Supplementary Methods and Materials
a) MISCAN-Colon Model Description

Model Overview

The Microsimulation Screening Analysis-Colon (MISCAN-Colon) model is a stochastic microsimulation model that is useful in explaining and predicting trends in CRC incidence and mortality and to quantify the effects and costs of primary prevention and screening for CRC.

The term 'microsimulation' implies that individuals are moved through the model one at a time (i.e. as individuals), 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.

MISCAN-Colon consists of 3 modules: a demography module, natural history module, and screening module (Figure 1). These parts are not physically separated in the program, but it is useful to consider them separately.

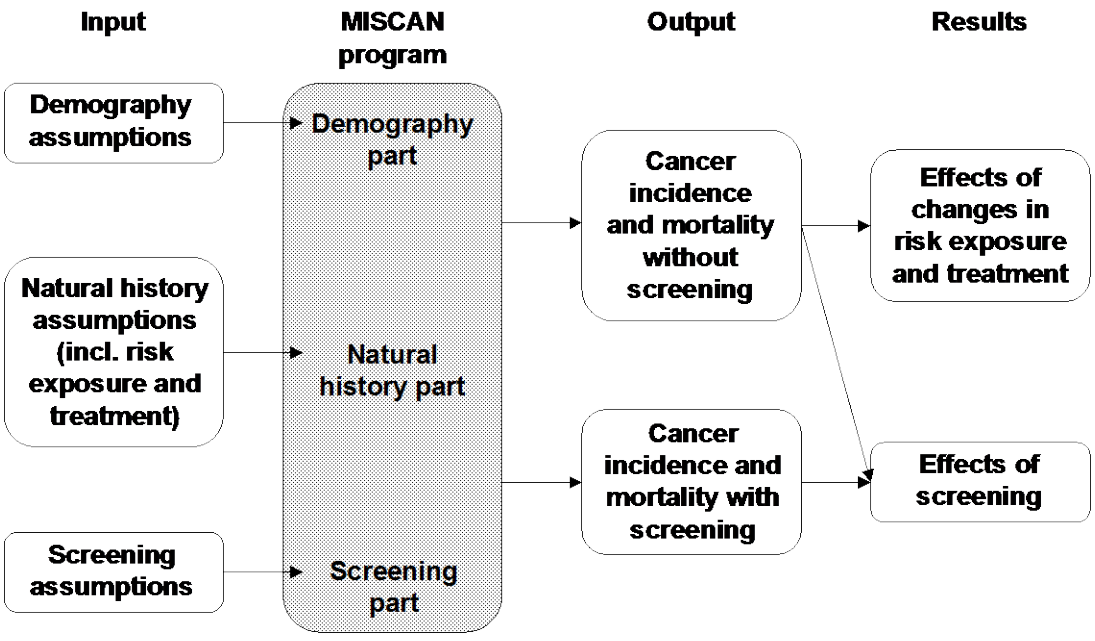

Figure 1: Structure of MISCAN-Colon

Demography Module

The demography module of MISCAN-Colon simulates individual life histories without colorectal cancer (CRC) 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-CRC death for each simulated individual. 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 CRC in the population. 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, CRC survival is simulated using age-, stage-, and localisation-specific survival estimates for clinically diagnosed CRC obtained from a study by Rutter and colleagues.[1] For individuals with synchronous CRCs at time of diagnosis, the survival of the most advanced cancer is used. The date of death for individuals with CRC is set to the earliest simulated death (either because of CRC or because of another cause).

