



FLEXKB DOCUMENT
Version: HI.001.11302018.9755
Document generated: 11/30/2018

CISNET COLORECTAL CANCER COLLABORATORS

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at <http://cisnet.cancer.gov/profiles>. The CISNET model profile topics are not necessarily meant to be read in sequential fashion, so the reader should feel free to skip around as their interests dictate.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

	RAND Corporation
	University of Minnesota
	Memorial Sloan Kettering / Erasmus



FLEXKB DOCUMENT
Version: HI.001.11302018.9752
Document generated: 11/30/2018

RAND CORPORATION

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at <http://cisnet.cancer.gov/profiles>. The CISNET model profile topics are not necessarily meant to be read in sequential fashion, so the reader should feel free to skip around as their interests dictate.



[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: [Reader's Guide](#).



READERS GUIDE

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5–10 minutes. Each contains links to more detailed information if required.



Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Component Overview

Describes the basic computational building blocks (components) of the RAND model.

- [Natural History Component](#)
- [Adenoma Risk Component](#)
- [Transition To Preclinical CRC Component](#)
- [Transition To Clinical CRC Component](#)

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Output Overview

Describes basic model outputs. Because we output complete information for our simulated population, we are free to choose a wide range of model outputs. Current model outputs are driven by comparisons with other CISNET models.

Results Overview

A guide to the results obtained from the model. At this time, our focus is on Bayesian calibration of model parameters.

Key References

A list of references used in the development of the model.



MODEL PURPOSE

SUMMARY

The Colorectal Cancer Simulated Population model for Incidence and Natural history (**CRC-SPIN**) was developed to explore trends in colorectal cancer (CRC) incidence and mortality, to compare the effectiveness of different screening modalities, and to extend results from clinical trials to mortality endpoints.



PURPOSE

CRC-SPIN contains three components that are used in combination to predict outcomes: a natural history model, a calibration component, and a screening component.

1) The **natural history model** describes the development of adenomas, preclinical cancers, clinically detected cancers, and survival after detection. *The purpose of the CRC-SPIN natural history model is to parsimoniously describe the natural history of colorectal cancer.* (see [Model Overview](#), the [Natural History Component](#) provides a brief description).

2) The **calibration component** is used to combine information from multiple targets to select good natural history model parameters. CRC-SPIN 1.0 was calibrated using an approximate Markov Chain Monte Carlo approach, with calibration based on data likelihoods (Rutter, Miglioretti, Savarino, 2009). CRC-SPIN 2.0 and later model versions were calibrated using an Incremental Mixture Approximate Bayesian Computation approach, which is a likelihood-free approach (Rutter, Ozik, DeYoreo, Collier, under review). The Bayesian methods used for calibration result in a sample from the posterior parameter distribution, which can be used to estimate the uncertainty of model predictions. *The purpose of the CRC-SPIN calibration component is to provide an objective, automated, data-based method for calibrating natural history model parameters. A secondary purpose is to obtain posterior distribution estimates of model parameters that can be used to describe uncertainty in model predictions.*

3) The **screening component** simulates the action of screening tests by simulating the occurrence of and outcomes from screening tests. CRC-SPIN simulates test performance that depends on disease characteristics. For example, the sensitivity of colonoscopy depends on lesion size. *The purpose of the CRC-SPIN screening component is to simulate and then compare model-predicted outcomes (such as incidence and mortality) under a range of screening scenarios.*



MODEL OVERVIEW

SUMMARY

The CRC–SPIN model simulates colorectal cancer disease trajectories for agents that are part of population, cohort, or sample.



PURPOSE

CRC–SPIN is used to examine the effect of screening on colorectal cancer (CRC) outcomes, including incidence and mortality. Additional details are provided in [Model Purpose](#).

BACKGROUND

CRC is the third leading cause of cancer death in the United States. Randomized controlled trials (RCTs) have shown that screening for CRC – using either fecal occult blood tests (FOBT) or flexible sigmoidoscopy – can reduce CRC–mortality. Evidence of the effectiveness of other tests is inferred from operating characteristics (sensitivity and specificity) or from observational studies (e.g., case–control studies). Although RCTs are a gold standard for evaluating the effectiveness of screening tests, it is impractical or impossible to use RCTs to answer the full range of health policy questions about CRC screening. This includes questions about the relative effectiveness of different CRC screening strategies. Microsimulation models like CRC–SPIN provide a method for addressing a broad range of questions about CRC screening.

MODEL DESCRIPTION

CRC–SPIN is a microsimulation model: it simulates individuals (or 'agents') but not interactions between agents. For each agent, CRC–SPIN simulates disease trajectories over a lifetime, including the occurrence and growth of adenomas, transition of adenomas to preclinical CRC, death from CRC, death from other causes, and the actions of screening on these trajectories. CRC–SPIN 1.0, developed in C#, is now retired. CRC–SPIN was updated and recalibrated in January 2018. CRC–SPIN 2.0 and beyond are written in R.

CRC–SPIN has four components:

1. adenoma risk;
2. adenoma growth;
3. transition from adenoma to preclinical cancer; and
4. transition from preclinical to clinical cancer (sojourn time).

Once CRC is clinically detected, CRC–SPIN stochastically assigns stage and size at detection, and survival given stage at detection. CRC–SPIN simulates events in continuous time, and simulates continuous (rather than categorical) adenoma and cancer size.

CRC–SPIN components are described in detail in the [Component Overview](#). Below, we describe key assumptions, model inputs, and model outputs.

Key Assumptions: CRC–SPIN 2.x is built on the assumption that all CRC arises through the adenoma–carcinoma process. (A CRC–SPIN version that incorporates the sessile serrated polyp disease pathway is under development.) Another key



assumption is that neither adenomas nor cancers regress, though adenomas can grow very slowly. CRC-SPIN specifies a minimum adenoma size of 1mm and a maximum adenoma size of 50mm. (Cancer size may be larger.)

Agents may develop multiple adenomas. Every adenoma has the potential to develop into preclinical cancer, so that agents may develop multiple colorectal cancers, and thus may have multiple hypothetical cancer death times. In the absence of screening, the first clinically detected cancer determines CRC survival. In the presence of screening, the first screen- or clinically-detected cancer determines CRC survival, though the removal of adenomas may prevent their transition to CRC.

CRC-SPIN incorporates the overall effect of changes in treatment on CRC survival, which is simulated using a model based on analysis of SEER data. CRC survival is a function of age, sex, cancer location (colon or rectum), stage, and year of diagnosis. CRC-SPIN does not simulate the impact of specific treatments on colorectal cancer outcomes, though this is a potential model extension.

CRC-SPIN is a 'parallel universe' model, and simulates outcomes for the same population under different screening scenarios. The screening component can accommodate complex screening scenarios, and is easily extended to incorporate new screening modalities. The screening component includes two general types of screening tests: an agent-level test that provides a single result for each agent, and a structural exam that provides a result for each adenoma (and an overall agent-level false positive rate). Colonoscopy is a special type of structural exam that can remove adenomas and preclinical cancers. (In some simulations lesions may also be removed at flexible sigmoidoscopy.) Agent-level tests include fecal-based tests of all types (gFOBT, FIT, stool DNA) and could include blood-based tests. Structural tests include flexible sigmoidoscopy, colonoscopy, CT colonography, and could include capsule tests.

A more detailed description of CRC-SPIN assumptions is described in [Assumption Overview](#).

Model Inputs: CRC-SPIN includes relatively few calibrated parameters (v1.0: 23, v2.x: 22, see [Parameter Overview](#)). Model *inputs* refer to information, based on empirical data, that is directly passed to the model. CRC-SPIN model inputs are:

- the distribution of adenomas over the large intestine (based on both autopsy and screening colonoscopy studies),
- the size distribution of clinically detected CRC (based on 1979 SEER data, prior to the diffusion of screening),
- the stage distribution of clinically detected CRC (based on 1979 SEER data), and
- CRC relative survival, a function of stage, location (colon or rectum), sex, and age at diagnosis (based on SEER data, see Rutter, Johnson, Feuer, et al, 2013)

Additional information about model inputs is provided in the [Assumption Overview](#).

Model Outputs: CRC-SPIN simulates life events histories for agents both with and without screening. Generated model outputs include: the prevalence and number of adenomas across agents, rates of preclinical cancer, rates of clinical cancer (by location, sex, and age), and mortality rates (by location, sex and age). Additional information is provided in [Output Overview](#).



RAND Corporation
Model Overview
Contributors

CONTRIBUTORS

Carolyn Rutter (PI), RAND Team (in alphabetic order:) Maria DeYoreo, Florentine Eloundou, Chris Maerzluft, Angel Martinez

past contributors: Jessica Hwang, Eric Johnson, Tracey Marsh, Diana Miglioretti, Chester Pabiniak, Jim Savarino



ASSUMPTION OVERVIEW

SUMMARY

This document describes basic assumptions made by the CRC–SPIN natural history and screening models.

BACKGROUND

Microsimulation models are complex and require assumptions about the functional form governing simulated process.

ASSUMPTION LISTING

The most basic model assumption is that all cancers arise from adenomas. (Development of a CRC–SPIN version that incorporates the sessile serrated pathway is underway.) Model assumptions for each CRC–SPIN component are described below.

Detailed Description of Model Assumptions

Adenoma initiation assumptions

CRC–SPIN uses a non–homogenous Poisson Process to simulate adenoma occurrence.

- Adenoma risk systematically varies with age and sex. Calibration of a CRC–SPIN model that allows adenoma risk to vary systematically by race is underway.
- Adenoma risk stochastically varies across agents (some have higher risk than others), and the distribution of agent–level baseline log–risk follows a normal distribution.
- Adenomas are independently located within each agent’s large intestine (e.g., we do not model an agent–level tendency to develop adenomas in a specific location.)
- The distribution of adenomas across the large intestine is uncalibrated and is based on findings from 9 autopsy studies and one colonoscopy study not included as calibration data. We assume that $P(\text{cecum})=0.08$, $P(\text{ascending colon})=0.23$, $P(\text{transverse colon})=0.24$, $P(\text{descending colon})=0.12$, $P(\text{sigmoid colon})=0.24$, $P(\text{rectum}) = 0.09$.

Adenoma growth assumptions

CRC–SPIN simulates adenoma growth using a Richard’s growth model (Tjørve, Tjørve, 2010). This model includes the Janoschek model (used in CRC–SPIN 1.0).

- Adenoma growth *parameters* are constant over time. This does not imply constant growth of adenomas over time.
- Adenomas do not regress.
- Adenoma growth parameters are independent within agents (for agents with multiple adenomas).
- The time to 10mm follows a Frèchet (type II extreme value) distribution.
- The minimum adenoma size is 1mm.
- The maximum adenoma size is 50mm.





Size at transition to cancer assumptions

CRC-SPIN simulates the size of adenoma transition to cancer using log-normal distribution.

- Cancer first grows within an adenoma, with the lesion size only increasing once the cancer 'overtakes' the adenoma.
- Most adenomas do not transition to cancer, and so most adenomas do not reach their simulated transition size.
- The minimum cancer size (size at transition) is 0.5mm. This is less than the 1mm adenoma size. Therefore, the minimum malignant lesion size is 1mm.
- The probability of transition to cancer is a function of adenoma size, sex, age at initiation, and location (colon v. rectum). (Calibration of a CRC-SPIN model that allows the size at adenoma transition to preclinical CRC to vary systematically by race is underway.)

Cancer growth assumptions

- Cancerous lesions grow exponentially. The exponential growth rate is a function of the size at transition (0.5mm), the size at clinical detection, and the time from initiation to clinical detection (sojourn time). Given the exponential model and the cancer growth parameter, cancer size can be calculated at any time during the preclinical detectable phase.

Sojourn time and stage at detection assumptions

- Sojourn time depends only on location within the large intestine (colon or rectum), and is independent across cancers within agents.
 - CRC-SPIN V1.0 used a log-normal model for sojourn time.
 - CRC-SPIN V2.x uses a Weibull model for sojourn time, with calibrated shape and location parameters, and a proportional hazards model used to capture differences in sojourn time by location.
Calibration of a CRC-SPIN model that allows sojourn time to vary systematically by race is underway.
- Stage and size at clinical detection are model inputs, and are based on 1979 SEER data that describe stage and size at clinical detection. The method for incorporating this information into the model depends on the version.
 - CRC-SPIN V1.0 simulated size at clinical detection then stage at clinical detection given size.
 - CRC-SPIN V2.x simulates stage at clinical detection then size at clinical detection given stage at detection.
- Size and stage at clinical detection are model inputs and are based on the SEER distribution of cancer size in 1975-1979, years prior to widespread CRC screening. CRC-SPIN 2.x uses stage at detection and the size at clinical detection stratified by stage. CRC-SPIN 1.0 used the overall size distribution and stage at detection given size at detection.

Survival assumptions



- CRC survival depends only on stage at diagnosis, age at diagnosis, location (colon or rectum), sex, and year of diagnosis.
- Survival following detection is a model input, and is based on relative survival conditional on stage at diagnosis, age at diagnosis and sex (as provided in Rutter, Johnson, Feuer et al. 2013).
- Future models that incorporate race will specify survival that also depends on race.



COMPONENT OVERVIEW

SUMMARY

This page describes the components of the CRC–SPIN natural history model.

OVERVIEW

There are four key components of the CRC–SPIN natural history model: 1) Adenoma risk; 2) Adenoma growth; 3) Size at transition to preclinical CRC; and 4) Time transition to clinical CRC and stage at diagnosis. Together, adenoma growth and size at transitioning to preclinical CRC determine the time to transition to CRC. After transition to clinical CRC, the model assigns stage at diagnosis and survival given stage at diagnosis.

CRC–SPIN is used to simulate events for individuals (or ‘agents’) in a population, sample, or cohort, by combining an age–sex distribution with a target population size. The age–sex distribution of simulated agents is a model input. The CRC–SPIN model can simulate population cohorts that have identical birthdays or have the same birth–year (or were born in a particular period). It is also possible to specify a sex–specific age distribution at a point in time, and then simulate these agents forward. The ability to specify more flexible age distributions is important for model calibration and validation.

COMPONENT LISTING

Adenoma Risk: CRC–SPIN simulates the occurrence of adenomas within agents using a non–homogenous Poisson process that allows adenoma risk to vary by age and sex (see [Adenoma Risk Component](#) for more details). The adenoma risk model is based on a Bayesian meta–analysis of 14 autopsy studies (Rutter, Miglioretti, Yu. 2007), which showed excellent fit to both the autopsy studies used for estimation, and to 4 screening colonoscopy studies used for validation.

Once adenomas are initiated, the CRC–SPIN model assigns their location using a multinomial distribution across 6 possible sites of the large intestine (from proximal to distal): 1) cecum; 2) ascending colon; 3) transverse colon; 4) descending colon; 5) sigmoid colon; 6) rectum. Overall location probabilities are not calibrated.

Adenoma Growth: The adenoma growth model is based on simulating the time it takes an adenoma to reach 10mm. This is then used in combination with a growth model to determine adenoma size at any point in time, which is needed to determine the outcomes of simulated tests. Adenoma size is also needed to determine the time at transition to preclinical CRC.

Size at Transition to Preclinical CRC: The model for transition to preclinical cancer is based loosely on autopsy studies of adenoma size and the presence of preclinical cancer. CRC–SPIN simulates the size at adenoma transition to preclinical invasive CRC using a lognormal model.

The **time from adenoma initiation to transition to preclinical cancer** is based on the combination of simulated adenoma growth and the simulated size at transition to preclinical cancer (see [Transition To Preclinical CRC Component](#) for more details).





Time to transition From Preclinical to Clinical CRC: CRC-SPIN V2.x uses a Weibull distribution for sojourn time. (CRC-SPIN 1.0 model used a log-Normal distribution.) The CRC-SPIN model does not include agent-level covariates in the sojourn-time model, though models that incorporate race will include an effect of race in the proportional hazards sojourn time model.

Cancer stage and survival are based on models that use Surveillance Epidemiology and End Results (SEER) data. In particular, we model the stage at clinical detection and then size conditional on stage. (The CRC-SPIN 1.0 model simulated cancer size, and then stage given size.) The **size during the preclinical detectable phase** is calculated assuming an exponential cancer growth model in combination with the size at transition to invasive cancer (0.5mm), the size at clinical detection, the time from initiation to clinical detection (sojourn time).

Survival after CRC detection is modeled as a function of age at diagnosis, sex, location (colon or rectum, stage, and year of diagnosis. Survival curves are based on analysis of SEER data. Models that include race will specify separate survival functions for black and white agents (in addition to effects of age at diagnosis, sex, location, stage, and year of diagnosis).



NATURAL HISTORY COMPONENT

SUMMARY

This document describes the Natural History model and the specific components we use to model agents' progression from a disease free state to diagnosis.



Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

OVERVIEW

The CRC–SPIN natural history model simulates adenoma development, growth and transition to cancer. CRC–SPIN allows disease processes to depend on age, sex, and adenoma location (colon or rectum), but does not incorporate other risk factors.

DETAILS

There are four key components of the CRC–SPIN natural history model: 1) Adenoma risk; 2) Adenoma growth; 3) Size at transition to preclinical CRC; and 4) Time transition to clinical CRC and stage at diagnosis. Together, adenoma growth and size at transitioning to preclinical CRC determine the time to transition to CRC. After transition to clinical CRC, the model assigns stage at diagnosis and survival given stage at diagnosis. These are described more fully in the [Model Overview](#) and in the separate model components ([Adenoma Risk Component](#), [Transition To Preclinical CRC Component](#), [Transition To Clinical CRC Component](#)).

RELEVANT ASSUMPTIONS

The most basic model assumption is that all cancers arise from adenomas. In addition, at this time, we assume that risk for adenomas depends only on sex and age, and does not otherwise vary over time. CRC–SPIN includes stochastic variability in risk, but does not link risk across components. For example, at any given size, fast growing adenomas are no more likely to transition to cancer than slow-growing adenomas. For a complete listing of assumptions see [Assumption Overview](#).

RELEVANT PARAMETERS

Parameters associated with the CRC–SPIN natural history model are described in the [Parameter Overview](#)

RELEVANT COMPONENTS

The separate components of the natural history model are described in the following pages:

- [Adenoma Risk Component](#) : A non-homogenous Poisson Process that allows risk to change with age and to depend on sex.
- [Transition To Preclinical CRC Component](#) : This model component is composed of two separate models, one describing adenoma growth and another describing the size at adenoma transition to preclinical cancer. CRC–SPIN simulates the time it takes for each adenoma to reach 10mm, and then simulates the size at any point in time using a Richards growth model that limits the maximum adenoma size to range from 1mm to 50mm. The size at transition to preclinical cancer is simulated using a lognormal model. Together, the growth model and the size at transition determine the time at adenoma transition to preclinical cancer.



- **Transition To Clinical CRC Component** : Sojourn time is modelled using a Weibull distribution that describes sojourn time and the variability of sojourn time across agents. The effect of location (colon or rectum) is incorporated through a proportional hazards model. (CRC-SPIN 1.0 used a log-normal distribution, with a two parameters for each location. CRC-SPIN 2.0 used a Weibull model with shape parameter set to 5 and one parameters for each location.)

Adenoma Stage and Survival, and Survival after CRC detection are uncalibrated model inputs (see [Component Overview](#)).

DEPENDENT OUTPUTS

The CRC-SPIN natural history model is a 'parallel universe' model, that simulates complete life histories for all agents. These life histories include: age at adenoma initiation, transition(s) to preclinical cancer, age(s) at clinical cancer detection, age at colorectal cancer death, and age at non-CRC death. Transition times and CRC death ages are calculated both with and without screening. CRC-SPIN uses a shared uniform random deviate to link survival when a cancer is screen-detected rather than clinically-detected. .



ADENOMA RISK COMPONENT

SUMMARY

The occurrence of adenomas is simulated using a non-homogenous Poisson process that allows risk to depend on sex, and to increase with age.

OVERVIEW

The CRC-SPIN adenoma risk model is based on a Bayesian meta-analysis of 14 autopsy studies (Rutter, Miglioretti, Yu, 2007). The meta-analytic model showed excellent fit to both the autopsy studies used for estimation, and to 4 screening colonoscopy studies used for validation.

DETAIL

Let $\psi_i(t)$ denote the i th agent's instantaneous risk of an adenoma at time t . The risk of developing adenomas differs for men and women and increases with age. To allow flexibility, CRC-SPIN describes log-risk as a piecewise linear function of age. The risk of an adenoma developing in the i th agent at time t is given by

$$\psi_i(t) = \exp \left(\alpha_{0i} + \alpha_1 \text{sex}_i + \sum_{k=1}^4 \delta(A_k < \text{age}_i(t) \leq A_{k+1}) \left\{ \text{age}_i(t) \alpha_{2k} + \sum_{j=2}^k A_j (\alpha_{2j-1} - \alpha_{2j}) \right\} \right)$$

where α_{0i} describes an agent's baseline risk; α_1 describes the difference in risk for women ($\text{sex}_i = 0$) relative men ($\text{sex}_i = 1$); α_{2k} describes changes in risk with age (in years) in the k th interval; and $\delta(\cdot)$ is an indicator function, with $\delta(x) = 1$ when x is true and $\delta(x) = 0$ otherwise.

Given $\psi_i(t)$, the number of adenomas an agent develops by time t , has a Poisson distribution with mean

$$\Psi_i(t) = \int_{20}^{\text{age}(t)} \psi_i(u) du \text{ given by}$$

$$\Psi_i(t) = e^{\alpha_{0i} + \alpha_1 \text{sex}_i} \sum_{k=1}^4 \left\{ \delta(\text{age}_i(t) > A_k) \left(\frac{e^{\alpha_{2k} \min(A_{k+1}, \text{age}_i(t))} - e^{\alpha_{2k} A_k}}{\alpha_{2k}} \right) \exp \left(\sum_{j=2}^k A_j (\alpha_{2j-1} - \alpha_{2j}) \right) \right\}$$

The baseline distribution of adenomas across the large intestine is based on combined information from 9 autopsy studies. These data were combined using a Bayesian Multinomial model with a Dirichlet prior for unknown probabilities. These baseline probabilities are: P(cecum)=0.08, P(ascending colon)=0.23, P(transverse colon)=0.24, P(descending colon)=0.12, P(sigmoid colon)=0.24, P(rectum) = 0.09, a distribution that is similar to the observed distribution in a relatively recent study of virtual and optical colonoscopy in a minimally screened population (Pickhardt et al. NEJM, 2003).

RELEVANT ASSUMPTIONS

The risk of developing adenomas in childhood is extremely low. The CRC-SPIN model does not simulate the development of adenomas until age 20. The CRC-SPIN adenoma model specifies $K = 4$ fixed age-risk intervals: [20,50), [50,60), [60,70), and ≥ 70 , so that $A_1 = 20$, $A_2 = 50$, $A_3 = 60$, $A_4 = 70$ and $A_5 = \infty$ (effectively 120 years old). Risk increases log-linearly within these age intervals.



- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References



Agent-level baseline risk (α_{0i}) results in clustering of adenomas within agents, so that high-risk agents develop more adenomas than low-risk agents. Agent-level baseline risk, α_{0i} , is assumed to be independently and identically distributed $\text{Normal}(\alpha_0, \sigma_\alpha)$ across agents.

RELEVANT PARAMETERS

The CRC-SPIN adenoma risk model includes 7 parameters:

- α_0 , Expected baseline log-risk
- σ_α , Standard deviation of baseline log-risk
- α_1 , The effect of sex on risk
- α_{2k} , $k = 1, \dots, 4$, The effect of age on risk.

RELEVANT COMPONENTS

The adenoma risk model starts the process that eventually leads to colorectal cancer. There are no subcomponents of this process. All subsequent adenoma processes (growth, transition to cancer) depend on the adenoma risk model.

DEPENDENT OUTPUTS

The number of adenomas within each agent over time, when each was initiated, and their locations in the large intestine.



TRANSITION TO PRECLINICAL CRC COMPONENT



- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References

SUMMARY

Transition to preclinical CRC is modeled as a function of adenoma size. Thus, the CRC-SPIN transition model is based on two sub-models, one for adenoma growth and another for cancer as a function of size.

OVERVIEW

Adenoma growth is modeled using the Richards growth model, parameterized in terms of the median time to reach 10mm. Transition to clinical CRC is modeled as a function of adenoma size, with transition probabilities based loosely on autopsy studies of size and presence of invasive cancer.

DETAIL

Adenoma growth model

Adenoma growth is simulated using the Richards growth model:

$$d_{ij}(t) = d_{\infty} \left[1 + \left(\left(\frac{d_0}{d_{\infty}} \right)^{1/p} - 1 \right) \exp(-\lambda_{ij}t) \right]^p$$

where d_{∞} is the maximum possible adenoma diameter, d_0 is the minimal detectable adenoma diameter, and λ_{ij} is the growth rate for the j th adenoma within the i th agent.

The Richards model is a general growth curve model that is primarily used in studies of animal growth. This model offers several advantages over other models of tumor growth. Unlike the Gompertz and logistic models, it allows relatively fast early growth with an asymptote at d_{∞} . Adenoma size is assumed to range from a minimum of $d_0 = 1\text{mm}$ to $d_{\infty} = 50\text{mm}$. CRC-SPIN 1.0 used a Janoschek model, with $p = 1$. CRC-SPIN 2.x treats p as a calibrated parameter.

