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Appendix 1

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Appendix 1: The MISCAN-Colon microsimulation model

Model Overview

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

The basic structure of MISCAN-Colon is illustrated in figure A1-1. Figure A1-1 clearly demonstrates that MISCAN-Colon consists of three parts:

- demography part
- natural history part
- screening part

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

Demography Part

The demography part of the model simulates individual life histories without colorectal cancer (CRC) to form a population. For each person, a date of birth and a date of death of other causes than CRC are simulated. The distribution of births and deaths can be adjusted to represent the population simulated.

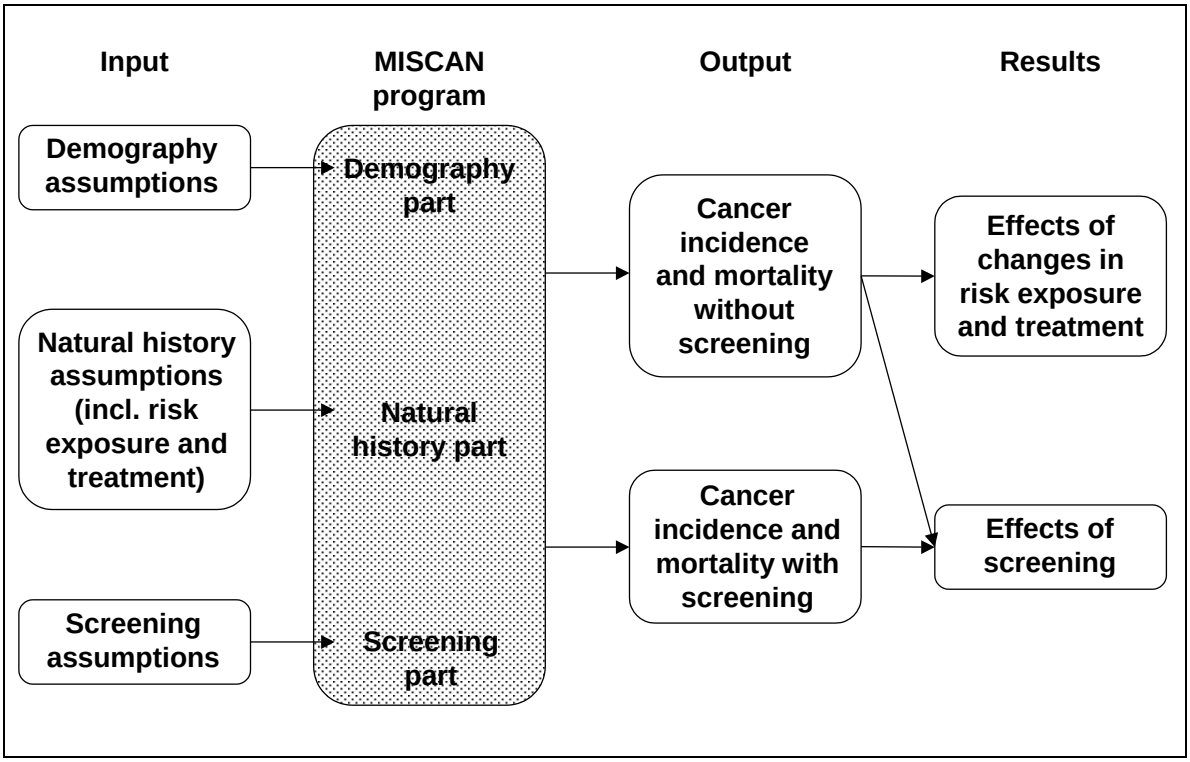

Figure A1-1: Structure of MISCAN-Colon

Natural History Part

The Natural History part of MISCAN-Colon simulates the development of CRC in the population. It was assumed that all CRCs develop according to the adenoma-carcinoma sequence of Morson[1] and Vogelstein[2] (Figure A1-2). For each individual in the simulated population a personal risk index is generated. Subsequently, adenomas are generated in the population according to this personal risk index and an age specific incidence rate of adenomas. This results in no adenomas for most persons and one or more adenomas for others. The distribution of adenomas over the colorectum is simulated according to the observed distribution of CRC incidence. Each of the adenomas can independently develop into CRC. Adenomas can progress in size from diminutive (1-5 mm) to small (6-9 mm) to large (10+ mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. The survival after clinical diagnosis depends on race, sex, period of diagnosis, and stage and location of the cancer.

