Combined Model Profile
Version: 1.0.00
Released: 2025-09-30

Colorectal Cancer Combined Model Profile

Individual Model Profiles

[Colorectal Cancer Simulated Population model for Incidence and Natural history (CRC-SPIN): Model Profile]
Fred Hutchinson Cancer Center
Version: 2.0.00
Released: 2025-09-30

[MIcrosimulation SCreening ANalysis Colorectal Cancer Model (MISCAN-Colon): Model Profile]
Erasmus University Medical Center/Memorial Sloan Kettering
Version: 1.0.00
Released: 2025-09-30

[Simulation Model of Colorectal Cancer (SimCRC): Model Profile]
Stanford University
Massachusetts General Hospital, Harvard University
University of Minnesota
Version: 1.0.00
Released: 2025-09-30

Suggested citation

CISNET Colorectal Working Group. Colorectal Cancer Combined Model Profile. [Internet] Sep 30, 2025. Cancer Intervention and Surveillance Modeling Network (CISNET). Available from: https://cisnet.cancer.gov/resources/files/mpd/colorectal/CISNET-colorectal-combined-model-profile-1.0.00-2025-09-30.pdf

Combined Model Profile Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.11302018.9755	2018-11-30	Historical release

Fred Hutchinson Cancer Center
Version: 2.0.00
Released: 2025-09-30

Colorectal Cancer Simulated Population model for Incidence and Natural history (CRC-SPIN): Model Profile

Fred Hutchinson Cancer Center

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Version Table

Version	Date	Notes
2.0.00	2025-09-30	Major update
1.0.00	2018-11-30	Historical release

Documentation Note: A major model update, which includes the serrated pathway, is underway and will be released upon publication.

Other Publications

- Rutter CM, Savarino JE. An Evidence-Based Microsimulation Model for Colorectal Cancer: Validation and Application. Cancer Epidemiology Biomarkers & Prevention. 2010 Aug;19(8):1992–2002. PMCID: PMC2919657
- Rutter CM, Ozik J, DeYoreo M, Collier N. Microsimulation model calibration using incremental mixture approximate Bayesian computation. The Annals of Applied Statistics. 2019 Dec 1;13(4):2189–2212. PMCID: PMC8534811
- DeYoreo M, Rutter CM, Ozik J, Collier N. Sequentially calibrating a Bayesian microsimulation model to incorporate new information and assumptions. BMC Med Inform Decis Mak. 2022 Jan 12;22(1):12. PMCID: PMC8756687

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Readers Guide

Fred Hutch Cancer Center

Reader's 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.

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

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

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.[1] CRC-SPIN 2.0 and later model versions were calibrated using an Incremental Mixture Approximate Bayesian Computation approach, which is a likelihood-free approach.[2] 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.*

References

1. Carolyn M. Rutter, Diana L. Miglioretti, James E. Savarino. Bayesian Calibration of Microsimulation Models. Journal of the American Statistical Association. 2009 Dec;104(488):1338–1350. PMCID: PMC2805837
2. Carolyn M. Rutter, Jonathan Ozik, Maria DeYoreo, Nicholson Collier. Microsimulation Model Calibration Using Incremental Mixture Approximate Bayesian Computation. The Annals of Applied Statistics. 2019 Dec;13(4):2189–2212. PMCID: PMC8534811

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[1])

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.

Contributors

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References

1. Carolyn M Rutter, Eric A Johnson, Eric J Feuer, Amy B Knudsen, Karen M Kuntz, Deborah Schrag. Secular Trends in Colon and Rectal Cancer Relative Survival. Journal of the National Cancer Institute. 2013 Dec;105(23):1806–1813. PMCID: PMC3848985

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(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.

Adenoma growth assumptions

CRC-SPIN simulates adenoma growth using a Richard's growth model.[1] 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.[2]
- Future models that incorporate race will specify survival that also depends on race.

References

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2. Carolyn M Rutter, Eric A Johnson, Eric J Feuer, Amy B Knudsen, Karen M Kuntz, Deborah Schrag. Secular Trends in Colon and Rectal Cancer Relative Survival. Journal of the National Cancer Institute. 2013 Dec;105(23):1806–1813. PMCID: PMC3848985

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.[1]

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}, $k = 1, \ldots, 4$. 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

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

References

1. Carolyn M. Rutter, Jonathan Ozik, Maria DeYoreo, Nicholson Collier. Microsimulation Model Calibration Using Incremental Mixture Approximate Bayesian Computation. The Annals of Applied Statistics. 2019 Dec;13(4):2189–2212. PMCID: PMC8534811

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Component Overview

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 transiting 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,[1] 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).

References

1. Carolyn M. Rutter, Onchee Yu, Diana L. Miglioretti. A Hierarchical Non-Homogenous Poisson Model for Meta-Analysis of Adenoma Counts. Statistics in Medicine. 2007 Jan;26(1):98–109. PMCID: PMC4189839

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 preclincal 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.

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 calibratedl using Incremental Mixture Approximate Bayesian Calibration (IMABC), a likelihood-free approach. Bayesian calibration has several advantages over frequentist calibration methods, including the ability to simultaneous 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.md"?TAId=58

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- Vanness DJ, Knudsen AB, Lansdorp-Vogelarr 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. PMCID: PMC3198218.
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- 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. PMCID: PMC5009464.
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Transition To Preclinical CRC component

Summary

Transition to preclinical CRC is modeled as a function of adenoma size. Thus, the CRC-SPIN transition model is based on 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 jth adenoma within the ith agent.[1]

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 = 1mm to d_∞ = 50mm. 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,

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

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 Frèchet 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[2] 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 on autopsy study results of Nusko and colleagues (1997).[3] 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.[4]

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:

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

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:

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

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: γ_0, $\gamma_1, \ldots, \gamma_7$, and σ_γ, the standard deviation of the underlying standard deviation.

Relative 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.

References

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Transition To Clinical CRC Component

Transition To Clinical CRC Component

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).

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

  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 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[1]

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*). # References 1. Carolyn M Rutter, Eric A Johnson, Eric J Feuer, Amy B Knudsen, Karen M Kuntz, Deborah Schrag. Secular Trends in Colon and Rectal Cancer Relative Survival. Journal of the National Cancer Institute. 2013 Dec;105(23):1806–1813. PMCID: PMC3848985

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Natural History Component

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.

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.

Detail

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 transiting 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 compents (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

Relative 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. .

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Log Normal

If $log(x)$ is Normally distributed with mean ξ and standard deviation ν, then x is Log Normally distributed with mean $\mu = exp(\xi + \frac{1}{2}\nu^2)$ and standard deivation $\tau\mu$, where $\tau = \sqrt{exp(\nu^2) - 1}$.

See Chapter 14 of Johnson and Kotz (1970), "Continuous Univariate Distributions - 1" (Wiley) for details.[1]
References

1. Johnson, Norman L, Kotz, Samuel. Continuous Univariate Distributions - 1. New York: John Wiley and Sons; 1970.

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Adenoma Risk Component

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.[1] 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 ith 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 ith agent at time t is given by

$$\psi_i(t) = exp\Big(\alpha_{0i} + \alpha_1 sex_i + \sum_{k=1}^{4} \delta(A_k < age_i(t) \leq A_{k+1})\Big\{age_i(t)\alpha_{2k} + \sum_{j=2}^{k} A_j(\alpha_{2\,j-1} - \alpha_{2j})\Big\}\Big)$$

where α_{0i} describes an agent's baseline risk; α_1 describes the difference in risk for women ($sex_i = 0$) relative men ($sex_i = 1$); α_{2k} describes changes in risk with age (in years) in the kth interval; and $\delta()$ 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 $\Psi_i(t) = \int_{20}^{age(t)} \psi_i(u)du$, given by

$$\Psi_i(t) = e^{\alpha_{0i}+\alpha_1 sex_i} \sum_{k=1}^{4}\Big\{\delta(age_i(t) > A_k)\Big(\frac{e^{\alpha_{2k} min(A_{k+1}, age_i(t))} - e^{\alpha_{2k}A_k}}{\alpha_{2k}}\Big) exp\Big(\sum_{j=2}^{k} A_j(\alpha_{2\,j-1} - \alpha_{2j})\Big)\Big\}$$

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.[2]

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 $\geq$ 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.