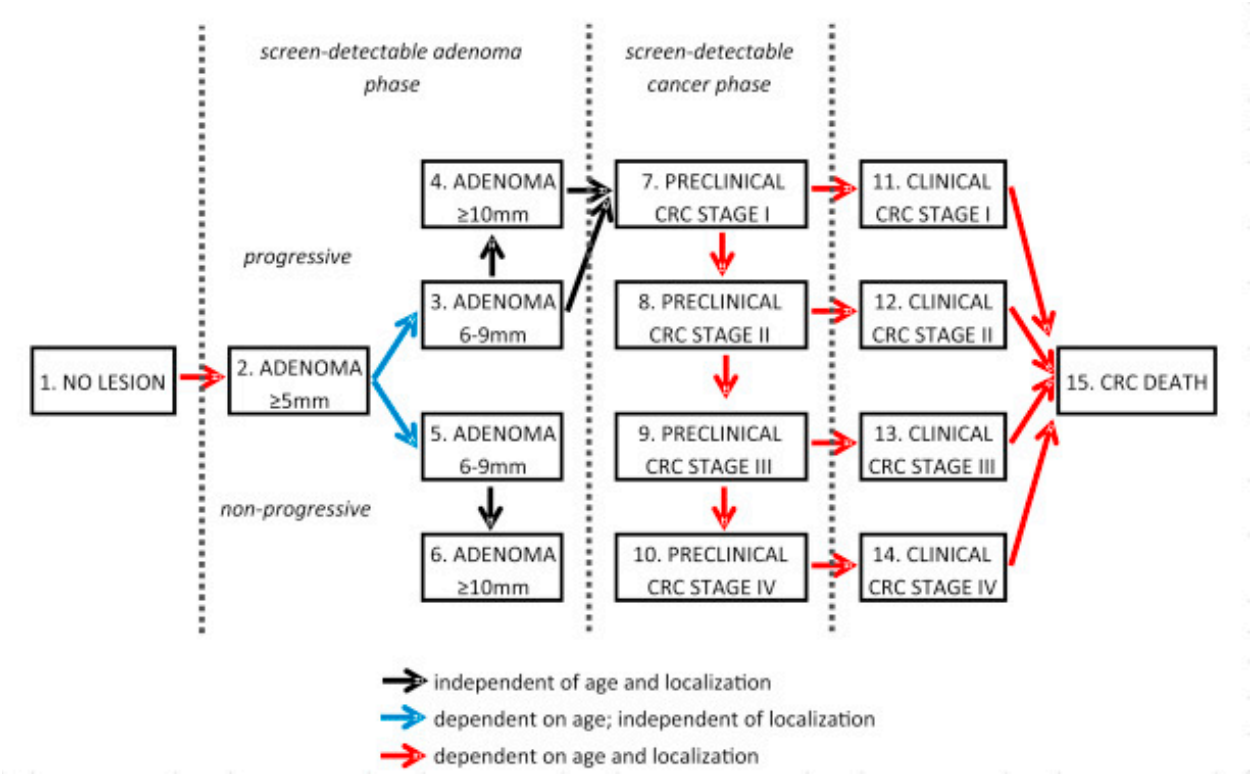

Figure 2: An overview of the natural history module of the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for CRC. Adenomas are categorised by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age.

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. The age-specific onset of adenomas and the of the personal risk index were calibrated to data on the prevalence and multiplicity distribution of adenomas as observed in autopsy studies (Figure 3).[2-11] The age-specific probability of adenoma-progressivity and the age- and localization-specific transition probabilities between preclinical cancer stages and between preclinical and clinical cancer stages were simultaneously calibrated to SEER data on the age-, stage-, and localization-specific incidence of CRC as observed before the introduction of screening (Figure 4).