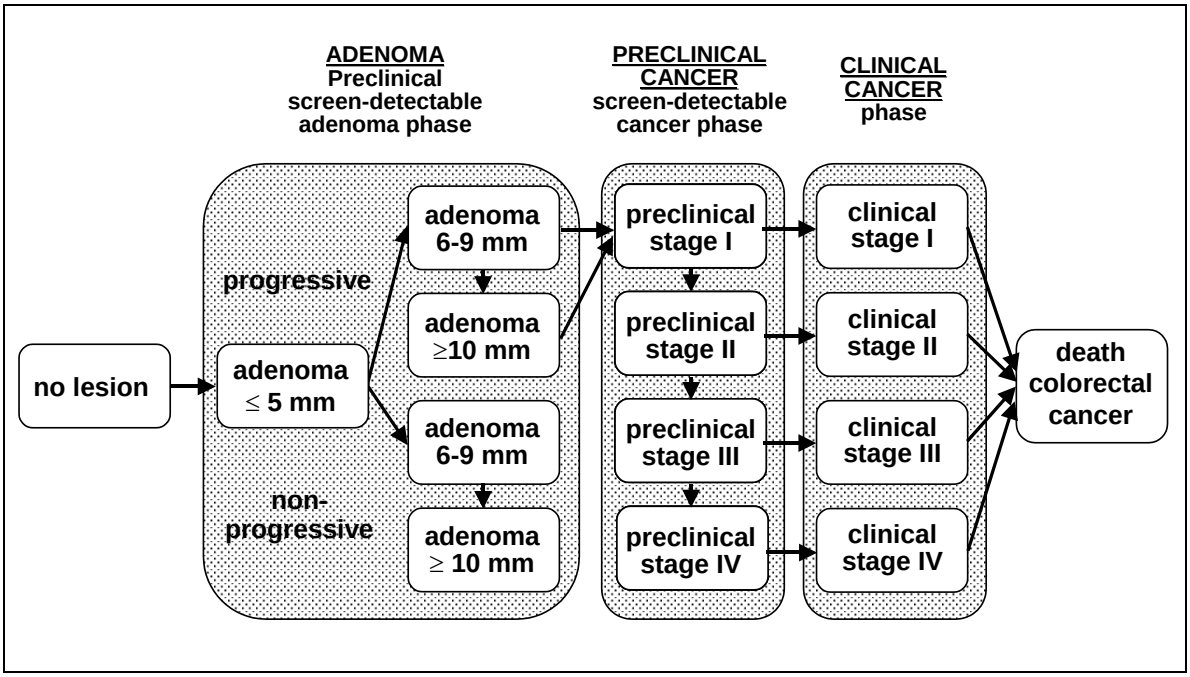

Figure A1-2: Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for CRC. Adenomas are categorised by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age.

Screening Part

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

Integration of the three model components

For each individual, the demography part of the model simulates a time of birth and a time of death of other causes than CRC, creating a life history without CRC (top line in figure A1-3a). Subsequently adenomas are simulated for that individual. For most individuals no adenomas are generated, for others one or more adenomas are generated. In the example in figure A1-3, the person develops two adenomas (2nd and 3rd line in figure A1-3a). The first adenoma arises at a certain age, grows into 6-9 mm and eventually becomes larger than 10 mm. However, this adenoma does not become cancer before the death of the person. The

second adenoma is a progressive adenoma. After having grown to 6-9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and diagnosis and eventually resulting in an earlier death from CRC. The life history without CRC and the development of the two adenomas in figure A1-3 together lead to the combined life history with CRC depicted in the bottom line. As this person dies from CRC before he dies from other causes, his death age is adjusted accordingly.