Clinical information is not available for growth model parameters. Instead, there is expert opinion about the expected time it takes and adenoma to reach 10mm and information about the size of detected adenomas. To better incorporate this information, the CRC-SPIN model specifies adenoma growth in terms of the time, in years, that it takes for an adenoma to reach 10mm,

$$t_{10mm} = -\frac{1}{\lambda} \ln \left(\frac{\left((10/d_{\infty})^{1/p} - 1 \right)}{\left((d_0/d_{\infty})^{1/p} - 1 \right)} \right)$$

t_{10mm} is simulated using a Frèchet (or Type 2 Extreme Value) distribution with scale parameter β_1 and scale parameter β_2 . The cumulative distribution function given by

$$F(t) = \exp \left(- \left(\frac{t}{\beta_1} \right)^{-\beta_2} \right)$$



for $t \geq 0$. This is equivalent to using a type I extreme value distribution on $\ln(t_{10mm})$. The Fréchet distribution has a long right tail but does not heavily weight small values that indicate fast growth.

Calibration of the CRC–SPIN 2.x model incorporated information about adenoma growth from a recent study that examined individuals with two screening colonoscopies that were approximately ten years apart (Ponugoti and Rex, 2017) and found that advanced adenomas were detected in only 3% of individuals at the second screening. Based on this, adenoma growth parameters were bounded so that the probability of an adenoma reaching 10mm within 10 years ranged from 0.001 to 0.25.

CRC–SPIN specifies separate growth distributions for colon and rectal adenomas, with parameters (β_{1c}, β_{2c}) and (β_{1r}, β_{2r}) , respectively.

Model for Size at Transition to Preclinical Cancer

Information about adenoma transition to preclinical invasive disease comes from autopsy and colonoscopy studies of adenomas examining the rate of preclinical invasive disease by adenoma size. The CRC–SPIN adenoma transition model is loosely based on an autopsy study results of Nusko and colleagues (1997). This study included information about preclinical cancer rates in the colon and rectum from 11380 adenomas removed endoscopically or by surgical resection between January 1978 and December 1993. Other information comes from a study of follow-up colonoscopy that provides evidence that the probability of transition depends on the age of the individual at the time of adenoma initiation (Yamaji et al., 2006).

Adenomas in the rectum appear to transition to cancer earlier than adenomas located in the colon. This possibility is further supported by clinical cancer rates. Relatively few adenomas occur in the rectum (approximately 9%), yet nearly a third of clinically detected colorectal cancers are located in the rectum (based on 1975–1979 SEER data).

CRC–SPIN uses a log–normal model for the size at adenoma transition as a function of sex, location, and age at adenoma initiation, that is, the log–size at transition preclinical invasive CRC has a normal distribution. CRC–SPIN 1.0 assumed that standard deviation of log–size at transition was 0.5, with mean:

$$\mu_\gamma = \gamma_0 + \gamma_1\delta_f + \gamma_2\delta_r + \gamma_3\delta_f\delta_r + (\gamma_4 + \gamma_5\delta_f + \gamma_6\delta_r + \gamma_7\delta_f\delta_r)(\text{age at initiation} - 50).$$

Where $\delta_f = 1$ if the agent is female and is zero if male, and $\delta_r = 1$ if the adenoma is located in the rectum and is zero if in the colon.

CRC–SPIN 2.x calibrates the standard deviation of the log–size at transition and assumes it has mean:

$$\mu_\gamma = \gamma_0 + \gamma_1\delta_f + \gamma_2\delta_r + \gamma_3\delta_f\delta_r + \gamma_4(\text{age at initiation} - 50) + \gamma_5(\text{age at initiation} - 50)^2$$

RELEVANT ASSUMPTIONS

Key assumptions made by the CRC–SPIN adenoma transition model are:



- Adenomas do not regress, though they may grow very slowly;
- The minimum adenoma size (size at initiation) is 1mm and the maximum *adenoma* size is 50mm;
- The probability of transition to cancer is a function of adenoma size, adenoma location, and age at adenoma initiation.
- The Richards model adequately describes adenoma growth, the type 2 extreme value distribution adequately describes the variability in time to 10mm across agents, and the Lognormal model adequately describes the probability of transition as a function of size.

RELEVANT PARAMETERS

A full description of the parameters included in this component is provided in our [Parameter Overview](#).

The CRC-SPIN adenoma transition model includes 11 parameters, 4 are associated with the adenoma growth and 7 are associated with the transition to invasive CRC.

Adenoma Growth:

- 4 parameters are associated with the Type 2 extreme value distribution used to model median time to 10mm: β_{1c} , β_{2c} , β_{1r} , and β_{2r} .

Transition to Preclinical (Invasive) CRC:

- 7 parameters are associated with the location-specific logistic regression models: $\gamma_0, \gamma_1, \dots, \gamma_7$, and σ_{γ_r} , the standard deviation of the underlying standard deviation.

RELEVANT COMPONENTS

The adenoma transition component includes two subcomponents, one describing adenoma growth and the other describing the transition of adenomas to cancer as a function of size.

DEPENDENT OUTPUTS

The growth model is used to simulate adenoma size at any point in time (size is used to determine the accuracy of some screening tests). The size at adenoma transition to preclinical invasive CRC is used to calculate the time/age at transition to preclinical cancer.

RELEVANT RESULTS

The key result from this component is the time from adenoma occurrence to transition to preclinical cancer. As noted above, adenoma size is also important because of its effect on screening accuracy.



TRANSITION TO CLINICAL CRC COMPONENT

RAND Corporation
Transition To Clinical CRC Component



- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References

TIME TO CLINICAL CANCER AND STAGE AT DETECTION

These components are described separately, below.

Time to Clinical Cancer

The time from preclinical detectable cancer to clinical disease is known as **sojourn time**. For modeling purposes, all preclinical cancer is detectable, and so sojourn time begins at the time of transition to preclinical cancer and ends at transition to clinically detectable cancer.

- CRC–SPIN 1.0 used a log–normal distribution for sojourn time.
- CRC–SPIN 2.x simulates sojourn time using a Weibull proportional hazards model. Both the shape and scale of the Weibull distribution are calibrated. The proportional hazard regression incorporates differences in sojourn time for adenomas in the colon and rectum, and will be used to simulate differences in sojourn time by risk factors (e.g., race).

$$F(t) = [1 - \exp(-(t/\mu_1)^{\mu_2})]^{\exp(\mu_3 \text{rectum}_i)}$$

Under this model, mean sojourn time is given by $[\mu_1 \Gamma(1 + 1/\mu_2)]^{\exp(\mu_3 \text{rectum}_i)}$.

Size and Stage at Detection

Size at clinical detection is needed to simulate cancer size during the preclinical detectable period. Cancer size affects the sensitivity of screening tests, especially endoscopic screen detection. Size at detection is also related to stage at detection which is used to simulate survival.

- CRC–SPIN 1.0 simulated size at clinical detection and then stage at detection conditional on size.
- CRC–SPIN 2.x simulates stage at clinical detection, and then size at detection conditional on stage. Simulating stage at clinical detection directly allows greater flexibility in specification of the stage distribution. Information about size and stage at clinical detection is based on SEER data from 1975–1979 (*i.e.*, prior to diffusion of colorectal cancer screening).

Survival

Our CRC–survival model is based on SEER data describing survival for cases diagnosed from 1975 to 2003. The CANSURV program (<http://srab.cancer.gov/cansurv/>) was used to estimate proportional hazard model that were stratified by location (colon or rectum) and AJCC stage with age and sex included as covariates. Models under development that incorporate race will specify that survival also depends on race using the same data (see: Rutter, Johnson, Feuer, et al., 2013).

Other–cause mortality was modeled using all–cause survival probabilities based on product–limit estimates for age and birth–year cohorts from the National Center for Health Statistics Databases (*US Life Tables, 2000*).



PARAMETER OVERVIEW

SUMMARY

This document describes calibrated CRC-SPIN parameters.

BACKGROUND

Parameters are tied to observed data through calibrated using incremental mixture approximate Bayesian computation (IMABC; Rutter, Ozik, DeYoreo, Collier, under review).

Calibration uses targets based on unscreened or minimally screened samples and populations. Model validation more readily incorporates information from screened samples and populations.

PARAMETER LISTING OVERVIEW

Natural History Model Parameters

Adenoma Risk: 7 Parameters (Adenoma Risk Component)

CRC-SPIN uses a non-homogeneous Poisson process to simulate adenoma occurrence

- Expected baseline log-risk: α_0
- Standard deviation of baseline log-risk: σ_α
- The effect of sex on risk: α_1
- The effect of age on risk: α_{2k} , $k = 1, \dots, 4$. CRC-SPIN simulates change in risk for 4 age groups: [20, 50), [50, 60), [60, 70), and ≥ 70 . Calibration results indicate that risk slows and may decline after age 70.

Adenoma Growth: 4 Parameters (Transition To Preclinical CRC Component)

CRC-SPIN simulates the time to reach 10mm using a Frèchet (Type 2 Extreme value) distribution for adenoma growth, assuming mutual independence for all parameters:

- β_{1c}, β_{1r} : shape parameters for adenomas in the colon and rectum, respectively
- β_{2c}, β_{2r} : scale parameters for adenomas in the colon and rectum, respectively

Adenoma Size at Transition to Preclinical CRC: 7 estimated Parameters (Transition To Preclinical CRC Component)

- Overall intercept, log-size at transition: γ_0
- Sex effect: γ_1
- Location effect (colon / rectum): γ_2
- Interaction between sex and location: γ_3
- (log) linear effect of age at initiation: γ_4
- (log) squared effect of age at initiation: γ_5
- standard deviation of log-size at transition: σ_γ



- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References



Time to Clinical Cancer Component: 3 Parameters (Transition To Clinical CRC Component)

- Weibull scale parameter: μ_1
- Weibull shape parameter: μ_2
- log-proportional hazards, sojourn time for rectal cancers: μ_3



OUTPUT OVERVIEW

SUMMARY

CRC-SPIN microsimulation model outputs.

OVERVIEW

The CRC-SPIN model results in a person- and adenoma-objects that contain the life event histories for the entire simulated population. For each agent, this includes the timing of adenoma occurrence, the timing of transition to preclinical cancer, the timing of transition to clinical cancer, stage and size at clinical detection, survival after detection, and other-cause death date. Summary results are based on post-simulation processing of these life histories. Adenoma and preclinical cancer size can be calculated at any point in time because the adenoma object includes adenoma and cancer growth rates, we can calculate

OUTPUT LISTING

Reports are often generated using annual summaries, which are generally aggregated by location (proximal colon, distal colon, rectum), age, sex and year. These summaries include:

- adenoma prevalence
- the average number of adenomas within individuals
- preclinical cancer prevalence
- clinical cancer prevalence
- colorectal cancer mortality
- overall mortality

CRC-SPIN has great flexibility, in terms of the outputs simulated from natural history trajectories. For example, because CRC-SPIN is a 'parallel universe' approach (modelling outcomes for agents both with and without screening), it is possible to calculate the simulated disease-free years attributable to screening.





RESULTS OVERVIEW

SUMMARY

Here, we provide a very brief overview of our calibration model and model applications.



Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

OVERVIEW

The Bayesian calibration approaches used for the CRC–SPIN model results in simulated draws from the posterior distribution of model parameters given calibration targets. The CRC–SPIN 1.0 model used a likelihood–based approach that used an approximate Markov Chain Monte Carlo approach. CRC–SPIN 2.x models are calibrated using Incremental Mixture Approximate Bayesian Calibration (IMABC), a likelihood–free approach. Bayesian calibration has several advantages over frequentist calibration methods, including the ability to simultaneously calibrate the model to multiple targets, incorporation of information via prior distributions, and the ability to simulate draws from the posterior distributions so that they can be used to inform parameter uncertainty and to propagate this uncertainty through the microsimulation model.

The CRC–SPIN 1.0 model has been used to estimate the comparative effectiveness of different screening regimens and has been validated through comparative modeling exercises within CISNET and through external validation to the UK Flexible Sigmoidoscopy study. The CRC–SPIN 2.x model updates this model and is used in publications after September 2018.

RESULTS LIST

Model results can be found in publications, listed below.

- Zauber AG, Knudsen AB, Rutter CM, Lansdorp–Vogelaar I, Savarino JE, van Ballegooijen M, Kuntz KM. Cost–Effectiveness of CT Colonography to Screen for Colorectal Cancer: Report to the Agency for Healthcare Research and Quality from the Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN, SimCRC, and CRC–SPIN Models. January 22, 2009. Available from: <https://www.cms.gov/medicare-coverage-database/details/technology-assessments-details.aspx?TAId=58>
- Rutter CM, Miglioretti DL, Savarino JE. Bayesian calibration of microsimulation models, *Journal of the American Statistical Association*, 2009; 104(488):1338–1350. PMID: PMC2805837.
- Rutter CM, Savarino JE. An evidence–based microsimulation model for colorectal cancer, *Cancer Epidemiology Biomarkers and Prevention*, 2010; 19(8):1992–2002. PMID: PMC2919657.



- Knudsen AB, Lansdorp–Vogelaar I, Rutter CM, Savarino JE, van Ballegooijen M, Kuntz KM, Zauber AG. Cost–Effectiveness of CT Colonography Screening for Colorectal Cancer among the Medicare Population, *Journal of the National Cancer Institute*, 2010; 102:1238–1252. PMID: PMC2923219.
- Berrington de González A, Kim KP, Knudsen AB, Lansdorp–Vogelaar I, Rutter CM, Smith–Bindman R, Yee J, Kuntz KM, van Ballegooijen M, Zauber AG, Berg CD. Radiation–related cancer risks from CT colonography screening: a risk–benefit analysis, accepted for publication, *American Journal of Roentgenology*, 2010; 196:816–823. PMID: PMC3470483.
- Kuntz KM, Lansdorp–Vogelaar I, Rutter CM, Knudsen AB, van Ballegooijen M, Savarino J, Feuer EJ, Zauber AG. A systematic analytical comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression, *Medical Decision Making*, 2011; 31:530–539. PMID: PMC3424513.
- van Ballegooijen M, Rutter CM, Knudsen AB, Zauber AG, Savarino J, Lansdorp–Vogelaar I, Feuer EJ, Kuntz KM. Clarifying differences between models for screening. The case of colorectal cancer, *Medical Decision Making*, 2011; 31:540–549. PMID: PMC3531980.
- Vanness DJ, Knudsen AB, Lansdorp–Vogelaar I, Rutter CM, Gareen IF, Herman BA, Kuntz KM, Zauber AG, van Ballegooijen M, Feuer EJ, Chen M, Johnson CD. Comparative Economic Evaluation of Data from the ACRIN National CT Colonography Trial with Three Cancer Intervention and Surveillance Modeling Network Microsimulations, *Radiology*, 2011; 261:487–498. PMID: PMC3198218.
- Rutter CM, Miglioretti DL, Savarino JE. Evaluating risk factor assumptions: a simulation–based approach. *BMC Medical Informatics and Decision Making*, 2011; 11:55. PMID: PMC3182875.
- Lansdorp–Vogelaar, Gulati R, Mariotto AB, Schechter CB, Heijnsdijk EA, Knudsen AB, van Ravesteijn NT, Wever EM, van Ballegooijen M, Rutter CM, Kuntz KM, Feuer EJ, Etzioni R, de Koning HJ, Zauber* AG, Mandelblatt* JS. Personalizing Age of Screening Cessation Based on Comorbidity – Results of Collaborative Modeling of Breast, Colorectal, and Prostate Cancer, *Annals of Internal Medicine*, 2014; 162(2):104–12. PMID: PMC4160041
- Zauber A, Knudsen A, Rutter CM, Lansdorp–Vogelaar I, Kuntz KM. Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collaborative Modeling Approach. Technical report for the Agency for Healthcare Research and Quality. AHRQ Publication No. 14–05203–EF–2, October 2015.

<http://www.uspreventiveservicestaskforce.org/Page/Document/modeling-report/colorectal-cancer-screening2>



- Rutter CM, Lansdorp–Vogelaar I, Knudsen AKB, Marsh T, Kuntz KM, van Ballegooijeen M, Zauber A. Validation of Models used to Inform Colorectal Cancer Screening Guidelines: Accuracy and Implications, Medical Decision Making, 2016; 36:604–614. PMID: PMC5009464.
- Knudsen AB, Zauber AG, Rutter CM, Naber SK, Doria–Rose VP, Pabiniak C, Johanson C, Fischer SE, Lansdorp–Vogelaar I, Kuntz KM. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US Preventive Services Task Force. JAMA. 2016 Jun 21; 315(23):2595–609. PMID: PMC5493310.
- Rutter CM, Kim JJ, Meester RGS, Sprague BL, Burger EA, Zauber AG, Ergun MA, Campos NG, Doubeni CA, Trentham–Dietz A, Sy S, Alagoz O, Stout NK, Lansdorp–Vogelaar I, Corley DA, Tosteson ANA. Effect of Time to Diagnostic Testing for Breast, Cervical, and Colorectal Cancer Screening Abnormalities on Screening Efficacy: A Modeling Study, Cancer Epidemiol Biomarkers Prev, 2018. PMID: PMC5809257 [Available on 2019–02–01]



KEY REFERENCES

BACKGROUND

- Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ.** Cancer statistics, 2004. *CA Cancer J Clin* 2004 Jan–2004 Feb 28;54(1):8–29.
- Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM.** Randomised controlled trial of faecal–occult–blood screening for colorectal cancer. *Lancet* 1996 Nov 30;348(9040):1472–7.
- Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O.** Randomised study of screening for colorectal cancer with faecal–occult–blood test. *Lancet* 1996 Nov 30;348(9040):1467–71.
- Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C.** A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult *BMJ* 1998;317:559–65.
- Winawer SJ.** A quarter century of colorectal cancer screening: progress and prospects. *J Clin Oncol* 2001 Sep 15;19(18 Suppl):6S–12S.
- Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS.** A case–control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992 Mar 5;326(10):653–7.
- Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM.** Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst* 1992 Oct 21;84(20):1572–5.
- Winawer SJ, Stewart ET, Zauber AG, Bond JH, Ansel H, Wayne JD, Hall D, Hamlin JA, Schapiro M, O'Brien MJ, et al.** A comparison of colonoscopy and double–contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. *N Engl J Med* 2000 Jun 15;342(24):1766–72.

ADENOMA RISK: NON–HOMOGENEOUS POISSON MODEL

- Cox DR, Miller HD.** (1965) *The theory of stochastic processes*, New York: Chapman and Hall.

ADENOMA RISK: AUTOPSY STUDIES CONTRIBUTING TO META–ANALYSIS

- Clark JC, Collan Y, Eide TJ, Esteve J, Ewen S, Gibbs NM, Jensen OM, Koskela E, MacLennan R, Simpson JG, Stalsberg H, Zaridze DG.** (1985) Prevalence of polyps in an autopsy series from areas with varying incidence of large–bowel cancer. *Int J Cancer*, 36, 179–186.
- Blatt LJ.** (1961) Polyps of the colon and rectum: Incidence and distribution. *Diseases of the Colon & Rectum*, 4, 277–282.
- Chapman I.** (1963) Adenomatous polypi of large intestine: Incidence and distribution. *Annals of Surgery*, 157, 223–226.
- Hughes LE.** (1968) The incidence of benign and malignant neoplasms of the colon and rectum: A post–mortem study. *Australian & New Zealand Journal of Surgery*, 38, 30–35.



- Stemmermann GN, Yatani R.** (1973) Diverticulosis and polyps of the large intestine. A necropsy study of Hawaii Japanese. *Cancer*, 31, 1260–1270.
- Eide TJ, Stalsberg H.** (1978) Polyps of the large intestine in Northern Norway. *Cancer*, 42, 2839–2848.
- Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM.** (1979) Adenomatous lesions of the large bowel. An autopsy survey. *Cancer*, 43, 1847–1857.
- Vatn MH, Stalsberg H.** (1982) The prevalence of polyps of the large intestine in Oslo: An autopsy study. *Cancer*, 49, 819–825.
- Williams AR, Balasooriya BAW, Day DW.** (1982) Polyps and cancer of the large bowel: A necropsy study in Liverpool. *Gut*, 23, 835–842.
- Bombi JA.** (1988) Polyps of the colon in Barcelona, Spain. *Cancer*, 61, 1472–1476.
- Johannsen LGK, Momsen O, Jacobsen NO.** (1989) Polyps of the large intestine in Aarhus, Demark. An autopsy study. *Scandinavian Journal of Gastroenterology*, 24, 799–806.
- Jass JR, Young PJ, Robinson EM.** (1992) Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. *Gut*, 33, 1508–1514.
- Szczepanski W, Urban A, Wierchowski W.** (1992) Colorectal polyps in autopsy material. Part I. Adenomatous polyps. *Pat Pol*, 43, 79–85.
- Paspatis GA, Papanikolaou N, Zois, E, Michalodimitrakis E.** (2001) Prevalence of polyps and diverticulosis of the large bowel in the Cretan population. An autopsy study. *Int J Colorectal Dis*, 16, 257–261.
- Rutter CM, Miglioretti DL, Yu O.** (2007) Adenoma risk meta analysis. *Statistics in Medicine*, 26: 98–109.

ADENOMA RISK: COLONOSCOPY STUDIES CONTRIBUTING TO VALIDATION

- DiSario JA, Foutch PG, Mai HD, Pardy K, Manne RK.** (1991) Prevalence and malignant potential of colorectal polyps in asymptomatic, average-risk men. *American Journal of Gastroenterology*, 86, 941–945.
- Rex DK, Lehman GA, Ulbright TM, Smith JJ, Pound DC, Hawes RH, Helper DJ, Wiersema MJ, Langefeld CD, Li W.** (1993) Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: Influence of age, gender, and family history. *American Journal of Gastroenterology*, 88, 825–831.
- Lieberman DA, Weiss DG, Bond JH, Anhen DJ, Garewal H, Chejfec G.** (2000) Use of colonoscopy to screen asymptomatic adults for colorectal cancer. *New England Journal of Medicine*, 343, 162–168.
- Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, Wong RK, Nugent PA, Mysliwiec PA, Schindler WR.** (2003) Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *New England Journal of Medicine*, 349, 2191–2200.
- Ponugoti PL, Rex DK.** (2017). Yield of a second screening colonoscopy 10 years after an initial negative examination in average-risk individuals. *Gastrointestinal endoscopy*, 85(1), 221–224.



ADENOMA GROWTH MODEL

Tjørve E, Tjørve KM. A unified approach to the Richards–model family for use in growth analyses: why we need only two model forms. *Journal of Theoretical Biology*. 2010 Dec 7;267(3):417–25.

TRANSITION FROM ADENOMA TO PRECLINICAL CANCER AS A FUNCTION OF SIZE

Nusko G, Mansmann U, Altendorf–Hofmann A, Groitl H, Wittekind C, Hahn EG. Risk of invasive carcinoma in colorectal adenomas assessed by size and site. *Int J Colorectal Dis* 1997;12(5):267–71.

Gillespie PE, Chambers TJ, Chan KW, Doronzo F, Morson BC, Williams CB. Colonic adenomas—a colonoscopy survey. *Gut* 1979 Mar;20(3):240–5.

Shinya H, Wolff WI. Morphology, anatomic distribution and cancer potential of colonic polyps. *Ann Surg* 1979 Dec;190(6):679–83.

CRC SURVIVAL

Rutter CM, Johnson E, Feuer R, Knudsen AB, Kuntz KM, Shrag D. Secular Trends in Colon and Rectal Cancer Survival, *JNCI*, 2013; 105(23): 1806–13.

BAYESIAN CALIBRATION

Gelman A, Stern HS, Carlin JB, Dunson DB, Vehtari A, Rubin DB. Bayesian data analysis. 2013, Chapman and Hall/CRC.

Gilks WR, Richardson S, Spiegelhalter DJ. Eds Markov Chain Monte Carlo in Practice. London, UK: Chapman & Hall; 1996; c1996.

Rutter CM, Miglioretti DL, Savarino JE (2009) Bayesian calibration of microsimulation models. *JASA*, 104: 1338–1350.

Rutter CM, Ozik J, DeYoreo M, Collier N. Microsimulation Model Calibration using Incremental Mixture Approximate Bayesian Computation. arXiv preprint arXiv:1804.02090. 2018. <http://arxiv.org/abs/1804.02090>.

CALIBRATION DATA

Surveillance, Epidemiology, and End Results (SEER) Program

(www.seer.cancer.gov), SEER*Stat Database: Incidence – SEER 9 Regs Public–Use, Nov 2003 Sub (1973–2001), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

Strul H, Kariv R, Leshno M, Halak A, Jakubowicz M, Santo M, Umansky M, Shirin H, Degani Y, Revivo M, Halpern Z, Arber N. The Prevalence Rate and Anatomic Location of Colorectal Adenoma and Cancer Detected by Colonoscopy in Average–Risk Individuals Aged 40–80 Years, *American Journal of Gastroenterology* 2006: 101: 255–262.

Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of Colonoscopy to Screen Asymptomatic Adults for Colorectal Cancer, *NEJM* 2000; 343:162–8.



Pickhardt PJ, Choi R, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, Wong RK, Nugent PA, Mysliwiec PA, Schindler WR. Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults, *NEJM* 2003; 349:2191–200.

Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of Advanced Proximal Neoplasms in Asymptomatic Adults According to the Distal Colorectal Findings, *NEJM* 2000: 343:169–74.

Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Results of Screening Colonoscopy Among persons 40 to 49 Years of Age, *NEJM* 2002; 346:1781–5.

Church JM. Clinical Significance of Small Colorectal Polyps, *Dis Colon Rectum* 2004; 47:481–485.

Odom SR, Duffy SD, Barone JE, Ghevariya V, McClane SJ. The Rate of Adenocarcinoma in Endoscopically Removed Colorectal Polyps, *The American Surgeon* 2005; 71:1024–1026



FLEXKB DOCUMENT
Version: HI.001.11302018.9752
Document generated: 11/30/2018

UNIVERSITY OF MINNESOTA

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at <http://cisnet.cancer.gov/profiles>. The CISNET model profile topics are not necessarily meant to be read in sequential fashion, so the reader should feel free to skip around as their interests dictate.