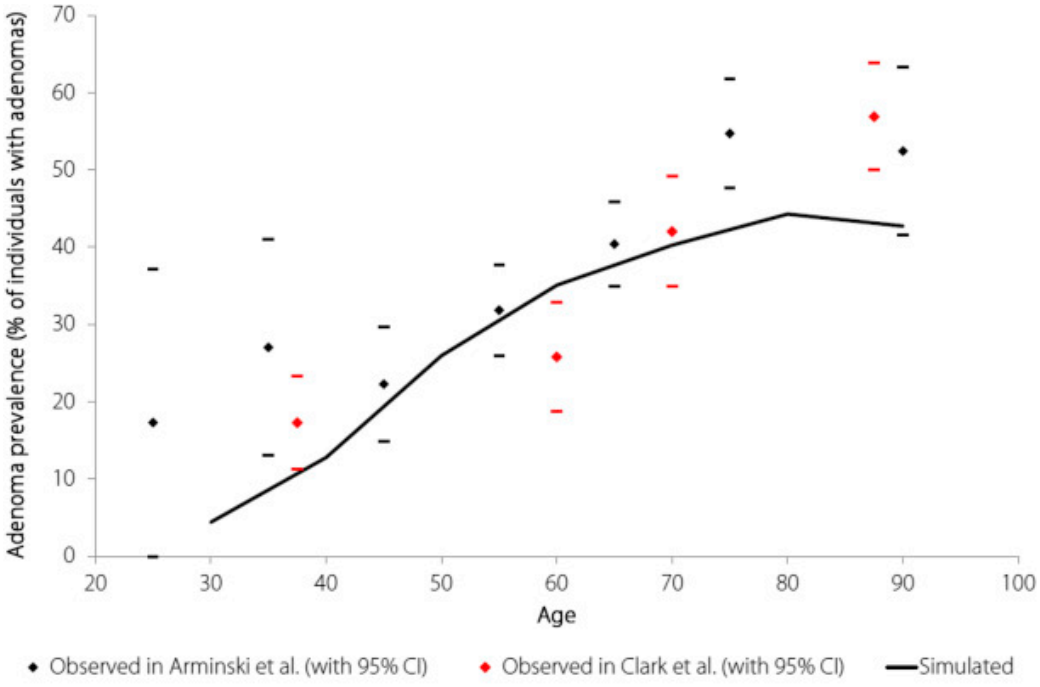

Figure 3: Adenoma prevalence observed in selected autopsy studies vs simulated by MISCAN-Colon (% of individuals with adenomas).*

*Observed results are shown only for the 2 largest studies on which the model has been calibrated.[2, 3] The model has additionally been calibrated to eight other autopsy studies.[4-11]

