
Single sigmoidoscopy	25	10	55	8	0.6	1000	278	94	3.2	4.3	7.9	0.19
Single colonoscopy	32	13	68	10	0.7	1000	1000	116	4.5	6.1	11.2	0.27
e. 5% colorectal cancer risk (50 cases per 1000 with a risk of dying of colorectal cancer of 1.6% (16 per 1000)).												
Biennial FIT	7	4	38	7	0.5	1688	150	53	1.6	2.1	3.9	0.09
Annual FIT	11	5	46	9	0.6	2650	204	71	2.1	2.9	5.3	0.13
Single sigmoidoscopy	26	13	55	10	0.7	1000	343	119	4.0	5.4	9.9	0.24
Single colonoscopy	33	16	68	13	0.9	1000	1000	147	5.6	7.7	14.0	0.33
f. 6% colorectal cancer risk (60 cases per 1000 with a risk of dying of colorectal cancer of 1.9% (19 per 1000)).												
Biennial FIT	7	4	37	8	0.6	1674	172	64	1.9	2.6	4.7	0.11
Annual FIT	11	7	46	10	0.7	2606	233	86	2.6	3.5	6.4	0.15
Single sigmoidoscopy	26	15	55	12	0.9	1000	406	146	4.8	6.6	12.0	0.29
Single colonoscopy	33	20	68	15	1.1	1000	1000	178	6.7	9.1	16.6	0.40
g. 7% colorectal cancer risk (70 cases per 1000 with a risk of dying of colorectal cancer of 2.2% (22 per 1000)).												
Biennial FIT	7	5	38	10	0.7	1661	194	75	2.2	3.0	5.5	0.13
Annual FIT	11	8	46	12	0.9	2564	260	100	3.0	4.1	7.5	0.18
Single sigmoidoscopy	26	19	56	15	1.0	1000	464	173	5.6	7.6	14.0	0.33
Single colonoscopy	33	23	69	18	1.3	1000	1000	210	7.7	10.4	19.0	0.45

Abbreviations: FIT, faecal immunochemical test; GI, gastrointestinal

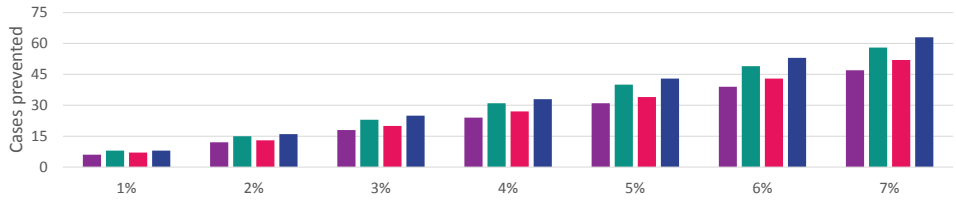
PART 3: MISCAN-COLON PREDICTIONS STRATIFIED FOR COLORECTAL CANCER RISK, AGE AND SEX WITH LIFETIME FOLLOW-UP

Supplementary Results Figure 4.3: MISCAN-Colon predictions of colorectal cancer a) mortality reduction and b) incidence reduction per 1000 individuals, using FIT, flexible sigmoidoscopy or colonoscopy. Results were stratified for CRC risk. Individuals were followed for a lifetime.

a. Colorectal cancer deaths prevented.



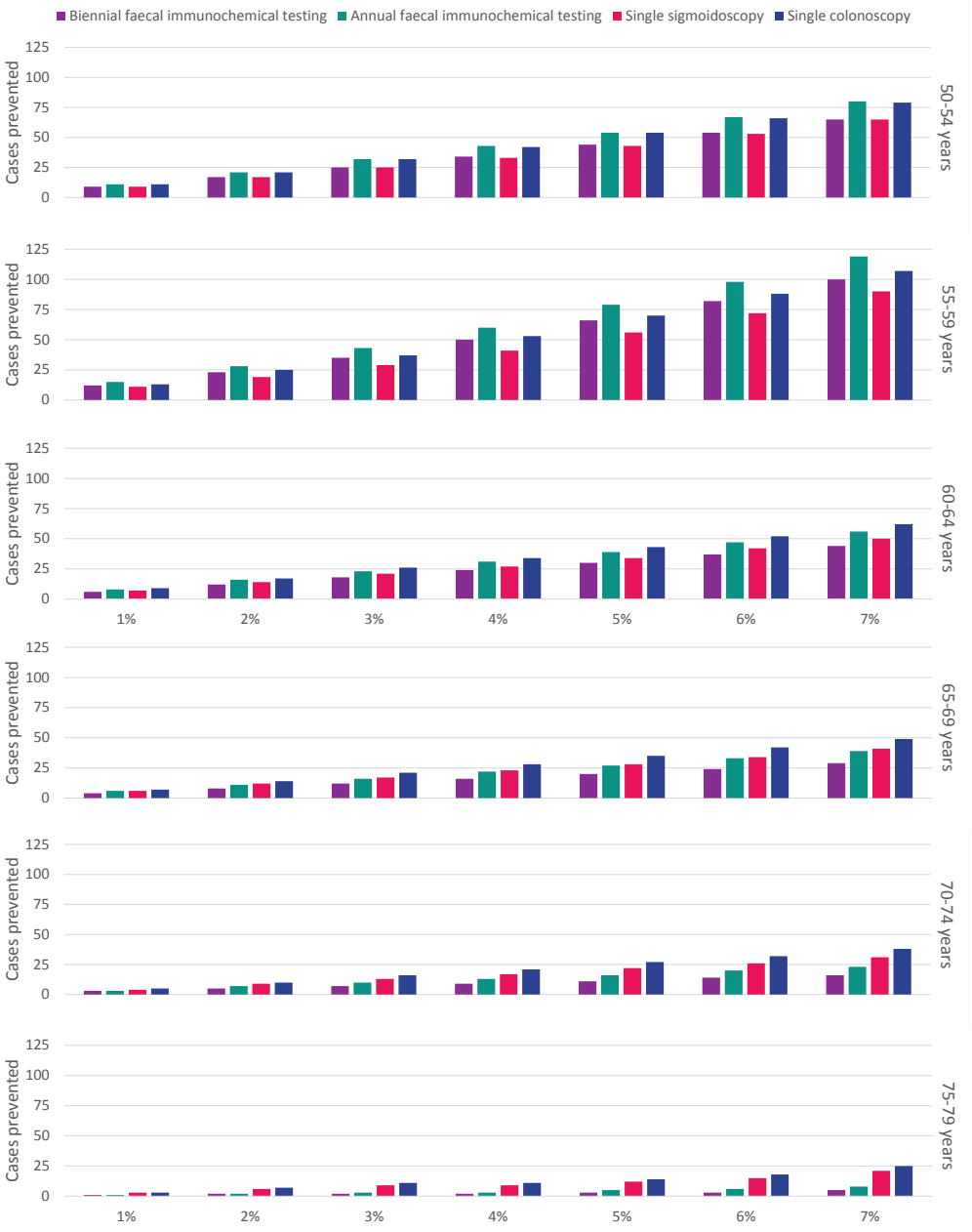
b. Colorectal cancer cases prevented.



Supplementary Results Figure 4.4: MISCAN-Colon predictions of colorectal cancer a) mortality reduction and b) incidence reduction per 1000 individuals, using FIT, flexible sigmoidoscopy or colonoscopy. Results were stratified for CRC risk and age. Individuals were followed for a lifetime.

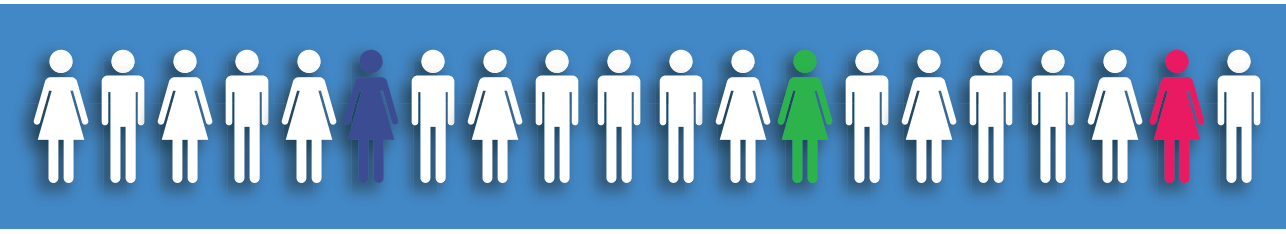
a. Colorectal cancer deaths prevented.

b. Colorectal cancer cases prevented.



CHAPTER 5

CALCULATION OF STOP AGES FOR COLORECTAL CANCER SCREENING BASED ON COMORBIDITIES AND SCREENING HISTORY



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ABSTRACT

Background and Aims: Routine screening for colorectal cancer is typically recommended until age 74 years. Although it has been proposed that screening stop age could be determined based on sex and comorbidity, less is known about the impact of screening history. We investigated the effects of screening history on selection of optimal age to stop screening.

Methods: We used the microsimulation model MISCAN-Colon to estimate harms and benefits of screening with biennial faecal immunochemical tests by sex, comorbidity status, and screening history. The optimal screening stop age was determined based on incremental number needed for 1 additional life-year per 1000 screened individuals compared to threshold provided by stopping screening at 76 years in the average-health population with perfect screening history (attended all required screening, diagnostic and follow-up tests) to biennial faecal immunochemical testing from age 50 years.

Results: For persons of age 76 years, 157 women and 108 men with perfect screening history would need to be screened to gain 1 life-year per 1000 screened individuals. Previously unscreened women with no comorbid conditions and no history of screening could undergo an initial screening through 90 years, whereas unscreened men could undergo initial screening through 88 years, before this balance is reached. As screening adherence improved or as comorbidities increased, the optimal age to stop screening decreased to a point that, regardless of sex, individuals with severe comorbidities and perfect screening history should stop screening at age 66 years or younger.

Conclusions: Based on the harm-benefit balance, optimal stop age for colorectal cancer screening ranges from 66 years for unhealthy individuals with perfect screening history to 90 years for healthy individuals without prior screening. These findings can be used to assist patients and clinicians in making decisions about screening participation.

INTRODUCTION

Colorectal cancer screening guidelines typically recommend screening for colorectal cancer in individuals at average risk between the ages of 50-74 years.[1] However, screening recommendations based solely on age do not consider the heterogeneity of the population and ignore other factors that play a role in the determination of harms and benefits of screening. Risk of colorectal cancer, for example, is affected by several factors including family history, sex, screening history, lifestyle, and comorbidity status.

Although some guidelines have recently suggested that screening could be offered to those aged over 74 depending on screening history and comorbidity[2, 3] there is little practical guidance on how to implement this. Previous studies investigating the impact of comorbidity on screening stop age were conducted in a setting of opportunistic colonoscopy screening, or assumed regular adherence to faecal immunochemical test (FIT) screening,[4-6] however this ignores the complexity and varied nature of screening history. In this analysis, we aimed to address this gap in knowledge.

Using microsimulation modelling, we investigated the impact that age, sex, comorbidity status, and screening history have on the possible benefits and harms of colorectal cancer screening. We used this information to determine the optimal age to stop screening for colorectal cancer and therefore provide recommendations for a more personalised approach to colorectal cancer screening cessation.

METHODS

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model to estimate the harms and benefits of undergoing one more screen by sex, age, comorbidity status, and screening history. The harms and benefits for each cohort were then compared to the average-health population, with perfect prior screening since age 50, having one more screen at age 74 and 76 years of age. Optimal age to stop screening was considered to be the age where the harm-benefit-ratio fell within this range.

MISCAN-COLON

MISCAN-Colon is a well-established microsimulation model for colorectal cancer developed at the Department of Public Health at Erasmus University Medical Centre (Rotterdam, the Netherlands).[7] The structure, underlying assumptions and data sources used to calibrate the model are described in detail in the **Model Appendix**. Briefly, the model simulates a large population of individuals from birth to death, first without and then with screening for colorectal cancer. As each simulated person ages, one or more adenomas may arise and some can progress in size from small (≤5 mm) to medium (6 to 9 mm) to large (≥ 10 mm). Medium

and large adenomas can develop into preclinical cancer and subsequently progress through stage I to IV. During each stage, symptoms may present and colorectal cancer may be diagnosed. Survival after a clinical diagnosis is determined by the person's age, the stage at diagnosis, and the location of the cancer.[8]

The introduction of screening may alter the simulated life histories through detection and removal of adenomas, which may prevent some cancer cases, or through detection of cancers at an earlier stage with more favourable survival. MISCAN-Colon quantifies the effectiveness, harms and costs of screening by comparing all simulated life histories with screening with the corresponding life histories without screening.

MISCAN-Colon was calibrated to match colorectal cancer incidence and stage distribution in Canada using incidence data from the Canadian cancer registry in 2001, which was prior to the introduction of population-based screening.[9] Additional model assumptions can be found in Table 5.1 and the Supplementary Methods.

SETTING

We assumed screening occurred in the Canadian setting. There is no national colorectal cancer screening program in Canada. Cancer screening is funded, organised and delivered at the provincial level and may co-exist with opportunistic screening. We therefore considered screening was taking place within an organised colorectal cancer screening program, commencing at age 50 years utilising biennial FIT, with opportunistic screening with colonoscopy.

We assumed that after a positive FIT result, a diagnostic colonoscopy was offered. Adenomas identified at screening or diagnostic colonoscopies were removed and the individual entered colonoscopy surveillance at intervals dependent on adenoma findings according to the surveillance recommendations from Ontario.[10] It was assumed that surveillance stopped at 85 years of age.

POPULATION

In the base-case analysis, we simulated 728 different cohorts of 10 million individuals varying them by sex, age (66, 68, …, 88, 90 years), comorbidity status (no, low, moderate, severe; Table 5.2), and screening history with FIT (no, some, reasonable, most or perfect prior screening) or colonoscopy (10 or 15 years prior). Simulated individuals were followed until death.

COMORBIDITY CONDITION SPECIFIC LIFETABLES

To develop Canadian specific comorbidity life tables, we took hazard ratios from comorbidity specific life tables from the United States[11] compared to the average life table, and applied these ratios to the 2010-2012 Canadian life tables[12] (Supplementary Methods Figures 5.1a-f).

We assumed that comorbid conditions influenced non-cancer life expectancy but did not influence cancer risk, progression, treatment, survival or complications.

SCREENING HISTORY

As adherence to screening varies, we assessed five prior screening scenarios with FIT: 1) no prior screening; 2) some prior screening; 3) reasonable prior screening; 4) most prior screening; 5) perfect prior screening. In the no prior screening scenario, we assumed that no colorectal cancer screening of any kind had occurred. Then, screening participation was increased stepwise by 25%, until perfect prior participation was achieved (Table 5.1). We considered adherence to screening to be randomly assigned across the lifespan and not dependent on participation in the previous screening round. In addition, we assessed screening with colonoscopy 10 and 15 years prior to the investigated stop age.

Attendance at diagnostic colonoscopy was assumed to be 79% for men and 78% for women based on observed rates in Ontario in 2015,[13] and if adenomas were diagnosed and removed, we assumed 80% adherence to surveillance guidelines.[14] This was altered in the perfect prior screening scenario, where we assumed that individuals had perfect adherence to diagnostic colonoscopy and any subsequent surveillance. To provide estimates for harms and benefits for a person considering screening, we assumed 100% participation in the screening, diagnostic and surveillance tests for the current screening episode.

TEST CHARACTERISTICS OF FIT AND COLONOSCOPY

We used the test characteristics of OC-Sensor (OC-Sensor Eiken Chemical co., Tokyo, Japan) based on data from the Dutch colorectal cancer screening program (Table 5.1).[15] Although Canadian provinces use different tests (including OC-Sensor and NS-Prime (Alfesa Pharma, Osaka, Japan)), FITs with similar positivity rates have been shown to perform similarly.[16, 17] We considered an overall positivity of 7.5% which equated to a cut-off level of 23 micrograms of haemoglobin per gram of faeces (µg Hb/g faeces) (Table 5.1). The FIT characteristics were adjusted to take into account the effect of systematic false-positive and false-negative results (that is, individuals without adenomas who test positive and adenomas do not bleed).[18]
The test characteristics of colonoscopy were based on a systematic review of polyp miss rates in tandem colonoscopy studies.[19] The lack of specificity of colonoscopy reflects the detection of hyperplastic polyps, which are not cancer precursors.[20] Complications of colonoscopy, including bleeding, perforation and death, were based on Canadian literature.[21, 22]

Table 5.1: Model Inputs: Test characteristics and participation assumptions associated with colorectal cancer screening.

Test characteristics	
Specificity and sensitivity of FIT [a]	
Specificity (per person)	96.7%
Sensitivity adenoma 1-5mm	0.0%
Sensitivity adenoma 6-9mm	17.6%
Sensitivity adenoma 10+ mm	34.0%
Sensitivity cancer long before clinical diagnosis	29.5%
Sensitivity cancer shortly before clinical diagnosis [b]	66.0%
Specificity and sensitivity of colonoscopy [c,d]	
Specificity	86%
Sensitivity adenoma 1-5mm	75%
Sensitivity adenoma 6-9mm	85%
Sensitivity adenoma 10+ mm	95%
Sensitivity preclinical cancer	95%
Complication of colonoscopy [e]	
Fatal perforation [f]	0.0074%
Bleeding [g]	0.1640%
Perforation [g]	0.0850%
Other [h]	0.3310%
Participation	
Participation in previous screening episodes	
No prior screening	0%
Some prior screening	25%
Reasonable prior screening	50%
Most prior screening	75%
Perfect prior screening	100%
Colonoscopy 10 years prior	0%
Colonoscopy 15 years prior	0%
Participation in current screening episode	100%
Participation with diagnostic colonoscopy [i]	
Males	79%
Females	78%
Participation in surveillance [j]	80%

Abbreviations: FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test

a. Specificity and sensitivity of FIT derived from data from the Dutch colorectal cancer screening program[15] and were adjusted to an overall positivity of 7.5% which equated to a cut-off level of 23 µg Hb/g faeces.
b. We assume that faecal screening is more sensitive in cancers towards the end of the occult bleeding period as they progress towards becoming symptomatic (i.e. visible bleeding) and clinically detectable.[23]
c. Specificity for colonoscopy is based on Schroy et al, 2013.[20] The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, which, in the case of colonoscopy leads to unnecessary polypectomy, which is associated with an increased risk complications.
d. Sensitivity of colonoscopy for the detection of adenomas and colorectal cancer within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies.[19]
e. Complications are conditional on polypectomy, and we assume that polypectomy is only performed if colonoscopy is positive.

f. Risk of dying from colonoscopy were based on Canadian literature.[22] A death was attributed to colonoscopy if it occurred within 30 days following an index colonoscopy.
g. Complications of colonoscopy were based on Canadian literature.[21, 22] A complication is considered as individuals who were admitted to hospital with colonoscopy related events during the 30 days following the index colonoscopy.
h. Other events include post-polypectomy syndrome, cardiac events, syncope/hypotension, gastrointestinal symptoms, splenic/hepatic hematoma, fall/injury, thrombophlebitis, hyponatremia, oesophageal variceal haemorrhage, and various other symptoms.
i. The participation with diagnostic colonoscopy after a positive faecal test is taken from Cancer Quality Council of Ontario[13] and is the same for all screening scenarios except under the assumption of perfect adherence to screening.
j. The participation rate for colonoscopy surveillance was assumed to be 80%, based on data from US clinical practice[14] and is the same for all screening scenarios except under the assumption of perfect adherence to screening where we assume 100% adherence to surveillance.

Table 5.2: Overview of comorbidity levels and associated conditions.

	Conditions included [a]
No comorbid conditions	None of the conditions listed for mild, moderate or severe
Low comorbid conditions	Myocardial infarction (MI), ulcer or rheumatologic disease
Moderate comorbid conditions	Peripheral vascular disease, cerebrovascular disease paralysis, diabetes, or combinations of mild conditions (with or without diabetes)
Severe comorbid conditions	AIDS, Chronic Obstructive Pulmonary Disease, cirrhosis, chronic hepatitis, chronic renal failure, dementia, congestive heart failure, or combinations of at least one moderate condition (except diabetes) with any mild or moderate condition

Abbreviations: AIDS, acquired immune deficiency syndrome
a. Comorbid conditions previously specified in Lansdorp-Vogelaar and colleagues, 2014.[4]

Analyses and Outcomes

For each cohort, we compared the harms and benefits of participating in FIT screening versus no further screening at their current age, considering sex, comorbidity status and screening history. The benefits of screening are provided as life years gained (LYG) and cancer deaths prevented (CDP) per 1000 women or men of a given age. Harms are expressed as the number of: i) colonoscopies; ii) complications from colonoscopy; iii) false-positive test results (i.e. negative diagnostic colonoscopies after positive FIT results); and iv) over-diagnosed cancer cases (i.e. cancers that would not have caused symptoms during a person's lifetime). The balance between harms and benefits is presented as the incremental number needed to screen per life-year gained (NNS/LYG). We also provide details on the incremental number needed to screen per CDP and the incremental number of colonoscopies per LYG and per CDP.

REFERENCE SCENARIO

To identify the optimal age to stop screening, we first established an acceptable balance of harms and benefits based on current screening recommendations (acceptable threshold) and then determined a threshold where the balance was no longer considered acceptable (upper threshold). To do this, we simulated a cohort of individuals aged 74 and 76 years with average health and life expectancy, who had perfectly adhered to biennial FIT screening, diagnostic and surveillance colonoscopies from age 50. We used this threshold because it is currently recommended and thus deemed acceptable.

The acceptable threshold was determined by assessing the harms and benefits FIT screening at age 74 compared to stopping screening at age 72. The upper threshold was determined by similarly evaluating a cohort of 76-year-olds, undergoing screening at age 76 compared to stopping screening at age 74 years. For each comorbidity level and screening history, the optimal age to stop screening was considered to be the age where the harm-benefit-ratio fell within the range between the acceptable and upper thresholds. Where no value or two values fell within the range, the age closest to the acceptable threshold was chosen.

SENSITIVITY ANALYSES

To assess the generalisability of our results, we conducted several sensitivity analyses to assess the impact of alternative screening histories. In the first instance we assessed historical screening using the less sensitive Hemoccult II,[23] a guaiac faecal occult blood test (gFOBT, Supplementary Methods Table 5.1), with FIT administered in the current screening episode. Secondly, we assessed historical screening where FIT was administered in the current and previous two screening episodes, but prior to that gFOBT was administered.

We also assessed scenarios of annual screening with FIT and 10-yearly screening with colonoscopy in accordance with practice in the US. Finally, we assessed the base case screening scenario using a FIT with a lower cut-off (15 µg Hb/g faeces) and therefore a higher overall positivity rate (9%). In these scenarios the acceptable thresholds were adjusted accordingly.

RESULTS

THRESHOLD RANGE TO STOP SCREENING

Screening 1000 women with average health and life expectancy at age 74 years (compared to stopping screening at 72 years), under the assumption of perfect prior screening with FIT since age 50, gained 6.9 LYs and prevented 0.9 colorectal cancer deaths (Table 5.3). In addition, there were 17.3 false-positive test results, 35.9 colonoscopies, 0.3 over-diagnosed cases of colorectal cancer and 0.1 complications of colonoscopy. Under these assumptions, 145

needed to be screened to gain one life year (acceptable threshold). An additional screen at age 76 (compared to stopping at 74 years) yielded fewer benefits thereby increasing the NNS/LYG to 157 (upper threshold (Figure 5.1a)). Screening in men followed the same pattern as in women, however, in general the gains in life years were higher, resulting in an acceptable and upper NNS/LYG threshold of 94 and 108 respectively (Table 5.3, Figure 5.1b).

SCREENING BASED ON SEX, COMORBIDITY, AND SCREENING HISTORY

Compared to perfectly screened 74-year-old women with average health, those with no comorbid conditions enjoyed greater benefits (7.8 LYG and 1.0 CDP). Although harms were similar, they experienced slightly less (0.2) over-diagnosed colorectal cancers (Supplementary Results Table 5.1a). This resulted in a more favourable balance between the harms and benefits (NNS/LYG: 129 (Figure 5.1a)). As comorbidity increased, the harms of screening also increased while the benefits decreased, worsening the harm-benefit ratio as indicated by the increased NNS/LYG (Supplementary Results Table 5.1a-g).

Women aged 74 years with no comorbid conditions and without prior screening, yielded substantially greater benefits (38.1 LYG and 4.9 CDP) than women aged 74 years with average health and perfect prior screening due to their increased risk and longer life-expectancy. This resulted in a substantially lower NNS/LYG (26.0) in this group (Figure 5.1c, Supplementary Results Table 5.1e). However, this group also experienced a noteworthy increase in harms. For example, there was 60% increase in the number of false-positive tests, a more than four-fold increase in the number of colonoscopies and over-diagnosed colorectal cancer cases and a more than six-fold increase in the number of complications of colonoscopy. As adherence to prior screening improved, both the harms and benefits of screening decreased, however benefits decreased to a greater extent, which resulted in an increase in the NNS/LYG (Supplementary Results Table 5.1b-f, Supplementary Results Figures 5.1a-e). In general, for women with a colonoscopy 10 years prior, the harms outweighed the benefits at or before the age of 74 years (Supplementary Results Table 5.1f). For women with a colonoscopy 15 years prior, the harms outweighed the benefits at or after the age of 74 years except for those with severe comorbidities (Supplementary Results Table 5.1g).

Screening in men followed the same pattern as in women, although in general they experienced both greater harms and greater benefits. However, as the benefits increased to a greater extent, the NNS/LYG was lower (Figures 5.1b and d, Supplementary Results Tables 5.2a-g, Supplementary Results Figures 5.2a-e).

Table 5.3: Reference scenario: harms and benefits of screening 1000 women and men with average health under the assumption of perfect prior screening adherence to biennial faecal immunochemical testing from age 50 years until age 74 or 76, and the balance between those harms and benefits. [a]

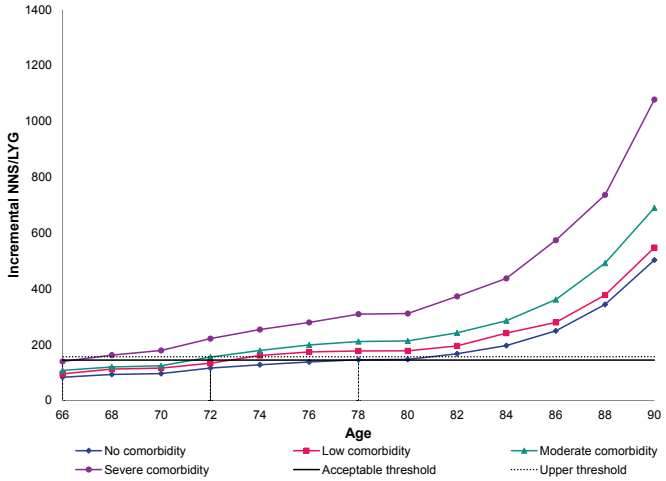
	Benefits [b]		Harms [b]				Balance [b]			
	Life-years gained, n [c]	Cancer deaths prevented, n	False-positive tests, n [d]	Over-diagnosed cases, n	Colonoscopies, n	Complications of colonoscopy, n	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Women										
Screening to age 74 [e]	6.9	0.9	17.3	0.3	35.8	0.1	145	1141	5.2	40.8
Screening to age 76 [f]	6.4	0.9	19.0	0.3	37.6	0.1	157	1147	5.9	43.1
Men										
Screening to age 74 [e]	10.6	1.5	15.3	0.6	47.4	0.2	94	659	4.5	31.3
Screening to age 76 [f]	9.2	1.4	17.4	0.7	50.3	0.2	108	690	5.4	34.7

Abbreviations: FIT, faecal immunochemical test; NNS/CDP, number needed to screen to prevent one colorectal cancer death; NNS/LYG, number needed to screen to gain one life year; NNSc/CDP, number needed to scope to prevent one colorectal cancer death; NNSc/LYG, number needed to scope to gain one life year
Note: These results are used to inform the acceptable and upper threshold to determine the optimal age to stop screening.

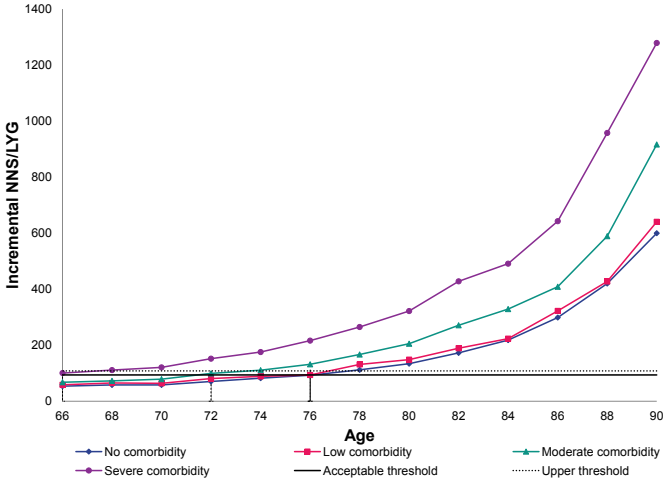
a. In this analysis we used a FIT positivity of 7.5% which equated to a cut-off level of 23 µg Hb/g. The FIT characteristics were adjusted to take into account the effect of systematic false-negative results.[18]
b. Results are per 1000 persons screened.
c. One life year gained per 1000 persons corresponds with 0.365 days gained per person.
d. A false-positive test is defined as a negative colonoscopy after a positive FIT.
e. Compared to stopping screening at age 72 years.
f. Compared to stopping screening at age 74 years.

Figure 5.1: Number needed to screen per life year gained by age and comorbidity level, for women (a, c) and men (b, d) with perfect prior FIT screening (a, b) and no prior screening (c, d).

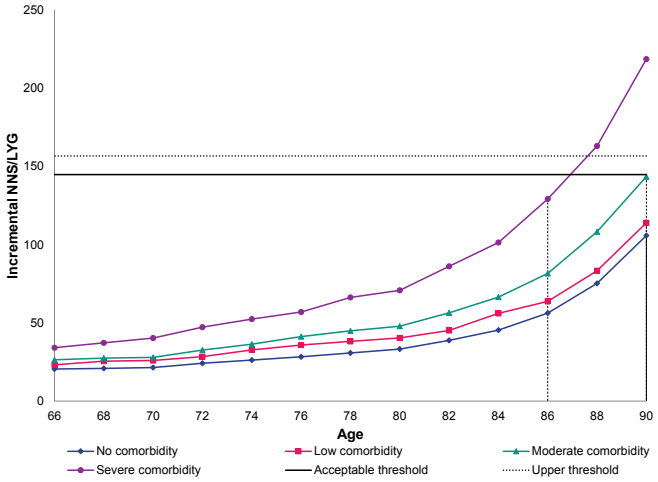
a



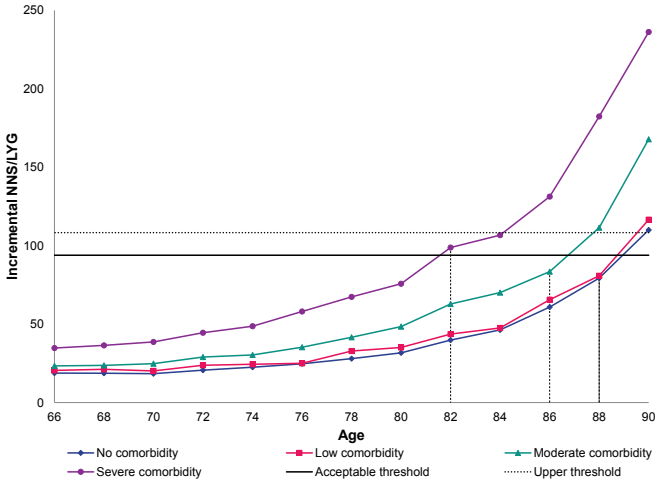
b



c



d



Abbreviations: NNS/LYG, number needed to screen to gain one life year

Each line represents the number needed to screen per life year gained over the ages 66 to 90 years for each level of comorbidity. The solid horizontal line represents the threshold for the number needed to screen per life year gained for screening in the average health population until the age of 74 years (acceptable threshold). The dashed line represents the threshold for the number needed to screen per life year gained for screening in the average health population until the age of 76 years (upper threshold). The recommended colorectal cancer screening stop age is defined by this range. Where two ages fall within the threshold range, the lowest of the two values is selected. Where no values fall within the threshold range, the age closest to the lowest level is selected. The vertical dashed lines indicate the age for each comorbidity group where screening provides a balance of harms and benefits similar to those aged 74 years with average health.

Age of last screen based on sex, comorbidity, and screening history

Men and women without comorbidities who had previously been screened with FIT and those with no or some prior FIT screening, regardless of comorbidity status, could screen past the recommended stop age, with age of last screen ranging from 76-90 years (Table 5.4). Those with severe comorbid conditions should consider having a last screening episode before the recommended stop age (66-70 years), unless they had no, some or reasonable prior screening, in which case they should continue to screen up to or past the recommended stop age (74-86 years).

For those who had a colonoscopy 10 years prior to the investigated stop age, regardless of sex or comorbidity, the last screening episode should occur at or before the age of 74 years. While for those who had a colonoscopy 15 years ago, screening stop age was dependent on both sex and comorbidity status and ranged from 66-83 years (Table 5.4).

Sensitivity analyses

Our results were robust to alterations in screening history with biennial gFOBT and FIT: the pattern of age of last screening remained the same as in the base-case scenario, however, the ages were slightly older (Supplementary Results Tables 5.3a-c, Supplementary Results Tables Table 5.5). For annual FIT screening, the stop ages were slightly lower. For colonoscopy screening, screening should stop earlier than the recommended screening stop age for those with severe comorbidities and at or just after the recommended screening stop age for those with no comorbidities (Supplementary Results Table 5.4).

Table 5.4: Suggested age of last screening episode for colorectal cancer based on the number needed to screen to gain one life year, by sex, comorbidity status and prior screening with biennial faecal immunochemical testing or colonoscopy. The faecal immunochemical test had a positivity of 7.5% (23 µg Hb/g faeces).

Screening History[a] / Comorbidity status[b]	Women				Men			
	No	Low	Mod	Sev	No	Low	Mod	Sev
Perfect Prior Screening with FIT	78	72	72	66	76	76	72	66
Most Prior Screening with FIT	84	82	78	70	80	80	76	70
Reasonable Prior Screening with FIT	86	84	82	76	82	82	78	74
Some Prior Screening with FIT	88	86	86	80	84	84	82	78
No Prior Screening	90	90	90	86	88	88	86	82
Colonoscopy 10 years prior	74	68	66	<66	73	72	69	<66
Colonoscopy 15 years prior	83	76	74	68	80	78	75	66

Abbreviations: FIT, faecal immunochemical test; Mod, moderate; Sev, severe

Key: Blue – stop screening later than recommended in guidelines; Green – stop screening in line with guidelines; Red – stop screening earlier than recommended in guidelines

a. Detailed descriptions of screening history are found in Table 5.1. In brief, perfect prior screening assumes 100% attendance in prior screening rounds, most prior screening assumes 75% attendance in prior screening rounds, reasonable prior screening assumes 50% attendance in prior screening rounds, some prior screening assumes 25% attendance in prior screening rounds and no prior screening assumes no attendance in prior screening rounds. For colonoscopy we assume screening occurred 10 and 15 years prior to the investigated stop age.

b. Detailed descriptions of comorbid conditions are found in Table 5.2. In brief there are four categories: no comorbidity, low comorbidity, moderate comorbidity and severe comorbidity.

DISCUSSION

According to our analysis, several groups may benefit from screening past the recommended stop age. For example, individuals without comorbidity, those who are screening naive or who had a colonoscopy 15 years ago and are without severe comorbidities could undergo screening until between 76-90 years of age. Screening these individuals after the recommended stop age presents an opportunity to reduce their risk of colorectal cancer and maximise the benefits of screening while maintaining an appropriate balance of harms. For others, such as those with severe comorbidity and most to perfect prior FIT screening, screening could stop earlier than currently recommended. This earlier than recommended stop age also applies to those with a colonoscopy 10 years prior, except for women without comorbidity. Continued screening in these individuals provides fewer benefits and increases unnecessary harms and burden compared to the average health population.

Our results are in line with previous findings that individuals with lower comorbidity and less intensive screening history will benefit from screening past the recommended stop age.[4, 5] However, our investigation builds on previous research by more comprehensively assessing the impact of screening history on optimal age to stop screening. This approach is more in keeping with "real life", where exposure to prior colorectal tests may be quite varied.

There are four noteworthy limitations to this investigation. First, rates of participation in prior screening were determined *a priori* and do not necessarily reflect what is happening in practice. More accurate data on actual patterns of adherence would be a useful addition. Second, by assuming that the population was at average risk for colorectal cancer, we did not consider the probable variation in risk. Colorectal cancer risk is affected by genetic profile, family history, lifestyle factors (such as smoking and obesity)[24, 25] and comorbid conditions (i.e. diabetes increases risk[26]). As these factors are likely to affect both the harms and benefits of screening, we believe they should be incorporated into future research. Third, our life tables came from a statistical analysis of administrative data provided by SEER and included a broad range of diseases such as AIDS which may seem less relevant than other diseases. However, that statistical analysis showed that having AIDS resulted in a higher probability of dying. Furthermore, the life tables do not include mortality for cancers, therefore our results may underestimate other-cause mortality rates and the harm-benefit ratio, but not the comparisons of the comorbid condition groups to the average health population. Finally, we did not include quality of life in our outcome measures. However, the purpose of this analysis was to separately assess the harms, burden and benefits of screening to allow individuals to make their own decisions about screening participation. Had we presented this, we would expect similar results as the thresholds would also have shifted.

Notwithstanding these limitations, there are several important implications of this investigation. Firstly, using MISCAN-Colon, a well-established, validated model for colorectal cancer screening,[7] we have developed a complex algorithm incorporating age, sex, comorbidity status, and screening history that allows for a comprehensive assessment of individuals within the population. In addition, by using life tables, which were based on administrative data and personal factors such as age, sex, comorbidity, and screening history, which are generally found in health administrative data, in the future screening participation recommendations could potentially be automated for use in the clinical setting (for example in a clinical decision support system).

Our results provide detailed guidance for clinicians and patients when discussing screening participation. For example, if a clinician was meeting with a 72-year-old women patient who has cardiovascular disease (considered as a moderate level of comorbidity) and who has participated 50% of prior screening rounds, our results indicate that she could participate in another screening round, as the benefits still outweigh the harms. However, for a man patient

aged 74 with chronic obstructive pulmonary disease (a severe comorbid condition) who has previously participated in 75% of screening episodes, our results indicate that the benefits of screening may no longer outweigh the potential harms, and he should consider stopping screening at this time. This guidance is based on the metric of NNS/LYG. However, should clinicians prefer to use another metric, they are available in the Supplementary Results. For example, using the balance of NNSc/CDP, our 72-year-old women noted above may consider stopping screening because this balance of harms and benefits is no longer favourable. Decisions to participate in screening should depend on individual patient preferences and our results help to facilitate this decision-making in an informed way. Furthermore, they can assist policy makers who are designing or updating existing colorectal cancer screening programs and guidelines, and addresses concerns that this evidence has been lacking for FIT-based screening programs.[27]

CONCLUSION

There is a growing body of evidence highlighting the benefits of personalising screening to optimise benefits and reduce harms. By providing reliable information about the possible benefits, harms and burden of screening, our results facilitate an evidence-based approach for formulating guidelines and making informed decisions about screening participation. Our research suggests that varying screening stop age from <66 to 90 years depending on age, sex, comorbidity status and screening history is a more efficient approach and results in better patient outcomes than one that is based on age alone. These results may assist patients and clinicians to make informed decisions about screening participation and could be used to inform future colorectal cancer screening program guidelines.

ACKNOWLEDGMENTS

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SUPPLEMENTARY METHODS

Supplementary Methods Table 5.1: Screen test characteristics.

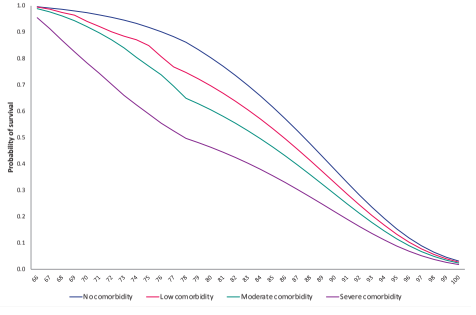
Screen test	Sensitivity (%)					Specificity (%)
	Adenoma ≤5mm	Adenoma 6-9mm	Adenoma ≥10mm	CRC early preclinical [a]	CRC late preclinical [a]	
FIT15 [b]	0.0	21.6	38.8	31.1	67.7	95.5
FIT23 [b]	0.0	17.6	34.0	29.5	66.0	96.7
gFOBT (Hemoccult II) [c]	0.0	1.3	6.5	18.2	50.8	98.0
Colonoscopy [d,e,f]	75.0	85.0	95.0	95.0	95.0	86.0

Abbreviations: CRC, colorectal cancer; FIT23, faecal immunochemical test, 23 µg Hb/g faeces cut-off value (7.5% positivity); FIT15, faecal immunochemical test, 15 µg Hb/g cut-off value (9% positivity)

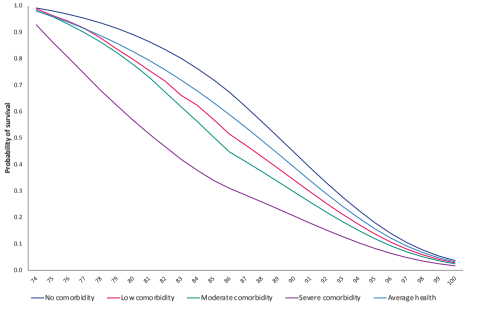
a. We assume that occult blood screening is more sensitive in cancers as they progress towards becoming symptomatic (visible bleeding) and clinically detectable.[23] For preclinical cancers which will become symptomatic within the same stage, assumed test sensitivity is higher.
b. Specificity and sensitivity of FIT derived from the Dutch colorectal cancer screening program.[15]
c. Specificity and sensitivity of gFOBT based on a prior calibration of the MISCAN model to three large gFOBT screening trials.[23]
d. Sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies.[19]
e. The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, where the non-adenomatous lesions are removed and therefore induce polypectomy and biopsy or lead to (unnecessary) referral with sigmoidoscopy. The evidence synthesis reported no specificity for endoscopy for any adenoma. Specificity for colonoscopy is therefore based on Schroy et al, 2013.[20]
f. We assume the same test characteristics for diagnostic colonoscopy as for screening colonoscopy.

Supplementary Methods Figure 5.1: Annual probability of survival by comorbidity condition for females (a, b, c,) and males (d, e, f) aged 66 (a, d), 74 (b, e) and 90 (c, f) years. At age 74 (b, e), survival for those with average health is also presented.

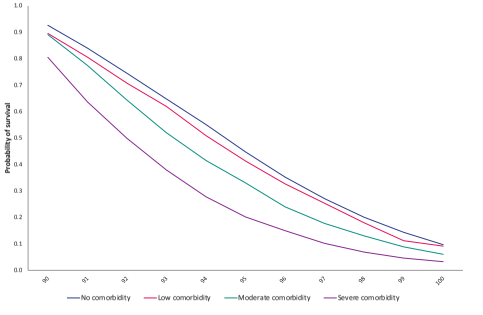
a. Females aged 66 with no, low, moderate or severe comorbidities.



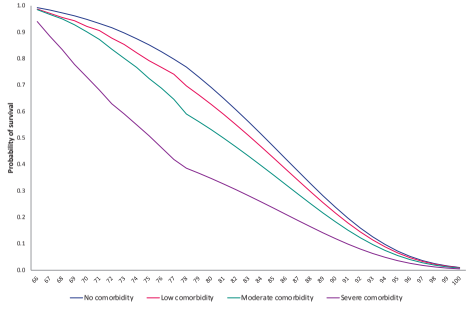
b. Females aged 74 with no, low, moderate or severe comorbidities and at average health.



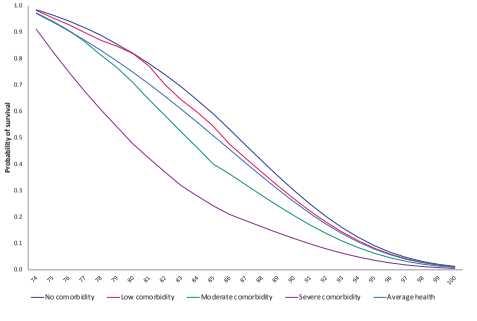
c. Females aged 90 with no, low, moderate or severe comorbidities.



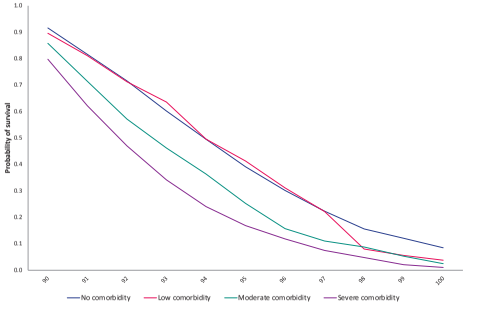
d. Males aged 66 with no, low, moderate or severe comorbidities.



e. Males aged 74 with no, low, moderate or severe comorbidities and at average health.



f. Males aged 90 with no, low, moderate or severe comorbidities.