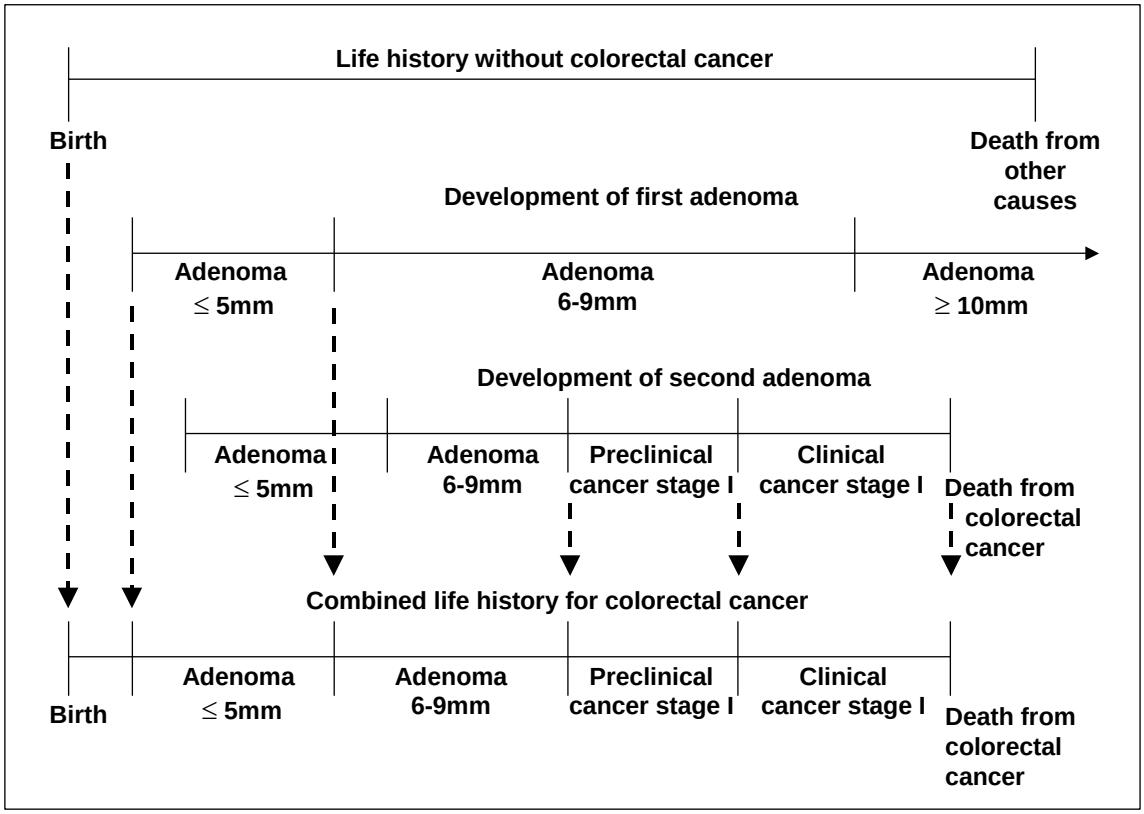

Figure A1-3a: Modelling natural history into life history

After the life history of a person is adjusted for CRC, the history will now be adjusted for the effects of screening. The effect of screening on life history is explained in figure A1-3b.The top line in this figure is the combined life history for CRC from figure A1-3a. The development of the separate adenomas is repeated in the second and third line. In this picture there is one screening intervention. During the screening both prevalent adenomas are detected and removed. This results in a combined life history for CRC and screening (bottom line). From the moment of screening the adenomas are removed and this individual becomes adenoma and carcinoma free. He does not develop cancer because the precursor lesion has been removed. Therefore the person dies from other causes and the effect of screening is the difference in life-years in the situation without screening and the situation

with screening. Of course many other possibilities could have occurred: a person could have developed new adenomas after the screening moment, or an adenoma could have been missed by the screening test, but in this case this individual really benefited from the screening intervention.