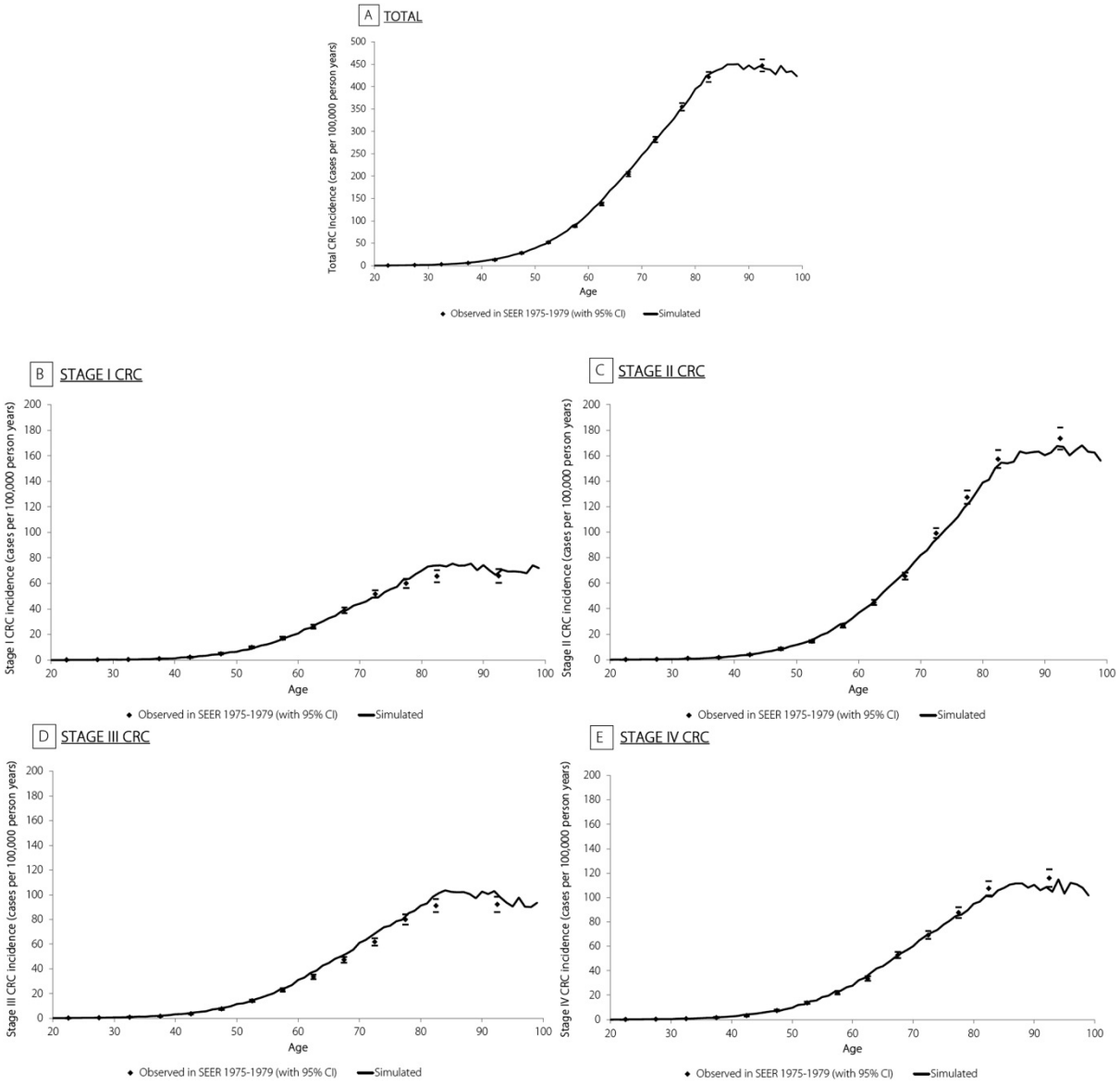

Figure 4: CRC incidence observed before the introduction of screening vs simulated by MISCAN-Colon (total (A), stage I CRC (B), stage II CRC (C), stage III CRC (D), stage IV CRC (E); cases per 100,000 person years).

The average durations of the preclinical cancer stages were calibrated to the rates of screen-detected and interval cancers observed in randomized controlled trials evaluating screening using 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 (i.e., the adenoma dwell-time) was calibrated to the rates of interval cancers (including surveillance detected cancers) observed in a randomized controlled trial evaluating once-only sigmoidoscopy screening (Figure 5).[16]

Furthermore, we assume: i) an equal overall dwell-time for adenomas developing into CRC from a medium size (30% of all CRCs) and from a large size (70% of all CRCs); exponential distribution for all durations in the adenoma and preclinical cancer phase; perfect correlation for the duration in the adenoma and preclinical cancer (meaning that if a small adenoma progresses rapidly to a medium-sized adenoma, it will also progress rapidly to a large adenoma or to a preclinical cancer stage I); and absence of correlation between durations in the adenoma phase and duration in the preclinical cancer phase.