SUPPLEMENTARY RESULTS

Supplementary Results Table 5.1: Benefits and harms of screening 1,000 females by age and comorbidity under varying prior screening assumptions with biennial faecal immunochemical testing or colonoscopy. The faecal immunochemical test had a positivity of 7.5% (23 µg Hb/g faeces).

a. Perfect prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	17.3	0.3	35.8	0.1	6.9	0.9	145	1141	5.2	40.8
	Screen through age 76 (vs. 74)	19.0	0.3	37.6	0.1	6.4	0.9	157	1147	5.9	43.1
No comorbidity	Screen through age 66	19.1	0.1	46.6	0.1	12.0	1.1	83	923	3.9	43.0
	Screen through age 68	17.5	0.1	40.9	0.1	10.7	1.0	93	965	3.8	39.5
	Screen through age 70	28.6	0.1	51.3	0.1	10.4	1.1	96	930	4.9	47.7
	Screen through age 72	17.4	0.2	38.9	0.1	8.6	1.0	116	1006	4.5	39.2
	Screen through age 74	17.3	0.2	36.2	0.1	7.8	1.0	128	1042	4.6	37.7
	Screen through age 76	19.0	0.2	38.2	0.1	7.3	1.0	138	1024	5.3	39.1
	Screen through age 78	16.8	0.3	33.5	0.1	6.8	1.0	146	1009	4.9	33.8
	Screen through age 80	27.0	0.4	45.6	0.1	6.8	1.1	147	918	6.7	41.9
	Screen through age 82	16.3	0.6	34.9	0.1	6.0	1.1	167	925	5.8	32.3
	Screen through age 84	16.2	0.7	35.9	0.1	5.1	1.0	197	958	7.1	34.4
	Screen through age 86	17.7	0.9	39.8	0.1	4.0	0.9	249	1057	9.9	42.1
	Screen through age 88	16.0	1.1	37.2	0.1	2.9	0.8	344	1237	12.8	46.0
	Screen through age 90	26.3	1.3	49.5	0.1	2.0	0.7	503	1506	24.9	74.5
Mild comorbidity	Screen through age 66	19.1	0.1	45.3	0.1	10.5	1.0	95	1026	4.3	46.4
	Screen through age 68	17.5	0.2	39.5	0.1	8.9	0.9	112	1114	4.4	44.0
	Screen through age 70	28.6	0.2	50.2	0.1	8.6	0.9	116	1077	5.8	54.1
	Screen through age 72	17.4	0.2	37.9	0.1	7.5	0.9	134	1138	5.1	43.2
	Screen through age 74	17.3	0.3	35.6	0.1	6.2	0.8	161	1232	5.7	43.8
	Screen through age 76	18.9	0.3	37.5	0.1	5.7	0.8	174	1214	6.5	45.5
	Screen through age 78	16.8	0.4	33.3	0.1	5.6	0.9	178	1146	5.9	38.2
	Screen through age 80	27.0	0.5	45.6	0.1	5.6	1.0	178	1034	8.1	47.1
	Screen through age 82	16.3	0.7	34.6	0.1	5.1	1.0	195	1037	6.8	35.9
	Screen through age 84	16.2	0.8	35.6	0.1	4.1	0.9	241	1100	8.6	39.2
	Screen through age 86	17.7	1.0	39.6	0.1	3.6	0.9	280	1129	11.1	44.8
	Screen through age 88	16.0	1.2	36.7	0.1	2.6	0.7	378	1344	13.8	49.3
	Screen through age 90	26.3	1.3	49.2	0.1	1.8	0.6	548	1617	26.9	79.5
Moderate comorbidity	Screen through age 66	19.1	0.2	44.1	0.1	9.3	0.9	108	1124	4.8	49.6
	Screen through age 68	17.5	0.2	39.1	0.1	8.3	0.9	120	1166	4.7	45.6
	Screen through age 70	28.6	0.2	49.8	0.1	8.0	0.9	124	1129	6.2	56.3
	Screen through age 72	17.4	0.3	37.2	0.1	6.4	0.8	155	1260	5.8	46.9
	Screen through age 74	17.4	0.3	35.4	0.1	5.6	0.8	179	1331	6.3	47.1
	Screen through age 76	18.9	0.4	37.1	0.1	5.0	0.8	199	1324	7.4	49.2
	Screen through age 78	16.8	0.5	33.1	0.1	4.7	0.8	211	1279	7.0	42.4
	Screen through age 80	27.0	0.6	45.3	0.1	4.7	0.8	213	1178	9.7	53.4
	Screen through age 82	16.3	0.8	34.3	0.1	4.1	0.8	242	1185	8.3	40.7
	Screen through age 84	16.3	1.0	35.4	0.1	3.5	0.8	285	1245	10.1	44.0
	Screen through age 86	17.7	1.1	39.3	0.1	2.8	0.7	361	1351	14.2	53.1
	Screen through age 88	16.1	1.3	36.4	0.1	2.0	0.6	492	1595	17.9	58.1
	Screen through age 90	26.3	1.4	48.7	0.1	1.4	0.5	690	1881	33.6	91.6
Severe comorbidity	Screen through age 66	19.1	0.2	41.4	0.1	7.2	0.7	140	1425	5.8	59.1
	Screen through age 68	17.5	0.3	36.8	0.1	6.1	0.7	163	1522	6.0	56.0
	Screen through age 70	28.6	0.3	47.5	0.1	5.6	0.7	179	1521	8.5	72.2
	Screen through age 72	17.4	0.4	35.0	0.1	4.5	0.6	222	1717	7.8	60.1
	Screen through age 74	17.4	0.4	33.7	0.1	3.9	0.6	254	1792	8.6	60.3
	Screen through age 76	19.0	0.5	35.7	0.1	3.6	0.6	280	1774	10.0	63.3
	Screen through age 78	16.8	0.6	32.2	0.1	3.2	0.6	309	1737	10.0	55.9
	Screen through age 80	27.0	0.8	44.5	0.1	3.2	0.6	311	1596	13.9	71.0
	Screen through age 82	16.3	1.0	33.5	0.1	2.7	0.6	373	1643	12.5	55.1
	Screen through age 84	16.2	1.2	34.4	0.1	2.3	0.6	437	1722	15.1	59.2
	Screen through age 86	17.7	1.4	38.2	0.1	1.7	0.5	574	1926	21.9	73.5
	Screen through age 88	16.1	1.5	35.4	0.1	1.4	0.5	737	2141	26.1	75.9
	Screen through age 90	26.2	1.7	47.6	0.1	0.9	0.4	1078	2675	51.3	127.4

b. Most prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	17.3	0.3	35.8	0.1	6.9	0.9	145	1141	5.2	40.8
	Screen through age 76 (vs. 74)	19.0	0.3	37.6	0.1	6.4	0.9	157	1147	5.9	43.1
No comorbidity	Screen through age 66	20.0	0.2	63.5	0.2	17.0	1.6	59	642	3.7	40.8
	Screen through age 68	19.2	0.2	56.7	0.2	15.7	1.5	64	655	3.6	37.1
	Screen through age 70	22.3	0.2	57.4	0.2	14.5	1.5	69	657	4.0	37.7
	Screen through age 72	22.5	0.3	56.1	0.2	12.5	1.4	80	696	4.5	39.1
	Screen through age 74	21.4	0.3	50.5	0.2	11.2	1.4	89	725	4.5	36.6
	Screen through age 76	20.3	0.4	48.3	0.2	10.0	1.4	100	739	4.8	35.7
	Screen through age 78	19.0	0.5	43.2	0.1	9.4	1.4	106	729	4.6	31.5
	Screen through age 80	20.1	0.6	44.7	0.1	9.1	1.5	110	687	4.9	30.8
	Screen through age 82	20.5	0.8	46.6	0.2	7.9	1.4	127	699	5.9	32.6
	Screen through age 84	20.1	1.1	47.5	0.2	6.9	1.4	144	708	6.9	33.6
	Screen through age 86	19.4	1.3	48.0	0.2	5.5	1.3	182	774	8.7	37.1
	Screen through age 88	18.7	1.6	48.1	0.2	4.0	1.1	250	901	12.0	43.3
	Screen through age 90	19.0	1.9	48.9	0.2	2.9	0.9	348	1074	17.0	52.6
Mild comorbidity	Screen through age 66	20.0	0.2	61.3	0.2	15.1	1.4	66	708	4.1	43.5
	Screen through age 68	19.2	0.3	54.7	0.2	13.1	1.3	76	755	4.2	41.3
	Screen through age 70	22.2	0.3	55.4	0.2	12.2	1.3	82	758	4.5	42.0
	Screen through age 72	22.5	0.3	54.5	0.2	10.6	1.3	94	795	5.1	43.3
	Screen through age 74	21.4	0.4	49.3	0.2	9.0	1.2	111	841	5.5	41.5
	Screen through age 76	20.2	0.5	47.3	0.1	7.9	1.1	126	872	6.0	41.2
	Screen through age 78	18.9	0.6	43.0	0.1	7.8	1.2	129	832	5.5	35.8
	Screen through age 80	20.0	0.7	44.5	0.1	7.5	1.3	133	780	5.9	34.7
	Screen through age 82	20.5	1.0	46.3	0.2	6.8	1.3	146	784	6.8	36.3
	Screen through age 84	20.1	1.2	47.2	0.2	5.7	1.3	175	799	8.2	37.7
	Screen through age 86	19.4	1.4	47.7	0.2	4.9	1.2	203	825	9.7	39.4
	Screen through age 88	18.7	1.8	47.3	0.2	3.6	1.0	276	985	13.0	46.5
	Screen through age 90	19.1	2.0	48.5	0.2	2.6	0.9	378	1143	18.3	55.4
Moderate comorbidity	Screen through age 66	20.0	0.3	59.5	0.2	13.2	1.3	76	784	4.5	46.6
	Screen through age 68	19.2	0.3	53.9	0.2	12.2	1.3	82	793	4.4	42.8
	Screen through age 70	22.2	0.3	54.8	0.2	11.4	1.2	88	800	4.8	43.9
	Screen through age 72	22.5	0.4	53.4	0.2	9.2	1.1	109	889	5.8	47.5
	Screen through age 74	21.4	0.4	49.0	0.1	8.2	1.1	123	904	6.0	44.3
	Screen through age 76	20.2	0.6	46.7	0.1	6.9	1.1	145	951	6.8	44.4
	Screen through age 78	19.0	0.7	42.7	0.1	6.5	1.1	153	931	6.5	39.7
	Screen through age 80	20.0	0.9	44.2	0.1	6.2	1.1	161	893	7.1	39.4
	Screen through age 82	20.5	1.1	46.0	0.1	5.6	1.1	180	888	8.3	40.8
	Screen through age 84	20.1	1.4	46.8	0.2	4.9	1.1	205	896	9.6	42.0
	Screen through age 86	19.4	1.6	47.1	0.2	3.8	1.0	261	976	12.3	45.9
	Screen through age 88	18.7	1.9	46.9	0.2	2.8	0.9	358	1175	16.8	55.1
	Screen through age 90	19.0	2.2	47.8	0.2	2.1	0.7	471	1337	22.5	63.9
Severe comorbidity	Screen through age 66	20.0	0.4	54.9	0.2	10.3	1.0	97	981	5.3	53.9
	Screen through age 68	19.2	0.4	49.9	0.2	9.0	1.0	112	1043	5.6	52.1
	Screen through age 70	22.2	0.5	51.0	0.2	7.9	0.9	127	1079	6.5	55.1
	Screen through age 72	22.5	0.6	50.0	0.1	6.3	0.8	158	1202	7.9	60.0
	Screen through age 74	21.4	0.7	46.2	0.1	5.6	0.8	179	1246	8.2	57.5
	Screen through age 76	20.2	0.8	44.6	0.1	5.0	0.8	201	1249	9.0	55.7
	Screen through age 78	19.0	0.9	41.3	0.1	4.5	0.8	224	1267	9.3	52.4
	Screen through age 80	20.0	1.2	43.0	0.1	4.2	0.8	238	1209	10.2	52.0
	Screen through age 82	20.5	1.4	44.8	0.1	3.7	0.8	270	1191	12.1	53.3
	Screen through age 84	20.1	1.7	45.4	0.2	3.2	0.8	315	1228	14.3	55.7
	Screen through age 86	19.4	2.0	45.6	0.2	2.5	0.7	407	1383	18.6	63.0
	Screen through age 88	18.7	2.3	45.6	0.2	1.9	0.6	532	1559	24.2	71.1
	Screen through age 90	19.0	2.5	46.3	0.2	1.4	0.5	707	1839	32.8	85.2

c. Reasonable prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	17.3	0.3	35.8	0.1	6.9	0.9	145	1141	5.2	40.8
	Screen through age 76 (vs. 74)	19.0	0.3	37.6	0.1	6.4	0.9	157	1147	5.9	43.1
No comorbidity	Screen through age 66	21.9	0.2	82.1	0.3	21.7	2.0	46	500	3.8	41.0
	Screen through age 68	21.1	0.3	73.9	0.2	20.3	2.0	49	503	3.6	37.2
	Screen through age 70	21.9	0.3	71.2	0.2	19.0	2.0	53	502	3.8	35.8
	Screen through age 72	22.4	0.4	69.6	0.2	16.3	1.9	61	531	4.3	37.0
	Screen through age 74	22.4	0.4	63.1	0.2	14.3	1.8	70	561	4.4	35.4
	Screen through age 76	21.9	0.5	60.4	0.2	13.0	1.8	77	567	4.6	34.2
	Screen through age 78	20.9	0.6	53.4	0.2	12.0	1.8	83	566	4.4	30.2
	Screen through age 80	20.6	0.8	52.7	0.2	11.4	1.8	88	550	4.6	28.9
	Screen through age 82	20.6	1.0	53.9	0.2	9.7	1.8	103	565	5.6	30.4
	Screen through age 84	20.7	1.3	55.5	0.2	8.5	1.7	118	577	6.5	32.0
	Screen through age 86	20.5	1.6	56.2	0.2	6.9	1.6	145	625	8.2	35.1
	Screen through age 88	20.2	2.0	57.0	0.2	5.1	1.4	196	710	11.2	40.4
	Screen through age 90	20.2	2.4	57.2	0.2	3.5	1.1	288	880	16.5	50.3
Mild comorbidity	Screen through age 66	21.9	0.3	79.1	0.3	19.1	1.8	52	550	4.1	43.5
	Screen through age 68	21.1	0.4	70.8	0.2	16.9	1.7	59	581	4.2	41.1
	Screen through age 70	21.9	0.4	68.3	0.2	15.8	1.7	63	580	4.3	39.6
	Screen through age 72	22.4	0.5	67.1	0.2	13.7	1.6	73	610	4.9	40.9
	Screen through age 74	22.5	0.6	61.4	0.2	11.4	1.5	88	669	5.4	41.1
	Screen through age 76	21.8	0.7	59.1	0.2	10.3	1.5	97	671	5.7	39.6
	Screen through age 78	20.9	0.7	53.0	0.2	9.8	1.5	102	653	5.4	34.6
	Screen through age 80	20.6	1.0	52.4	0.2	9.3	1.6	108	625	5.6	32.8
	Screen through age 82	20.6	1.2	53.5	0.2	8.4	1.6	119	630	6.4	33.7
	Screen through age 84	20.7	1.5	55.0	0.2	7.0	1.5	143	651	7.8	35.8
	Screen through age 86	20.5	1.8	56.1	0.2	6.2	1.5	162	667	9.1	37.4
	Screen through age 88	20.2	2.2	55.9	0.2	4.6	1.3	216	773	12.1	43.2
	Screen through age 90	20.2	2.6	56.7	0.2	3.2	1.1	312	940	17.7	53.3
Moderate comorbidity	Screen through age 66	21.9	0.3	76.4	0.2	16.9	1.6	59	607	4.5	46.4
	Screen through age 68	21.1	0.4	69.7	0.2	15.7	1.6	64	613	4.4	42.7
	Screen through age 70	21.9	0.4	67.3	0.2	14.6	1.6	69	615	4.6	41.4
	Screen through age 72	22.5	0.5	65.7	0.2	12.1	1.5	83	665	5.4	43.7
	Screen through age 74	22.5	0.6	60.9	0.2	10.3	1.4	97	707	5.9	43.0
	Screen through age 76	21.8	0.7	58.3	0.2	9.0	1.4	112	739	6.5	43.0
	Screen through age 78	20.9	0.9	52.5	0.2	8.2	1.4	121	736	6.4	38.7
	Screen through age 80	20.6	1.1	52.0	0.2	7.8	1.4	129	711	6.7	37.0
	Screen through age 82	20.6	1.3	53.1	0.2	6.7	1.4	148	728	7.9	38.6
	Screen through age 84	20.7	1.7	54.6	0.2	5.9	1.4	169	736	9.2	40.1
	Screen through age 86	20.5	2.0	55.3	0.2	4.9	1.3	206	783	11.4	43.3
	Screen through age 88	20.2	2.5	55.4	0.2	3.6	1.1	280	923	15.5	51.2
	Screen through age 90	20.2	2.8	55.8	0.2	2.6	0.9	389	1094	21.7	61.1
Severe comorbidity	Screen through age 66	21.9	0.5	69.9	0.2	13.0	1.3	77	768	5.4	53.7
	Screen through age 68	21.2	0.6	63.9	0.2	11.5	1.3	87	799	5.5	51.0
	Screen through age 70	21.9	0.7	61.5	0.2	10.2	1.2	98	827	6.0	50.9
	Screen through age 72	22.4	0.8	60.4	0.2	8.4	1.1	120	908	7.2	54.9
	Screen through age 74	22.5	0.9	56.8	0.2	7.2	1.0	139	960	7.9	54.6
	Screen through age 76	21.8	1.0	55.1	0.2	6.4	1.0	156	972	8.6	53.5
	Screen through age 78	20.9	1.2	50.6	0.2	5.5	1.0	182	1017	9.2	51.5
	Screen through age 80	20.6	1.5	50.3	0.2	5.3	1.0	190	969	9.5	48.7
	Screen through age 82	20.6	1.8	51.5	0.2	4.4	1.0	225	991	11.6	51.0
	Screen through age 84	20.7	2.2	52.7	0.2	3.8	1.0	261	1015	13.8	53.5
	Screen through age 86	20.5	2.5	53.2	0.2	3.0	0.9	332	1118	17.7	59.4
	Screen through age 88	20.2	2.9	53.7	0.2	2.4	0.8	416	1250	22.3	67.1
	Screen through age 90	20.2	3.2	53.9	0.2	1.7	0.7	582	1496	31.3	80.6

d. Some prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	17.3	0.3	35.8	0.1	6.9	0.9	145	1141	5.2	40.8
	Screen through age 76 (vs. 74)	19.0	0.3	37.6	0.1	6.4	0.9	157	1147	5.9	43.1
No comorbidity	Screen through age 66	24.2	0.3	117.5	0.4	30.8	2.9	32	348	3.8	40.9
	Screen through age 68	23.8	0.4	107.1	0.4	28.5	2.8	35	351	3.8	37.6
	Screen through age 70	23.7	0.4	102.9	0.4	27.5	2.9	36	344	3.7	35.4
	Screen through age 72	23.8	0.5	100.5	0.4	23.4	2.7	43	364	4.3	36.6
	Screen through age 74	23.8	0.6	90.4	0.3	20.9	2.6	48	377	4.3	34.1
	Screen through age 76	23.5	0.7	86.3	0.3	18.8	2.6	53	387	4.6	33.4
	Screen through age 78	22.9	0.9	74.6	0.3	17.4	2.6	57	390	4.3	29.1
	Screen through age 80	22.5	1.1	72.4	0.3	16.1	2.6	62	385	4.5	27.9
	Screen through age 82	22.1	1.5	73.1	0.3	13.7	2.5	73	397	5.3	29.1
	Screen through age 84	21.9	1.9	73.9	0.3	11.5	2.4	87	420	6.4	31.1
	Screen through age 86	21.9	2.4	74.5	0.3	9.2	2.2	109	459	8.1	34.2
	Screen through age 88	21.8	2.9	75.3	0.3	7.0	1.9	143	520	10.7	39.1
	Screen through age 90	21.7	3.4	75.0	0.3	4.9	1.6	204	621	15.3	46.6
Mild comorbidity	Screen through age 66	24.2	0.4	112.7	0.4	27.0	2.6	37	385	4.2	43.4
	Screen through age 68	23.8	0.5	101.7	0.4	23.6	2.5	42	406	4.3	41.3
	Screen through age 70	23.7	0.6	97.7	0.3	22.6	2.5	44	401	4.3	39.2
	Screen through age 72	23.8	0.7	96.3	0.3	19.9	2.4	50	415	4.8	39.9
	Screen through age 74	23.8	0.8	87.3	0.3	16.8	2.2	60	447	5.2	39.0
	Screen through age 76	23.5	1.0	84.1	0.3	14.8	2.2	67	462	5.7	38.8
	Screen through age 78	22.9	1.1	73.9	0.3	14.1	2.2	71	454	5.3	33.5
	Screen through age 80	22.6	1.4	71.9	0.3	13.2	2.3	76	439	5.5	31.6
	Screen through age 82	22.2	1.7	72.3	0.3	11.8	2.2	85	446	6.1	32.2
	Screen through age 84	21.9	2.2	73.1	0.3	9.4	2.1	106	479	7.8	35.0
	Screen through age 86	21.9	2.5	74.1	0.3	8.2	2.0	122	493	9.0	36.6
	Screen through age 88	21.8	3.2	73.7	0.3	6.4	1.8	157	563	11.6	41.5
	Screen through age 90	21.7	3.6	74.2	0.3	4.6	1.5	219	662	16.2	49.1
Moderate comorbidity	Screen through age 66	24.2	0.5	108.3	0.4	23.9	2.4	42	423	4.5	45.8
	Screen through age 68	23.8	0.5	100.1	0.3	22.0	2.3	45	429	4.5	43.0
	Screen through age 70	23.7	0.6	96.2	0.3	20.9	2.3	48	426	4.6	41.0
	Screen through age 72	23.8	0.8	93.8	0.3	17.3	2.2	58	462	5.4	43.3
	Screen through age 74	23.8	0.9	86.2	0.3	15.0	2.1	67	487	5.8	42.0
	Screen through age 76	23.5	1.1	82.7	0.3	12.9	2.0	77	507	6.4	41.9
	Screen through age 78	22.9	1.2	73.2	0.3	11.9	2.0	84	508	6.1	37.2
	Screen through age 80	22.6	1.6	71.2	0.3	11.1	2.0	90	498	6.4	35.4
	Screen through age 82	22.2	1.9	71.6	0.3	9.5	2.0	106	512	7.6	36.7
	Screen through age 84	21.9	2.4	72.3	0.3	8.0	1.8	125	541	9.0	39.1
	Screen through age 86	21.9	2.9	72.9	0.3	6.4	1.7	156	584	11.4	42.6
	Screen through age 88	21.8	3.5	73.0	0.3	4.9	1.5	204	668	14.9	48.8
	Screen through age 90	21.7	3.9	72.9	0.3	3.6	1.3	274	778	20.0	56.7
Severe comorbidity	Screen through age 66	24.1	0.7	98.2	0.3	18.6	1.9	54	534	5.3	52.4
	Screen through age 68	23.7	0.8	90.7	0.3	16.3	1.8	61	558	5.6	50.6
	Screen through age 70	23.7	1.0	87.0	0.3	14.6	1.7	69	577	6.0	50.2
	Screen through age 72	23.8	1.1	84.9	0.3	11.9	1.6	84	633	7.1	53.7
	Screen through age 74	23.8	1.3	79.2	0.3	10.6	1.5	94	652	7.5	51.6
	Screen through age 76	23.5	1.5	76.8	0.3	9.6	1.5	104	664	8.0	51.0
	Screen through age 78	22.9	1.7	70.0	0.3	8.2	1.5	122	685	8.6	47.9
	Screen through age 80	22.6	2.1	68.4	0.3	7.5	1.5	133	673	9.1	46.0
	Screen through age 82	22.2	2.5	68.9	0.3	6.2	1.4	162	708	11.2	48.7
	Screen through age 84	21.9	3.1	69.5	0.3	5.2	1.4	191	741	13.3	51.4
	Screen through age 86	21.9	3.6	69.7	0.3	4.1	1.2	244	823	17.0	57.4
	Screen through age 88	21.8	4.1	70.3	0.3	3.2	1.1	308	905	21.6	63.6
	Screen through age 90	21.7	4.6	69.9	0.3	2.4	0.9	413	1066	28.9	74.5

e. No prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	17.3	0.3	35.8	0.1	6.9	0.9	145	1141	5.2	40.8
	Screen through age 76 (vs. 74)	19.0	0.3	37.6	0.1	6.4	0.9	157	1147	5.9	43.1
No comorbidity	Screen through age 66	27.8	0.6	190.3	0.7	48.8	4.7	20	214	3.9	40.8
	Screen through age 68	27.7	0.7	179.6	0.7	47.8	4.8	21	208	3.8	37.3
	Screen through age 70	27.7	0.8	178.7	0.7	46.6	5.0	21	199	3.8	35.5
	Screen through age 72	27.5	1.0	180.1	0.7	41.3	4.9	24	203	4.4	36.6
	Screen through age 74	27.3	1.2	165.0	0.7	38.2	4.9	26	204	4.3	33.7
	Screen through age 76	26.9	1.4	161.2	0.7	35.3	4.9	28	203	4.6	32.8
	Screen through age 78	26.3	1.7	137.4	0.6	32.5	4.9	31	205	4.2	28.2
	Screen through age 80	25.9	2.1	132.5	0.6	30.1	4.9	33	204	4.4	27.0
	Screen through age 82	25.6	2.8	135.5	0.6	25.8	4.8	39	210	5.3	28.4
	Screen through age 84	25.2	3.6	137.8	0.6	22.0	4.6	45	218	6.3	30.1
	Screen through age 86	25.0	4.6	139.4	0.6	17.8	4.2	56	236	7.8	32.9
	Screen through age 88	24.8	5.7	140.0	0.6	13.3	3.7	75	269	10.5	37.6
	Screen through age 90	24.7	6.9	140.0	0.6	9.4	3.1	106	318	14.8	44.5
Mild comorbidity	Screen through age 66	27.8	0.7	181.2	0.7	43.1	4.2	23	237	4.2	42.9
	Screen through age 68	27.7	0.9	169.5	0.6	39.1	4.1	26	241	4.3	40.9
	Screen through age 70	27.7	1.1	168.8	0.6	38.5	4.3	26	231	4.4	39.1
	Screen through age 72	27.5	1.3	171.6	0.7	35.2	4.3	28	231	4.9	39.7
	Screen through age 74	27.3	1.5	158.6	0.6	30.6	4.2	33	241	5.2	38.2
	Screen through age 76	26.9	1.9	155.6	0.6	27.9	4.2	36	241	5.6	37.4
	Screen through age 78	26.4	2.1	135.7	0.6	26.2	4.2	38	238	5.2	32.3
	Screen through age 80	25.9	2.5	131.5	0.6	24.8	4.3	40	233	5.3	30.6
	Screen through age 82	25.6	3.3	133.8	0.6	22.1	4.2	45	236	6.0	31.5
	Screen through age 84	25.2	4.1	136.0	0.6	17.8	4.0	56	250	7.6	34.0
	Screen through age 86	25.0	4.9	138.4	0.6	15.7	3.9	64	256	8.8	35.4
	Screen through age 88	24.8	6.2	136.2	0.6	12.0	3.4	83	293	11.3	40.0
	Screen through age 90	24.7	7.3	138.1	0.6	8.8	3.0	114	338	15.7	46.6
Moderate comorbidity	Screen through age 66	27.8	0.8	173.8	0.6	37.9	3.8	26	261	4.6	45.4
	Screen through age 68	27.7	1.0	166.4	0.6	36.4	3.9	27	255	4.6	42.4
	Screen through age 70	27.7	1.1	165.9	0.6	35.8	4.1	28	244	4.6	40.5
	Screen through age 72	27.4	1.4	166.5	0.7	30.7	3.9	33	256	5.4	42.6
	Screen through age 74	27.3	1.7	156.6	0.6	27.5	3.9	36	259	5.7	40.6
	Screen through age 76	26.9	2.1	152.7	0.6	24.3	3.8	41	265	6.3	40.5
	Screen through age 78	26.4	2.4	134.0	0.6	22.3	3.8	45	266	6.0	35.7
	Screen through age 80	25.9	2.9	129.7	0.6	20.9	3.8	48	263	6.2	34.1
	Screen through age 82	25.6	3.7	132.1	0.6	17.7	3.7	56	272	7.5	35.9
	Screen through age 84	25.2	4.6	134.1	0.6	15.0	3.5	66	284	8.9	38.1
	Screen through age 86	25.0	5.6	135.4	0.6	12.3	3.3	82	304	11.1	41.2
	Screen through age 88	24.8	6.8	134.4	0.6	9.2	2.9	108	350	14.6	47.0
	Screen through age 90	24.7	7.9	135.0	0.6	7.0	2.5	143	397	19.4	53.5
Severe comorbidity	Screen through age 66	27.8	1.2	155.8	0.6	29.3	3.0	34	330	5.3	51.4
	Screen through age 68	27.7	1.4	148.5	0.6	26.9	3.0	37	333	5.5	49.5
	Screen through age 70	27.6	1.7	147.3	0.6	24.8	3.0	40	331	5.9	48.8
	Screen through age 72	27.5	2.0	147.8	0.6	21.2	2.8	47	351	7.0	51.9
	Screen through age 74	27.3	2.4	141.3	0.6	19.1	2.8	52	355	7.4	50.2
	Screen through age 76	26.9	2.8	139.6	0.6	17.6	2.8	57	352	7.9	49.2
	Screen through age 78	26.4	3.3	126.4	0.5	15.1	2.7	66	365	8.4	46.1
	Screen through age 80	25.9	4.0	123.4	0.5	14.1	2.8	71	358	8.7	44.2
	Screen through age 82	25.6	4.8	125.6	0.5	11.6	2.7	86	373	10.8	46.9
	Screen through age 84	25.2	5.9	127.1	0.6	9.9	2.6	101	390	12.9	49.6
	Screen through age 86	25.0	7.0	127.6	0.6	7.7	2.3	129	429	16.5	54.7
	Screen through age 88	24.8	8.0	128.0	0.6	6.1	2.1	163	472	20.9	60.5
	Screen through age 90	24.7	9.2	127.7	0.6	4.6	1.8	219	544	27.9	69.4

f. Colonoscopy 10 years prior.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	17.3	0.3	35.8	0.1	6.9	0.9	145	1141	5.2	40.8
	Screen through age 76 (vs. 74)	19.0	0.3	37.6	0.1	6.4	0.9	157	1147	5.9	43.1
No comorbidity	Screen through age 66	30.8	0.1	52.7	0.1	8.6	0.7	117	1403	6.1	73.9
	Screen through age 67	30.8	0.1	52.3	0.1	8.4	0.7	119	1396	6.2	73.0
	Screen through age 68	30.8	0.1	50.7	0.1	8.2	0.7	121	1378	6.2	69.9
	Screen through age 69	30.8	0.1	50.7	0.1	8.1	0.7	124	1338	6.3	67.9
	Screen through age 70	30.8	0.1	50.5	0.1	7.9	0.7	127	1335	6.4	67.4
	Screen through age 71	30.7	0.1	50.5	0.1	7.4	0.7	134	1354	6.8	68.4
	Screen through age 72	30.7	0.1	50.4	0.1	7.1	0.7	140	1348	7.1	68.0
	Screen through age 73	30.7	0.1	48.6	0.1	6.9	0.7	145	1362	7.0	66.2
	Screen through age 74	30.6	0.1	48.7	0.1	6.7	0.7	150	1356	7.3	66.0
	Screen through age 75	30.6	0.2	48.5	0.1	6.4	0.7	156	1368	7.6	66.4
	Screen through age 76	30.3	0.2	48.8	0.1	6.0	0.7	165	1367	8.1	66.7
	Screen through age 77	30.1	0.2	49.0	0.1	5.9	0.7	170	1343	8.4	65.8
	Screen through age 78	29.9	0.2	46.9	0.1	5.7	0.8	176	1324	8.2	62.1
	Screen through age 79	29.7	0.3	47.4	0.1	5.6	0.8	178	1284	8.4	60.9
	Screen through age 80	29.5	0.3	47.5	0.1	5.5	0.8	181	1237	8.6	58.7
	Screen through age 81	29.3	0.3	48.1	0.1	5.3	0.8	188	1222	9.1	58.7
	Screen through age 82	29.0	0.4	48.8	0.1	5.3	0.9	188	1167	9.2	57.0
	Screen through age 83	28.8	0.4	48.3	0.1	5.1	0.9	195	1160	9.4	56.0
	Screen through age 84	28.6	0.5	49.1	0.1	5.2	0.9	193	1105	9.5	54.2
	Screen through age 85	28.5	0.6	49.6	0.1	5.1	0.9	197	1078	9.8	53.4
	Screen through age 86	28.5	0.6	49.4	0.1	4.4	0.8	228	1178	11.2	58.1
	Screen through age 87	28.6	0.6	49.2	0.1	3.8	0.8	264	1280	13.0	62.9
	Screen through age 88	28.7	0.7	49.2	0.1	3.3	0.7	304	1392	15.0	68.4
	Screen through age 89	28.7	0.7	49.1	0.1	2.9	0.7	344	1481	16.9	72.7
	Screen through age 90	28.8	0.7	48.7	0.1	2.5	0.6	403	1610	19.6	78.4
Mild comorbidity	Screen through age 66	30.8	0.1	51.7	0.1	7.6	0.6	132	1542	6.8	79.7
	Screen through age 67	30.8	0.1	51.3	0.1	7.2	0.6	139	1544	7.1	79.3
	Screen through age 68	30.8	0.1	49.8	0.1	6.8	0.6	147	1580	7.3	78.7
	Screen through age 69	30.8	0.1	49.9	0.1	6.8	0.7	148	1529	7.4	76.3
	Screen through age 70	30.8	0.1	49.7	0.1	6.5	0.7	154	1524	7.7	75.7
	Screen through age 71	30.7	0.1	49.4	0.1	5.8	0.6	171	1595	8.5	78.8
	Screen through age 72	30.7	0.2	49.7	0.1	6.2	0.7	162	1512	8.1	75.1
	Screen through age 73	30.7	0.2	48.1	0.1	5.7	0.6	174	1559	8.4	75.0
	Screen through age 74	30.7	0.2	48.3	0.1	5.5	0.6	181	1552	8.7	74.9
	Screen through age 75	30.6	0.2	48.0	0.1	5.4	0.6	185	1561	8.9	75.0
	Screen through age 76	30.4	0.2	48.3	0.1	4.9	0.6	205	1589	9.9	76.8
	Screen through age 77	30.1	0.2	48.6	0.1	4.9	0.6	206	1550	10.0	75.3
	Screen through age 78	29.9	0.3	46.7	0.1	4.6	0.7	216	1534	10.1	71.7
	Screen through age 79	29.7	0.3	47.1	0.1	4.7	0.7	215	1463	10.1	68.9
	Screen through age 80	29.5	0.3	47.3	0.1	4.6	0.7	216	1372	10.2	65.0
	Screen through age 81	29.3	0.4	48.0	0.1	4.5	0.7	222	1353	10.7	64.9
	Screen through age 82	29.0	0.4	48.7	0.1	4.6	0.8	215	1290	10.5	62.8
	Screen through age 83	28.8	0.5	48.2	0.1	4.6	0.8	216	1241	10.4	59.8
	Screen through age 84	28.6	0.6	48.9	0.1	4.4	0.8	229	1235	11.2	60.4
	Screen through age 85	28.5	0.6	49.4	0.1	4.7	0.9	214	1153	10.6	56.9
	Screen through age 86	28.5	0.6	49.3	0.1	4.0	0.8	251	1250	12.4	61.7
	Screen through age 87	28.6	0.7	49.0	0.1	3.5	0.7	289	1359	14.2	66.6
	Screen through age 88	28.7	0.7	48.9	0.1	3.0	0.7	330	1487	16.1	72.7
	Screen through age 89	28.7	0.7	49.1	0.1	2.7	0.6	364	1551	17.9	76.1
	Screen through age 90	28.8	0.8	48.6	0.1	2.3	0.6	432	1690	21.0	82.0
Moderate comorbidity	Screen through age 66	30.8	0.1	50.9	0.1	6.8	0.6	148	1668	7.5	84.9
	Screen through age 67	30.8	0.1	50.8	0.1	6.4	0.6	155	1659	7.9	84.3
	Screen through age 68	30.8	0.1	49.6	0.1	6.2	0.6	160	1655	8.0	82.1
	Screen through age 69	30.8	0.1	49.6	0.1	6.2	0.6	162	1629	8.0	80.8
	Screen through age 70	30.8	0.1	49.4	0.1	6.1	0.6	164	1588	8.1	78.5
	Screen through age 71	30.7	0.2	49.3	0.1	5.6	0.6	178	1626	8.8	80.1
	Screen through age 72	30.7	0.2	49.1	0.1	5.4	0.6	184	1644	9.0	80.8
	Screen through age 73	30.7	0.2	47.8	0.1	5.2	0.6	193	1667	9.2	79.7
	Screen through age 74	30.6	0.2	48.0	0.1	5.0	0.6	200	1658	9.6	79.6
	Screen through age 75	30.6	0.2	47.9	0.1	4.7	0.6	215	1680	10.3	80.4
	Screen through age 76	30.4	0.2	48.1	0.1	4.3	0.6	232	1701	11.2	81.8
	Screen through age 77	30.1	0.3	48.2	0.1	4.2	0.6	239	1690	11.5	81.5
	Screen through age 78	29.9	0.3	46.6	0.1	4.0	0.6	253	1669	11.8	77.8
	Screen through age 79	29.7	0.3	47.0	0.1	4.0	0.6	252	1608	11.9	75.6
	Screen through age 80	29.5	0.4	47.1	0.1	3.9	0.6	258	1577	12.1	74.3
	Screen through age 81	29.3	0.4	47.8	0.1	3.8	0.7	263	1511	12.6	72.2
	Screen through age 82	29.0	0.5	48.4	0.1	3.8	0.7	261	1440	12.6	69.7
	Screen through age 83	28.8	0.6	48.1	0.1	3.7	0.7	274	1424	13.1	68.4
	Screen through age 84	28.7	0.6	48.7	0.1	3.7	0.7	269	1387	13.1	67.6
	Screen through age 85	28.5	0.7	49.3	0.1	3.7	0.8	274	1322	13.5	65.1
	Screen through age 86	28.5	0.7	49.1	0.1	3.3	0.7	307	1419	15.1	69.7
	Screen through age 87	28.6	0.8	48.8	0.1	2.8	0.6	363	1573	17.7	76.8
	Screen through age 88	28.7	0.8	48.8	0.1	2.5	0.6	397	1667	19.4	81.3
	Screen through age 89	28.7	0.8	48.7	0.1	2.3	0.6	440	1756	21.4	85.6
	Screen through age 90	28.8	0.8	48.4	0.1	2.0	0.5	507	1893	24.5	91.6

Severe comorbidity	Screen through age 66	30.8	0.2	49.2	0.1	5.3	0.5	190	2054	9.3	101.1
	Screen through age 67	30.8	0.2	48.9	0.1	4.9	0.5	206	2103	10.1	102.9
	Screen through age 68	30.8	0.2	47.9	0.1	4.6	0.5	217	2123	10.4	101.7
	Screen through age 69	30.8	0.2	48.0	0.1	4.5	0.5	222	2078	10.7	99.8
	Screen through age 70	30.8	0.2	47.8	0.1	4.3	0.5	230	2073	11.0	99.0
	Screen through age 71	30.7	0.2	47.7	0.1	4.1	0.5	242	2084	11.6	99.4
	Screen through age 72	30.7	0.3	47.5	0.1	3.8	0.5	262	2174	12.5	103.3
	Screen through age 73	30.6	0.3	46.8	0.1	3.6	0.5	278	2184	13.0	102.1
	Screen through age 74	30.6	0.3	46.8	0.1	3.6	0.5	277	2115	13.0	99.0
	Screen through age 75	30.6	0.3	46.7	0.1	3.3	0.5	299	2176	14.0	101.7
	Screen through age 76	30.4	0.3	46.9	0.1	3.2	0.5	313	2185	14.7	102.5
	Screen through age 77	30.1	0.4	47.2	0.1	3.0	0.5	335	2162	15.8	102.1
	Screen through age 78	29.9	0.4	46.0	0.1	2.8	0.5	359	2174	16.5	100.1
	Screen through age 79	29.7	0.4	46.4	0.1	2.9	0.5	350	2070	16.2	96.1
	Screen through age 80	29.5	0.5	46.5	0.1	2.8	0.5	357	2006	16.6	93.3
	Screen through age 81	29.3	0.6	47.1	0.1	2.6	0.5	382	2017	18.0	94.9
	Screen through age 82	29.0	0.6	47.8	0.1	2.7	0.5	375	1872	17.9	89.4
	Screen through age 83	28.8	0.7	47.5	0.1	2.6	0.5	389	1846	18.5	87.6
	Screen through age 84	28.6	0.8	48.2	0.1	2.6	0.6	378	1748	18.2	84.3
	Screen through age 85	28.5	0.9	48.6	0.1	2.6	0.6	384	1688	18.7	82.1
	Screen through age 86	28.6	0.9	48.5	0.1	2.3	0.5	443	1828	21.5	88.7
	Screen through age 87	28.6	0.9	48.4	0.1	2.1	0.5	482	1935	23.4	93.7
	Screen through age 88	28.7	0.9	48.4	0.1	1.9	0.5	538	2042	26.0	98.8
	Screen through age 89	28.7	1.0	48.3	0.1	1.6	0.5	618	2184	29.9	105.5
	Screen through age 90	28.8	1.0	47.9	0.1	1.4	0.4	701	2390	33.6	114.5

g. Colonoscopy 15 years prior.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	17.3	0.3	35.8	0.1	6.9	0.9	145	1141	5.2	40.8
	Screen through age 76 (vs. 74)	19.0	0.3	37.6	0.1	6.4	0.9	157	1147	5.9	43.1
No comorbidity	Screen through age 66	31.2	0.1	61.7	0.1	12.2	1.0	82	1022	5.1	63.1
	Screen through age 67	31.2	0.1	60.8	0.1	11.7	1.0	86	1029	5.2	62.5
	Screen through age 68	31.3	0.1	58.0	0.1	11.3	1.0	88	1039	5.1	60.3
	Screen through age 69	31.4	0.1	57.5	0.1	10.9	1.0	91	1035	5.3	59.5
	Screen through age 70	31.4	0.1	56.6	0.1	10.3	0.9	97	1054	5.5	59.7
	Screen through age 71	31.4	0.1	56.5	0.1	9.8	0.9	102	1063	5.7	60.1
	Screen through age 72	31.3	0.2	56.2	0.1	9.4	0.9	106	1073	6.0	60.3
	Screen through age 73	31.3	0.2	53.8	0.1	9.1	0.9	110	1080	5.9	58.1
	Screen through age 74	31.3	0.2	53.8	0.1	9.0	0.9	112	1064	6.0	57.2
	Screen through age 75	31.2	0.2	53.5	0.1	8.7	0.9	115	1066	6.2	57.0
	Screen through age 76	30.9	0.2	53.7	0.1	8.4	1.0	118	1051	6.4	56.4
	Screen through age 77	30.7	0.3	53.9	0.1	8.2	1.0	123	1034	6.6	55.7
	Screen through age 78	30.5	0.3	51.3	0.1	8.1	1.0	124	1017	6.3	52.2
	Screen through age 79	30.3	0.3	51.8	0.1	8.1	1.0	124	981	6.4	50.8
	Screen through age 80	30.1	0.4	51.8	0.1	7.9	1.1	126	950	6.5	49.3
	Screen through age 81	29.9	0.4	52.3	0.1	7.3	1.0	137	969	7.2	50.7
	Screen through age 82	29.7	0.5	52.9	0.1	7.0	1.0	142	965	7.5	51.1
	Screen through age 83	29.6	0.5	52.6	0.1	6.5	1.0	153	975	8.1	51.3
	Screen through age 84	29.4	0.6	53.3	0.1	6.3	1.0	158	962	8.4	51.3
	Screen through age 85	29.3	0.7	53.7	0.1	5.9	1.0	170	982	9.1	52.7
	Screen through age 86	29.0	0.8	54.4	0.1	5.7	1.0	177	983	9.6	53.4
	Screen through age 87	28.9	0.9	55.0	0.2	5.5	1.0	182	980	10.0	53.9
	Screen through age 88	28.7	1.0	54.4	0.2	5.2	1.0	191	1003	10.4	54.6
	Screen through age 89	28.5	1.1	55.1	0.2	5.3	1.0	189	980	10.4	53.9
	Screen through age 90	28.4	1.2	55.4	0.2	5.1	1.0	195	997	10.8	55.2
Mild comorbidity	Screen through age 66	31.2	0.1	60.4	0.1	10.7	0.9	93	1111	5.6	67.1
	Screen through age 67	31.2	0.1	59.4	0.1	10.0	0.9	100	1140	5.9	67.8
	Screen through age 68	31.3	0.2	56.9	0.1	9.6	0.9	104	1159	5.9	65.9
	Screen through age 69	31.3	0.2	56.4	0.1	9.4	0.9	107	1154	6.0	65.1
	Screen through age 70	31.4	0.2	55.6	0.1	8.8	0.8	114	1177	6.3	65.4
	Screen through age 71	31.4	0.2	55.2	0.1	8.0	0.8	125	1233	6.9	68.1
	Screen through age 72	31.3	0.2	55.3	0.1	8.2	0.8	122	1192	6.7	65.9
	Screen through age 73	31.3	0.2	53.2	0.1	7.6	0.8	131	1232	7.0	65.5
	Screen through age 74	31.3	0.2	53.2	0.1	7.4	0.8	135	1206	7.2	64.2
	Screen through age 75	31.2	0.3	52.9	0.1	7.3	0.8	138	1214	7.3	64.2
	Screen through age 76	31.0	0.3	53.0	0.1	6.9	0.8	145	1201	7.7	63.7
	Screen through age 77	30.7	0.3	53.4	0.1	6.9	0.9	144	1166	7.7	62.2
	Screen through age 78	30.5	0.3	51.1	0.1	6.7	0.9	150	1154	7.7	58.9
	Screen through age 79	30.3	0.4	51.4	0.1	6.7	0.9	149	1111	7.7	57.1
	Screen through age 80	30.1	0.4	51.7	0.1	6.7	0.9	150	1064	7.7	55.0
	Screen through age 81	29.9	0.5	52.2	0.1	6.1	0.9	163	1086	8.5	56.7
	Screen through age 82	29.7	0.6	52.7	0.1	6.2	0.9	162	1057	8.5	55.8
	Screen through age 83	29.6	0.6	52.5	0.1	5.9	1.0	169	1042	8.9	54.8
	Screen through age 84	29.4	0.7	53.1	0.1	5.4	0.9	184	1066	9.8	56.7
	Screen through age 85	29.3	0.8	53.5	0.1	5.5	1.0	182	1044	9.7	55.8
	Screen through age 86	29.1	0.9	54.3	0.1	5.2	1.0	191	1032	10.4	56.1
	Screen through age 87	28.9	1.0	54.8	0.2	5.0	1.0	200	1046	11.0	57.3
	Screen through age 88	28.7	1.1	54.0	0.2	4.8	0.9	207	1072	11.2	57.9
	Screen through age 89	28.5	1.1	55.0	0.2	5.0	1.0	199	1018	10.9	56.0
	Screen through age 90	28.4	1.2	55.3	0.2	4.9	1.0	203	1032	11.2	57.0
Moderate comorbidity	Screen through age 66	31.2	0.2	59.3	0.1	9.6	0.8	104	1211	6.2	71.9
	Screen through age 67	31.2	0.2	58.6	0.1	9.2	0.8	109	1218	6.4	71.3
	Screen through age 68	31.3	0.2	56.5	0.1	9.0	0.8	112	1210	6.3	68.3
	Screen through age 69	31.3	0.2	56.0	0.1	8.7	0.8	115	1211	6.5	67.9
	Screen through age 70	31.4	0.2	55.3	0.1	8.3	0.8	121	1225	6.7	67.7
	Screen through age 71	31.4	0.2	55.0	0.1	7.7	0.8	129	1258	7.1	69.2
	Screen through age 72	31.3	0.2	54.8	0.1	7.3	0.8	137	1279	7.5	70.1
	Screen through age 73	31.3	0.2	52.9	0.1	7.0	0.8	144	1306	7.6	69.1
	Screen through age 74	31.3	0.3	53.0	0.1	6.8	0.8	148	1282	7.8	68.0
	Screen through age 75	31.2	0.3	52.7	0.1	6.2	0.8	161	1323	8.5	69.7
	Screen through age 76	30.9	0.3	52.8	0.1	6.0	0.8	166	1303	8.8	68.7
	Screen through age 77	30.7	0.4	52.9	0.1	6.0	0.8	165	1271	8.7	67.3
	Screen through age 78	30.5	0.4	51.0	0.1	5.9	0.8	170	1241	8.7	63.2
	Screen through age 79	30.3	0.4	51.3	0.1	5.9	0.8	170	1213	8.7	62.3
	Screen through age 80	30.1	0.5	51.4	0.1	5.8	0.8	173	1187	8.9	61.0
	Screen through age 81	29.9	0.6	52.0	0.1	5.3	0.8	190	1208	9.9	62.8
	Screen through age 82	29.7	0.6	52.4	0.1	5.1	0.8	196	1193	10.3	62.6
	Screen through age 83	29.6	0.7	52.3	0.1	4.7	0.8	211	1203	11.1	63.0
	Screen through age 84	29.4	0.8	53.0	0.1	4.8	0.8	210	1179	11.1	62.5
	Screen through age 85	29.3	0.9	53.3	0.1	4.4	0.8	226	1183	12.1	63.1
	Screen through age 86	29.1	1.0	54.0	0.1	4.4	0.9	229	1175	12.4	63.5
	Screen through age 87	28.9	1.1	54.5	0.2	4.2	0.8	236	1188	12.9	64.7
	Screen through age 88	28.7	1.2	53.8	0.2	4.1	0.8	244	1198	13.2	64.5
	Screen through age 89	28.6	1.3	54.5	0.2	4.3	0.9	234	1149	12.7	62.6
	Screen through age 90	28.4	1.4	54.9	0.2	4.3	0.9	233	1134	12.8	62.3

Severe comorbidity	Screen through age 66	31.1	0.2	56.7	0.1	7.4	0.7	135	1503	7.6	85.3
	Screen through age 67	31.2	0.2	56.1	0.1	7.0	0.7	144	1528	8.1	85.7
	Screen through age 68	31.2	0.3	54.3	0.1	6.7	0.6	150	1558	8.1	84.5
	Screen through age 69	31.3	0.3	53.9	0.1	6.5	0.6	155	1554	8.3	83.7
	Screen through age 70	31.4	0.3	53.1	0.1	6.0	0.6	167	1590	8.9	84.5
	Screen through age 71	31.3	0.3	53.0	0.1	5.7	0.6	176	1611	9.3	85.5
	Screen through age 72	31.3	0.3	52.7	0.1	5.2	0.6	191	1665	10.1	87.8
	Screen through age 73	31.3	0.4	51.6	0.1	4.9	0.6	202	1672	10.4	86.2
	Screen through age 74	31.2	0.4	51.6	0.1	4.9	0.6	203	1628	10.5	84.0
	Screen through age 75	31.2	0.4	51.3	0.1	4.8	0.6	210	1648	10.8	84.6
	Screen through age 76	31.0	0.4	51.5	0.1	4.7	0.6	213	1628	11.0	83.8
	Screen through age 77	30.7	0.5	51.6	0.1	4.4	0.6	226	1630	11.7	84.1
	Screen through age 78	30.5	0.5	50.2	0.1	4.2	0.6	235	1608	11.8	80.8
	Screen through age 79	30.2	0.6	50.6	0.1	4.3	0.7	232	1529	11.7	77.4
	Screen through age 80	30.1	0.7	50.8	0.1	4.2	0.7	237	1498	12.0	76.0
	Screen through age 81	29.9	0.7	51.2	0.1	3.9	0.6	258	1540	13.2	78.9
	Screen through age 82	29.7	0.8	51.7	0.1	3.7	0.7	272	1525	14.1	78.8
	Screen through age 83	29.6	0.9	51.6	0.1	3.5	0.7	283	1511	14.6	78.0
	Screen through age 84	29.4	1.0	52.3	0.1	3.5	0.7	290	1495	15.1	78.1
	Screen through age 85	29.3	1.1	52.5	0.1	3.3	0.7	306	1499	16.1	78.8
	Screen through age 86	29.1	1.2	53.2	0.1	3.2	0.7	315	1493	16.8	79.5
	Screen through age 87	28.9	1.3	53.9	0.2	3.2	0.7	310	1458	16.7	78.6
	Screen through age 88	28.7	1.4	53.2	0.1	3.2	0.7	314	1458	16.7	77.6
	Screen through age 89	28.6	1.5	53.7	0.2	3.3	0.7	304	1411	16.4	75.8
	Screen through age 90	28.5	1.6	54.1	0.2	3.4	0.7	295	1379	16.0	74.7

Abbreviations: Av, average health; NNS/LYG, number needed to screen to gain one life-year; NNS/CDP, number needed to screen to prevent one cancer death; NNSc/LYG, number needed to scope to gain one life-year; NNSc/CDP, number needed to scope to prevent one cancer death

Details of comorbid conditions are found in Table 5.2.

Shaded row represents the age for each comorbidity group at which screening provided similar harms and benefits as provided by the threshold of NNS/LYG for females with perfect screening history with biennial FIT and with average life expectancy at age 74.