UNIVERSITY
OF MINNESOTA

Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: [Reader's Guide](#).



READERS GUIDE

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5–10 minutes. Each contains links to more detailed information if required.



UNIVERSITY
OF MINNESOTA

Readers Guide

Model Overview

Assumption Overview

Parameter Overview

Component Overview

Output Overview

Results Overview

Key References

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

Output Overview

Definitons and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Key References

A list of references used in the development of the model.



MODEL PURPOSE

SUMMARY

This page summarizes the overall goal of the Simulation Model of Colorectal Cancer (SimCRC) Model.



UNIVERSITY
OF MINNESOTA

Readers Guide

Model Overview

Assumption Overview

Parameter Overview

Component Overview

Output Overview

Results Overview

Key References

PURPOSE

The SimCRC Model can be run in one of two ways. It can simulate the US population from birth to death, and track the full US population from 1970 to a future year (e.g. 2020), or it can run a single birth cohort. The type of model run varies depending on the purpose of the model application.

The Model contains:

1. a natural history component that tracks the adenoma–carcinoma sequence as a function of age, sex, race, and risk factors (see [Risk Factors CRC](#));
2. a screening component that allows for the detection and removal of adenomas and possibly an early diagnosis of preclinical CRC; and
3. a treatment component for all persons diagnosed with CRC.

The Model specifically incorporates:

1. population–level trends in risk factors for CRC and the underlying relationship between each risk factor and colorectal disease;
2. population–level trends in CRC screening participation rates and each test’s ability to detect and remove adenomas and preclinical cancers; and
3. trends in the use of 5–fluorouracil (5FU) based chemotherapy and projected use of newer chemotherapy agents and their impact on cancer–specific mortality, as well improvements in cancer–specific survival over time not explained by chemotherapy trends.

The primary model outcomes when running a population–based simulation are the predicted number of cases of CRC and the number of deaths from CRC per 100,000 persons, standardized to the 2000 population, which can then be compared with actual incidence data from the Surveillance, Epidemiology, and End Results (SEER) program and mortality data from the US Vital Statistics. The primary model outcomes when running a birth cohort simulation are the number of life years gained with screening compared to without screening per 1000 persons screened. See [Model Overview](#) for a more detailed description of the Model.



MODEL OVERVIEW

SUMMARY

This document provides an overview of the structure of the SimCRC Model and its components.



UNIVERSITY
OF MINNESOTA

Readers Guide

Model Overview

Assumption Overview

Parameter Overview

Component Overview

Output Overview

Results Overview

Key References

PURPOSE

The SimCRC Model was initially developed to examine the relative contribution of changes in risk factors, screening and treatment on the overall population trends in CRC incidence and mortality. Subsequent uses of the model have targeted policy questions for cancer control. See [Model Purpose](#) for more details.

BACKGROUND

Colorectal cancer (CRC) is the second most common cause of cancer-related death in the United States. Although the incidence rate of CRC increased from 1973 through 1985, it has declined steadily since 1985. However, this decline in incidence has been greater for white Americans compared with African Americans. Possible reasons for the decreasing trends in incidence and mortality of CRC include lifestyle changes (e.g., less consumption of red meat),^{1,2,3,4,5,6,7,8} increased screening (resulting in the detection and removal of adenomas and a favorable stage-shift at cancer diagnosis),

^{9,10,11,12,13,14,15} or new treatment regimens (e.g., new adjuvant therapies).^{16,17,18,19,20}

In addition to examining the relative contributions of risk factors, screening, and treatment on cancer trends, simulation models provide a tool for incorporating multiple sources of data to examine outcomes associated with different screening and treatment policies. Screening rates in the US continue to be lower than that for other cancers and it is not possible to conduct randomized controlled trials of all of the possible screening strategies possible. Models can provide a useful tool for evaluating screening alternatives in the average-risk population. Further, comparing the results of the results from three independently-developed models lends robustness to the model results.

MODEL DESCRIPTION

The model is based on a prior model that was designed as a cohort model to evaluate the cost-effectiveness of screening.²¹ The SimCRC Model was originally designed specifically to examine population trends over time in that it simulates the US population from 1970 to 2020. The model can also be used to simulate a single birth cohort, which is typically used to evaluate alternative screening policies. Model components include:

1. population demographics,
2. risk factor trends,
3. screening dissemination,
4. treatment dissemination and other improvements in cancer-specific survival,
5. natural history of colorectal cancer,
6. screening mechanism, and
7. post-CRC diagnosis.

More details on population demographics, natural history of colorectal cancer, the screening mechanism, and post-CRC diagnosis is provided in [Assumption Overview](#).

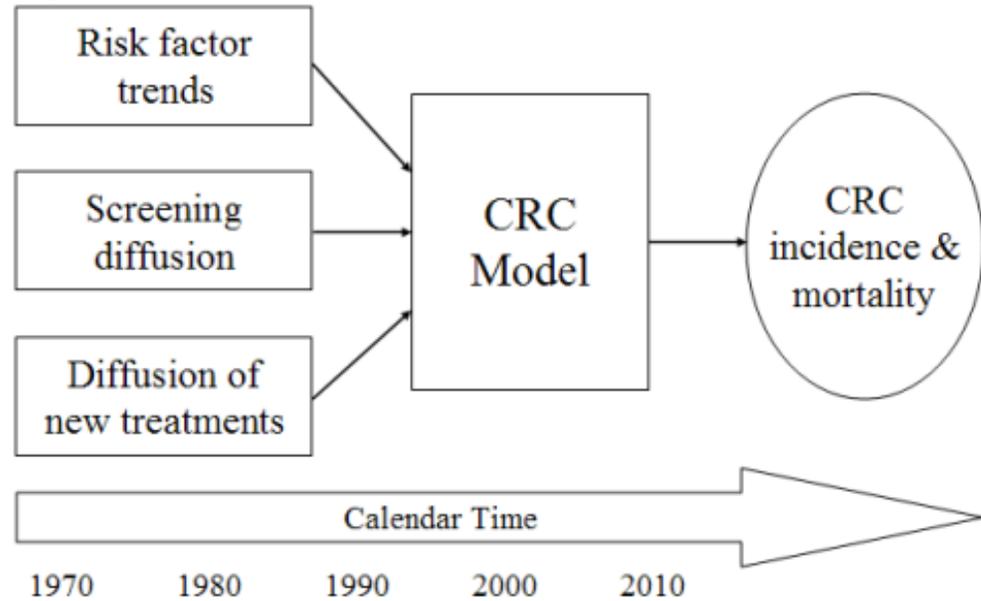


Variables used to model risk factor trends, screening dissemination, and treatment dissemination are provided in [Parameter Overview](#), with detailed descriptions provided in the [Component Overview](#). The key outcomes of the model are incident CRC cases and CRC deaths each each calendar year, standardized to the 2000 US population.

The SimCRC Model is population-based microsimulation model of the US population that can be used to forecast incidence and mortality associated with CRC. In addition it can simulate the outcomes for a single birth cohort. The model tracks the US population from birth to death. For each simulated person, SimCRC first generates a time of birth and a time of death from causes other than CRC. Next, SimCRC generates adenomas within the individual, with the age of onset for each adenoma drawn from a cumulative probability function that depends on sex, race, age, and an individual risk index that captures whether a person tends to produce more (or fewer) adenomas than average. SimCRC includes an optional risk factor module that allows individual-level risk factors to influence adenoma incidence (i.e., specific values for each of eight CRC risk factors, see [Risk Factors CRC](#)). SimCRC simulates three adenoma sizes (1–5mm, 6–9mm, 10+mm) and six locations (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum). All adenomas start small and can transition through larger size categories. The timing of transitions between adenoma size categories depends on age, sex, location (proximal colon, distal colon, rectum) and (optionally) eight modifiable risk factors. Medium and large adenomas may progress to preclinical CRC, although most will not in a person's lifetime. Progression depends on sex, race, and adenoma location. SimCRC can be (optionally) implemented to allow progression to preclinical CRC to depend on eight risk factors and birth year.

Overlaid on this natural history of colorectal disease (no disease to adenoma to preclinical cancer to clinical cancer) is a screening mechanism. If a screening test is performed in a particular year, then a person with an underlying adenoma has a chance of having it detected and removed, or a person with preclinical cancer may have it detected at an earlier stage than clinical detection. When modeling population trends, the chance that a screening test is performed depends on the age, sex, race and birth year of the simulated individual and these screening probabilities are derived to reflect the dissemination of screening (fecal occult blood test, sigmoidoscopy, or both) in the US between 1970 and 2000, with projection to 2020. When modeling screening strategies, the chance that a screening test is performed depends on the screening algorithm and assumptions about adherence. Simulated persons diagnosed with CRC

(by symptoms or by screening) are assigned a cancer-specific mortality rate, which depends on age, sex, stage at diagnosis, location of cancer (colon vs. rectum), year of diagnosis and (optionally) race.



Schematic Diagram of the Population Trends Analysis

CONTRIBUTORS

Karen Kuntz
Amy Knudsen
Claire Wang
Graham Colditz
Charles Fuchs
Jane Weeks
Milton Weinstein

REFERENCES:

- ¹ Giovannucci, E., Stampfer, MJ., Colditz, GA., Rimm, EB., Trichopoulos, D., Rosner, BA., Speizer, FE., Willett, WC. "Folate, methionine, and alcohol intake and risk of colorectal adenoma" in *J Natl Cancer Inst* 1993; 85: 875-884
- ² Giovannucci, E., Rimm, EB., Stampfer, MJ., Colditz, GA., Ascherio, A., Willett, WC. "Intake of fat, meat, and fiber in relation to risk of colon cancer in men" in *Cancer Research* 1994; 54: 2390-2397
- ³ Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC "Physical activity, obesity, and risk for colon cancer and adenoma in men" in *Ann Intern Med* 1995; 122: 327-334
- ⁴ Giovannucci, E., Egan, KM., Hunter, DJ., Stampfer, MJ., Colditz, GA., Willett, WC., Speizer, FE. "Aspirin and the risk of colorectal cancer in women" in *N Engl J Med* 1995; 333: 609-614
- ⁵ Giovannucci, E., Martinez, ME. "Tobacco, colorectal cancer, and adenomas: a review of the evidence" in *J Natl Cancer Inst* 1996; 88: 1717-1730
- ⁶ Giovannucci, E., Stampfer, MJ., Colditz, GA., Hunter, DJ., Fuchs, C., Rosner, BA, Speizer, FE., Willett, WC. "Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study" in *Intern Med* 1998; 129: 517-524
- ⁷ Grodstein, F., Martinez, ME., Platz, EA., Giovannucci, E., Colditz, GA., Kautzky, M., Fuchs, C., Stampfer, M. "Postmenopausal hormone use and risk for colorectal cancer and adenoma" in *Ann Intern Med* 1998; 128: 705-712



- 8 Martinez, ME., Giovannucci, E., Spiegelman, D., Hunter, DJ., Willett, WC., Colditz, GA. "Leisure-time physical activity, body size, and colon cancer in women" in *J Natl Cancer Inst* 1997; 89: 948
- 9 Mandel, J.S., Church, T.R., Bond, J.H., Ederer, F., Geisser, M.S., Mongin, S.J., Schuman, LM. "The effect of fecal occult-blood screening on the incidence of colorectal cancer." in *N Engl J Med* 2000; 343: 1603-1607
- 10 Hardcastle, J.D., Chamberlain, J.O., Robinson, M.H.E., Moss, S.M., Amar, S.S., Balfour, T.W., James, P.D., Mangham, C.M. "Randomised controlled trial of faecal-occult-blood screening for colorectal cancer." in *Lancet* 1996; 348: : 1472-1477
- 11 Jorgensen, O.D., Kronborg, O., Fenger, C. "A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds." in *Gut* 2002; 20: : 29-32
- 12 Atkin, WS., Cuzick, J., Northover, JM., Whynes, DK., "Prevention of colorectal cancer by once-only sigmoidoscopy" in *Lancet* 1993; 341: 736-740
- 13 Selby, J., Friedman, G., Quesenberry, C., Weiss, N. "A case-control study of screening sigmoidoscopy and mortality from colorectal cancer." in *N Engl J Med* 1992; 326: : 653-657
- 14 Brenner, H., Arndt, V., Sturmer, T., Stegmaier, C., Ziegler, H., Dhom G. "Long lasting reduction of risk of colorectal cancer following screening endoscopy." in *Br J Cancer* 2001; 85: : 972-976
- 15 Winawer SJ., Zauber AG., Ho MN., O'Brien, MJ., Gottlieb, LS., Sternberg, SS., Wayne, JD., Schapiro, M., Bond, JH., Panish, JF. "Prevention of colorectal cancer of colonoscopic polypectomy. The National Polyp Study Workgroup" in *N Engl J Med* 1993; 329: 1997-1981
- 16 Saltz, L.B., Cox, J.V., Blanke, C., et al. "Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group." in *N Engl J Med* 2000; 343: : 905-914
- 17 de Gramont, A., Figuer, A., Seymour, M., et al. "Leucovorin and fluorouracil with or without oxaliplatin as first-Line treatment in advanced colorectal cancer." in *J Clin Oncol* 2000; 18: 2937-2947
- 18 Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., Bets, D., Mueser, M., Harstrick, A., Verslype, C., Chau, I., Van Cutsem, E. "Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer." in *N Engl J Med* 2004; 351: : 337-345
- 19 Hurwitz, H., Fehrenbacher, L., Novotny, W., et al. "Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer." in *N Engl J Med* 2004; 350: 2335-2342
- 20 Schrag, D. "The price tag on progress - chemotherapy for colorectal cancer" in *N Engl J Med* 2004; 351: : 317-319
- 21 Frazier, AL., Colditz, GA., Fuchs, CS., Kuntz, KM. "Cost-effectiveness of screening for colorectal cancer in the general population" in *JAMA* 2000; 284: 1954-1961



ASSUMPTION OVERVIEW

SUMMARY

This section outlines the key assumptions of the SimCRC Model.

BACKGROUND

The structure of SimCRC relies on a number of assumptions. While the natural history component of the model is based on the adenoma–carcinoma sequence,^{1 2 3} we need to make several assumptions about how that is operationalized structurally. In addition, we assume that all CRC arises from an adenoma and we do not explicitly model hyperplastic polyps.

ASSUMPTION LISTING

Population Demographics

SimCRC is a compilation of multiple cohorts defined by age, sex, race, and calendar year; the size of each cohort is based on US Census data. Each birth cohort is analyzed one individual at a time as a first–order microsimulation starting at birth, where we assume no adenomas can develop until age 20. Non–cancer–specific mortality rates are based on the US life tables and are a function of age, sex, race, and calendar year. Population migration is not explicitly modeled.

Natural History of Colorectal Disease (prior to diagnosis)

The natural history model describes the progression of underlying disease in an unscreened population. It models the transitions from normal colonic epithelium to low–risk adenomas (defined as 1–5 mm in size), from low–risk to medium–risk adenomas (defined as 6–9mm in size), from medium–risk to high–risk adenomas (defined as ≥ 10 mm in size), from medium– or high–risk adenomas to preclinical cancer (stages I–IV), and from preclinical to symptom–detected CRC. This disease process is allowed to progress separately for three segments of the CRC tract (i.e., the proximal colon, the distal colon, and the rectum) and we allow for up to six lesions in the proximal colon and 3 lesions in the distal colon and the rectum for a maximum of 12 lesions per person. See [Parameter Overview](#) for key variables in the natural history model.

The model incorporates (optionally) the effects of eight modifiable risk factors associated with CRC (see [Risk Factors CRC](#)). Risk factors are allowed to have an effect on: 1) the development of an adenoma, and/or 2) the progression of an adenoma to preclinical cancer. In addition to these known risk factors we also assign a risk index based on a Truncated Normal distribution with a mean of 1 and variance v . The magnitude of this factor affects the risk of developing an adenoma.

Screening Mechanism

A simulated person who has an underlying adenoma or preclinical cancer has a chance of having it detected during a screening year as a function of his or her adherence rate and the sensitivity of the test.^{4,5,6} Test sensitivity varies as a function of adenoma size and presence of preclinical cancer. Test specificity is defined as the probability of having a positive test among persons without any adenomas or preclinical CRC.





CRC screening tests vary in terms of their test characteristics, reach, and risk. For example, FOBTs have the ability to detect a lesion in any segment of the colorectal system, but tends to have relatively poorer test characteristics compared with the other screening modalities. We assume that colonoscopy is recommended for all person with a positive FOBT. Sigmoidoscopy can only detect lesions located in the distal colon or rectum, although with better test characteristics within its reach. If any lesion is found the person is then referred to colonoscopy. The test sensitivity of colonoscopy is also lesion-based; however, colonoscopy has the ability to detect lesions throughout the colorectal system. Colonoscopy is also associated with a small mortality risk due to the risk of perforations during the procedure.

We assume that all adenomas that are detected during colonoscopy are removed via polypectomy. All persons who have had a high-risk adenoma (i.e. at least one large adenoma or three or more adenomas of any size) detected and removed are placed on colonoscopic surveillance every 3 years, and those with low-risk adenomas detected and removed are placed on colonoscopic surveillance every 5 years.

Diagnosed CRC

Once a person is diagnosed with CRC, either by symptom detection or by screening, they enter a "diagnosis" submodel. We track diagnosed patients on a monthly basis (as opposed to a yearly basis prior to diagnosis) and do not continue to keep track of risk factors or screening. CRC patients are assigned a cancer-specific mortality rate (in addition to their mortality rate from the life tables), which is a function of age and stage at diagnosis, location of cancer (colon vs. rectum), year of diagnosis, and use of adjuvant chemotherapy. There are two trends that are relevant for CRC patients: (1) cancer-specific mortality has decreased over time independent of known effective therapies and (2) the development of new effective therapies has increased.

REFERENCES:

- ¹ Morson, B. "The polyp-cancer sequence in the large bowel" in *Proc R Soc Med* 1974; 67: 451-457
- ² Fenoglio, CM., Lane, N. "The anatomical precursor of colorectal carcinoma" in *Cancer* 1974;34:819-823. 1974; 34: 819-823
- ³ Kronborg, O., Fenger, C. "Clinical evidence for the adenoma-carcinoma sequence." in *Eur J Cancer* 1999; 8: Suppl 1: S73-86
- ⁴ Allison, J., Ransom, L., Adrain, A. "A comparison of fecal occult-blood tests for colorectal-cancer screening" in *N Engl J Med* 1996; 334: 155-159
- ⁵ Rex, D.K., Cutler, C.S., Lemmel, G.T., Rahmani, E.Y., Clark, D.W., Helper, D.J., Lehman, G.A., Mark, D.G. "Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies." in *Gastroenterology* 1997; 112: : 24-28
- ⁶ Hixson, L., Fennerty, M., Sampliner, R., Garewal, H. "Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps" in *Gastrointest Endosc* 1991; 37: 127-127



PARAMETER OVERVIEW

SUMMARY

This section describes the key parameters in the SimCRC Model.

BACKGROUND

We have several model components that have their own sets of parameters.

1. Parameters that describe the US population dynamics over time.
2. A set of natural history parameters that describe the progression of colorectal disease in a simulated individual. These parameters were estimated through calibration (see [Calibration Method](#)).
3. Parameters that describe the risk factor status of a simulated individual (see [Risk Factors CRC](#)), the manner in which risk factors can change over time (see [Risk Factor Drifts](#)) and parameters that are specific for the risk factor effects on underlying disease progression (see [Risk Factor Effect Method](#)).
4. Parameters that describe the test characteristics of the screening tests that are modeled as well as parameters that describe screening dissemination in the US.
5. Parameters relevant for patients diagnosed with CRC, including the dissemination of adjuvant chemotherapy.

PARAMETER LISTING OVERVIEW

Population Parameters (see Population Demographics in [Component Overview](#))

1. number of persons in the US, by age, sex, race and calendar year
2. life table values for each birth cohort

Natural History Parameters (see [Natural History](#))

1. health state descriptors describing the adeno–carcinoma sequence
2. annual probability of transitioning from no disease to low–risk adenoma (function of age, location, risk index, risk factors (optional); see [Adenoma Incidence](#))
3. annual probability of transitioning from low–risk adenoma to medium–risk adenoma (function of location)
4. annual probability of transitioning from low–risk adenoma to medium–risk adenoma (function of location)
5. annual probability of transitioning from medium– or high–risk polyp to stage 1 preclinical cancer (function of age, location, risk factors (optional); see [Adenoma Progression](#))
6. annual probability of transitioning from stage i to stage $i+1$ preclinical cancer ($i=1,2,3$; function of stage and location)
7. annual probability of preclinical cancer becoming symptom detected (function of stage and location)

Risk Factor Parameters (see Risk Factor Trends in [Component Overview](#))

1. vector of values for each risk factor
2. multiway distributions of risk factor prevalence in 1970, by age range, sex and race



UNIVERSITY
OF MINNESOTA

Readers Guide

Model Overview

Assumption Overview

Parameter Overview

Component Overview

Output Overview

Results Overview

Key References



3. multiway distributions of risk factor prevalence for 25-year-old individuals in 1971 and beyond, by sex and race
4. distributions for each continuous RF category (used to assign risk factor values)
5. menopause status for a simulated woman and time since menopause (linked with hormone replacement therapy use)
6. multipliers for each of the continuous risk factors (body mass index, red meat consumption, fruit and vegetable consumption, physical activity) to reflect cohort-specific changes each year, by age, birth year, sex and race
7. annual probabilities of uptake among non-users or of quitting among users (for smoking, multivitamin use, and aspirin use) to reflect cohort-specific changes each year, by age, birth year, sex and race
8. annual probabilities of uptake among non-users or quitting among users for hormone replacement therapy use to reflect cohort-specific changes each year, by year of menopause, time since menopause and race

Screening Parameters (see [Screening Dissemination and Screening Effectiveness in Component Overview](#))

1. annual probability of getting screened in a year if previously unscreened, by age, birth year, sex and race (for trends analysis)
2. distribution of screening modalities among screened persons (FOBT, sigmoidoscopy, both, colonoscopy) (for trends analysis)
3. distribution of screening behavior among screened persons (low, moderate, high), which influences compliance with a screening strategy
4. probabilities that a person with a low-risk or medium-risk adenoma will be put on surveillance
5. sensitivities and specificities of all screening tests (by disease status)
6. mortality risk associated with colonoscopy

CRC Diagnosis Parameters (see [Treatment Dissemination and Diagnosis Model in Component Overview](#))

1. indicator variable to indicate whether cancer has been diagnosed
2. age, stage, location and year of diagnosis
3. time since diagnosis in months
4. probability that a newly diagnosed CRC patient or a newly metastatic patient receives chemotherapy (function of age, sex, race, stage, location, year) (for trends analysis)
5. monthly cancer-specific mortality rates (function of age at diagnosis, stage, location, treatment, year)
6. hazard ratio associated with treatment (function of age and stage)

Output Parameters (see [Output Overview](#))

1. risk factor categories for a given year, as an external check and Healthy People 2010 website graphs (see [Healthy People 2010](#))
2. incidence CRC cases and CRC deaths
3. adenomas and preclinical cancer
4. screening results and findings



COMPONENT OVERVIEW

SUMMARY

This document outlines the key components of the SimCRC Model.

OVERVIEW

Major inputs into the model include (1) population demographics, (2) changes in risk factors over time for a cohort, (3) changes in CRC screening over time, and (4) changes in CRC treatment over time. The natural history model (see [Natural History](#)) tracks the underlying progression of colorectal disease from normal colonic tissue to development of adenomatous polyps to invasive cancer. Cancer incidence is affected by the presence or absence of certain risk factors, and by screening. Cancer-specific mortality is affected by incidence and treatment post-diagnosis. Key model outputs are provided in [Output Overview](#).

COMPONENT LISTING

Population Demographics

The simulated population consists of all persons 25 years or older at some point between 1970 and the last calendar year of a given simulation (e.g., 2000). The simulated population can therefore be broken into two types of cohorts:

1. Prevalent cohorts: all US persons 25–90 years of age in 1970. These cohorts consist of people born in years 1880–1945 (total of 66 birth cohorts per sex and race category).
2. Incident cohorts: new 25-year-old individuals who join the target population every year after 1970 (e.g., 1971–2000). These cohorts are born in years 1946–1975 (total 30 birth cohorts per sex and race category).

Simulated persons face an annual rate of death from non-CRC causes each year based on their age, sex, race and birth year. These rates are based on the US life tables.

Risk Factor Trends

For all birth cohorts, including prevalent and incident ones, individuals are assigned initial risk factor values for each of eight risk factors (see [Risk Factors CRC](#)) by random draw from an age (in decades), sex, and race-specific multiway distribution of the eight risk factors (see [Risk Factor Distribution](#)). This is done in either 1970 for the prevalent cohorts or the year when the i^{th} incident cohort turns 25 years old (1970+i). A simulated person starts with his/her initial risk factor (RF) profile and then “drifts” with annual changes in each risk factor (see [Risk Factor Drifts](#)) that are a function of age, sex, race and birth year and reflect US population trends. The model allows for three basic scenarios to be modeled for 1970–2000:

1. cohort-specific changes; risk factors change with age and year (default)
2. age-specific changes; risk factors change with age but not year (used for Base Case analyses)
3. no changes in risk factors over time (since 1970)

Screening Dissemination

Based on data from the National Health Interview Survey (NHIS) we have incorporated the probability of being screened in any given year, based on age, sex, race and calendar year among persons who have never been screened. Persons who





will undergo screening are then assigned one of four recommended screening strategies: annual FOBT, sigmoidoscopy every five years, annual FOBT and sigmoidoscopy every five years, or colonoscopy every ten years, based on the current recommendations. To account for the fact that screened individuals do not tend to follow recommended screening schedules, we assign a screening behavior to screened persons (i.e., low, moderate, high) that is linked with adherence rates that dictate the probability that he or she will undergo a scheduled screening test. While there are no national data that provide the level of detail necessary for describing screening behavior, we input reasonable assumptions and then calibrate the Model outputs to NHIS data regarding questions asked about a persons history of being screened with FOBT within the past two years or ever screened with endoscopy (by age range, sex and race).