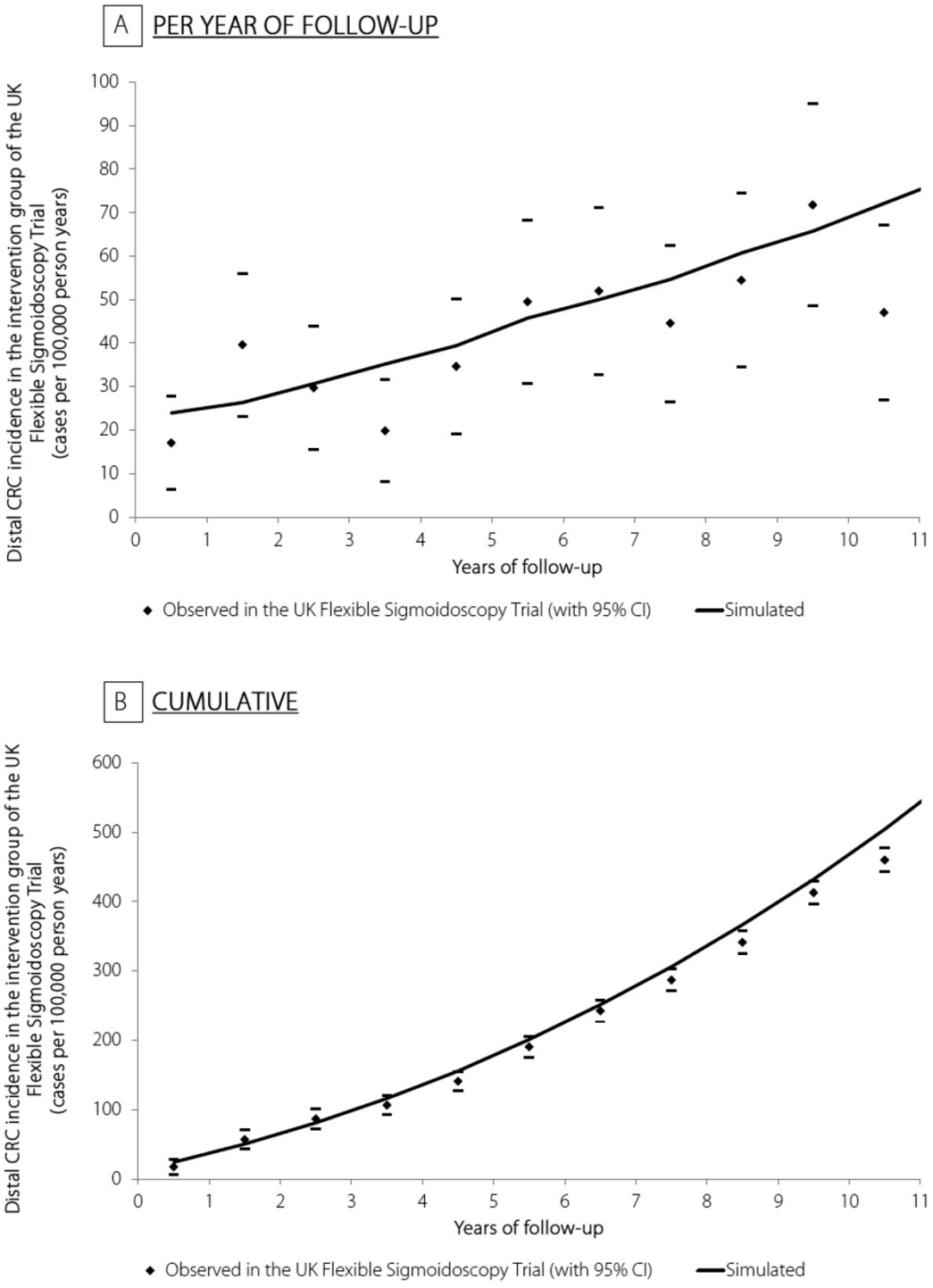

Figure 5: Distal CRC incidence observed in the intervention group of the UK Flexible Sigmoidoscopy Trial vs simulated by MISCAN-Colon (per year of follow-up (A), cumulative (B); cases per 100,000 person years).

Screening Module

Screening interrupts the development of CRC 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 CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening. The effects of different screening policies can be compared by applying them to identical natural histories. As seen in RCTs on guaiac faecal occult blood testing, the stage-specific survival of screen-detected CRC was more favourable compared with clinically detected CRC, 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. These cancers were always assigned the survival of a clinically diagnosed stage IV cancer.

In addition to modelling positive health effects of screening, we can also model colonoscopy-related complications, over-diagnosis and over-treatment of CRC (ie, the detection and treatment of cancers that would not have been diagnosed without screening).[17-19]

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 CRC, creating a life history without adenomas or CRC.

In patient A in Figure 6, the natural history module generates an adenoma. This adenoma progresses into preclinical cancer (diagnosed as stage II CRC because of symptoms) and results in CRC death before non-CRC 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 CRC and CRC death prevented. Hence, in Patient A, the positive effect of the screening intervention is indicated by the green arrow and represents the increased LYG 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 CRC in a scenario without screening

(see life history 2). However, during the simulated screening examination (blue arrow) CRC is screen-detected in stage I and for this patient, the screening results in over-diagnosis and overtreatment of CRC: in this situation, screening does not prolong life, but it does result in additional LYs with CRC care (over-treatment) as indicated by the red arrow.