Supplementary Results Table 5.2: Benefits and harms of screening 1,000 males by age and comorbidity under varying prior screening assumptions with biennial faecal immunochemical testing or colonoscopy. The faecal immunochemical test had a positivity of 7.5% (23 µg Hb/g faeces).

a. Perfect prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	15.3	0.6	47.4	0.2	10.6	1.5	94	659	4.5	31.3
	Screen through age 76 (vs. 74)	17.4	0.7	50.3	0.2	9.2	1.4	108	690	5.4	34.7
No comorbidity	Screen through age 66	17.5	0.3	58.2	0.2	18.6	1.8	54	550	3.1	32.0
	Screen through age 68	15.6	0.3	52.5	0.2	17.2	1.8	58	546	3.1	28.7
	Screen through age 70	25.5	0.4	63.9	0.2	17.2	1.9	58	514	3.7	32.8
	Screen through age 72	15.4	0.4	52.2	0.2	14.2	1.8	70	556	3.7	29.0
	Screen through age 74	15.3	0.5	48.5	0.2	12.1	1.7	82	590	4.0	28.6
	Screen through age 76	17.4	0.6	51.4	0.2	10.8	1.6	93	616	4.8	31.7
	Screen through age 78	15.2	0.7	42.5	0.2	8.9	1.5	112	670	4.8	28.5
	Screen through age 80	24.8	0.8	52.9	0.2	7.5	1.4	134	729	7.1	38.6
	Screen through age 82	15.0	0.9	41.5	0.1	5.8	1.2	172	846	7.2	35.1
	Screen through age 84	15.1	1.0	41.4	0.1	4.6	1.1	218	949	9.0	39.3
	Screen through age 86	17.7	1.2	44.8	0.2	3.3	0.9	299	1125	13.4	50.4
	Screen through age 88	15.2	1.3	40.2	0.1	2.4	0.7	420	1385	16.9	55.7
	Screen through age 90	25.2	1.4	50.7	0.2	1.7	0.6	600	1735	30.4	88.0
Mild comorbidity	Screen through age 66	17.5	0.3	56.9	0.2	17.1	1.7	59	588	3.3	33.4
	Screen through age 68	15.6	0.4	51.2	0.2	15.3	1.7	65	596	3.3	30.5
	Screen through age 70	25.5	0.4	62.9	0.2	15.6	1.8	64	548	4.0	34.5
	Screen through age 72	15.4	0.5	51.1	0.2	12.3	1.6	81	608	4.1	31.1
	Screen through age 74	15.3	0.6	48.2	0.2	11.2	1.6	89	623	4.3	30.0
	Screen through age 76	17.4	0.7	51.0	0.2	10.7	1.6	94	624	4.8	31.8
	Screen through age 78	15.2	0.8	42.4	0.1	7.6	1.4	131	739	5.6	31.3
	Screen through age 80	24.8	0.9	52.8	0.2	6.7	1.3	148	776	7.8	41.0
	Screen through age 82	15.0	1.0	41.5	0.1	5.3	1.1	189	873	7.9	36.2
	Screen through age 84	15.1	1.0	41.2	0.1	4.5	1.0	223	973	9.2	40.1
	Screen through age 86	17.7	1.2	44.7	0.2	3.1	0.8	322	1191	14.4	53.2
	Screen through age 88	15.2	1.3	40.0	0.1	2.3	0.7	428	1392	17.1	55.7
	Screen through age 90	25.2	1.4	50.7	0.2	1.6	0.6	640	1780	32.5	90.2
Moderate comorbidity	Screen through age 66	17.5	0.4	55.2	0.2	14.8	1.5	68	645	3.7	35.6
	Screen through age 68	15.6	0.4	50.1	0.2	13.8	1.6	73	639	3.6	32.0
	Screen through age 70	25.5	0.5	61.2	0.2	12.7	1.6	79	631	4.8	38.6
	Screen through age 72	15.4	0.6	49.2	0.2	10.1	1.4	99	701	4.9	34.5
	Screen through age 74	15.3	0.7	46.8	0.2	9.0	1.4	111	730	5.2	34.1
	Screen through age 76	17.4	0.8	49.7	0.2	7.6	1.3	132	774	6.6	38.5
	Screen through age 78	15.2	0.9	41.9	0.1	6.0	1.1	167	874	7.0	36.6
	Screen through age 80	24.8	1.0	52.3	0.2	4.9	1.0	206	957	10.8	50.1
	Screen through age 82	15.0	1.2	40.8	0.1	3.7	0.9	271	1123	11.1	45.9
	Screen through age 84	15.1	1.2	40.6	0.1	3.0	0.8	329	1255	13.4	51.0
	Screen through age 86	17.7	1.4	44.1	0.2	2.4	0.7	409	1408	18.0	62.0
	Screen through age 88	15.2	1.4	39.6	0.1	1.7	0.6	589	1738	23.3	68.8
	Screen through age 90	25.2	1.6	49.5	0.1	1.1	0.4	917	2341	45.4	115.9
Severe comorbidity	Screen through age 66	17.5	0.6	50.2	0.2	9.9	1.1	101	894	5.0	44.9
	Screen through age 68	15.6	0.7	45.5	0.2	9.0	1.1	111	909	5.1	41.3
	Screen through age 70	25.5	0.8	56.9	0.2	8.3	1.1	121	899	6.9	51.1
	Screen through age 72	15.4	0.9	45.0	0.2	6.6	1.0	152	991	6.8	44.6
	Screen through age 74	15.3	1.0	43.4	0.2	5.7	1.0	176	1046	7.6	45.4
	Screen through age 76	17.4	1.2	46.4	0.2	4.6	0.9	217	1132	10.0	52.5
	Screen through age 78	15.2	1.2	40.2	0.1	3.8	0.8	265	1265	10.7	50.9
	Screen through age 80	24.8	1.4	50.9	0.2	3.1	0.7	322	1377	16.4	70.0
	Screen through age 82	15.0	1.5	39.3	0.1	2.3	0.6	428	1622	16.8	63.8
	Screen through age 84	15.1	1.5	39.2	0.1	2.0	0.6	491	1737	19.3	68.1
	Screen through age 86	17.7	1.7	42.7	0.1	1.6	0.5	643	1976	27.5	84.5
	Screen through age 88	15.2	1.7	38.0	0.1	1.0	0.4	958	2514	36.4	95.6
	Screen through age 90	25.2	1.8	48.7	0.1	0.8	0.3	1279	2972	62.3	144.8

b. Most prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	15.3	0.6	47.4	0.2	10.6	1.5	94	659	4.5	31.3
	Screen through age 76 (vs. 74)	17.4	0.7	50.3	0.2	9.2	1.4	108	690	5.4	34.7
No comorbidity	Screen through age 66	18.1	0.4	74.6	0.3	24.4	2.4	41	414	3.1	30.9
	Screen through age 68	17.3	0.5	70.3	0.2	23.6	2.5	42	397	3.0	27.9
	Screen through age 70	19.9	0.6	72.6	0.3	22.7	2.6	44	387	3.2	28.1
	Screen through age 72	19.9	0.7	72.8	0.3	19.5	2.5	51	406	3.7	29.6
	Screen through age 74	18.8	0.8	66.3	0.2	16.9	2.3	59	427	3.9	28.3
	Screen through age 76	18.1	0.9	64.6	0.2	15.0	2.3	67	441	4.3	28.5
	Screen through age 78	17.3	1.1	56.2	0.2	12.7	2.1	79	475	4.4	26.7
	Screen through age 80	18.6	1.2	56.5	0.2	10.6	1.9	94	514	5.3	29.1
	Screen through age 82	19.2	1.4	57.0	0.2	8.3	1.7	121	591	6.9	33.7
	Screen through age 84	18.8	1.5	56.4	0.2	6.7	1.5	149	647	8.4	36.5
	Screen through age 86	18.4	1.8	55.4	0.2	4.9	1.3	205	780	11.4	43.2
	Screen through age 88	17.9	2.0	53.9	0.2	3.7	1.1	273	924	14.7	49.8
	Screen through age 90	18.5	2.1	53.5	0.2	2.5	0.9	397	1156	21.3	61.8
Mild comorbidity	Screen through age 66	18.1	0.5	72.6	0.3	22.4	2.3	45	444	3.2	32.2
	Screen through age 68	17.3	0.5	68.6	0.2	21.0	2.3	48	433	3.3	29.7
	Screen through age 70	19.9	0.6	71.1	0.2	20.7	2.4	48	414	3.4	29.4
	Screen through age 72	19.9	0.7	71.3	0.2	16.9	2.3	59	440	4.2	31.4
	Screen through age 74	18.8	0.8	65.9	0.2	15.7	2.2	64	449	4.2	29.6
	Screen through age 76	18.1	0.9	64.1	0.2	14.8	2.2	67	451	4.3	28.9
	Screen through age 78	17.3	1.2	56.1	0.2	10.8	1.9	92	525	5.2	29.4
	Screen through age 80	18.6	1.3	56.4	0.2	9.5	1.8	105	551	5.9	31.1
	Screen through age 82	19.2	1.4	57.0	0.2	7.6	1.6	132	609	7.5	34.7
	Screen through age 84	18.8	1.6	56.3	0.2	6.5	1.5	153	664	8.6	37.4
	Screen through age 86	18.4	1.8	55.2	0.2	4.6	1.2	220	816	12.1	45.0
	Screen through age 88	17.9	2.0	53.7	0.2	3.6	1.1	280	925	15.0	49.7
	Screen through age 90	18.5	2.2	53.5	0.2	2.3	0.8	429	1190	22.9	63.6
Moderate comorbidity	Screen through age 66	18.1	0.5	70.1	0.2	19.4	2.0	52	491	3.6	34.4
	Screen through age 68	17.3	0.6	66.8	0.2	18.7	2.1	54	469	3.6	31.3
	Screen through age 70	19.9	0.8	68.5	0.2	17.0	2.1	59	471	4.0	32.3
	Screen through age 72	19.9	0.9	68.5	0.2	14.0	2.0	72	502	4.9	34.4
	Screen through age 74	18.8	1.0	63.9	0.2	12.6	1.9	79	525	5.1	33.5
	Screen through age 76	18.1	1.2	62.1	0.2	10.4	1.8	96	561	6.0	34.8
	Screen through age 78	17.3	1.4	55.3	0.2	8.6	1.6	117	618	6.5	34.2
	Screen through age 80	18.6	1.6	55.7	0.2	6.9	1.5	145	672	8.1	37.5
	Screen through age 82	19.2	1.8	56.0	0.2	5.2	1.3	192	787	10.7	44.1
	Screen through age 84	18.8	1.9	55.4	0.2	4.5	1.2	224	852	12.4	47.2
	Screen through age 86	18.4	2.1	54.2	0.2	3.6	1.0	281	967	15.3	52.5
	Screen through age 88	18.0	2.3	53.1	0.2	2.6	0.9	382	1157	20.3	61.4
	Screen through age 90	18.5	2.5	51.7	0.2	1.6	0.6	616	1542	31.9	79.7
Severe comorbidity	Screen through age 66	18.1	0.9	62.6	0.2	13.0	1.5	77	676	4.8	42.3
	Screen through age 68	17.2	1.0	59.9	0.2	12.2	1.5	82	671	4.9	40.2
	Screen through age 70	19.9	1.2	62.4	0.2	11.2	1.5	89	661	5.6	41.2
	Screen through age 72	19.9	1.3	62.3	0.2	9.2	1.4	109	710	6.8	44.3
	Screen through age 74	18.8	1.5	58.9	0.2	7.9	1.3	126	755	7.4	44.4
	Screen through age 76	18.1	1.7	57.4	0.2	6.3	1.2	158	824	9.0	47.3
	Screen through age 78	17.4	1.9	52.8	0.2	5.4	1.1	186	891	9.9	47.1
	Screen through age 80	18.6	2.1	53.6	0.2	4.5	1.0	220	969	11.8	51.9
	Screen through age 82	19.2	2.3	53.6	0.2	3.3	0.9	306	1147	16.4	61.5
	Screen through age 84	18.9	2.4	53.4	0.2	2.9	0.9	340	1169	18.2	62.4
	Screen through age 86	18.4	2.5	52.3	0.2	2.3	0.7	440	1362	23.0	71.2
	Screen through age 88	18.0	2.7	50.7	0.2	1.6	0.6	629	1676	31.9	85.0
	Screen through age 90	18.5	2.8	50.4	0.2	1.1	0.5	871	1995	43.9	100.4

c. Reasonable prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	15.3	0.6	47.4	0.2	10.6	1.5	94	659	4.5	31.3
	Screen through age 76 (vs. 74)	17.4	0.7	50.3	0.2	9.2	1.4	108	690	5.4	34.7
No comorbidity	Screen through age 66	19.7	0.5	91.7	0.3	29.2	2.9	34	344	3.1	31.6
	Screen through age 68	18.9	0.6	86.8	0.3	29.0	3.1	35	325	3.0	28.2
	Screen through age 70	19.5	0.7	87.0	0.3	28.0	3.2	36	314	3.1	27.3
	Screen through age 72	20.0	0.8	88.0	0.3	24.1	3.0	42	329	3.7	29.0
	Screen through age 74	19.8	1.0	81.0	0.3	21.2	2.9	47	340	3.8	27.5
	Screen through age 76	19.5	1.2	79.2	0.3	18.9	2.8	53	353	4.2	27.9
	Screen through age 78	19.0	1.4	68.8	0.3	16.1	2.6	62	379	4.3	26.1
	Screen through age 80	19.1	1.6	67.3	0.3	13.4	2.4	75	409	5.0	27.5
	Screen through age 82	19.2	1.9	67.5	0.3	10.6	2.2	94	462	6.4	31.2
	Screen through age 84	19.5	2.1	67.8	0.3	8.8	2.0	114	502	7.7	34.0
	Screen through age 86	19.5	2.4	67.0	0.3	6.4	1.7	157	599	10.5	40.1
	Screen through age 88	19.3	2.7	65.5	0.3	4.7	1.4	211	713	13.8	46.7
	Screen through age 90	19.6	2.9	64.7	0.2	3.3	1.1	302	879	19.6	56.9
Mild comorbidity	Screen through age 66	19.7	0.6	89.1	0.3	26.9	2.7	37	368	3.3	32.8
	Screen through age 68	18.9	0.7	84.4	0.3	25.6	2.8	39	355	3.3	29.9
	Screen through age 70	19.5	0.8	85.2	0.3	25.7	3.0	39	335	3.3	28.5
	Screen through age 72	20.0	0.9	85.8	0.3	20.9	2.8	48	358	4.1	30.7
	Screen through age 74	19.8	1.1	80.5	0.3	19.5	2.8	51	359	4.1	28.9
	Screen through age 76	19.5	1.2	78.5	0.3	18.7	2.8	54	359	4.2	28.2
	Screen through age 78	19.0	1.5	68.5	0.3	13.7	2.4	73	420	5.0	28.8
	Screen through age 80	19.1	1.7	67.2	0.3	12.1	2.3	83	435	5.6	29.2
	Screen through age 82	19.2	1.9	67.3	0.3	9.6	2.1	104	480	7.0	32.3
	Screen through age 84	19.5	2.2	67.5	0.3	8.6	1.9	117	514	7.9	34.7
	Screen through age 86	19.5	2.5	66.8	0.3	5.9	1.6	169	630	11.3	42.1
	Screen through age 88	19.4	2.7	65.2	0.3	4.6	1.4	216	718	14.1	46.9
	Screen through age 90	19.5	2.9	64.7	0.2	3.1	1.1	323	899	20.9	58.2
Moderate comorbidity	Screen through age 66	19.7	0.7	85.9	0.3	23.4	2.5	43	404	3.7	34.7
	Screen through age 68	18.9	0.8	82.3	0.3	22.8	2.6	44	384	3.6	31.6
	Screen through age 70	19.5	1.0	81.9	0.3	21.0	2.6	48	383	3.9	31.4
	Screen through age 72	20.0	1.1	82.2	0.3	17.3	2.4	58	413	4.8	34.0
	Screen through age 74	19.8	1.3	77.7	0.3	15.5	2.4	64	422	5.0	32.8
	Screen through age 76	19.5	1.5	76.1	0.3	13.1	2.2	76	448	5.8	34.1
	Screen through age 78	19.0	1.8	67.4	0.3	10.8	2.0	93	491	6.2	33.1
	Screen through age 80	19.1	2.1	66.3	0.3	8.7	1.9	115	531	7.6	35.2
	Screen through age 82	19.2	2.4	66.2	0.3	6.6	1.6	151	620	10.0	41.0
	Screen through age 84	19.5	2.5	66.4	0.3	5.8	1.5	172	658	11.4	43.7
	Screen through age 86	19.5	2.8	65.6	0.3	4.7	1.4	213	740	14.0	48.6
	Screen through age 88	19.4	3.0	64.4	0.2	3.4	1.1	294	883	18.9	56.9
	Screen through age 90	19.5	3.4	62.2	0.2	2.1	0.8	470	1190	29.2	74.0
Severe comorbidity	Screen through age 66	19.7	1.1	76.1	0.3	15.7	1.8	64	565	4.9	43.0
	Screen through age 68	18.9	1.3	73.2	0.3	15.0	1.8	67	541	4.9	39.6
	Screen through age 70	19.5	1.5	73.4	0.3	13.5	1.9	74	538	5.4	39.5
	Screen through age 72	20.0	1.7	74.0	0.3	11.4	1.7	88	580	6.5	42.9
	Screen through age 74	19.8	1.9	71.0	0.3	9.8	1.6	102	607	7.3	43.1
	Screen through age 76	19.5	2.2	69.6	0.3	8.0	1.5	125	659	8.7	45.9
	Screen through age 78	19.0	2.5	64.1	0.2	6.7	1.4	148	711	9.5	45.6
	Screen through age 80	19.0	2.7	63.3	0.2	5.6	1.3	178	771	11.3	48.8
	Screen through age 82	19.2	3.0	63.1	0.2	4.2	1.1	235	876	14.9	55.3
	Screen through age 84	19.5	3.1	63.5	0.2	3.8	1.1	261	906	16.6	57.6
	Screen through age 86	19.5	3.4	63.0	0.2	3.0	1.0	333	1042	21.0	65.7
	Screen through age 88	19.3	3.7	61.3	0.2	2.1	0.8	479	1281	29.3	78.4
	Screen through age 90	19.6	3.8	60.5	0.2	1.5	0.7	649	1522	39.3	92.1

d. Some prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	15.3	0.6	47.4	0.2	10.6	1.5	94	659	4.5	31.3
	Screen through age 76 (vs. 74)	17.4	0.7	50.3	0.2	9.2	1.4	108	690	5.4	34.7
No comorbidity	Screen through age 66	21.7	0.6	122.0	0.4	37.9	3.8	26	263	3.2	32.1
	Screen through age 68	21.2	0.8	116.7	0.4	37.0	4.0	27	249	3.2	29.1
	Screen through age 70	21.1	0.9	116.8	0.4	36.7	4.2	27	236	3.2	27.6
	Screen through age 72	21.0	1.1	118.1	0.4	32.1	4.1	31	246	3.7	29.1
	Screen through age 74	20.9	1.4	108.8	0.4	28.4	3.9	35	254	3.8	27.6
	Screen through age 76	20.8	1.6	106.7	0.4	25.6	3.8	39	261	4.2	27.8
	Screen through age 78	20.7	1.9	92.4	0.4	22.3	3.6	45	274	4.2	25.4
	Screen through age 80	20.7	2.3	90.2	0.4	18.7	3.4	53	295	4.8	26.6
	Screen through age 82	20.6	2.7	90.3	0.4	14.9	3.0	67	330	6.0	29.8
	Screen through age 84	20.6	3.0	91.0	0.4	12.4	2.8	81	358	7.3	32.5
	Screen through age 86	20.8	3.5	90.2	0.4	9.2	2.4	109	417	9.8	37.6
	Screen through age 88	20.9	4.0	89.1	0.4	6.9	2.0	145	492	12.9	43.8
	Screen through age 90	20.9	4.4	87.4	0.4	4.9	1.6	206	607	18.0	53.1
Mild comorbidity	Screen through age 66	21.7	0.7	118.4	0.4	34.6	3.5	29	282	3.4	33.4
	Screen through age 68	21.2	0.9	113.4	0.4	32.9	3.7	30	271	3.4	30.7
	Screen through age 70	21.0	1.1	114.1	0.4	33.6	4.0	30	253	3.4	28.8
	Screen through age 72	21.0	1.3	115.0	0.4	28.0	3.7	36	267	4.1	30.8
	Screen through age 74	20.9	1.5	107.9	0.4	26.3	3.7	38	267	4.1	28.8
	Screen through age 76	20.8	1.7	105.7	0.4	25.3	3.8	40	266	4.2	28.1
	Screen through age 78	20.7	2.1	92.0	0.4	18.9	3.3	53	304	4.9	28.0
	Screen through age 80	20.7	2.5	90.0	0.4	16.9	3.2	59	314	5.3	28.2
	Screen through age 82	20.6	2.8	90.2	0.4	13.6	2.9	74	340	6.6	30.7
	Screen through age 84	20.6	3.1	90.6	0.4	12.1	2.7	83	367	7.5	33.3
	Screen through age 86	20.8	3.6	89.7	0.4	8.5	2.3	118	441	10.6	39.6
	Screen through age 88	20.9	4.0	88.7	0.4	6.8	2.0	148	493	13.1	43.7
	Screen through age 90	20.9	4.4	87.4	0.4	4.6	1.6	218	618	19.0	54.0
Moderate comorbidity	Screen through age 66	21.7	0.9	113.6	0.4	30.3	3.2	33	311	3.8	35.3
	Screen through age 68	21.2	1.0	110.2	0.4	29.3	3.4	34	295	3.8	32.6
	Screen through age 70	21.0	1.3	109.2	0.4	27.2	3.4	37	291	4.0	31.8
	Screen through age 72	21.0	1.6	109.5	0.4	22.7	3.2	44	311	4.8	34.0
	Screen through age 74	21.0	1.8	103.7	0.4	21.1	3.2	47	312	4.9	32.4
	Screen through age 76	20.8	2.1	102.0	0.4	17.9	3.0	56	331	5.7	33.8
	Screen through age 78	20.7	2.5	90.4	0.4	14.9	2.8	67	354	6.1	32.0
	Screen through age 80	20.7	3.0	88.6	0.4	12.4	2.6	80	382	7.1	33.8
	Screen through age 82	20.6	3.4	88.3	0.4	9.4	2.3	106	442	9.4	39.0
	Screen through age 84	20.6	3.7	88.8	0.4	8.3	2.2	120	464	10.6	41.2
	Screen through age 86	20.8	4.1	87.9	0.4	6.7	1.9	148	515	13.0	45.3
	Screen through age 88	20.9	4.5	87.2	0.4	4.9	1.6	202	611	17.6	53.2
	Screen through age 90	20.9	5.1	83.8	0.3	3.2	1.2	308	806	25.8	67.5
Severe comorbidity	Screen through age 66	21.7	1.4	99.8	0.4	20.3	2.3	49	432	4.9	43.1
	Screen through age 68	21.2	1.7	96.8	0.4	19.0	2.4	53	422	5.1	40.8
	Screen through age 70	21.1	2.0	96.8	0.4	17.5	2.4	57	414	5.5	40.1
	Screen through age 72	21.0	2.3	97.5	0.4	14.8	2.3	67	436	6.6	42.5
	Screen through age 74	21.0	2.7	93.7	0.4	13.1	2.2	76	452	7.1	42.4
	Screen through age 76	20.8	3.1	92.5	0.4	11.0	2.1	91	480	8.4	44.4
	Screen through age 78	20.7	3.5	85.4	0.3	9.3	1.9	108	516	9.2	44.1
	Screen through age 80	20.7	3.9	84.1	0.3	8.0	1.8	126	548	10.6	46.1
	Screen through age 82	20.6	4.3	83.8	0.3	6.0	1.6	167	628	14.0	52.7
	Screen through age 84	20.6	4.6	84.4	0.3	5.5	1.6	182	638	15.4	53.9
	Screen through age 86	20.8	5.0	84.1	0.3	4.3	1.4	233	728	19.6	61.2
	Screen through age 88	20.9	5.4	82.3	0.3	3.0	1.1	333	894	27.4	73.5
	Screen through age 90	20.9	5.7	81.1	0.3	2.3	1.0	428	1031	34.7	83.6

e. No prior screening with biennial FIT.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	15.3	0.6	47.4	0.2	10.6	1.5	94	659	4.5	31.3
	Screen through age 76 (vs. 74)	17.4	0.7	50.3	0.2	9.2	1.4	108	690	5.4	34.7
No comorbidity	Screen through age 66	24.9	0.9	180.6	0.7	53.3	5.4	19	184	3.4	33.2
	Screen through age 68	24.6	1.1	177.2	0.7	53.4	5.8	19	171	3.3	30.3
	Screen through age 70	24.4	1.4	181.5	0.7	54.3	6.3	18	159	3.3	28.8
	Screen through age 72	24.0	1.8	187.7	0.7	48.5	6.2	21	161	3.9	30.1
	Screen through age 74	23.8	2.2	175.8	0.7	44.4	6.2	23	161	4.0	28.3
	Screen through age 76	23.6	2.7	175.7	0.7	40.5	6.2	25	162	4.3	28.5
	Screen through age 78	23.4	3.3	152.3	0.7	35.7	5.9	28	168	4.3	25.7
	Screen through age 80	23.3	4.0	149.9	0.7	31.5	5.8	32	174	4.8	26.0
	Screen through age 82	23.2	4.9	153.3	0.7	25.1	5.2	40	193	6.1	29.6
	Screen through age 84	23.1	5.5	157.2	0.7	21.6	4.9	46	203	7.3	31.9
	Screen through age 86	23.1	6.6	158.4	0.7	16.4	4.3	61	232	9.6	36.8
	Screen through age 88	23.1	7.7	158.8	0.7	12.6	3.8	79	266	12.6	42.2
	Screen through age 90	23.1	8.6	159.0	0.7	9.1	3.2	110	315	17.5	50.1
Mild comorbidity	Screen through age 66	24.9	1.1	174.8	0.7	48.8	5.1	20	197	3.6	34.4
	Screen through age 68	24.6	1.3	171.4	0.7	47.2	5.3	21	187	3.6	32.1
	Screen through age 70	24.4	1.6	176.6	0.7	49.6	5.9	20	169	3.6	29.9
	Screen through age 72	24.0	2.0	182.2	0.7	42.1	5.7	24	176	4.3	32.0
	Screen through age 74	23.8	2.4	174.3	0.7	41.0	5.9	24	169	4.3	29.5
	Screen through age 76	23.6	2.9	173.8	0.7	40.0	6.0	25	165	4.3	28.8
	Screen through age 78	23.4	3.6	151.5	0.7	30.4	5.4	33	186	5.0	28.2
	Screen through age 80	23.3	4.3	149.4	0.7	28.5	5.4	35	185	5.2	27.7
	Screen through age 82	23.2	5.0	153.0	0.7	22.9	5.0	44	199	6.7	30.4
	Screen through age 84	23.1	5.7	156.4	0.7	21.0	4.8	48	208	7.4	32.6
	Screen through age 86	23.1	6.9	157.4	0.7	15.3	4.1	66	245	10.3	38.5
	Screen through age 88	23.1	7.7	158.0	0.7	12.4	3.8	81	265	12.8	41.9
	Screen through age 90	23.1	8.7	158.7	0.7	8.6	3.1	117	321	18.5	51.0
Moderate comorbidity	Screen through age 66	24.9	1.2	167.4	0.6	42.8	4.6	23	217	3.9	36.3
	Screen through age 68	24.6	1.5	166.1	0.6	42.2	4.9	24	204	3.9	33.8
	Screen through age 70	24.4	1.9	168.3	0.7	40.3	5.1	25	195	4.2	32.9
	Screen through age 72	24.1	2.4	172.9	0.7	34.4	4.9	29	203	5.0	35.1
	Screen through age 74	23.8	2.9	166.9	0.7	32.9	5.1	30	198	5.1	33.0
	Screen through age 76	23.6	3.5	167.1	0.7	28.3	4.9	35	206	5.9	34.3
	Screen through age 78	23.4	4.2	148.2	0.6	24.0	4.6	42	218	6.2	32.3
	Screen through age 80	23.3	5.1	146.8	0.6	20.7	4.4	48	225	7.1	33.0
	Screen through age 82	23.2	6.1	149.3	0.7	15.9	3.9	63	258	9.4	38.5
	Screen through age 84	23.1	6.7	152.9	0.7	14.3	3.8	70	265	10.7	40.5
	Screen through age 86	23.1	7.6	153.5	0.7	12.0	3.5	83	289	12.8	44.4
	Screen through age 88	23.1	8.7	154.7	0.7	9.0	3.0	111	332	17.2	51.4
	Screen through age 90	23.1	10.0	150.4	0.7	6.0	2.3	168	427	25.3	64.3
Severe comorbidity	Screen through age 66	24.9	2.0	145.3	0.6	28.8	3.3	35	302	5.1	43.9
	Screen through age 68	24.6	2.4	144.3	0.6	27.4	3.5	36	290	5.3	41.8
	Screen through age 70	24.4	3.0	147.5	0.6	25.9	3.6	39	278	5.7	41.1
	Screen through age 72	24.0	3.6	151.5	0.6	22.5	3.5	45	288	6.7	43.6
	Screen through age 74	23.8	4.2	148.4	0.6	20.5	3.5	49	289	7.2	42.8
	Screen through age 76	23.6	5.0	149.4	0.6	17.2	3.3	58	302	8.7	45.2
	Screen through age 78	23.4	5.8	138.3	0.6	14.8	3.2	67	316	9.3	43.8
	Screen through age 80	23.3	6.7	138.0	0.6	13.2	3.1	76	324	10.5	44.7
	Screen through age 82	23.2	7.7	140.2	0.6	10.1	2.7	99	366	13.9	51.3
	Screen through age 84	23.2	8.4	144.1	0.6	9.4	2.7	107	366	15.4	52.7
	Screen through age 86	23.1	9.3	145.4	0.7	7.6	2.5	131	406	19.1	59.0
	Screen through age 88	23.1	10.4	144.1	0.7	5.5	2.1	182	481	26.3	69.3
	Screen through age 90	23.2	11.1	144.5	0.7	4.2	1.8	236	551	34.1	79.6

f. Colonoscopy 10 years prior.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	15.3	0.6	47.4	0.2	10.6	1.5	94	659	4.5	31.3
	Screen through age 76 (vs. 74)	17.4	0.7	50.3	0.2	9.2	1.4	108	690	5.4	34.7
No comorbidity	Screen through age 66	27.8	0.2	64.1	0.2	15.9	1.4	63	691	4.0	44.3
	Screen through age 67	27.9	0.2	63.3	0.2	15.0	1.4	67	708	4.2	44.8
	Screen through age 68	28.0	0.2	60.3	0.2	14.2	1.4	70	722	4.2	43.6
	Screen through age 69	28.1	0.2	59.7	0.2	13.5	1.4	74	738	4.4	44.0
	Screen through age 70	28.2	0.2	58.9	0.2	13.1	1.4	77	741	4.5	43.6
	Screen through age 71	28.3	0.3	58.7	0.2	11.9	1.3	84	785	4.9	46.1
	Screen through age 72	28.3	0.3	58.5	0.2	11.2	1.2	89	801	5.2	46.8
	Screen through age 73	28.3	0.3	55.8	0.1	10.6	1.2	94	812	5.3	45.3
	Screen through age 74	28.3	0.3	55.9	0.1	10.0	1.2	100	829	5.6	46.3
	Screen through age 75	28.3	0.3	55.6	0.1	9.6	1.2	104	832	5.8	46.3
	Screen through age 76	28.3	0.4	55.7	0.1	8.7	1.1	115	872	6.4	48.5
	Screen through age 77	28.3	0.4	55.7	0.1	8.1	1.1	123	892	6.9	49.7
	Screen through age 78	28.3	0.4	52.5	0.1	7.6	1.1	131	922	6.9	48.4
	Screen through age 79	28.3	0.4	52.6	0.1	7.1	1.0	141	956	7.4	50.3
	Screen through age 80	28.4	0.5	52.6	0.1	6.6	1.0	152	970	8.0	51.0
	Screen through age 81	28.4	0.5	52.6	0.1	5.8	1.0	172	1047	9.0	55.1
	Screen through age 82	28.5	0.5	52.5	0.1	5.4	0.9	186	1098	9.8	57.7
	Screen through age 83	28.5	0.6	50.8	0.1	4.8	0.9	208	1162	10.6	59.0
	Screen through age 84	28.6	0.5	50.8	0.1	4.5	0.8	222	1185	11.3	60.3
	Screen through age 85	28.6	0.6	50.7	0.1	4.1	0.8	246	1260	12.5	63.9
	Screen through age 86	28.7	0.6	50.7	0.1	3.6	0.7	278	1343	14.1	68.0
	Screen through age 87	28.8	0.6	50.6	0.1	3.2	0.7	310	1452	15.7	73.5
	Screen through age 88	28.9	0.7	50.5	0.1	2.9	0.7	350	1525	17.7	77.0
	Screen through age 89	29.0	0.7	50.4	0.1	2.5	0.6	402	1648	20.2	83.0
	Screen through age 90	29.1	0.7	50.1	0.1	2.3	0.6	444	1746	22.2	87.4
Mild comorbidity	Screen through age 66	27.8	0.2	62.9	0.2	14.5	1.4	69	737	4.3	46.4
	Screen through age 67	27.9	0.2	62.5	0.2	14.1	1.3	71	744	4.4	46.5
	Screen through age 68	28.0	0.3	59.5	0.2	12.7	1.3	79	781	4.7	46.4
	Screen through age 69	28.1	0.3	59.3	0.2	12.9	1.3	77	761	4.6	45.1
	Screen through age 70	28.2	0.3	58.3	0.2	12.1	1.3	82	779	4.8	45.4
	Screen through age 71	28.2	0.3	58.4	0.2	11.4	1.2	88	804	5.1	46.9
	Screen through age 72	28.2	0.3	57.9	0.2	9.9	1.2	101	851	5.8	49.3
	Screen through age 73	28.2	0.3	55.6	0.1	9.5	1.1	105	871	5.9	48.4
	Screen through age 74	28.3	0.3	55.7	0.1	9.3	1.2	107	865	6.0	48.2
	Screen through age 75	28.3	0.4	55.5	0.1	9.4	1.2	106	844	5.9	46.8
	Screen through age 76	28.3	0.4	55.5	0.1	8.6	1.1	116	887	6.4	49.2
	Screen through age 77	28.3	0.4	55.5	0.1	7.7	1.1	130	926	7.2	51.3
	Screen through age 78	28.3	0.4	52.4	0.1	6.7	1.0	150	995	7.9	52.1
	Screen through age 79	28.3	0.5	52.5	0.1	6.2	1.0	162	1036	8.5	54.4
	Screen through age 80	28.3	0.5	52.6	0.1	6.1	1.0	165	1015	8.6	53.4
	Screen through age 81	28.4	0.5	52.6	0.1	5.5	0.9	182	1078	9.6	56.7
	Screen through age 82	28.5	0.5	52.5	0.1	5.0	0.9	200	1122	10.5	58.9
	Screen through age 83	28.5	0.6	50.8	0.1	4.5	0.8	220	1203	11.2	61.0
	Screen through age 84	28.6	0.6	50.8	0.1	4.4	0.8	225	1210	11.4	61.4
	Screen through age 85	28.6	0.6	50.8	0.1	4.5	0.8	222	1190	11.3	60.4
	Screen through age 86	28.7	0.6	50.6	0.1	3.4	0.7	298	1405	15.1	71.1
	Screen through age 87	28.8	0.7	50.5	0.1	3.2	0.7	316	1468	16.0	74.2
	Screen through age 88	28.9	0.7	50.5	0.1	2.8	0.6	357	1539	18.0	77.7
	Screen through age 89	29.0	0.7	50.3	0.1	2.4	0.6	419	1687	21.1	84.9
	Screen through age 90	29.1	0.7	50.0	0.1	2.2	0.6	461	1772	23.1	88.6
Moderate comorbidity	Screen through age 66	27.8	0.3	61.6	0.2	12.8	1.2	78	801	4.8	49.3
	Screen through age 67	27.9	0.3	60.8	0.2	11.9	1.2	84	828	5.1	50.3
	Screen through age 68	28.0	0.3	58.5	0.2	11.3	1.2	88	841	5.2	49.3
	Screen through age 69	28.1	0.3	57.8	0.2	10.5	1.2	96	869	5.5	50.3
	Screen through age 70	28.2	0.3	57.1	0.2	9.9	1.1	101	882	5.7	50.4
	Screen through age 71	28.2	0.3	56.9	0.1	9.1	1.1	109	923	6.2	52.5
	Screen through age 72	28.2	0.4	56.7	0.1	8.3	1.0	120	955	6.8	54.2
	Screen through age 73	28.2	0.4	54.9	0.1	8.1	1.0	123	961	6.7	52.8
	Screen through age 74	28.2	0.4	54.9	0.1	7.8	1.0	129	974	7.1	53.5
	Screen through age 75	28.3	0.4	54.8	0.1	7.0	1.0	142	1004	7.8	55.0
	Screen through age 76	28.3	0.5	54.7	0.1	6.3	0.9	158	1063	8.6	58.2
	Screen through age 77	28.3	0.5	54.7	0.1	5.9	0.9	170	1090	9.3	59.6
	Screen through age 78	28.3	0.5	52.1	0.1	5.3	0.9	188	1146	9.8	59.7
	Screen through age 79	28.3	0.5	52.3	0.1	4.7	0.8	211	1204	11.0	63.0
	Screen through age 80	28.3	0.6	52.2	0.1	4.6	0.8	216	1195	11.3	62.4
	Screen through age 81	28.4	0.6	52.2	0.1	4.1	0.8	244	1278	12.7	66.7
	Screen through age 82	28.5	0.7	52.2	0.1	3.7	0.7	269	1366	14.1	71.3
	Screen through age 83	28.5	0.7	50.6	0.1	3.3	0.7	303	1450	15.3	73.3
	Screen through age 84	28.6	0.7	50.6	0.1	3.3	0.7	303	1429	15.3	72.4
	Screen through age 85	28.6	0.7	50.5	0.1	3.1	0.7	324	1496	16.3	75.5
	Screen through age 86	28.7	0.7	50.4	0.1	2.8	0.6	354	1577	17.8	79.5
	Screen through age 87	28.8	0.7	50.3	0.1	2.4	0.6	417	1742	21.0	87.6
	Screen through age 88	28.9	0.8	50.3	0.1	2.2	0.6	450	1803	22.6	90.7
	Screen through age 89	29.0	0.8	50.2	0.1	1.9	0.5	522	1953	26.2	98.0
	Screen through age 90	29.1	0.8	49.6	0.1	1.6	0.5	615	2149	30.5	106.5

Severe comorbidity	Screen through age 66	27.9	0.5	57.6	0.2	8.6	0.9	116	1093	6.7	62.9
	Screen through age 67	28.0	0.5	57.1	0.2	8.0	0.9	126	1129	7.2	64.4
	Screen through age 68	28.1	0.5	55.3	0.1	7.5	0.9	133	1157	7.4	64.0
	Screen through age 69	28.2	0.5	54.8	0.1	7.0	0.8	144	1185	7.9	64.9
	Screen through age 70	28.2	0.5	54.2	0.1	6.7	0.8	150	1191	8.1	64.6
	Screen through age 71	28.2	0.5	54.0	0.1	6.1	0.8	164	1261	8.9	68.1
	Screen through age 72	28.2	0.6	53.8	0.1	5.6	0.8	178	1291	9.6	69.5
	Screen through age 73	28.3	0.6	52.8	0.1	5.4	0.8	186	1306	9.8	68.9
	Screen through age 74	28.3	0.6	52.7	0.1	5.1	0.8	198	1330	10.4	70.2
	Screen through age 75	28.3	0.6	52.7	0.1	4.7	0.7	212	1352	11.2	71.3
	Screen through age 76	28.3	0.6	52.8	0.1	4.1	0.7	247	1433	13.0	75.6
	Screen through age 77	28.3	0.7	52.8	0.1	3.8	0.7	263	1476	13.9	77.9
	Screen through age 78	28.3	0.7	51.2	0.1	3.5	0.7	282	1531	14.5	78.4
	Screen through age 79	28.3	0.7	51.3	0.1	3.4	0.6	298	1564	15.3	80.2
	Screen through age 80	28.4	0.8	51.3	0.1	3.1	0.6	321	1592	16.4	81.7
	Screen through age 81	28.4	0.8	51.3	0.1	2.8	0.6	362	1686	18.5	86.5
	Screen through age 82	28.5	0.8	51.2	0.1	2.5	0.6	403	1764	20.6	90.4
	Screen through age 83	28.5	0.8	50.0	0.1	2.2	0.5	452	1886	22.6	94.2
	Screen through age 84	28.6	0.8	50.1	0.1	2.4	0.6	420	1797	21.0	90.0
	Screen through age 85	28.6	0.9	50.0	0.1	2.3	0.5	433	1837	21.7	91.9
	Screen through age 86	28.7	0.9	50.0	0.1	2.0	0.5	499	1989	24.9	99.3
	Screen through age 87	28.8	0.9	49.8	0.1	1.8	0.5	566	2149	28.2	107.1
	Screen through age 88	28.9	0.9	49.7	0.1	1.6	0.4	638	2268	31.7	112.8
	Screen through age 89	29.0	0.9	49.6	0.1	1.4	0.4	692	2364	34.3	117.4
	Screen through age 90	29.1	0.9	49.2	0.1	1.3	0.4	749	2476	36.9	121.9

g. Colonoscopy 15 years prior.

		HARMS				BENEFITS		BALANCE			
		False-positive tests	Over-diagnosed cases	Colonoscopies	Complications	Life-years gained	Cancer deaths prevented	NNS/LYG	NNS/CDP	NNSc/LYG	NNSc/CDP
Av	Screen through age 74 (vs. 72)	15.3	0.6	47.4	0.2	10.6	1.5	94	659	4.5	31.3
	Screen through age 76 (vs. 74)	17.4	0.7	50.3	0.2	9.2	1.4	108	690	5.4	34.7
No comorbidity	Screen through age 66	28.3	0.3	72.8	0.2	18.7	1.7	53	581	3.9	42.3
	Screen through age 67	28.1	0.3	74.2	0.2	19.3	1.8	52	550	3.9	40.8
	Screen through age 68	27.9	0.3	72.9	0.2	19.9	1.9	50	517	3.7	37.7
	Screen through age 69	27.7	0.4	74.8	0.2	20.7	2.0	48	488	3.6	36.5
	Screen through age 70	27.6	0.4	76.1	0.2	21.4	2.2	47	461	3.6	35.1
	Screen through age 71	27.8	0.4	74.6	0.2	18.9	2.0	53	505	4.0	37.7
	Screen through age 72	28.0	0.5	73.1	0.2	17.3	1.9	58	532	4.2	38.9
	Screen through age 73	28.1	0.5	68.1	0.2	16.0	1.8	62	559	4.2	38.1
	Screen through age 74	28.2	0.5	67.3	0.2	14.8	1.7	67	579	4.5	39.0
	Screen through age 75	28.4	0.5	66.2	0.2	14.1	1.7	71	598	4.7	39.6
	Screen through age 76	28.5	0.5	66.0	0.2	13.3	1.6	75	613	4.9	40.4
	Screen through age 77	28.5	0.6	65.7	0.2	12.4	1.6	81	634	5.3	41.6
	Screen through age 78	28.6	0.6	60.9	0.2	11.8	1.5	85	653	5.2	39.8
	Screen through age 79	28.7	0.6	60.9	0.2	11.0	1.5	91	677	5.5	41.2
	Screen through age 80	28.8	0.7	60.5	0.2	10.5	1.4	95	691	5.8	41.8
	Screen through age 81	28.8	0.7	60.5	0.2	9.2	1.3	109	753	6.6	45.6
	Screen through age 82	28.9	0.7	60.5	0.2	8.6	1.3	116	780	7.0	47.2
	Screen through age 83	28.9	0.8	59.0	0.2	8.0	1.2	125	815	7.4	48.1
	Screen through age 84	29.0	0.8	59.2	0.2	7.8	1.2	128	816	7.6	48.3
	Screen through age 85	29.0	0.8	59.1	0.2	7.1	1.2	141	855	8.3	50.5
	Screen through age 86	29.2	0.9	58.9	0.2	6.6	1.1	152	903	9.0	53.2
	Screen through age 87	29.3	0.9	58.8	0.2	6.2	1.1	162	949	9.5	55.8
	Screen through age 88	29.5	0.9	56.6	0.2	5.7	1.0	176	996	10.0	56.3
	Screen through age 89	29.6	1.0	56.3	0.2	5.1	0.9	196	1062	11.0	59.7
	Screen through age 90	29.7	1.0	56.0	0.2	4.9	0.9	203	1101	11.4	61.7
Mild comorbidity	Screen through age 66	28.3	0.3	71.5	0.2	17.1	1.6	58	618	4.2	44.2
	Screen through age 67	28.1	0.4	73.2	0.2	18.2	1.7	55	575	4.0	42.1
	Screen through age 68	27.9	0.4	71.6	0.2	17.6	1.8	57	563	4.1	40.3
	Screen through age 69	27.7	0.4	74.1	0.2	19.7	2.0	51	505	3.8	37.4
	Screen through age 70	27.6	0.5	75.0	0.2	19.9	2.1	50	482	3.8	36.2
	Screen through age 71	27.8	0.5	74.1	0.2	18.0	1.9	56	518	4.1	38.4
	Screen through age 72	27.9	0.5	72.2	0.2	15.6	1.8	64	564	4.6	40.8
	Screen through age 73	28.1	0.5	67.8	0.2	14.5	1.7	69	594	4.7	40.3
	Screen through age 74	28.2	0.5	67.1	0.2	14.0	1.7	71	602	4.8	40.4
	Screen through age 75	28.4	0.5	66.0	0.2	13.8	1.6	72	606	4.8	40.0
	Screen through age 76	28.5	0.6	65.6	0.2	13.2	1.6	76	623	5.0	40.9
	Screen through age 77	28.5	0.6	65.3	0.2	11.8	1.5	85	656	5.5	42.8
	Screen through age 78	28.6	0.7	60.8	0.2	10.4	1.4	96	704	5.8	42.8
	Screen through age 79	28.7	0.7	60.7	0.2	9.8	1.4	102	728	6.2	44.2
	Screen through age 80	28.8	0.7	60.4	0.2	9.8	1.4	102	722	6.2	43.6
	Screen through age 81	28.8	0.7	60.5	0.2	8.7	1.3	116	780	7.0	47.2
	Screen through age 82	28.9	0.7	60.5	0.2	8.2	1.3	123	794	7.4	48.1
	Screen through age 83	28.9	0.8	59.0	0.2	7.6	1.2	132	843	7.8	49.8
	Screen through age 84	29.0	0.8	59.1	0.2	7.6	1.2	131	835	7.7	49.3
	Screen through age 85	29.0	0.8	59.1	0.2	7.7	1.2	130	820	7.7	48.5
	Screen through age 86	29.2	0.9	58.8	0.2	6.2	1.1	160	937	9.4	55.1
	Screen through age 87	29.3	0.9	58.6	0.2	6.0	1.0	166	964	9.7	56.5
	Screen through age 88	29.5	0.9	56.5	0.2	5.6	1.0	178	1000	10.0	56.5
	Screen through age 89	29.6	1.0	56.2	0.2	5.0	0.9	201	1089	11.3	61.2
	Screen through age 90	29.7	1.0	56.0	0.2	4.8	0.9	208	1115	11.7	62.4
Moderate comorbidity	Screen through age 66	28.3	0.4	69.7	0.2	15.1	1.5	66	674	4.6	47.0
	Screen through age 67	28.1	0.4	70.9	0.2	15.3	1.6	65	640	4.6	45.4
	Screen through age 68	27.9	0.5	70.3	0.2	15.8	1.7	63	604	4.4	42.5
	Screen through age 69	27.8	0.5	71.7	0.2	15.9	1.7	63	577	4.5	41.4
	Screen through age 70	27.6	0.6	73.0	0.2	16.4	1.8	61	547	4.5	39.9
	Screen through age 71	27.8	0.6	71.6	0.2	14.5	1.7	69	598	4.9	42.8
	Screen through age 72	27.9	0.6	70.2	0.2	13.0	1.6	77	636	5.4	44.6
	Screen through age 73	28.1	0.6	66.7	0.2	12.6	1.5	80	653	5.3	43.6
	Screen through age 74	28.2	0.6	65.8	0.2	11.8	1.5	85	677	5.6	44.6
	Screen through age 75	28.4	0.7	64.9	0.2	10.6	1.4	95	714	6.1	46.4
	Screen through age 76	28.4	0.7	64.5	0.2	10.1	1.4	99	736	6.4	47.5
	Screen through age 77	28.5	0.7	64.1	0.2	9.4	1.3	107	766	6.8	49.1
	Screen through age 78	28.6	0.8	60.4	0.2	8.7	1.3	115	795	7.0	48.0
	Screen through age 79	28.7	0.8	60.4	0.2	7.9	1.2	126	827	7.6	49.9
	Screen through age 80	28.8	0.8	60.2	0.2	7.8	1.2	129	829	7.7	49.9
	Screen through age 81	28.8	0.9	60.1	0.2	6.7	1.1	148	907	8.9	54.5
	Screen through age 82	28.9	0.9	60.1	0.2	6.2	1.0	162	960	9.7	57.7
	Screen through age 83	28.9	1.0	58.7	0.2	5.9	1.0	171	992	10.0	58.2
	Screen through age 84	29.0	1.0	58.8	0.2	6.0	1.0	168	984	9.9	57.9
	Screen through age 85	29.1	1.0	58.7	0.2	5.6	1.0	177	1007	10.4	59.1
	Screen through age 86	29.2	1.0	58.6	0.2	5.4	1.0	186	1036	10.9	60.7
	Screen through age 87	29.3	1.0	58.3	0.2	4.9	0.9	204	1111	11.9	64.8
	Screen through age 88	29.5	1.0	56.2	0.2	4.7	0.9	212	1132	11.9	63.6
	Screen through age 89	29.6	1.1	56.0	0.2	4.3	0.8	234	1211	13.1	67.8
	Screen through age 90	29.7	1.2	55.4	0.2	4.0	0.8	253	1292	14.0	71.5

Severe comorbidity	Screen through age 66	28.3	0.6	64.8	0.2	10.4	1.1	97	914	6.3	59.2
	Screen through age 67	28.1	0.7	65.9	0.2	10.4	1.2	96	869	6.3	57.2
	Screen through age 68	27.9	0.7	65.4	0.2	10.5	1.2	95	830	6.2	54.3
	Screen through age 69	27.7	0.8	66.8	0.2	10.6	1.3	94	791	6.3	52.9
	Screen through age 70	27.6	0.9	68.0	0.2	11.0	1.3	91	746	6.2	50.7
	Screen through age 71	27.8	0.9	66.9	0.2	9.8	1.2	102	814	6.9	54.5
	Screen through age 72	27.9	0.9	65.9	0.2	8.9	1.2	113	858	7.4	56.5
	Screen through age 73	28.1	0.9	63.6	0.2	8.5	1.1	118	884	7.5	56.2
	Screen through age 74	28.2	0.9	62.8	0.2	7.9	1.1	127	916	8.0	57.5
	Screen through age 75	28.4	1.0	62.1	0.2	7.4	1.1	135	935	8.4	58.1
	Screen through age 76	28.5	1.0	61.8	0.2	6.8	1.0	147	978	9.1	60.5
	Screen through age 77	28.5	1.0	61.5	0.2	6.4	1.0	156	1013	9.6	62.3
	Screen through age 78	28.6	1.0	59.1	0.2	6.1	1.0	165	1046	9.7	61.8
	Screen through age 79	28.7	1.1	59.0	0.2	5.8	0.9	174	1071	10.3	63.2
	Screen through age 80	28.8	1.1	58.8	0.2	5.5	0.9	181	1078	10.6	63.4
	Screen through age 81	28.8	1.1	58.9	0.2	4.8	0.9	208	1164	12.3	68.5
	Screen through age 82	28.9	1.2	58.9	0.2	4.6	0.8	218	1184	12.8	69.7
	Screen through age 83	28.9	1.2	57.8	0.2	4.3	0.8	235	1250	13.6	72.3
	Screen through age 84	29.0	1.2	58.1	0.2	4.6	0.8	219	1190	12.7	69.1
	Screen through age 85	29.0	1.2	58.0	0.2	4.5	0.8	222	1203	12.9	69.8
	Screen through age 86	29.2	1.2	57.8	0.2	4.2	0.8	238	1241	13.7	71.7
	Screen through age 87	29.3	1.2	57.7	0.2	4.0	0.8	252	1310	14.6	75.6
	Screen through age 88	29.5	1.3	55.4	0.2	3.6	0.7	275	1366	15.2	75.7
	Screen through age 89	29.6	1.3	55.2	0.2	3.5	0.7	289	1416	15.9	78.2
	Screen through age 90	29.7	1.3	54.9	0.2	3.4	0.7	294	1451	16.2	79.7

Abbreviations: Av, average health; NNS/LYG, number needed to screen to gain one life-year; NNS/CDP, number needed to screen to prevent one cancer death; NNSc/LYG, number needed to scope to gain one life-year; NNSc/CDP, number needed to scope to prevent one cancer death

Details of comorbid conditions are found in Table 5.2.

Shaded row represents the age for each comorbidity group at which screening provided similar harms and benefits as provided by the threshold of NNS/LYG for males with perfect screening history with biennial FIT and with average life expectancy at age 74.

Supplementary Results Table 5.3: Suggested age of last screening episode for colorectal cancer based on the number needed to screen to gain one life year, by sex, comorbidity status and prior screening. The faecal immunochemical test had a positivity of 7.5% (23 µg Hb/g faeces).

a. Prior screening with biennial guaiac faecal occult blood testing and faecal immunochemical testing for the current screening episode.

Screening History[a] /	Females				Males			
Comorbidity status[b]	No	Low	Mod	Sev	No	Low	Mod	Sev
Perfect Prior Screening with gFOBT	86	86	84	80	84	84	80	76
Most Prior Screening with gFOBT	88	88	86	82	86	86	82	78
Reasonable Prior Screening with gFOBT	88	88	86	84	86	86	84	80
Some Prior Screening with gFOBT	90	90	88	84	88	88	86	80
No Prior Screening with gFOBT	90	90	90	86	88	88	86	82

b. Prior screening with biennial guaiac faecal occult blood testing and faecal immunochemical testing in the previous two and current screening episodes.

Screening History[a] /	Females				Males			
Comorbidity status[b]	No	Low	Mod	Sev	No	Low	Mod	Sev
Perfect Prior Screening with gFOBT and FIT in last 2 screens	82	76	74	70	78	76	74	68
Most Prior Screening with gFOBT and FIT in last 2 screens	86	84	82	76	82	82	78	74
Reasonable Prior Screening with gFOBT and FIT in last 2 screens	88	86	86	80	84	84	80	76
Some Prior Screening with gFOBT and FIT in last 2 screens	90	88	88	84	86	86	84	80
No Prior Screening with gFOBT and FIT in last 2 screens	90	90	90	86	88	88	86	82

c. Prior screening with annual faecal immunochemical testing.