Treatment Dissemination

The probability that a simulated person with a new diagnosis of CRC receives chemotherapy is modeled as a function of stage at diagnosis, age, sex, race and calendar year. These treatment patterns are based on analyses of the SEER–Medicare linked dataset, and are extrapolated for patients aged less than 65 years at diagnosis. We estimated the probability of receiving adjuvant chemotherapy with 5FU for patients who are diagnosed with stage II rectal cancer or stage III colon or rectal cancer. In general, white patients are more likely to get treatment compared with black patients, younger patients are more likely to get treatment compared with older patients, stage III patients are more likely to get treatment compared with stage II patients, and the overall chance of getting treatment increases with time. Starting in the year 2000 we modeled the probability of receiving FOLFOX therapy instead of 5FU. We also estimated the probability of receiving chemotherapy for patients who are diagnosed with metastatic CRC. We modeled the dissemination of irinotecan starting in 1996, oxaliplatin starting in 2001, and the newer therapies (cetuximab and bevacizumab) starting in 2004. Projections of these dissemination probabilities are based on anticipated diffusion patterns into the population on the basis of the 5FU experience.

To account for changes that are not explained by dissemination of chemotherapy regimens we model cancer–specific mortality as a function of the period in which the cancer was diagnosed (1975–1982; 1983–1987; 1988–1990; 1991–1995; 1996–1999). The treatment effects due to the dissemination of chemotherapy are adjusted out of each of the period–specific relative survival curves.

Screening Effectiveness

The ability of a screening test to decrease CRC incidence and mortality is modeled through the removal of adenomas by colonoscopy and the early detection of preclinical cancer. The screening component is run simultaneously with the Natural History Model (see [Natural History](#)), which keeps track of the underlying disease status of each simulated individual. The true disease status of the patient, along with the test characteristics, will determine whether or not a test is positive or negative. Ultimately, the adenoma–carcinoma sequence can only be interrupted by removal of an adenoma by colonoscopy. For example, a person with a positive sigmoidoscopy finding who fails to be adherent with a follow–up colonoscopy will not benefit from that screening test.

Diagnosis Model

Patients who are diagnosed with CRC in the Model, either by symptom detection or by a positive colonoscopy result, enter the Diagnosis Model. Each month, they face a



monthly cancer-specific mortality rate that is a function of sex, the stage at diagnosis, age at diagnosis, year of diagnosis, time since diagnosis, and race (optional). These rates are based on Cox proportional hazards models for relative survival applied to SEER survival data. The SimCRC Model also has a separate post-diagnosis model that simulates the risk of subsequent metastatic recurrence and only allows cancer deaths to occur following an unresectable metastatic recurrence.



OUTPUT OVERVIEW

SUMMARY

This document describes the general outputs of the SimCRC Model.

OVERVIEW

The SimCRC Model provides estimates of the number of incidence cases of diagnosed CRC and cancer-specific deaths per calendar year, as a function of sex and race. These outputs will be reported as age-standardized values.

The model also generates specific Base Case outputs to compare with the model outputs from the other two CISNET models, as well as several outputs that allow for calibration or validation of model inputs (see [Results Overview](#)).

OUTPUT LISTING

Base Case I

Base Case I assumes that no screening is performed, that risk factors change only with age and not birth year, and that cancer-specific mortality does not change with time or treatment. Specific outputs generated are as follows, where age is in five-year age groups and calendar year is 1978–2000:

1. number of incidence cases by age groups, sex, race, stage, location and calendar year (1978–2000)
2. number of CRC deaths by age, sex, race, location and calendar year
3. population size by age, sex, race and calendar year
4. adenoma prevalence by age, sex, race, size, location and calendar year
5. number of preclinical cancers by age, sex, race, stage, location and calendar year
6. number of prevalent cases in 1978, by age, sex, race, stage and location

Base Case II

Base Case II overlays a simple screening assumption onto the assumptions of Base Case I. Specifically, we allow for a single screening event with 100% compliance beginning in Year 1980 for those age 65. We consider 3 tests – colonoscopy, flexible sigmoidoscopy, and fecal occult blood test with and without surveillance (colonoscopy every five years for those with an adenoma found). Specific outputs generated are as follows, where age is in five-year age groups (unless indicated otherwise) and calendar year is 1978–2000:

1. number of screen-detected cases by age, sex, race, stage, location and calendar year
2. number of symptom-detected cases by age, sex, race, stage, location and calendar year
3. number of CRC deaths by age, sex, race, location and calendar year
4. population size by age, sex, race and calendar year
5. number of screenees by result (positive vs. negative), sex, race and calendar year
6. number of persons receiving a surveillance or follow-up test by age (65, 70, 75, ... 95, 100+), sex, race and calendar year
7. number of adenomas detected by age, sex, race, size, location and calendar year





Risk Factor Calibration

For risk factor calibrations, the model outputs the following information for every simulated person for a specified Output Year (e.g., 1991).

1. age group, sex, race, risk factor value of each of eight risk factors, weighting factor (indicates the number of persons in the US population represented by the simulated person)

We compare the 1973, 1978, 1991, and 2001 risk factor distributions (by age, sex, race) outputted by the model with the observed distributions from the four waves of NHANES. We are also generating output of the implied risk factor trends using this output mechanism for Healthy People 2010, and are providing input data for the other modeling groups.

Screen Behavior Calibration

For screen behavior calibrations, the model outputs the following information for every simulated person for specified Output Years between 1987 and 2010 to match NHIS data on screening.

1. number of person who have ever been screened, by age group, sex, race and calendar year
2. number of person who have ever been screened by endoscopy, by age group, sex, race and calendar year
3. number of person who have ever been screened by fecal occult blood test, by age group, sex, race and calendar year
4. number of person who have been screened by fecal occult blood test within the past two years, by age group, sex, race and calendar year

CISNET Runs

For the CISNET analysis (1970–2000) or the Healthy People 2010 analysis (1970–2020) we output the following:

1. number of incident CRC cases by five–year age group, sex, race, stage, location and calendar year
2. number of CRC deaths by five–year age group, sex, race, location and calendar year
3. population size by age, sex, race and calendar year



RESULTS OVERVIEW

SUMMARY

This section summarizes the key analyses done during the development of the SimCRC Model, as well as initial results from the (relatively) completed model.

OVERVIEW

There are five general categories of model results

1. Model Development Results

- We have several analyses that pertain to developing a small piece of the SimCRC modeling puzzle. For example, the methods that we used to determine the effects of the risk factors on the underlying progression of colorectal disease, or the approach that we took for calibrating the natural history model.
- Base Case Results
- There are several Base Case analyses that have been done for purposes of comparing outputs across the three CRC CISNET models.
- Trends Results
- We have initial results that explain the observed CRC trends over the past three decades. These results utilize all aspects of the model to generate results.
- Policy–Relevant Analyses
- Analyses that addresses a particular policy–relevant question.
- Miscellaneous Analyses
- These include analyses that are not relevant to the above four categories.

RESULTS LIST

Model Development

1. Methods used to estimate cohort–specific risk factor drifts using the example of body mass index (see [Risk Factor Drift Method](#))
2. Methods used to estimate risk factor effects on the underlying natural history of colorectal disease (see [Risk Factor Effect Method](#))
3. Calibration methods for natural history model parameters (see [Calibration Method](#))

Trends Analysis

1. Examining CRC trends (see [Examining Trends](#))

Policy–Relevant Analyses

1. Analysis of the degree to which meeting upstream Healthy People 2010 goals for risk factors and screening achieve the downstream goal for CRC mortality (see [Healthy People 2010](#))
2. Projections of the impact in 2015 of optimistic disseminations about the use of computerized tomographic (CT) colonography (see [Policy Relevant Analyses](#))





Miscellaneous Analyses

1. Evaluating the impact of using different estimates of non-cancer-specific mortality on the relative proportion of cancer-specific mortality (see [Non Cancer Mortality](#))
2. Evaluating the impact of the US policy to fortify grains with folate (see [Folate Trends](#))



RISK FACTORS CRC

The model incorporates the effects of eight modifiable risk factors associated with CRC: body mass index (kg/m²), physical activity level (met-hours per week), fruit and vegetable consumption (servings per day), multivitamin use (yes/no), smoking status (number of cigarettes per day), red meat consumption (servings per day), aspirin use (yes/no), and postmenopausal hormone replacement therapy use (yes/no). Risk factors are categorized as shown below for purposes of estimating multiway distributions of risk factor prevalence (by ten-year age group, sex, race, and calendar year).

Risk Factor	Categories
Body mass index	
Physical activity	0; 0.01–1.9; 2.0–9.9; 10.0+
Fruit and vegetable consumption	0–1.9; 2.0–3.9; 4.0–5.9; 6.0–7.9; 8.0+
Multivitamin use	non-user; user
Current smoker	non-user; user
Red meat consumption	0–0.104; 0.105–0.43; >0.43
Aspirin use	non-user; user
Hormone replacement therapy	non-user; user

If a person is designated a smoker they are then assigned a number of cigarettes per day on the basis of age-specific population distributions and are assumed to maintain that level of intensity for as long they smoke.



CALIBRATION METHOD

The model is calibrated by simulating the life histories of cohorts of individuals under a given set of parameter values and comparing the model–predicted outcomes with observed data on: (1) the prevalence and number of adenomas by age and sex from a meta–analysis of autopsy studies; (2) the location and size/histology of lesions from two colonoscopy screening studies ^{1 2}; and (3) the stage– and location–specific incidence of CRC by age, sex, and race from SEER. We assumed that each set of observed data follows a multinomial distribution and calculated two likelihoods for each measure: (1) the likelihood of generating the observed data with a particular set of parameter values (i.e., the observed likelihood) and (2) the likelihood obtained if the model exactly predicted the observed data (i.e., the maximum likelihood). Goodness of fit (GOF) scores were calculated as -2 times the difference between the observed and maximum log likelihoods. An overall GOF score that evaluated the simultaneous fit to the three sets of observed data was calculated by summing the individual GOF scores; a parameter set with a lower overall GOF score provides a better simultaneous fit to the observed data. We used the Nelder and Mead Simplex algorithm to explore the parameter space; this is a direct–search approach to finding the minima of a function. The model with the best fit from the simultaneous optimization underpredicts adenoma prevalence at younger ages and overpredicts at older ages. However, all predictions are very close to falling within one standard error of the observed data. The best–fitting model also provides an excellent fit to the overall risk of developing CRC by age.

REFERENCES:

- ¹ Imperiale, T.F., Wagner, D.R., Lin, C.Y., Larkin, G.N., Rogge, J.D., Ransohoff, D.F. “Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings.” in *N Engl J Med* 2000; 343: : 169-174
- ² Lieberman, D.A., Weiss, D.G., Bond, J.H., Ahnen, D.J., Garewal, H., Chejfec, G. “Use of colonoscopy to screen asymptomatic adults for colorectal cancer.” in *N Engl J Med* 2000; 343: 162-168



RISK FACTOR DRIFTS

A simulated person starts with his/her initial risk factor (RF) profile and then “drifts” with annual changes in each risk factor. For continuous risk factors: $RF(\text{year } X+1) = RF(\text{year } X) * \text{drift}(\text{born } Y, \text{ age } A, \text{ sex, race})$; $X=Y+A$. Thus, a RF drift value greater than 1 indicates an increase, equal to 1 indicates no change, and less than 1 indicates a decrease. For dichotomous variables, the drift values are either annual probabilities of quitting usage (negative values) among users or annual probabilities of initiating usage (positive values) among non-users.

Estimates of these risk factor drifts were derived from analyses of multiple waves of the National Health and Nutrition Examination Survey (NHANES). We compiled three waves of NHANES (NHANES I, 1971–1975; NHANES II, 1976–1980; NHANES III, 1988–1994) and fit parametric polynomial regression models with age and calendar year as explanatory variables. To estimate risk factor drifts for a particular birth cohort over time, we used our models, increasing age and year simultaneously, to obtain expected RF changes as the cohort ages. (See [Risk Factor Drift Method](#) for details.)

Model checks have been done to compare predicted RF cumulative frequency plots for 1978 with those from NHANES II data, predicted RF cumulative frequency plots for 1991 with those from NHANES III data, and predicted RF cumulative frequency plots for 2001 with those from NHANES 1999–2002. Model predictions tend to be close to the observed data.



RISK FACTOR EFFECT METHOD

We used data from the Nurses' Health Study (NHS) ¹ and the Health Professionals' Follow-up Study (HPFS) ² to derive two stage-specific risk functions that describe the relationship between the CRC risk factors and: 1) the development of an adenoma, and 2) the progression of an adenoma to preclinical cancer. The NHS began in 1976, when 121,700 registered nurses 30 to 55 years of age returned a mailed questionnaire that included details on risk factors for breast and other cancers. Follow-up questionnaires mailed every two years identify incident cancers and collect detailed information on diet, physical activity, smoking history, and other exposures. The HPFS began in 1986 when approximately 51,500 male health professionals 40–75 year of age were recruited to study the dietary etiologies of heart disease and cancer. Risk factors for various cancers were collected at baseline. Incident cancers are identified by follow-up questionnaires, which have response rates of 90% for every two-year cycle. Using data from these two cohort studies, we fit logistic regression models that describe the relationship between CRC risk factors and the diagnosis of CRC, adjusted for screening. Although the data from the NHS and the HPFS provide evidence on the relationship between risk factors and the diagnosis of CRC in an unscreened population of women and men, respectively, the natural history component of the SimCRC Model requires the specification of the influence of risk factors on the underlying progression of disease. To derive the necessary stage-specific risk functions, we use a combination of simulation modeling with epidemiological analysis.

Evidence suggests that three of the risk factors – aspirin use, multivitamin use, and smoking – act primarily on initial adenoma development, since it is the exposure to these risk factors 10 to 15 years prior to CRC diagnosis that is significant. For the stage-specific risk functions we assumed a logistic function for the relationship between adenoma incidence (i.e., risk function 1) and adenoma progression (i.e., risk function 2) and defined all variables in terms of current status (e.g., current aspirin user, current smoker). However, in the logistic regression models that we estimated from the cohort studies, the three risk factors with early effects were defined differently, that is, using the duration of aspirin use, the duration of multivitamin use, and the number of years since smoking was started.

We utilized the basic structure of our natural history model to empirically estimate the effect of CRC risk factors on the unobserved states of colorectal disease. This was accomplished by first specifying starting values for the risk factor effects (via the two stage-specific risk functions), and then generating a hypothetical dataset of women or men with characteristics that mimic the NHS or the HPFS, respectively, in terms of age distribution and risk factor information (e.g., smoking behavior observed during the study). We then analyzed this simulated dataset using regression methods analogous to those used for the cohort study data to estimate the simulated relationship between the risk factors, as defined in the cohort studies (e.g., duration of aspirin use), and diagnosed CRC. The starting values for the risk factor effects were then revised and the simulation process repeated in an iterative fashion until the relationship between the duration of aspirin use and diagnosed colorectal cancer in the simulated dataset matched the analogous relationship observed in the cohort studies.

REFERENCES:

- ¹ Colditz, GA. "The Nurses' Health Study: a cohort of women followed since 1976" in JAMA 1995; 50: 40-44, 63



University of Minnesota
Risk Factor Effect Method
References:

² Rimm, E.B., Giovannucci, E., Willett, W.C., Colditz, G.A., Ascherio, A., Rosner, B., Stampfer, M.J. "Prospective study of alcohol consumption and risk of coronary disease in men." in *Lancet* 1991; 338: 464-468



NATURAL HISTORY

SUMMARY

This document focuses on the natural history component of SimCRC Model. It describes how we model the underlying progression of colorectal disease, as well as how we incorporate risk factors.

OVERVIEW

Our natural history model is a microsimulation model that tracks the development of adenomatous polyps and their progression to underlying cancer within the proximal colon, distal colon, and rectum for cohorts of 25-year-old individuals. We calibrate the model by simulating the life histories of cohorts of individuals under multiple sets of parameter values and comparing model-predicted outcomes with observed data on adenomas (prevalence, location, type) and CRC (incidence, location, stage) using a likelihood-based approach (see [Calibration Method](#)). This model also includes risk factors and their effects on disease progression (see [Risk Factor Effect Method](#)).

Our SimCRC Model tracks multiple cohorts of individuals in order to simulate the US population aged 25 and older starting in 1970 and projecting out to 2020. The parameters that effect the underlying progression of disease are from the calibrated cohort model.

DETAILS

States Tracked by the Model

For each of three locations (proximal colon, distal colon, and rectum) and subsites within each location (6 for proximal colon, 3 for distal colon, 3 for rectum), one of the following disease states is allowed:

1. disease free,
2. adenoma (low-risk, medium-risk, or high-risk),
3. preclinical cancer (by stage), and
4. clinical (diagnosed) cancer (by stage).

Temporal Aspects

Each year we allow a non-diseased colorectal segment to develop a low-risk adenoma, a low-risk adenoma to progress to a medium-risk adenoma, a medium-risk adenoma to progress to a high-risk adenoma, a high-risk adenoma to progress to preclinical stage I cancer, preclinical stage I cancer to preclinical stage II cancer, preclinical stage II cancer to preclinical stage III cancer, and preclinical stage III cancer to preclinical stage IV cancer. Individuals with preclinical cancer can be symptom detected and transition to a clinical (diagnosed) cancer state (of the same stage). In any year and from any state, individuals can die of non-CRC causes (based on age, sex, race, and year). Individuals with cancer can also die from CRC-related causes.

Key Attributes

Variables that affect the transitions among health states are age, sex, race, risk factors (see [Risk Factors CRC](#)), a "propensity" factor, and location (proximal colon, distal colon, rectum).



UNIVERSITY
OF MINNESOTA

[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)



RELEVANT ASSUMPTIONS

There are a number of assumptions that we make.

1. All colorectal cancers arise from adenomas.
2. We do not allow for adenoma regression.
3. Disease progression is independent of calendar year once we adjust for the risk factor effects.
4. We allow for one additional person-specific parameter that affects the chance of developing an adenoma (a propensity factor) in addition to the effects of the risk factors.

RELEVANT PARAMETERS

See [Parameter Overview](#).

RELEVANT COMPONENTS

The Natural History Model forms the basis of the SimCRC Model. The Risk Factor Trends component of the overall model provides information to the Natural History Model about the current risk factor values of each simulated person, thus allowing risk factors and trends in risk factors to have an impact on the underlying progression of disease.

Overlaid on the Natural History Model is a Screening Component, one that represents screening dissemination in the US and thus dictates the chance that a simulated individual will undergo a screening test (as a function of age, sex, race and birth year). The other screening component determines the effectiveness of a screening test by its ability to identify and remove an adenoma (based on the sensitivity of the test or sequence of tests) or to diagnose preclinical cancer.

The Natural History Model endpoint is diagnosed CRC (or death from other causes). Once a person is diagnosed with CRC they enter a Diagnosis Model.

See [Component Overview](#) for more details.

DEPENDENT OUTPUTS

The primary outputs from the Natural History Model are Base Case I outputs on adenoma prevalence and cancer incidence (see [Output Overview](#)).

RELEVANT RESULTS

See [Calibration Method](#) and [Output Overview](#) (Base Case I).



ADENOMA INCIDENCE

The annual probability of transitioning from no disease (ND) to low-risk adenoma (LRA) within a subsite of the colorectal track is a function of age, sex, propensity factor and risk factors:

$$Pr(\text{ND} \rightarrow \text{LRA}) = \frac{1}{1 + \exp(-\alpha - \gamma - \beta_{age} * age - \beta'_{r,f} * X)}$$



UNIVERSITY
OF MINNESOTA

[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)

α is an intercept term and varies by location (proximal cancer, distal cancer, rectum) and sex. γ is a propensity factor that is randomly drawn for each simulated individual from the same distribution with variance σ . β_{age} dictates the age effect on adenoma incidence and varies by location and sex. α , σ , and β_{age} are estimated via the natural history calibration (see [Calibration Method](#)).

$\beta_{r,f}$ is a vector of parameters that describe the effect of a particular risk factor on adenoma incidence and varies by location and sex. These parameters are estimated in a separate calibration exercise in conjunction with analyses of the Nurses' Health Study and Health Professionals' Follow-up Study (see [Risk Factor Effect Method](#)). X is the vector of risk factor values for a simulated person for a particular year (see [Parameter Overview](#) for risk factor parameters).



ADENOMA PROGRESSION

The annual probability of transitioning from high-risk adenoma (HRA) to stage I preclinical colorectal cancer (PCC) within a subsite of the colorectal track is a function of age, sex, and risk factors:

$$Pr(\text{HRA} \rightarrow \text{PCC}) = \frac{1}{1 + \exp(-\alpha - \beta_{age} * age - \beta'_{rf} * X)}$$



UNIVERSITY
OF MINNESOTA

[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)

α is an intercept term and varies by location (proximal cancer, distal cancer, rectum) and sex. β_{age} dictates the age effect on adenoma progression and varies by location and sex. α and β_{age} are estimated via the natural history calibration (see [Calibration Method](#)).

β_{rf} is a vector of parameters that describe the effect of a particular risk factor on adenoma progression and varies by location and sex. These parameters are estimated in a separate calibration exercise in conjunction with analyses of the Nurses' Health Study and Health Professionals' Follow-up Study (see [Risk Factor Effect Method](#)). X is the vector of risk factor values for a simulated person for a particular year (see [Parameter Overview](#) for risk factor parameters).



University of Minnesota
Healthy People 2010



UNIVERSITY
OF MINNESOTA

[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)

HEALTHY PEOPLE 2010

National health goals currently exist for a number of the health behaviors associated with CRC, and for CRC screening. Healthy People 2010 is a set of health objectives set forth by the US Department of Health and Human Services for the nation to achieve over the first decade of the new century. The objectives aim to increase the quality and length of life, and eliminate health disparities. The Healthy People 2010 goals include targets for obesity, physical activity, smoking, folate intake for women of child-bearing age, fruit and vegetable consumption, CRC screening, and CRC mortality.

Using the SimCRC Model, we conducted a formal analyses to determine the extent to which the Healthy People 2010 cancer mortality goals are achievable. The results of these analyses were presented at the NCI in June, 2004. Two modeling groups focused on the CRC-related goals. Specifically, we used our models to link the Healthy People 2010 risk factor and screening goals with the CRC mortality goal of reducing the CRC mortality rate to 13.9 deaths per 100,000. To do this, we generated model-predicted CRC mortality rates in 2010 assuming that risk factor levels and screening rates do not change from their 2000 values. Then we predicted CRC mortality assuming the Healthy People 2010 risk factor and/or screening targets are met by the year 2010. We found that if risk factors and screening rates do not change from the 2000 values, CRC mortality in 2010 would be 19.4 deaths per 100,000. If the Healthy People 2010 risk factor and screening targets are met by 2010, CRC mortality would fall to 17.7 CRC deaths per 100,000. We found that if the current trends in risk factors and screening continue through 2010, we would achieve 65% of the reduction in CRC mortality needed to reach the Healthy People 2010 goal.



RISK FACTOR DISTRIBUTION

For prevalent cohorts (i.e., persons 25 years of age or older in 1970) we randomly draw from age (in decades), sex, and race-specific multiway distributions of the eight risk factors (categorized). The matrices that represent the multiway distributions contains 4800 cells representing the probability of a US person in each 24 demographic group in 1970 fits into a particular risk factor profile. The number of cells (i.e., 4800) is determined by the number of categories for each risk factor: 5 (body mass index) \times 4 (physical activity) \times 5 (fruit and vegetable consumption) \times 2 (multivitamin use) \times 2 (smoking status) \times 3 (red meat consumption) \times 2 (aspirin use) \times 2 (hormone replacement use). Once a particular risk factor category is determined for a simulated individual, an actual value within that category is randomly assigned for continuously-defined risk factors based on the distribution with the category (e.g., a person in the body mass index category defined as 18.5–24.9 may be assigned a value of 22.3).

The multiway distributions were first derived from NHANES III (1988–1994). We then assume that the relative interactions among risk factors from NHANES III are the same in 1970 and implement an iterative proportional fitting algorithm using the marginal distributions estimated for 1970 (e.g., the marginal distribution for body mass index is the proportions of the 1970 population that fall into each of the five body mass index categories) and the multiway distributions from 1988–1994 to obtain multiway distributions for 1970 (one for each of 24 demographic groups).

For incident cohorts we randomly draw from a sex and race-specific multiway distribution that is generated for persons aged 26–34 years during the model simulation from all of the prevalent cohorts and prior incident cohorts. The risk factors that are drawn from these distributions are adjusted backwards using the risk factor drifts to distinguish a 25-year-old individual from a 26–34 year-old group.



RISK FACTOR DRIFT METHOD

Each year, the risk factor values for each simulated person are updated based on age-, sex-, race- and birth year-specific changes over time, or drifts. Estimates of these risk factor drifts were derived from analyses of multiple waves of the National Health and Nutrition Examination Survey (NHANES). We illustrate our basic approach to estimating risk factor drifts with an example using body mass index (BMI). We adopted a similar approach for estimating risk factor drifts for the other risk factors, although each individual risk factor analysis varied somewhat depending upon the availability of the risk factor information in NHANES I.