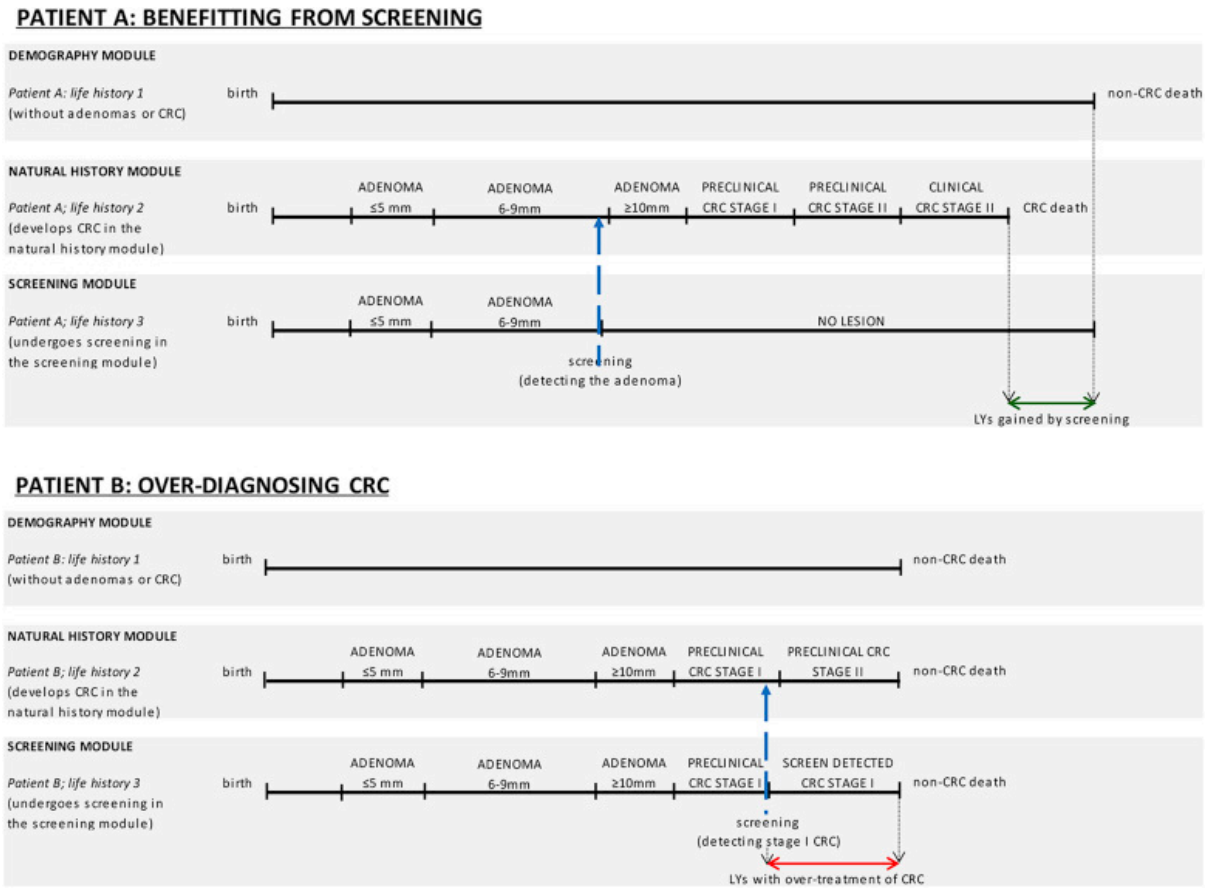

Figure 6: Integrating modules: two example patients (A and B).

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 CRC by calendar year and age

Natural history

1. CRC cases by calendar year, stage and age
2. CRC deaths by calendar year and age
3. Life-years lived with CRC 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 CRC 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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Supplementary Methods and Materials
b) MISCAN-Colon Model Quantification

Model Parameters

The quantification of the demography and natural history parameters in the model may vary depending on the population simulated. The following data is the description of the model quantification used in the present analysis.

Demography Parameters

In all analyses, a cohort of individuals born in 1980 were modelled with age specific all-cause mortality based on 2013-2015 life tables from the Australian Bureau of Statistics.[20] These life tables include CRC mortality and the demography part simulates mortality from causes other than CRC. However, no adjustment was made to the life tables because the percentage of CRC mortality in overall mortality is small and the data on CRCs deaths by age, gender and race are sparse.

Natural History Parameters

The parameters for natural history model which could not be directly estimated from data, or fit to reference data, were established based on expert opinion. 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, a model structure was devised in agreement with the currently accepted model of the adenoma–carcinoma sequence. It was assumed that all cancers are preceded by adenomas.