Screening History[a] /	Females				Males			
Comorbidity status[b]	No	Low	Mod	Sev	No	Low	Mod	Sev
Perfect Prior Screening with FIT	81	74	72	68	77	76	73	67
Most Prior Screening with FIT	85	83	82	72	81	80	77	72
Reasonable Prior Screening with FIT	87	86	84	77	83	82	80	76
Some Prior Screening with FIT	89	89	87	84	87	86	83	80
No Prior Screening with FIT	90	90	90	90	90	90	90	88

Abbreviations: FIT, faecal immunochemical test; Mod, moderate; Sev, severe

Key: Blue – stop screening later than recommended in guidelines; Green – stop screening in line with guidelines; Red – stop screening earlier than recommended in guidelines.

a. Details of screening history are found in Table 5.1.

b. Details of comorbid conditions are found in Table 5.2.

Supplementary Results Table 5.4: Suggested age of last screening episode for colorectal cancer based on the number needed to screen to gain one life year, by sex, comorbidity status and prior screening with colonoscopy. Current screening is with colonoscopy.

Screening History[a] /	Females				Males			
Comorbidity status[b]	No	Low	Mod	Sev	No	Low	Mod	Sev
Screening Colonoscopy 10 years prior	75	74	73	70	76	75	74	70

Abbreviations: Mod, moderate; Sev, severe
Key: Blue – stop screening later than recommended in guidelines; Green – stop screening in line with guidelines; Red – stop screening earlier than recommended in guidelines.
a. Details of screening history are found in Table 5.1.
b. Details of comorbid conditions are found in Table 5.2.

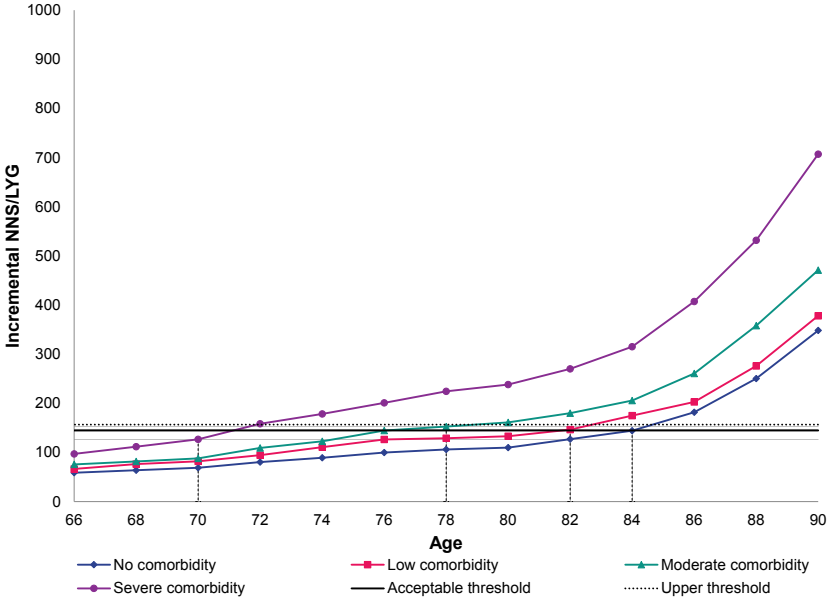
Supplementary Results Table 5.5: Suggested age of last screening episode for colorectal cancer based on the number needed to screen to gain one life year, by sex, comorbidity status and prior screening with biennial faecal immunochemical testing or colonoscopy. The faecal immunochemical test had a positivity of 9% (15 µg Hb/g faeces).

Screening History[a] /	Females				Males			
Comorbidity status[b]	No	Low	Mod	Sev	No	Low	Mod	Sev
Perfect Prior Screening with FIT	82	74	72	68	76	76	72	68
Most Prior Screening with FIT	84	84	80	72	80	80	76	72
Reasonable Prior Screening with FIT	86	86	84	76	82	82	78	74
Some Prior Screening with FIT	88	88	86	82	86	84	82	78
No Prior Screening with FIT	90	90	90	88	90	88	88	84
Screening Colonoscopy 10 years prior	81	74	72	66	76	76	72	66
Screening Colonoscopy 15 years prior	87	84	81	72	82	81	78	73

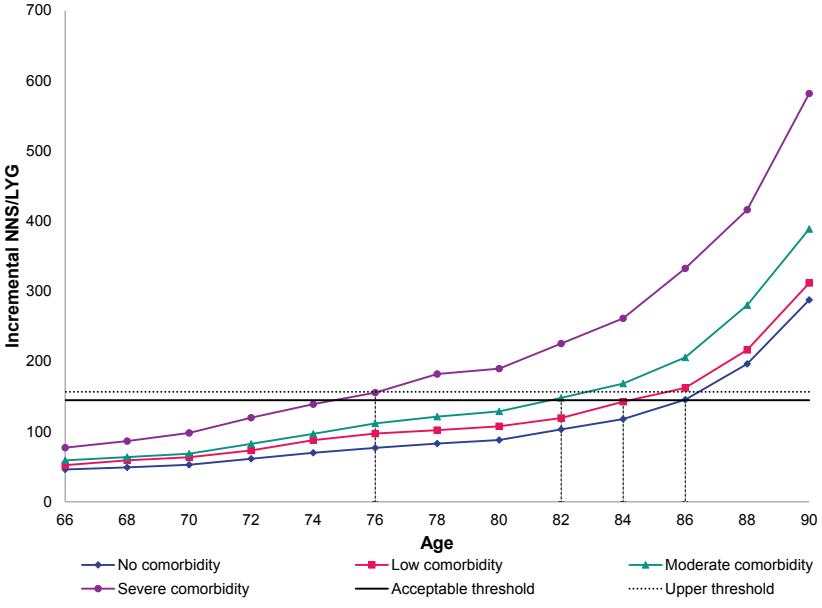
Abbreviations: FIT, faecal immunochemical test; Mod, moderate; Sev, severe
Key: Blue – stop screening later than recommended in guidelines; Green – stop screening in line with guidelines; Red – stop screening earlier than recommended in guidelines.
a. Details of screening history are found in Table 5.1.
b. Details of comorbid conditions are found in Table 5.2.

Supplementary Results Figure 5.1: Number needed to screen per life year gained for females by age and comorbidity level under varying prior screening assumptions.

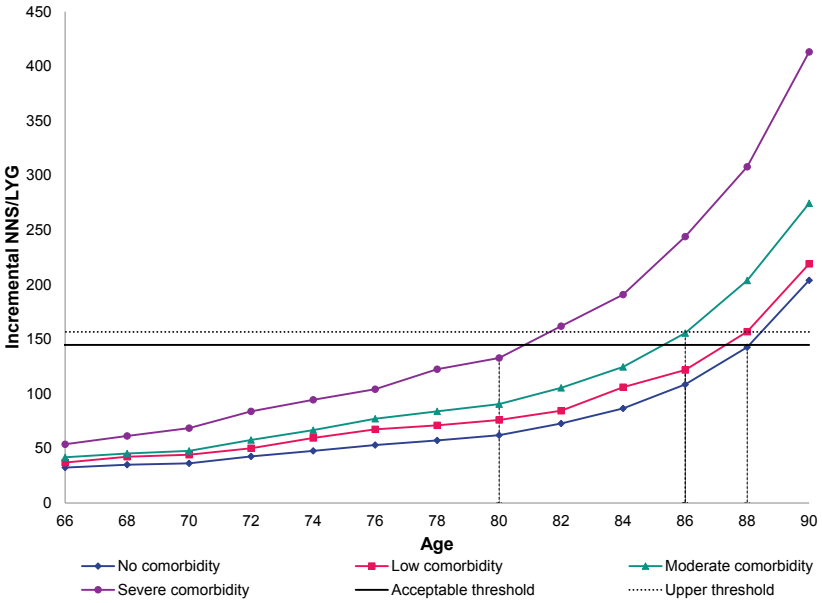
a. Most prior screening with FIT.



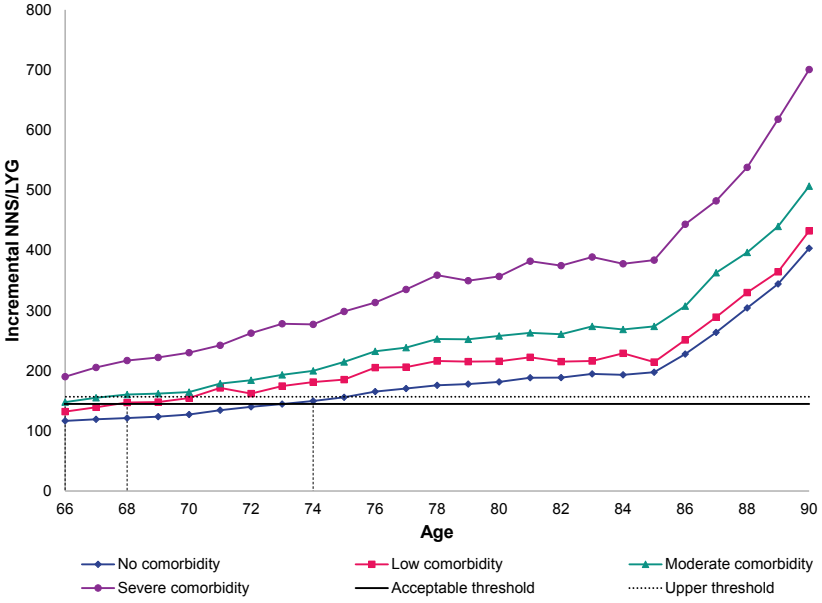
b. Reasonable prior screening with FIT.



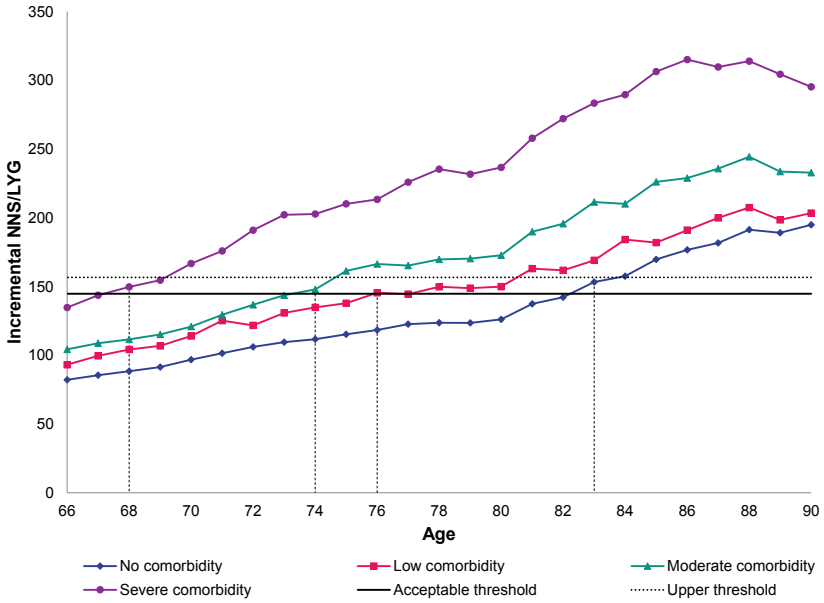
c. Some prior screening with FIT.



d. Colonoscopy 10 years prior.



e. Colonoscopy 15 years prior.

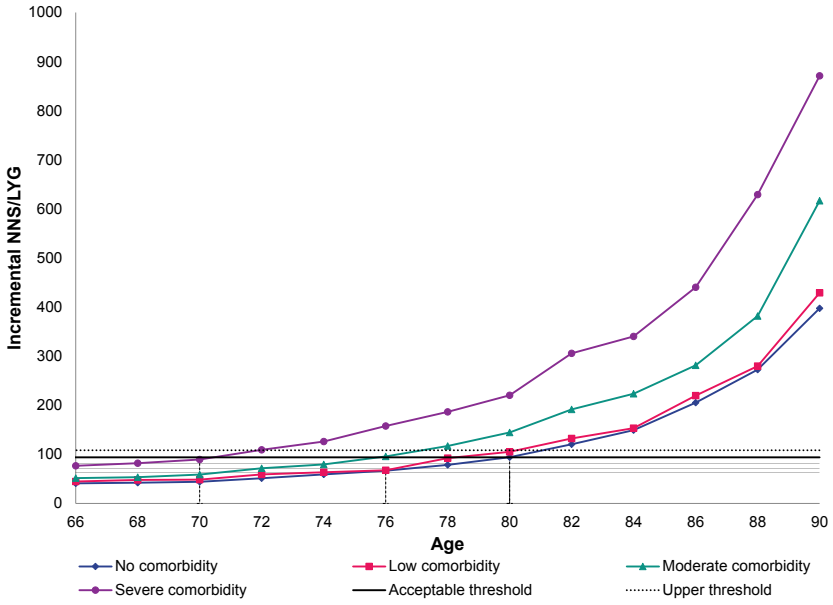


Abbreviations: NNS/LYG, number needed to screen to gain one life year

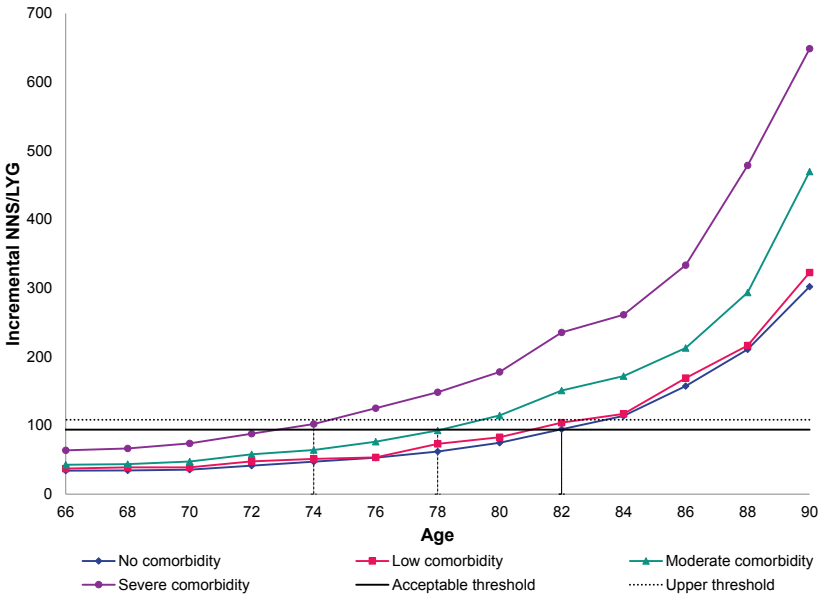
Each coloured line represents the number needed to screen per life year gained over the ages 66 to 90 for each level of comorbidity. The solid horizontal line represents the threshold for the number needed to screen per life year gained for screening in the average health population until the age of 74 (acceptable threshold). The dashed line represents the threshold for the number needed to screen per life year gained for screening in the average health population until the age of 76 (upper threshold). The recommended CRC screening stop-age is defined by this range. Where two ages fall within the threshold range, the lowest of the two values is selected. Where no values fall within the threshold range, the age closest to the lowest level is selected. The vertical dashed lines indicate the age for each comorbidity group where screening provides a balance of harms and benefits similar to those aged 74 with average health.

Supplementary Results Figure 5.2: Number needed to screen per life year gained for males by age and comorbidity level under varying prior screening assumptions.

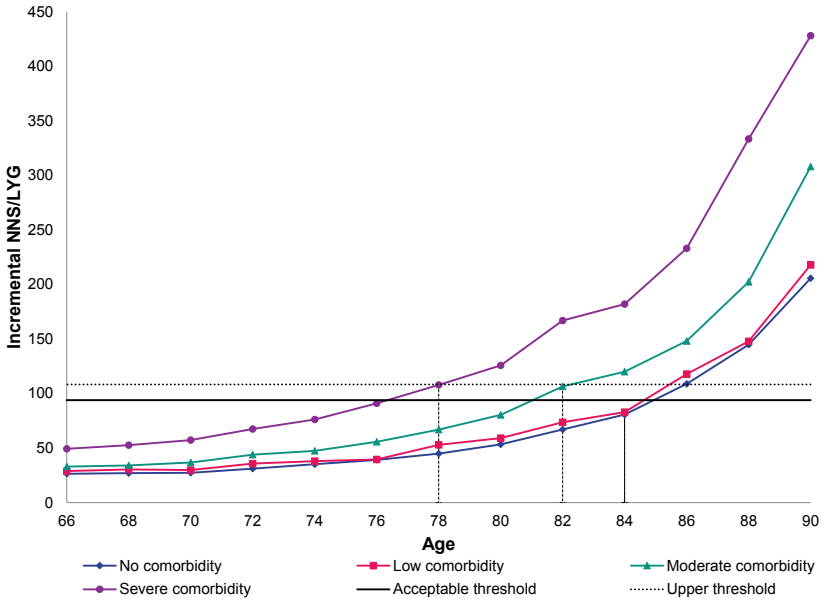
a. Most prior screening with FIT.



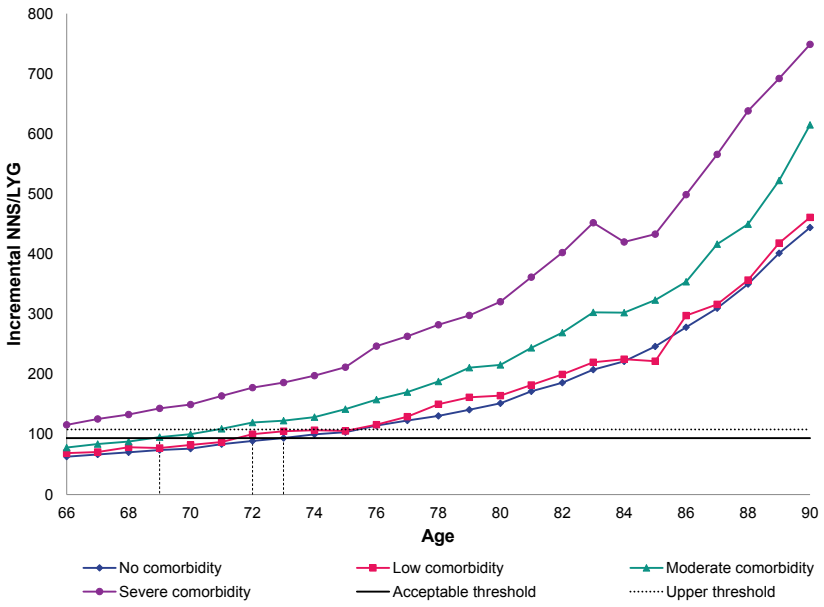
b. Reasonable prior screening with FIT.



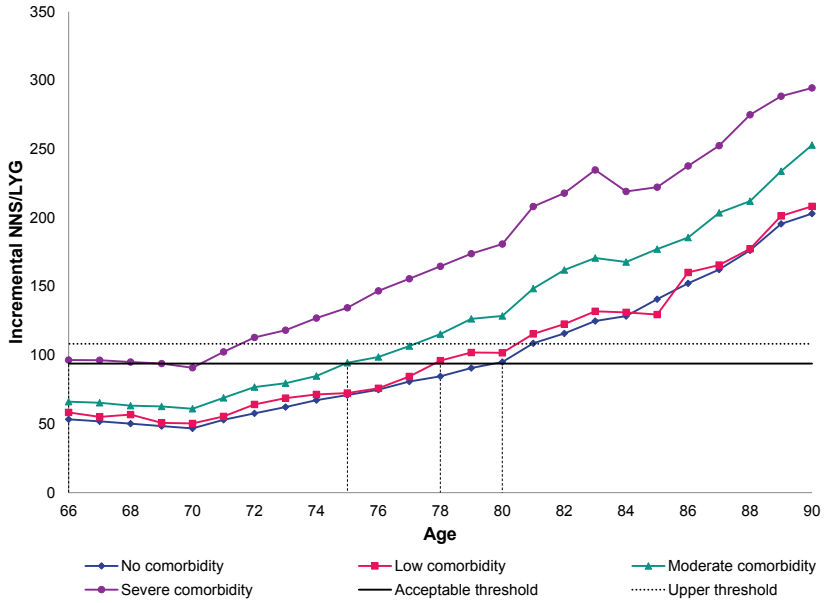
c. Some prior screening with FIT.



d. Colonoscopy 10 years prior.



e. Colonoscopy 15 years prior.

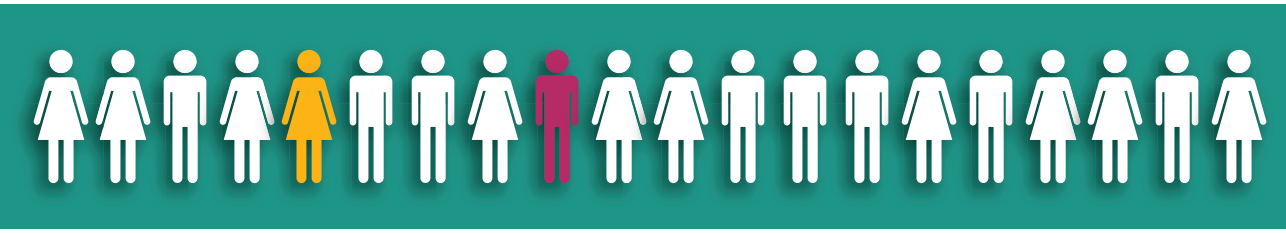


Abbreviations: NNS/LYG, number needed to screen to gain one life year

Each coloured line represents the number needed to screen per life year gained over the ages 66 to 90 for each level of comorbidity. The solid horizontal line represents the threshold for the number needed to screen per life year gained for screening in the average health population until the age of 74 (acceptable threshold). The dashed line represents the threshold for the number needed to screen per life year gained for screening in the average health population until the age of 76 (upper threshold). The recommended CRC screening stop-age is defined by this range. Where two ages fall within the threshold range, the lowest of the two values is selected. Where no values fall within the threshold range, the age closest to the lowest level is selected. The vertical dashed lines indicate the age for each comorbidity group where screening provides a balance of harms and benefits similar to those aged 74 with average health.

CHAPTER 6

COST-EFFECTIVENESS OF PERSONALISED SCREENING FOR COLORECTAL CANCER BASED ON POLYGENIC RISK AND FAMILY HISTORY



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ABSTRACT

Background: There is growing evidence for personalising colorectal cancer screening based on risk factors. We compared the cost-effectiveness of personalised colorectal cancer screening based on polygenic risk and family history to uniform screening.

Methods: Using the MISCAN-Colon model, we simulated a cohort of 100 million 40-year-olds, offering them uniform or personalised screening. Individuals were categorised based on polygenic risk and family history of colorectal cancer. We varied screening strategies by start age, interval and test and estimated costs, and quality-adjusted life years (QALY). In our analysis we: i) assessed the cost-effectiveness of uniform screening; ii) developed personalised screening scenarios based on optimal screening strategies by risk group; and iii) compared the cost-effectiveness of both.

Results: At a willingness-to-pay threshold of $50,000/QALY, the optimal uniform screening scenario was annual faecal immunochemical testing (FIT) from ages 50-74 years, whereas for personalised screening the optimal screening scenario consisted of annual and biennial FIT screening except for those at highest risk who were offered 5-yearly colonoscopy from age 50 years. Although these scenarios gained the same number of QALYs (17,887), personalised screening was not cost effective, costing an additional $428,953 due to costs associated with determining risk (assumed to be $240 per person). Personalised screening was cost effective when these costs were less than ~$48.

Conclusion: Uniform colorectal cancer screening currently appears more cost effective than personalised screening based on polygenic risk and family history. However, cost-effectiveness is highly dependent on the cost of determining risk.

Impact: Personalised screening could become increasingly viable as costs for determining risk decrease.

INTRODUCTION

Screening has been shown to be a cost effective method to reduce the incidence and mortality of colorectal cancer.[1-4] In countries with population screening programs, screening for colorectal cancer is based on age,[5] with separate screening recommendations for those with a positive family history.[6] However, genetic susceptibility also plays an important role in colorectal cancer risk and it has been suggested that, when combined with family history, this may improve risk prediction and diagnosis.[7, 8]

Genome-wide association studies have shown that polygenic factors, such as common, low risk genetic variants or single-nucleotide polymorphisms (SNP), play a significant role in defining colorectal cancer risk due to their relatively high prevalence in the population.[9-12] In isolation, SNPs are only weakly associated with colorectal cancer risk; however, cumulatively they explain substantial variation in risk.[9, 13] A polygenic test can be used to estimate someone's polygenic risk score based on the absence or presence of specific risk alleles. Such a risk score can be used to identify individuals at several times lower and greater (0.49-3.40) colorectal cancer risk than the average population.[14]

Compared with age-based screening, personalised screening provides an opportunity to stratify the population allowing screening to be tailored to an individual's risk.[15] This would allow for those at lower risk to start screening later and or have longer screening intervals, whereas those at higher risk could start screening earlier, undergo more intensive screening or both.[9, 15-17] Personalised screening also provides opportunities to detect cancers in younger at-risk individuals, who are currently excluded from age-based screening despite being at increased risk.[18-20] In this way, personalised screening has the potential to reduce the harms of screening while maintaining, or even increasing, its benefits in addition to improving its cost-effectiveness.

Previous research has demonstrated the efficacy of stratifying the population for screening based on age and polygenic risk,[21, 22] or in combination with other factors including family history.[7, 23] However, no studies have evaluated the cost-effectiveness of such risk-stratified screening compared with uniform screening for colorectal cancer. To address this gap in knowledge, we investigated the impact of personalising colorectal cancer screening, based on polygenic risk and family history and compared its cost-effectiveness to uniform screening.

METHODS AND MATERIALS

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon)[24] model to estimate the costs, benefits and harms of different uniform screening strategies as well as personalised screening strategies that were based on polygenic risk and family history of colorectal cancer.

MISCAN-COLON

MISCAN-Colon is a well-established microsimulation model for colorectal cancer developed at the Department of Public Health, Erasmus University Medical Center.[24] The structure, underlying assumptions, and data sources used to calibrate the model are detailed in the **Model Appendix**. In brief, the model simulates a large population of individuals from birth to death, first without and then with screening for colorectal cancer. As each simulated person ages, one or more adenomas may arise and some can progress in size from small (<5 mm) to medium (6-9 mm) to large (>10 mm). Some adenomas develop into preclinical cancer and subsequently progress through cancer stages I to IV. During each stage symptoms may present and colorectal cancer may be diagnosed. The introduction of screening may alter the simulated life histories through detection and removal of adenomas or through detection of colorectal cancer at an earlier stage with a more favourable survival. By comparing the life histories of a simulated population being screened to the corresponding life histories in a simulated population not screened, MISCAN-Colon quantifies the effectiveness and the costs of screening.

MISCAN-Colon was calibrated to match the age-specific incidence of colorectal cancer in Australia before the introduction of biennial faecal immunochemical test (FIT) screening for those aged 50 to 74 years in 2006.[25] Stage distribution, localisation of cancers in the colorectum, and five-year relative survival after clinical diagnosis of a cancer were based on Australian literature.[26, 27] Additional assumptions of the MISCAN-Colon model are presented in Table 6.1 and the **Model Appendix**.

SIMULATED POPULATION

For this analysis, we simulated a cohort of 100 million 40-year-olds, with life expectancy as observed in Australia in 2013-2015.[28] Individuals were followed for a lifetime, until a maximum age of 100 years, at which point they are all assumed to be dead.

RISK STRATIFICATION

Using previous research, the population was stratified *a priori* into five risk groups based on their quintile of polygenic risk score (based on 45 SNPs shown to increase colorectal cancer risk) and their first-degree family history of colorectal cancer (Table 6.2).[14] The expected prevalence of each of the five categories in the general population was based on a random assignment of 1,000 people given a 20% probability of being in any SNP quintile and a 10% probability of having at least one first-degree relative with colorectal cancer.[29] The relative risk (RR) of developing colorectal cancer (compared with the average population risk) for each risk group was based on the combined RR of each quintile of polygenic risk score and family history based on observed virtual independence of the two factors.[14] The five risk groups were defined as “very low” (RR<0.5), “low” (RR between 0.5-0.9), “average” (RR between 0.9-1.2),

"high" (RR between 1.2-1.8), and "very high" (RR >1.8). We assumed no other differences in life expectancy, colorectal cancer stage distribution, survival, or screening performance characteristics between the risk groups.

SCREENING AND SURVEILLANCE

In addition to a scenario without screening, we modelled 25 different screening strategies, varying screening start age (40, 46, 50, 54 or 60 years), test (FIT or colonoscopy), and interval (annual, biennial or triennial screening for FIT, and every 5 or 10 years for colonoscopy). For all FIT analyses, we assumed a positivity of 7.7% based on rates observed in the Queensland Bowel Cancer Screening Program between August 2006 and December 2010.[30, 31] Screening was always assumed to stop at age 74 years. Surveillance intervals and stop age for all scenarios were based on the Australian National Health and Medical Research Council Clinical Practice Guidelines for Surveillance Colonoscopy.[32]

PARTICIPATION

Screening programmes can be assessed under the assumption of perfect adherence or observed adherence. In the first analyses, we assumed perfect adherence to all screening, diagnostic, and surveillance tests. Subsequently, we estimated the costs and effects of screening at adherence levels currently observed in Australia.

For the latter analysis, we simulated participation rates as reported by the Australian National Bowel Cancer Screening Program (NBCSP), a biennial FIT screening program, in 2017 (Table 6.1).[33] Participation with annual and triennial FIT and with primary colonoscopy screening was set at the same screening participation rates. Age-specific participation rates were provided in five-year age intervals between 50 and 74 years. As data were not available for screening participation for individuals aged 40-49 years, participation was assumed to be equal to those aged 50-54 years. We assumed that 76.0% of individuals who had previously attended screening would attend again in the next screening round, whereas 19.7% of individuals who had not attended in the previous round would now attend based on data from the NBCSP.[33]

A positive FIT requires a consultation with a primary care provider, such as a general practitioner (GP) to discuss test results and obtain a referral for colonoscopy. For the observed adherence analyses, it was assumed that 90% of FIT positive cases would attend this appointment.[26] In addition, attendance at diagnostic colonoscopy was age-specific ranging from 68.2% to 72.3% based on outcomes from the NBCSP.[33] The participation rate for colonoscopy surveillance was assumed to be 80%.[34]

Table 6.1: Model Inputs: Test characteristics, participation assumptions, utility losses and costs associated with colorectal cancer screening and treatment.

Test characteristics	
Specificity and sensitivity of FIT [a]	
Specificity (per person)	95.0%
Sensitivity adenoma 1-5 mm	0.0%
Sensitivity adenoma 6-9 mm	9.0%
Sensitivity adenoma 10+ mm	32.0%
Sensitivity cancer long before clinical diagnosis [b]	36.5%
Sensitivity cancer shortly before clinical diagnosis [b]	72.8%
Specificity and sensitivity of colonoscopy [c, d]	
Specificity	86%
Sensitivity adenoma 1-5 mm	75%
Sensitivity adenoma 6-9 mm	85%
Sensitivity adenoma 10+ mm	95%
Sensitivity preclinical cancer	95%
Complication of colonoscopy [e]	
Fatal complication [f]	0.040%
General complication [g]	
50–54	0.096%
55–59	0.080%
60–64	0.054%
65–69	0.127%
70–74	0.073%
Participation	
Uptake of initial screening offer [h]	
50–54	28.5%
55–59	36.8%
60–64	43.2%
65–69	43.5%
70–74	52.5%
Uptake of rescreening [h]	
Previously attended	76.0%
Previously not attended	19.7%
Attendance at General Practitioner [i]	90.0%
Uptake of diagnostic test [h]	
50–54	72.3%
55–59	71.6%
60–64	71.4%
65–69	70.6%
70–74	68.2%
Adherence to surveillance [j]	80.0%

Utility loss (QALYs) [k]				
Per FIT	0			
Per colonoscopy [l]	0.00274			
Per complication of colonoscopy [m]	0.01918			
Per LY with colorectal cancer Care [n, o]	Initial Care	Continuing Care	Terminal care (Death colorectal cancer)	Terminal care (Death OC)
Stage I	0.12	0.05	0.70	0.05
Stage II	0.18	0.05	0.70	0.05
Stage III	0.24	0.24	0.70	0.24
Stage IV	0.70	0.70	0.70	0.70
Costs (2016 $AUD) [p]				
Per FIT invitation [q]				17.35
Per returned FIT [r]				22.60
Per GP visit [s]				37.05
Per colonoscopy (same day) [t]				1,627
Polygenic test [u]				200
Per complication of colonoscopy [v]				9,027
Treatment by stage and location [w, x, y]				
Stage I CC (without bevacizumab)				31,107
Stage I RC (without bevacizumab)				41,619
Stage II CC (without bevacizumab)				43,776
Stage III CC (without bevacizumab)				79,375
Stage II/III RC (without bevacizumab)				86,317
Stage IV colorectal cancer without bevacizumab				71,156
Stage IV colorectal cancer with bevacizumab				81,403

Abbreviations: CC, Colon Cancer; colorectal cancer, Colorectal Cancer; FIT, faecal immunochemical test; GP, General Practitioner; OC, Other Cause; QALY, Quality-Adjusted Life Year; RC, Rectal Cancer; LY, Life Year

a. Specificity and sensitivity of FIT derived from results of Queensland Health report.[31]
b. We assume that FIT screening is more sensitive in cancers as they progress towards becoming symptomatic (visible bleeding) and clinically detectable. For preclinical cancers which will become symptomatic within the same stage, assumed test sensitivity is higher.
c. The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, where the non-adenomatous lesions are removed and therefore induce polypectomy and biopsy or lead to (unnecessary) referral with sigmoidoscopy. The evidence synthesis reported no specificity for endoscopy for any adenoma. Specificity for colonoscopy is therefore based on Schroy et al, 2013.[35]
d. Sensitivity of colonoscopy for the detection of adenomas and colorectal cancer within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies.[36]
e. Complications are conditional on polypectomy, and we assume that polypectomy is only performed if colonoscopy is positive.
f. Fatal perforation taken from Viiala et al, 2003[37] and includes only deaths from colonoscopies performed in outpatients within 30 days of, and attributed to, colonoscopy.
g. Age-specific rate of complication taken from National Bowel Cancer Screening Monitoring report.[33] A complication is considered as an unplanned hospital admission within 30-days of a diagnostic colonoscopy.
h. Uptake of screening, rescreening and participation in diagnostic follow up taken from National Bowel Cancer Screening Monitoring report.[33]
i. Attendance at general practitioner for referral to colonoscopy taken from Tran et al, 2011.[26]
j. Attendance at surveillance colonoscopies assumed to be 80% based on Colquhoun et al, 2003.[34]
k. The loss of quality of life associated with a particular event.
l. Equal to 2 days per colonoscopy at a utility of 0.5.
m. Complications associated with hospitalisation with 30 days of colonoscopy were assumed to be equal to 14 days at a utility of 0.5.

n. Care for colorectal cancer 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 colorectal cancer patients dying from colorectal cancer and colorectal cancer 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.
o. 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 colorectal cancer, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV colorectal cancer, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for colorectal cancer, we assumed the utility loss for LYs with initial care for stage IV colorectal cancer. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.
p. Costs are from a health systems perspective and do not include patient time costs. All costs are presented in Australian dollars ($AUD) and are indexed to 2016 prices.
q. FIT price based on the pricing of a commercially available alternative.[39]
r. The cost to analyse a specimen based in Australian Medicare Benefits Schedule.[40]
s. Cost to visit GP taken from Australian Medicare Benefits Schedule.[41]
t. Costs for colonoscopy are calculated based on information available from Independent Hospital Pricing Authority.[42]
u. Cost of polygenic test based on a commercially available polygenic test for breast cancer.[43]
v. Costs for complications of colonoscopy are calculated based on information available from Independent Hospital Pricing Authority.[42]
w. Cost of treatment taken from Ananda et al, 2016.[44]
x. Proportion of rectal cancer assumed to be 30.81%.[27]
y. Proportion of Stage IV cancers treated with bevacizumab assumed to be 50%.[44]

Table 6.2: Stratification of individuals according to polygenic risk and family history of colorectal cancer. [a]

Risk group	Risk category	Description	RR	PP(%)
Very Low	1	Lowest quintile for polygenic risk and no colorectal cancer in first degree relatives	0.47	20
Low	2	Second lowest quintile for polygenic risk and no colorectal cancer in first degree relatives	0.72	23
Average	3	Lowest quintile for polygenic risk and at least one colorectal cancer in first degree relative OR middle quintile for polygenic risk and no colorectal cancer in first degree relatives	0.93	18
	4	Second highest quintile for polygenic risk and no colorectal cancer in first degree relatives	1.14	14
High	5	Second lowest quintile for polygenic risk and at least one colorectal cancer in first degree relatives	1.45	3
	6	Middle quintile for polygenic risk and at least one colorectal cancer in first degree relative OR highest quintile for polygenic risk and no colorectal cancer in first degree relatives	1.70	18
Very High	7	Second highest quintile for polygenic risk and at least one colorectal cancer in first degree relatives	2.31	2
	8	Highest quintile for polygenic risk and at least one colorectal cancer in first degree relatives	3.40	2

Abbreviations: PP, Population percentage; RR, Relative risk, risk of colorectal cancer in category compared with the average risk of colorectal cancer

a. Stratification based on Jenkins et al.[14]

Assumptions for costs and utilities

The cost of screening with FIT was based on commercially available kits.[39] This cost includes the test, postage, and test processing fees. The cost to analyse a FIT specimen was based on the Australian Medicare Benefits Schedule (MBS).[40] The cost of attending a GP to obtain a referral for colonoscopy (standard consult) is set in the MBS.[41] The cost for colonoscopy and complications from colonoscopy was obtained from the Independent Hospital Pricing Authority report on costs in Australian public hospitals.[42] Costs for cancer care were based on costs of cancer treatment in the Australian setting.[44] All costs are presented in Australian dollars ($AUD), standardised to 2016 prices using the consumer price index where necessary.[45]

To determine risk, we assumed all individuals underwent assessment for family history of colorectal cancer and polygenic testing prior to the commencement of colorectal cancer screening. We assumed assessment for family history of colorectal cancer would be undertaken by a GP and cost the same as a standard consult (Table 6.1).[41] In addition, we assumed polygenic testing would cost $200 based on a commercially available polygenic test for breast cancer.[43]

The assumed utility loss due to colorectal cancer screening was 0.00274 quality-adjusted life years (QALY) per colonoscopy (1.5 days at 0.5 utility) and 0.001918 QALYs per complication of colonoscopy (14 days at 0.5 utility, Table 6.1). We also assumed that life years (LY) with colorectal cancer care are of lower quality than those without colorectal cancer care.[38] We assumed no disutility from determining or knowing polygenic risk score.

Model outcomes

For all scenarios, the model estimated health effects such as colorectal cancer incidence and colorectal cancer mortality, and required resources such as the number of screening and surveillance tests performed between ages 40 and 74 years. From these outcomes, we calculated costs, life years, and QALYs lived with each strategy. Costs, life years, and QALYs were discounted at an annual rate of 5%, as is recommended in Australia.[46] Undiscounted results are presented in the Supplementary Results (Table 6.6, Figure 6.8).

Analyses

Our analysis consisted of four parts. First, we determined costs, benefits, and harms of the aforementioned screening strategies applied to the population as a whole (uniform screening). We plotted the uniform screening scenarios in a cost-effectiveness plane and performed an incremental cost-effectiveness analysis to see which scenarios were efficient.

Second, we followed the above steps for each risk group and used these results to determine the efficient screening strategies for each risk group. Then, we combined the efficient

screening strategies for all risk groups and ordered them from least expensive to most expensive. Using this list, we developed a series of optimally personalised screening scenarios. As each personalised screening scenario can be a combination of different strategies for each risk subgroup, there will be many more personalised screening scenarios.

Third, we compared the outcomes of uniform and personalised screening to establish which method would yield better results. We did this by plotting all uniform and personalised screening scenarios in a single cost-effectiveness plane and by performing an incremental cost-effectiveness analysis to see whether personalised screening or uniform screening was most efficient.

Finally, we applied imperfect participation rates to uniform and personalised screening scenarios to determine their impact in a "real-world" scenario. The benefits and costs of screening were compared with the same population undergoing no screening.

At each step, scenarios with the highest incremental cost-effectiveness ratio (ICER) under a threshold of $50,000 per QALY gained were identified as the optimally cost-effective strategy as this is a commonly used willingness-to-pay (WTP) threshold in Australia.

Sensitivity analyses

In sensitivity analyses, we assessed the impact of weighting QALYs by age[47] (we applied age-adjusted health-related quality of life so that quality of life deceased with increasing age) and discounting our results at 3% rather than 5% as this is a common international discounting rate.[48] In addition, we explored the impact of changes in screening participation for personalised screening, holding the participation of uniform screening at current levels. To do this, we increased and decreased age-specific participation of the initial screening offer by 10 percentage points and adjusted the participation of rescreening.

Due to the uncertainty surrounding costs for determining risk profile, we also included a sensitivity analysis where these costs were excluded. Using this information, we conducted a threshold analysis to estimate the maximum cost for determining risk profile where personalised screening would be considered cost effective compared to uniform screening, at a WTP of $50,000 per QALY gained.

Results

Uniform screening

Compared with no screening, the uniform screening scenarios (Table 6.3a) reduced colorectal cancer incidence by 22%-69% (18-58 fewer colorectal cancer cases per 1,000 individuals) and mortality by 35%-79% (10-23 fewer colorectal cancer deaths). These scenarios yielded 0.11%-0.32% more QALYs (20-58 additional QALYs) and costs increased by 0.5%-424% ($6,409-

$5,277,930) per 1,000 individuals. These screening scenarios increased colonoscopy demand by 383-6,927 colonoscopies per 1,000 individuals (Table 6.3a). Several uniform screening scenarios were on the efficient frontier (Supplementary Results Figure 6.1). Using a WTP threshold of $50,000 per QALY gained, the optimal uniform screening scenario was annual FIT from 50 to 74 years (ICER $43,174). Although close to the efficient frontier, biennial FIT screening from 50 to 74 years, the screening program currently implemented in Australia, was dominated. Colonoscopy screening scenarios were the most effective, however, they also had the highest ICERs.

Optimal screening strategies per risk group

The efficient frontier included many of the same strategies for each risk group; however, the ICERs differed substantially (Supplementary Results Table 6.1, Supplementary Results Figures 6.2a-e). For example, annual screening with FIT from 54 to 74 years was on the efficient frontier for all risk groups; however, the ICERs ranged from $86,929 for those at very low risk to $3,687 for those at very high risk. Considering a WTP threshold of $50,000 per QALY gained, the optimal screening strategy for those at very low risk was biennial FIT from 54 to 74 years (ICER $33,639), whereas for those at highest risk, the optimal strategy was 5-yearly colonoscopy from 50 to 74 years (ICER $39,568). Biennial FIT screening was only on the efficient frontier for the very low risk group (ICER $63,911).

Personalised screening

Using these efficient strategies, 39 personalised screening scenarios were created (Table 4). These scenarios (Table 6.5a) reduced colorectal cancer incidence by 4%-68% (3-57 fewer colorectal cancer cases per 1,000 individuals) and mortality by 5%-79% (2-23 fewer deaths). In addition, they yielded 0.02%-0.32% more QALYs (3-58 additional QALYs) and increased costs by 19%-432% ($233,599-$5,330,249). The personalised screening scenarios increased colonoscopy demand by 45-6,698 colonoscopies per 1,000 individuals (Table 6.5a).

At a WTP threshold of $50,000 per QALY gained, the optimal personalised screening scenario consisted of the following: those at very low risk or low risk, screening should start at age 54 years with biennial and annual FIT, respectively, those at average and high risk, screening should start at age 50 years with annual FIT, and those at very high risk, screening should start at age 50 years with 5-yearly colonoscopy (ICER $45,682).

Table 6.3: Costs and effects (discounted at 5%) per 1,000 simulated 40-year-olds of all uniform screening scenarios assuming a) perfect adherence and b) realistic adherence.

a. Assuming perfect adherence.

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
No Screening			0	84	0.07	84	29	17,872	17,847	1,234,089	
FIT	60	3	3,981	467	0.24	66	19	17,889	17,867	1,240,498	317
FIT	60	2	5,935	576	0.27	62	16	17,892	17,871	1,256,805	4,314
FIT	54	3	5,571	561	0.28	64	18	17,894	17,873	1,304,332	Dominated
FIT	60	1	9,954	777	0.34	56	15	17,895	17,875	1,327,965	Dominated
FIT	54	2	8,101	695	0.32	59	16	17,898	17,878	1,343,651	11,768
FIT	50	3	6,990	625	0.30	63	17	17,897	17,877	1,371,842	Dominated
FIT	50	2	9,473	759	0.34	59	15	17,901	17,881	1,436,505	Dominated
FIT	46	3	7,789	660	0.29	63	17	17,898	17,878	1,462,077	Dominated
FIT	54	1	13,381	953	0.40	53	14	17,902	17,884	1,480,562	23,324
FIT	46	2	10,767	811	0.35	59	16	17,902	17,883	1,556,681	Dominated
FIT	50	1	15,397	1,042	0.43	53	14	17,905	17,887	1,634,262	43,174
FIT	40	3	9,187	707	0.30	64	18	17,899	17,879	1,635,282	Dominated
FIT	40	2	12,532	868	0.36	60	16	17,903	17,884	1,789,931	Dominated
COL	60	10	0	2,198	0.60	42	11	17,900	17,881	1,789,986	Dominated
FIT	46	1	17,171	1,109	0.44	54	14	17,906	17,889	1,830,442	122,612
COL	60	5	0	3,048	0.82	37	10	17,902	17,883	2,117,448	Dominated
FIT	40	1	19,338	1,165	0.44	57	16	17,906	17,888	2,201,540	Dominated
COL	54	10	0	2,928	0.86	39	10	17,907	17,889	2,294,199	Dominated
COL	50	10	0	3,245	0.91	37	9	17,911	17,893	2,706,770	Dominated
COL	54	5	0	4,540	1.16	31	7	17,911	17,894	3,016,912	Dominated
COL	46	10	0	3,341	1.01	39	10	17,912	17,895	3,181,465	Dominated
COL	50	5	0	5,012	1.24	29	7	17,916	17,899	3,664,480	184,883
COL	40	10	0	4,269	1.09	36	9	17,916	17,898	4,319,443	Dominated
COL	46	5	0	5,700	1.35	30	7	17,919	17,902	4,593,188	349,139
COL	40	5	0	7,011	1.57	26	6	17,924	17,904	6,462,019	648,900

b. Assuming realistic adherence.

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
No Screening			0	84	0.07	84	29	17,872	17,847	1,234,089	Dominated
FIT	60	3	1,952	228	0.14	77	24	17,879	17,855	1,249,846	1,936
FIT	60	2	3,022	285	0.16	74	23	17,881	17,857	1,259,357	3,446
FIT	54	3	2,488	255	0.15	76	24	17,880	17,857	1,278,301	Dominated
FIT	60	1	5,427	398	0.21	69	20	17,885	17,863	1,292,600	6,544
FIT	54	2	3,931	328	0.18	73	22	17,884	17,860	1,300,838	Dominated
FIT	50	3	3,253	288	0.17	75	23	17,882	17,859	1,310,216	Dominated
FIT	50	2	4,721	361	0.19	72	22	17,885	17,863	1,346,432	Dominated
FIT	46	3	3,691	305	0.16	75	23	17,883	17,860	1,351,925	Dominated
FIT	54	1	7,355	478	0.24	67	19	17,890	17,868	1,373,779	15,702
FIT	46	2	5,504	390	0.20	72	22	17,887	17,864	1,407,164	Dominated
FIT	40	3	4,500	332	0.17	75	23	17,884	17,861	1,435,530	Dominated
FIT	50	1	8,779	529	0.26	66	19	17,892	17,871	1,459,998	29,326
COL	60	10	0	987	0.30	65	21	17,884	17,862	1,460,994	Dominated
FIT	40	2	6,651	425	0.21	72	22	17,888	17,866	1,528,067	Dominated
COL	54	10	0	1,048	0.35	67	21	17,884	17,862	1,550,987	Dominated
FIT	46	1	10,156	573	0.27	66	19	17,894	17,873	1,572,125	56,064
COL	60	5	0	1,413	0.45	60	18	17,887	17,865	1,592,938	Dominated
COL	50	10	0	1,176	0.37	65	21	17,886	17,864	1,679,843	Dominated
FIT	40	1	12,108	626	0.28	67	19	17,895	17,874	1,792,630	151,031
COL	54	5	0	1,825	0.55	57	17	17,890	17,869	1,821,556	Dominated
COL	46	10	0	1,215	0.43	66	21	17,887	17,865	1,831,735	Dominated
COL	50	5	0	2,040	0.60	55	17	17,893	17,873	2,050,622	Dominated
COL	40	10	0	1,622	0.47	62	19	17,890	17,868	2,218,841	Dominated
COL	46	5	0	2,377	0.67	53	16	17,896	17,876	2,395,405	Dominated
COL	40	5	0	2,986	0.79	50	15	17,901	17,880	3,102,085	221,941

Abbreviations: COL, colonoscopy; CRC, colorectal cancer, FIT, faecal immunological test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Grey shading highlights uniform screening scenarios on the efficient frontier prior to considering personalised screening.

a. Results are discounted at an annual rate of 5%.

b. Costs are presented in Australian Dollars ($AUD).

UNIFORM SCREENING VERSUS PERSONALISED SCREENING

When compared, personalised and uniform screening scenarios similarly reduced colorectal cancer incidence and mortality and yielded similar QALYs. Personalised screening more efficiently allocated colonoscopy demand; however, it cost more than uniform screening, due to the cost of determining risk. Although several scenarios from each type of screening were on the efficient frontier (Figure 6.1a), all of the personalised screening scenarios had an ICER above $100,000 and would therefore not be considered cost effective. At a WTP threshold of $50,000 per QALY gained, the optimal screening scenario was annual FIT screening from 50 to 74 years.

REALISTIC ADHERENCE

As might be expected, the application of realistic participation rates decreased the health benefits as well as the costs of all screening scenarios. At this level of participation, none of the personalised screening scenarios were cost effective compared with uniform screening (Figure 6.1b).

SENSITIVITY ANALYSES

Our results were not sensitive to changes in discounting, weighting of QALYs or adjustments to rates of participation (Supplementary Results Tables 6.2-6.5, Supplementary Results Figures 6.3-6.6). However, excluding the costs of determining polygenic risk had a significant impact on our results with personalised screening dominating uniform screening scenarios at both perfect (Figure 6.1c) and realistic adherence (Supplementary Results Figure 6.7). The threshold analysis indicated that for personalised screening to be cost effective compared to uniform screening at the WTP of $50,000 per QALY gained, the cost for determining risk should not exceed $47.52 (Supplementary Results Table 6.8).

DISCUSSION

We investigated the impact of personalising colorectal cancer screening based on polygenic risk and family history. We found that uniform screening was equally effective (cancers and deaths prevented) but more cost effective than personalised screening. Although personalised and uniform screening showed similar reductions in colorectal cancer incidence and mortality and similar gains in QALYs, personalised screening incurred additional costs resulting from the whole population undergoing testing to determine their colorectal cancer risk.

Table 6.4: Specifics of the personalised screening scenarios, when costs and QALYs are discounted at 5%. All screening ends at or before the age of 74 years.