We compiled three waves of NHANES (NHANES I, 1971–1975; NHANES II, 1976–1980; NHANES III, 1988–1994) to model secular trends in risk factors at the population level. We fit parametric polynomial regression models with age and calendar year as explanatory variables to predict population mean BMI by age and year. These models adjust for the characteristics of the sampling structures of the different waves (i.e., strata, clusters, and unequal probability of sampling). We accounted for the differences in BMI patterns by race and sex by fitting separate models for four demographic subgroups: white men, white women, black men, and black women. The fitted regression models allow for interpolation as well as extrapolation to make projections for any given age and calendar year, allowing for different age effects in different years. We used these models to predict mean BMI values for individuals aged 20 to 90 years in calendar years 1970–2000. To evaluate how well our model projects beyond the three NHANES survey periods, we compared our fitted mean BMI values in year 2000 for each subgroup with the mean BMI values from the recently released NHANES 1999–2000 data. The model predictions for the year 2000 were very close to the actual national estimates from NHANES 1999–2000. In 23 out of 28 age–race–sex groups, the predicted BMI values fell within the 95% confidence limits of the observed BMI means.

To estimate risk factor drifts for a particular birth cohort over time, we used our model, increasing age and year simultaneously, to obtain expected BMI means as the cohort ages. We then derived annual percent changes in mean BMI for each birth cohort. To verify the face validity of these values, we compared them to observed longitudinal BMI changes in two large-scale follow-up studies: Nurses' Health Study (NHS) and Health Professionals' Follow-up Study (HPFS). We compared three birth cohorts of white women from the starting NHS cohort (in 1976) and three birth cohorts of white men from the starting HPFS cohort (in 1986), using our model-based longitudinal projections. Although we do not expect the mean BMI of these two selected groups to be representative of average US persons, we anticipate that the longitudinal weight changes will share similar patterns. As expected, the mean BMI among the NHS cohorts was 2.26–6.21 kg (4.99–13.69 lb) lower than the predicted US population for average white women 1.65 meters (5' 4") in height. When we applied the predicted cohort-specific annual changes derived from our models to each cohort using their 1976 baseline BMI means, the projected BMI in 2000 was within 5% of their observed BMI in 1998. Similarly, the mean BMI for the three HPFS cohorts was 3.71 to 8.19 kg (6.69–14.75 lb) lower than the predicted population means for white men 1.75 meters (5' 9") in height for comparable birth years. Applying cohort-specific annual changes to their starting mean BMI, the model-predicted BMI in 2000 was within 4% of the observed values. The above comparisons provide external validity for applying our longitudinal projections to subpopulations.



EXAMINING TRENDS

We have completed an initial analysis of the CRC trends. During the period 1978 to 2000, approximately 2.52 million Americans were diagnosed with CRC and 1.25 million died from the disease. Our model estimates that the observed number of incident cases represents a 4.7% reduction from the estimated number that would have occurred if there had been no secular trends in risk factors and no dissemination of screening over this time period (8.6% reduction in 2000). Changes in risk factors alone account for 31.5% of the overall reduction, and 67.3% is attributable to screening. The number of cancer deaths represents a 13.1% reduction from the estimated number that would have occurred in the absence of changes in risk factors, screening, and treatment (22.0% reduction in 2000). Advancements in treatment alone account for 59.9% of the reduction, while risk factors and screening account for 7.8% and 30.7% of the decline, respectively. From these analyses, we conclude that screening and advancements in treatment have played significant roles in the declines in CRC incidence and mortality. Our results suggest that cancer control policies should focus their efforts on ensuring that patients with CRC receive the best-available care, and on increasing screening dissemination rates. Even with only 34% of the population ages 50 years and older undergoing endoscopy in the past decade, the dissemination of screening has played a significant role in decreasing both CRC incidence and mortality. Widespread adoption of screening could make significant inroads at reducing the burden of CRC.



POLICY RELEVANT ANALYSES

Cost-effectiveness analysis of Stool DNA for the Centers for Medicare and Medicaid Services

In 2007 the Centers for Medicare and Medicaid Services (CMS) requested a cost-effectiveness analysis to assist in a National Coverage Determination for stool DNA screening for CRC. MISCAN and SimCRC modelers performed a cost-effectiveness analysis of stool DNA testing (both version 1.0 and PreGen-Plus™) among the average-risk Medicare population to determine whether stool DNA testing could be cost-effective compared with CRC screening tests currently reimbursed by CMS ¹. Both models predicted that stool DNA testing every three or five years was both less effective and more costly than the currently recommended CRC screening strategies. Screening with the stool DNA test could be cost-effective at per-test cost \$40 to \$60 for 3-yearly stool DNA testing, depending on the simulation model used. The findings were consistent across the models and were relatively insensitive to changes in stool DNA test characteristics.

Decision Analysis for age to begin, age to end, intervals of screening, and screening test for the USPSTF

In another policy-relevant analysis, the US Preventive Services Task Force (USPSTF) requested a decision analysis to inform decisions about CRC screening, specifically to determine the age to begin screening, the age to end screening, and screening intervals ². This was the first time the USPSTF used a decision analysis in combination with a systematic evidence review to inform their decisions. The CISNET-CRC models provided standardized comparisons of 145 screening strategies using the best available evidence for consideration by USPSTF. Several of these screening strategies gave similar gains in life-years, provided that there is equally high adherence for all aspects of the screening process. Under these conditions, the best screening strategies were high-sensitivity FOBT (Hemoccult SENZA or IFOBT) performed annually, sigmoidoscopy performed every 5 years with Hemoccult SENZA performed every 2 to 3 years, or colonoscopy performed every 10 years. Annual FOBT with a lower-sensitivity test (Hemoccult II) and sigmoidoscopy alone resulted in fewer life-years gained relative to other strategies. These analyses showed that stopping screening at age 75 after consecutive negative screenings since age 50 provides almost the same benefit as stopping at age 85 but with substantially fewer colonoscopy resources and risk of complications.

Evaluation of CT-colonography for the Centers for Medicare and Medicaid Services

In May 2008 CMS requested a cost-effectiveness analysis to assist National Coverage Determination for CT colonography screening for CRC ³. The three CISNET-CRC modeling groups showed that with perfect adherence to each test type, the predicted life-years gained from screening for CRC with 5-yearly CT colonography were slightly less than predicted life-years gained from 10-yearly colonoscopy, and if reimbursed at approximately the same rate as colonoscopy screening (i.e. 488 USD per scan relative to 498 USD for colonoscopy without polypectomy), CT colonography was predicted to be the most costly of the screening strategies considered. Screening with CT colonography was predicted to be a cost-effective CRC screening option for the Medicare population if the cost per scan were 105–208 USD, or if the availability of CT colonography screening would entice a large fraction of the unscreened population to adopt screening. The predictions were consistent across the models and were relatively insensitive to changes in CT colonography sensitivity and specificity, screening interval, and lesion size threshold for referring an individual for a follow-up



colonoscopy for polypectomy. On May 12, 2009 CMS released its decision not to cover CT colonography screening for Medicare enrollees; this decision was partially informed by our analysis.

Evaluation of CT Colonography for the Institute for Clinical and Economic Review (ICER)

Dr. Knudsen used the SimCRC model to estimate the incremental cost–effectiveness of CT colonography screening for the Institute for Clinical and Economic Review (ICER)⁴. Their analysis showed that compared to no screening, CT colonography every five years from age 50–75 with referral to colonoscopy for individuals with lesions ≥ 6 mm provides good value for money, with an incremental cost per life year gained of \$1500. However, when compared directly with colonoscopy every ten years over this age range, CT colonography every five years was more expensive and only slightly more effective than colonoscopy, with a cost–effectiveness ratio greater than \$500,000 per life year gained. An incremental cost per life year saved of \$100,000 could be achieved for CT colonography if the exam cost were approximately 47% that of colonoscopy. The results of this analysis were used to inform the Washington State Health Care Authority’s decision on coverage of CT colonography for state Medicaid enrollees and state employees.

Evaluation of CT Colonography for ACRIN

The CISNET–CRC team has collaborated with the American College of Radiology Imaging Network (ACRIN) to evaluate the cost–effectiveness of CT colonography as performed in the NCTC trial⁵. The NCTC trial was a large multi–site study to assess the accuracy of CT colonography for CRC screening in the general population and in community–based practices. All three modeling groups collaborated with CISNET–CRC affiliate member Dr. Vanness to conduct the cost–effectiveness analysis. We simulated survival and lifetime costs for screening 50 year–olds in the US with CT colonography every five or ten years and compared them to those from guideline concordant screening using colonoscopy, sigmoidoscopy, Hemoccult SENSAs, and IFOBT and to those with no screening. Perfect and reduced screening adherence scenarios were considered. We found screening with CT colonography likely to be net–beneficial compared to no screening but more costly and less effective than other non–CT colonography screening approaches.

Evaluation of CT Colonography for potential radiation exposure

CISNET–CRC modelers also assisted in analyses addressing concerns about risks of radiation–induced cancers that might result from using CT colonography for routine CRC screening⁶. The CISNET–CRC modelers collaborated with Dr. Amy Berrington (NCI) to estimate the ratio of CRCs prevented to cancers induced (benefit–risk ratio) associated with CT colonography screening every five years from age 50–80. Radiation–related cancer risk was estimated using risk projection models based on the National Research Council’s BEIR VII committee’s report and screening protocols from the ACRIN NCTC trial. The three CISNET–CRC models were used to estimate the potential reduction in CRC cases and deaths from CT colonography screening. The estimated number of radiation–related cancers from 5–yearly CT colonography screening from age 50–80 was 150 cases per 100,000 individuals. The estimated number of CRCs prevented by 5–yearly CT colonography screening from age 50–80 ranged across the three microsimulation models from 3580 to 5190 per 100,000, giving a benefit–risk ratio that varied from 24:1 to 35:1. The benefit–risk ratios for cancer deaths were even higher than the ratios for cancer cases. These models suggest that the benefits from CT colonography screening every five years from age 50–80 clearly



outweigh the radiation risks.

Evaluation of Screening Programs, Including Follow-up

Several industrialized nations recommend the use of FOBT to screen for CRC but guidelines often do not specify whether individuals with a false-positive test result should continue with FOBT screening or switch to 10-yearly colonoscopy screening. The SimCRC group, led by a visiting scholar from the University of Heidelberg, Dr. Ulrike Haug, compared the effectiveness of different strategies for follow-up of patients with a false positive FOBT (Hemoccult II, Hemoccult SENSAs or IFOBT), including continued FOBT screening versus switching to screening colonoscopy⁷. A sensitivity analysis was conducted to examine the effect of assuming conditional dependence of sequential testing among people without adenomas or CRC. The preliminary analysis shows that switching to screening colonoscopy is the better strategy for managing patients with a false positive FOBT result, especially in view of the uncertainty regarding conditional independence of sequential testing among people with a previous false positive.

The SimCRC modeling team estimated the comparative effectiveness of different strategies for following individuals with a negative screening colonoscopy⁸. Guidelines recommend that individuals with a negative screening colonoscopy repeat colonoscopy screening in ten years. However, the impact of this versus other follow-up strategies on health and economic outcomes is uncertain. The SimCRC modelers compared four management strategies, starting at age 60, for individuals with a negative colonoscopy at age 50: no further screening; annual IFOBT; 5 yearly CT colonography; and 10-yearly colonoscopy. They found that continuing screening with colonoscopy every 10 years was the most effective strategy for reducing the burden of CRC. In settings with limited resources and/or limited colonoscopy capacity, resuming screening at age 60 with annual IFOBT is also a reasonable approach. If the unit cost of CT colonography were less than \$342, CT colonography every 5 years would also be advantageous from a cost-effectiveness standpoint.

The MISCAN and SimCRC modeling teams are evaluating the potential cost implications for Medicare, Medicaid, and private payers from increased CRC screening among pre-Medicare individuals (i.e., individuals aged 50–64 years). Increased screening among this group is likely to result in earlier detection of CRC as well as prevention of CRC from adenoma detection and removal. Both these factors may reduce treatment costs. This work is being performed for the CDC.

The MISCAN and SimCRC modeling groups collaborated with NCI to create a CRC Mortality Projections Website. This site provides a modeling tool that projects future trends in CRC mortality and evaluates how potential increases in prevention, screening, and access to state-of-the-science cancer treatment may affect future mortality trends. It is intended for policy, legislative, and cancer-control planning staff at the federal, state, and local levels, as well as advocacy and professional groups. It features descriptions of and links to the Healthy People 2010 objectives relevant to CRC. Results show that almost half of all CRC mortality can be eliminated by 2020 by more fully utilizing cancer-control opportunities that we know are effective. Lower levels of utilization will substantially reduce those gains. While increased use of state-of-the-art treatment has the most immediate impact on mortality, over the longer term screening has the largest impact. Changing the risk factor profile of the US population to optimistic, but still realistic, levels will take many years to influence CRC mortality trends, but the benefits extend well beyond CRC. Additional information can be found online at cisnet.cancer.gov/projections/colorectal.



Quality of care guidelines

Several additional pieces of work by CISNET–CRC team members focused on clinical guidelines. Drs. Kuntz and Schrag worked with the Cancer Care Quality Measurement Project, an interagency initiative to develop quality-of-care measures for cancer care for evaluation by the National Quality Forum ⁹. To assist the National Quality Forum, the diagnostic component of SimCRC was used to assess the relative contribution of four processes of care for improving cancer outcomes. SimCRC predicts that increasing appropriate use of chemotherapy in the adjuvant and metastatic settings is likely to provide a substantial reduction in CRC mortality. Improving CRC care delivery by increasing the intensity of post-treatment surveillance or chemotherapy subsequent to metastectomy will likely have minimal impact on reducing cancer mortality at the population level.

Global screening programs

The SimCRC team is collaborating with Dr. Gabriel Leung to evaluate the cost-effectiveness of population-based screening for CRC in Hong Kong. A version of the SimCRC natural history model was modified to match data from Hong Kong on CRC incidence (lower than the US) and stage distribution (more advanced disease than the US). The modified model also incorporates Hong Kong life tables and reflects clinical practice in Hong Kong. The results show that annual screening with IFOBT is effective and provides good value for money. This research was presented at the International Health Economics Association.

REFERENCES:

- ¹ Lansdorp-Vogelaar, I., Kuntz, K.M., Knudsen, A.B., Wilschut, J., Zauber, A.G., van Ballegooijen, M. "Stool DNA testing to screen for colorectal cancer in the Medicare population: A cost-effectiveness analysis." in *Annals of internal medicine* 2010; 153.6: 368-377
- ² Zauber, A.G., Lansdorp-Vogelaar, I., Knudsen, A.B., Wilschut, J., van Ballegooijen, M., Kuntz, K.M. "Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force." in *Ann Intern Med* 2008; 149: 9: 659-69
- ³ Knudsen, A.B., Lansdorp-Vogelaar, I., Rutter, C.M., Savarino, J.E., van Ballegooijen, M., Kuntz, K.M., Zauber, A.G. "Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the Medicare population." in *J Nat Cancer Inst* 2010; 102: 16: 1238-52
- ⁴ Pearson, S.D., Knudsen, A.B., Scherer, R.W., Weissberg, J., Gazelle, G.S. "Assessing the comparative effectiveness of a diagnostic technology: CT colonography." in *Health Affairs* 2008; 27: 6: 1503-14
- ⁵ Vanness, D.J., Knudsen, A.B., Lansdorp-Vogelaar, I., Rutter, C.M., Gareen, I.F., Herman, B.A., Kuntz, K.M., Zauber, A.G., van Ballegooijen, M., Feuer, E.J., Chen, M.H., Johnson, C.D. "Comparative Economic Evaluation of the American College of Radiology Imaging Network National CT Colonography Trial with three CISNET Microsimulations." in *Radiology* 2011; 261: 2: 487-98
- ⁶ Berrington de Gonzalez, A., Kim, K.P., Knudsen, A.B., Lansdorp-Vogelaar, I., Rutter, C.M., Smith-Bindman, R., Yee, J., Kuntz, K.M., van Ballegooijen, M., Zauber, A.G., Berg, C.D. "Radiation-related cancer risks from CT colonography screening: A risk-benefit analysis." in *Am J Roentgenol* 2011; 196: 4: 816-23
- ⁷ Haug, U., Knudsen, A.B., Kuntz, K.M. "How should individuals with a false-positive fecal occult blood test for colorectal cancer be managed? A decision analysis." in *Int J Cancer* 2012; 131: : 2094-102
- ⁸ Knudsen, A.B., Hur, C., Gazelle, G.S., Schrag, D., McFarland, B., Kuntz, K.M. "Rescreening of individuals with a negative colonoscopy: A comparative effectiveness analysis." in *Ann Intern Med* 2012; 157: : 611-20



University of Minnesota
Policy Relevant Analyses
References:

⁹ Kuntz, K.M., Stout, N.K., Schrag, D. "Simulating Clinical Outcomes Associated with Quality Measures in the Treatment of Colorectal Cancer. A Report to the National Cancer Institute." 2006;



University of Minnesota
Non Cancer Mortality

NON CANCER MORTALITY

We constructed a simple Markov model to evaluate the impact of the relative proportion of mortality at 5-years attributed to cancer depending on whether we obtained estimates of non-cancer related mortality from: (1) the US general population using life table data from the National Center for Health Statistics, or (2) cause-specific estimates from SEER. For 60-69 year old patients with CRC, overall mortality was 43% at 5 years. Using a life table method to partition mortality, 36% of patients had deaths attributed to cancer and 7% died from other causes. In contrast, the cause-specific method assigned 32% of the cohort to cancer-related and 12% to cancer-unrelated deaths. We concluded that the strategy used to partition mortality may have an impact on the results of decision analyses.



UNIVERSITY
OF MINNESOTA

[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)



FOLATE TRENDS

The 1998 mandate to fortify enriched grain products with folic acid in the US was aimed to help prevent neural tube defects among pregnant women. To evaluate the increase in folate in the population after fortification, we analyzed food, supplement, and total folate intake by gender, age, and race/ethnicity using data from two waves of the NHANES, one before and one after the policy was adopted. We compared pre- and post-fortification distributions of total folate intake and proportions of the population consuming more than 400 and 1,000 mcg/day of total folate. Overall, daily food and total folate intake increased by approximately 100 mcg/day after fortification. The proportion of younger women consuming greater than 400 mcg/day of folate has increased since fortification, but has not yet reached the 50% target: 28% (pre-fortification) vs. 33% (post-fortification) in white women; 19% vs. 23% in African American women; and 15% vs. 28% of Mexican-American women. Among older populations who may be at risk of B-12 deficiency masking, the percent that are consuming over 1,000 mcg/day (the tolerable upper limit) increased after fortification for whites and African American men, but remained unchanged for African American women and decreased for Mexican-Americans.

We also developed a Markov model to simulate the effect of pre-versus-post fortification changes in folate consumption on incidence of neural tube defects (NTDs), myocardial infarctions (MIs), colon cancers, and B-12 masking. In each one-year cycle, persons face age-, gender-, race/ethnicity-, and folate-specific risks of developing any one of the four health outcomes (multiple events allowed), of staying disease-free, or of dying. We calculated population burden of disease for non-Hispanic whites, non-Hispanic blacks, and Mexican-Americans aged 15 and older among the civilian, non-institutionalized U.S. population. The model predicted that in one year after fortification, the following disease events would be averted: 181 NTDs; 30,541 MIs; and 5,933 colon cancers. On the other hand, fortification was predicted to cause 96 new cases of B-12 masking per year. There were substantial variations by race/ethnicity, with whites showing greater percent reductions in disease risk as compared to blacks and Mexican-Americans, due to the larger changes in folate intake after fortification seen in whites. Whites also experienced the greatest numbers facing increased risk from B-12 masking, again due to their larger increases in folate intake after fortification.



KEY REFERENCES

- Allison, J., Ransom, L., Adrain, A.** (1996) A comparison of fecal occult–blood tests for colorectal–cancer screening in *N Engl J Med*:334, p 155–159
- Atkin, WS., Cuzick, J., Northover, JM., Whynes, DK.** (1993) Prevention of colorectal cancer by once–only sigmoidoscopy in *Lancet*:341, p 736–740
- Berrington de Gonzalez, A., Kim, K.P., Knudsen, A.B., Lansdorp–Vogelaar, I., Rutter, C.M., Smith–Bindman, R., Yee, J., Kuntz, K.M., van Ballegooijen, M., Zauber, A.G., Berg, C.D.** (2011) Radiation–related cancer risks from CT colonography screening: A risk–benefit analysis. in *Am J Roentgenol* 196:4, p 816–23
- Brenner, H., Arndt, V., Sturmer, T., Stegmaier, C., Ziegler, H., Dhom G.** (2001) Long lasting reduction of risk of colorectal cancer following screening endoscopy. in *Br J Cancer* 85, p 972–976
- Colditz, GA.** (1995) The Nurses’ Health Study: a cohort of women followed since 1976 in *JAMWA*:50, p 40–44, 63
- Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., Bets, D., Mueser, M., Harstrick, A., Verslype, C., Chau, I., Van Cutsem, E.** (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan–refractory metastatic colorectal cancer. in *N Engl J Med* 351, p 337–345
- Fenoglio, CM., Lane, N.** (1974) The anatomical precursor of colorectal carcinoma in *Cancer* 1974;34:819–823.:34, p 819–823
- Frazier, AL., Colditz, GA., Fuchs, CS., Kuntz, KM.** (2000) Cost–effectiveness of screening for colorectal cancer in the general population in *JAMA*:284, p 1954–1961
- Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC** (1995) Physical activity, obesity, and risk for colon cancer and adenoma in men in *Ann Intern Med*:122, p 327–334
- Giovannucci, E., Egan, KM., Hunter, DJ., Stampfer, MJ., Colditz, GA., Willett, WC., Speizer, FE.** (1995) Aspirin and the risk of colorectal cancer in women in *N Engl J Med*:333, p 609–614
- Giovannucci, E., Martinez, ME.** (1996) Tobacco, colorectal cancer, and adenomas: a review of the evidence in *J Natl Cancer Inst*:88, p 1717–1730
- Giovannucci, E., Rimm, EB., Stampfer, MJ., Colditz, GA., Ascherio, A., Willett, WC.** (1994) Intake of fat, meat, and fiber in relation to risk of colon cancer in men in *Cancer Research*:54, p 2390–2397
- Giovannucci, E., Stampfer, MJ., Colditz, GA., Hunter, DJ., Fuchs, C., Rosner, BA, Speizer, FE., Willett, WC.** (1998) Multivitamin use, folate, and colon cancer in women in the Nurses’ Health Study in *Intern Med*:129, p 517–524
- Giovannucci, E., Stampfer, MJ., Colditz, GA., Rimm, EB., Trichopoulos, D., Rosner, BA., Speizer, FE., Willett, WC.** (1993) Folate, methionine, and alcohol intake and risk of colorectal adenoma in *J Natl Cancer Inst*:85, p 875–884
- Grodstein, F., Martinez, ME., Platz, EA., Giovannucci, E., Colditz, GA., Kautzky, M., Fuchs, C., Stampfer, M.** (1998) Postmenopausal hormone use and risk for colorectal cancer and adenoma in *Ann Intern Med*:128, p 705–712
- Hardcastle, J.D., Chamberlain, J.O., Robinson, M.H.E., Moss, S.M., Amar, S.S., Balfour, T.W., James, P.D., Mangham, C.M.** (1996) Randomised controlled trial of faecal–occult–blood screening for colorectal cancer. in *Lancet* 348, p 1472–1477

- Haug, U., Knudsen, A.B., Kuntz, K.M.** (2012) How should individuals with a false-positive fecal occult blood test for colorectal cancer be managed? A decision analysis. in *Int J Cancer* 131, p 2094–102
- Hixson, L., Fennerty, M., Sampliner, R., Garewal, H.** (1991) Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps in *Gastrointest Endosc*:37, p 127–127
- Hurwitz, H., Fehrenbacher, L., Novotny, W., et al.** (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. in *N Engl J Med* 350:2335–2342,
- Imperiale, T.F., Wagner, D.R., Lin, C.Y., Larkin, G.N., Rogge, J.D., Ransohoff, D.F.** (2000) Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. in *N Engl J Med* 343, p 169–174
- Jorgensen, O.D., Kronborg, O., Fenger, C.** (2002) A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. in *Gut* 20, p 29–32
- Knudsen, A.B., Hur, C., Gazelle, G.S., Schrag, D., McFarland, B., Kuntz, K.M.** (2012) Rescreening of individuals with a negative colonoscopy: A comparative effectiveness analysis. in *Ann Intern Med* 157, p 611–20
- Knudsen, A.B., Lansdorp–Vogelaar, I., Rutter, C.M., Savarino, J.E., van Ballegooijen, M., Kuntz, K.M., Zauber, A.G.** (2010) Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the Medicare population. in *J Nat Cancer Inst* 102:16, p 1238–52
- Kronborg, O., Fenger, C.** (1999) Clinical evidence for the adenoma–carcinoma sequence. in *Eur J Cancer* 8:Suppl 1, p S73–86
- Kuntz, K.M., Stout, N.K., Schrag, D.** (2006) Simulating Clinical Outcomes Associated with Quality Measures in the Treatment of Colorectal Cancer. A Report to the National Cancer Institute.,
- Lansdorp–Vogelaar, I., Kuntz, K.M., Knudsen, A.B., Wilschut, J., Zauber, A.G., van Ballegooijen, M.** (2010) Stool DNA testing to screen for colorectal cancer in the Medicare population: A cost-effectiveness analysis. in *Annals of internal medicine*:153.6, p 368–377
- Lieberman, D.A., Weiss, D.G., Bond, J.H., Ahnen, D.J., Garewal, H., Chejfec, G.** (2000) Use of colonoscopy to screen asymptomatic adults for colorectal cancer. in *N Engl J Med*:343, p 162–168
- Mandel, J.S., Church, T.R., Bond, J.H., Ederer, F., Geisser, M.S., Mongin, S.J., Schuman, LM.** (2000) The effect of fecal occult–blood screening on the incidence of colorectal cancer. in *N Engl J Med*:343, p 1603–1607
- Martinez, ME., Giovannucci, E., Spiegelman, D., Hunter, DJ., Willett, WC., Colditz, GA.** (1997) Leisure-time physical activity, body size, and colon cancer in women in *J Natl Cancer Inst*:89, p 948
- Morson, B.** (1974) The polyp–cancer sequence in the large bowel in *Proc R Soc Med*:67, p 451–457
- Pearson, S.D., Knudsen, A.B., Scherer, R.W., Weissberg, J., Gazelle, G.S.** (2008) Assessing the comparative effectiveness of a diagnostic technology: CT colonography. in *Health Affairs* 27:6, p 1503–14
- Rex, D.K., Cutler, C.S., Lemmel, G.T., Rahmani, E.Y., Clark, D.W., Helper, D.J., Lehman, G.A., Mark, D.G.** (1997) Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. in *Gastroenterology* 112, p 24–28
- Rimm, E.B., Giovannucci, E., Willett, W.C., Colditz, G.A., Ascherio, A., Rosner, B., Stampfer, M.J.** (1991) Prospective study of alcohol consumption and risk of coronary disease in men. in *Lancet* 338:464–468,