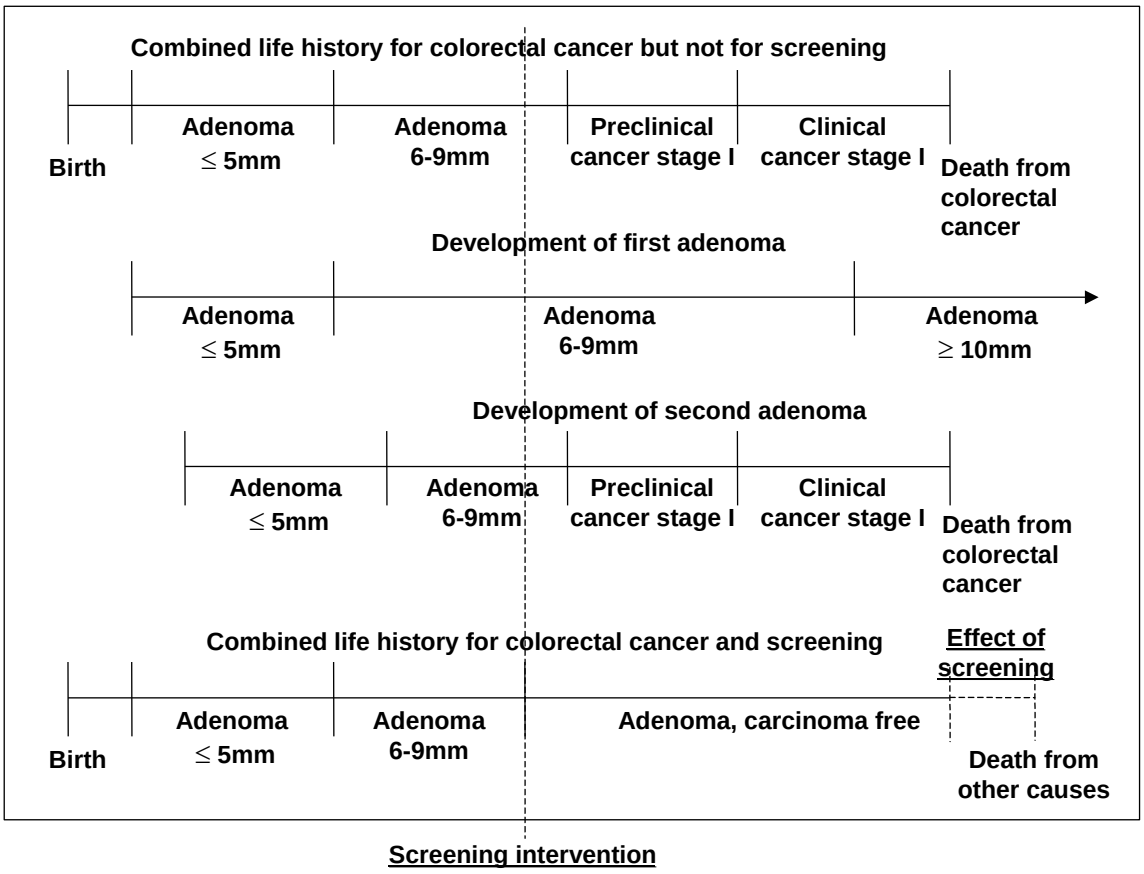

Figure A1-3b: Modelling screening into life history

Model Quantification

Demography Parameters

There are two types of demography parameters: birth tables and life tables. Birth tables were modelled on individuals born between 1911 and 2011 (inclusive) with the distribution of births so that the 2011 Australian population was matched by gender and age.[3]