Screening Strategy	Risk Groups				
	Very Low	Low	Average	High	Very High
PS1	NoScr	NoScr	NoScr	NoScr	FIT-60-1
PS2	NoScr	NoScr	NoScr	NoScr	FIT-54-1
PS3	NoScr	NoScr	NoScr	FIT-60-2	FIT-54-1
PS4	NoScr	NoScr	NoScr	FIT-60-1	FIT-54-1
PS5	NoScr	NoScr	NoScr	FIT-54-2	FIT-54-1
PS6	NoScr	NoScr	NoScr	FIT-54-1	FIT-54-1
PS7	NoScr	NoScr	FIT-60-2	FIT-54-1	FIT-54-1
PS8	NoScr	NoScr	FIT-54-2	FIT-54-1	FIT-54-1
PS9	NoScr	NoScr	FIT-54-2	FIT-54-1	FIT-50-1
PS10	NoScr	FIT-60-2	FIT-54-2	FIT-54-1	FIT-50-1
PS11	NoScr	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1
PS12	NoScr	FIT-54-2	FIT-54-1	FIT-54-1	FIT-50-1
PS13	NoScr	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1
PS14	FIT-54-3	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1
PS15	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1
PS16	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1	COL-54-5
PS17	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1	COL-50-5
PS18	FIT-54-2	FIT-54-1	FIT-54-1	FIT-50-1	COL-50-5
PS19	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5
PS20	FIT-54-2	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5
PS21	FIT-50-2	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5
PS22	FIT-50-2	FIT-50-1	FIT-50-1	COL-50-5	COL-50-5
PS23	FIT-50-2	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5
PS24	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5
PS25	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5
PS26	FIT-50-1	FIT-50-1	FIT-46-1	COL-50-5	COL-46-5
PS27	FIT-50-1	FIT-50-1	FIT-46-1	COL-50-5	COL-40-5
PS28	FIT-50-1	FIT-50-1	FIT-46-1	COL-46-5	COL-40-5
PS29	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5	COL-40-5
PS30	FIT-50-1	FIT-46-1	COL-50-5	COL-46-5	COL-40-5
PS31	FIT-46-1	FIT-46-1	COL-50-5	COL-46-5	COL-40-5
PS32	FIT-46-1	FIT-46-1	COL-50-5	COL-40-5	COL-40-5
PS33	FIT-46-1	FIT-46-1	COL-46-5	COL-40-5	COL-40-5
PS34	FIT-46-1	COL-50-5	COL-46-5	COL-40-5	COL-40-5
PS35	FIT-46-1	COL-46-5	COL-46-5	COL-40-5	COL-40-5
PS36	FIT-46-1	COL-46-5	COL-40-5	COL-40-5	COL-40-5
PS37	COL-50-5	COL-46-5	COL-40-5	COL-40-5	COL-40-5
PS38	COL-50-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5
PS39	COL-46-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5

Abbreviations: COL, colonoscopy; FIT, faecal immunochemical test, NoScr, no screening
Screening strategies: Screening test-screening start age-screening interval

Table 6.5: Costs and effects (discounted at 5%) of per 1,000 simulated 40-year-olds of all personalised screening scenarios assuming a) perfect adherence and b) realistic adherence.

a. Assuming perfect adherence.

Screening Strategy	FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
No Screening	0	84	0.07	84	29	17,872	17,847	1,234,089	
PS01	360	130	0.09	81	27	17,874	17,850	1,467,668	Dominated
PS02	515	141	0.10	81	27	17,875	17,851	1,471,312	Dominated
PS03	1,722	276	0.16	73	23	17,882	17,859	1,505,808	Dominated
PS04	2,554	324	0.18	71	22	17,883	17,860	1,513,829	Dominated
PS05	2,190	305	0.18	72	23	17,884	17,861	1,520,843	Dominated
PS06	3,322	368	0.20	70	22	17,885	17,863	1,542,584	Dominated
PS07	5,226	525	0.27	63	18	17,891	17,871	1,628,434	Dominated
PS08	5,920	562	0.28	63	18	17,893	17,873	1,656,571	Dominated
PS09	6,017	568	0.28	63	18	17,894	17,873	1,662,780	15,998
PS10	7,406	663	0.32	59	16	17,897	17,877	1,734,789	19,167
PS11	7,898	687	0.33	59	16	17,898	17,878	1,756,804	19,251
PS12	9,596	770	0.35	57	15	17,899	17,880	1,801,421	24,261
PS13	10,057	792	0.36	57	15	17,900	17,881	1,834,425	28,076
PS14	11,189	859	0.38	55	14	17,902	17,884	1,911,354	32,041
PS15	11,700	881	0.39	55	14	17,902	17,884	1,924,610	33,605
PS16	11,089	991	0.43	52	14	17,903	17,885	1,952,870	38,059
PS17	11,089	1,023	0.44	52	13	17,903	17,885	1,978,086	39,563
PS18	12,293	1,078	0.45	51	13	17,904	17,886	2,013,777	39,692
PS19	12,939	1,106	0.46	51	13	17,905	17,887	2,063,215	45,682
PS20	13,382	1,125	0.47	51	13	17,905	17,888	2,098,112	63,213
PS21	13,646	1,136	0.47	51	13	17,906	17,888	2,116,904	64,062
PS22	10,378	1,951	0.68	43	11	17,909	17,893	2,487,033	81,839
PS23	10,378	1,969	0.69	43	11	17,910	17,893	2,519,388	82,386
PS24	11,148	2,001	0.69	43	11	17,910	17,893	2,534,168	86,970
PS25	11,518	2,017	0.70	43	11	17,910	17,894	2,564,321	95,845
PS26	12,085	2,037	0.70	43	11	17,911	17,894	2,627,025	127,618
PS27	12,085	2,100	0.71	43	11	17,911	17,895	2,699,821	135,361
PS28	12,085	2,209	0.74	43	11	17,912	17,896	2,880,990	172,640
PS29	6,575	3,465	0.99	35	9	17,915	17,899	3,469,210	180,219
PS30	6,964	3,480	0.99	35	9	17,915	17,899	3,512,866	181,642
PS31	7,289	3,492	1.00	35	9	17,916	17,899	3,549,627	226,549
PS32	7,289	3,804	1.05	34	8	17,917	17,901	3,943,469	282,951

PS33	7,289	4,017	1.09	34	8	17,918	17,902	4,238,838	349,821
PS34	3,372	4,929	1.25	30	7	17,920	17,903	4,694,318	370,115
PS35	3,372	5,105	1.28	30	7	17,920	17,903	4,915,213	696,391
PS36	3,372	5,531	1.35	29	7	17,922	17,904	5,515,822	707,094
PS37	0	6,328	1.47	27	6	17,922	17,904	5,935,615	1,808,159
PS38	0	6,612	1.51	27	6	17,923	17,904	6,365,416	2,057,076
PS39	0	6,782	1.54	27	6	17,923	17,905	6,564,338	3,860,049

b. Assuming realistic adherence.

Screening Strategy	FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
No Screening	0	84	0.07	84	29	17,872	17,847	1,234,089	
PS01	203	107	0.08	82	28	17,873	17,848	1,473,736	Dominated
PS02	283	112	0.08	82	28	17,874	17,849	1,475,367	Dominated
PS03	908	168	0.11	79	26	17,877	17,853	1,521,883	Dominated
PS04	1,402	198	0.13	77	25	17,878	17,854	1,523,703	Dominated
PS05	1,101	180	0.12	78	25	17,878	17,854	1,529,310	Dominated
PS06	1,814	218	0.14	76	25	17,880	17,856	1,538,207	Dominated
PS07	2,783	282	0.17	73	23	17,882	17,859	1,623,617	Dominated
PS08	3,074	296	0.17	73	22	17,883	17,860	1,637,150	Dominated
PS09	3,134	299	0.18	73	22	17,883	17,861	1,640,166	Dominated
PS10	3,834	337	0.19	71	21	17,885	17,862	1,705,874	Dominated
PS11	4,042	345	0.19	71	21	17,885	17,863	1,716,293	Dominated
PS12	5,140	393	0.21	69	20	17,887	17,865	1,740,403	Dominated
PS13	5,447	405	0.22	69	20	17,888	17,866	1,757,876	26,955
PS14	5,946	428	0.23	68	20	17,889	17,867	1,820,048	Dominated
PS15	6,239	439	0.23	68	20	17,889	17,867	1,827,488	Dominated
PS16	5,897	479	0.25	67	20	17,889	17,867	1,832,472	Dominated
PS17	5,897	494	0.25	67	20	17,889	17,867	1,840,654	Dominated
PS18	6,688	525	0.26	66	19	17,890	17,869	1,861,200	Dominated
PS19	7,144	541	0.27	66	19	17,891	17,869	1,888,754	37,121
PS20	7,468	552	0.27	66	19	17,891	17,870	1,909,081	43,619
PS21	7,625	557	0.27	66	19	17,891	17,870	1,918,670	50,380
PS22	5,787	873	0.37	62	18	17,892	17,871	2,021,485	Dominated
PS23	5,787	885	0.37	62	18	17,892	17,872	2,032,352	Dominated
PS24	6,320	903	0.37	61	18	17,893	17,872	2,043,097	Dominated
PS25	6,598	911	0.38	61	18	17,893	17,872	2,060,946	Dominated
PS26	7,039	925	0.38	61	18	17,893	17,873	2,096,862	Dominated
PS27	7,039	955	0.39	61	18	17,894	17,873	2,123,266	Dominated
PS28	7,039	1,016	0.41	60	17	17,895	17,875	2,188,845	61,316

PS29	3,785	1,489	0.51	56	17	17,895	17,875	2,342,739	Dominated
PS30	4,097	1,499	0.52	56	17	17,895	17,875	2,368,540	Dominated
PS31	4,366	1,507	0.52	56	17	17,895	17,875	2,390,967	Dominated
PS32	4,366	1,654	0.55	55	16	17,897	17,877	2,539,024	Dominated
PS33	4,366	1,759	0.58	55	16	17,898	17,878	2,648,884	148,949
PS34	2,029	2,100	0.64	53	16	17,898	17,878	2,770,951	Dominated
PS35	2,029	2,182	0.66	53	16	17,898	17,878	2,854,071	Dominated
PS36	2,029	2,380	0.69	52	15	17,899	17,879	3,081,587	268,852
PS37	0	2,675	0.74	51	15	17,899	17,879	3,196,125	Dominated
PS38	0	2,805	0.76	50	15	17,900	17,880	3,359,342	Dominated
PS39	0	2,883	0.78	50	15	17,900	17,880	3,434,699	677,027

Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; PS, personalised screening; QALY, quality-adjusted life years

Grey shading highlights screening scenarios on the efficient frontier prior to considering uniform screening.

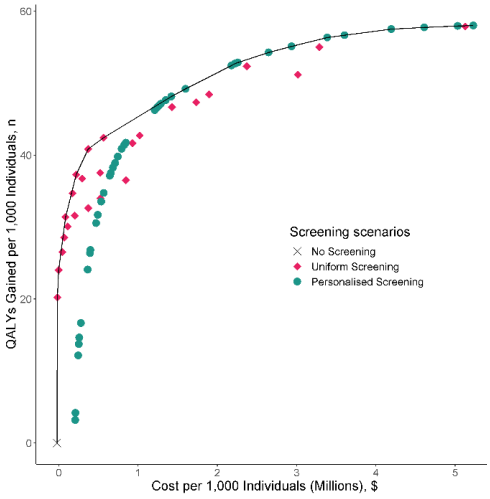
a. Results are discounted at an annual rate of 5%.

b. Costs are presented in Australian Dollars ($AUD).

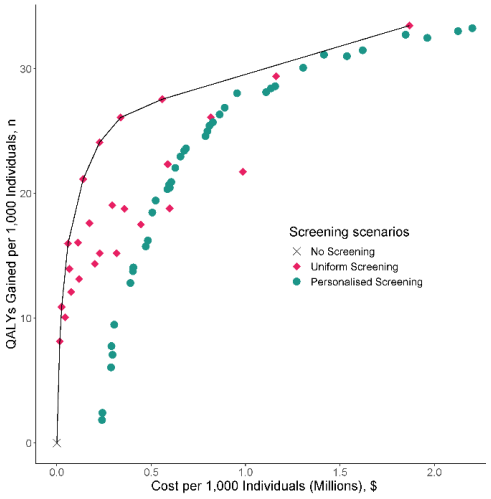
c. The personalised screening scenarios are described in Table 6.4.

Figure 6.1: Costs and quality-adjusted life years (discounted at 5%) per 1,000 40-year-olds for all uniform and personalised colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies[a] assuming: a) perfect adherence; b) realistic adherence and c) perfect adherence and no costs associated with determining risk.

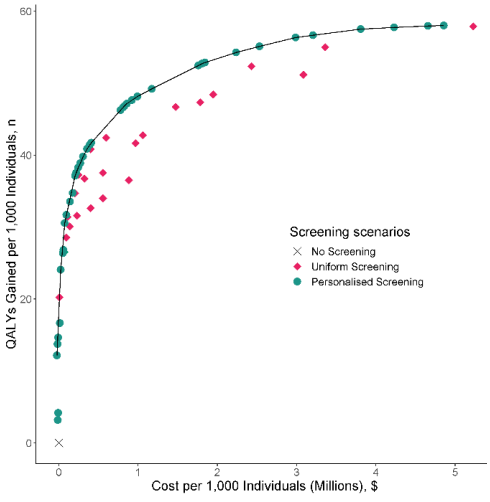
a. Perfect adherence.



b. Realistic adherence.



c. Perfect adherence and no costs for determining risk.



Abbreviations: QALY, quality-adjusted life years

Note: A description of the personalised screening scenarios can be found in Table 6.4.

a. Discounted costs and life years gained reflect total costs and life years gained of a screening program, accounting for time preference for present over future outcomes. Quality-adjusted life years gained are plotted on the y-axis, and total costs are plotted on the x-axis. Each possible screening strategy is represented by a point. Strategies that form the solid line connecting the points lying left and upward are the economically rational subset of choices. This line is called the efficient frontier. The inverse slope of the line represents the incremental cost-effectiveness ratio of the connected strategies. Points lying to the right and beneath the line represent the dominated strategies.

The concept of personalised screening is promising and has previously been shown to be more effective than a strategy based on age alone.[7, 21-23] Our results add support to these findings. However, our results do not align with recent findings that risk-stratified screening based on polygenic risk profile for breast cancer is cost effective compared with the standard age-based screening program.[49] This discrepancy may be due to differences in the discriminatory performance of risk-stratification algorithms or differences in the cost for determining risk, which was substantially lower in this analysis (£50 or ~$90) than in ours (~$240). However, it is difficult to accurately determine how much of the cost for establishing risk should be allocated to a screening program. The cost of polygenic testing varies widely[50] and there is potential to combine testing for other cancers. Given this difficulty and because cost-effectiveness of personalised screening is highly dependent on these additional costs, we assessed the impact of excluding them. We found that when these costs were excluded, personalised screening was cost effective. The threshold analysis suggested that at a WTP of $50,000 per QALY gained, the cost to determine risk should not exceed ~$48, which is significantly lower than the cost assumed in this analysis.

The effectiveness of personalised screening will be affected by the precision with which the population is stratified.[15] This will be affected by both the accuracy of the metric used to stratify the population and the proportion of the population willing to undertake polygenic testing. Although our results appear unfavourable, the advantage of screening based on polygenic risk and family history remains limited largely because the current contribution of known SNPs to colorectal cancer risk is modest.[9, 10, 51] As new SNPs are identified, the discriminatory utility of polygenic testing will increase and the performance of risk assessment based on this metric could improve.[15] The inclusion of other factors in risk assessment, such as obesity and smoking status, may also enhance the discriminatory performance of personalised screening.[13, 52, 53] It may also be pertinent to consider results from an individual's screening history. As these factors will vary over an individual's lifespan, assessment of risk may need to become more dynamic in nature, and although such inclusions will present challenges, they will likely improve the harm–benefit ratio of colorectal cancer screening.

In addition, although genetic testing for colorectal cancer has been shown to be acceptable to the community,[54] individuals may not always be willing to undergo testing, for a variety of reasons, including concerns over privacy, possible misuse of data, and potential negative psychological impacts of findings.[55-57] For this analysis, we assumed all individuals would undergo testing to determine their risk profile; however, due consideration of how to manage this issue is required.

The benefits of population screening are largely dependent on participation. With many countries already experiencing suboptimal levels of participation in routine age-based screening for colorectal cancer,[33, 58] personalised screening presents an interesting

proposition. On the one hand, increasing the complexity of screening may reduce participation in screening, thereby diminishing the modest benefits. However, individuals at increased risk of colorectal cancer have been shown to be more compliant to screening guidelines than those at average risk,[59] suggesting that the provision of risk information may assist in screening uptake.[16, 60] Coupled with evidence that involvement of GPs improves participation in colorectal cancer screening,[61] a simple risk assessment has the potential to positively affect screening participation.[62] When we applied realistic rates of participation, we found that personalised screening remained suboptimal compared to uniform screening, even when participation in personalised screening was improved (Supplementary Results Figure 6.6). This suggests that at present, increasing participation in uniform screening will likely yield better results.

Screening effectiveness will also be affected by the choice of screening test and screening frequency. This will largely be determined by a health systems capacity to provide a given intervention to its population. Our analysis indicates that screening scenarios utilising colonoscopy are the most effective scenarios. However, as would be expected, these scenarios significantly increase colonoscopy utilisation. Although personalised screening more efficiently allocated colonoscopy utilisation compared to uniform screening, such increases in demand will likely be infeasible, especially in countries with limited colonoscopy capacity.

Moving from an age-based screening program will result in a redistribution of the harms and benefits. This raises ethical issues as although personalised screening may be optimal at a population level, individuals may experience increased harms or reduced benefits as a result of their screening protocol. As would be expected, our analysis indicates that when individuals undergo less frequent screening (either by starting screening later or by having a longer screening interval) they experience higher colorectal cancer incidence and mortality. However, this will be partly offset by a reduction in other harms such as invasive tests, false-positive test results, adverse events, anxiety, and inconvenience. These concerns hold for the inclusion of younger individuals, although recent evidence suggests that their inclusion is favourable.[63]

Limitations exist with our research. First, we only considered a limited number of risk categories. Effectiveness and cost-effectiveness could be further improved as the discriminatory performance of risk stratification improves. Second, we only included a limited number of low-intensity screening strategies. It is possible that other low-intensity screening strategies, such as one-off colonoscopy or less frequent FIT screening would be more efficient. Third, we did not compare the (cost-) effectiveness of stratifying the population based on family history alone. However, as the aim of this research was to explore the possible implications of combining SNPs and family history in a risk assessment, and, as determining polygenic risk is assumed to be quite expensive, such a comparison would potentially make

this analysis look even less cost effective. Finally, there is some uncertainty regarding the assumptions for participation in screening. We assumed that participation in screening of any form would be equal to participation in uniform biennial FIT screening. However this is unlikely as participation in screening varies widely.[5] Unfortunately, to date, there are few data examining multiple screening modalities within one population to adequately address this concern.

In summary, this research presents an exploration of the possible impact of personalised screening for colorectal cancer based on polygenic risk and family history. Our results suggest that although personalising screening based on colorectal cancer risk is slightly more effective than screening based on age alone, it is currently not necessarily cost effective. Cost-effectiveness of personalised screening will depend on the costs of determining risk and the magnitude of the benefits of personalisation. Our analysis suggests that the currently assumed cost of determining risk is too high compared to the gains, and costs must be substantially lower for personalised screening to become cost effective. The balance of cost and benefits will be contingent on the discriminatory performance of risk-stratification algorithms on polygenic risk and family history, which remains sub-optimal.

However, we cannot ignore the changing landscape that advances in technology provide and, as improvements in risk stratification occur and costs for polygenic testing decrease, personalising screening will become an increasingly cost effective and attractive option. This consortium of researchers, and others, have previously called for the concept of personalised screening to be brought to the attention of key stakeholders.[15, 64] Our research seeks to highlight the possible implications of personalised screening based on risk assessment, which we believe can and will play a significant role in improving our screening programs. As such, we reiterate our call that key stakeholders carefully consider the evidence for personalised screening in order to effectively plan for the future.

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SUPPLEMENTARY RESULTS

Supplementary Results Table 6.1: Risk group level cost and effects (discounted at 5%) of 25 screening scenarios and a scenario without screening, per 1,000 simulated 40-year-olds, assuming perfect adherence.

a. Effects of screening for the very low risk group.

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
No Screening			0	36	0.03	36	12	17,910	17,899	531,056	
FIT	60	3	4,087	294	0.11	28	8	17,917	17,908	841,686	Dominated
FIT	60	2	6,110	385	0.13	26	7	17,919	17,909	881,028	Dominated
FIT	54	3	5,661	370	0.14	27	7	17,920	17,911	915,641	31,995
FIT	50	3	7,061	428	0.15	26	7	17,921	17,912	989,979	Dominated
FIT	54	2	8,219	482	0.16	25	6	17,921	17,913	981,909	33,639
FIT	60	1	10,181	559	0.17	24	6	17,920	17,911	983,128	Dominated
FIT	46	3	7,835	460	0.15	26	7	17,922	17,913	1,075,629	Dominated
FIT	50	2	9,538	538	0.17	25	6	17,923	17,914	1,075,858	63,911
FIT	46	2	10,778	588	0.18	25	6	17,923	17,915	1,192,966	Dominated
FIT	54	1	13,384	701	0.20	22	6	17,923	17,915	1,149,747	86,929
FIT	40	3	9,205	511	0.16	27	7	17,922	17,913	1,243,293	Dominated
FIT	50	1	15,233	778	0.22	22	6	17,925	17,917	1,300,489	96,014
FIT	40	2	12,485	649	0.19	25	7	17,924	17,915	1,417,130	Dominated
FIT	46	1	16,858	841	0.24	23	6	17,925	17,917	1,484,265	226,884
COL	60	10	0	1,978	0.34	18	5	17,922	17,913	1,527,701	Dominated
FIT	40	1	18,889	909	0.24	24	7	17,925	17,917	1,833,001	Dominated
COL	60	5	0	2,868	0.52	16	4	17,923	17,913	1,923,484	Dominated
COL	54	10	0	2,808	0.52	17	4	17,925	17,916	2,090,952	Dominated
COL	50	10	0	2,991	0.55	16	4	17,927	17,917	2,480,460	Dominated
COL	46	10	0	3,069	0.66	17	4	17,928	17,918	2,939,036	Dominated
COL	54	5	0	4,556	0.80	13	3	17,927	17,917	2,958,508	Dominated
COL	50	5	0	4,828	0.84	13	3	17,929	17,919	3,582,891	1,793,697
COL	40	10	0	4,003	0.70	15	4	17,929	17,918	4,102,124	Dominated
COL	46	5	0	5,681	0.97	13	3	17,930	17,919	4,577,339	3,977,790
COL	40	5	0	6,824	1.14	12	3	17,932	17,918	6,435,949	Dominated

b. Effects of screening for the low risk group.

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
No Screening			0	57	0.05	57	20	17,893	17,876	840,912	
FIT	60	3	4,042	372	0.17	45	13	17,905	17,890	1,124,633	Dominated
FIT	60	2	6,037	471	0.19	42	11	17,907	17,892	1,153,974	19,124
FIT	54	3	5,625	455	0.20	44	12	17,909	17,894	1,195,225	Dominated
FIT	60	1	10,097	658	0.25	38	10	17,909	17,895	1,242,543	Dominated
FIT	54	2	8,175	577	0.23	40	11	17,911	17,897	1,249,685	19,258
FIT	50	3	7,035	515	0.22	43	12	17,911	17,897	1,266,575	Dominated
FIT	50	2	9,519	636	0.24	40	11	17,913	17,900	1,343,028	Dominated
FIT	46	3	7,821	549	0.21	43	12	17,911	17,898	1,353,677	Dominated
FIT	54	1	13,410	815	0.29	36	9	17,914	17,901	1,404,854	39,685
FIT	46	2	10,784	687	0.26	40	11	17,914	17,901	1,461,318	Dominated
FIT	40	3	9,203	597	0.22	44	12	17,912	17,898	1,524,008	Dominated
FIT	50	1	15,338	897	0.32	36	9	17,916	17,904	1,556,566	63,213
FIT	40	2	12,517	746	0.26	41	11	17,915	17,902	1,689,545	Dominated
FIT	46	1	17,029	960	0.33	37	10	17,917	17,905	1,746,359	182,494
COL	60	10	0	2,087	0.46	29	8	17,912	17,899	1,751,467	Dominated
FIT	40	1	19,117	1,022	0.33	39	11	17,917	17,904	2,104,788	Dominated
COL	60	5	0	2,961	0.66	26	7	17,914	17,900	2,116,045	Dominated
COL	54	10	0	2,858	0.68	26	7	17,917	17,905	2,284,883	Dominated
COL	50	10	0	3,113	0.71	25	6	17,920	17,907	2,688,824	Dominated
COL	54	5	0	4,549	0.96	21	5	17,920	17,907	3,086,369	Dominated
COL	46	10	0	3,197	0.82	27	7	17,921	17,908	3,155,140	Dominated
COL	50	5	0	4,923	1.02	20	5	17,923	17,910	3,726,554	370,130
COL	40	10	0	4,129	0.88	24	6	17,924	17,909	4,306,323	Dominated
COL	46	5	0	5,688	1.14	20	5	17,926	17,912	4,686,894	695,898
COL	40	5	0	6,920	1.33	18	4	17,929	17,912	6,555,452	2,053,361

c. Effects of screening for the average risk group.

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
No Screening			0	83	0.07	83	28	17,873	17,848	1,211,915	
FIT	60	3	3,988	464	0.24	65	18	17,889	17,868	1,462,876	Dominated
FIT	60	2	5,948	573	0.27	61	16	17,892	17,871	1,480,195	11,509
FIT	54	3	5,580	556	0.27	64	18	17,894	17,874	1,527,861	Dominated
FIT	60	1	9,987	776	0.34	56	14	17,896	17,876	1,552,752	Dominated
FIT	54	2	8,119	690	0.31	59	16	17,898	17,879	1,568,124	12,402
FIT	50	3	7,001	619	0.30	62	17	17,897	17,877	1,595,055	Dominated
FIT	50	2	9,492	753	0.33	59	15	17,901	17,882	1,661,451	Dominated
FIT	46	3	7,800	654	0.29	63	17	17,899	17,879	1,685,377	Dominated
FIT	54	1	13,427	950	0.40	53	14	17,902	17,884	1,707,549	24,290
FIT	46	2	10,786	805	0.35	59	16	17,902	17,884	1,781,135	Dominated
FIT	40	3	9,197	701	0.29	64	18	17,899	17,880	1,858,394	Dominated
FIT	50	1	15,446	1,037	0.42	53	14	17,905	17,888	1,862,042	45,573
FIT	40	2	12,549	861	0.35	60	16	17,903	17,884	2,013,880	Dominated
COL	60	10	0	2,210	0.61	42	11	17,900	17,881	2,017,744	Dominated
FIT	46	1	17,217	1,103	0.44	54	14	17,907	17,889	2,057,988	128,069
COL	60	5	0	3,065	0.82	37	9	17,902	17,884	2,345,635	Dominated
FIT	40	1	19,373	1,158	0.43	57	16	17,906	17,888	2,427,946	Dominated
COL	54	10	0	2,920	0.86	38	10	17,907	17,890	2,518,294	Dominated
COL	50	10	0	3,253	0.91	37	9	17,911	17,894	2,936,137	Dominated
COL	54	5	0	4,540	1.16	30	7	17,912	17,895	3,241,023	Dominated
COL	46	10	0	3,344	1.00	39	10	17,913	17,895	3,410,330	Dominated
COL	50	5	0	5,029	1.24	29	7	17,916	17,899	3,896,161	180,213
COL	40	10	0	4,275	1.08	35	9	17,916	17,898	4,548,108	Dominated
COL	46	5	0	5,697	1.35	29	7	17,919	17,902	4,819,181	349,629
COL	40	5	0	7,028	1.56	26	6	17,924	17,905	6,696,070	708,260

d. Effects of screening for the high risk group.

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
No Screening			0	135	0.11	135	46	17,832	17,792	1,975,690	
FIT	60	2	5,749	777	0.42	99	27	17,864	17,830	2,139,982	4,300
FIT	60	3	3,870	649	0.38	106	30	17,859	17,824	2,148,370	Dominated
FIT	60	1	9,707	1,007	0.52	90	23	17,870	17,837	2,178,183	5,141
FIT	54	3	5,474	762	0.43	103	29	17,867	17,834	2,200,583	Dominated
FIT	54	2	7,976	919	0.48	96	25	17,873	17,842	2,211,588	7,751
FIT	50	3	6,913	833	0.46	101	27	17,872	17,839	2,261,428	Dominated
FIT	50	2	9,403	991	0.51	95	25	17,878	17,847	2,303,291	Dominated
FIT	54	1	13,369	1,217	0.61	86	22	17,881	17,851	2,315,132	10,752
FIT	46	3	7,739	870	0.45	102	28	17,874	17,842	2,356,947	Dominated
FIT	46	2	10,752	1,046	0.53	96	25	17,880	17,850	2,427,374	Dominated
FIT	50	1	15,562	1,321	0.65	86	22	17,885	17,857	2,472,317	28,069
FIT	40	3	9,167	914	0.45	103	29	17,875	17,843	2,534,984	Dominated
COL	60	10	0	2,425	0.88	68	18	17,877	17,847	2,551,250	Dominated
FIT	40	2	12,580	1,098	0.53	98	26	17,881	17,851	2,670,407	Dominated
FIT	46	1	17,495	1,391	0.66	87	23	17,887	17,859	2,682,285	Dominated
COL	60	5	0	3,231	1.13	59	15	17,880	17,852	2,806,337	Dominated
COL	54	10	0	3,059	1.22	62	16	17,888	17,861	2,996,730	Dominated
FIT	40	1	19,807	1,436	0.65	92	26	17,886	17,858	3,076,509	Dominated
COL	50	10	0	3,507	1.30	59	15	17,894	17,868	3,430,659	Dominated
COL	54	5	0	4,524	1.53	49	12	17,895	17,870	3,565,696	Dominated
COL	46	10	0	3,623	1.37	63	17	17,897	17,871	3,922,409	Dominated
COL	50	5	0	5,199	1.66	46	11	17,902	17,878	4,235,107	81,838
COL	40	10	0	4,544	1.49	57	14	17,903	17,877	5,033,423	Dominated
COL	46	5	0	5,719	1.76	48	12	17,907	17,883	5,097,948	172,568
COL	40	5	0	7,201	2.03	42	10	17,915	17,890	6,973,676	282,915

e. Effects of screening for the very high risk group.

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
No Screening			0	222	0.18	222	76	17,756	17,689	3,296,374	Dominated
FIT	60	1	9,016	1,358	0.81	144	37	17,822	17,768	3,209,564	Dominates
FIT	60	2	5,345	1,101	0.68	159	42	17,813	17,756	3,231,453	Dominated
FIT	54	2	7,610	1,292	0.78	152	40	17,829	17,777	3,268,440	Dominated
FIT	60	3	3,638	950	0.62	170	48	17,805	17,746	3,283,787	Dominated
FIT	54	1	12,890	1,638	0.95	136	34	17,841	17,793	3,300,695	3,687
FIT	54	3	5,237	1,107	0.70	165	45	17,819	17,764	3,309,921	Dominated
FIT	50	2	9,101	1,386	0.83	151	39	17,837	17,786	3,355,258	Dominated
FIT	50	3	6,679	1,195	0.75	161	43	17,827	17,774	3,358,728	Dominated
COL	60	10	0	2,657	1.25	112	29	17,832	17,784	3,432,092	Dominated
FIT	50	1	15,306	1,775	1.02	136	35	17,850	17,804	3,455,984	14,182
FIT	46	3	7,548	1,240	0.73	163	44	17,831	17,778	3,461,465	Dominated
FIT	46	2	10,529	1,453	0.86	152	40	17,842	17,793	3,485,059	Dominated
COL	60	5	0	3,352	1.53	99	25	17,837	17,791	3,580,870	Dominated
FIT	40	3	9,027	1,283	0.74	165	45	17,833	17,781	3,655,055	Dominated
FIT	46	1	17,489	1,867	1.05	138	36	17,854	17,809	3,680,416	Dominated
FIT	40	2	12,465	1,506	0.86	156	42	17,844	17,795	3,745,337	Dominated
COL	54	10	0	3,314	1.75	102	26	17,852	17,809	3,810,691	Dominated
FIT	40	1	20,104	1,909	1.03	146	40	17,853	17,808	4,123,967	Dominated
COL	54	5	0	4,510	2.06	84	20	17,863	17,823	4,162,832	38,064
COL	50	10	0	3,835	1.88	97	24	17,862	17,821	4,233,917	Dominated
COL	46	10	0	4,025	1.95	102	26	17,868	17,828	4,751,928	Dominated
COL	50	5	0	5,329	2.28	77	18	17,875	17,839	4,793,549	39,568
COL	46	5	0	5,780	2.40	80	20	17,884	17,848	5,602,818	82,326
COL	40	10	0	4,909	2.13	94	23	17,877	17,838	5,831,509	Dominated
COL	40	5	0	7,334	2.75	70	16	17,897	17,862	7,423,645	135,377

Abbreviations: COL, colonoscopy; CRC, colorectal cancer, FIT, faecal immunological test; QALY, quality-adjusted life years

Note: details of the risk groups can be found in Table 6.2.

Grey shading highlights strategies on the efficient frontier.

a. Results are discounted at an annual rate of 5%.

b. Costs are presented in Australian Dollars ($AUD).

Supplementary Results Table 6.2: Costs and effects of all a) uniform screening scenarios and b) personalised screening scenarios per 1,000 simulated 40-year-olds, assuming perfect adherence when costs are discounted at 5% and QALYs are discounted and weighted by age.

a. Effects of uniform screening scenarios.

Screening Strategy			FITs	COL	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[bc]	ICER[c]
Test	Start Age	Interval									
No Screening			0	84	0.07	84	29	15,176	15,156	1,234,089	
FIT	60	3	3,981	467	0.24	66	19	15,190	15,172	1,240,498	413
FIT	60	2	5,935	576	0.27	62	16	15,192	15,175	1,256,805	5,643
FIT	54	3	5,571	561	0.28	64	18	15,194	15,177	1,304,332	Dominated
FIT	60	1	9,954	777	0.34	56	15	15,195	15,178	1,327,965	Dominated
FIT	54	2	8,101	695	0.32	59	16	15,197	15,181	1,343,651	14,720
FIT	50	3	6,990	625	0.30	63	17	15,196	15,180	1,371,842	Dominated
FIT	50	2	9,473	759	0.34	59	15	15,199	15,183	1,436,505	Dominated
FIT	46	3	7,789	660	0.29	63	17	15,197	15,181	1,462,077	Dominated
FIT	54	1	13,381	953	0.40	53	14	15,200	15,185	1,480,562	29,828
FIT	46	2	10,767	811	0.35	59	16	15,200	15,185	1,556,681	Dominated
FIT	50	1	15,397	1,042	0.43	53	14	15,202	15,188	1,634,262	52,279
FIT	40	3	9,187	707	0.30	64	18	15,198	15,182	1,635,282	Dominated
FIT	40	2	12,532	868	0.36	60	16	15,201	15,186	1,789,931	Dominated
COL	60	10	0	2,198	0.60	42	11	15,198	15,182	1,789,986	Dominated
FIT	46	1	17,171	1,109	0.44	54	14	15,204	15,190	1,830,442	139,134
COL	60	5	0	3,048	0.82	37	10	15,200	15,184	2,117,448	Dominated
FIT	40	1	19,338	1,165	0.44	57	16	15,204	15,189	2,201,540	Dominated
COL	54	10	0	2,928	0.86	39	10	15,204	15,189	2,294,199	Dominated
COL	50	10	0	3,245	0.91	37	9	15,207	15,192	2,706,770	Dominated
COL	54	5	0	4,540	1.16	31	7	15,207	15,193	3,016,912	Dominated
COL	46	10	0	3,341	1.01	39	10	15,208	15,194	3,181,465	Dominated
COL	50	5	0	5,012	1.24	29	7	15,211	15,197	3,664,480	251,583
COL	40	10	0	4,269	1.09	36	9	15,211	15,196	4,319,443	Dominated
COL	46	5	0	5,700	1.35	30	7	15,214	15,199	4,593,188	427,976
COL	40	5	0	7,011	1.57	26	6	15,217	15,201	6,462,019	869,224

b. Effects of personalised screening scenarios.[d]

Screening Strategy	FITs	COL	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[bc]	ICER[c]
No Screening	0	84	0.07	84	29	15,176	15,156	1,234,089	
PS01	360	130	0.09	81	27	15,178	15,159	1,467,668	Dominated
PS02	515	141	0.10	81	27	15,179	15,160	1,471,312	Dominated
PS03	1,722	276	0.16	73	23	15,184	15,166	1,505,808	Dominated
PS04	2,554	324	0.18	71	22	15,185	15,167	1,513,829	Dominated
PS05	2,190	305	0.18	72	23	15,186	15,168	1,520,843	Dominated
PS06	3,322	368	0.20	70	22	15,187	15,169	1,542,584	Dominated
PS07	5,226	525	0.27	63	18	15,192	15,175	1,628,434	Dominated
PS08	5,920	562	0.28	63	18	15,193	15,177	1,656,571	Dominated
PS09	6,017	568	0.28	63	18	15,193	15,177	1,662,780	20,620
PS10	7,898	687	0.33	59	16	15,197	15,181	1,756,804	24,788
PS12	10,057	792	0.36	57	15	15,198	15,183	1,834,425	32,204
PS11	10,800	825	0.37	56	15	15,198	15,183	1,837,112	Dominated
PS13	11,189	859	0.38	55	14	15,200	15,185	1,911,354	41,373
PS14	11,700	881	0.39	55	14	15,200	15,185	1,924,610	43,491
PS15	11,788	885	0.39	55	14	15,200	15,186	1,933,583	49,167
PS16	11,089	1,023	0.44	52	13	15,201	15,186	1,978,086	Dominated
PS17	11,398	1,037	0.44	52	13	15,202	15,187	1,999,556	50,356
PS18	12,293	1,078	0.45	51	13	15,202	15,187	2,013,777	51,739
PS19	12,939	1,106	0.46	51	13	15,202	15,188	2,063,215	55,162
PS20	13,382	1,125	0.47	51	13	15,203	15,189	2,098,112	76,583
PS21	13,646	1,136	0.47	51	13	15,203	15,189	2,116,904	78,423
PS22	13,646	1,154	0.47	51	13	15,203	15,189	2,149,259	98,736
PS23	14,052	1,169	0.48	52	14	15,204	15,190	2,193,345	98,758
PS24	10,378	1,969	0.69	43	11	15,206	15,193	2,519,388	108,054
PS25	11,518	2,017	0.70	43	11	15,206	15,193	2,564,321	118,157
PS26	12,085	2,037	0.70	43	11	15,207	15,193	2,627,025	144,858
PS27	12,085	2,100	0.71	43	11	15,207	15,194	2,699,821	168,462
PS28	12,085	2,209	0.74	43	11	15,208	15,195	2,880,990	Dominated
PS29	12,473	2,223	0.74	43	11	15,208	15,195	2,924,646	208,087
PS30	6,964	3,480	0.99	35	9	15,211	15,197	3,512,866	244,752
PS31	7,289	3,492	1.00	35	9	15,211	15,197	3,549,627	264,513
PS32	7,289	3,804	1.05	34	8	15,212	15,199	3,943,469	358,974
PS33	7,289	4,017	1.09	34	8	15,213	15,199	4,238,838	429,957
PS34	3,372	4,929	1.25	30	7	15,214	15,200	4,694,318	522,899
PS35	3,372	5,105	1.28	30	7	15,214	15,200	4,915,213	882,218
PS36	3,372	5,531	1.35	29	7	15,216	15,201	5,515,822	951,617
PS37	3,372	5,814	1.39	29	7	15,216	15,201	5,945,624	3,457,466
PS38	0	6,612	1.51	27	6	15,217	15,201	6,365,416	3,689,986
PS39	0	6,782	1.54	27	6	15,217	15,201	6,564,338	6,542,166

Abbreviations: COL, colonoscopy; CRC, colorectal cancer, FIT, faecal immunological test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Grey shading highlights screening scenarios on the efficient frontier.

a. Life years and QALYs are discounted at 5% and weighted by age.
b. Costs are discounted at 5%.
c. Costs are presented in Australian Dollars ($AUD).
d. The personalised screening scenarios are described in Supplementary Results Table 6.3.

Supplementary Results Table 6.3: Specifics of the personalised screening scenarios when costs are discounted at 5% and QALYs are discounted at 5% and weighted by age. All screening ends at or before the age of 74 years.

Screening Strategy	Risk Groups				
	Very Low	Low	Average	High	Very High
PS1	NoScr	NoScr	NoScr	NoScr	FIT-60-1
PS2	NoScr	NoScr	NoScr	NoScr	FIT-54-1
PS3	NoScr	NoScr	NoScr	FIT-60-2	FIT-54-1
PS4	NoScr	NoScr	NoScr	FIT-60-1	FIT-54-1
PS5	NoScr	NoScr	NoScr	FIT-54-2	FIT-54-1
PS6	NoScr	NoScr	NoScr	FIT-54-1	FIT-54-1
PS7	NoScr	NoScr	FIT-60-2	FIT-54-1	FIT-54-1
PS8	NoScr	NoScr	FIT-54-2	FIT-54-1	FIT-54-1
PS9	NoScr	NoScr	FIT-54-2	FIT-54-1	FIT-50-1
PS10	NoScr	FIT-60-2	FIT-54-2	FIT-54-1	FIT-50-1
PS11	NoScr	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1
PS12	NoScr	FIT-54-2	FIT-54-1	FIT-54-1	FIT-50-1
PS13	NoScr	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1
PS14	FIT-54-3	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1
PS15	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1
PS16	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1	COL-54-5
PS17	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1	COL-50-5
PS18	FIT-54-2	FIT-54-1	FIT-54-1	FIT-50-1	COL-50-5
PS19	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5
PS20	FIT-54-2	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5
PS21	FIT-50-2	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5
PS22	FIT-50-2	FIT-50-1	FIT-50-1	COL-50-5	COL-50-5
PS23	FIT-50-2	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5
PS24	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5
PS25	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5
PS26	FIT-50-1	FIT-50-1	FIT-46-1	COL-50-5	COL-46-5
PS27	FIT-50-1	FIT-50-1	FIT-46-1	COL-50-5	COL-40-5
PS28	FIT-50-1	FIT-50-1	FIT-46-1	COL-46-5	COL-40-5
PS29	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5	COL-40-5
PS30	FIT-50-1	FIT-46-1	COL-50-5	COL-46-5	COL-40-5
PS31	FIT-46-1	FIT-46-1	COL-50-5	COL-46-5	COL-40-5
PS32	FIT-46-1	FIT-46-1	COL-50-5	COL-40-5	COL-40-5
PS33	FIT-46-1	FIT-46-1	COL-46-5	COL-40-5	COL-40-5
PS34	FIT-46-1	COL-50-5	COL-46-5	COL-40-5	COL-40-5
PS35	FIT-46-1	COL-46-5	COL-46-5	COL-40-5	COL-40-5
PS36	FIT-46-1	COL-46-5	COL-40-5	COL-40-5	COL-40-5
PS37	COL-50-5	COL-46-5	COL-40-5	COL-40-5	COL-40-5
PS38	COL-50-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5
PS39	COL-46-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5

Abbreviations: COL, Colonoscopy; FIT, faecal immunochemical test; NoScr, no screening
Screening strategies: screening test-screening start age-screening interval

Supplementary Results Table 6.4: Costs and effects of all a) uniform screening scenarios and b) personalised screening scenarios per 1,000 simulated 40-year-olds, assuming perfect adherence when costs and QALYs are discounted at 3%.

a. Uniform screening scenarios.

Screening Strategy			FITs	COL	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[b]
Test	Start Age	Interval									
No Screening			0	84	0.07	84	29	24,044	23,998	2,131,337	Dominated
FIT	60	3	3,981	467	0.24	66	19	24,081	24,042	2,039,884	Dominates
FIT	60	2	5,935	576	0.27	62	16	24,088	24,050	2,047,061	861
FIT	54	3	5,571	561	0.28	64	18	24,091	24,054	2,108,708	Dominated
FIT	60	1	9,954	777	0.34	56	15	24,095	24,060	2,142,041	Dominated
FIT	54	2	8,101	695	0.32	59	16	24,099	24,064	2,144,612	7,275
FIT	50	3	6,990	625	0.30	63	17	24,096	24,060	2,178,311	Dominated
FIT	50	2	9,473	759	0.34	59	15	24,103	24,069	2,250,511	Dominated
FIT	46	3	7,789	660	0.29	63	17	24,098	24,062	2,279,045	Dominated
FIT	54	1	13,381	953	0.40	53	14	24,108	24,076	2,323,627	15,069
FIT	46	2	10,767	811	0.35	59	16	24,105	24,072	2,381,682	Dominated
FIT	40	3	9,187	707	0.30	64	18	24,098	24,063	2,452,550	Dominated
FIT	50	1	15,397	1,042	0.43	53	14	24,112	24,081	2,501,392	32,204
FIT	40	2	12,532	868	0.36	60	16	24,106	24,072	2,616,871	Dominated
FIT	46	1	17,171	1,109	0.44	54	14	24,113	24,083	2,716,181	Dominated
COL	60	10	0	2,198	0.60	42	11	24,105	24,072	2,815,371	Dominated
FIT	40	1	19,338	1,165	0.44	57	16	24,111	24,079	3,085,943	Dominated
COL	60	5	0	3,048	0.82	37	10	24,110	24,078	3,338,895	Dominated
COL	54	10	0	2,928	0.86	39	10	24,118	24,088	3,455,297	Dominated
COL	50	10	0	3,245	0.91	37	9	24,124	24,095	3,893,169	98,778
COL	46	10	0	3,341	1.01	39	10	24,126	24,098	4,338,784	Dominated
COL	54	5	0	4,540	1.16	31	7	24,127	24,099	4,560,398	Dominated
COL	50	5	0	5,012	1.24	29	7	24,134	24,108	5,259,267	110,258
COL	40	10	0	4,269	1.09	36	9	24,132	24,104	5,491,543	Dominated
COL	46	5	0	5,700	1.35	30	7	24,139	24,112	6,281,315	234,415
COL	40	5	0	7,011	1.57	26	6	24,147	24,119	8,165,431	285,040

b. Personalised screening scenarios.[c]

Screening Strategy	FITs	COL	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[b]
No Screening	0	84	0.07	84	29	24,044	23,998	2,131,337	
PS01	1,568	264	0.16	73	23	24,064	24,022	2,325,151	Dominated
PS02	1,722	276	0.16	73	23	24,066	24,024	2,328,301	Dominated
PS03	2,554	324	0.18	71	22	24,068	24,028	2,334,210	Dominated
PS04	4,457	481	0.25	64	19	24,082	24,044	2,388,587	5,634
PS05	5,226	525	0.27	63	18	24,086	24,049	2,421,113	6,202
PS06	5,920	562	0.28	63	18	24,089	24,053	2,452,809	7,685
PS07	7,309	658	0.32	59	16	24,096	24,061	2,517,012	7,840
PS08	7,406	663	0.32	59	16	24,097	24,062	2,524,438	10,732
PS09	7,898	687	0.33	59	16	24,098	24,064	2,550,682	12,607
PS10	8,715	739	0.34	57	15	24,102	24,068	2,612,964	Dominated
PS11	10,414	822	0.37	55	14	24,104	24,072	2,671,669	15,773
PS12	10,728	837	0.37	55	14	24,105	24,073	2,689,632	16,721
PS13	10,117	947	0.42	53	14	24,107	24,075	2,725,078	19,526
PS14	10,577	968	0.42	53	14	24,108	24,076	2,763,970	21,599
PS15	11,089	991	0.43	52	14	24,109	24,077	2,782,499	22,238
PS16	11,089	1,023	0.44	52	13	24,110	24,078	2,811,605	26,284
PS17	12,293	1,078	0.45	51	13	24,111	24,080	2,860,808	26,934
PS18	12,939	1,106	0.46	51	13	24,112	24,082	2,918,096	34,370
PS19	13,203	1,117	0.46	51	13	24,113	24,082	2,939,743	44,551
PS20	13,646	1,136	0.47	51	13	24,113	24,083	2,979,627	46,083
PS21	10,378	1,595	0.61	46	12	24,117	24,089	3,226,411	46,622
PS22	10,378	1,951	0.68	43	11	24,121	24,093	3,465,361	52,016
PS23	11,148	1,983	0.69	42	11	24,121	24,094	3,491,503	56,483
PS24	11,148	2,001	0.69	43	11	24,122	24,094	3,526,082	60,225
PS25	11,518	2,017	0.70	43	11	24,122	24,095	3,560,357	68,807
PS26	11,518	2,079	0.71	42	11	24,123	24,096	3,633,921	76,512
PS27	6,575	2,788	0.87	37	9	24,127	24,100	4,079,776	96,653
PS28	6,575	3,356	0.97	34	8	24,130	24,104	4,518,470	109,516
PS29	6,575	3,465	0.99	35	9	24,132	24,106	4,711,626	121,339
PS30	6,575	3,776	1.05	34	8	24,134	24,109	5,113,837	149,883
PS31	3,047	4,286	1.14	31	7	24,136	24,110	5,459,786	176,486
PS32	3,372	4,299	1.14	31	7	24,136	24,111	5,498,219	190,456
PS33	3,372	4,715	1.21	30	7	24,138	24,112	5,839,990	199,604
PS34	3,372	4,929	1.25	30	7	24,140	24,114	6,163,155	230,476
PS35	3,372	5,355	1.32	29	7	24,142	24,116	6,770,919	305,621
PS36	3,372	5,531	1.35	29	7	24,143	24,116	7,016,964	410,008
PS37	0	6,328	1.47	27	6	24,144	24,118	7,613,850	511,280
PS38	0	6,612	1.51	27	6	24,146	24,118	8,044,907	557,935
PS39	0	6,782	1.54	27	6	24,146	24,119	8,270,010	1,157,855
PS40	0	7,011	1.57	26	6	24,147	24,119	8,639,531	1,798,841

Abbreviations: COL, colonoscopy; CRC, colorectal cancer, FIT, faecal immunological test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Grey shading highlights screening scenarios on the efficient frontier.

a. Results are discounted at 3%.

b. Costs are presented in Australian Dollars ($AUD).

c. The personalised screening scenarios are described in Supplementary Results Table 6.5.

Supplementary Results Table 6.5: Specifics of the personalised screening scenarios by willingness-to-pay threshold when cost and QALYs are discounted by 3%. All screening ends at or before the age of 74 years.