- Saltz, L.B., Cox, J.V., Blanke, C., et al.** (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. in *N Engl J Med* 343, p 905–914
- Schrag, D.** (2004) The price tag on progress – chemotherapy for colorectal cancer in *N Engl J Med* 351, p 317–319
- Selby, J., Friedman, G., Quesenberry, C., Weiss, N.** (1992) A case–control study of screening sigmoidoscopy and mortality from colorectal cancer. in *N Engl J Med* 326, p 653–657
- Smith, R.A., Cokkinides, V., Eyre, H.J.** (2003) American Cancer Society Guidelines for the early detection of cancer, 2003. in *CA Cancer J Clin* 53, p 27–43
- Vanness, D.J., Knudsen, A.B., Lansdorp–Vogelaar, I., Rutter, C.M., Gareen, I.F., Herman, B.A., Kuntz, K.M., Zauber, A.G., van Ballegooijen, M., Feuer, E.J., Chen, M.H., Johnson, C.D.** (2011) Comparative Economic Evaluation of the American College of Radiology Imaging Network National CT Colonography Trial with three CISNET Microsimulations. in *Radiology* 261:2, p 487–98
- Winawer SJ., Zauber AG., Ho MN., O’Brien, MJ., Gottlieb, LS., Sternberg, SS., Waye, JD., Schapiro, M., Bond, JH., Panish, JF.** (1993) Prevention of colorectal cancer of colonoscopic polypectomy. The National Polyp Study Workgroup in *N Engl J Med*:329, p 1997–1981
- Winawer, S.J., Fletcher, R., Rex, D., Bond, J., Burt, R., Ferrucci, J., Ganiats, T., Levin, T., Woolf, S., Johnson, D., Kirk, L., Litin, S., Simmam, C.** (2003) Colorectal cancer screening and surveillance: clinical guidelines and rationale – update based on new evidence. in *Gastroenterology* 124, p 544–560
- Zauber, A.G., Lansdorp–Vogelaar, I., Knudsen, A.B., Wilschut, J., van Ballegooijen, M., Kuntz, K.M.** (2008) Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. in *Ann Intern Med* 149:9, p 659–69
- de Gramont, A., Figier, A., Seymour, M., et al.** (2000) Leucovorin and fluorouracil with or without oxaliplatin as first–Line treatment in advanced colorectal cancer. in *J Clin Oncol* 18:2937–2947,
-



FLEXKB DOCUMENT
Version: HI.001.11302018.9754
Document generated: 11/30/2018

MEMORIAL SLOAN KETTERING / ERASMUS



[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at <http://cisnet.cancer.gov/profiles>. The CISNET model profile topics are not necessarily meant to be read in sequential fashion, so the reader should feel free to skip around as their interests dictate.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: [Reader's Guide](#).



READERS GUIDE

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5–10 minutes. Each contains links to more detailed information if required.



Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

Output Overview

Definitons and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Key References

A list of references used in the development of the model.



MODEL PURPOSE

SUMMARY

This document describes in broad terms, the purpose(s) for which the MISCAN–Colon model was developed.



PURPOSE

Trends in colorectal cancer incidence and mortality and the (potential) impact of interventions depend on many kinds of factors related to the biology of the adenoma–carcinoma sequence, the characteristics of the population, and the potential impact and usage of primary prevention, early detection and treatment. A simulation model is a helpful tool to estimate the effect of each of the listed factors on cancer incidence and mortality. MISCAN–Colon is developed to analyze trends in colorectal cancer due to changes in lifestyle, improvement of treatment and implementation of screening strategies.

The purpose of MISCAN–Colon can be described in three specific aims:

1. to simulate colorectal cancer incidence and mortality according to observed figures
2. to estimate the absolute and relative contribution of CRC cancer screening, risk factors and improved therapy on observed cancer incidence and mortality trends
3. to predict how changes in lifestyle, CRC screening and treatment practices will impact on future incidence and mortality

The development of colorectal cancer is based on the adenoma–carcinoma sequence of Morson ¹ and Vogelstein ² and is an important underlying assumption of the model.

REFERENCES:

- ¹ Morson, B “The polyp-cancer sequence in the large bowel” in Proc R Soc Med 1974; 67: : 451-7
- ² Vogelstein, B, Fearon, ER, Hamilton, SR, Kern, SE, Preisinger, AC, et al. “Genetic alterations during colorectal-tumor development. ” in N Engl J Med 1988; 319: 9: 525-32



MODEL OVERVIEW

SUMMARY

MISCAN–Colon is designed to analyze trends in colorectal cancer. MISCAN–Colon is a micro–simulation model, consisting of three parts:

- demography part
- natural history part
- screening part



Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

Based on assumptions on trends in demography, risk exposure, natural history, treatment, screening dissemination and impact of screening MISCAN–Colon simulates cancer incidence and mortality by stage, age and calendar year.

PURPOSE

MISCAN–Colon is developed to analyze trends in colorectal cancer due to changes in lifestyle, improvement of treatment and implementation of screening strategies. See [Model Purpose](#) for more details.

BACKGROUND

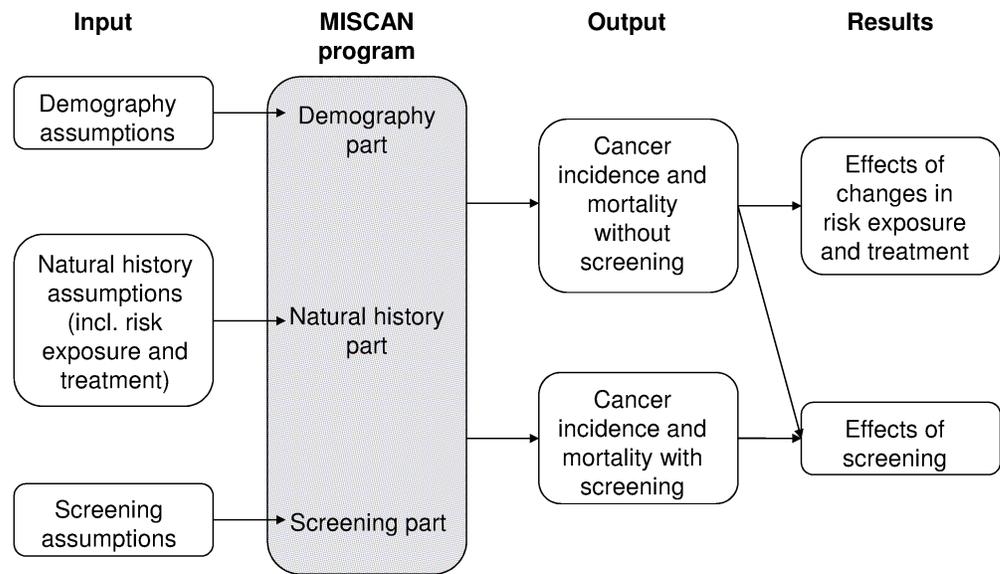
The Microsimulation Screening Analysis (MISCAN) computer program has been used for simulating cancers of the breast, cervix, colon and prostate ^{1,2,3,4,5}. MISCAN–Colon will simulate a population of persons in which colorectal cancer and its precursor lesion, the adenomatous polyp, develop, resulting in "clinical" diagnosis, treatment, and possible death from this disease. Different assumptions on risk exposure and treatment and their influence on cancer incidence and mortality can be simulated. The output of the program can be used among others to compare situations with and without screening, or different screening policies with each other.

By combining demographic and epidemiological information from the Surveillance, Epidemiology and End Results (SEER) program, information on lifestyle and risk factors and information on screening dissemination, we will gain insight into what extent the observed trends in incidence and mortality of colorectal cancer can be explained by screening. Also the effects of other factors such as changes in treatment and lifestyle (risk exposure) will be studied. Using the knowledge gathered during the project, MISCAN–Colon will reproduce the total US population to predict effects of future cancer control strategies on a population level. The results may be used for public health policy making.

MODEL DESCRIPTION

The basic structure of MISCAN–Colon is illustrated in figure 1. It describes the way in which effects of risk exposure and improvement of treatment are modeled and how effects of different screening strategies are estimated. By running MISCAN–Colon on different assumptions on for example risk exposure, the effects of risk exposure on cancer incidence and mortality and optimal screening policy can be evaluated.

FIGURE 1: Structure of MISCAN-Colon



MISCAN-Colon is a micro-simulation program, generating individual life histories. 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.

Figure 1 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.

MISCAN-Colon first generates a series of individual life histories in the demography part to form a population according to the [Demography Parameters](#) (e.g. the life table). Each person in the population consists of a date of birth and a date of death from other causes than colorectal cancer.

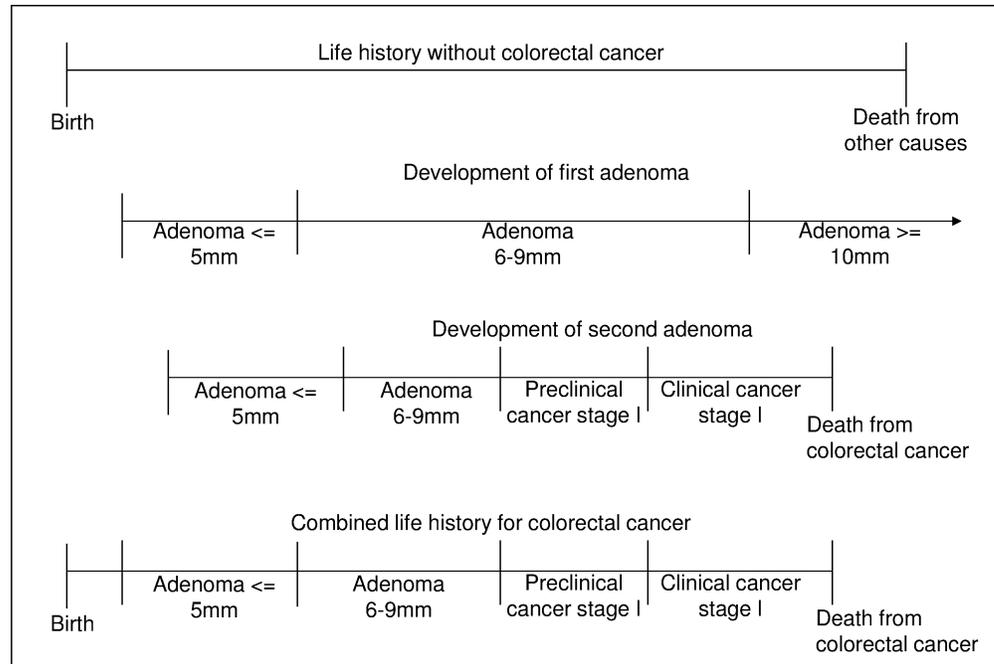
Subsequently the [Natural History Component](#) part of MISCAN-Colon simulates colorectal cancer histories (natural histories) for each individual life history separately. We based our natural history model on the adenoma-carcinoma sequence of Morson ⁶ and Vogelstein ⁷. This means that adenomas are generated according to a personal risk index and an age specific incidence rate, resulting in no adenomas for most persons and 1 or more adenomas for others. Some of these adenomas develop into colorectal cancer, depending on the Natural History Parameters. The development from adenoma into cancer covers different stages. Each disease state represents a state in a Markov process. This is a generalized Markov process in the sense that

- other than exponential distributions in each disease state are possible,
- distributions are age dependent
- distributions are calendar time dependent
- intervention by screening is possible

The survivorship of a person is generated according to the Survival Parameters, once an adenoma has developed into clinical colorectal cancer.

The life history of each person is altered according to the natural history that is simulated for that person. This means that the state a person is in is the same as the state of the most advanced adenoma or carcinoma he has. If he dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly. This procedure is explained in figure 2a. In this example the life history of a person is shown who develops two adenomas. One of these adenomas develops into a cancer and causes death before the age of death from other causes. The combination of life history without colorectal cancer and the development of adenomas is shown in the bottom line: combined life history for colorectal cancer.

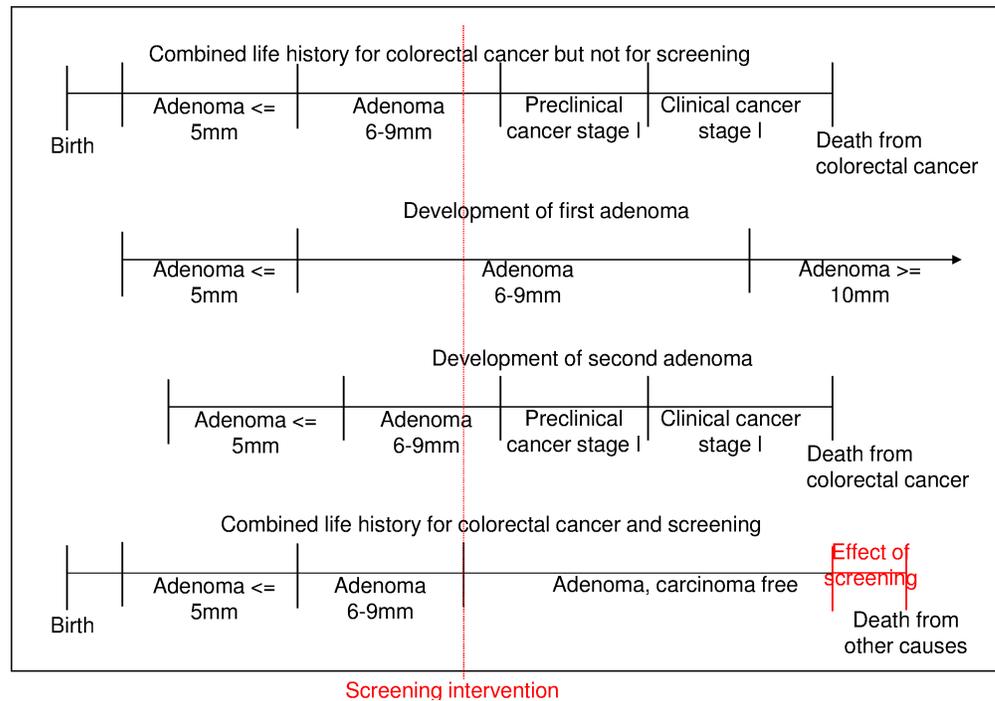
FIGURE 2A: Modeling natural history into life history



In the third part of the program, screening for colorectal cancer is simulated. After the life history of a person is adjusted for colorectal cancer, the history will now be adjusted for the effects of screening. The screening part is simultaneously run with the natural history part, making detection of adenomas and carcinomas in different states possible. The aggregated changes in life history constitute the effectiveness of the screening. The effect of screening on life history is explained in figure 2b.

The top line in this figure is the combined life history for colorectal cancer from figure 2a. The development of the separate adenomas is shown in the second and third line. In this picture there is one screening intervention. During the screening both prevalent adenomas are detected and removed. This results in a combined life history for colorectal cancer and screening (bottom line), where the person is adenoma–carcinoma free after the screening intervention. The effect of screening is now equal to the lifeyears gained by the screening intervention.

FIGURE 2B: Modeling screening into life history



The effects of different screening policies can be compared by applying them to identical natural histories. If one is solely interested in modeling the natural history of disease, the screening part is not necessary.

CONTRIBUTORS

Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands

- Marjolein van Ballegooijen
- Rob Boer
- J. Dik F. Habbema
- Franka Loeve
- Gerrit J. van Oortmarssen
- Iris Vogelaar

Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

- Ann Zauber

REFERENCES:

- ¹ Akker-van Marle, ME, van den, Ballegooijen, M, van Oortmarssen, GJ, van Boer, R, Habbema, JDF "Cost-effectiveness of cervical cancer screening: comparison of screening policies" in *J Natl Cancer Inst* 2002; 94: : 193-204
- ² Loeve, F, Boer, R, Oortmarssen, GJ, van Ballegooijen, M, van Habbema, JDF "The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening" in *Comput Biomed Res* 1999; 32: : 13-33
- ³ Loeve, F, Brown, ML, Boer, R, Ballegooijen, M, van Oortmarssen, GJ, van Habbema, JDF "Endoscopic colorectal cancer screening: a cost-saving analysis " 2000; 92: 7: 557-63



- ⁴ Koning, HJ, de Boer, R, Warmerdam, PG, Beemsterboer, PMM, Maas, PJ van der "Quantitative interpretation of age-specific mortality reductions from the Swedish breast cancer-screening trials " in J Natl Cancer Inst 1995; 87: 16: 1217-23
- ⁵ Habbema, JD, Oortmarsen, GJ van, Lubbe, JT, Maas, PJ van der "The MISCAN simulation program for the evaluation of screening for disease " in Comput Methods Programs Biomed 1985; 20: 1: 79-93
- ⁶ Morson, B "The polyp-cancer sequence in the large bowel" in Proc R Soc Med 1974; 67: : 451-7
- ⁷ Vogelstein, B, Fearon, ER, Hamilton, SR, Kern, SE, Preisinger, AC, et al. "Genetic alterations during colorectal-tumor development. " in N Engl J Med 1988; 319: 9: 525-32

ASSUMPTION OVERVIEW

SUMMARY

Overview of the main assumptions used in the present version of the MISCAN–Colon model.



BACKGROUND

A model is defined as a simplified representation of a complex process. Because of lack of data or to prevent the model from becoming too complicated, simplifying assumptions have to be made in all models.

In each of the three parts of the MISCAN–Colon program assumptions are made:

- assumptions on demography
- assumptions on natural history
- assumptions on screening.

Model validation is an important tool for testing the model assumptions. During validation we use MISCAN–Colon to simulate for example a trial situation and compare the observed trial outcomes with the model outputs. Discrepancies between the trial and simulated outcomes are further investigated. If external reasons are not sufficient to explain discrepancies, the model parameters are re–examined. If re–estimating the model parameters does not lead to a good fit of model output and observations, the assumptions are reconsidered.

ASSUMPTION LISTING

Demography Assumptions

Demography Assumptions focus on the actuarial characteristics of the population. The following assumptions on demography are made:

- the life table differs per birth cohort
- death from colorectal cancer and death from other causes are considered independent from each other

Natural History Assumptions

Natural History assumptions focus on the initiation, progression and response to treatment of colorectal cancer in the model. Natural history includes assumptions on:

- Colorectal cancer development
- Adenoma incidence
- Multiplicity of adenomas
- Adenoma types
- Non–progressive adenomas
- Progressive adenomas and cancer
- Transition probabilities
- State durations
- Anatomical site of adenomas
- Survival rates

A more detailed description of the natural history assumptions can be found in [Natural](#)

History Assumptions.

Screening Assumptions

Screening assumptions focus on all aspects of screening, including compliance and operational characteristics of the screening process. Assumptions are listed in detail below:

- *Sensitivity of screening* – The sensitivity for all tests depends on location, state and size of the lesion. It is also possible to assume systematic error on screening results. There can be systematic errors for certain persons or lesions.
- *Reach of screening* – It is possible to limit the reach of screening tests by indicating the probability for a test to reach a certain localization in the large bowel.
- *Impact of early detection and treatment after screening* – In case of detection and removal of an adenoma, it is assumed that the adenoma is prevented from growing into a cancer. In case of detection of a cancer, a screen detected cancer can be detected in the same stage as it would have become clinical in the absence of screening, or it can be detected in an earlier stage. In the former case, we assume the same stage specific survival for screen-detected as for clinically detected cancers. In the latter case, we assume the stage specific survival of one stage earlier for screen-detected cancers. For each screen-detected lesion a new survival is generated.
- *Surveillance* – MISCAN-Colon enables the user to define a surveillance-scheme after detection of an adenoma during screening or surveillance. Surveillance will be modeled according to current guidelines. A description of these guidelines can be found in the next layer of the Model Profile.

PARAMETER OVERVIEW

SUMMARY

Provides a complete overview of the parameters used to quantify the MISCAN–Colon model.



Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

BACKGROUND

The MISCAN–Colon model uses four types of parameters: demography parameters, natural history parameters, screening parameters and output parameters.

PARAMETER LISTING OVERVIEW

Demography Parameters

1. number of birth cohorts
2. proportion of the population in each birth cohort
3. for each birth cohort parameters of its birth table
4. for each birth cohort the parameters of its life table

Natural History Parameters

1. adenoma–carcinoma sequence states
2. age specific adenoma incidence rate by birth cohort
3. parameters for the distribution of the individual risk index
4. distribution of adenomas over the colorectal sites
5. probability for an adenoma to be progressive
6. parameters for the transition probability of non–progressive adenomas for each state
7. parameters for the duration distribution of non–progressive adenomas for each state
8. parameters for the transition probability of progressive lesions for each state
9. parameters for the duration distribution of progressive lesions for each state
10. correlation between duration in subsequent states
11. parameters for survival after clinical diagnosis by age at diagnosis, year of diagnosis, stage of disease and localization of the cancer

Screening Test Parameters

1. parameters for the dissemination of screening
2. reach, sensitivity, specificity of different screening tests
3. dependency of test outcomes on previous test outcomes of the same individual
4. parameters for survival after screen detected diagnosis
5. surveillance after screen–detected adenomas

Output Parameters

1. adenoma states required in the output
2. age groups required in the output

3. parameters for life years in initial therapy
4. parameters for life years with terminal care
5. number of persons to be simulated

Categories

The above parameters can be divided into three categories:

- parameters that are directly estimated from available data
- parameters for which no data (or only limited data) are available
- parameters that will be varied to fit reference data

TABLE 1 shows which parameters belong to each of these categories.

Parameters that are directly estimated from available data	Parameters for which no data (or only limited data are available)	Parameters that will be varied to fit reference data (calibrated)
demography	duration distribution in preclinical states	probability for an adenoma to be progressive
distribution of lesions over large bowel	transition probabilities from preclinical non-invasive states	individual risk index
survival after clinical diagnosis	correlation between durations in subsequent states	incidence rate of adenomas
sensitivity, specificity and reach of screening tests	dependency of test outcomes	transition probabilities from preclinical invasive states to clinical states
distribution of cancers over invasive stages	survival after screen detected diagnosis	screening dissemination
Relative risk associated with risk and protective factors	–	–
Prevalence of risk and protective factors	–	–
Treatment dissemination	–	–
Hazard ratios of treatment	–	–

The parameters are based on literature (see: [References For Model Parameters](#)), expert opinion and SEER data.

COMPONENT OVERVIEW

SUMMARY

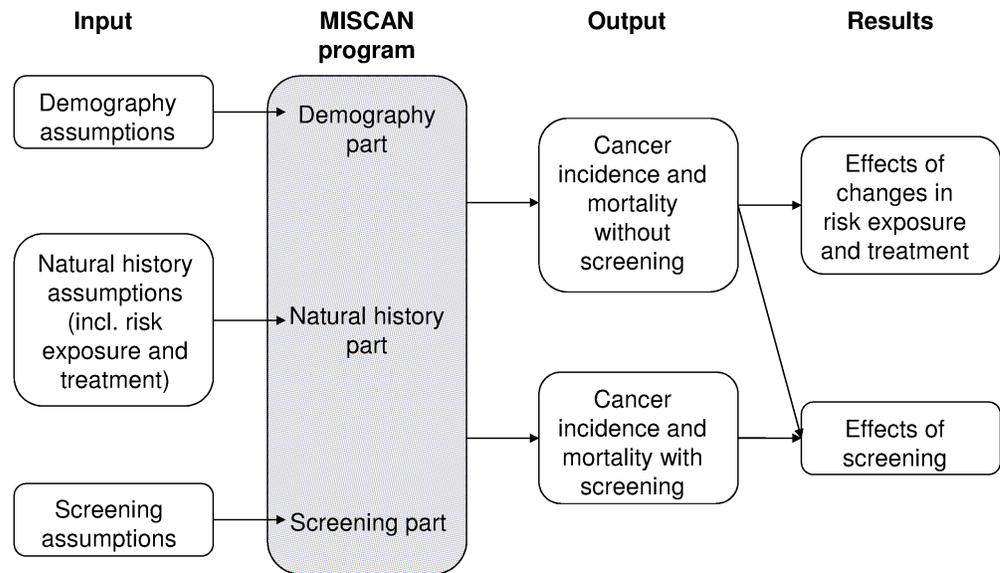
Overview of the major components in the MISCAN–Colon model.

OVERVIEW

As described in the [Model Overview](#) document, the MISCAN–Colon model contains three primary components: Demography, [Natural History Component](#) and Screening.



- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References



COMPONENT LISTING

Demography Component

The demography component simulates a population of individual life histories, according to the demography parameters. The demography parameters are:

- birth table parameters (<http://seer.cancer.gov/popdata>)
- life table life table parameters (National Center for Health Statistics)

Each individual in the population consists of a date of birth and age of death.

Natural History Component

Subsequently the Natural History part of MISCAN–Colon simulates colorectal cancer histories (natural histories) for each individual life history separately. Adenomas are generated according to an individual risk index and age–specific incidence rate. The age–specific adenoma incidence rate depends on exposure to risk factors and therefore varies by birth cohort. Some of these adenomas develop into colorectal cancer, depending on the natural history parameters (see [Parameter Overview](#)). The development from adenoma into cancer covers different stages. The survivorship of a person once an adenoma has developed into clinical colorectal cancer, depends on year of diagnosis, age at diagnosis, localization of the cancer and stage of disease. The life history of each person is altered according to the natural history that is simulated for that person. If he dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly.



Screening Component

The screening component is simultaneously run with the [Natural History Component](#), making detection of adenomas and carcinomas in different states possible. Screening in the model potentially affects all preclinical disease stages, resulting either in removal of an adenoma and preventing CRC or early detection of a preclinical carcinoma, possibly in an earlier stage resulting in a favorable stage shift and thus improved prognosis. The effectiveness of screening depends on the screening parameters (see [Parameter Overview](#)).

OUTPUT OVERVIEW

SUMMARY

Overview of the outputs generated by the MISCAN–Colon model.

OVERVIEW

The MISCAN–Colon model simulates among others the Base Case outputs. In case the screening part is activated MISCAN–Colon also provides output on screening effects. It is also possible to consider quality of life. This also generates extra output.

OUTPUT LISTING

The output component produces the final output of the model:

Base Case

1. Incidence counts by calendar year, location, stage and age in five year age groups
2. Mortality counts by calendar year and age in five year age groups
3. Population on July 1 of each calendar year by age in five year age groups
4. Adenoma prevalence by calendar year, location, size, sex and age in five year age groups
5. CRC prevalence by calendar year, stage, location and age in five year age groups

Screening

6. Number of invitations for screen tests, diagnostic tests, surveillance tests and number of opportunistic screen tests for each year
7. Number of positive and negative test results per preclinical state and per year
8. Total number of life years, life years lost due to cancer, number of specific deaths and non-specific deaths
9. Number of screenings that prevented cancer by year of screening
10. Number of screenings that detected cancer early by year of screening
11. Number of surveillance tests that prevented cancer by year of surveillance
12. Number of surveillance tests that detected cancer early by year of surveillance
13. Number of life years gained due to screening by year of screening

Quality of life

14. Total number of life years in surveillance
15. Total number of life years with initial therapy after screen–detected or clinical invasive cancer for each state
16. Total number of life years with terminal care before death from other causes
17. Total number of life years with terminal care before death from colorectal cancer





RESULTS OVERVIEW

SUMMARY

Describes the general results obtained from the MISCAN–Colon output.

OVERVIEW

One of the strengths of the MISCAN–Colon model is that it has been validated against several large screening trials, and we will continue to update the model when new data becomes available. This document shortly describes the main validation studies that were performed with the model to date. Subsequently, a list is provided of all studies that were published with the validated model.

RESULTS LIST

Validation of the MISCAN–Colon model

*The Kaiser validation study*¹ CoCaP is a large program of sigmoidoscopy screening conducted by Kaiser Permanente of Northern California (KPNC), a large non–profit Health Maintenance Organization. We compared the model predicted and observed cancer incidence after screening to assess the assumptions for the sensitivity of sigmoidoscopy to detect adenomas and CRC. Many combinations of sensitivity and duration of adenomas were consistent with the observed findings. These assessments will be modeled subsequently when data on repeat screenings are available.

*National Polyp Study data: evidence for regression of adenomas*² The data of the National Polyp Study, a large longitudinal study on surveillance of adenoma patients, is used for testing assumptions on the adenoma–carcinoma sequence. The observed adenoma and colorectal cancer incidence in the National Polyp Study were compared with the simulated outcomes of the MISCAN–Colon model of epidemiology and control of colorectal cancer for the U.S. population based on expert opinion. Variants of this model were explored in order to identify assumptions on the adenoma–carcinoma sequence that are consistent with the study observations. The high observed adenoma detection rates at surveillance and low observed colorectal cancer incidence in the National Polyp Study could only be explained by assuming a high incidence rate of adenomas accompanied by regression of adenomas. The National Polyp Study data suggest that adenoma prevalence results from a dynamic process of both formation as well as regression of adenomas. This lowers the expectations for the effects of colorectal cancer screening strategies that focus on adenoma detection.

*Metasynthesis validation study of 3 randomized FOBT trials*³ Data of the Minnesota, Funen, and Nottingham FOBT trials were used to compare expected model outcomes and observed data on screen detected cancers and adenomas, interval cancers and mortality. All three trials are randomized controlled trials of FOBT screening where participants were offered annual screening (Minnesota only), biennial screening or usual care. All three trials have shown a significant mortality reduction ranging from 15% to 33%. Adjusting the model for differences in design and background incidence between trials, we tried to find one disease model that simultaneously fit all three studies. Parameters varied were FOBT sensitivity and dwelling time of preclinical cancer stages. Assuming a fixed sensitivity of FOBT for all cancer stages would imply short dwelling times for the local stages, and long dwelling times for the advanced stages. Despite the short estimated dwelling time, too many Dukes A cancers were still found expected in consecutive screening rounds. Varying sensitivity of FOBT by stage



- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References



gave better results for Dukes A cancers detected, but still resulted in too many Dukes A cancers found expected in consecutive screening rounds. We therefore proposed a novel hypothesis that sensitivity is higher for the stage in which the cancer would have been diagnosed in the absence of screening than for earlier stages. This hypothesis, with a high sensitivity shortly before diagnosis when the cancer is likely to bleed, gave the best fit to results of the randomized controlled trials of Minnesota, Nottingham and Funen.

Healthy People 2010^{4,5} The Healthy People consortium acknowledged the burden of colorectal cancer and formulated the target of reducing colorectal cancer mortality from 21.2 per 100,000 in 1998 with 34% by 2010. We used the MISCAN-COLON micro-simulation model to examine the possibilities for reaching the Healthy People 2010 colorectal cancer mortality goal when assuming various trends in risk factor prevalence, screening participation and improvements in CRC treatment.

For this project the model was calibrated to reproduce the 1975 to 1979 age-specific CRC incidence rates, which were representative of the U.S. population prior to the introduction of screening. Subsequently, by adding the observed trends in risk-factor prevalence and screening and treatment use from 1975 to 2000, a population was generated with the characteristics of the 2000 U.S. population. The model predictions for CRC incidence and mortality from 1975 until 2000 all were within 6% of the observed incidence and mortality in the U.S.

*United Kingdom Flexible Sigmoidoscopy Study (Manuscript in preparation)*⁶

We validated the MISCAN-Colon model, as well as two other CISNET CRC microsimulation models, against outcomes from the United Kingdom Flexible Sigmoidoscopy Study (UKFSS), a randomized controlled trial that examined the effectiveness of one-time flexible sigmoidoscopy screening to reduce CRC mortality.⁷ All three models accurately predicted the relative effect of one-time flexible sigmoidoscopy on CRC mortality ten years after screening. However, the models predicted absolute mortality and the effect of screening on disease incidence with varying degrees of success. One major difference between the models is 'dwell time', the average time from adenoma initiation to presentation with clinical CRC, simulated as 25.8 years for CRC-SPIN, 25.2 years for SimCRC, and 10.6 years for MISCAN. MISCAN predicted too many screen-detected cancers and higher 10-year CRC incidence rates than estimated, especially in the control group, but 10-year CRC mortality rates that were slightly lower than estimated. The shorter dwell time specified by the MISCAN model resulted in predicted CRC incidence in the intervention group that 'caught up' too quickly to incidence rates the control group. When the MISCAN model was updated to incorporate a longer transition time and then recalibrated, the updated model predicted hazard rates for both 10-year CRC incidence and mortality that were within the study error bounds

Applications of the MISCAN-Colon model

The MISCAN-Colon model has been applied to a wide range of applications falling into three general areas: directly informing policy, indirectly informing policy, and informing model assumptions. Much of this work has been carried out through additional funding provided by the Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), United States Department of Veterans Affairs (VA), and the Agency for Healthcare Research and Quality (AHRQ).

Applications that Directly Inform Policy



MISCAN (as well as other CISNET–Colon models) have been used to inform US National Policy, specifically USPSTF CRC screening guidelines⁸ and CMS reimbursement decisions for CRC screening tests.^{9,10,11,12,13} The model has also been used to inform US State Policy. This includes a project supported by the CDC to assist state groups as they implement cancer–control programs. The model was used to identify optimal screening scenarios for underserved rural areas of South Carolina with a limited budget for screening and significant distances to endoscopy centers.¹⁴ We also worked with the American Cancer Society and state health departments in New Jersey and Louisiana to estimate how differences in risk factors, screening, and treatment explain the differences in CRC mortality in those states (manuscript in preparation). Finally, the model has also been used to inform international policy recommendations. We are working with researchers in Ontario and Alberta, Canada (two manuscripts in preparation) as well as Australia¹⁵ to project outcomes and resources for population–based screening programs being tested in these regions. In addition, we work closely with the Dutch government to inform the recently introduced national FIT screening program.^{16,17,18}

Applications that Indirectly Inform Policy

Many of our applications have examined policy–focused issues resulting in publications in high–profile journals including New England Journal of Medicine,¹⁹ JAMA Internal Medicine²⁰, Annals of Internal Medicine^{8,10,21,22}, and Journal of the National Cancer Institute.^{23,12,24} These papers have examined various facets of CRC including the impact of comorbidity²¹ and family history^{25,26} on screening benefit, black–white disparities in CRC incidence and mortality^{27,28}, the potential impact of over–use of screening²⁰ and potential stopping ages^{8,22}, productivity savings from CRC prevention,²⁹ the costs and relative benefits of CTC screening^{30,12,31} and the potential effect of radiation exposure with CTC.³² In addition, we have worked with the Healthy People 2010 initiative to describe CRC incidence and mortality to trends and project the effect of changes in screening and risk factors on these trends.⁴ and the MISCAN model was used for the 2009 report on the status of cancer⁵ to address the potential benefit of screening the entire US population for CRC according to current guidelines.

Applications that Inform Model Assumptions

Applications that provide insight into model performance and relationships between assumptions and model output are critical to thoughtful model application. Several studies have been performed to validate the accuracy of the model (described in section "Validation of the MISCAN–Colon model" above). In addition, two studies on comparisons between CISNET–Colon models highlighted differences between the models.^{33,34}

REFERENCES:

- 1 Loeve, F., Boer, R., van Ballegooijen, M., van Oortmarssen, G. J., Habbema, J. D. F. "Final Report MISCAN-COLON Microsimulation Model for Colorectal Cancer: Report to the National Cancer Institute Project No. NO1-CN55186" in Department of Public Health, Erasmus University. Rotterdam, The Netherlands. 1998;
- 2 Loeve F, Zauber AG, Van Ballegooijen M, Van Oortmarssen GJ, Winawer SJ, Habbema JD "National Polyp Study data: evidence for regression of adenomas." in International Journal of Cancer 2004; 111: 4: 633-9



- 3 Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, Zauber AG, Habbema JDF "A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials" in *Cancer* 2009; 115: 11: 2410-9
- 4 Vogelaar I, van Ballegooijen M, Schrag D, Boer R, Winawer SJ, Habbema JDF, Zauber AG. "How much can current interventions reduce colorectal cancer mortality in the U.S.? Mortality projections for scenarios of risk-factor modification, screening, and treatment." in *Cancer* 2006; 107: 7: 1624-33
- 5 Edwards BK, Ward E, Kohler BA, Ehemann C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. "Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates" in *Cancer* 2010; 116: 3: 544-73
- 6 Rutter CM, Knudsen AB, Marsh TL, Doria-Rose VP, Johnson E, Pabiniak C, Kuntz KM, van Ballegooijen M, Zauber AG, Lansdorp-Vogelaar I. "Validation to Inform Model Structure: Results from Three Colorectal Cancer Microsimulation Models" in [Manuscript in preparation] 2015;
- 7 Atkin, W. S., Edwards, R., Kralj-Hans, I., Wooldrage, K., Hart, A. R., Northover, J. M., Parkin, D. M., Wardle, J., Duffy, S. W., Cuzick, J., U.K. Flexible Sigmoidoscopy Trial Investigators "Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial" in *Lancet* 2010; 375: 9726: 1624-33
- 8 Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM "Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force." in *Ann Intern Med* 2008; 149: 9: 659-69
- 9 Zauber AG, Lansdorp-Vogelaar I, Wilschut J, Knudsen AB, van Ballegooijen M, Kuntz KM. "Cost-Effectiveness of DNA Stool Testing to Screen for Colorectal Cancer: Report to AHRQ and CMS from the Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN and SimCRC Models" in Online report 2007;
- 10 Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, Wilschut JA, Zauber AG, van Ballegooijen M. "Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis." in *Ann Intern Med* 2010; 153: 6: 368-77
- 11 Zauber AG, Knudsen AB, Rutter CM, et al. "Cost-Effectiveness of CT Colonography to Screen for Colorectal Cancer." in Online report 2009;
- 12 Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Savarino JE, van Ballegooijen M, Kuntz KM, Zauber AG. "Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the medicare population." in *J Natl Cancer Inst* 2010; 102: 16: 1238-52
- 13 van Ballegooijen M, Habbema JDF, Boer R, Zauber AG, Brown ML. "Report to the Agency for Healthcare Research and Quality: a comparison of the cost-effectiveness of fecal occult blood tests with different test characteristics in the context of annual screening in t" in Online report 2003;
- 14 van der Steen A, Knudsen AB, van Hees F, Walter GP, Berger FG, Daguise VG, Kuntz KM, Zauber AG, van Ballegooijen M, Lansdorp-Vogelaar I. "Optimal Colorectal Cancer Screening in States' Low-Income, Uninsured Populations-The Case of South Carolina." in *Health Serv Res.* 2014 Oct 16. doi: 10.1111/1475-6773.12246. [Epub ahead of print]
- 15 Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. "Optimising the expansion of the National Bowel Cancer Screening Program." in *Med J Aust* 2014; 201: 8: 456-61
- 16 Wilschut JA, Hol L, Dekker E, Jansen JB, Van Leerdam ME, Lansdorp-Vogelaar I, Kuipers EJ, Habbema JD, Van Ballegooijen M. "Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening." in *Gastroenterology* 2011; 141: 5: 1648-55

- 17 Wilschut JA, Habbema JD, van Leerdam ME, Hol L, Lansdorp-Vogelaar I, Kuipers EJ, van Ballegooijen M "Fecal occult blood testing when colonoscopy capacity is limited." in *J Natl Cancer Inst* 2011; 103: 23: 1741-51
- 18 Goede SL, van Roon AH, Reijerink JC, van Vuuren AJ, Lansdorp-Vogelaar I, Habbema JD, Kuipers EJ, van Leerdam ME, van Ballegooijen M. "Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening." in *Gut* 2013; 62: 5: 727-34
- 19 Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Wayne JD. "Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths" in *N Engl J Med* 2012; 366: 8: 687-96
- 20 van Hees F, Zauber AG, Klabunde CN, Goede SL, Lansdorp-Vogelaar I, van Ballegooijen M. "The appropriateness of more intensive colonoscopy screening than recommended in medicare beneficiaries: a modeling study." in *JAMA Intern Med* 2014; 174: 10: 1568-76
- 21 Lansdorp-Vogelaar I, Gulati R, Mariotto AB, Schechter CB, de Carvalho TM, Knudsen AB, van Ravesteyn NT, Heijnsdijk EA, Pabiniak C, van Ballegooijen M, Rutter CM, Kuntz KM, Feuer EJ, Etzioni R, de Koning HJ, Zauber AG, Mandelblatt JS. "Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits." in *Ann Intern Med* 2014; 161: 2: 104-12
- 22 van Hees F, Habbema JD, Meester RG, Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG. "Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis." in *Ann Intern Med* 2014; 160: 11: 750-9
- 23 Loeve, F, Brown, ML, Boer, R, Ballegooijen, M, van Oortmarssen, GJ, van Habbema, JDF "Endoscopic colorectal cancer screening: a cost-saving analysis " 2000; 92: 7: 557-63
- 24 Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JDF, Kuipers EJ "Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening" in *J Natl Cancer Inst* 2009; 101: 20: 1412-22
- 25 Wilschut JA, Steyerberg EW, van Leerdam ME, Lansdorp-Vogelaar I, Habbema JD, van Ballegooijen M. "How much colonoscopy screening should be recommended to individuals with various degrees of family history of colorectal cancer?" in *Cancer* 2011; 117: 18: 4166-74
- 26 Ramsey SD, Wilschut J, Boer R, van Ballegooijen M. "A decision-analytic evaluation of the cost-effectiveness of family history-based colorectal cancer screening programs." in *Am J Gastroenterol* 2010; 105: 8: 1861-9
- 27 Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut JA, Winawer SJ, Habbema JDF, "Individualizing colonoscopy screening by sex and race" in *Gastrointest Endosc* 2009; 70: 1: 96-108
- 28 Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, van Ballegooijen M, Zauber AG, Jemal A. "Contribution of screening and survival differences to racial disparities in colorectal cancer rates." in *Cancer Epidemiol Biomarkers Prev* 2012; 21: 5: 728-36
- 29 Bradley CJ, Lansdorp-Vogelaar I, Yabroff KR, Dahman B, Mariotto A, Feuer EJ, Brown ML. "Productivity savings from colorectal cancer prevention and control strategies." in *Am J Prev Med* 2011; 41: 2: e5-e14
- 30 Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut JA, Habbema JDF. "At what costs will screening with CT colonography be competitive? A cost-effectiveness approach." in *Int J Cancer* 2009; 124: 5: 1161-8
- 31 Vanness DJ, Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Gareen IF, Herman BA, Kuntz KM, Zauber AG, van Ballegooijen M, Feuer EJ, Chen MH, Johnson CD. "Comparative economic evaluation of data from the ACRIN National CT Colonography Trial with three cancer intervention and surveillance modeling network microsimulations." in *Radiology* 2011; 261: 2: 487-98



- 32 Berrington de González A, Kim KP, Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Smith-Bindman R, Yee J, Kuntz KM, van Ballegooijen M, Zauber AG, Berg CD "Radiation-related cancer risks from CT colonography screening: a risk-benefit analysis." in Am J Roentgenol 2011; 196: 4: 816-23
- 33 Kuntz KM, Lansdorp-Vogelaar I, Rutter CM, Knudsen AB, van Ballegooijen M, Savarino JE, Feuer EJ, Zauber AG "A systematic comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression." in Med Decis Making 2011; 31: 4: 530-9
- 34 van Ballegooijen M, Rutter CM, Knudsen AB, Zauber AG, Savarino JE, Lansdorp-Vogelaar I, Boer R, Feuer EJ, Habbema JD, Kuntz KM. "Clarifying differences in natural history between models of screening: the case of colorectal cancer." in Med Decis Making 2011; 31: 4: 540-9

NATURAL HISTORY COMPONENT

SUMMARY

This document describes the Natural History Component of the model and discusses aspects of the patient's progression from a disease free state to diagnosis.

OVERVIEW

MISCAN–Colon consists of three parts: the demography part, the natural history part and the screening part. At the beginning of each run a population is simulated. Each person consists of a date of birth and date of death. For each person a personal risk index is generated. Based on this risk index and the age specific incidence rate the ages at which lesions develop are generated. At the generated ages lesions start in the begin–state corresponding to the type of lesion.

The development of the lesion depends on the type of lesion (non–progressive / progressive), the transition probabilities and the duration distribution. The duration is assumed to be exponentially distributed.

The assumptions of the natural history of colorectal cancer are based on literature (see [References For Model Parameters](#)), expert opinion and SEER–data.

DETAILS

States tracked by the model

MISCAN–Colon distinguishes the following states of the disease process:

Disease free state

- no lesion

Non–progressive states

- non–progressive adenoma
- non–progressive adenoma 6–9mm
- non–progressive adenoma ≥ 10 mm

Preclinical non–invasive states

- progressive adenoma
- progressive adenoma 6–9mm
- progressive adenoma ≥ 10 mm

Preclinical invasive states

- preclinical colorectal cancer, stage I
- preclinical colorectal cancer, stage II
- preclinical colorectal cancer, stage III
- preclinical colorectal cancer, stage IV

Clinical invasive states

- clinical colorectal cancer, stage I
- clinical colorectal cancer, stage II
- clinical colorectal cancer, stage III



[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)

- clinical colorectal cancer, stage IV

Temporal aspects

The possible transitions between the different states are explained in figures 1 and 2:

FIGURE 1: Non–progressive adenoma sequence

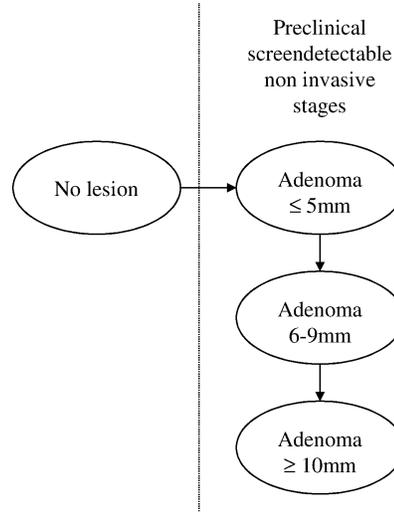
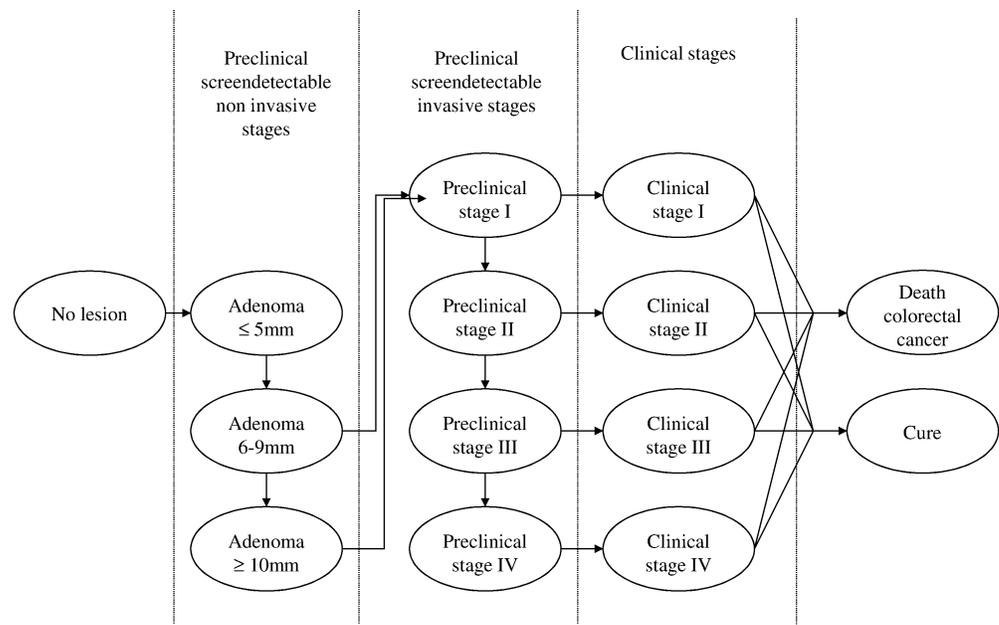


FIGURE 2: Adenoma–carcinoma sequence for progressive adenomas



All states in the above figure have a certain transition probability and duration distribution. The transition probabilities through different preclinical states are given. The transition probabilities from the preclinical states to the clinical states are based on stage distribution in SEER data.



The duration distribution is assumed to be dependent on the age of a person and location of the lesion. All durations are assumed to be exponentially distributed. We assume a positive correlation between duration in successive states.

Key attributes

Adenoma incidence and development depend on:

- a. age
- b. gender
- c. race
- d. location
- e. personal risk index
- f. risk factor exposure

Adenoma localization options

Adenomas and cancers are modeled to be continuously distributed over the bowel. In the output they are categorized according to the part of the bowel they are in. MISCAN-Colon distinguishes the following parts of the large bowel:

1. Rectum
2. Rectosigmoid + Rectosigmoid junction
3. Sigmoid
4. Descending colon
5. Hepatic flexure + transverse colon + splenic flexure
6. Ascending colon
7. Cecum

RELEVANT ASSUMPTIONS

The most important assumptions on natural history concern:

- development of colorectal cancer
- multiplicity of adenomas
- age dependent adenoma incidence
- existence of non-progressive and progressive adenomas
- transition probabilities and duration distribution per state

A more extensive description of the assumptions can be found in [Natural History Assumptions](#).

The reduction in cancer mortality due to screening in MISCAN-Colon is realized in two ways. First of all it is assumed that a removed adenoma will not develop into a cancer anymore. On top of that a cancer can be detected at an earlier stage (stage-shift) with potentially better survival.

RELEVANT PARAMETERS

The parameters used to simulate natural history are:

- adenoma states
- age specific adenoma incidence rate
- parameters for the individual risk index
- distribution of adenomas over the colon and rectum

- probability for an adenoma to be progressive
- parameters for the transition probability of non–progressive adenomas for each state
- parameters for the duration distribution of non–progressive adenomas for each transition
- parameters for the transition probability of progressive lesions for each state
- parameters for the duration distribution of progressive lesions for each transition
- correlation between duration in subsequent states

All input–parameters for MISCAN–Colon are described in the [Parameter Overview](#).