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 Normal(α_0,σ_α) 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
- $\alpha_{2k}, k = 1, \ldots, 4$, The effect of age on risk.

Relative 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.

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MIcrosimulation SCreening ANalysis Colorectal Cancer Model (MISCAN-Colon): Model Profile

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.03122015.70025	2015-12-03	Historical release

Other Publications

- Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res. 1999;32(1):13-33. doi:10.1006/cbmr.1998.1498
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Reader's 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.

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

Definitions 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 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.

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1. Morson, B. The polyp-cancer sequence in the large bowel. Proc R Soc Med. 1974;67:451–7.
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Erasmus MC/Memorial Sloan Kettering
Model Overview

Model Overview

Summary

MISCAN-Colon is designed to analyze trends in colorectal cancer. MISCAN-Colon is a microsimulation model, consisting of three parts:

- Demography part
- Natural history part
- Screening part

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

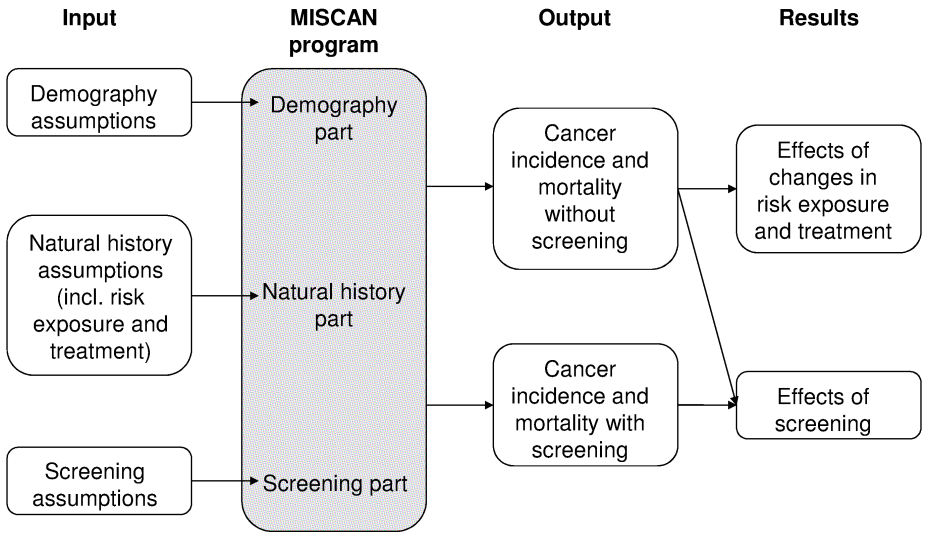
The MIcrosimulation SCreening ANalysis (MISCAN) computer program has been used for simulating cancers of the breast, cervix, colon, stomach, prostate, as well as for dementia [1-7]. MISCAN-Colon will simulate a population of persons in which colorectal cancer and its precursor lesion, the adenomatous 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 microsimulation 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.

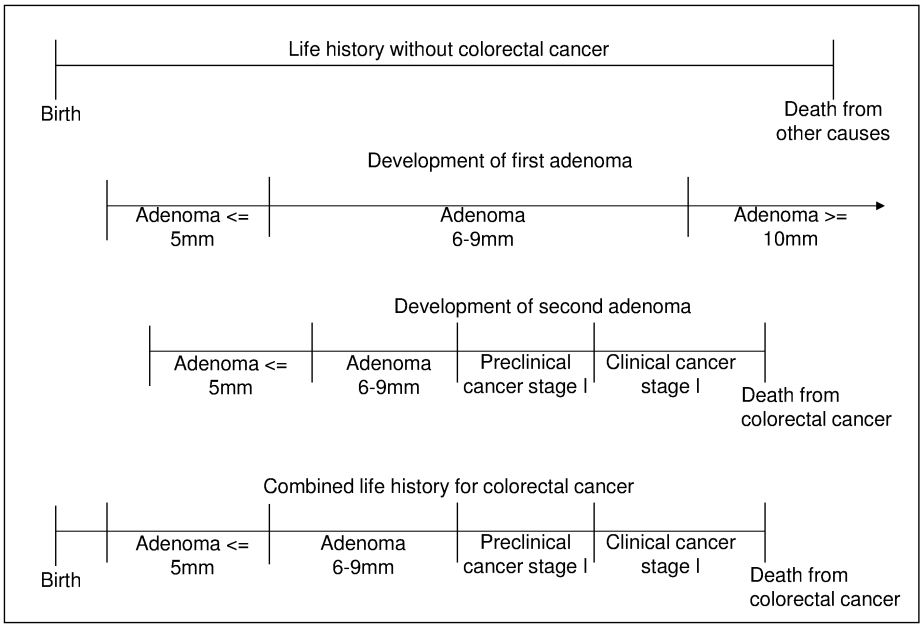
Subsequently the Natural History Component part of MISCAN-Colon simulates colorectal cancer histories (natural histories) for each individual life history separately. We based our natural history model on the adenoma-carcinoma sequence of Morson [8] and Vogelstein [9]. This means that adenomas are generated 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:

- non-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 they have. If they die from colorectal cancer before they die from other causes, their 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.

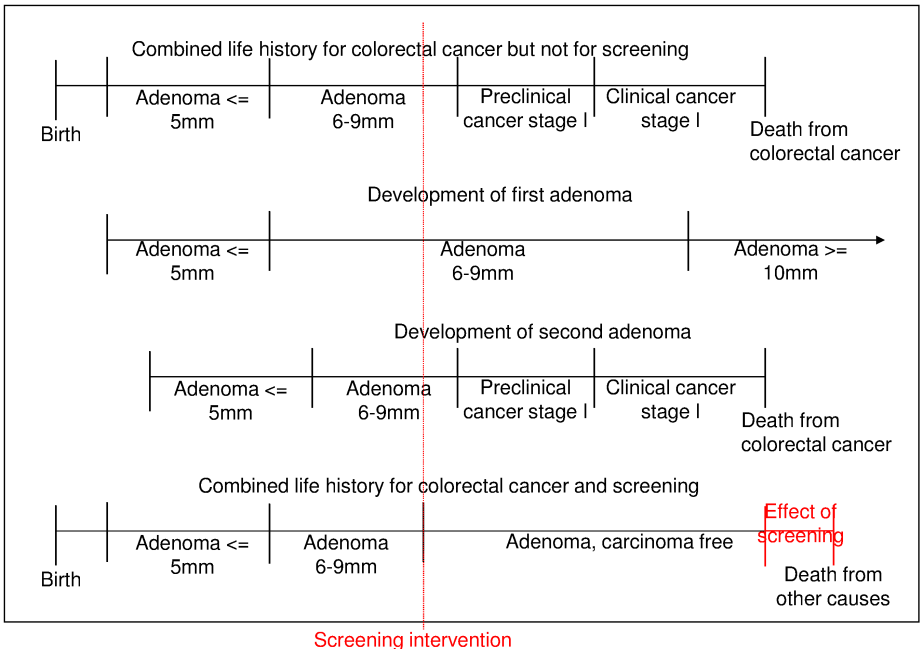
Figure 2a: Modeling natural history into life history



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.