Screening Strategy	Risk Groups				
	Very Low	Low	Average	High	Very High
PS1	NoScr	NoScr	NoScr	FIT-60-2	FIT-60-1
PS2	NoScr	NoScr	NoScr	FIT-60-2	FIT-54-1
PS3	NoScr	NoScr	NoScr	FIT-60-1	FIT-54-1
PS4	NoScr	NoScr	FIT-60-2	FIT-60-1	FIT-54-1
PS5	NoScr	NoScr	FIT-60-2	FIT-54-1	FIT-54-1
PS6	NoScr	NoScr	FIT-54-2	FIT-54-1	FIT-54-1
PS7	NoScr	FIT-60-2	FIT-54-2	FIT-54-1	FIT-54-1
PS8	NoScr	FIT-60-2	FIT-54-2	FIT-54-1	FIT-50-1
PS9	NoScr	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1
PS10	FIT-60-74-3	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1
PS11	FIT-60-74-3	FIT-54-2	FIT-54-1	FIT-54-1	FIT-50-1
PS12	FIT-54-3	FIT-54-2	FIT-54-1	FIT-54-1	FIT-50-1
PS13	FIT-54-3	FIT-54-2	FIT-54-1	FIT-54-1	COL-54-5
PS14	FIT-54-3	FIT-54-2	FIT-54-1	FIT-50-1	COL-54-5
PS15	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1	COL-54-5
PS16	FIT-54-2	FIT-54-2	FIT-54-1	FIT-50-1	COL-50-5
PS17	FIT-54-2	FIT-54-1	FIT-54-1	FIT-50-1	COL-50-5
PS18	FIT-54-2	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5
PS19	FIT-50-2	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5
PS20	FIT-50-2	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5
PS21	FIT-50-2	FIT-50-1	FIT-50-1	COL-50-10	COL-50-5
PS22	FIT-50-2	FIT-50-1	FIT-50-1	COL-50-5	COL-50-5
PS23	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5	COL-50-5
PS24	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5
PS25	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5
PS26	FIT-50-1	FIT-50-1	FIT-50-1	COL-50-5	COL-40-5
PS27	FIT-50-1	FIT-50-1	COL-50-10	COL-50-5	COL-40-5
PS28	FIT-50-1	FIT-50-1	COL-50-5	COL-50-5	COL-40-5
PS29	FIT-50-1	FIT-50-1	COL-50-5	COL-46-5	COL-40-5
PS30	FIT-50-1	FIT-50-1	COL-50-5	COL-40-5	COL-40-5
PS31	FIT-50-1	COL-50-10	COL-50-5	COL-40-5	COL-40-5
PS32	FIT-46-1	COL-50-10	COL-50-5	COL-40-5	COL-40-5
PS33	FIT-46-1	COL-50-5	COL-50-5	COL-40-5	COL-40-5
PS34	FIT-46-1	COL-50-5	COL-46-5	COL-40-5	COL-40-5
PS35	FIT-46-1	COL-50-5	COL-40-5	COL-40-5	COL-40-5
PS36	FIT-46-1	COL-46-5	COL-40-5	COL-40-5	COL-40-5
PS37	COL-50-5	COL-46-5	COL-40-5	COL-40-5	COL-40-5
PS38	COL-50-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5
PS39	COL-46-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5
PS40	COL-40-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5

Abbreviations: COL, Colonoscopy; FIT, faecal immunochemical test; NoScr, no screening
Screening strategies: screening test-screening start age-screening interval

Supplementary Results Table 6.6: Costs and effects of all a) uniform screening scenarios and b) personalised screening scenarios per 1,000 simulated 40-year-olds, assuming perfect adherence when costs and QALYs are undiscounted.

a. Uniform screening scenarios.

Screening Strategy			FITs	COL	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[b]
Test	Start Age	Interval									
No Screening			0	84	0.07	84	29	24,044	23,998	2,131,337	Dominated
FIT	60	2	5,935	576	0.27	62	16	43,149	43,049	4,739,664	Dominates
FIT	60	3	3,981	467	0.24	66	19	43,126	43,020	4,817,049	Dominated
FIT	54	2	8,101	695	0.32	59	16	43,176	43,084	4,850,988	3,179
FIT	60	1	9,954	777	0.34	56	15	43,173	43,081	4,852,104	Dominated
FIT	54	3	5,571	561	0.28	64	18	43,150	43,050	4,886,396	Dominated
FIT	50	3	6,990	625	0.30	63	17	43,164	43,067	4,935,602	Dominated
FIT	50	2	9,473	759	0.34	59	15	43,186	43,096	4,987,686	Dominated
FIT	46	3	7,789	660	0.29	63	17	43,165	43,069	5,077,689	Dominated
FIT	54	1	13,381	953	0.40	53	14	43,204	43,121	5,087,843	6,415
FIT	46	2	10,767	811	0.35	59	16	43,189	43,100	5,150,353	Dominated
FIT	40	3	9,187	707	0.30	64	18	43,164	43,067	5,270,930	Dominated
FIT	50	1	15,397	1,042	0.43	53	14	43,212	43,131	5,322,533	22,161
FIT	40	2	12,532	868	0.36	60	16	43,185	43,095	5,416,504	Dominated
FIT	46	1	17,171	1,109	0.44	54	14	43,211	43,130	5,590,545	Dominated
COL	60	10	0	2,198	0.60	42	11	43,205	43,125	5,984,373	Dominated
FIT	40	1	19,338	1,165	0.44	57	16	43,197	43,113	6,003,156	Dominated
COL	54	10	0	2,928	0.86	39	10	43,238	43,166	6,946,819	Dominated
COL	60	5	0	3,048	0.82	37	10	43,222	43,147	7,040,041	Dominated
COL	50	10	0	3,245	0.91	37	9	43,253	43,185	7,349,473	38,029
COL	46	10	0	3,341	1.01	39	10	43,254	43,185	7,669,729	Dominated
COL	40	10	0	4,269	1.09	36	9	43,271	43,205	8,919,959	Dominated
COL	54	5	0	4,540	1.16	31	7	43,268	43,203	9,072,841	Dominated
COL	50	5	0	5,012	1.24	29	7	43,287	43,226	9,720,205	56,975
COL	46	5	0	5,700	1.35	30	7	43,295	43,234	10,917,234	Dominated
COL	40	5	0	7,011	1.57	26	6	43,313	43,255	12,815,034	106,718

b. Personalised screening scenarios.[c]

Screening Strategy	FITs	COL	Complications	CRC Incidence	CRC Mortality	Life Years[b]	Total QALYs[b]	Total Costs[bc]	ICER[b]
No Screening	0	84	0.07	84	29	43,001	42,869	5,460,172	Dominated
PS03	6,148	668	0.31	58	15	43,161	43,065	4,919,457	Dominates
PS01	4,871	594	0.29	60	17	43,146	43,047	4,922,589	Dominated
PS02	5,330	617	0.30	60	16	43,149	43,052	4,926,793	Dominated
PS04	6,916	713	0.33	57	15	43,171	43,079	4,959,849	3,026
PS05	7,611	750	0.34	56	15	43,179	43,089	4,995,978	3,359
PS06	7,611	776	0.36	56	15	43,183	43,094	5,015,775	4,277
PS07	8,103	801	0.37	56	15	43,187	43,099	5,049,437	6,193
PS08	9,802	884	0.40	54	14	43,196	43,111	5,128,736	6,850
PS09	10,206	902	0.40	53	14	43,198	43,113	5,147,483	7,753
PS10	10,206	950	0.41	53	14	43,201	43,117	5,177,225	7,789
PS11	10,628	969	0.42	52	14	43,203	43,120	5,210,998	10,596
PS12	10,628	1,002	0.43	52	13	43,205	43,123	5,246,635	12,905
PS13	11,832	1,056	0.44	51	13	43,210	43,129	5,323,387	13,478
PS14	9,025	1,443	0.57	46	12	43,221	43,145	5,562,545	14,690
PS15	9,025	1,537	0.59	46	12	43,226	43,151	5,674,015	17,799
PS16	9,671	1,565	0.60	46	12	43,229	43,155	5,749,938	24,226
PS17	9,935	1,576	0.60	46	12	43,230	43,156	5,776,707	24,681
PS18	9,935	1,932	0.68	43	11	43,241	43,170	6,180,918	27,246
PS19	10,704	1,964	0.68	42	11	43,243	43,172	6,235,349	28,675
PS20	11,148	1,983	0.69	42	11	43,244	43,174	6,284,712	29,170
PS21	11,148	2,063	0.71	42	11	43,247	43,178	6,397,904	32,093
PS22	6,205	2,772	0.86	37	9	43,260	43,195	7,046,014	37,125
PS23	6,575	2,788	0.87	37	9	43,261	43,196	7,086,658	41,179
PS24	6,575	3,356	0.97	34	8	43,272	43,209	7,849,972	56,864
PS25	6,575	3,776	1.05	34	8	43,281	43,220	8,480,538	61,177
PS26	3,047	4,286	1.14	31	7	43,287	43,228	9,020,556	68,106
PS27	3,047	4,703	1.21	30	7	43,292	43,234	9,620,268	98,538
PS28	3,047	5,342	1.32	29	7	43,301	43,243	10,611,955	109,959
PS29	0	5,785	1.38	28	6	43,304	43,246	11,134,728	149,697
PS30	0	5,801	1.40	28	6	43,304	43,247	11,171,639	150,421
PS31	0	6,260	1.47	27	6	43,308	43,251	11,894,768	172,055
PS32	0	6,612	1.51	27	6	43,311	43,253	12,415,828	208,145
PS33	0	7,011	1.57	26	6	43,313	43,255	13,052,084	327,048

Abbreviations: COL, colonoscopy; CRC, colorectal cancer, FIT, faecal immunological test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Grey shading highlights screening scenarios on the efficient frontier.

a. Results are undiscounted.

b. Costs are presented in Australian Dollars ($AUD).

c. The personalised screening scenarios are described in Supplementary Results Table 6.7.

Supplementary Results Table 6.7: Specifics of the personalised screening scenarios by willingness-to-pay threshold, when costs and QALYs are undiscounted. All screening ends at or before the age of 74 years.

Screening Strategy	Risk Groups				
	Very Low	Low	Average	High	Very High
PS1	NoScr	FIT-60-3	FIT-60-2	FIT-60-1	COL-60-10
PS2	NoScr	FIT-60-2	FIT-60-2	FIT-60-1	COL-60-10
PS3	FIT-60-3	FIT-60-2	FIT-60-2	FIT-60-1	COL-60-10
PS4	FIT-60-3	FIT-60-2	FIT-60-2	FIT-54-1	COL-60-10
PS5	FIT-60-3	FIT-60-2	FIT-54-2	FIT-54-1	COL-60-10
PS6	FIT-60-3	FIT-60-2	FIT-54-2	FIT-54-1	COL-54-10
PS7	FIT-60-3	FIT-54-2	FIT-54-2	FIT-54-1	COL-54-10
PS8	FIT-60-3	FIT-54-2	FIT-54-1	FIT-54-1	COL-54-10
PS9	FIT-60-2	FIT-54-2	FIT-54-1	FIT-54-1	COL-54-10
PS10	FIT-60-2	FIT-54-2	FIT-54-1	FIT-54-1	COL-54-5
PS11	FIT-54-2	FIT-54-2	FIT-54-1	FIT-54-1	COL-54-5
PS12	FIT-54-2	FIT-54-2	FIT-54-1	FIT-54-1	COL-50-5
PS13	FIT-54-2	FIT-54-1	FIT-54-1	FIT-54-1	COL-50-5
PS14	FIT-54-2	FIT-54-1	FIT-54-1	COL-54-10	COL-50-5
PS15	FIT-54-2	FIT-54-1	FIT-54-1	COL-50-10	COL-50-5
PS16	FIT-54-2	FIT-54-1	FIT-50-1	COL-50-10	COL-50-5
PS17	FIT-50-2	FIT-54-1	FIT-50-1	COL-50-10	COL-50-5
PS18	FIT-50-2	FIT-54-1	FIT-50-1	COL-50-5	COL-50-5
PS19	FIT-54-1	FIT-54-1	FIT-50-1	COL-50-5	COL-50-5
PS20	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5	COL-50-5
PS21	FIT-54-1	FIT-50-1	FIT-50-1	COL-50-5	COL-40-5
PS22	FIT-54-1	FIT-50-1	COL-50-10	COL-50-5	COL-40-5
PS23	FIT-50-1	FIT-50-1	COL-50-10	COL-50-5	COL-40-5
PS24	FIT-50-1	FIT-50-1	COL-50-5	COL-50-5	COL-40-5
PS25	FIT-50-1	FIT-50-1	COL-50-5	COL-40-5	COL-40-5
PS26	FIT-50-1	COL-50-10	COL-50-5	COL-40-5	COL-40-5
PS27	FIT-50-1	COL-50-5	COL-50-5	COL-40-5	COL-40-5
PS28	FIT-50-1	COL-50-5	COL-40-5	COL-40-5	COL-40-5
PS29	COL-50-10	COL-50-5	COL-40-5	COL-40-5	COL-40-5
PS30	COL-46-10	COL-50-5	COL-40-5	COL-40-5	COL-40-5
PS31	COL-46-10	COL-40-5	COL-40-5	COL-40-5	COL-40-5
PS32	COL-50-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5
PS33	COL-40-5	COL-40-5	COL-40-5	COL-40-5	COL-40-5

Abbreviations: COL, Colonoscopy; FIT, faecal immunochemical test; NoScr, no screening
Screening strategies: screening test-screening start age-screening interval

Supplementary Results Table 6.8: Threshold analysis: estimated cost of determining polygenic risk when personalised screening would be equally cost-effective to uniform annual screening from 50-74 years.

Scenario [a]	Cost [b]	Incremental cost compared to uniform screening	QALYs	Incremental QALYs compared to uniform screening	Incremental costs required to be cost-effective compared to uniform screening [c]	Difference between actual costs and required costs to be cost-effective [d]	Estimated cost to determine risk per individual
FIT-1-50-74	$1,634,262		17887.34				
PS14	$1,437,254	-$197,008	17883.63	-3.71	-$185,413	$11,595	$11.59
PS15	$1,450,510	-$183,752	17884.03	-3.31	-$165,690	$18,062	$18.06
PS16	$1,478,770	-$155,493	17884.77	-2.57	-$128,564	$26,929	$26.93
PS17	$1,503,986	-$130,277	17885.41	-1.93	-$96,695	$33,581	$33.58
PS18	$1,539,677	-$94,585	17886.31	-1.03	-$51,734	$42,851	$42.85
PS19	$1,589,115	-$45,147	17887.39	0.05	$2,377	$47,524	$47.52
PS20	$1,624,012	-$10,250	17887.94	0.60	$29,979	$40,229	$40.23
PS21	$1,642,804	$8,542	17888.23	0.89	$44,647	$36,104	$36.10

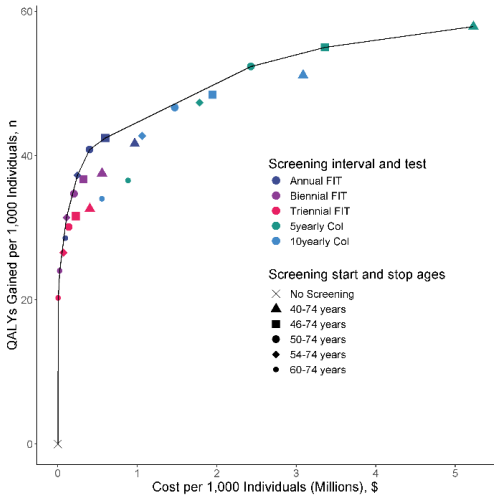
Abbreviations: FIT, faecal immunochemical test; FIT-1-50-74, Single sample FIT from 50-74 years; QALY, quality-adjusted life years

a. Only scenarios with positive threshold costs are included.
b. Costs for determining risk are excluded.
c. Calculated by multiplying the incremental number of QALYs by the willingness-to-pay threshold of $50,000.
d. Calculated by subtracting the incremental cost compared to uniform screening from the incremental costs required to be cost-effective compared to uniform screening.

A note on cost-effectiveness planes: Discounted costs and life years gained reflect total costs and life years gained of a screening program, accounting for time preference for present over future outcomes. Quality-adjusted life years gained are plotted on the y-axis, and total costs are plotted on the x-axis. Each possible screening strategy is represented by a point. Strategies that form the solid line connecting the points lying left and upward are the economically rational subset of choices. This line is called the efficient frontier. The inverse slope of the line represents the incremental cost-effectiveness ratio of the connected strategies. Points lying to the right and beneath the line represent the dominated strategies.

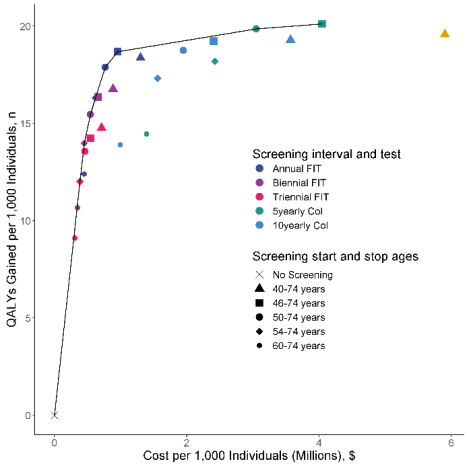
Abbreviations: Col, colonoscopy; FIT, faecal immunochemical test; QALY, quality-adjusted life years

Supplementary Results Figure 6.1: Costs and quality-adjusted life years (discounted at 5%) per 1,000 40-year-olds assuming perfect adherence for 25 uniform colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies.

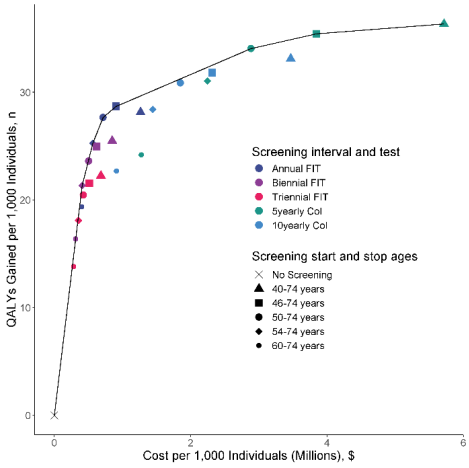


Supplementary Results Figure 6.2: Risk group level costs and quality-adjusted life years (discounted at 5%) per 1,000 40-year-olds assuming perfect adherence for 25 colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies.

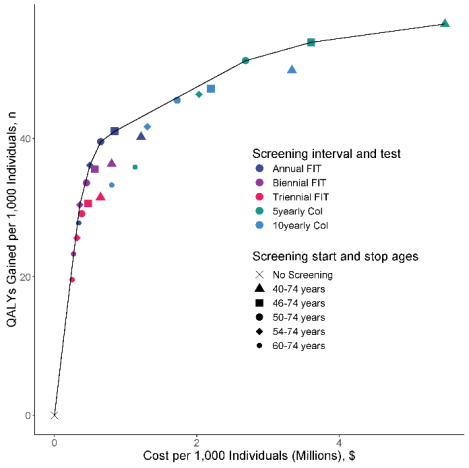
a. Very low risk



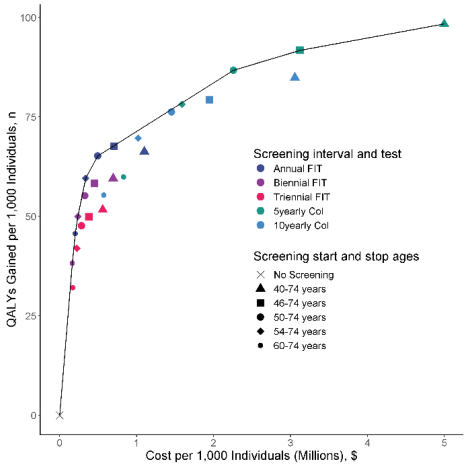
b. Low risk.



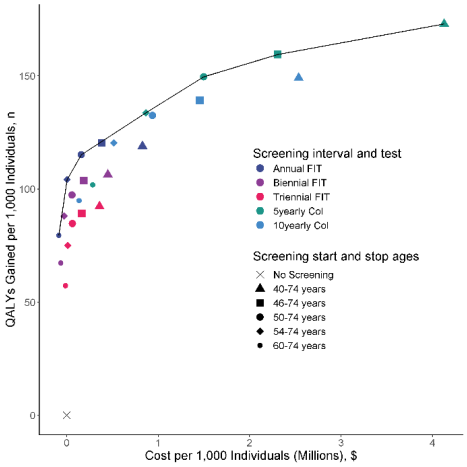
c. Average risk.



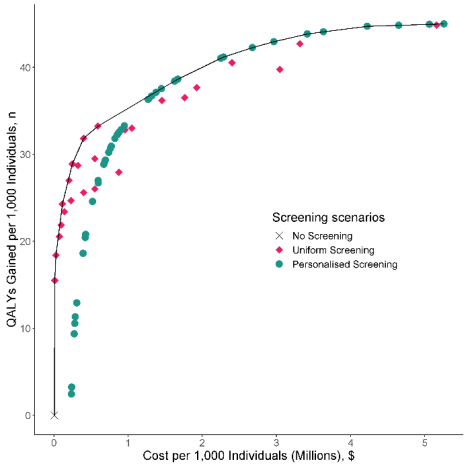
d. High risk.



e. Very high risk.

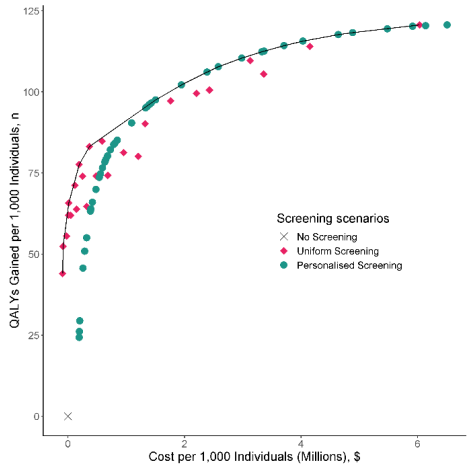


Supplementary Results Figure 6.3: Costs (discounted at 5%) and quality-adjusted life years (discounted at 5% and weighted by age) per 1,000 40-year-olds assuming perfect adherence for all uniform and personalised colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies.



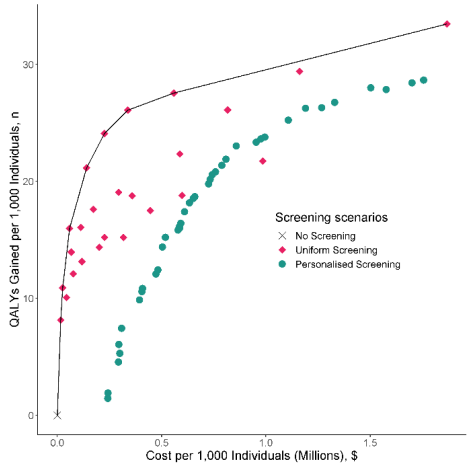
Note: A description of the personalised screening scenarios can be found in Supplementary Results Table 6.3.

Supplementary Results Figure 6.4: Costs and quality-adjusted life years (discounted at 3%) per 1,000 40-year-olds assuming perfect adherence for all uniform and personalised colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies.



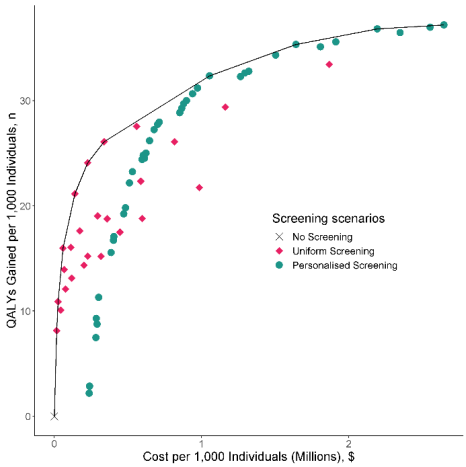
Note: A description of the personalised screening scenarios can be found in Supplementary Results Table 6.5.

Supplementary Results Figure 6.5: Costs and quality-adjusted life years (discounted at 5%) per 1,000 40-year-olds assuming realistic participation for uniform screening and lowered adherence for personalised colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies.



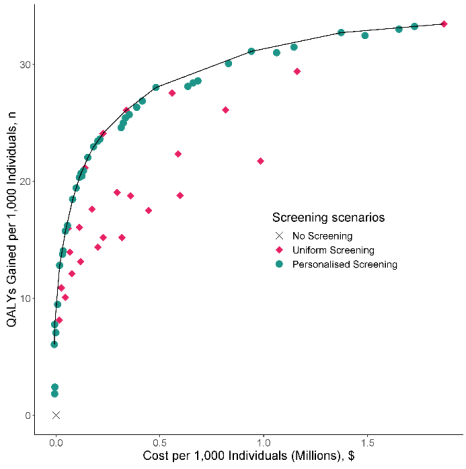
Note: A description of the personalised screening scenarios can be found in Table 6.4 of the manuscript.

Supplementary Results Figure 6.6: Costs and quality-adjusted life years (discounted at 5%) per 1,000 40-year-olds assuming realistic participation for uniform screening and higher adherence for personalised colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies.



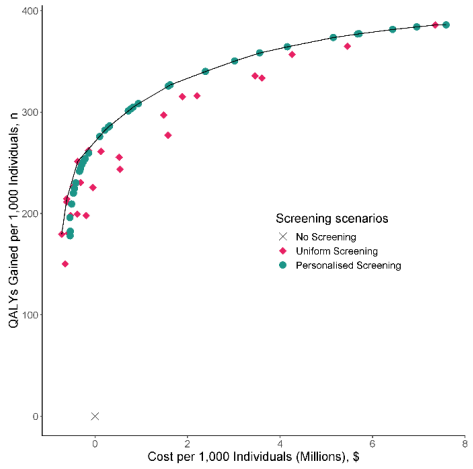
Note: A description of the personalised screening scenarios can be found in Table 6.4 of the manuscript.

Supplementary Results Figure 6.7: Costs and quality-adjusted life years (discounted at 5%) per 1,000 40-year-olds assuming realistic adherence for all uniform and personalised colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies. Costs for determining polygenic risk are excluded.



Note: A description of the personalised screening scenarios can be found in Table 6.4 of the manuscript.

Supplementary Results Figure 6.8: Costs and quality-adjusted life years (undiscounted) per 1,000 40-year-olds assuming perfect adherence for all uniform and personalised colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies.



Note: A description of the personalised screening scenarios can be found in Supplementary Results Table 6.7.

GENERAL DISCUSSION

Throughout this thesis we have investigated multiple methods for optimising colorectal cancer screening programs. In this chapter, we will answer the research questions proposed in the Introduction and provide an interpretation of our findings. We present methodological considerations and address challenges to achieving optimal screening programs. Finally, we discuss future directions for research and modelling, and highlight our general conclusions and recommendations based on the research described in this thesis.

PATHWAYS TO OPTIMAL SCREENING PROGRAMS

Within this thesis we have investigated two pathways to optimise colorectal cancer screening programs. The first is to optimise uniform screening programs to ensure they are designed and implemented to achieve the best possible outcomes for the average risk population. The second pathway addresses what we believe to be the future of screening – personalisation.

PART I: OPTIMISATION OF UNIFORM SCREENING PROGRAM

WHAT IS THE OPTIMAL SCREENING PROGRAM TO IDENTIFY LYNCH SYNDROME FOR THOSE WHO ARE DIAGNOSED WITH COLORECTAL CANCER?

The optimal screening pathway to identify Lynch syndrome includes mismatch repair immunohistochemistry followed by MLH1 methylation (if indicated) and germline testing for incident colorectal cancers diagnosed in those aged under 70 years. Screening those over 70 years requires ongoing investigation.

Although Lynch syndrome screening is widely recognised as important, the optimal screening strategy to identify new cases remains a hotly debated topic. There is limited consensus on the optimal screening pathway and whether screening should be universally applied to all colorectal cancer diagnoses or limited by an age-at-diagnosis threshold.[1-3]

In **Chapter 1**, we aimed to address this gap in knowledge.[4] In the first instance, we assessed two commonly followed tumour screening pathways to identify Lynch syndrome. Secondly, we assessed the cost-effectiveness from a health systems perspective of universal screening compared to three age-at-diagnosis thresholds (Screening<50, Screening<60 and Screening<70).

Our results suggest that the screening pathway including MMR immunohistochemistry followed by *MLH1* methylation (if indicated) and germline testing is more cost effective than the alternative pathway that includes testing with *BRAF* V6006E. Moreover, we found that it is cost effective to screen for Lynch syndrome up until the age of 70 years. Universal screening was not considered to be cost effective, as no additional Lynch syndrome cases were detected

in this age group but the cost of screening is significantly more. This finding should, however, be interpreted with caution as patients over 70 years with Lynch Syndrome were under-represented in the studied population and none of those included had been diagnosed with Lynch syndrome.[5] As Lynch syndrome does occur in colorectal cancer patients above 70 years,[6] our results may not be a true reflection of the costs and outcomes for this age group.

Our research was part of a broader conversation about the need to address the poor implementation of universal screening for Lynch syndrome in Australia. Shortly after our publication was released, the Royal College of Pathologists of Australasia (RCPA) submitted an application to the Australian Medical Services Advisory Council (MSAC) seeking to have germline testing and genetic counselling for Lynch syndrome (and other hereditable mutations which increase the risk of colorectal and endometrial cancers) covered by the Medical Benefits Scheme (MBS, Australia's public health insurance scheme).[7] The application requested that these items be covered for both the initial patient and their at-risk family members. In 2019, MSAC approved the RCPA application with changes to the MBS coming into effect in May 2020.[8] The importance of this development cannot be overstated. The inclusion of germline testing and genetic counselling on the MBS should significantly improve the referral pathway and improve the identification of people at increased risk of colorectal cancer due to Lynch syndrome and other genetic disorders. Since our publication, modelling investigations in Australia have shown universal screening for Lynch syndrome to be cost effective.[9] In addition, the Australasian Gastrointestinal Pathology Society has published a consensus statement supporting universal screening for Lynch syndrome[10] and the RCPA has put support behind the process.[11] However a national testing policy is still lacking, and although funding will now be available for germline testing and genetic counselling, other steps in the tumour screening pathway remain unfunded. For universal screening to be successfully implemented, these issues will need to be addressed.

How could Shanghai optimise its colorectal cancer screening initiative?

The Shanghai screening program could be optimised by switching to a validated screening test, reducing the test cut-off, increasing the screening frequency and extending the eligibility age range.

Despite relatively low incidence and mortality of colorectal cancer, due to its large population, China is a noteworthy contributor to the global burden of colorectal cancer.[12, 13] Moreover, as incidence and mortality is rising steadily,[14] colorectal cancer represents a significant public health challenge for the country. In an effort to reduce the burden of colorectal cancer, the Shanghai Municipal Government implemented a community-based colorectal cancer

screening program in 2013.[15] The program invited individuals aged 50-74 years to participate in colorectal cancer screening, offering triennial screening using a locally manufactured faecal immunochemical test (FIT) and a risk questionnaire. Results from the initial rounds of screening[15, 16] have highlighted several challenges for the screening program, and call into question whether the program is optimal for the population. To determine what the optimal screening program might look like, we assessed the performance of the existing screening program against a program using standardised and validated FITs (**Chapter 2**). In addition, we varied program characteristics including test cut-off, screening interval and screening start- and stop age.

Our results suggest that although the screening program currently implemented in Shanghai is effective at reducing colorectal cancer incidence and mortality, it is not the most optimal program. Compared to using strategies utilising validated screening tests, the strategies utilising the Shanghai tests were generally more expensive and required substantially more colonoscopies. We found that the Shanghai screening program could be optimised by utilising a validated, single sample FIT, with a cut-off of 10 µg Hb/g, with screening occurring annually from ages 45-80 years. However, given the suboptimal participation in screening and diagnostic colonoscopy seen in the existing program, implementing a program that is longer in duration and requires a greater number of repeat screens may not be optimal in practice. Such a program may diminish the already low participation rate. In addition, the program may experience 'screening fatigue', where motivation to participate is reduced due to a false perception of decreased colorectal cancer risk after several negative screening test results.[17, 18] These issues highlight the need to balance what is optimal in theory with what is practical in the "real world".

The Shanghai screening program is unique in that it offers triennial screening with FIT.[19] This strategy was selected after a comprehensive evaluation of the capacity of health resources of the region.[15] Colonoscopy capacity is likely to be a key driver in the selection of a triennial screening program. Therefore, it is feasible that an alternative screening program, which requires similar or lower colonoscopy demand than the existing program but with greater gains and fewer harms, would be desirable. Our investigation found several cost-effective alternatives which met these criteria, all of which used the validated FIT (including the optimal strategy mentioned above). Depending on desired outcomes, several other strategies could also be selected, however, all of these alternatives utilise a validated FIT. As such, these results may be relevant to jurisdictions with limited health resources which are considering implementing colorectal cancer screening. In addition, they are relevant to other low incidence jurisdictions as they indicate that, even in this setting, screening is a cost-effective method for reducing colorectal cancer burden.

WHAT IS THE OPTIMAL IMPLEMENTATION SCHEDULE OF THE NATIONAL BOWEL CANCER SCREENING PROGRAM IN AUSTRALIA?

By implementing the National Bowel Cancer Screening Program on an expedited 5-year timeline, many thousands of unnecessary colorectal cancer deaths could be averted.

The implementation of the Australian National Bowel Cancer Screening Program (NBCSP) was long and complicated. Colorectal cancer screening was first recommended in 1997 by the Australian Health Technology Advisory Committee.[20] In 1999, the Australian National Health and Medical Research Council (NHMRC) recommended biennial screening with FIT for individuals aged 50-74 years.[21, 22] However, the program wasn't commenced until 2006, and at this time just two age groups were invited (those aged 55 and 65).[23] During the following years, various commitments to extend the program were made, but there was no commitment to full implementation in line with NHMRC guidelines. This was despite evidence that those screened within the program were diagnosed with colorectal cancer at earlier stages, compared to those presenting symptomatically[24, 25] and a modelling study showing that full implementation of the NBCSP was cost effective.[26]

In 2012 the Australian Government committed to the full implementation.[27] Although the commitment was welcomed by advocacy and stakeholder groups, the protracted time line (full implementation would not be achieved until 2034) caused concern. It was at this time that we initiated research into the optimal implementation timeline for the NBCSP (**Chapter 3**).[28]

Our research compared the originally proposed implementation timeline to a series of alternatives. Not surprisingly, our findings indicate that although the protracted timeline would prevent colorectal cancer deaths (approximately 61,000), an expedited timeline, where full implementation was achieved by 2020, would increase the number of preventable deaths (to approximately 70,000) over the subsequent 40-year period. Our results demonstrate the drastic effect an implementation timeline can have on mortality and morbidity thereby highlighting the importance of appropriate selection.

The results of this research had far reaching consequences in the policy sphere in Australia. In 2013, the preliminary results were utilised during the election campaign, with the then leader of the opposition and shadow health minister pledging to spend $46 million to implement biennial FIT screening for individuals aged 50-74 by 2020 if elected.[29, 30] This party went on to win the election and in their 2014-15 budget announced $95.9 million to complete the implementation.[31] Full implementation of biennial screening was achieved in 2019.

This research highlights the importance of quantitative data in the advocacy arena – after nearly 20 years of advocacy efforts, it was this research that resulted in a paradigm shift in colorectal cancer screening in Australia.[32] Our results provide a strong argument to act with immediacy. The importance of relevant and timely evidence-based research to advocate for changes to public policy cannot be underestimated.

PART II: OPTIMISATION THROUGH PERSONALISATION

WHICH SCREENING MODALITY WILL OFFER THE BEST OUTCOMES TO INDIVIDUALS BASED ON THEIR BACKGROUND RISK OF COLORECTAL CANCER?

The assessed screening strategies were equally effective at reducing colorectal cancer mortality over a 15-year follow-up period, regardless of baseline risk. A single colonoscopy or sigmoidoscopy was more effective at reducing colorectal cancer incidence. As risk of colorectal cancer increases, so too do the benefits and harms, although the benefits increase to a greater extent. Our results were sensitive to the follow-up period – when lifetime follow-up was assessed, larger reductions in colorectal cancer incidence and mortality were predicted.

It remains unknown which screening modality will provide the optimal balance between benefits, burden and harms when baseline risk of colorectal cancer is considered. It is assumed that colonoscopy and FIT screening will perform at least as well as flexible sigmoidoscopy and guaiac faecal occult blood testing given their test characteristics, but empirical evidence is lacking. As screening effectiveness is influenced by baseline risk, investigation into how it affects the balance between benefits, burden and harms is warranted.

To determine the optimal screening strategy, in **Chapter 4** we assessed the benefits, burdens and harms of screening a population cohort aged 50-79 years, stratified by baseline 15-year colorectal cancer risk (1-7%).[33] We investigated four screening strategies: annual FIT; biennial FIT; a single sigmoidoscopy; and a single colonoscopy and followed individuals for 15 years. This work was part of a suite of research undertaken as part of the British Medical Journal's Rapid Recommendations project. The Rapid Recommendations project aims to provide trustworthy practice guidelines by responding to new, potentially practice-changing, evidence in a timely manner.

Our results suggest that, regardless of baseline risk, all strategies reduce colorectal cancer incidence and mortality. Although a single colonoscopy or sigmoidoscopy is more effective at reducing colorectal cancer incidence, all strategies are similarly effective at reducing colorectal cancer mortality. As would be expected, screening burden was greatest for those undergoing annual FIT screening, and harms were proportional to the number of

colonoscopies, which were highest in the colonoscopy screening strategy. Although the relative reduction in colorectal cancer incidence and mortality were similar, there was substantial variation in the absolute reductions. For example, at 3% colorectal cancer risk, the relative reduction in incidence was 5-34% which in absolute terms translates to 1-3 colorectal cancer cases prevented. When colorectal cancer risk increases to 6%, the relative reduction in incidence was the same as for 3% risk (5-34%), but the reduction in absolute terms translates to 3-21 colorectal cancer cases prevented. This means that there is a more unfavourable balance between the harms and the benefits for those at lower risk compared to those at higher risk.

When published, this suite of papers caused quite a stir internationally. This was largely because the Rapid Recommendations panel suggested against screening for those with a 15-year colorectal cancer risk of less than 3%.[34] This suggests that guidelines which recommend screening for all individuals starting at age 50 years, when the risk of colorectal cancer in the next 15 years is between 1-2%,[35-37] may in fact be over-screening their population. However, at present, there is no evidence to support such a threshold. In addition, as this recommendation was based on results of 15 years of follow up (the time frame requested by the panel as it allowed the model predictions to be validated against trial data[38]), it should be interpreted with some caution. Colorectal cancer develops slowly (the time from an asymptomatic polyp to a symptom detectable colorectal cancer is estimated to take between 10-25 years[39, 40]). As the full benefits of screening are achieved over the longer term, a longer period of follow up is warranted. Although longer follow up may have altered the benefit threshold defined by the panel, there is every possibility that individuals at lower risk may have reached this threshold. Our results were sensitive to this assumption – when lifetime follow up was assessed, the model predicted larger absolute reductions in colorectal cancer incidence and mortality for all screening strategies and at younger ages, annual FIT screening was more effective at reducing colorectal cancer incidence and mortality than a single colonoscopy.

HOW IS AGE-TO-STOP SCREENING AFFECTED BY COMORBIDITY AND PRIOR SCREENING HISTORY?

The optimal age-to-stop screening varies significantly based on an individual's comorbidity status and prior screening history. For those with severe comorbidity or a strong history of screening, the harms of screening outweigh the benefits at or before the age of 66 years. However, for those without comorbidity or who were previously unscreened, screening could continue until past the recommended stop age, in some cases up to 90 years of age.

Recent screening guidelines suggest that screening could be offered to those aged over 74 years, recommending that decisions to participate should consider screening history and comorbidity.[41, 42] Although recommended, there is little practical guidance or reliable tools to assist in making these decisions. The diversity of screening programs[19] and evidence that screening is not always targeted at those most likely to benefit,[43-47] highlight the need for improved guidance regarding the optimal age-to-stop screening. To assist in the development of such guidelines, we conducted an analysis to determine the optimal age-to-stop screening based on sex, age, comorbidity status and screening history (**Chapter 5**).[48] We modelled a cohort of individuals for each combination of sex, age (66-90 years), comorbidity status (no, low, moderate, severe), and screening history with FIT (no, some, reasonable, most or perfect prior screening) or colonoscopy (10 or 15 years prior), simulating 624 scenarios in total.

This investigation found that the optimal screening stop age depends heavily on individual factors such as comorbidity and screening history. The optimal screening stop age can be personalised to the age where the benefits of screening no longer outweigh the harms and varies from <66 to 90 years. Our results demonstrate that select groups, such as individuals without comorbidities or those who have not previously undergone screening could benefit from screening past the recommended stop age and, in some cases, screening could even continue up to 90 years of age. Conversely, those with severe comorbidity or a strong history of prior screening could stop earlier than currently recommended and, in some instances, this was before the age of 66 years.

While our results are in line with previous investigations,[49, 50] by addressing the complex nature of screening history, they are more in keeping with the "real life" scenarios faced by clinicians and participants. Moreover, by providing reliable information about the possible benefits, harms and burden of screening, they support informed decision-making in relation to screening participation. Given the complex nature of our analysis, clinicians and participants may find it challenging to integrate our findings into clinical practice. Therefore, to facilitate their use, we suggest that future screening participation recommendations could be automated. One way to do this would be to develop a clinical decision support system. Such systems aim to improve clinical decision-making by generating personalised patient recommendations based on an individual's specific characteristics.[51] Used at point of care and integrated into clinical workflows,[52, 53] they have considerable potential to improve the practice of medicine. Using our results within a clinical decision support system supports an evidence-based approach for decisions about screening participation.

IS IT COST EFFECTIVE TO IMPLEMENT RISK STRATIFIED SCREENING BASED ON POLYGENIC RISK AND FAMILY HISTORY COMPARED TO UNIFORM, ONE-SIZE-FITS-ALL, SCREENING?

Personalised screening is slightly more effective than uniform screening, however, at this stage, it is not more cost effective. This is due to the costs associated with determining an individual's risk of colorectal cancer and the suboptimal performance of the risk stratification algorithm. As costs decrease, and risk stratification algorithms improve, screening based on polygenic risk and family history will become a viable option.

It is now recognised that genetic susceptibility related to low risk genetic variants, or single-nucleotide polymorphisms (SNPs), play a significant role in colorectal cancer incidence. Although demonstrated to be an effective tool for stratifying the population,[54-58] the cost-effectiveness has yet to be established. We therefore explored the impact of stratifying the population by risk of colorectal cancer based on polygenic risk and family history and compared its effectiveness and cost-effectiveness to uniform screening (**Chapter 6**).[59]

Our results suggest that although personalised screening is slightly more effective than uniform screening in terms of reductions in incidence and mortality, uniform screening is more cost effective. Overall, personalised screening costs more than uniform screening due to the costs associated with determining colorectal cancer risk. However, our results were sensitive to our assumptions of costs for determining risk. When these costs were excluded, personalised screening was more cost effective that uniform screening. This finding is pertinent as, although we assumed costs that were comparable to those currently available and used in literature, the true cost of determining risk remains unknown as the cost of polygenic testing varies widely[60] and there is possibility to share such costs with other cancer screening programs. Moreover, although our results appear unfavourable at present, the discriminatory performance of risk stratification algorithms based on polygenic risk and family history remains suboptimal. This is largely because the current contribution of known SNPs to colorectal cancer risk is modest,[61-63] and the heritability of colorectal cancer remains largely unexplained.[63] However, as new SNPs are identified, the discriminatory performance of polygenic testing will increase and the utility of risk assessment based on this metric should improve.[64]

This study represents an early exploration of the potential benefits of risk stratified screening incorporating family history and polygenic risk. While our results suggest that uniform screening is currently more cost effective than personalised screening, our investigation highlights important future opportunities for screening based on this metric. As technology advances, costs for determining risk decrease, and improvements in risk stratification occur, we believe that personalised screening will become an increasingly cost effective and

attractive option. Despite the potential health gains, personalising screening will introduce a range of new and significant challenges for population screening policy makers. These fundamental economic, ethical and policy issues must be identified and resolved before personalised screening could be implemented.

METHODOLOGICAL CONSIDERATIONS

The majority of studies in this thesis have used the MISCAN-colon model to simulate the effects of potential colorectal cancer screening policy changes. MISCAN-Colon has been used extensively to guide public health research and policies for more than two decades. It has influenced policy around the globe, including in Australia,[28] the Netherlands,[65] Canada[66] and the USA.[67, 68] However, like all research, there are strengths and limitations and in light of this, the findings of this thesis should be interpreted with caution.

STRENGTHS OF MISCAN-COLON

MODEL VALIDATION AND CALIBRATION

One of the major strengths of the MISCAN-Colon model is that it has been extensively externally validated. The model has successfully replicated the results of large screening and surveillance studies, such as the randomised trials of guaiac faecal occult blood testing in Minnesota, Funen, and Nottingham,[69] the CoCap sigmoidoscopy study,[70] and the National Polyp Study.[71] The MISCAN-Colon model was able to explain observed colorectal cancer incidence and mortality trends in the United States when accounting for risk factor trends, screening practice, and chemotherapy.[72] MISCAN-Colon has successfully replicated the colorectal cancer incidence and mortality reduction of two large flexible sigmoidoscopy screening trials – the United Kingdom Flexible Sigmoidoscopy Screening trial[73] and the Norwegian Colorectal Cancer Prevention trial.[74] This comprehensive validation of the model supports its reliability and suggests that it can be a useful tool to aid decision making on colorectal cancer screening.

Validation and calibration of the model also help to explain the unobservable parameters. For example, the average preclinical duration of colorectal cancer was estimated using data from the Nottingham, Minnesota, and Funen trials on the effectiveness of screening with guaiac faecal occult blood test.[69] Similarly, data from the United Kingdom Flexible Sigmoidoscopy Screening trial which assessed the effectiveness of one-time sigmoidoscopy screening was used to estimate the average adenoma dwell-time.[73]

Although identified as a key strength of the MISCAN-Colon model, ongoing validation and calibration is a critical iterative process that ensures model accuracy. As new evidence becomes available, it will provide opportunities to test the underlying structure and accuracy of assumptions of the model, the results of which will allow further refinement and

improvement of the model. For example, although the effectiveness of screening for colorectal cancer has been demonstrated in randomised control trials of guaiac faecal occult blood testing and sigmoidoscopy,[38, 75-78] this evidence is lacking for colonoscopy and faecal immunochemical testing. Although colonoscopy and faecal immunochemical testing are likely to be at least as effective, there are currently no published randomised controlled trials to support this assumption. Fortunately, this evidence will soon be available as randomised controlled trials assessing the effectiveness of colonoscopy and faecal immunochemical testing are soon to be published.[79, 80] These investigations will provide important future opportunities for validation of the MISCAN-Colon model.

In addition, there is uncertainty about the development of colorectal cancer over time. Although individuals with adenomas are recommended to undergo colonoscopy surveillance to prevent subsequent colorectal cancer, the relationship between adenomas at colonoscopy and long-term colorectal cancer incidence remains unclear. While investigations where adenomas were removed at colonoscopy have shown a decrease in colorectal cancer incidence (with median follow up durations of 7.7-13 years), [81, 82] modelling by our research group has suggested that, despite the removal of adenomas, colorectal cancer incidence will increase over a lifetime.[83] There is no empirical evidence to support this finding as investigations with a follow up period longer than 20 years are lacking. Ongoing follow up of existing investigations into the impact of the removal of adenomas on colorectal incidence and mortality[81, 82] will help to provide the data required to evaluate this finding. In addition, the long term follow up of investigations assessing the impact of screening will allow us to more accurately estimate the long term effectiveness of screening.[38, 75]

INCLUSION OF SYSTEMATIC FALSE POSITIVITY AND SYSTEMATIC FALSE NEGATIVITY OF STOOL-BASED TESTS

It was previously assumed that consecutive screening rounds utilising faecal occult blood tests were independent of each other. This suggested that the gains in sensitivity which occurred when screening programs moved from guaiac to immunochemical stool tests would be retained over all screening rounds. However, an investigation by colleagues in our team established that this assumption was incorrect.[84] Using data from multiple rounds of the Dutch FIT screening trials, the authors found that individuals with a false positive test result in one screening round were at increased risk of having another false positive test result (probably due to other conditions that cause bleeding such as haemorrhoids) in the subsequent screening round. In addition, those with a false negative test result were at increased risk of having another false negative test result (probably because they have a type of adenoma that is less likely to bleed). This indicates that a proportion of adenomas are systematically missed by repeat FIT screening, thereby reducing its efficacy. By including the impact of systematic false negative and systematic false positive results in our analyses, we are able to more accurately assess the effectiveness of FIT screening programs. This is particularly important in

analyses where FIT is compared to other screening modalities, such as in **Chapters 5** and **6**, where we compare FIT and colonoscopy screening. At present, MISCAN-Colon is the only microsimulation model that assesses the impact of systematic test characteristics.

LIMITATIONS OF MISCAN-COLON

Despite the usefulness and benefits of using MISCAN-Colon to inform policy questions, there remain methodological issues that require due consideration.

WEAKNESSES OF THE NATURAL HISTORY COMPONENT

Although colorectal cancer is now known to arise from both the conventional adenoma-carcinoma sequence and the serrated-polyp pathway, MISCAN-Colon currently only simulates the adenoma-carcinoma sequence as a carcinogenic pathway. At the time MISCAN-Colon was developed, serrated polyps were not considered to be an important contributor to colorectal cancer and therefore the serrated-polyp pathway was not explicitly simulated. The pathway is indirectly simulated as the development of colorectal cancer was calibrated to the UK flexible sigmoidoscopy screening trial which included both conventional and serrated polyps[73] and detection is reflected in the lack of specificity of colonoscopy. However, as it is now suggested that the serrated-polyp pathway may account for up to 30% of all colorectal cancers,[85-87] their inclusion in the natural history component of the model is warranted. While the inclusion of this pathway has been shown to have very limited impact on the effectiveness of FIT screening[88] and is unlikely to impact the results in the analyses contained within this thesis, its incorporation is important for comparing screening effectiveness across a range of modalities with varying sensitivity for serrated lesions. For example, the multi-target stool DNA test has been shown to have an increased sensitivity for sessile serrated lesions compared to the FIT.[89, 90] As the model currently does not include the serrated-polyp pathway, the cost-effectiveness of the multi-target stool DNA test compared to FIT may potentially be underestimated.

Our research group is currently working on incorporating a separate pathway for serrated lesions into the natural history component of MISCAN-Colon, however including this pathway will not be without its challenges. Although it is now considered an important pathway in the development of colorectal cancer, we have only recently been able to gather enough information about their natural history and outcomes. Compared to the more common adenomatous polyp, sessile serrated polyps are more likely to be located in the proximal colon and are less likely to bleed.[85-87] In addition, there does not appear to be a relationship between prevalence and age.[91] While approximately half of individuals with a sessile serrated polyp will also have conventional adenomas, fewer are diagnosed with multiple sessile serrated polyps compared to individuals with a typical adenoma. These clinical features impact the effectiveness of different screening modalities and therefore the inclusion of the sessile

serrated polyp pathway may have implications for both the effectiveness and cost-effectiveness of colorectal cancer screening.

Despite the significant gains in knowledge of the sessile serrated polyp pathway, there remains noteworthy uncertainty regarding the risk of progression, detectability and recurrence of serrated lesions and the survival associated with the cancers that they cause. As such, their incorporation will require several assumptions which will need to be rigorously validated. Exploring these uncertainties and assumptions will enable us to gain insight into the natural history of this pathway, which will ultimately improve our understanding of the sessile serrated polyp pathway and the accuracy of the MISCAN-Colon model.