The average duration between onset of a progressive adenoma and the transition to preclinical cancer was estimated based on the interval cancer rate after a once-only sigmoidoscopy in a randomized controlled trial from the United Kingdom.[16] The duration of cancer in preclinical stages was estimated based on the results of three large randomised controlled screening trails.[15] This resulted in the average duration of 2.5 years, 2.5 years, 3.7 years, and 1.5 years, for stages I-IV respectively, with a total average duration of 6.7 years because not every cancer reaches stage IV before clinical diagnosis. All durations were governed by an exponential probability distribution. Durations in each of the invasive cancer stages as well as durations in the stages of the non-invasive adenomas were assumed to be 100% associated with each other, but the durations in invasive stages as a whole were independent of durations in non-invasive adenoma stages that precede cancer. These assumptions resulted in an exponential distribution of the total duration of progressive non-invasive adenomas and of the total duration of preclinical cancer, which has also been used in other cancer screening models.[21, 22]

Based on expert opinion, it is assumed that 30% of the cancers arise from adenomas of 6–9 mm and that 70% arise from larger adenomas. The incidence of progressive adenomas was chosen to reproduce the CRC incidence by age, stage, and localisation in Australia in 2006 as this was prior to the commencement of the National Bowel Cancer Screening Program.[23] The preclinical incidence of non-progressive adenomas that will never grow into cancer was varied until the simulated prevalence of all adenomas matched with data from autopsy studies.[2-11]

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.[24] 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 CRCs in Australia.[25]

Five-year relative survival after clinical diagnosis of CRC was based on literature available in the Australian setting.[26] The stage-specific survival of patients with screen-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage, except if screen-detection occurs in the same stage as the cancer would have been diagnosed without screening.[27] In that case, survival is assumed to be similar to survival of one stage more favourable (i.e. stage II cancer gets stage I survival). Only if screen-detected in stage IV, we assume no possibility for within-stage shift and stage IV screen detected cancers always have the same survival as clinically diagnosed cancers in stage IV. Removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma.

Table 1 contains a detailed summary of the natural history input values and data- sources.

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

Model parameter	Value	Source
Heterogeneity of risk for adenomas over the general population	Gamma distributed, mean 1, variance gender-dependent Age 60: • 1 or more 20% • 2 or more 6% • 3 or more 2% Age 90: • 1 or more 37% • 2 or more 17% • 3 or more 9%	Fit to multiplicity distribution of adenomas in autopsy studies[2-11]
Adenoma incidence per year	Age, gender and race dependent varying from 0-26% per year	Fit to adenoma prevalence in autopsy studies[2-11] Cancer incidence from AIHW[23]
Probability that a new adenoma is progressive	Dependent on age at onset, varying from 0-31%	Fit to adenoma prevalence in autopsy studies[2-11] Cancer incidence from AIHW[23]
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	6.7 years	Estimated from FOBT trials[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)[24] • 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
Localisation distribution of adenomas and cancer	Rectum: 0.3081 Distal colon: 0.3492 Proximal colon: 0.3427	Australian literature[25]
5-year survival after clinical diagnosis of CRC	Based on stage of diagnosis • Stage I = 84% • Stage II = 77% • Stage III= 64% • Stage IV = 19%	Australian literature[26]

Abbreviations: AIHW = Australian Institute of Health and Welfare; CRC = colorectal cancer; FOBT = faecal occult blood test

Screening Parameters

Data and assumptions for FIT Screening

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 (Table 2).[28] Sensitivity and specificity were chosen so that simulated positivity rates and positive predictive values matched the observed rates to within 0.1%. The sensitivity of FIT 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). In addition, the effect of systematic false positive and negative FIT results were taken into account.[29]

Table 2: Simulated and observed positivity rates and positive predictive values of FIT[a]

Parameter	Simulated %	Observed %
Overall FIT positivity rate	7.7	7.7
Positives without histopathologically confirmed adenomas or cancer	47.4	47.7
Positives with adenomas	48.2	48.0
Positives with advanced adenomas	25.6	26.0
Positives with confirmed cancer	4.4	4.3

a. Simulated and observed positivity rates and positive predictive values of FIT derived from calibration of positivity and detection rates observed in the Queensland Bowel Health Cancer Screening Program between August 2006 and December 2010[28]

Data and assumptions for colonoscopy

For colonoscopy procedures the caecal intubation rate was assumed to be 95%.[30-32] 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) has been estimated as 16%.[33] 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 CRC.[34] At detection, lesions are removed immediately. Removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma.

Risks of complications reported in organised screening programs[35-37] are lower than those reported for general practice colonoscopies.[38, 39] The major complications of colonoscopy are perforations (which can occur with or without polypectomy), serosal burns, bleeds requiring transfusion and bleeds not requiring transfusion.[35-39] Complications of colonoscopy were based

on hospital admissions within 30 days of assessment colonoscopy and were stratified by age.[40] Risk of dying from colonoscopy was based on Australian literature.[41] Additional assumptions of the MISCAN-Colon model can be found in Table 3.