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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 [1]. A description of the parameters specifying these guidelines can be found in the Parameter Overview section.

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Parameter Overview

Parameter Overview

Summary

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

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 the 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. age groups required in the output
2. year groups required in the output
3. number of persons to be simulated
4. overall seed for reproducibility or seeds for specific model parts

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.

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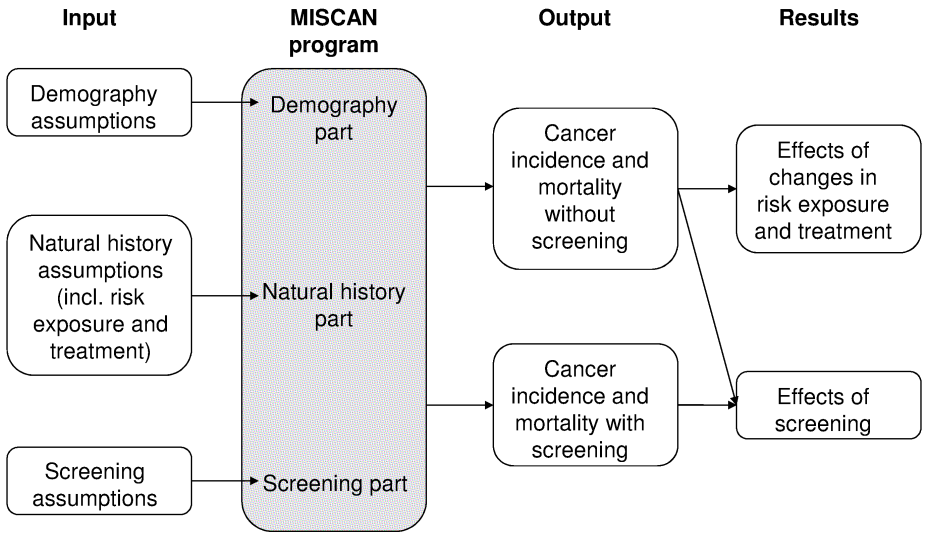
Component Overview

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.



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 has 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 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 they die from colorectal cancer before they die from other causes, their 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.

Output Listing

The following outputs can be calculated based on the final output of the model:

Base Case

1. Incidence counts by calendar year, location, stage and age
2. Mortality counts by calendar year and age
3. Population counts by each calendar year by age
4. Adenoma prevalence by calendar year, location, size, sex and agegroups
5. CRC prevalence by calendar year, stage, location and age

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 for the U.S. population. 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 in consecutive screening rounds. Varying sensitivity of FOBT by stage gave better results for Dukes A cancers detected, but still resulted in too many Dukes A cancers found 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 microsimulation model to examine the possibilities of 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, 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 [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 research and policy questions, supporting decision-making in colorectal cancer (CRC) screening at national, state, and international levels. These applications fall into three main areas: directly informing policy, indirectly informing policy, and advancing model methodology and validation.

Applications that Directly Inform Policy

MISCAN-Colon has been used to inform CRC screening policy in the United States and internationally. The model has directly informed national guidelines, such as those issued by the US Preventive Services Task Force [8,9], and contributed to policy decisions regarding the implementation and optimization of screening programs at both state and international levels [10-13]. For example, the model was used to identify optimal screening scenarios for underserved rural areas of South Carolina [14], and to estimate how differences in risk factors, screening, and treatment explain CRC mortality differences in New Jersey and Louisiana (manuscript in preparation). Internationally, MISCAN-Colon has supported projects in Canada and Australia, and has been used to inform the Dutch national FIT screening program. The model has also evaluated the impact of policy changes, such as the introduction of new screening modalities, adjustments to screening intervals, and responses to public health emergencies like the COVID-19 pandemic [15-20].

Applications that Indirectly Inform Policy

Many MISCAN-Colon applications have examined policy-relevant issues by evaluating and optimizing CRC screening strategies, as well as assessing cost-effectiveness. Studies have assessed the effectiveness of different screening intervals, starting and stopping ages [21-23], and the use of risk factors such as comorbidity and family history to personalize screening recommendations [24-28]. The model has compared the benefits of various screening modalities (e.g., FIT, colonoscopy, sigmoidoscopy) [29-32], and explored the impact of adherence, demographic differences, and emerging technologies [33,34].

The model has also been used extensively to assess the cost-effectiveness of CRC screening strategies, including the introduction of new tests, risk-stratified approaches, and programmatic changes [35-44]. These analyses have informed reimbursement decisions, guided the adoption of innovative technologies, and provided evidence for the efficient allocation of healthcare resources. By quantifying both the costs and health outcomes associated with different screening options, MISCAN-Colon has helped ensure that policy decisions are grounded in value-based care.

Model Assumptions, Methodology, and Validation

Applications that provide insight into model performance and relationships between assumptions and model output are critical to thoughtful model application. MISCAN-Colon has undergone rigorous validation and methodological development. Studies in this area have focused on external and predictive validation, comparative modeling, and the refinement of key model assumptions [6,45,46,47,48,49,50,51,52,53,54,55,56,57,58]. This body of work underpins the model's use in high-stakes policy settings and supports its ongoing evolution in response to new scientific evidence and analytic challenges.

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Natural History Component

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 has 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 ReferencesForModelParameters), expert opinion and SEER-data.

Detail

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 <=5mm
- non-progressive adenoma 6-9mm
- non-progressive adenoma >=10mm

Preclinical non-invasive states

- progressive adenoma <=5mm
- progressive adenoma 6-9mm
- progressive adenoma >=10mm

Preclinical invasive states

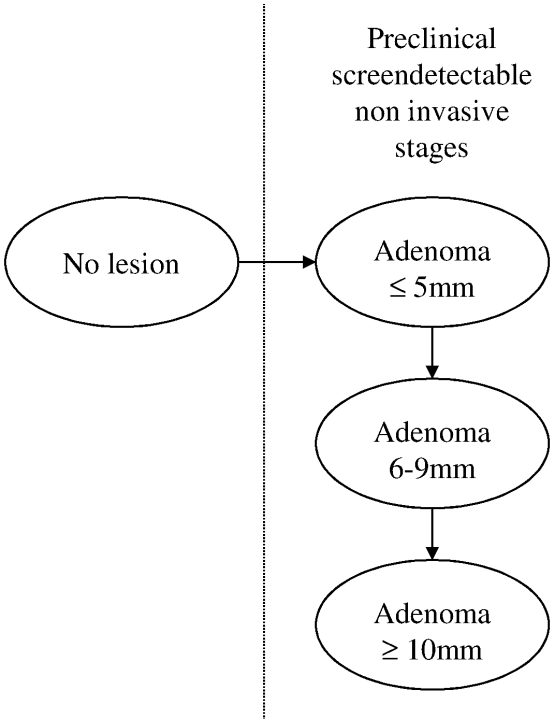
- preclinical colorectal cancer, stage I
- preclinical colorectal cancer, stage II
- preclinical colorectal cancer, stage III
- preclinical colorectal cancer, stage IV

Clinical invasive states

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

Temporal aspects
The possible transitions between the different states are explained in Figures 1 below and Figure 1 of the Natural History Assumptions section.

Figure 1: Non-progressive adenoma sequence



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
3. Sigmoid
4. Descending Colon
5. Transverse Colon
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. In MISCAN, we use an adaptation of the Nelder and Mead Simplex Method [1,2]or genetic algorithms 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.