SCOPE OF SCREENING AND SURVEILLANCE COMPONENTS

Although the screening and surveillance components of the MISCAN-Colon model are extensively developed, there remains opportunity to broaden their scope. While the screening component can comprehensively assess the impact of a single screening test, it is currently unable to model opportunistic and programmatic screening occurring in the same population. This is pertinent for a variety of situations including where multiple screening tests are available (such as the US); or where programs are transitioning from opportunistic screening or operate in hybrid environments where screening can be performed outside the program (such as Australia and Canada).

Within the surveillance component it is possible to differentiate adenomas by multiplicity and size, however, it is currently not possible to include the molecular characteristics of lesions. This will become increasingly important as new surveillance guidelines now include molecular characteristics as a method to stratify the surveillance strategies.[92, 93] We hope to be able to add molecular characteristics such as dysplasia and villous aspect to our model in the future.

UNCERTAINTY IN MODEL ASSUMPTIONS

Although MISCAN-Colon has repeatedly been verified as a reliable tool for informing colorectal cancer screening, it is important to note that the accuracy of a model's predictions reflects the quality of their assumptions. Where possible, our assumptions are informed by empirical data from sources such as cancer registries, mortality databases, randomised control trials and cohort studies. However, this is not always feasible as some parameters are not directly observable and for others data is scarce and difficult to obtain. In these circumstances, we are required to make assumptions which increases the uncertainty of our model predictions.

One noteworthy assumption is the application of adherence patterns. Compared to other screening programs such as breast and cervical cancer screening, colorectal cancer screening programs are relatively new. This means that we are unable to discern long term patterns of screening adherence. Although in **Chapters 2** and **6** we use repeat adherence based on real

data, the data is limited in scope in that is it provided in 5-yearly intervals and as screening only started in Australia in 2006, it is limited in duration. Understanding patterns of adherence is important as it is a key determinant of screening effectiveness and therefore the estimated impact of a screening program should be determined based on this. In order to determine optimal screening, we often use perfect adherence. This allows us to estimate the impact of screening among individuals who are willing to participate in all screening and follow up tests where indicated. Although perfect adherence is improbable and the estimated effects of colorectal cancer screening are likely to be overestimated and unrealistic, it is important from an ethical viewpoint, as otherwise those who adhere to the guidelines would be over screened.

A second noteworthy assumption relates to the costs associated with screening. Costs are an important driver of cost-effectiveness and it is therefore important that assumptions accurately reflect real life. Unfortunately, cost data is often scarce or difficult to obtain, thereby limiting accurate estimates. Although our cost assumptions are usually based on data available in the public domain, these are not always an accurate reflection of the real costs. For example, in **Chapter 6** we base the cost of the FIT on a commercially available FIT and the cost of a polygenic testing on a commercially available polygenic test for breast cancer. In both instances, these costs are unlikely to reflect the true cost as screening programs will have commercial contracts with test providers which would likely result in reduced costs. Moreover, in the case of the polygenic test, it is possible that a single test would be used to assess polygenic risk for multiple diseases and therefore it is difficult to accurately determine how much of the cost for establishing risk should be allocated to a colorectal cancer screening program. In **Chapter 2,** we relied on expert opinion as the costs of the FIT was not publicly available. To alleviate these issues, we often conduct sensitivity analyses where we adjust the costs to assess their impact on our findings. For example, in **Chapter 1** we provided lower and upper cost estimates by assuming a 50% reduction and two-fold increase in costs associated with screening for Lynch syndrome. Likewise, in **Chapter 2** we assessed the impact of changes to the cost of the FIT to the same degree and our results were robust to these changes.

To increase transparency, we declare and justify our assumptions by providing detailed information to explain how and why they were derived and used. This provides readers with clarity, ensuring they can accurately interpret and understand our assumptions and allows opportunities for readers to dispute or suggest other more relevant or appropriate sources.

ACHIEVING OPTIMAL SCREENING PROGRAMS – THE IMPORTANCE OF MODELS

Underscoring our findings is the importance of models in answering policy questions. As screening expands globally, new screening tests and technologies are developed, improvements in cancer therapies are made, changes in costs occur and opportunities for personalisation are identified, decision analyses using microsimulation models will be critical. It is highly unlikely that any country could undertake the number of pilot studies required to determine the optimal screening strategy for their population. It is even more unlikely that there will be enough empirical evidence to unquestionably choose one screening strategy over another. Although modelling should never replace randomised control trials or other methods of gathering empirical data, modelling offers a feasible alternative to expensive and protracted clinical trials and allows policy makers to make screening policy decisions in an informed and transparent manner.

In an effort to improve cancer outcomes across Europe, our group, in collaboration with several European partners, established EU-TOPIA (Towards improved screening for breast, cervical and colorectal cancer in all of Europe).[94] EU-TOPIA aims to evaluate and quantify the harms and benefits of screening programs for breast, cervical, and colorectal cancer and identify ways to improve health outcomes and increase equity. To do this, the group developed an open, online, and user-friendly tool (the "EU- TOPIA evaluation tool" available at https:\\miscan.eu-topia.org). Incorporating the validated structure of the MISCAN-Colon model,[95] the tool allows European researchers and policymakers to use country-specific data (demographic, epidemiological, and cancer screening information) to simulate and assess the future benefits of colorectal cancer screening in their countries and the impact of changes and improvements to their screening programs.[95]

CHALLENGES TO ACHIEVING OPTIMAL SCREENING PROGRAMS

Within this thesis we have investigated several pathways which will help to optimise colorectal cancer screening programs. Despite the benefits, challenges exist in achieving this desired outcome. Below we identify and discuss the implications of some of these challenges.

ENSURING THE BEST UNIFORM SCREENING PROGRAMS

The investigations contained within the first part of this thesis, and several others from our research group,[65-68] demonstrate the importance of selecting the appropriate program characteristics and implementation timelines for uniform screening programs. Although program characteristics are key to ensuring program effectiveness, implemented colorectal cancer screening programs differ significantly in terms of screening tests, referral threshold for follow-up testing, target age ranges and screening intervals.[19] This reflects the diverse interpretation of existing evidence by policy makers and the need to consider local priorities,

resource capacity and costs. The values and preferences of the population undergoing screening also need to be considered as they affect screening uptake.[96]

For example, in **Chapter 2** we demonstrate that although the screening strategy used in the Shanghai screening program was effective at reducing colorectal cancer incidence and mortality, the benefits of screening were increased and the burden reduced under an alternative screening strategy utilising a validated FIT. However, this strategy expands the target age range and reduces the interval of screening. Therefore, despite this strategy being optimal in theory, it may not be optimal in practice given the already low participation in screening in Shanghai. As effectiveness of screening is largely determined by participation, ensuring adequate adherence to the screening program would likely yield better results.

Our results in **Chapter 3** show that an implementation timeline of a screening program has a significant impact on incidence and mortality.[28] Although choosing an expedited timeline will avoid unnecessary burden of colorectal cancer in the population, the optimal implementation timeline will largely be determined by health system capacity. Implementing a screening program too quickly may result in demand outstripping supply, the consequence of which will be delayed diagnosis and treatment. Timely access to diagnosis and treatment is essential as delays have been shown to have a clinically relevant effect, increasing cancer incidence and mortality, and decreasing the overall benefits of screening.[97, 98] An appropriate implementation timeline will circumvent demand outstripping supply and ensure appropriate use of health system resources. Political landscape and adequate funding models may also play a role.

In addition, organised screening programs may face organisational challenges. For screening to achieve its full benefit, population registries need to be complete and fully functional so that the screening program can effectively reach the target population. Real-time monitoring and evaluation systems are required to allow ongoing assessment of screening outcomes and if necessary enable adjustment to the screening program so that it achieves its intended impact. Quality assurance measures, which ensure the quality of the screening program need to be defined and regularly reported against to ensure all elements of the screening program are appropriately functioning. Identifying and addressing organisational and stakeholder barriers to screening programs will help to ensure their optimal implementation and uptake.

CHALLENGES TO PERSONALISATION

Although the benefits of colorectal cancer screening are well-established, until recently, research in this field has largely focussed on the effectiveness of uniform, one size fits all, screening in the “average” population. However, by ignoring other factors that play a role in the determination of risk this approach does not consider the heterogeneity of the population. Despite the importance of improving uniform screening programs, it is increasingly recognised

that individuals differ and, as a consequence, they may not benefit equally from the same screening protocol. Within a uniform screening program, it is likely that those at higher risk are under-screened while those at lower risk are over-screened. Moreover, the vast majority of individuals who undergo screening will have no neoplastic findings.[99] These individuals shoulder the burden and potential harms associated with screening participation, but forgo receiving its benefits. This provides a compelling argument to investigate methods that will reduce the burden on those who are least at risk and identify those individuals that will benefit most from screening.

Personalisation of screening is an emerging method to optimise colorectal cancer screening programs. In theory, personalised screening offers an opportunity to improve the effectiveness of colorectal cancer screening programs by providing screening recommendations which are tailored to an individual's unique circumstances.[100, 101] Using this approach, an individual's characteristics are used to predict the benefits, burden, harms, and costs of screening. In this way, personalised screening has the potential to not only reduce harms and increase the benefits of screening, its implementation may help to redistribute and preserve scarce health care resources.

Although our investigations in **Chapters 4, 5,** and **6** demonstrate the potential gains to be made by personalising screening, to date there are no population level screening programs that offer such recommendations. There are several challenges that screening programs must consider before personalised screening can be implemented. Within this section, we address a selection of these challenges. However, regardless of the challenges, efforts to improve the selection of candidates for cancer screening through personalisation warrants continued investigation and we believe that personalisation will play an important role in improving future screening programs.

DETERMINING BASELINE RISK

Risk of colorectal cancer is affected by several factors that are often not independent of each other. Accurately determining an individual's baseline risk is therefore a complex process that is affected by several factors including the selection and implementation of risk prediction models, the establishment of accurate information and the impact of acquiring additional information on screening uptake.

Risk prediction models are frequently used to predict an individual's risk of a disease based on known risk factors. They help to identify individuals most likely to benefit from screening, or other health intervention. The advantage of using risk prediction models is that they incorporate multiple variables. However, at present, the discriminatory performance of risk prediction models remains suboptimal.[102] Moreover, there are noteworthy challenges to their implementation. For example, there are several colorectal cancer risk prediction models available. Although the models demonstrate similar discriminatory performance,[102, 103]

decision makers must first choose the most appropriate model for their population. Once a model has been selected, due consideration must be given to the of cut-off points which will change the nature and/ or frequency of screening. There have also been difficulties in translating simple risk estimates into clinically meaningful estimates of benefit.[104, 105] Our investigation in **Chapter 4**[33] was, in part, an attempt to alleviate this issue.

In the analysis, we used the QCancer Calculator.[106] This model was chosen for several reasons.[34] Firstly, the model has been internally and externally validated and discriminatory performance is considered to be one of the best for both men and women.[107, 108] Secondly, the calculator predicted risk estimate over a 15-year time horizon, which was deemed important as it enabled the validation of our modelled predictions against trial data. Finally, the calculator is available online and only includes risk factors that are routinely collected. Although this model was chosen for several valid reasons, it may not be appropriate in all settings. We provided results stratified by baseline 15-year colorectal cancer risk (1-7%) for those aged 50-79 years. In doing this, we did not address the challenges in determining appropriate cut-offs (although this was addressed in a corresponding investigation[34]), nor did we address how the calculator may be implemented in practice.

Challenges also exist in establishing accurate information on family history and risk factors. In our investigations into personalised screening using these measures (**Chapters 4** and **6**) we assume that all individuals were accurately assessed for family history of colorectal cancer and honestly reported other risk factors – however this is unlikely the case in practice. Family history and patient risk factors are generally self-reported, a method that is subject to a number of biases, which can lead to an underestimation of risk.[109, 110] Moreover, availability of this information may be limited or not readily accessible. As the effectiveness of personalised screening will be impacted by the precision with which the population is stratified, methods to improve the accuracy of these metrics warrant investigation. Consideration will need to be given to the variation of risk factors over an individual's lifespan.

In recent years, genome-wide association studies have identified a number of single-nucleotide polymorphisms (SNPs) associated with colorectal cancer risk. In isolation, SNPs are only weakly associated with colorectal cancer risk, however, combining multiple SNPs into a polygenic risk score has been shown to explain substantial variation in risk.[62, 111, 112] Although our investigation into the cost-effectiveness of personalised screening based on polygenic risk and family history (**Chapter 6**) suggests that, at present, the discriminatory performance of risk stratification based on this metric is currently suboptimal, we believe that this tool holds great promise in the future. As additional SNPs associated with colorectal cancer risk are discovered, which since our analysis have risen from 45[112] to 100,[113] the utility of this measure should improve. In addition, as demand for genetic testing increases, costs for determining

polygenic risk will likely decrease. Both of these eventualities have shown personalised screening incorporating polygenic risk to be cost effective compared to uniform screening.[114]

Finally, the gathering of additional information to determine an individual's risk, may impact participation. Although many risk factors are routinely collected in healthcare settings, there is a possibility that this requirement may present a barrier to screening participation. Furthermore, to establish a polygenic risk score a once in a lifetime genetic test is required. Although it has been demonstrated that genetic testing for colorectal cancer is acceptable to the community,[115] this does not mean that all individuals will be willing to undergo testing. Valid concerns have been raised over privacy and confidentiality of identifiable personal data and its possible misuse.[116, 117] If individuals do not consent to testing, the effectiveness of risk stratification may be diminished. There are also other economic, ethical and policy issues that will need to be resolved before personalised screening incorporating genetic information could be implemented.[117] These include, but are not limited to, logistical issues such as secure sample storage, ethical considerations about consent to access to genetic, lifestyle and medical records over an individual's lifetime and ethical and policy matters pertaining to the management of incidental findings and reporting of the variants of unknown significance identified as a result of genetic testing.[118]

IMPLEMENTATION OF PERSONALISED SCREENING RECOMMENDATIONS

Implementation of personalised screening guidelines may be problematic without the appropriate tools to assist health care practitioners and individuals to assess risk and make appropriate, informed decisions. Thus, before personalised screening could be implemented, such tools would need to be developed. For example, in **Chapter 5**,[48] we suggest using the results of our investigation to develop an electronic clinical decision support system. More simply, a generic matrix containing appropriate information related to bands of relative risk based on personal risk factors (including factors such as age, screening history, comorbidity and polygenic risk) and screening strategy (including screening test, starting ages, stopping ages and intervals). These tools would need to be assessed for validity and reliability before being implemented on a larger scale.

Program organisation may also need to be reconsidered. In opportunistic settings, potential screenees generally meet with their health care provider and screening may be offered. This presents an obvious opportunity for personalisation to occur. Implementing personalised screening might be more challenging in an organised screening program as this face to face opportunity is generally not available. In such a setting, investment in a comprehensive health education campaign may help to alleviate this issue.

IMPACT OF PROVIDING RISK INFORMATION ON SCREENING UPTAKE

There is strong evidence that the provision of personalised risk information improves informed consent and accuracy of perceived risk, however, the evidence for improving screening uptake remains weak.[119] When personalised risk information for colorectal cancer is presented as a categorised risk (e.g. 'low', 'medium', 'high') it has been shown to elicit a small but significant increase in uptake of screening,[120-122] however, the same effect is not achieved when risk information is provided using a numerical risk score[123] or a personal risk factor list.[124-129] Similar results are seen across a range of screening tests.[119] However, these analyses did not provide information on genetic risk of colorectal cancer. Incorporating this information has a positive effect on willingness to start screening[130] as well as alter health-related behaviours.[130-133] This suggests that the included risk factors and the manner in which risk information is communicated is important. As changes in health-related behaviour may ultimately result in reductions in colorectal cancer incidence and mortality, further investigation into this is warranted.

ADHERENCE TO PERSONALISED SCREENING RECOMMENDATIONS

Ideally, the provision of risk information would encourage individuals to participate in screening according to their recommended program. However, in an investigation of women's attitudes towards modified frequency of mammography screening based on genetic risk, 85% of women were willing to participate in more frequent screening, however only 59% were willing to undergo less frequent screening.[134] If individuals do not adhere to their personalised screening strategy (i.e. if those at lower risk are not willing to undergo less intense screening where indicated), it remains uncertain whether the expected benefits will be achieved. For the benefits of personalised screening to be realised, it is essential that individuals be willing to follow their personalised screening strategies.

Moving to personalised screening from a universal screening program will naturally increase the program complexity. This has the potential to create confusion and it remains unknown what impact it would have on screening adherence. For example, it is feasible that individuals within the same household could have different screening protocols. Any increase in effectiveness provided by personalised screening recommendations could easily be offset by potential reductions in screening participation. As developing a clear, concise message may be difficult, it will be important for policy makers to investigate methods to effectively communicate this complicated message and improve health literacy.

Furthermore, as cancer risk is higher in individuals who do not attend screening, increasing adherence to current screening guidelines will potentially yield better results than personalised screening. Encouragingly, individuals at increased risk of colorectal cancer, whose recommended screening and surveillance guidelines differ from the average risk

population, have been shown to be more compliant to screening guidelines.[135, 136] This offers hope that personalised screening recommendations could improve screening adherence.

FUTURE PATHWAYS TO OPTIMISE SCREENING

Although the work described in this thesis highlights various pathways to optimise colorectal cancer screening, cancer screening is a dynamic and rapidly developing field of research. Screening is expanding across the globe, new screening tests and technologies are being developed, and improvements in cancer therapies are being achieved. Such developments give rise to several opportunities for future research using modelling to determine their potential benefits. In the following section, a selection of these opportunities is discussed.

IMPROVE SCREENING AND SURVEILLANCE FOR LYNCH SYNDROME

Although Lynch syndrome is only responsible for a small proportion of colorectal cancers, its identification can save lives. While international consensus recommends universal screening for Lynch syndrome,[1-3] our analysis in **Chapter 1** suggests that screening for Lynch syndrome should occur in all individuals diagnosed with colorectal cancer who are aged below 70 years (noting those aged over 70 years were under-represented in our study population). In addition, our investigation did not assess the impact on testing first degree relatives. While a subsequent modelling study has shown this to be cost effective for those aged below 70 years,[137] future research should investigate the effectiveness of Lynch syndrome screening and cascade testing in the older population.

Despite the recommendation of universal screening, globally significant disparity in the implementation of Lynch syndrome screening exists.[138-143] In the United States, just 28% of individuals diagnosed with colorectal cancer undergo MMR testing,[139] while in Australia, less than 50% of accredited pathology services have implemented universal tumour screening and a variety of screening protocols are in use.[140] In the United Kingdom, the National Health Service faces similar issues relating to the diversity of screening protocols and the implementation of screening for Lynch syndrome has been described as “patchy and inconsistent”, with many different screening protocols in use[143] and in Canada, identification of potential cases of Lynch syndrome depends largely on individual clinicians,[142] as there is no standardised and integrated approach to identifying patients with Lynch syndrome.[141, 142] Consequently, Lynch syndrome often remains unidentified and underdiagnosed.[141, 142] Future research will need to identify setting specific barriers to implementation and investigate ways to overcome them. This will likely include the development of standardised testing policies to ensure program quality and consistency, provision of adequate funding and resources and improved education for healthcare providers.[142-144]

In those diagnosed with Lynch syndrome, intensive surveillance has been demonstrated to reduce colorectal cancer mortality. At present, surveillance guidelines recommend annual to biennial colonoscopy, commencing between the ages of 20-25 years.[1-3] However, improved understanding of the mutations that cause Lynch syndrome suggests that this approach may not be optimal. Lynch syndrome is an inherited condition caused by a mutation in one of four mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) and EPCAM deletion.[145] Risk of colorectal cancer and age of disease onset vary by mutation type, suggesting that surveillance could be stratified. For example, the risk of colorectal cancer is lower and the age of diagnosis is later in carriers of MSH6 or PMS2 mutations, suggesting that cancer surveillance could be offered from a later age.[146, 147] It may also be possible to extend the surveillance interval, with recent investigations finding that colonoscopy every one to two years does not result in lower incidence of colorectal cancer in MLH1 and MSH2 carriers compared to surveillance every three years.[148, 149] Further investigation into the benefits and impact of risk stratified surveillance for those with Lynch syndrome is warranted.

Personalise by previous FIT result

Screening with FIT could also be personalised by using the findings of the previous screening round. An investigation using the results from the first two rounds of the Dutch colorectal cancer screening program established that haemoglobin detected in the stool was a strong predictor for future cancer risk.[150] Compared to those without blood detected in their stool, individuals with a haemoglobin level between 15 and 47 µg Hb/g faeces in the first round were 23 times more likely to be detected with an advanced neoplasia in the second round. Similar results were found in Italy.[151] This suggests that individuals with higher concentrations of faecal haemoglobin could be invited to screen earlier than currently recommended, while those with lower concentrations may not need to screen as frequently. As data pertaining to the faecal haemoglobin concentration may be present in screening program registries, personalising screening recommendations based on this metric is quite feasible. Our group is currently working to establish a randomised controlled trial to demonstrate the feasibility, acceptability and superiority of personalised screening based on faecal haemoglobin concentration.

Combine risk factors to refine personalisation

Personalised screening recommendations are becoming increasingly feasible and desirable. While in **Chapters 5, 6,** and **7** we investigate opportunities to personalise colorectal cancer screening, there remains significant opportunity to refine personalisation. To accomplish this, it will be necessary to develop a comprehensive model that considers as much relevant information as possible to improve the discriminatory accuracy of risk stratification algorithms. While this should include many of the risk factors addressed in the investigations

contained within this thesis, it will be important to combine these factors as this will provide a more precise estimate of the true benefits of personalised screening.

The most comprehensive risk prediction model currently available includes family history, 19 lifestyle and environmental factors and 63 SNPs associated with increased risk of colorectal cancer.[152] Unfortunately, even with such a comprehensive risk prediction model there is room for improvement of the discriminatory accuracy. The growing number of SNPs associated with colorectal cancer risk should improve the discriminatory performance of risk stratification algorithms.

Moreover, this model does not include important risk factors such as an individual's health status (comorbidity) and screening history. Our work demonstrates that these factors are highly predictive of colorectal cancer risk and screening benefit which substantially impacts screening effectiveness (**Chapter 5**).[48-50] However, in our analysis, personalisation was based on grouping individuals into broad comorbidity and screening history categories. Although the comorbidity conditions were based on administrative data from SEER,[153] they were relatively general and somewhat limited in scope in so far as they only factored in the most common medical conditions and did not include cancer. In future, it may be pertinent to assess comorbidity using the Charlson comorbidity index, which may be more commonly used in practice. Moreover, the screening histories were simplified into five discrete groups which is unlikely to reflect what is happening in practice. Such broad categorisation will need to be refined to ensure true personalisation is achieved.

Although complex, machine learning can assist in the determination of risk profiles and microsimulation models like MISCAN-Colon can be used to determine the optimal screening strategies. This will include screening start and stop ages, interval and test. Such work should provide guidance in the colorectal cancer screening policy landscape and ultimately result in changes to clinical practice and improvements in public health.

Optimise surveillance

As individuals with adenomas are recommended to undergo colonoscopy surveillance to prevent subsequent colorectal cancer, surveillance colonoscopies account for a considerable proportion of ongoing colonoscopy demand. Adherence to surveillance colonoscopy guidelines is important to ensure effectiveness and efficiency of surveillance and maintain adequate access. Unfortunately, surveillance guidelines are often not accurately adhered to – investigations in Canada and the Netherlands report the that close to 50% of surveillance colonoscopies are performed earlier than recommended.[98, 154]

While a large proportion of individuals are seen too often, there are others who are referred to colonoscopy who experience significant delays in access.[155-157] As noted above, such delays have been associated with increases in colorectal cancer incidence and mortality.[97, 98] As

colonoscopy capacity is an essential component of an effective screening program, interventions aimed at improving adherence to surveillance guidelines, thereby ensuring its optimal use, are warranted.

A more personalised approach to surveillance may assist in achieving this outcome. Surveillance intervals are commonly based on adenoma characteristics such as the number, size, villosity and dysplasia grade found at the most recent colonoscopy.[158-160] Recent surveillance guidelines in the Netherlands have moved towards a more personalised approach to surveillance intervals. The Dutch guidelines stratify patients by an adenoma risk score (0-5) derived from a range of individual adenoma characteristics.[161] This more nuanced approach to surveillance should improve decisions on repeat colonoscopy by identifying which patients should be offered less, or more intensive, surveillance. Importantly, it has been shown to reduce colonoscopy demand without compromising the effectiveness of surveillance in terms of colorectal cancer detection and life-years gained.[162]

However, by basing surveillance intervals solely on adenoma characteristics determined at the most recent colonoscopy, earlier or overall colonoscopy results, and their impact on risk of subsequent colorectal cancer, are not considered. For example, the recurrence of advanced adenoma at second surveillance is consistently higher in patients with high-risk adenomas at most recent colonoscopy than in patients with low-risk adenomas.[160, 163] These individuals may therefore benefit from a shorter interval between surveillance colonoscopies. The new Australian surveillance guidelines now differentiate between the initial diagnostic colonoscopy and the subsequent two surveillance colonoscopies,[92] recommending different surveillance intervals dependent of the findings of up to two previous colonoscopies. Further refinements to this strategy are possible, and our research group is part of an investigation assessing the of the risk of colorectal cancer in individuals based on findings over multiple surveillance colonoscopies.[164]

CONCLUSIONS

Based on the results of the studies described in this thesis, we derived the following conclusions:

- The optimal screening pathway to identify Lynch Syndrome includes MMR immunohistochemistry followed by MLH1 methylation (if indicated) and germline testing. Screening should be restricted to those under 70 years. (**Chapter 1**)
- Although the screening program that is currently implemented in Shanghai is effective at reducing colorectal cancer incidence and mortality, using a validated test would result in improved efficiency. (**Chapter 2**)
- Protracted implementation timelines result in unnecessary disease burden. While consideration needs to be given to resources, screening should be implemented in an expedited manner. (**Chapter 3**)
- The background risk of colorectal cancer influences the effectiveness of colorectal cancer screening, such that the absolute benefit of screening increases with increasing risk. (**Chapter 4**)
- All screening strategies are effective at reducing colorectal cancer mortality over 15 years follow-up. Follow-up time impacts the magnitude of effect – a longer follow-up (lifetime) results in larger reductions in colorectal cancer incidence and mortality. (**Chapter 4**)
- An individual's comorbidity and screening history are important determinants of the balance of harms and benefits of screening and can be used to establish the optimal age to stop screening. Individuals without comorbidities or who are screening naïve could continue screening past the recommended stop age, in some cases up to 90 years of age. Others, such as those who have severe comorbidities or high levels of participation should consider stopping screening earlier. (**Chapter 5**)
- Although personalised screening based on polygenic risk and family history is an effective method to reduce colorectal cancer incidence and mortality, with the current discriminatory performance and cost of determining colorectal cancer risk, it is not cost effective compared to uniform screening. This may change as more common genetic variants associated with colorectal cancer are discovered or as the cost of determining risk decreases. (**Chapter 6**)

RECOMMENDATIONS

Based on these conclusions, we formulated the following recommendations:

In Australia, all colorectal cancer cases below the age of 70 years should be tested for Lynch syndrome using immunohistochemistry followed by MLH1 methylation (if indicated) and germline testing.

The cost-effectiveness of screening for Lynch syndrome in those over the age of 70 years should be further investigated.

Countries with low incidence should also consider the benefits of implementing screening, as even in this setting screening can be a cost-effective method to reduce colorectal cancer related incidence and mortality.

To avoid unnecessary deaths from colorectal cancer, the implementation of screening programs should not be unnecessarily delayed.

Decisions about when to stop screening should be based on an individual's screening history and comorbidity. To assist clinicians and participant in making these decisions, decision aids should be developed.

Research into the discovery of additional common genetic variants that are associated with colorectal cancer risk is warranted to improve the discriminatory performance of risk stratification using this measure.

To improve the discriminatory performance of risk stratification, personalised screening guidelines should contain a comprehensive set of factors including screening history, comorbidity, polygenic risk, family history and environment and lifestyle risk factors.

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MODEL APPENDIX

INTRODUCTION

This appendix provides a detailed description of the MISCAN-Colon model, outlining the assumptions and the parameters that inform the model. In brief, it describes the model structure and details the quantification of model parameters that are common to all analyses. Parameters that differ between the individual chapters are presented in the final part of the appendix.

MODEL OVERVIEW

The Microsimulation Screening Analysis-Colon (MISCAN-Colon) model is a stochastic, semi-Markov, microsimulation model that is useful in explaining and predicting trends in colorectal cancer incidence and mortality and to quantify the effects and costs of primary prevention of colorectal cancer, screening for colorectal cancer and surveillance.

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. Possible events are birth and death of a person, adenoma incidence and transitions from one state of disease to another.

MODEL STRUCTURE AND QUANTIFICATION OF COMMON PARAMETERS

At two expert meetings at the National Cancer Institute (Bethesda, Maryland, United States of America) held on June 5–7, 1996, and May 12–13, 1997, the structure of the model was devised in agreement with the currently accepted model of the adenoma–carcinoma sequence. MISCAN-Colon consists of 3 modules: a demography module, natural history module, and screening module (Figure 1). Although these parts are not physically separated in MISCAN-Colon, it is useful to consider them separately.

DEMOGRAPHY MODULE

The demography module of MISCAN-Colon simulates individual life histories without colorectal cancer to form a population. Using birth tables and life tables representative of the population under consideration, the model draws a date of birth and a date of non-colorectal cancer death for each simulated individual. Life tables often include mortality related to colorectal cancer. However, as the percentage of colorectal cancer mortality in overall

mortality is small and the data on colorectal cancer deaths by age, sex and race are sparse, no adjustment to the life tables is made. The model restricts the maximum age a person can achieve to 100 years.

NATURAL HISTORY MODULE

In the natural history module, MISCAN-Colon simulates the development of colorectal cancer in the population. It was assumed that all colorectal cancers are preceded by adenomas. As each simulated individual ages, one or more adenomas may develop (Figure 2). These adenomas can be either progressive or non-progressive and both can grow in size from small (≤5 mm), to medium (6–9 mm), to large (≥10 mm). Only progressive adenomas can develop into preclinical cancer and these may progress through stages I to IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. After clinical diagnosis, colorectal cancer survival is simulated using age-, stage-, and localisation-specific survival estimates for clinically diagnosed colorectal cancer specific to the population being modelled. For individuals with synchronous colorectal cancers at time of diagnosis, the survival of the most advanced cancer is used. The date of death for individuals with colorectal cancer is set to the earliest simulated death either because of colorectal cancer or because of another causes (see Demography model).

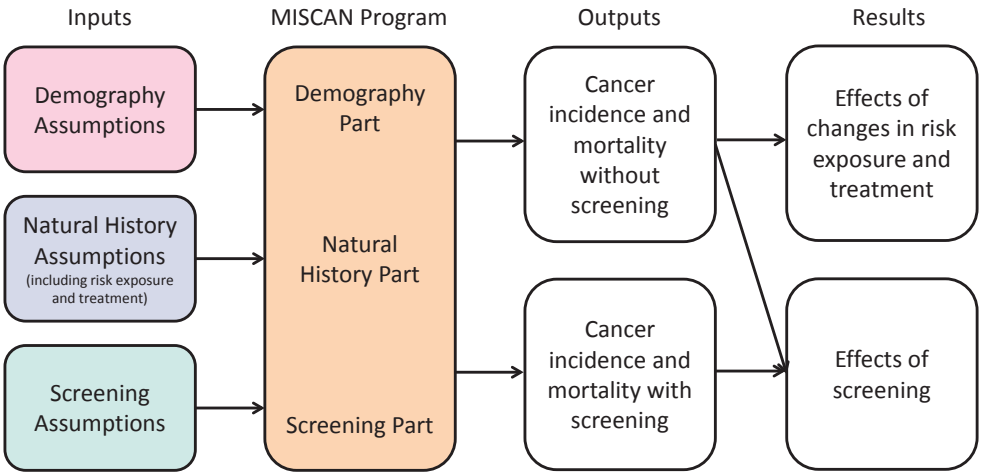


Figure 1: Structure of MISCAN-Colon.

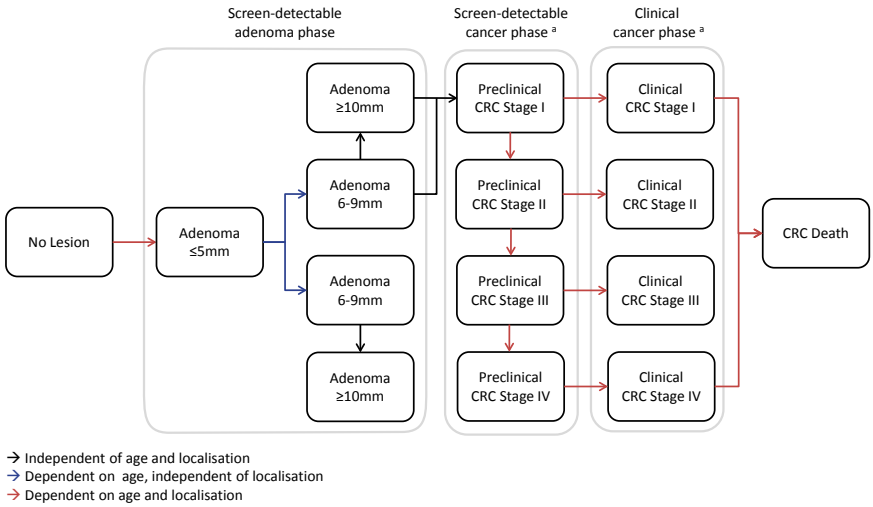


Figure 2: Schematic representation of the natural history module of the MISCAN-Colon model.

Abbreviations: CRC, colorectal cancer
The arrows between the states show which types of transitions can occur. In every state before death, a transition to "death from other causes" can occur (state and connect arrows not shown).
a. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for colorectal cancer.

An individual's risk of developing adenomas depends on the individual's age and a personal risk index. As a result, most individuals will not develop adenomas, whilst others develop many. The distribution of adenomas over the colon and rectum is assumed to equal the distribution of cancers observed before the introduction of screening and is specific to the population under consideration. The age-specific onset of adenomas and the personal risk index were calibrated to data on the prevalence and multiplicity distribution of adenomas as observed in autopsy studies (Figure 3).[1-10] The preclinical incidence of non-progressive adenomas (adenomas that will never grow into cancer) was varied until the simulated prevalence of all adenomas matched with data from autopsy studies.[1-10] The size distribution of adenomas over all ages was assumed to be 73% for stages less than or equal to 5 mm, 15% for stages 6–9 mm, and 12% for stages greater than or equal to 10 mm.[11] The age-specific probability that an adenoma will progress and the age- and localisation-specific transition probabilities between preclinical cancer stages and between preclinical and clinical cancer stages are specific to the population under consideration as observed before the introduction of screening.

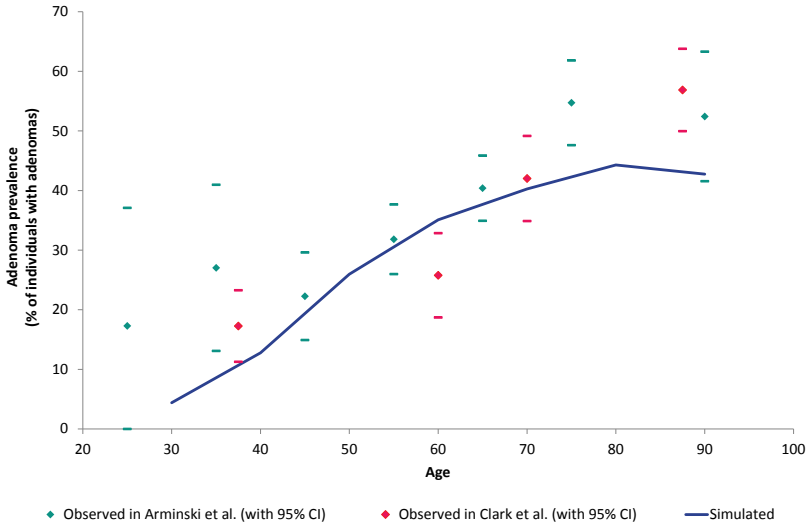


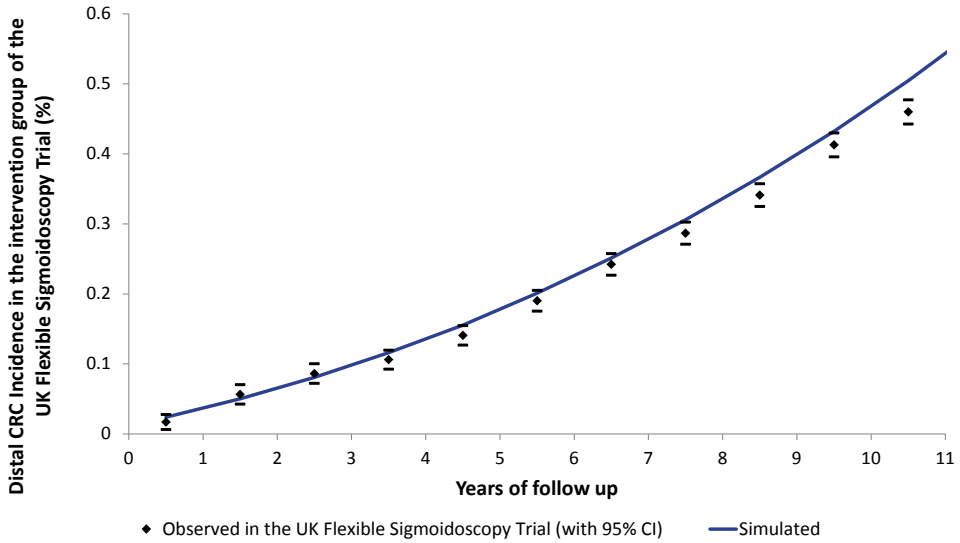
Figure 3: Adenoma prevalence observed in selected autopsy studies vs simulated by MISCAN-Colon (% of individuals with adenomas). Observed results are shown only for the 2 largest studies on which the model has been calibrated.[1, 2] The model has also been calibrated to eight other autopsy studies.[3-10]

The average durations of the preclinical cancer stages were calibrated to the rates of screen-detected and interval cancers observed in randomised controlled trials evaluating screening using guaiac faecal occult blood tests.[12-14] This exercise has been described extensively in a publication by Lansdorp-Vogelaar and colleagues.[15] The average duration from the emergence of an adenoma until progression into preclinical cancer (the adenoma dwell-time) was estimated based on the interval cancer rate observed in a randomised controlled trial evaluating once-only sigmoidoscopy screening (Figure 4).[16]

Based on expert opinion, we assume an equal overall dwell-time for adenomas developing into colorectal cancer from a medium size (30% of all colorectal cancers) and from a large size (70% of all colorectal cancers). Durations within the adenoma phase and within the preclinical phase were assumed to be perfectly correlated (meaning that if a small adenoma progresses rapidly to a medium-sized adenoma, it will also progress rapidly to a large adenoma or into colorectal cancer. However, we assume an absence of correlation between durations in the adenoma phase and duration in the preclinical cancer phase (meaning that a rapidly growing adenoma does not necessarily develop into a rapidly progressing cancer.).

Table 1 summarises the natural history parameters common to all of the analyses in this thesis.

a. Incidence per year of follow-up.



b. Cumulative incidence.

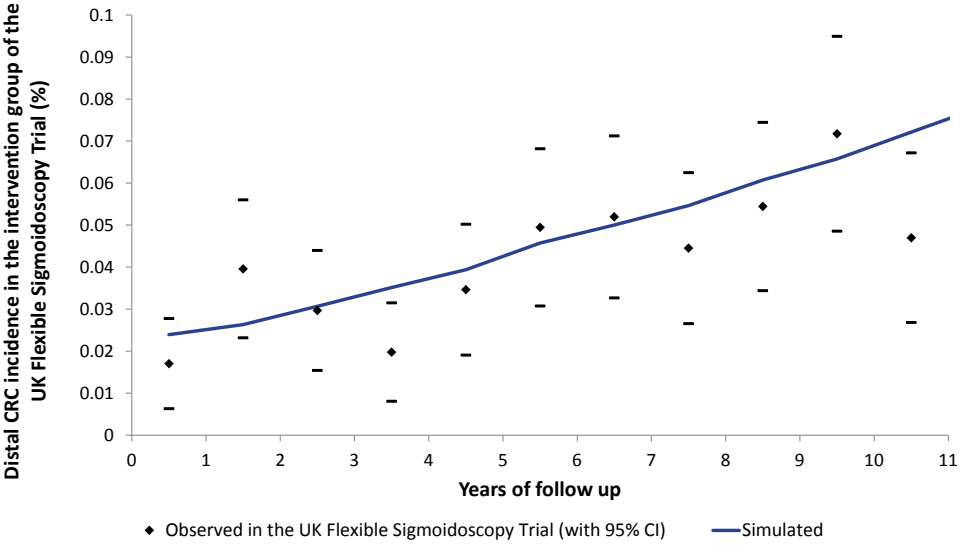


Figure 4: Distal colorectal incidence observed in the intervention group of the UK Flexible Sigmoidoscopy Trial vs simulated by MISCAN-Colon for a) incidence per year of follow-up and b) incidence cumulative. Incidence is measured as cases per 100,000 person years).

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

Model parameter	Value	Source
Regression of adenomas	No significant regression of adenomas	Expert opinion
Mean duration of development of progressive adenomas to preclinical cancer	14 years	Estimated from randomized controlled trial of once-only sigmoidoscopy[16]
Mean duration of preclinical cancer	Stage I: 2.5 years Stage II: 2.5 year Stage III: 3.7 years Stage IV: 1.5 year Overall: 6.7 years	Estimated from faecal occult blood test trials[12-15]
Per cent of non-progressive adenomas that stay 6-9mm	25%	Fit to size distribution of adenomas in colonoscopy trial (corrected for colonoscopy sensitivity)[11] • 1-5mm: 73% • 6-9mm: 15% • 10+mm: 12%
Per cent of non-progressive adenomas that become 10mm or larger	75%	
Per cent of cancers that develops from 6-9mm adenoma and from 10+mm adenoma	30% develop from 6-9mm 70% develop from 10+mm	Expert opinion
Survival after screen detection of cancer	As after clinical diagnosis in the same stage, or one stage better in case of screen detection in same state as without screening (within-stage shift)	Faecal immunochemical test trial[17]

SCREENING MODULE

Screening interrupts the development of colorectal cancer and therefore alters some of the simulated life histories. With screening, some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage than with clinical diagnosis which offers a more favourable survival. In this way, screening prevents colorectal cancer incidence or colorectal cancer death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening. The effects of different screening policies can be compared by applying them to identical natural histories. As seen in randomised controlled trials on guaiac faecal occult blood testing, the stage-specific survival of screen-detected colorectal cancer was more favourable compared with clinically detected colorectal cancer, even after the lead-time bias correction.[15]

We therefore assign screen-detected cancers that would have been clinically detected in the same stage the survival corresponding to a cancer that is one stage less progressive. For example, a cancer which is screen-detected in stage II, that would also have been clinically diagnosed in stage II, is assigned the survival of a clinically diagnosed stage I cancer. The only exceptions were screen-detected stage IV cancers. For these cancers we assume no possibility for within-stage shift and they are therefore assigned the same survival as a clinically diagnosed cancer stage IV. The removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma.

In addition to modelling the positive health effects of screening, we also model colonoscopy-related complications, over-diagnosis and over-treatment of colorectal cancer (for example, the detection and treatment of cancers that would not have been diagnosed without screening).[18-20] Risks of complications reported in organised screening programs[21-23] are lower than those reported for general practice colonoscopies.[24, 25] The major complications of colonoscopy are perforations (which can occur with or without polypectomy), serosal burns, bleeds requiring transfusion and bleeds not requiring transfusion.[21-25] For the purposes of these analyses, complications are conditional on polypectomy,[18] and we assume that polypectomy is only performed if colonoscopy is positive.

The sensitivity of the stool tests for cancer was split to take into account the variance in test sensitivity at different time points before clinical diagnosis (shortly before and longer before). It was assumed that the probability a colorectal cancer bleeds, and thus the sensitivity of stool tests for colorectal cancer, depends on the time until clinical diagnosis, hence the distinction between ‘early’ and ‘late’ preclinical colorectal cancer. This is to be expected when cancers that bleed do so increasingly over time, starting with occult blood loss and progressing to clinically visible bleeding.[15] In addition, the effect of systematic false negative stool tests (that

is, individuals with adenomas that do not bleed) and systematic false positive (individuals who always test positive but do not have adenomas) results were taken into account.[26]

In all analyses, it was assumed that after a positive stool test result, a diagnostic colonoscopy was offered. Adenomas identified at both screening and diagnostic colonoscopies were removed and the individual entered colonoscopy surveillance at intervals dependent on adenoma findings. Surveillance intervals are adjusted to the setting which is being investigated.

For colonoscopy procedures the caecal intubation rate was assumed to be 95%.[27-29] The percentage of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after colonoscopy (colonoscopy lack of specificity) was estimated as 10% in **Chapter 3**.[30] This was increased to 16% in **Chapters 2, 4, 5** and **6**.[31] This percentage was assumed to be independent of the screening round.

The sensitivity for each lesion within reach was based on back-to-back colonoscopy studies increasing from 75% for small adenomas (≤5 mm) to 85% for medium-sized adenomas (6-9 mm) and to 95% for large adenomas (≥10 mm) and colorectal cancer.[32] At detection, lesions are removed immediately. Removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma. We assume the same test characteristics for screening, diagnostic and surveillance colonoscopies.

INTEGRATION OF THE MODEL COMPONENTS

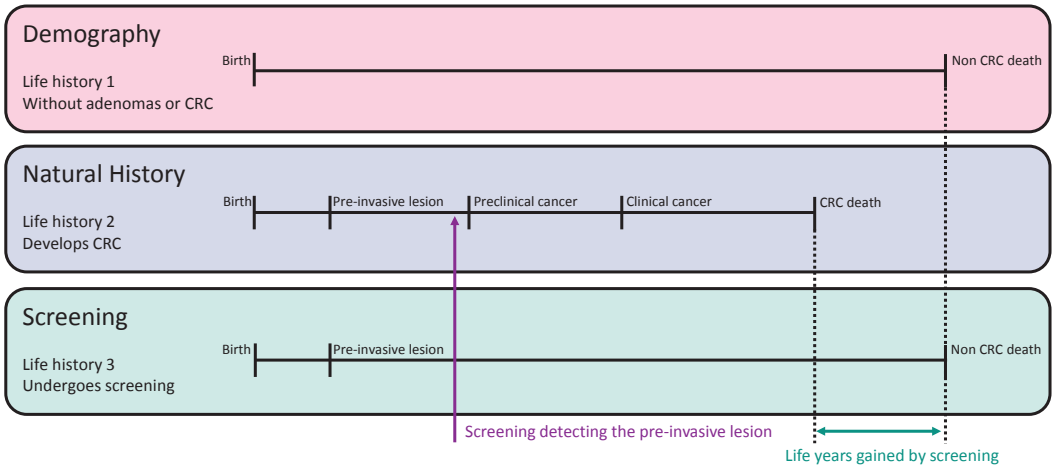
For each individual, the demography module of MISCAN-Colon simulates a date of birth and a date of death of other causes than colorectal cancer, creating a life history without adenomas or colorectal cancer.

For Patient A in Figure 5, the natural history module generates an adenoma. This adenoma progresses into preclinical cancer (diagnosed as stage II colorectal cancer because of symptoms) and results in colorectal cancer death before non-colorectal cancer death would have occurred. However, in the screening module, a screening examination is introduced (indicated by the blue arrow). During this examination, the adenoma is detected and then removed, and both colorectal cancer and colorectal cancer death prevented. Hence, in Patient A, the positive effect of the screening intervention is indicated by the green arrow and represents the increased life years gained for this patient because of screening.

Patient B also develops an adenoma, and although this adenoma does progress into preclinical cancer, Patient B would never have been diagnosed with colorectal cancer in a scenario without screening (see Life history 2). However, during the simulated screening examination (purple arrow) colorectal cancer is screen-detected in stage I and for this patient, the screening results in over-diagnosis and overtreatment of colorectal cancer: in this situation,

screening does not prolong life, but it does result in additional life years with colorectal cancer care (overtreatment) as indicated by the red arrow.

Patient A



Patient B

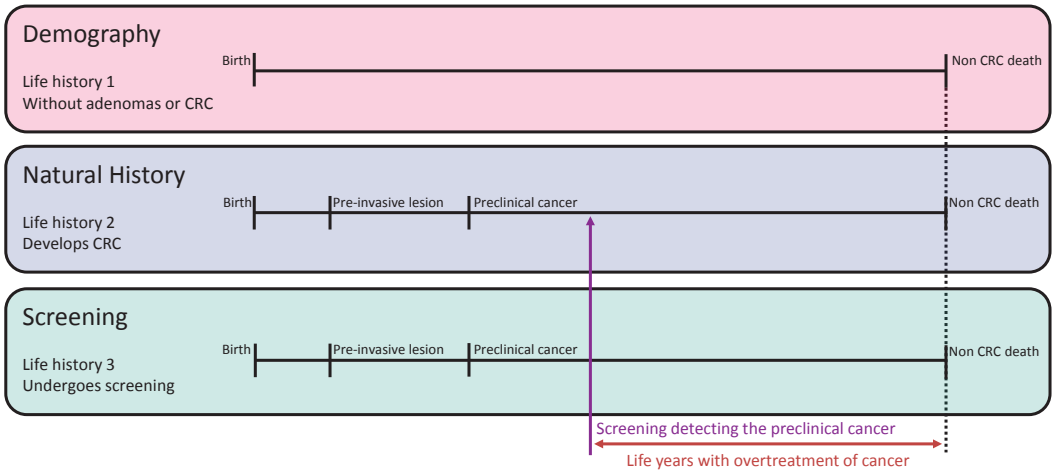


Figure 5: Integrating modules: two example individuals (A and B).

CHAPTER SPECIFIC DIFFERENCES IN MODEL QUANTIFICATION

The quantification of the demography, natural history and screening parameters in the model vary depending on the simulated population. The following section provides a description of the parameters unique to each chapter. Table 2 provides a summary of the demography, natural history and screening parameters used in the analyses in this thesis

CHAPTER 2

In **Chapter 2**, a cohort of 45-year-old males and females in China was modelled. Life tables were based on data from China's 6th population census in 2010 (most recent available data).[33]

Colorectal cancer incidence and mortality data was estimated from data sourced from Shanghai Municipal Center for Disease Control and Prevention.[34] The incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localisation in Shanghai.[34-36] The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of colorectal cancers as reported by the Shanghai Municipal Center for Disease Control and Prevention.[36] Stage-specific survival was based on data from 2015 in Shanghai.[35] The survival data was divided into colon and rectal cancer, and the data was transformed into a weighted colorectal cancer survival for use in MISCAN-Colon.