Follow-up and surveillance

For all strategies, it was assumed that after a positive FIT result, a diagnostic colonoscopy was offered. Adenomas identified at both screening and diagnostic colonoscopies were removed and the individual entered surveillance based on the National Health and Medical Research Council (NHMRC) approved guidelines.[42] If no adenomas were found during colonoscopy, the individual was invited to rescreen with a FIT after 2 years.[42] It was assumed that surveillance stopped at 75 years of age.[42]

The stage-specific survival of patients with screen-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage, except if screen-detection occurs in the same stage as the cancer would have been diagnosed without screening.[27] In that case, survival is assumed to be similar to survival of one stage more favourable (i.e. stage II cancer gets stage I survival). Only if screen-detected in stage IV, we assume no possibility for within-stage shift and stage IV screen detected cancers always have the same survival as clinically diagnosed cancers in stage IV.

Utility losses associated with CRC

Based on expert opinion, the assumed loss in quality of life due to screening was zero quality adjusted life years (QALYs) for FIT screening and 0.00274 (equal to 2 days per colonoscopy at a utility of 0.5) QALYs for screening with colonoscopy. Complications resulting in hospitalisation within 30 days after colonoscopy were assumed to result in a 0.5 reduction in quality of life during 14 days (0.01918 QALYs). Life with CRC was assumed to be of lower quality than life without CRC,[43] and utilities were based on stage of CRC (Table 4).

Table 3: Main screening assumptions in the MISCAN-Colon model

Parameter	Value	Source
Sensitivity of FIT[a]	Dependent on stage of disease • Adenoma 1-5mm: 0% • Adenoma 6-9mm: 9% • Adenoma 10+ mm: 32% • Preclinical cancer (long before clinical diagnosis): 36.5% • Preclinical cancer (shortly before clinical diagnosis): 72.8%	Queensland Bowel Health Cancer Screening Program Report [28]
Specificity of FIT (per person)	95%	Queensland Bowel Health Cancer Screening Program Report [28]
Positivity rate of FIT	7.7%	Queensland Bowel Health Cancer Screening Program Report[28]
Positive predictive values of FIT	Without histopathologically confirmed adenomas or cancer: 47.4% With adenomas: 48.2% With advanced adenomas: 25.6% With confirmed cancer: 4.4%	Queensland Bowel Health Cancer Screening Program Report [28]
Sensitivity of colonoscopy[b,c]	Dependent on stage of disease • Adenoma 1-5mm: 75% • Adenoma 6-9mm: 85% • Adenoma 10+ mm: 95% • Preclinical cancer: 95%	Back-to-back colonoscopy studies[34]
Specificity of colonoscopy[b,d]	86%	International literature[33]
Caecal intubation rate	95%	International literature[30, 31, 32]
Complication rate with colonoscopy[e]		
Fatal complication[f]	0.4 per 1,000 colonoscopies	Australian Data [41]
General complication[g]	Age-specific • 50–54: 9.6% • 55–59: 8.0% • 60–64: 5.4% • 65–69: 12.7% • 70–74: 7.3%	National Bowel Cancer Screening Program[40]
Probability to develop cancer from removed adenoma	0%	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)	FIT trial[27]

Abbreviations: CRC = colorectal cancer; FIT = faecal immunochemical test

a. 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
b. We assume the same test characteristics for diagnostic colonoscopy as for screening colonoscopy
c. 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[34]
d. 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. Ann Intern Med 2013[33]
e. Complications are conditional on polypectomy, and we assume that polypectomy is only performed if colonoscopy is positive
f. Fatal complication taken from Viiala et al, 2003[41] 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.[40] A complication is considered as an unplanned hospital admission within 30-days of a diagnostic colonoscopy in people aged 50-74 years

Table 4: Utility losses associated with CRC screening and treatment

UTILITY LOSS (QALYs) [a]				
Per FIT	0			
Per colonoscopy [b]	0.00274			
Per complication of colonoscopy [c]	0.01918			
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

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. Complications associated with hospitalisation with 30 days of colonoscopy were assumed to be equal to 14 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.[43] 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

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