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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 develop 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 adenomas[1]: non-progressive and progressive adenomas. The probability for an adenoma to be progressive is age-dependent.

[1]Note:

- 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
Non-progressive adenomas never develop into an invasive state. These lesions can only transit through the states: adenoma <=5mm, adenoma 6-9mm and adenoma >=10mm. Some of the non-progressive adenomas never develop into an adenoma >=10mm.

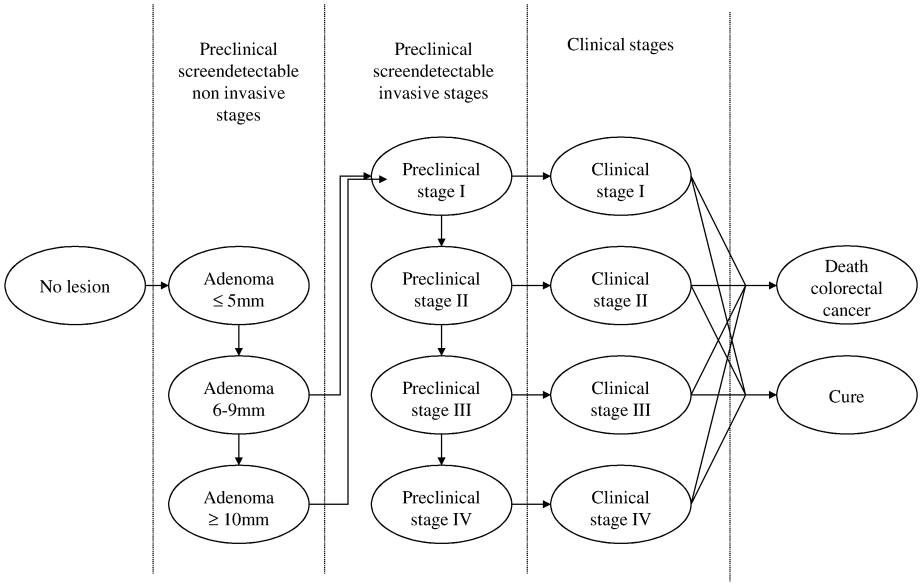
Progressive adenomas and cancer

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 <= 5mm
2. progressive adenoma 6-9mm
3. progressive adenoma >= 10mm
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



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
3. Sigmoid
4. Descending Colon
5. Transverse Colon
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 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.

Planned Model Extensions

Future updates to the model will incorporate additional lesion states, such as adenomas with high-grade dysplasia, tubular, tubulovillous, and villous adenomas. A distinct pathway for sessile serrated lesions, including hyperplastic polyps, is also under development.

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Simulation Model of Colorectal Cancer (SimCRC): Model Profile

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.03112015.70108	2015-03-11	Historical release

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Readers Guide

Reader's 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.

Parameter Overview
Describes the basic parameter set used to inform the model.

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

Output Overview
Definitions and methodologies for the basic model outputs.

Results Overview
A guide to the results obtained from the model.

Policy-Relevant Analyses
A guide to analyses with the model that were designed to inform policy decisions.

Methods-Relevant Analyses
A guide to relevant methodologic work.

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

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Model Purpose

Summary

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

Purpose

Simulation models can project outcomes for a population or cohort under several counterfactual scenarios to provide insight into an intervention or policy. SimCRC describes the evolution of the natural history of colorectal cancer (CRC) as discrete event state transitions in continuous time. For each simulated individual, 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, age, and an individual risk index that captures whether a person tends to produce more (or fewer) adenomas than average. Once initiated, each adenoma is assigned a location in the large intestine according to the location distribution of adenomas in autopsy studies, as well as an adenoma growth index that allows some adenomas to grow faster (or slower) than average. Some adenomas may progress to a Stage I preclinical CRC; a preclinical CRC can then progress to a more advanced stage or become symptomatic. SimCRC can be run in one of two ways: it can simulate multiple US population birth cohorts, resulting in output representative of the full cross section of the US population by calendar year (i.e., a "population-based simulation"), or it can simulate a single birth cohort from birth to death (i.e., a "single cohort simulation"). The type of model run varies depending on the purpose of the model application.

SimCRC contains:

1. population demographic;
2. a natural history component that tracks the adenoma-carcinoma sequence;
3. a screening component that allows for the detection and removal of adenomas during a screening year based on the test sensitivities and possibly an early diagnosis of preclinical CRC;
4. a surveillance module that follows individuals for a specified period after diagnosis with adenomas;
5. a cancer-specific survival module for all persons diagnosed with CRC.

The primary outcomes when running a population-based simulation include the model-predicted number of cases of CRC and the annual number of deaths from CRC among the US population by year. The primary outcomes when running a single cohort simulation include the model-predicted number of CRC cases, number of CRC deaths, and life years per 1000 persons alive at a given starting age. See Model Overview for a more detailed description of the Model.

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Model Overview

Summary

This document provides an overview of the structure of the Simulation Model of Colorectal Cancer (SimCRC) and its components.

Purpose

SimCRC 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.

Background

Colorectal cancer (CRC) is the second most common cause of cancer death in the United States. The age-adjusted CRC incidence rate each year has decreased from 66.2 per 100,000 persons in 1985 to 35.7 per 100,000 in 2019, representing a 46% decline over a span of 34 years.[1] This success is largely due to changes in risk factors in the population, such as decreased smoking rates and increased aspirin use[2], as well as increased uptake of screening.[3] CRC screening reduces cancer incidence by finding and removing precancerous lesions (i.e., adenomas and sessile serrated lesions), thereby preventing their progression to cancer. Screening also reduces cancer-related mortality by detecting cancers at earlier, more treatable stages. The US Preventive Services Task Force recommends that average-risk persons should be screened for CRC with one of several recommended tests starting at age 45 and ending at age 75 years.[4] The younger start age was informed in large part by the increased numbers of diagnosed persons who are younger than age 50.[5] Persons who have a precancerous finding(s) detected by screening are recommended to undergo colonoscopy surveillance, where surveillance intervals depend on the risk of the adenoma finding (e.g., adenoma size and number).[6]

Several clinical trials have shown that CRC screening strategies are effective in terms of reducing CRC incidence and mortality,[7] however, several currently-available CRC screening strategies have not been evaluated in trials. Because there are a many screening tests available, with several options for screening interval, start age, and stop age, clinical trials will unlikely be able to evaluate all possible strategies. Microsimulation models provide a tool for incorporating multiple sources of data (e.g., data from randomized trials, observational studies, and test accuracy studies). Models that are well validated to the resutls from existing trials provide an opportunity to project the health outcomes associated with a wide range of screening strategies that are not directly evaluated in a trial. Furthermore, comparing the results from multiple independently-developed models provides invaluable information. When the models agree, comparative modeling studies lend robustness to the model results. When the models yield different conclusions, these studies shed light on the areas where more data are needed.

Model Description

SimCRC is a microsimulation model of the adenoma-carcinoma sequence and the effects of screening that can be used to forecast incidence and mortality associated with CRC over the lifetimes of a single birth cohort or for the US population as a whole, by year. For each simulated person, SimCRC first generates a time of birth and a time of death from causes other than CRC.

SimCRC generates adenomas within an individual, with the age of onset for each adenoma drawn from a cumulative probability function that depends on sex, age, and an individual risk index that captures whether a person tends to produce more (or fewer) adenomas than average. Once initiated, each adenoma is assigned a location in the large intestine according to the location distribution of adenomas in autopsy studies. SimCRC simulates three adenoma categories: small/diminutive (1 to <6mm), medium (6 to <10mm), and large ($\geq$ 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. Each adenoma is randomly assigned an adenoma-specific growth index based on a truncated distribution that allows between-adenoma variability

in the probability of transitioning to larger sizes. The timing of transitions between adenoma size categories depends on age, sex, and location (proximal colon, distal colon, rectum). Medium and large adenomas may progress to preclinical CRC, although most will not in a person's lifetime. Progression depends on sex, and adenoma location.