Life expectancy was modelled on data from the Australian Bureau of Statistics 2009 Life Tables.[4] These life tables include CRC mortality and the demography part simulates mortality from other causes 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 NCI on June 5–7, 1996, and May 12–13, 1997, a model structure was devised in agreement with the currently accepted model of the adenoma–carcinoma sequence. It was assumed that all cancers are preceded by adenomas. The average duration of cancer in preclinical stages I–IV was 2.5 years, 2.5 year, 3.7 years, and 1.5 years, respectively, which resulted in a total average duration of 6.7 years because not every cancer reaches stage IV before clinical diagnosis. These sojourn times were based on a simultaneous estimation of sojourn time and FOBT sensitivity from the three large randomized controlled trials on FOBT screening.[5] The average duration of the development from adenoma 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.[6] 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.[7, 8]

It was 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. 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.[9-18] 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.[19]

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.[20] Five-year relative survival after clinical diagnosis of CRC was based on literature available in the Australian setting.[21]

Table 2 contains a summary of the model input values and its data-sources.

Table A1-2: Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance gender-dependent	Fit to multiplicity distribution of adenomas in autopsy studies:[22] 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%
Adenoma incidence per year	Age, gender and race dependent varying from 0-26% per year	Fit to adenoma prevalence in autopsy studies [9-18]
Probability that a new adenoma is progressive	Dependent on age at onset, varying from 0-31%	Fit to adenoma prevalence in autopsy studies [9-18] Cancer incidence taken 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[6]*
Mean duration of preclinical cancer	6.7 years	Estimated from large randomised controlled FOBT trials[5]
Per cent of non-progressive adenomas that stay 6-9mm	25%	Fit to size distribution of adenomas in colonoscopy study (corrected for lack of sensitivity)[19]
Per cent of non-progressive adenoma that become 10mm or larger	75%	Fit to size distribution of adenomas in colonoscopy study (corrected for lack of sensitivity)[19]
Per cent of cancers that develops from 6-9mm adenoma and from 10+mm adenoma	30% of cancer develops from 6-9 mm, 70% from 10+mm	Expert opinion
Localisation distribution of adenomas and cancer		Taken from Australian literature[20]
5-year survival after clinical diagnosis of CRC		Taken from Australian literature[21]

* To be estimated from randomized controlled endoscopy trials, in progress.

Screening Parameters

The iFOBT 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.[24] 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 iFOBT 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).

Caecal intubation rate was assumed to be 95%.[25-27] The sensitivity of colonoscopy for each lesion within realized reach was based on back-to-back colonoscopy studies: 75% in adenomas less than or equal to 5 mm, 85% in adenomas 6–9 mm, and 95% in adenomas greater than or equal to 10 mm and cancers.[28] At detection, lesions are removed immediately. The percentage of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after colonoscopy has been estimated from Kaiser data:[29] 10%. This percentage was assumed to be independent of the screening round.

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.[30] 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. Risks of complications reported in organised screening programs[31-33] are lower than those reported for general practice colonoscopies.[34, 35] The major complications of colonoscopy are perforations (which can occur with or without polypectomy), serosal burns, bleeds requiring transfusion and bleeds not requiring transfusion.[31-35] A rate of death among persons was estimated as 0.4 per 10,000 colonoscopies.[36]

Table A1-3: Main screening assumptions in the MISCAN-Colon model

Parameter	Value	Source
Sensitivity of iFOBT	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 [24]
Specificity of iFOBT (per person)	95%	Queensland Bowel Health Cancer Screening Program Report [24]
Positivity rate of iFOBT	7.7%	Queensland Bowel Health Cancer Screening Program Report[24]
Positive predictive values of iFOBT	Without histo-pathologically 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 [24]
Sensitivity of colonoscopy	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[28]
Cecal intubation rate	95%	General practice [25, 26] and guidelines[27]
Complication rate with colonoscopy Perforation Serosal burn Bleed with transfusion Bleed without transfusion	2.4 per 1,000 colonoscopies 0.7 per 1,000 0.3 per 1,000 0.4 per 1,000 1.1 per 1,000	Organised screening programs[31-33] and general practice[34, 35]
Fatal complication rate with colonoscopy	0.1 per 1,000 colonoscopies	Prospective endoscopy study[36]
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)	FOBT trial[30]

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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