Calibration

The assumptions of the natural history of colorectal cancer are based on literature (see [References For Model Parameters](#)), expert opinion and SEER–data. Not all parameters can be obtained directly from data. These parameters must be calibrated to fit actual data. These parameters include for instance age–specific adenoma incidence. The adenoma incidence will be varied until simulated adenoma prevalence and colorectal cancer incidence reflect actual data. We use in MISCAN a built–in optimization method, which is an adaptation of the Nelder and Mead Simplex Method ^{1,2} to optimize these and other parameters. A complete list of parameters to be calibrated depends on data available and will be determined during the process.

Validation

Different model specifications are simulated and the output of these different models is compared to actual data. The goodness of fit of model assumptions is evaluated by the deviance, which compares outcomes of the model with actual data. The outcomes that can be evaluated are for example the cancer incidence by age, the stage distribution of clinical cancers and the prevalence of adenomas. The MISCAN–Colon model has been validated on different data sources in the US and Europe (see [Results Overview](#)).

DEPENDENT OUTPUTS

The outputs most dependent on natural history are:

- cancer incidence
- cancer stage distributions
- cancer mortality

RELEVANT RESULTS

The results of MISCAN–Colon provide solid policy recommendations based on evaluation of simulated effects of risk factors, improved therapy and screening interventions.

REFERENCES:

- 1 Nelder, JA, Mead, R “A simplex method of function minimization” in Computer Journal 1965; 7: : 308-312
- 2 Neddermeijer HG, Piersma N, van Oortmarssen GJ, Habbema JDF, Dekker R. “Comparison of response surface methodology and the Nelder and Mead simplex method for optimization in microsimulation models” in Econometric Institute 1999;

NATURAL HISTORY ASSUMPTIONS

SUMMARY

This document describes the assumptions inherent in the modeling of disease initiation and progression.

OVERVIEW

Much of the natural history of disease is unobserved and parameters cannot be measured directly. To be able to model natural history of colorectal cancer, assumptions have to be made. The model assumptions are based on expert opinion by consensus of a group of clinical experts in the field of colorectal cancer.

See also [Assumption Overview](#), [Natural History Component](#)

DETAIL

The [Natural History Component](#) assumptions are listed in detail below.

Colorectal cancer development

Colorectal cancer always grows from an adenoma

Adenoma incidence

It is possible for individuals to develop multiple adenomas. In the whole population risk differences are present: some people will never grow an adenoma while others have more than one. This risk difference is modeled by the introduction of a risk index for each individual. A high-risk index indicates a high probability to develop adenomas. The risk index is randomly drawn from a gamma distribution.

Adenoma incidence also varies with age. The age-specific adenoma incidence rate can differ by birth cohort to reflect differences in relative risk between birth cohorts.

Multiple adenomas

Development of a new adenoma in a person is assumed to be independent of the number of adenomas already present. The development of this adenoma is also independent of the development of other adenomas.

Adenoma types

MISCAN-COLON distinguishes two types of adenomas¹: non-progressive and progressive adenomas. The probability for an adenoma to be progressive is age-dependent.

Note 1:

- Hyperplastic polyps are not modeled because we assume that hyperplastic polyps never grow into a cancer. Since their removal has no influence on incidence and mortality they are not included in MISCAN-COLON. In cost-effectiveness analyses the costs of removal of hyperplastic polyps will be accounted for.
- Flat adenomas are implicitly modeled as progressive adenomas that have short duration before developing into invasive states.

Non-progressive adenomas



[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Key References](#)

Non–progressive adenomas never develop into an invasive state. These lesions can only transit through the states: adenoma ≤ 10 mm. Some of the non–progressive adenomas never develop into an adenoma ≥ 10 mm.

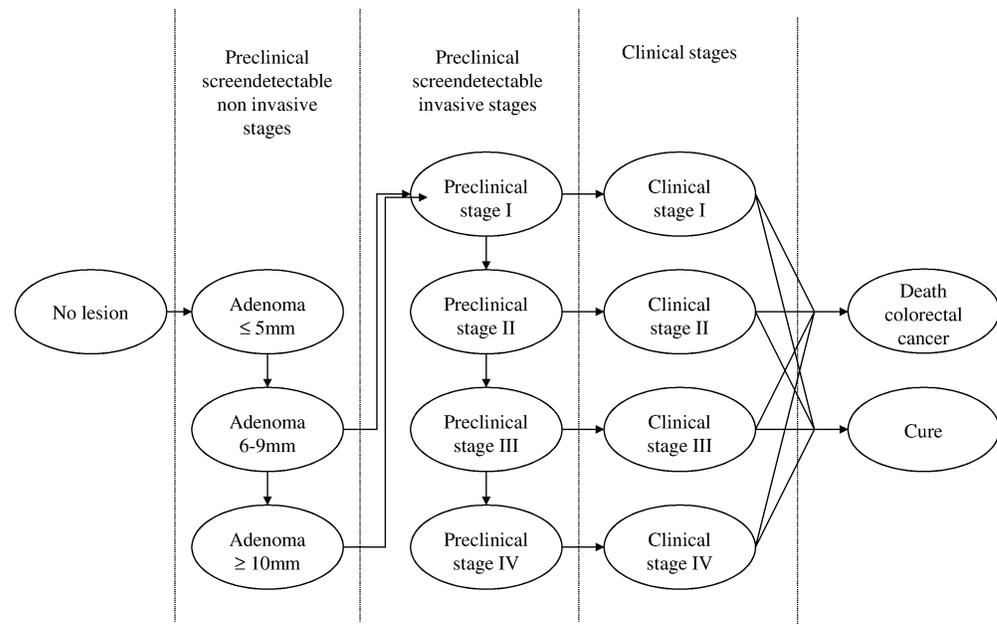
Progressive adenomas and cancer

Progressive adenomas are assumed to eventually develop into colorectal cancer (although a person may die from other causes before the cancer actually has developed). In this development the following states are possible:

1. progressive adenoma
2. progressive adenoma 6–9mm
3. progressive adenoma ≥ 10 mm
4. preclinical colorectal cancer, stage I
5. preclinical colorectal cancer, stage II
6. preclinical colorectal cancer, stage III
7. preclinical colorectal cancer, stage IV
8. clinical colorectal cancer, stage I
9. clinical colorectal cancer, stage II
10. clinical colorectal cancer, stage III
11. clinical colorectal cancer, stage IV

Possible transitions between the different states are explained in figure 1:

Figure 1: Adenoma–carcinoma sequence for progressive adenomas



Adaptation in the CISNET project: We will consider extending the adenoma–carcinoma sequence with extra adenoma states. These states depend on the histology in the adenoma. Possible adenomas that are added, are adenomas with high–grade dysplasia, tubular, tubular–villous and villous adenomas. In addition, we will consider adding a separate pathway for sessile serrated lesions, which would include hyperplastic polyps.

Transition probabilities

Each transition in figure 1 has a certain probability to occur. The transition probabilities can depend on age of the patient and localization of the adenoma. Transition probabilities are independent of risk exposure.

State duration

All transitions above have a certain duration distribution. This distribution can be assumed dependent of age and location of the lesion. We assume all durations to be exponentially distributed. We assume a positive correlation between duration in successive states. Durations are independent of risk exposure.

Anatomical site of adenomas

For every adenoma an anatomical site is determined. The anatomical site of a new polyp is independent of the anatomical site of previous polyps. We distinguish the following sites of the large bowel:

1. Rectum
2. Rectosigmoid + rectosigmoid junction
3. Sigmoid
4. Descending Colon
5. Hepatic Flexure + transverse colon + splenic flexure
6. Ascending colon
7. Cecum

Cancer incidence for which localization is not otherwise specified is proportionally distributed over the possible localizations. The site distribution for progressive and non–progressive adenomas is assumed to be equal.

Survival rates

After clinical diagnosis of one cancer all adenomas and cancers in a certain person are assumed to be clinical. The model generates a stage–specific survival for the most advanced clinically diagnosed cancer. The patient dies from colorectal cancer at the moment this colorectal cancer reaches death. Survival depends on year of diagnosis, age at diagnosis, localization of the cancer and stage of disease.

REFERENCES FOR MODEL PARAMETERS

Below is a list of references used in parameter estimation. For a complete list of references see: [Key References](#).



Readers Guide
Model Overview
Assumption Overview
Parameter Overview
Component Overview
Output Overview
Results Overview
Key References

- Atkin, W. S., Edwards, R., Kralj-Hans, I., Wooldrage, K., Hart, A. R., Northover, J. M., Parkin, D. M., Wardle, J., Duffy, S. W., Cuzick, J., U.K. Flexible Sigmoidoscopy Trial Investigators** (2010) Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial in *Lancet* 375:9726, p 1624–33
- Disario, JA, Foutch, PG, Mai, HD, Pardy, K, Manne, RK** (1991) Prevalence and malignant potential of colorectal polyps in asymptomatic, average-risk men in *Am J Gastroenterol* 86, p 941–5
- Hardcastle, JD, Chamberlain, J, Sheffield, J, Balfour, TW, Armitage, NC, Thomas, WM** (1989) Randomised, controlled trial of faecal occult blood screening for colorectal cancer in *Lancet* i, p 1160–4
- Hardcastle, JD, Chamberlain, JO, Robinson, MH, Moss, SM, Amar, SS, Balfour, TW, James, PD, Mangham, CM** (1996) Randomised controlled trial of faecal-occult-blood screening for colorectal cancer in *Lancet* 348:9040, p 1472–7
- Johnson, DA, Gurney, MS, Volpe, RJ, Jones, DM, VanNess, MM, Chobanian, SJ** (1990) A prospective study of the prevalence of colonic neoplasms in asymptomatic patients with an age-related risk in *Am, J Gastroenterol* 85, p 969–74
- Koretz, RL** (1993) Malignant polyps: are they sheep in wolves' clothing? in *Ann Intern Med* 118, p 63–8
- Kronborg, O, Fenger, C, Olsen, J, Bech, K, Søndergaard, O** (1989) Repeated screening for colorectal cancer with fecal occult blood test. A prospective study at Funen, Denmark. in *Scand J Gastroenterol* 24, p 599–606
- Kronborg, O, Fenger, C, Olsen, J, Jorgensen, OD, Søndergaard, O** (1996) Randomised study of screening for colorectal cancer with faecal-occult-blood test. in *Lancet* 348, p 1467–71
- Lieberman, DA, Smith, FW** (1991) Screening for colon malignancy with colonoscopy in *Am J Gastroenterol* 86, p 946–51
- Mandel, JS, Bond, JH, Church, TR, Snover, DC, Bradley, M, Schuman, LM** (1993) Reducing mortality from colorectal cancer by screening for fecal occult blood in *N Engl J Med* 328, p 1365–71
- Neugut, AI, Pita, S** (1988) Role of sigmoidoscopy in screening for colorectal cancer: a critical review in *Gastroenterology* 95, p 492–9
- Neugut, AI, Young, GP** (1996) Screening for colorectal cancer: an overview. In: *Prevention and early Detection of Colorectal Cancer*
- Rex, DK, Lehman, GA, Hawes, RH, Ulbright, TM, Smith, JJ** (1991) Screening colonoscopy in asymptomatic average-risk persons with negative fecal occult blood tests. in *Gastroenterology* 100, p 64–7



Rickert, RR, Auerbach, O, Garfinkel, L, Hammond, EC, Frasca, JM (1979)
Adenomatous lesions of the large bowel in *Adenomatous lesions of the large bowel*
Cancer 43, p 1847–57

Thomas, WM, Hardcastle, JD, Walker, AR (1992) Screening for colorectal carcinoma: an analysis of the sensitivity of haemoccult.
in *Br J Surg* 79, p 833–5

Williams, AR, Balasooriya, BAW, Day, DW (1982) Polyps and cancer of the large bowel: a necropsy study in Liverpool in *Gut* 23, p 835–42



KEY REFERENCES

- Akker-van Marle, ME, van den, Ballegooijen, M, van Oortmarsen, GJ, van Boer, R, Habbema, JDF** (2002) Cost-effectiveness of cervical cancer screening: comparison of screening policies in *J Natl Cancer Inst* 94, p 193–204
- Atkin, W. S., Edwards, R., Kralj-Hans, I., Wooldrage, K., Hart, A. R., Northover, J. M., Parkin, D. M., Wardle, J., Duffy, S. W., Cuzick, J., U.K. Flexible Sigmoidoscopy Trial Investigators** (2010) Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial in *Lancet* 375:9726, p 1624–33
- Berrington de González A, Kim KP, Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Smith-Bindman R, Yee J, Kuntz KM, van Ballegooijen M, Zauber AG, Berg CD** (2011) Radiation-related cancer risks from CT colonography screening: a risk-benefit analysis. in *Am J Roentgenol* 196:4, p 816–23
- Bradley CJ, Lansdorp-Vogelaar I, Yabroff KR, Dahman B, Mariotto A, Feuer EJ, Brown ML.** (2011) Productivity savings from colorectal cancer prevention and control strategies. in *Am J Prev Med* 41:2, p e5–e14
- Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I.** (2014) Optimising the expansion of the National Bowel Cancer Screening Program. in *Med J Aust* 201:8, p 456–61
- Disario, JA, Foutch, PG, Mai, HD, Pardy, K, Manne, RK** (1991) Prevalence and malignant potential of colorectal polyps in asymptomatic, average-risk men in *Am J Gastroenterol* 86, p 941–5
- Edwards BK, Ward E, Kohler BA, Ehemann C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA.** (2010) Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates in *Cancer* 116:3, p 544–73
- Goede SL, van Roon AH, Reijerink JC, van Vuuren AJ, Lansdorp-Vogelaar I, Habbema JD, Kuipers EJ, van Leerdam ME, van Ballegooijen M.** (2013) Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening. in *Gut* 62:5, p 727–34
- Habbema, JD, Oortmarsen, GJ van, Lubbe, JT, Maas, PJ van der** (1985) The MISCAN simulation program for the evaluation of screening for disease in *Comput Methods Programs Biomed* 20:1, p 79–93
- Hardcastle, JD, Chamberlain, J, Sheffield, J, Balfour, TW, Armitage, NC, Thomas, WM** (1989) Randomised, controlled trial of faecal occult blood screening for colorectal cancer in *Lancet* i, p 1160–4
- Hardcastle, JD, Chamberlain, JO, Robinson, MH, Moss, SM, Amar, SS, Balfour, TW, James, PD, Mangham, CM** (1996) Randomised controlled trial of faecal-occult-blood screening for colorectal cancer in *Lancet* 348:9040, p 1472–7
- Johnson, DA, Gurney, MS, Volpe, RJ, Jones, DM, VanNess, MM, Chobanian, SJ** (1990) A prospective study of the prevalence of colonic neoplasms in asymptomatic patients with an age-related risk in *Am, J Gastroenterol* 85, p 969–74
- Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Savarino JE, van Ballegooijen M, Kuntz KM, Zauber AG.** (2010) Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the medicare population. in *J Natl Cancer Inst* 102:16, p 1238–52

- Koning, HJ, de Boer, R, Warmerdam, PG, Beemsterboer, PMM, Maas, PJ van der** (1995) Quantitative interpretation of age-specific mortality reductions from the Swedish breast cancer-screening trials in *J Natl Cancer Inst* 87:16, p 1217–23
- Koretz, RL** (1993) Malignant polyps: are they sheep in wolves' clothing? in *Ann Intern Med* 118, p 63–8
- Kronborg, O, Fenger, C, Olsen, J, Bech, K, Søndergaard, O** (1989) Repeated screening for colorectal cancer with fecal occult blood test. A prospective study at Funen, Denmark. in *Scand J Gastroenterol* 24, p 599–606
- Kronborg, O, Fenger, C, Olsen, J, Jorgensen, OD, Søndergaard, O** (1996) Randomised study of screening for colorectal cancer with faecal-occult-blood test. in *Lancet* 348, p 1467–71
- Kuntz KM, Lansdorp-Vogelaar I, Rutter CM, Knudsen AB, van Ballegooijen M, Savarino JE, Feuer EJ, Zauber AG** (2011) A systematic comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression. in *Med Decis Making* 31:4, p 530–9
- Lansdorp-Vogelaar I, Goede SL, Ma J, Xiau-Cheng W, Pawlish K, van Ballegooijen M, Jemal A.** (2014) State disparities in colorectal cancer rates – contribution of risk factors, screening and survival differences in *Manuscript under review.*,
- Lansdorp-Vogelaar I, Gulati R, Mariotto AB, Schechter CB, de Carvalho TM, Knudsen AB, van Ravesteyn NT, Heijnsdijk EA, Pabiniak C, van Ballegooijen M, Rutter CM, Kuntz KM, Feuer EJ, Etzioni R, de Koning HJ, Zauber AG, Mandelblatt JS.** (2014) Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits. in *Ann Intern Med* 161:2, p 104–12
- Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, Wilschut JA, Zauber AG, van Ballegooijen M.** (2010) Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. in *Ann Intern Med* 153:6, p 368–77
- Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, van Ballegooijen M, Zauber AG, Jemal A.** (2012) Contribution of screening and survival differences to racial disparities in colorectal cancer rates. in *Cancer Epidemiol Biomarkers Prev* 21:5, p 728–36
- Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, Zauber AG, Habbema JDF** (2009) A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials in *Cancer* 115:11, p 2410–9
- Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut JA, Habbema JDF.** (2009) At what costs will screening with CT colonography be competitive? A cost-effectiveness approach. in *Int J Cancer* 124:5, p 1161–8
- Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut JA, Winawer SJ, Habbema JDF** (2009) Individualizing colonoscopy screening by sex and race in *Gastrointest Endosc* 70:1, p 96–108
- Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JDF, Kuipers EJ** (2009) Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening in *J Natl Cancer Inst* 101:20, p 1412–22
- Lieberman, DA, Smith, FW** (1991) Screening for colon malignancy with colonoscopy in *Am J Gastroenterol* 86, p 946–51

- Loeve F, Zauber AG, Van Ballegooijen M, Van Oortmarsen GJ, Winawer SJ, Habbema JD** (2004) National Polyp Study data: evidence for regression of adenomas. in *International Journal of Cancer* 111:4, p 633–9
- Loeve, F, Boer, R, Oortmarsen, GJ, van Ballegooijen, M, van Habbema, JDF** (1999) The MISCAN–COLON simulation model for the evaluation of colorectal cancer screening in *Comput Biomed Res* 32, p 13–33
- Loeve, F, Brown, ML, Boer, R, Ballegooijen, M, van Oortmarsen, GJ, van Habbema, JDF** (2000) Endoscopic colorectal cancer screening: a cost–saving analysis
92:7, p 557–63
- Loeve, F., Boer, R., van Ballegooijen, M., van Oortmarsen, G. J., Habbema, J. D. F.** (1998) Final Report MISCAN–COLON Microsimulation Model for Colorectal Cancer: Report to the National Cancer Institute Project No. NO1–CN55186 in *Department of Public Health, Erasmus University. Rotterdam, The Netherlands.*,
- Mandel, JS, Bond, JH, Church, TR, Snover, DC, Bradley, M, Schuman, LM** (1993) Reducing mortality from colorectal cancer by screening for fecal occult blood in *N Engl J Med* 328, p 1365–71
- Morson, B** (1974) The polyp–cancer sequence in the large bowel in *Proc R Soc Med* 67, p 451–7
- Nagengast FM, Kaandorp CJ** (2001) Revised CBO guideline 'Follow–up after polypectomy' in *Nederlands Tijdschrift voor de Geneeskunde* 145:42, p 2022–5
- Neddermeijer HG, Piersma N, van Oortmarsen GJ, Habbema JDF, Dekker R.** (1999) Comparison of response surface methodology and the Nelder and Mead simplex method for optimization in microsimulation models in *Econometric Institute,*
- Nelder, JA, Mead, R** (1965) A simplex method of function minimization in *Computer Journal* 7, p 308–312
- Neugut, AI, Pita, S** (1988) Role of sigmoidoscopy in screening for colorectal cancer: a critical review in *Gastroenterology* 95, p 492–9
- Neugut, AI, Young, GP** (1996) Screening for colorectal cancer: an overview. In: *Prevention and early Detection of Colorectal Cancer*
- Ramsey SD, Wilschut J, Boer R, van Ballegooijen M.** (2010) A decision–analytic evaluation of the cost–effectiveness of family history–based colorectal cancer screening programs. in *Am J Gastroenterol* 105:8, p 1861–9
- Rex, DK, Lehman, GA, Hawes, RH, Ulbright, TM, Smith, JJ** (1991) Screening colonoscopy in asymptomatic average–risk persons with negative fecal occult blood tests. in *Gastroenterology* 100, p 64–7
- Rickert, RR, Auerbach, O, Garfinkel, L, Hammond, EC, Frasca, JM** (1979) Adenomatous lesions of the large bowel in *Adenomatous lesions of the large bowel*
Cancer 43, p 1847–57
- Rutter CM, Knudsen AB, Marsh TL, Doria–Rose VP, Johnson E, Pabiniak C, Kuntz KM, van Ballegooijeen M, Zauber AG, Lansdorp–Vogelaar I.** (2015) Validation to Inform Model Structure: Results from Three Colorectal Cancer Microsimulation Models in [*Manuscript in preparation*],
- Thomas, WM, Hardcastle, JD, Walker, AR** (1992) Screening for colorectal carcinoma: an analysis of the sensitivity of haemoccult. in *Br J Surg* 79, p 833–5

- Vanness DJ, Knudsen AB, Lansdorp–Vogelaar I, Rutter CM, Gareen IF, Herman BA, Kuntz KM, Zauber AG, van Ballegooijen M, Feuer EJ, Chen MH, Johnson CD.** (2011) Comparative economic evaluation of data from the ACRIN National CT Colonography Trial with three cancer intervention and surveillance modeling network microsimulations. in *Radiology* 261:2, p 487–98
- Vogelaar I, van Ballegooijen M, Schrag D, Boer R, Winawer SJ, Habbema JDF, Zauber AG.** (2006) How much can current interventions reduce colorectal cancer mortality in the U.S.? Mortality projections for scenarios of risk-factor modification, screening, and treatment. in *Cancer* 107:7, p 1624–33
- Vogelstein, B, Fearon, ER, Hamilton, SR, Kern, SE, Preisinger, AC, et al.** (1988) Genetic alterations during colorectal–tumor development. in *N Engl J Med* 319:9, p 525–32
- Williams, AR, Balasooriya, BAW, Day, DW** (1982) Polyps and cancer of the large bowel: a necropsy study in Liverpool in *Gut* 23, p 835–42
- Wilschut JA, Habbema JD, van Leerdam ME, Hol L, Lansdorp–Vogelaar I, Kuipers EJ, van Ballegooijen M** (2011) Fecal occult blood testing when colonoscopy capacity is limited. in *J Natl Cancer Inst* 103:23, p 1741–51
- Wilschut JA, Hol L, Dekker E, Jansen JB, Van Leerdam ME, Lansdorp–Vogelaar I, Kuipers EJ, Habbema JD, Van Ballegooijen M.** (2011) Cost–effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. in *Gastroenterology* 141:5, p 1648–55
- Wilschut JA, Steyerberg EW, van Leerdam ME, Lansdorp–Vogelaar I, Habbema JD, van Ballegooijen M.** (2011) How much colonoscopy screening should be recommended to individuals with various degrees of family history of colorectal cancer? in *Cancer* 117:18, p 4166–74
- Zauber AG, Knudsen AB, Rutter CM, et al.** (2009) Cost–Effectiveness of CT Colonography to Screen for Colorectal Cancer. in *Online report*,
- Zauber AG, Lansdorp–Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM** (2008) Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. in *Ann Intern Med* 149:9, p 659–69
- Zauber AG, Lansdorp–Vogelaar I, Wilschut J, Knudsen AB, van Ballegooijen M, Kuntz KM.** (2007) Cost–Effectiveness of DNA Stool Testing to Screen for Colorectal Cancer: Report to AHRQ and CMS from the Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN and SimCRC Models in *Online report*,
- Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp–Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Wayne JD.** (2012) Colonoscopic polypectomy and long–term prevention of colorectal–cancer deaths in *N Engl J Med* 366:8, p 687–96
- van Ballegooijen M, Habbema JDF, Boer R, Zauber AG, Brown ML.** (2003) Report to the Agency for Healthcare Research and Quality: a comparison of the cost–effectiveness of fecal occult blood tests with different test characteristics in the context of annual screening in t in *Online report*,
- van Ballegooijen M, Rutter CM, Knudsen AB, Zauber AG, Savarino JE, Lansdorp–Vogelaar I, Boer R, Feuer EJ, Habbema JD, Kuntz KM.** (2011) Clarifying differences in natural history between models of screening: the case of colorectal cancer. in *Med Decis Making* 31:4, p 540–9
- van Hees F, Habbema JD, Meester RG, Lansdorp–Vogelaar I, van Ballegooijen M, Zauber AG.** (2014) Should colorectal cancer screening be considered in elderly persons without previous screening? A cost–effectiveness analysis. in *Ann Intern Med* 160:11, p 750–9



MSK/Erasmus
Key References

van Hees F, Zauber AG, Klabunde CN, Goede SL, Lansdorp–Vogelaar I, van Ballegooijen M. (2014) The appropriateness of more intensive colonoscopy screening than recommended in medicare beneficiaries: a modeling study. in *JAMA Intern Med* 174:10, p 1568–76

van der Steen A, Knudsen AB, van Hees F, Walter GP, Berger FG, Daguise VG, Kuntz KM, Zauber AG, van Ballegooijen M, Lansdorp–Vogelaar I. Optimal Colorectal Cancer Screening in States' Low–Income, Uninsured Populations–The Case of South Carolina. in *Health Serv Res.* 2014 Oct 16. doi: 10.1111/1475–6773.12246. [Epub ahead of print],