Progression through preclinical cancer stages I through stage IV (distant metastasis) depends on sex and location. At each preclinical stage, SimCRC simulates whether there is a transition to symptomatic and clinically detected cancer as a function of stage and preclinical cancer location. After clinical detection, SimCRC simulates the survival time to death from CRC using relative survival estimates from SEER, utilizing an approach common across the three CISNET CRC models.

CRC survival time depends on age, calendar year, stage at detection, cancer location (colon or rectum), and sex. For individuals with synchronous CRCs at the time of diagnosis, SimCRC uses the stage-specific survival of the cancer with the highest stage. For all individuals with CRC, their death date is set to the earliest simulated death date (either due to CRC or other causes).[8]

Overlaid on the natural history of colorectal disease is a screening mechanism that allows for the detection of adenoma(s) and preclinical CRC(s). The likelihood of detection is a function of the screening modality (e.g., fecal immunochemical test [FIT], colonoscopy, or sigmoidoscopy) and the sensitivity of the test for lesions of a given size, and in the case of endoscopic tests, the reach of the scope. When modeling screening strategies, the chance that a screening test is performed depends on the screening algorithm (e.g., age to begin screening, age to end screening, and screening interval) 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), and year of diagnosis.

We assume all adenomas detected during colonoscopy are completely removed via polypectomy, although the model also has the ability to simulate incomplete resection. We assume that individuals with an adenoma detected are recommended to undergo colonoscopic surveillance. The frequency of surveillance is allowed to vary by the size and number of adenomas detected at the two most recent colonoscopies, thereby enabling the option for surveillance to be performed consistent with the 2020 US Multi-Society Task Force on Colorectal Cancer recommendations.[6] Simulated individuals are allowed to be adherent or non-adherent with surveillance. The model can also be run assuming no surveillance of individuals who have had adenomas detected.

Model Calibration

SimCRC 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;[9] (2) the location and size/histology of lesions from two colonoscopy screening studies [10,11]; and (3) the stage- and location-specific incidence of CRC by age and sex 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 simulated annealing algorithm to explore the parameter space; this is a direct-search approach to finding the minima of a function.

Model Validation

SimCRC has been validated by comparing model predictions with results from studies that were not used in model calibration, namely, randomized trials of colorectal cancer screening. The findings of these validation studies are described below.

Validation of Models Used to inform Colorectal Cancer Screening Guidelines: Accuracy and Implications

*Authors: C. M. Rutter, A. B. Knudsen, T. L. Marsh, V. P. Doria-Rose, E. Johnson, C. Pabiniak, K. M. Kuntz, M. van Ballegooijen, A. G. Zauber, I. Lansdorp-Vogelaar, *
Year: 2016

In this study led by Rutter et al. each model simulated 2000 replications of this study of once-only flexible sigmoidoscopy screening among adults aged 55 to 64 years and estimated hazard ratios and 95% credible intervals for CRC incidence and CRC mortality after 10 years of follow-up. We focus here on the findings with 'SimCRC'; the model accurately predicted the 10-year reduction in CRC incidence and CRC mortality (see the figure below). The study was published in *Medical Decision Making* in July 2016. DOI: 10.1177/0272989X15622642.

Source: Rutter et al. *Medical Decision Making* 2016;36(5):604-614

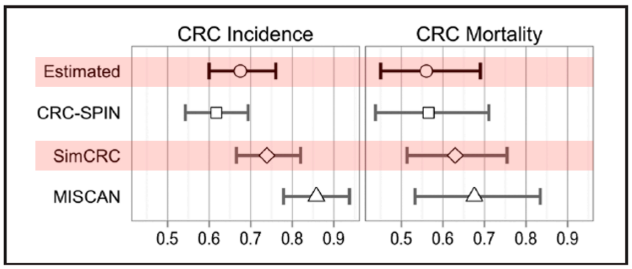

Figure 2 Hazard ratios: study-estimated and model-predicted intervention effects, with 95% percentile intervals for model predictions and 95% confidence intervals for estimates. Both estimated and predicted hazard ratios compare screening-adherent intervention participants to control participants who underwent no screening. CRC, colorectal cancer; CRC-SPIN, CISNET: Colorectal Cancer Simulated Population model for Incidence and Natural history; MISCAN, Microsimulation Screening Analysis; SimCRC, Simulation Model of Colorectal Cancer.

Validation of Colorectal Cancer Models on Long-term Outcomes from a Randomized Controlled Trial
Authors: M. DeYoreo, I. Lansdorp-Vogelaar, A. B. Knudsen, K. M. Kuntz, A. G. Zauber, C. M. Rutter
Year: 2020

Building on the study by Rutter et al. described above, DeYoreo et al. (2020)[12] updated the validation of the three CISNET CRC models with 17-year follow-up from the United Kingdom Flexible Sigmoidoscopy Screening Trial of once-only screening.[13] Focusing here on the findings with 'SimCRC', this study demonstrated SimCRC's ability to accurately predict long-term reductions in CRC incidence and CRC mortality (see figure below), supporting its use in evaluating CRC screening strategies. The study was published in *Medical Decision Making* in November 2020. DOI: 10.1177/0272989X20961095.

Source: DeYoreo et al. *Medical Decision Making* 2020;40(8):1034-1040

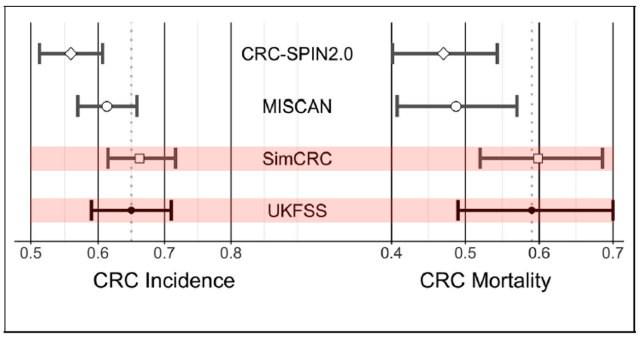

Figure 1 Hazard ratios. The United Kingdom Flexible Sigmoidoscopy Screening (UKFSS) Trial–estimated and model-predicted hazard ratios for intervention effects. Point estimates as well as 95% confidence or credible intervals for model predictions and 95% confidence intervals for estimates are displayed. Both estimated and predicted hazard ratios compare the screened intervention group participants to control participants who underwent no screening.

NordICC Trial Results in Line with Expected Colorectal Cancer Mortality Reduction After Colonoscopy: A Modeling Study

*Authors: D. M. N. van den Berg, P. Nascimento de Lima, A. B. Knudsen, C. M. Rutter, D. Weinberg, I. Lansdorp-Vogelaar, on behalf of the CISNET-Colon group, *

Year: 2023

In this study led by van den Berg et al.(2023)[14], the three CISNET CRC models simulated CRC incidence and CRC mortality reductions from a once-only screening colonoscopy. Model results were generated for two scenarios of adherence with the screening colonoscopy, 42% and 100%. Model-predicted outcomes after 10 years of follow-up were compared with the intention-to-screen and per-protocol results, respectively, from the Nordic-European Initiative on Colorectal Cancer (NordICC) randomized trial of once-only screening colonoscopy that achieved a 42% uptake of colonoscopy among the group invited to screening.[15] We focus here on the findings with 'SimCRC': for both the 42% adherence scenario (akin to the trial's intention-to-screen analysis) and the 100% adherence scenario (akin to the trial's per-protocol analysis), the 'SimCRC'-predicted reductions in CRC incidence accurately predicted trial results, further lending validating the model's ability to predict long-term outcomes with screening. The study was published in *Gastroenterology* in October 2023. DOI: 10.1053/j.gastro.2023.06.035.