We estimated the test characteristics of the Shanghai screening program so that the model predicted positivity and detection rates for advanced neoplasia are similar to those observed in the first three years of screening in Pudong (2013-2015, data provided by the Pudong Centre for Disease Control). The test characteristics of the validated FITs were fitted to the positivity and detection rates of advanced neoplasia observed in the first screening round of two Dutch randomised trials, which utilised the OC-Sensor micro (Eiken Chemical, Tokyo, Japan).[37-40] To estimate the test characteristics we followed the approach described in Goede and colleagues.[41] The characteristics differ to those previously presented as the natural history of the MISCAN-Colon model has been updated since this publication.[42]

Information on complications arising from colonoscopy are scarce in China. We only reported perforations associated with polypectomy[43] as we were unable to find any information of deaths associated with colonoscopy. Complications of colonoscopy were based on hospital admissions within 30 days of index colonoscopy. We modelled surveillance consistent with the European Society of Gastrointestinal Endoscopy Guidelines.[44] We simulated these guidelines because there is conflicting advice in China about the post diagnostic colonoscopy pathway (including when to return to screening and the surveillance pathway),[45-49] and the Asia Pacific Consensus Group did not provide precise guidelines on interval of surveillance, other than to suggest that such intervals should be tailored to the risk level.[50] Therefore, individuals with low risk findings (less than 3 low risk (less than 10mm) adenomas at primary

screening) did not receive any surveillance while individuals with high-risk findings were offered surveillance with colonoscopy after three years, and thereafter repeated colonoscopies with intervals of three to five years depending on the findings. It was assumed that surveillance stopped at 80 years of age.

CHAPTER 3

In **Chapter 3**, we simulated the Australian population from 1911 and 2011 (inclusive) with births distributed to match the 2011 Australian population by sex and age.[51] Life expectancy was modelled on data from the Australian Bureau of Statistics 2009 life tables.[52]

Incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localisation in Australia in 2006 as this was prior to the commencement of the National Bowel Cancer Screening Program.[53-55] The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of colorectal cancers in Australia.[53] Five-year relative survival after clinical diagnosis of colorectal cancer was based on literature available in the Australian setting.[54]

In absence of high quality nation-wide data, the FIT characteristics were adjusted to simulate the positivity and detection rates observed in the Queensland Bowel Health Cancer Screening Program between August 2006 and December 2010.[56] Sensitivity and specificity were chosen so that simulated positivity rates and positive predictive values matched the observed rates to within 0.1%. The effects of systematic false negative and systematic false positive stool test results were not taken into account in this analysis.

Risk of complications were based on estimates reported in organised screening programs.[21-23] Risk of dying from colonoscopy was based on Australian literature.[57] Surveillance was based on the National Health and Medical Research Council approved guidelines.[58] If no adenomas were found during the colonoscopy, the individual was invited to re-screen with FIT after five years.[59] It was assumed that surveillance stopped at 75 years of age.

CHAPTER 4

In **Chapter 4**, we simulated seven population cohorts consisting of men and women aged 50-79 years with a 15-year colorectal cancer risk varying from 1% to 7%. Life expectancy was based on sex-specific lifetables for 2007, the middle of the Norwegian Colorectal Cancer Prevention trial period, from Statistics Norway.[60]

We developed a version of the MISCAN-Colon model calibrated to the sex-, age-, stage-, and localisation-specific colorectal cancer incidence and survival as observed in Norway during the timeframe of the Norwegian Colorectal Cancer Prevention trial (1999-2011), using data provided by the Norwegian Cancer Registry.[61] The age-specific onset of adenomas in MISCAN-

Colon for all ages was adjusted to match the 15-year colorectal cancer risk in seven cohorts. The modelled risk levels were chosen to cover the majority of individuals under consideration for this study (healthy people aged 50 to 79 years), but still with a manageable number of risk levels. We used the range of risk levels found when applying the QCancer® risk prediction model to the UK Biobank cohort as guidance.[62] The simulated risk levels from 1% to 7% cover approximately 90% of the colorectal cancer risk levels found in the UK Biobank cohort (personal communication UK Biobank researcher Juliet Usher-Smith). We confirmed that the chosen risk levels also cover the range of risk levels observed in the general population, by comparing the risk levels with the 15 year colorectal cancer risk ranges found in two large population-based cancer databases.[63, 64] Data from the UK Biobank were also used to validate the QCancer® prediction model for colorectal cancer. The QCancer® Calculator is an open-access online tool that aims to predict individual colorectal cancer risk based on risk factors such as medical history, lifestyle factors, and ethnicity.[65]

A FIT cut-off of 20 µg Hb/g faeces was chosen as this is used in many screening programmes.[66] Sensitivity and specificity of the screening tests were based on diagnostic test accuracy studies.[67] Age-specific risks for complications associated with colonoscopy were derived from Surveillance, Epidemiology, and End-Results Medicare data.[18-20] Only complications requiring hospital admission within 30 days after the colonoscopy were taken into account.

We modelled surveillance consistent with the European Society of Gastrointestinal Endoscopy Guidelines.[44] Individuals with low risk findings (less than 3 low risk (less than 10mm) adenomas at primary screening) did not receive any surveillance while individuals with high-risk findings were offered surveillance with colonoscopy after three years, and thereafter repeated colonoscopies with intervals of three to five years depending on the findings. It was assumed that surveillance stopped at 80 years of age.

CHAPTER 5

In **Chapter 5**, a cohort of 50-year-old males and females was modelled. To develop Canadian specific comorbidity life tables, we took hazard ratios from comorbidity specific life tables from the United States[68] compared to the average life table, and applied this ratio to the 2010-2012 Canadian life tables from Statistic Canada.[69]

The incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localisation in Ontario in 2001 as this was prior to the commencement of screening.[70] The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of colorectal cancers in Ontario in 2001.[70]

As stage-specific data on colorectal cancer relative survival were not available for Ontario, we assumed the same age- and stage-specific colorectal cancer relative survival as observed in

the Surveillance, Epidemiology, and End-Results database in the US, in the period 2000-2003.[71]

The test characteristics of the faecal immunochemical test (FIT) used in this analysis were based on the test characteristics of faecal occult blood (FOB)-Gold (Sentinel, Italy) based on data from the Dutch colorectal cancer screening program.[72] The FIT cut-offs were chosen to match an overall FIT positivity of 7.5% (main analysis) and 9.0% (sensitivity analysis). The characteristics of the guaiac faecal occult blood test (Hemoccult II, only used in sensitivity analyses) were based on a prior calibration of the MISCAN model to three large gFOBT screening trials.[15]

Complications of colonoscopy were based on hospital admissions within 30 days of index colonoscopy and were based on Canadian literature.[73, 74] Risk of dying from colonoscopy was based on Canadian literature.[74] A death was attributed to colonoscopy if it occurred within 30 days following an index colonoscopy. We modelled surveillance according to evidence based provincial screening program surveillance guidelines from Ontario.[75] If no adenomas were found during a diagnostic colonoscopy (i.e. after a positive stool test), then the individual was invited to rescreen with a stool test after 10 years. It was assumed that surveillance stopped at 85 years of age.

CHAPTER 6

In **Chapter 6**, we modelled a cohort of 40-year-old males and females with age specific all-cause mortality based on 2013-2015 life tables from the Australian Bureau of Statistics.[76] As in **Chapter 3**, the incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localisation in Australia in 2006 as this was prior to the commencement of the National Bowel Cancer Screening Program.[53-55] The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of colorectal cancers in Australia.[53] Five-year relative survival after clinical diagnosis of colorectal cancer was based on literature available in the Australian setting.[54]

The FIT characteristics were adjusted to simulate the positivity and detection rates observed in the Queensland Bowel Health Cancer Screening Program between August 2006 and December 2010.[56] Complications of colonoscopy were based on hospital admissions within 30 days of assessment colonoscopy and were stratified by age.[77] Risk of dying from colonoscopy was based on Australian literature.[78] Surveillance was based on the National Health and Medical Research Council approved guidelines.[79] If no adenomas were found during colonoscopy, the individual was invited to rescreen with a FIT after 2 years.[79] It was assumed that surveillance stopped at 75 years of age.[79]

Table 2: Differences of the demography, natural history and screening parameters used in the analyses of this thesis.

Demography parameters	**Chapter 2**	**Chapter 3**	**Chapter 4**	**Chapter 5**	**Chapter 6**
Population modelled	Chinese 45-year-old males and females	Australian population from 1911 and 2011 (inclusive) with births distributed to match the 2011 Australian population by sex and age[51]	Norwegian population cohort consisting of men and women aged 50-79 years	Canadian 50-year-old males and females	Australian 40-year-old males and females
Life expectancy	China's 6th population census, 2010[33]	Australian Bureau of Statistics 2009 life tables[52]	Sex-specific lifetables for 2007 from Statistics Norway[60]	Age and sex-specific comorbidity life tables, derived from US comorbidity specific life tables[68] and life tables from Statistics Canada[69]	Australian Bureau of Statistics 2013-2015 life tables[76]
Natural history parameters	**Chapter 2**	**Chapter 3**	**Chapter 4**	**Chapter 5**	**Chapter 6**
Distribution of risk for adenomas over the general population	Fit to multiplicity distribution of adenomas in autopsy studies[1-10] and cancer incidence from Shanghai in 2015[34]	Fit to multiplicity distribution of adenomas in autopsy studies[1-10] and cancer incidence from Australia in 2012[55]	Fit to adenoma prevalence in autopsy studies[1-10, 80]	Fit to multiplicity distribution of adenomas in autopsy studies[1-10] and cancer incidence from Ontario in 2001[70]	Fit to multiplicity distribution of adenomas in autopsy studies[1-10]
Adenoma incidence per year	Fit to adenoma prevalence in autopsy studies[1-10] and cancer incidence from Shanghai in 2015[34]	Fit to adenoma prevalence in autopsy studies[1-10] and cancer incidence from Australia in 2012[55]	Fit to adenoma prevalence in autopsy studies[1-10, 80] and varied to match risk-profile	Fit to adenoma prevalence in autopsy studies[1-10] and cancer incidence from Ontario in 2001[70]	Fit to adenoma prevalence in autopsy studies[1-10] and cancer incidence from Australia in 2012[55]
Probability that a new adenoma is progressive	Fit to adenoma prevalence in autopsy studies[1-10]	Fit to adenoma prevalence in autopsy studies[1-10]	Fit to adenoma prevalence in autopsy studies[1-10, 80]	Fit to adenoma prevalence in autopsy studies[1-10]	Fit to adenoma prevalence in autopsy studies[1-10]
Localisation distribution of adenomas and cancer	Estimated from Shanghai cancer incidence in 2015[34]	Estimated from Australian literature[53]	Norwegian Cancer Registry[61]	Estimated from Ontario cancer incidence in 2001[70]	Estimated from Australian literature[53]
Stage distribution	Estimated from stage distribution in Shanghai[34-36]	Estimated from Australian literature[53, 55]	Norwegian Cancer Registry[61]	Estimated from stage distribution in Ontario[70]	Estimated from Australian literature[53, 55]
Survival after clinical diagnosis of CRC	5-year survival estimated from data from 2015 in Shanghai[35]	5-year survival estimated from Australian literature[54]	Norwegian Cancer Registry[61]	10-year survival estimated from the SEER database from 2000-2003[71]	5-year survival estimated from Australian literature[54]

Screening parameters	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6
Characteristics of guaiac faecal occult blood test [a]	Not applicable	Not applicable	Not applicable	Lansdorp-Vogelaar, 2009[15]	Not applicable
Characteristics of FIT [a]	Calibrated to data provided by the Pudong Centre for Disease Control and Dutch randomised trials[37-40]	Queensland Bowel Health Cancer Screening Program Report[56]	Imperiale, 2014[67]	Dutch colorectal cancer screening program[72]	Queensland Bowel Health Cancer Screening Program Report [56]
Specificity of colonoscopy [b,c]	Schroy, 2013[31]	Levin, 1999[30]	Schroy, 2013[31]	Schroy, 2013[31]	Schroy, 2013[31]
Sensitivity of colonoscopy [b]	Back-to-back colonoscopy studies[32]	Back-to-back colonoscopy studies[32]	Back-to-back colonoscopy studies[32]	Back-to-back colonoscopy studies[32]	Back-to-back colonoscopy studies[32]
Caecal intubation rate	General practice[27, 28] and guidelines[29]	General practice[27, 28] and guidelines[29]	General practice[27, 28] and guidelines[29]	General practice[27, 28] and guidelines[29]	General practice[27, 28] and guidelines[29]
Complications rate with colonoscopy [d]	Shi, 2015[43]	Organised screening programs[21-23] and general practice[24, 25]	SEER-Medicare data[18-20]	Hilsden, 2015[73] Rabeneck, 2008[74]	National Bowel Cancer Screening Program[77]
Fatal complication rate with colonoscopy	Not modelled	Prospective endoscopy study[57]	SEER-Medicare data[18-20]	Rabeneck, 2008[74]	Viiala, 2003[78]
Surveillance	European Society of Gastrointestinal Endoscopy Guidelines[44]	National Health and Medical Research Council approved guidelines[58]	European Society of Gastrointestinal Endoscopy Guidelines[44]	Guidelines from Ontario[75]	National Health and Medical Research Council approved guidelines[79]

Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; NORCCAP, Norwegian Colorectal Cancer Prevention; SEER, Surveillance, Epidemiology, and End-Results

a. We assume that occult blood screening is more sensitive in cancers as they progress towards becoming symptomatic (visible bleeding) and clinically detectable.[15] For preclinical cancers which will become symptomatic within the same stage, assumed test sensitivity is higher.
b. We assume the same test characteristics for screening, diagnostic and surveillance colonoscopies.
c. The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, where the non-adenomatous lesions are removed and therefore induce polypectomy and biopsy.
d. Complications are conditional on polypectomy, and we assume that polypectomy is only performed if colonoscopy is positive.

MODEL OUTPUTS

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

DEMOGRAPHY

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

NATURAL HISTORY

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

SCREENING

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

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SUMMARY

PATHWAYS FOR OPTIMISING COLORECTAL CANCER SCREENING

Colorectal cancer is an important global public health issue. With over 1.8 million new diagnoses in 2018, colorectal cancer was the third leading cause of cancer incidence. Each year, almost half of all colorectal cancer patients die from the disease, making it the second leading cause of cancer-related deaths. Traditionally thought of as a disease of the "western world", incidence of colorectal cancer is rising in populations historically considered to be at low risk. This change is largely a result of temporal trends such as population ageing and improved standards of living, which has resulted in the adoption of the Western lifestyle including changes in dietary habits and a rise in modifiable risk factors such as smoking, alcohol consumption, obesity, and lack of physical activity.

Although individuals in westernised countries generally experience greater risk of colorectal cancer, globally the overall burden of colorectal cancer is unevenly distributed. Increased incidence, coupled with large population size means that lower incidence countries are noteworthy contributors to the global burden. For example, in 2018, China accounted for almost a third of all colorectal cancer cases and deaths. In comparison, Australia and the Netherlands collectively contributed less than 2% of cases and 1.5% of deaths.

Encouragingly, the burden of colorectal cancer can be reduced with screening. With its long sojourn time and effective treatment options, colorectal cancer is especially suitable for screening. However, although screening has been recommended by several health organisations and medical associations worldwide, it has not been universally implemented. Screening programs have predominantly been introduced in Western countries which generally have higher colorectal cancer incidence and more available resources. However, this is changing, with a growing number of middle-income countries introducing screening in recent years.

Colorectal cancer screening programs differ markedly throughout the world, reflecting differences in decision-making processes and uncertainty about which strategy is best. Although some variation is not entirely unexpected given that risk of colorectal cancer varies significantly around the world, the extent of variety suggests there may be room to improve screening programs. Risk of colorectal cancer risk not only varies between countries, it also varies between individuals. There are a range of lifestyle, environmental and genetic risk factors that are known to effect risk and it is increasingly recognised that individuals may not benefit equally from the same screening protocol. While this suggests that screening may be optimised if these personal risk factors were considered, it is currently unknown to what extent personalisation could further improve screening outcomes.

Decision models, such as MISCAN-Colon, are useful tools to assist in identifying optimal policies to reduce colorectal cancer incidence and mortality. These models are able to

evaluate multiple screening strategies quantifying future outcomes, resource demand and costs of screening.

In this thesis we investigate pathways to improve colorectal cancer screening programs. In the first part, we explore pathways to optimise uniform screening programs and ensure they are designed and implemented to achieve the best possible outcomes for the average risk population. In the second part, we investigate personalisation as a pathway to improve colorectal cancer screening programs.

PART I: OPTIMISATION OF UNIFORM SCREENING PROGRAM

Although proven to be effective, uniform screening programs, where the same strategy is applied to the entire target population, can still be optimised. Consideration should be given to the selection of appropriate program characteristics (including screening modality, frequency and start and stop ages) as well as the implementation timeline. The selection of appropriate program characteristics and implementation timeline are key to ensuring program effectiveness and an optimal balance of benefits to burdens and harms.

In **Chapter 1**, we investigated the optimal screening program for identifying Lynch syndrome in those who are diagnosed with colorectal cancer. Although Lynch syndrome is only responsible for a small proportion of colorectal cancers, carriers experience an increased lifetime risk for colorectal cancer and the mutation puts them at risk of other cancers. Screening for Lynch syndrome is widely recognised as important as the identification of Lynch syndrome aids clinical decision-making in cancer patients and can help identify at risk relatives, potentially saving their lives. Despite this, there is limited consensus on the optimal screening pathway and whether screening should be universally applied to all colorectal cancer diagnoses or limited by an age-at-diagnosis threshold. In our investigation we assessed two commonly followed tumour screening pathways to identify Lynch syndrome (mismatch repair immunohistochemistry (MMR IHC) followed by either a*MLH1* methylation test or a *BRAF* V600E mutation test), and explored the effectiveness of universal screening compared to three age-at-diagnosis thresholds (Screening<50, Screening<60 and Screening<70). Based on our results, the optimal screening pathway to identify Lynch syndrome includes MMR IHC followed by *MLH1* methylation (if indicated) and germline testing for colorectal cancers diagnosed in those aged under 70 years. Although not found to be cost effective in our study, we believe screening those over 70 years requires ongoing investigation, as cases in this age cohort were under-represented in our investigation.

In **Chapter 2** we explored opportunities to optimise the recently initiated colorectal cancer program in Shanghai, China. Both incidence and mortality of colorectal cancer are relatively low in China, however, due to its large population it is a noteworthy contributor to the global burden of colorectal cancer. Shanghai, one of the largest and most developed cities in China,

experiences some of the highest colorectal cancer incidence and mortality in China. In an effort to reduce the burden of colorectal cancer, the Shanghai Municipal Government implemented a colorectal cancer screening program in 2013, offering triennial screening using a locally manufactured faecal immunochemical test (FIT) and a risk questionnaire to individuals aged 50-74 years. However, as uptake is low, it is uncertain if this is the optimal screening program for the population. To determine what the optimal screening program might look like, we assessed the performance of the existing screening program against a program using standardised and validated FITs, varying program characteristics including test cut-off, screening interval and screening start- and stop age. Our results show that also in lower-incidence setting such as Shanghai, CRC screening can be cost-effective. Although the screening program currently implemented in Shanghai is effective at reducing colorectal cancer incidence and mortality, it could be further optimised by transitioning to a validated screening test and, depending on desired outcomes, test cut-off could be reduced, screening frequency could be increased and the age range could be expanded. Such a program could be more effective, less costly and require lower colonoscopy capacity than the current program. Depending on desired outcomes, several strategies could be selected, however, all of these alternatives utilise a validated FIT. These results may be relevant to other low incidence jurisdictions as they indicate that, even in this setting, screening is a cost-effective method for reducing colorectal cancer burden.

Our investigation in **Chapter 3** highlights the significant impact the implementation timeline of a screening program has on incidence and mortality. In Australia, the implementation of the National Bowel Cancer Screening Program was long and complicated. Although the federal government eventually committed to fully implement the screening program, the protracted time line (it was initially slated to take nearly 30 years to achieve full implementation of biennial screening with FIT for those age 50-74 years) caused concern. We therefore investigated the impact of this protracted timeline and compared it to a series of feasible alternative implementation timelines to determine the optimal implementation timeline in terms of mortality reduction. Not surprisingly, our findings suggested that although the protracted timeline would prevent colorectal cancer deaths (approximately 61,000), an expedited timeline, where full implementation was achieved by 2020, would substantially increase the number of preventable deaths (to approximately 70,000) over the subsequent 40-year period. These results provide a strong argument for policy makers to act with immediacy and resulted in the federal government committing to an expediated timeline with full implementation of the screening program achieved within five years.

PART II: OPTIMISATION THROUGH PERSONALISATION

Despite the importance of improving uniform screening programs, it is increasingly recognised that individuals differ and may not benefit equally from a uniform screening strategy. This presents an opportunity to tailor screening to the individual rather than the average population. Despite the potential gains to be made by personalising screening, at present there are no population level screening programs that offer such recommendations. Therefore, this emerging method to optimise colorectal cancer screening programs requires further investigation.

In **Chapter 4** we address the question of which screening modality provides the best outcomes for individuals based on their background risk of colorectal cancer. As screening effectiveness is influenced by baseline risk, investigating how it affects the balance between benefits, burden and harms is warranted. To do this, we assessed the impact of screening on a population of individuals aged 50-79 years, with varying baseline 15-year colorectal cancer risk (1%-7%). We considered four screening strategies: annual FIT; biennial FIT; a single sigmoidoscopy; and a single colonoscopy and followed individuals for 15 years. We found that, regardless of baseline risk, all of the assessed screening strategies were equally effective at reducing colorectal cancer mortality over a 15-year follow-up period. A single colonoscopy or sigmoidoscopy was more effective at reducing colorectal cancer incidence. As risk of colorectal cancer increases, so too do the benefits and harms, although the benefits increase to a greater extent. We also assessed the impact of lifetime follow-up, finding that a longer follow-up up resulted in larger reductions in colorectal cancer incidence and mortality. This is likely due to the slow developing nature of colorectal cancer (the time from an asymptomatic polyp to a symptom detectable colorectal cancer is estimated to take between 10-25 years).

Although colorectal cancer screening guidelines typically recommend screening for colorectal cancer in individuals at average risk between the ages of 50-74 years, the optimal age to stop screening is affected by both general health status (comorbidity) and screening history. Our research group has previously shown that screening stop age is impacted by these factors, however, an investigation considering the complexity and varied nature of screening history was lacking. Our investigation in **Chapter 5** was aimed at addressing this gap in knowledge. We found that the optimal age to stop screening varies from <66 to 90 years, depending on comorbidity and screening history. For example, individuals without comorbidities or those who have not previously undergone screening may benefit from screening past the recommended stop age, and in some cases could continue screening up to 90 years of age. Conversely, those with severe comorbidity or a strong history of prior screening could stop earlier than currently recommended and, in some instances, this was before the age of 66 years. As these results address the complex nature of screening history, they are more in keeping with the “real life” scenarios faced by clinicians and participants. By providing reliable

information about the possible benefits, harms and burden of screening, they support informed decision-making in relation to screening participation.

Finally, in **Chapter 6**, we present an early exploration of the potential benefits of risk stratified screening incorporating family history and polygenic risk. Colorectal cancer risk was determined by individuals undergoing a polygenic test (used to reveal the presence or absence of SNPs) and an assessment for family history of colorectal cancer. Future colorectal cancer screening was determined based on this information. To determine the optimal screening program, we compared the costs and effects of personalised screening based on risk to those of uniform screening. We found that while personalised screening was slightly more effective than uniform screening, at this stage, it is not more cost effective. This is due to the costs associated with determining an individual's risk of colorectal cancer and the suboptimal performance of the risk stratification algorithm. We noted that as costs to determine risk decrease, and the discriminatory performance of risk stratification algorithms improve, screening based on polygenic risk and family history will become a viable option. Despite the potential health gains, personalising screening will introduce a range of new and significant challenges for population screening policy makers. These fundamental economic, ethical and policy issues must be identified and resolved before personalised screening could be implemented.

CONCLUSIONS

Based on the results of the studies described in this thesis, we derived the following conclusions:

- The optimal screening pathway to identify Lynch Syndrome includes MMR immunohistochemistry followed by MLH1 methylation (if indicated) and germline testing. Screening should be restricted to those under 70 years. (**Chapter 1**)
- Although the screening program that is currently implemented in Shanghai is effective at reducing colorectal cancer incidence and mortality, using a validated test would result in improved efficiency. (**Chapter 2**)
- Protracted implementation timelines result in unnecessary disease burden. While consideration needs to be given to resources, screening should be implemented in an expedited manner. (**Chapter 3**)
- The background risk of colorectal cancer influences the effectiveness of colorectal cancer screening, such that the absolute benefit of screening increases with increasing risk. (**Chapter 4**)
- All screening strategies are effective at reducing colorectal cancer mortality over 15 years follow-up. Follow-up time impacts the magnitude of effect – a longer follow-up (lifetime) results in larger reductions in colorectal cancer incidence and mortality. (**Chapter 4**)
- An individual's comorbidity and screening history are important determinants of the balance of harms and benefits of screening and can be used to establish the optimal age to stop screening. Individuals without comorbidities or who are screening naïve could continue screening past the recommended stop age, in some cases up to 90 years of age. Others, such as those who have severe comorbidities or high levels of participation should consider stopping screening earlier. (**Chapter 5**)
- Although personalised screening based on polygenic risk and family history is an effective method to reduce colorectal cancer incidence and mortality, with the current discriminatory performance and cost of determining colorectal cancer risk, it is not cost effective compared to uniform screening. This may change as more common genetic variants associated with colorectal cancer are discovered or as the cost of determining risk decreases. (**Chapter 6**)

RECOMMENDATIONS

Based on these conclusions, we formulated the following recommendations:

In Australia, all colorectal cancer cases below the age of 70 years should be tested for Lynch syndrome using immunohistochemistry followed by MLH1 methylation (if indicated) and germline testing.

The cost-effectiveness of screening for Lynch syndrome in those over the age of 70 years should be further investigated.

Countries with low incidence should also consider the benefits of implementing screening, as even in this setting screening can be a cost-effective method to reduce colorectal cancer related incidence and mortality.

To avoid unnecessary deaths from colorectal cancer, the implementation of screening programs should not be unnecessarily delayed.

Decisions about when to stop screening should be based on an individual's screening history and comorbidity. To assist clinicians and participant in making these decisions, decision aids should be developed.

Research into the discovery of additional common genetic variants that are associated with colorectal cancer risk is warranted to improve the discriminatory performance of risk stratification using this measure.

To improve the discriminatory performance of risk stratification, personalised screening guidelines should contain a comprehensive set of factors including screening history, comorbidity, polygenic risk, family history and environment and lifestyle risk factors.

SAMENVATTING

STRATEGIEËN OM DARMKANKER SCREENING TE OPTIMALISEREN

Darmkanker is wereldwijd een groot gezondheidsprobleem. In 2018 kregen 1,8 miljoen personen de diagnose darmkanker, waarmee het de derde meest voorkomende kanker was. Jaarlijks overlijdt ongeveer de helft van de darmkanker patiënten aan de ziekte, waarmee het de tweede meest voorkomende oorzaak is van overlijden aan kanker. Voorheen was darmkanker vooral een probleem in de Westerse wereld, maar tegenwoordig neemt ook in niet-Westerse landen de incidentie van darmkanker sterk toe. De oorzaken hiervan liggen in de vergrijzing van de bevolking en verbeterde leefomstandigheden die gepaard gaan met het overnemen van een Westerse leefstijl: Westers dieet en toename van risicofactoren als roken, alcoholconsumptie en onvoldoende beweging.

Ondanks dat personen in de Westerse wereld nog steeds het hoogste risico hebben op het ontwikkelen van darmkanker, is wereldwijd de ziektelast niet evenredig verdeeld. De toename van de incidentie in combinatie met de grootte van de bevolking zorgt ervoor dat landen met een lage incidentie toch een groot aandeel hebben in de totale ziektelast. Het totaal aantal ziekte- en sterfgevallen ten gevolge van darmkanker in China bedroeg bijvoorbeeld een derde van het totaal aantal gevallen in de wereld in 2018. Ter vergelijking: Australië en Nederland samen waren in hetzelfde jaar maar verantwoordelijk voor respectievelijk 2% van het totaal aantal ziektegevallen en 1,5% van het totaal aantal sterfgevallen in de wereld.

De ziektelast veroorzaakt door darmkanker kan worden verminderd door screening. Vanwege de langzame groei van darmkanker en goede behandelmogelijkheden is darmkanker een geschikte ziekte om op te screenen. Screening wordt geadviseerd door verschillende gezondheidsorganisaties, maar is nog niet wereldwijd ingevoerd. Met name landen in het Westen hebben een darmkanker screeningsprogramma ingevoerd. Deze landen hebben vaak een hoge darmkanker incidentie en beschikken over de juiste middelen om te screenen. In de afgelopen jaren is er ook een toename van nieuwe screeningsprogramma's in middeninkomenslanden.

De opzet van screeningsprogramma's verschilt wereldwijd. Dit is het gevolg van keuzes die gemaakt worden tijdens het ontwikkelingsproces van de programma's en wisselende visies op de beste strategieën voor screening. Ondanks het feit dat sommige verschillen verklaard kunnen worden door een verschil in achtergrondrisico, lijkt er toch ruimte te zijn voor verbetering. Het risico op darmkanker verschilt niet alleen tussen landen, maar ook tussen individuen. Er is een verscheidenheid aan leefstijl, omgevings- en genetische factoren waarvan bekend is dat ze bijdragen aan een verhoogd risico op darmkanker. De voordelen van screening kunnen daarom verschillen tussen individuen. Dit suggereert dat screening mogelijk verbeterd zou kunnen worden als die afgestemd wordt op persoonlijke risicofactoren. Tot op

heden is niet bekend in hoeverre het personaliseren van screening inderdaad een positieve bijdrage kan leveren aan het screeningsprogramma.

Rekenkundige beslismodellen, zoals het door Erasmus MC ontwikkelde MISCAN-colon, kunnen gebruikt worden om de optimale screeningsstrategie te bepalen. Deze modellen kunnen verschillende screening strategieën doorrekenen en zo de lange-termijn voor- en nadelen en bijbehorende capaciteit en kosten kwantificeren.

In dit proefschrift evalueren we verschillende manieren om darmkanker screening te optimaliseren. In het eerste gedeelte evalueren hoe we screening kunnen optimaliseren voor de algemene bevolking als geheel (uniforme screening), terwijl we in het tweede gedeelte onderzoeken of het personaliseren van screening kan leiden tot verdere verbetering van darmkanker screening.

PART I: OPTIMALISEREN VAN EEN UNIFORM SCREENINGSPROGRAMMA

Ondanks het feit dat bewezen is dat een uniforme screeningsstrategie effectief is, blijft er veelal ruimte over voor verbetering. Men kan veranderingen in de programma opzet overwegen, (screeningtest, frequentie en start en stop leeftijd) evenals het aanpassen van de duur van implementatiefase. Het kiezen van de juiste strategie en doorlooptijd van de implementatiefase zijn cruciaal voor de effectiviteit van het programma en een goede balans tussen de voor- en nadelen van screening.

In **hoofdstuk 1** hebben we onderzocht wat de optimale strategie is om bij personen met de diagnose darmkanker het Lynch-syndroom vast te stellen. Ondanks dat een laag percentage van alle darmkankers wordt veroorzaakt door het Lynch-syndroom, hebben dragers van dit gen een sterk verhoogd risico op het ontwikkelen van darmkanker gedurende hun leven. Ook hebben ze een verhoogd risico op het krijgen van andere soorten kanker. Screening op Lynch-syndroom is belangrijk om de drager te identificeren, wat helpt bij de klinische besluitvorming en het vaststellen van de mutatie bij familieleden. Er is echter beperkte consensus wat de optimale screeningsstrategie is en of screening op Lynch mutaties moet worden uitgevoerd bij alle personen die de diagnose darmkanker hebben gekregen of alleen voor bepaalde leeftijdscategorieën. In hoofdstuk 1 hebben we twee veel gebruikte screeningsstrategieën voor Lynch-syndroom vergeleken: mismatch repair immunohistochemistry (MMR IHC) gevolgd door *een ''MLH1* methylation test'' en MMR IHC gevolgd door een ''*BRAF V600E*'' mutation test. We vergeleken de effectiviteit van screening van iedereen met darmkanker met drie strategieën, waarbij de leeftijd op moment van diagnose bepaalde of er op Lynch-syndroom gescreend moest worden (<50 jaar, <60 jaar en <70 jaar). De resultaten toonden aan dat de optimale screeningsstrategie voor Lynch-Syndroom bestond uit testen op MMR IHC gevolgd door de MLH1 methylation test voor personen met darmkanker die jonger waren dan 70 jaar op het moment van diagnose. Screening voor personen ouder dan 70 jaar bleek

niet kosteneffectief in onze studie, maar dit kwam mogelijk door een ondervertegenwoordiging van deze leeftijdsgroep binnen de onderzoekspopulatie. Nader onderzoek naar deze leeftijdscategorie is daarom noodzakelijk.

In **hoofdstuk 2** hebben we mogelijkheden bekeken om een nieuw darmkanker screeningsprogramma in Shanghai, China te optimaliseren. Shanghai is één van de grootste en meest ontwikkelde steden van China en de incidentie van en sterfte aan darmkanker behoren tot de hoogste in China. In 2013, heeft de Shanghai Municipal Government een darmkanker screeningsprogramma ingevoerd, waarbij er driejaarlijkse een FIT (van een Chinese fabrikant), samen met een vragenlijst om het risico op darmkanker te bepalen, wordt aangeboden aan personen in de leeftijd van 50-74 jaar. De deelname is echter laag en het is onbekend wat de optimale screeningsstrategie is voor de doelgroep. Om de optimale screeningsstrategie te bepalen, hebben we de het huidige programma vergeleken met een programma waarbij gestandaardiseerde en gevalideerde FIT testen worden gebruikt. Daarnaast hebben we gekeken naar de uitkomsten wanneer we veranderingen aanbrachten in de afkapwaarde, het screeningsinterval, en de leeftijdscategorie waarin mensen werden uitgenodigd om deel te nemen aan screening. De resultaten toonden aan dat in steden of landen met een relatief lage incidentie, zoals in Shanghai, darmkanker screening een bijdrage kunne leveren aan het terugdringen van de ziektelast van darmkanker en kosteneffectief kan zijn. Het programma in Shanghai zou verder geoptimaliseerd kunnen worden door een gevalideerde FIT te gebruiken, de afkapwaarde te verlagen, het screeningsinterval te verkorten en de leeftijdsgroepen die worden uitgenodigd voor screening uit te breiden. Een dergelijk geoptimaliseerd programma kan effectiever zijn dan het huidige programma, kost minder geld en heeft minder coloscopiecapaciteit nodig. Afhankelijk van de gewenste uitkomst van het screeningsprogramma bestaan er verschillende efficiënte screeningsstrategieën, maar al deze alternatieven gebruiken een gevalideerde FIT test. Deze resultaten zijn relevant voor andere regio's met een lage darmkanker incidentie die screening overwegen, omdat ze aantonen dat screening ook dan kosteneffectief kan zijn in het verlagen van de darmkanker incidentie en sterfte.

In **hoofdstuk 3** toonden we aan dat de duur van de implementatiefase van aan screeningsprogramma een significante invloed kan hebben op darmkanker incidentie en sterfte. De invoering van het National Bowel Cancer Screening program in Australië was een lang en gecompliceerd proces. Na het besluit van de overheid om een screeningsprogramma in te voeren, was de geplande doorlooptijd 30 jaar. Deze langdurige periode voor de volledige invoering van een landelijk screeningsprogramma met tweejaarlijkse FIT voor personen in de leeftijdscategorie van 50 tot 74 jaar oud was een zorgwekkende situatie. Wij hebben daarom geëvalueerd wat de invloed van deze lange doorlooptijd is op darmkanker sterfte. We vergeleken dit met haalbare alternatieve doorlooptijden om de optimale doorlooptijd te bepalen. Uit de resultaten bleek dat ook bij een (lange) implementatiefase van 40 jaar sterfte

aan darmkanker kon worden voorkomen (ongeveer 61.000 doden), maar dat bij een versnelde implementatiefase waarbij het programma volledig werd uitgerold in 5 jaar, veel meer doden ten gevolge van darmkanker voorkomen konden worden (tot ongeveer 70.000 doden). Deze resultaten hebben ertoe bijgedragen dat de Australische overheid inderdaad voor een versnelde invoering heeft gekozen waarbij het programma volledig uitgerold was binnen 5 jaar.

PART II: OPTIMALISEREN DOOR GEPERSONALISEERDE SCREENING

Ondanks het belang van het verbeteren van uniforme screeningsprogramma's, wordt er steeds vaker erkend dat personen verschillen in hun risico op darmkanker en dat daarom de voordelen van screening bij een uniforme screeningsstrategie niet gelijk zijn voor iedereen. Dit suggereert dat het individualiseren van screening in plaats van het richten op de algehele bevolking effectief zou kunnen zijn. Ondanks de mogelijke voordelen van gepersonaliseerde screening zijn er op dit moment geen georganiseerde screeningsprogramma's die dit aanbevelen. Om deze veelbelovende screeningsstrategie, met de potentie om darmkanker screening verder te optimaliseren, in kaart te brengen, is verdere analyse vereist.

In **hoofdstuk 4** behandelden we de vraag welke screeningstest voor de beste uitkomsten zorgt indien rekening gehouden wordt met het risico op darmkanker van een individu. Daarom is het belangrijk om de invloed van het dit risico op de balans tussen de voor- en nadelen van screening te onderzoeken. We hebben dit geëvalueerd door vier verschillende screeningsstrategieën te evalueren in personen van 50 tot 79 jaar met een 15-jaars cumulatief risico op darmkanker variërend van 1%-7%: jaarlijkse FIT, tweejaarlijkse FIT, eenmalige sigmoïdoscopie en eenmalige coloscopie. We hebben de screening strategieën gesimuleerd voor een periode van 15 jaar. Ongeacht het veronderstelde achtergrondrisico, leidden al deze screeningsstrategieën tot een eenzelfde relatieve afname in darmkanker sterfte. Een eenmalige sigmoïdoscopie of coloscopie waren wel effectiever in het verlagen van de darmkanker incidentie. Wanneer het risico op darmkanker toeneemt, wegen de absolute voordelen van screening meer op tegen de nadelen. Bij een levenslange follow-up in plaats van een periode van 15 jaar, was er een grotere afname in darmkanker incidentie en sterfte voor alle testen. Dit wordt verklaard door de langzame groei van darmkanker (de ontwikkeling van een asymptomatische poliep tot een symptomatische darmkanker wordt geschat tussen de 10 en 25 jaar).

In de richtlijnen voor darmkankerscreening wordt meestal geadviseerd om personen met een gemiddeld darmkanker risico te screenen van 50 tot 74 jaar, maar de optimale leeftijd om te stoppen met screenen wordt beïnvloed door de algemene gezondheidstoestand (comorbiditeit) van een individu en of deze persoon eerder heeft deelgenomen aan screening en wat de uitkomsten hiervan waren (screeningsgeschiedenis). Onze onderzoeksgroep heeft dit in het verleden al geanalyseerd, maar toen is er nog geen rekening gehouden met de

complexiteit en verschillen in screening geschiedenis. In **hoofdstuk 5** hebben we de optimale leeftijd om te stoppen met screening daarom nader onderzocht. We toonden aan dat de optimale stopleeftijd varieerde van 66 tot 90 jaar, afhankelijk van de aanwezigheid van comorbiditeit en screeningsgeschiedenis. Personen zonder comorbiditeit of personen die niet eerder meegedaan hebben aan screening, kunnen bijvoorbeeld baat hebben bij screening na de nu geadviseerde leeftijd om te stoppen met screening, waarbij sommigen zelfs nog baat hebben bij screening tot en met de leeftijd van 90 jaar. Omgekeerd gold hetzelfde: personen met ernstige comorbiditeit of die regelmatig screening hebben ondergaan, kunnen mogelijk vóór de geadviseerde stopleeftijd stoppen. Doordat deze analyse de complexiteit van mogelijke screeningsgeschiedenissen meeneemt, zijn ze direct toepasbaar in situaties in de dagelijkse praktijk. Met behulp van deze resultaten over mogelijke voor- en nadelen van screening kunnen deelnemers in samenspraak met hun artsen een geïnformeerde keuze maken over het al dan niet continueren van screening.

In het laatste hoofdstuk, **hoofdstuk 6,** hebben we een eerste analyse uitgevoerd over mogelijke voordelen van volledig gepersonaliseerde screening op basis van familiegeschiedenis en polygene risicoscore (bepaald met behulp van DNA-test op aan- of afwezigheid van Single Nucleotide Polymorphisms). Voor deze analyse hebben we de bevolking in vijf quintielen van risico opgedeeld op basis van die polygene risico score en familiegeschiedenis en voor ieder van die kwantielen de optimale screeningsstrategie bepaald. Vervolgens hebben we de kosten en effecten van deze gepersonaliseerde strategie gebaseerd op risico, vergeleken met die van uniforme screening. Ondanks dat gepersonaliseerde screening iets effectiever was dan uniforme screening, was het niet kosteneffectiever. Dit is te wijten aan de kosten die verbonden zijn aan het vaststellen van het individuele risico en het relatief beperkte onderscheidend vermogen van de polygene risicoscore. Indien de kosten van de risicobepaling zouden afnemen en het onderscheidend vermogen van de risicobepaling verbetert, kan screening op basis van polygeen risico en relevante familiegeschiedenis een goed alternatief zijn. Ondanks de veelbelovende voordelen, leidt gepersonaliseerde screening ook tot veel nieuwe uitdagingen voor beleidsmakers van screeningsprogramma's. Deze fundamentele economische, ethische en politieke vraagstukken moeten eerst in kaart gebracht worden voordat gepersonaliseerde screening kan worden ingevoerd.

CONCLUSIES

Op basis van de resultaten gepresenteerd in dit proefschrift kunnen de volgende conclusies worden getrokken:

- De optimale screeningsstrategie voor het vaststellen van het Lynch syndroom bestaat uit MMR immunohistochemistry, gevolgd door MLH1 methylation en testen op kiembaanmutaties indien van toepassing. (**Hoofdstuk 1**)
- Ondanks dat het huidige screeningsprogramma in Shanghai effectief is in het verlagen van darmkanker incidentie en sterfte, zou het gebruik van een gevalideerde test de effectiviteit verder kunnen verbeteren. (**Hoofdstuk 2**)
- Lange doorlooptijd van de implementatiefase resulteert in een onnodige ziektelast. De implementatie van een screeningsprogramma moet zo snel als de beschikbare middelen toelaten, worden ingevoerd. (**Hoofdstuk 3**)
- Het risico op darmkanker heeft invloed op de effectiviteit van darmkanker screening: de absolute voordelen van screening nemen toe met het risico op darmkanker. (**Hoofdstuk 4**)
- Alle screeningsstrategieën zijn effectief in het verlagen van de darmkanker sterfte over een periode van 15 jaar. De follow-up duur heeft invloed op de grootte van het effect: een langere follow-up tijd (levenslang) resulteerde in een grotere afname van darmkanker incidentie en sterfte. (**Hoofdstuk 4**)
- Comorbiditeit en screeningsgeschiedenis van een persoon dragen bij aan de balans tussen de voor- en nadelen van screening en kunnen daarom gebruikt worden voor het bepalen van de optimale leeftijd om te stoppen met screening. Personen zonder comorbiditeit of personen die niet eerder meegedaan hebben aan screening, kunnen baat hebben bij screening voorbij de geadviseerde stopleeftijd, soms zelfs tot de leeftijd van 90 jaar. Voor andere personen, bijvoorbeeld die met ernstige comorbiditeit of die regelmatig gescreend zijn, kunnen mogelijk vóór de geadviseerde stopleeftijd stoppen. (**Hoofdstuk 5**)
- Gepersonaliseerde screening gebaseerd op polygeen risico en relevante familiegeschiedenis kan effectief zijn in het verlagen van darmkanker incidentie en sterfte, maar met het huidig onderscheidend vermogen en de bijkomende kosten is het niet kosteneffectiever dan uniforme screening. Dit kan veranderen indien meer genetische varianten geassocieerd met darmkanker ontdekt worden of als de kosten voor het vaststellen van het risico afnemen. (**Hoofdstuk 6**)

AANBEVELINGEN

Op basis van bovenstaande conclusies kunnen de volgende aanbevelingen worden gedaan:

In Australië moeten alle personen met een darmkanker diagnose voor de leeftijd van 70 jaar getest worden op het Lynch-syndroom door middel MMR immunohistochemistry, gevolgd door MLH1 methylation en testen op kiembaanmutaties indien van toepassing.

De kosteneffectiviteit van screening op Lynch-syndroom in personen ouder dan 70 jaar moet verder onderzocht worden.

Landen met een lage darmkanker incidentie zouden de voordelen van het invoeren van een screeningsprogramma moeten overwegen, omdat is aangetoond dat screening ook in deze situaties een kosteneffectieve methode kan zijn voor het verlagen van de darmkanker incidentie en sterfte.

Om onnodige overlijdens als gevolg van darmkanker te voorkomen, moet de invoering van een screeningsprogramma niet onnodig vertraagd worden.

Beslissingen omtrent stoppen met screening moeten gebaseerd worden op de screeningsgeschiedenis van een individu en diens comorbiditeit. Om artsen en deelnemers te helpen in het maken van deze beslissingen, moeten er keuzehulp instrumenten worden ontwikkeld.

Er moet verder onderzoek gedaan worden om nieuwe genetische varianten geassocieerd met de ontwikkeling van darmkanker te ontdekken, zodat het onderscheidend vermogen van risicostratificatie verbeterd kan worden.

Om het onderscheidend vermogen van risicostratificatie te verbeteren, moeten richtlijnen voor gepersonaliseerde screening een uitgebreide set van factoren bevatten, zoals screeningsgeschiedenis, comorbiditeit, polygeen risico, relevante familiegeschiedenis, en risicofactoren als omgeving en leefstijl.

About the author

CURRICULUM VITAE

Dayna Cenin (née Ward) was born in Attadale, Western Australia, on January 13th 1981. After finishing her undergraduate studies in exercise and health sciences, Dayna completed a Graduate Diploma in Education and worked as a health and physical education teacher in Western Australia and the United Kingdom between 2005 and 2011. During 2010-11, she completed a Master of Public Health, graduating with distinction, at the University of Western Australia. During this period, she was employed to manage the transition of the Western Australian Birth Defects Register and the Western Australian Cerebral Palsy Register to the statutory body Western Australian Register of Developmental Anomalies. In 2011, she joined UNICEF in Ghana as an Australian Youth Ambassador for Development to coordinate local community-based health services.

From 2012-2015, Dayna was the Coordinator of the Bowel Cancer Education Program at Cancer Council Western Australia. In 2013, Dayna was the lead author on a modelling study that estimated the benefits of bringing forward the implementation of Australia's National Bowel Cancer Screening Program by 14 years compared with the government plan at the time (Chapter 3 of this thesis). A pre-publication summary prompted the newly elected Australian Government to support the study's recommended scenario and invest $95.9 million into fast-tracking the program's implementation.

In 2016, Dayna moved with her family from Perth to Rotterdam where she joined the Department of Public Health at Erasmus Medical Center as a Scientific Researcher. Under the supervision of Assistant Professor Iris Lansdorp-Vogelaar, her research has focussed on optimising and personalising screening interventions to prevent colorectal cancer. She has a strong interest in using research to drive evidence-based health policy.

List of Publications

In this thesis

Cenin DR, Naber SK, Lansdorp-Vogelaar I, Jenkins MA, Buchanan DD, Preen DB, Ee, HC, O'Leary, P. Costs and outcomes of Lynch syndrome screening in the Australian colorectal cancer population. J Gastroenterol Hepatol. 2018;33(10):1737-44.

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PHD PORTFOLIO

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PhD Period: 2015-2020

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Promotor: Professor Dr. Harry J. de Koning

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Academic Courses	**Year**	**Workload (ECTS)**
Health Economics Department of Public Health, University of Western Australia, Perth, Australia (Grade 7.4/10)	2015	1.4
Linked Data Department of Public Health, University of Western Australia, Perth, Australia (Grade 8.1/10)	2015	1.4
Planning and Evaluation of Screening Netherlands Institute for Health Sciences, Erasmus University, Rotterdam, the Netherlands (Grade 7.5/10)	2016	1.4
Conceptual Foundation of Epidemiologic Study Design Netherlands Institute for Health Sciences, Erasmus University, Rotterdam, the Netherlands	2017	0.7
Introduction to Data-Analysis Netherlands Institute for Health Sciences, Erasmus University, Rotterdam, the Netherlands	2017	0.7
Regression Analysis Netherlands Institute for Health Sciences, Erasmus University, Rotterdam, the Netherlands	2017	1.4
Health Technology Assessment Erasmus School of Health Policy & Management, Erasmus University, Rotterdam, the Netherlands (Grade 9.1/10)	2018	5.0
Decision Modelling Using R Decision Analysis in R for Technologies in Health (DARTH) Workgroup, Leiden, the Netherlands	2018	1.0
Comparative Health Policy Erasmus School of Health Policy & Management, Erasmus University, Rotterdam, the Netherlands (Grade 8.7/10)	2018/19	5.0
General Courses		
Integrity in Research Erasmus Medical Center, Rotterdam, the Netherlands	2017	0.3
Biomedical English Writing and Communication Department of Medical Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, the Netherlands	2018-19	1.4
LogFrame: the basis for good project writing Research and Development Office, Erasmus Medical Center, Rotterdam, the Netherlands	2018	0.3

Seminars and workshops	Year	Workload (ECTS)
Seminars		
Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands	2016-19	3.1
Workshop: When is it too expensive?		
Erasmus School of Health Policy & Management, Erasmus University, Rotterdam, the Netherlands	2017	0.3
Fresh Science: Media and communication training		
Science in Public, Fremantle, Australia	2019	0.6
Oral Presentations		
World Cancer Congress, UICC, Paris, France	2016	0.6
World Endoscopy Organization, Vienna, Austria	2018	0.6
United European Gastroenterology Week, Vienna Austria	2018	0.6
Behavioural Research in Cancer Control, Perth, Australia	2019	1.0
International Cancer Screening Conference, Rotterdam, the Netherlands	2019	0.6
Poster Presentations		
Digestive Diseases Week, Chicago, USA	2017	0.3
International Cancer Screening Conference, Maryland (USA) x 2	2017	0.6
Conferences		
World Endoscopy Organization, Vienna, Austria (1 day)	2016	0.3
World Cancer Congress, UICC, Paris, France (3 days)	2016	1.0
World Endoscopy Organization, Chicago, USA (1 day)	2017	0.3
Digestive Diseases Week, Chicago, USA (4 days)	2017	1.4
World Endoscopy Organization, Vienna, Austria (1 day)	2018	0.3
United European Gastroenterology Week, Vienna, Austria (3 days)	2018	1.0
Behavioural Research in Cancer Control, Perth, Australia (3 days)	2019	1.0
International Cancer Screening Conference, Rotterdam, the Netherlands (3 days)	2019	1.0
World Endoscopy Organization, online (half day)	2020	0.2
Teaching/Supervision		
Project Supervisor: Bachelor of Econometrics, Erasmus University, Rotterdam, the Netherlands	2016-17	1.0
Other		
Design, development and management of a User Reference Manual for the MISCAN model	2016-17	3.0
Design and development of a parameter documentation for the MISCAN model	2018	1.0
Peer review activities	2016-20	1.1

Dankwoord

DANKWOORD

And so here it is! The project I never thought I would start and once I started, I never thought I would finish! Hoorah! No PhD is the journey of a single individual. It is full of significant people who contribute an enormous amount to the final product, sometimes unwittingly.

For me this journey started with the encouragement and support of two key individuals, Melissa Ledger and Terry Slevin. Without your quiet and unwavering belief in me as a public health researcher, this journey would never have begun. And while there have certainly been moments (many moments!) when I have cursed you, I am grateful to you both for helping me get to where I am today.

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Thanks to all who shared the ride.

Dayna

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