Source: van den Berg et al. *Gastroenterology* 2023;165(8):1077-1079

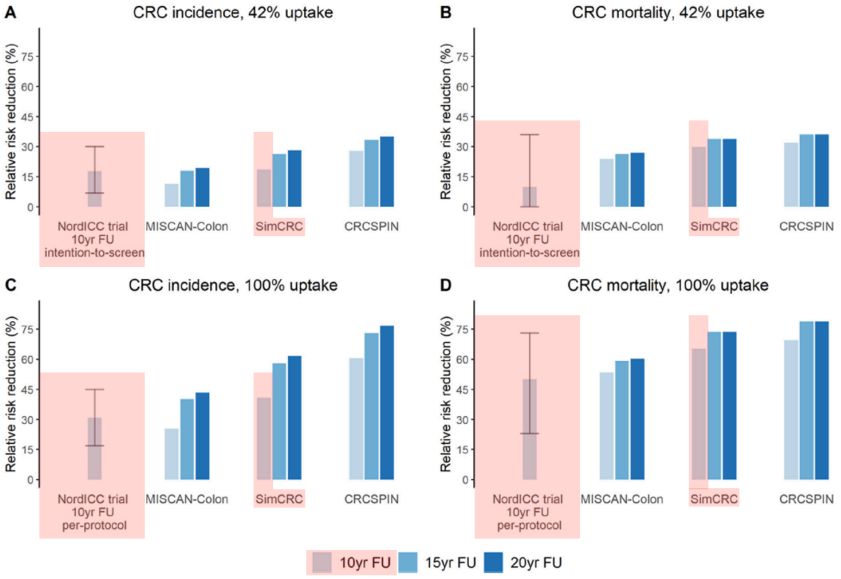

Figure 1. Relative risk reductions in CRC incidence (*A*, *C*) and CRC mortality (*B*, *D*) compared to no screening for 2 different uptake scenarios (42% and 100% uptake) and 3 different follow-up durations (10, 15, and 20 years). CRCSPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural History; FU, follow-up; MISCAN-Colon, Microsimulation Screening Analysis Colorectal Cancer; SimCRC, Simulation model of Colorectal Cancer.

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Assumption Overview

Summary

This section outlines the key assumptions of the Simulation Model of Colorectal Cancer (SimCRC)

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,[1-3] we need to make several assumptions about how that sequence is operationalized and how it is impacted by screened.

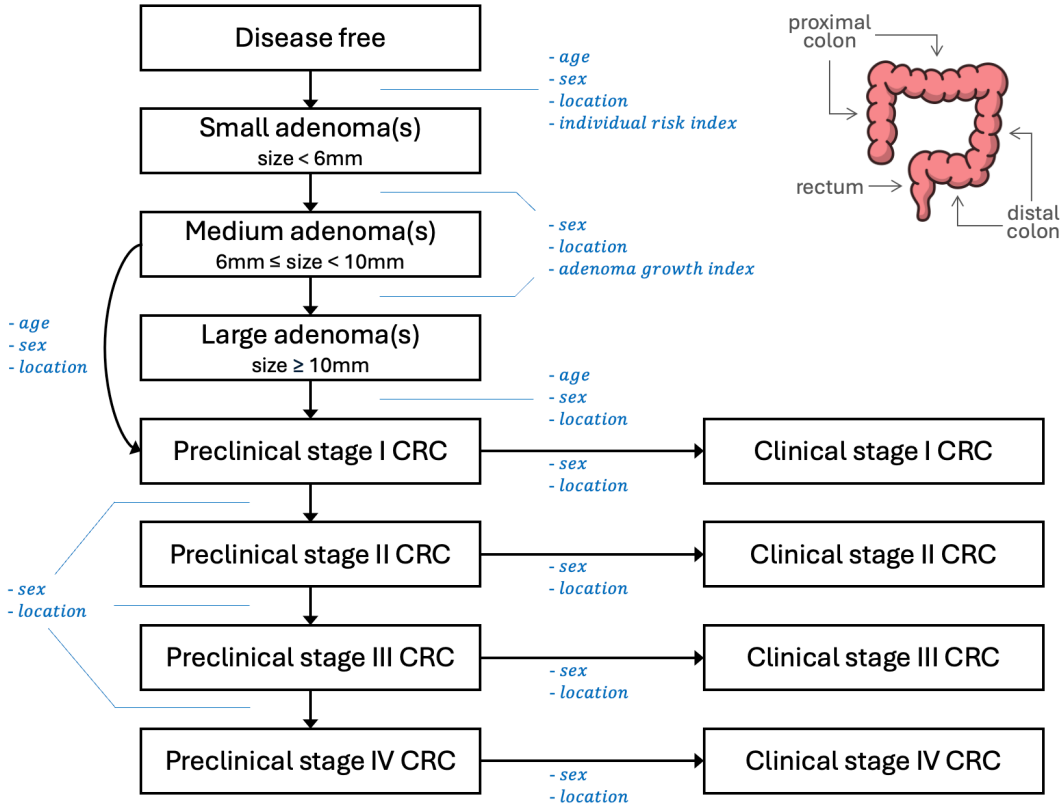
We are currently updating the model to incorporate the sessile-serrated polyp pathway.

Assumption Listing

Population Demographics
SimCRC is a compilation of multiple birth cohorts defined by age, sex, and birth 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 US life tables and are a function of age, sex, and calendar year or birth year (depending on the analysis). Population migration is not simulated.

Natural History of Colorectal Disease (prior to diagnosis)
The natural history model describes the onset and progression of adenomas in an unscreened population. It simulates the transitions from normal colonic epithelium to small/diminutive adenomas (defined as 1 to < 6 mm in size), from small to medium size adenomas (defined as 6 to < 10 mm in size), from medium to large size adenomas (defined as $\geq$ 10 mm in size), from medium or large adenomas to preclinical stage I cancer, 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). Regression of adenomas is not allowed. We assume that all adenomas have the chance of progressing to CRC, although most will not in a person's lifetime. See Parameter Overview for key variables in the natural history model.

We assign an individual risk index based on a truncated normal distribution with a mean of 1 and variance (v) that is determined in model calibration. The magnitude of this factor affects the risk of developing an adenoma. We also assign each adenoma a growth index that allows variability in the risk of transitioning to larger adenoma size categories.



Screening Mechanism

A simulated person who has an underlying adenoma or preclinical cancer has a chance of having it detected by screening. 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.

SimCRC simulates multiple types of screening tests: non-invasive tests (i.e., stool- and blood-based tests); imaging-based tests (i.e., computed tomographic colonography); and endoscopic tests (i.e., sigmoidoscopy and colonoscopy). These tests vary in terms of their test performance characteristics (i.e., sensitivity and specificity) and risk.[4] We assume that small adenomas do not bleed, so that the chance that a person with only small adenoma(s) has a positive fecal occult blood test (FOBT) or FIT is given by the test's lack of specificity. We assume that stool-, blood-, and imaging-based tests have the ability to detect a lesion in any segment of the colorectal system, but that endoscopic tests only have the ability to detect lesions that are within the reach of the scope. For all tests, the sensitivity depends on lesion size and type. We assume that the sensitivity of stool- and blood-based tests is based on the size of the most advanced lesion that an individual has, whereas the sensitivity for imaging and endoscopic tests is lesion-based. We simulate the risk of complications from colonoscopy, including a small risk of mortality from perforation during the procedure. The model structure insures that individuals undergoing a non-colonoscopy screening test can only benefit from the test if abnormal test results are followed up by a colonoscopy.

We assume that all adenomas that are detected during colonoscopy are removed via polypectomy, although the model also allows for incomplete resection. We also assume that individuals who have had adenoma detected and removed are recommended to undergo routine surveillance with colonoscopy. The model has flexibility to implement different surveillance intervals based on the size and number of adenomas detected at the two most recent colonoscopies. It also allows for imperfect adherence with surveillance, as well as the simulation of continued screening after detection and removal of adenomas.

Diagnosed CRC

Once patients are diagnosed with CRC, either by symptom detection or by screening, they 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) and year of diagnosis.[5] For simulated individuals

with multiple cancerous lesions, the model assigns survival according to the cancer with the most advanced stage. We assume that individuals cannot die from cancer during their lead time.

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Parameter Overview

Summary

This section describes the key parameters in the the Simulation Model of Colorectal Cancer (SimCRC).

Background

SimCRC has several components, each with their own sets of parameters.

1. Parameters that describe the US population dynamics over time.
2. Natural history parameters that describe the progression of colorectal disease in a simulated individual.
3. Parameters that describe screening test performance characteristics, as well as parameters that describe screening dissemination in the US.
4. Parameters that dictate the relative survival for patients diagnosed with CRC.

Parameter Listing Overview

Population Parameters (see Population Demographics in Component Overview)

1. Number of persons in the US, by age, sex, and calendar year
2. Age-, sex-, and birth-year-specific risks of all-cause death.

Natural History Parameters

1. Annual probability of developing small adenoma (function of age, sex, and person-specific adenoma risk index)
2. Annual probability that a small adenoma transitions to a to medium adenoma (function of sex, location, and lesion-specific growth index)
3. Annual probability that a medium adenoma transitions to a large adenoma (function of sex, location, and lesion-specific growth index)
4. Annual probability that a large adenoma transitions to preclinical stage I colorectal cancer (function of age, sex, and location)
5. Annual probabilities that a cancer of stage i transitions to stage i+1 preclinical cancer (i=1,2,3; function of stage and location)
6. Annual probability that a preclinical cancer is detected by symptoms detected (function of stage and location)

Screening Parameters (see Screening Dissemination and Screening Effectiveness in Component Overview)

1. Annual probability of undergoing a first screening test, by birth year, age, and sex.
2. Distribution of screening modalities among screened persons (e.g., FOBT, FIT, sigmoidoscopy, CT colonography, colonoscopy), by calendar year.
3. Probabilities that a person with adenoma(s) detected and removed at colonoscopy will be recommended to undergo colonoscopy surveillance.
4. Probability that a person who has previously been screened returns for repeat screening, by sex, screening modality, and time since last screen.
5. Probability that a person who has been recommended to undergo surveillance undergoes surveillance, by the size and number of adenomas detected and removed at the two most recent colonoscopies and the time since the most recent colonoscopy.
6. Probability that a person who has been screened with one modality and remains eligible for screening changes to a different screening modality, by screening modality, age, and year.
7. Sensitivities (for adenomas by size category and for CRC) and specificity for small adenomas, by screening modeling (and optionally, by sex, age group, and lesion location).
8. Risk of non-fatal complications of screening, by screening modality and age.
9. Mortality risk associated with colonoscopy.

CRC Mortality Parameters

1. Monthly cancer-specific mortality rate (function of age at diagnosis, year of diagnosis, stage, location, an time since diagnosis)

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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 CRC screening over time, and (3) changes in CRC mortality over time. The natural history model tracks the underlying progression of colorectal disease from normal colonic tissue to development of adenomatous polyps to invasive cancer. Cancer incidence is affected 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.

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, 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 interupted by removal of an adenoma by colonoscopy. For example, a person with a positive FIT finding who fails to be adherent with a follow-up colonoscopy will not benefit from that screening test.

CRC Mortality Model
Patients who are diagnosed with CRC in the Model, either by symptom detection or by a positive colonoscopy result, enter the CRC Mortality 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 [1].

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Output Overview

Summary

This section lists the key outputs of the Simulation Model of Colorectal Cancer (SimCRC).

Model Outputs

SimCRC generates life histories for each simulated individual. In addition, it outputs the following summary measures:

1. Incident CRC cases by age, sex, location, stage, and year.
2. CRC deaths by age, sex, location, stage, and year.
3. Prevalence of adenomas by age, sex, location, size, and year.
4. Prevalence of preclinical cancer by age, sex, location, stage, and year.
5. Deaths from complications of colonoscopy, by age, sex, and year.
6. Deaths from causes other than CRC and complications of colonoscopy, by age, sex, and year.
7. Screening tests by age, sex, year, screening modality, and test result.
8. Follow-up colonoscopies by sex, year, and finding.
9. Surveillance colonoscopies by sex, year, and finding.
10. Overdiagnosed adenomas (detected adenomas that, in the absence of screening, would not have become a symptom-detected CRC before death), by sex.
11. Overdiagnosed CRC (screen-detected CRC that, in the absence of screening, would not have been detected by symptoms before death), by sex.
12. Person-years by age, sex, and year.
13. Person-years with diagnosed CRC, by age, sex, stage at diagnosis, phase of care (initial, terminal by cause of death, continuing), and year.
14. Population by age, sex, and year.

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Results Overview

Results Overview

Summary

This section describes the results of analyses perfomed using the Simulation Model of Colorectal Cancer (`SimCRC`) and methodologic studies done in the development of the model. The original model is programmed in C++ and includes only the adenoma-carcinoma sequence. We are in the process of recoding the model in R and adding the serrated polyp pathway to CRC.

Model-based Analyses

There are two general categories of model-based analyses with SimCRC:

1. Policy-Relevant Analyses
2. Methods-Relevant Analyses

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Policy Relevant Analyses

Policy Relevant Analyses

Estimation of Cancer Deaths Averted From Prevention, Screening, and Treatment Efforts, 1975-2020

*Authors: Goddard KAB, Feuer EJ, Mandelblatt JS, Meza R, Holford TR, Jeon J, Lansdorp-Vogelaar I, Gulati R, Stout NK, Howlader N, **Knudsen AB**, Miller D, Caswell-Jin JL, Schechter CB, Etzioni R, Trentham-Dietz A, Kurian AW, Plevritis SK, Hampton JM, Stein S, Sun LP, Umar A, Castle PE*

Year: 2025

Goddard et al. (2025)[1] extended outputs from published models developed by the Cancer Intervention and Surveillance Modeling Network to estimate the contributions of different interventions across the cancer-control continuum to averting deaths from breast, cervical, colorectal, lung, and prostate cancers over the period from 1975 to 2020. The models estimated that 5.94 million cancer deaths were averted for breast, cervical, colorectal, lung, and prostate cancers combined. Cancer prevention and screening efforts averted 8 of 10 of these deaths (4.75 million averted deaths). The relative contributions of prevention (excluding the preventive effects of colorectal anc cervical cancer screening), screening, and treatment varied by cancer site. Screening accounted for 25% of breast cancer deaths averted. Averted cervical cancer deaths were nearly completely achieved through screening and removal of cancer precursors as treatment advances were modest during the study period. Averted colorectal cancer deaths were achieved through screening and removal of precancerous polyps or early detection in 79% and treatment advances in 21%. Most lung cancer deaths were avoided by smoking reduction (98%) because screening uptake was low and treatment largely palliative before 2014. Screening contributed to 56% of averted prostate cancer deaths. The authors concluded that over the past 45 years, cancer prevention and screening accounted for most cancer deaths averted for these causes, and that efforts to further reduce the burden of cancer in the US will require increased dissemination of effective interventions and new technologies and discoveries.

This study was published in *JAMA Oncology* in 2025. DOI: 10.1001/jamaoncol.2024.5381

Characteristics of a Cost-Effective Blood Test for Colorectal Cancer Screening

*Authors: Nascimento de Lima P, van den Puttelaar R, **Knudsen AB**, Hahn AI, **Kuntz KM**, Ozik J, Collier N, **Alarid-Escudero F**, Zauber AG, Inadomi JM, Lansdorp-Vogelaar I, Rutter CM*

Year: 2024

Nascimento de Lima et al. (2024)[2] investigated the conditions under which blood-based biomarker tests could be as effective and cost-effective as established colorectal cancer (CRC) screening methods like annual fecal immunochemical testing (FIT) or decennial colonoscopy. Utilizing three Cancer Intervention and Surveillance Modeling Network (CISNET) microsimulation models, the study evaluated various scenarios by varying test sensitivity for detecting CRC (74%-92%) and advanced adenomas (10%-50%), screening intervals (1-3 years), and test costs ($25-$500). Results indicated that a blood test with 92% CRC sensitivity and 50% advanced adenoma sensitivity, conducted every three years, could yield 117-162 quality-adjusted life-years (QALYs) gained per 1,000 individuals. However, to be cost-effective, such a test would need to be priced below $125. The authors concluded that blood tests meeting only the minimum performance criteria set by the Centers for Medicare & Medicaid Services (CMS) are less effective and more costly compared to existing screening methods. Therefore, they should not be recommended for patients who are candidates for colonoscopy or FIT. To be a viable alternative, blood tests would require higher sensitivity for advanced adenomas and lower costs.

This study was published in *Journal of the National Cancer Institute* in 2024. DOI: 10.1093/jnci/djae124.

Effectiveness and Cost-Effectiveness of Colorectal Cancer Screening With a Blood Test That Meets the Centers for Medicare & Medicaid Services Coverage Decision

*Authors: van den Puttelaar R, de Lima PN, **Knudsen AB**, Rutter CM, **Kuntz KM**, de Jonge L, **Alarid-Escudero F**, Lieberman D, Zauber AG, Hahn AI, Inadomi JM, Lansdorp-Vogelaar I*

Year: 2024

Van den Puttelaar et al. (2024) [3] evaluated the clinical effectiveness and cost-effectiveness of a hypothetical blood-based test for colorectal cancer (CRC) screening that meets the Centers for Medicare & Medicaid Services (CMS) coverage criteria—minimum 74% sensitivity for CRC detection and 90% specificity. Using three established microsimulation models (MISCAN-Colon, CRC-SPIN, and SimCRC), the authors compared triennial blood-based screening (ages 45–75) to no screening, annual fecal immunochemical testing (FIT), triennial multitarget stool DNA (mt-sDNA) testing combined with FIT, and colonoscopy every 10 years.

The models showed that compared to no screening, blood-based testing reduced CRC incidence and mortality and was cost-effective with an incremental cost-effectiveness ratio (ICER) of 25, 600–43,700 per quality-adjusted life-year (QALY) gained. However, when compared to guideline-endorsed strategies, blood-based screening was both more costly and less effective—even in sensitivity analyses where its uptake was 20 percentage points higher than FIT. For example, FIT provided 5–24 additional QALYs and saved 3.2–3.5 million per 1,000 individuals relative to the blood test.

The study concluded that despite the potential for increased screening participation, a blood test meeting CMS's minimum performance criteria is not cost-effective compared with existing CRC screening strategies. Improved test sensitivity—particularly for precancerous lesions—and lower costs would be needed for blood-based screening to be a viable alternative.

This study was published in *Gastroenterology* in 2024. DOI: 10.1053/j.gastro.2024.02.012.

NordICC Trial Results in Line with Expected Colorectal Cancer Mortality Reduction After Colonoscopy: A Modeling Study

*Authors: van den Berg DMN, Nascimento de Lima P, **Knudsen AB**, Rutter CM, Weinberg D, Lansdorp-Vogelaar I, on behalf of the CISNET-Colon group*

Year: 2023

In this study led by van den Berg et al.,(2023)[4] the three Cancer Intervention and Surveillance Modeling Network (CISNET) CRC models were used to predict the long-term CRC outcomes of the Nordic-European Initiative on Colorectal Cancer (NordICC) randomized trial of once-only screening colonoscopy.[5] The study reported an 18% reduction in CRC incidence and a 10% reduction in CRC mortality after 10 years of follow-up -- reductions that were less than those anticipated based on findings from observational studies and modeling analyses. Reductions were higher in adjusted per-protocol analyses (31% and 50% reductions, respectively). The authors simulated the screening uptake observed in the trial (42% of invited individuals) and predicted outcomes for the intention-to-screen analysis and the per-protocol analysis after 10, 15, and 20 years of follow-up. They found that model-predicted CRC incidence and CRC mortality reductions after 10 years of follow-up were similar to those reported in the trial for both the intention-to-screen and per-protocol analyses. They also predicted that the effectiveness of screening would increase over time, with incidence reductions of 43% to 77% and CRC mortality reductions of 60% to 79% (per-protocol analysis) after 20 years of follow-up.

The study was published in *Gastroenterology* in 2023. DOI: 10.1053/j.gastro.2023.06.035

Estimated US cancer deaths prevented with increased use of lung, colorectal, breast, and cervical cancer screening

*Authors: **Knudsen AB**, Kim JJ, Mandelblatt JM, Meza R, Trentham-Dietz A, Zauber AG, Castle PE, Feuer EJ.*

Year: 2023

Knudsen et al. (2023)[6] used previously published outputs from Cancer Intervention and Surveillance Modeling Network (CISNET) models to estimate the number of US cancer deaths that could be prevented from a 10-percentage-point increase in uptake of US Preventive Services Task Force (USPSTF)-recommended screening strategies for lung, colorectal, breast, and cervical cancer. The authors estimated that a 10-percentage-point increase in screening use would prevent 1,010 lung cancer deaths, 11,070 colorectal cancer deaths, 1,790

breast cancer deaths, and 1,710 cervical cancer deaths over the lifetimes of eligible US residents at the recommended age to begin screening in 2021. Copared to a proxy for the expected lifetime number of lung, colorectal, female breast, and cervical cancer deaths if current trends in screening and treatment were to continue, these deaths averted represent a 1% reduction in lung cacner deaths, and 21% reduction in colorectal cancer deaths, a 4% reduction in breast cancer deaths, and a 40% reduction in cervical cancer deaths. The authors concluded that the Biden Administration's Cancer Moonshot goal of reducing cancer mortality by 50% over the 25-year period from 2022 to 2047 cannot be achieved by focusing on overall increases in screening uptake alone.

This study was published in *JAMA Network Open* in 2023. DOI: 10.1001/jamanetworkopen.2023.44698..

Reevaluating the Evidence for Intensive Postoperative Extracolonic Surveillance for Nonmetastatic Colorectal Cancer

Authors: Popp J, Weinberg DS, Enns E, Nyman JA, Beck JR, ***Kuntz KM***

Year: 2022

Popp et al. (2022)[7] critically examined the clinical value and economic implications of intensive postoperative extracolonic surveillance in patients with nonmetastatic colorectal cancer (CRC). The study employed a microsimulation model to assess the potential survival benefits of intensive surveillance strategies, such as routine computed tomography (CT) scans and carcinoembryonic antigen (CEA) assays, compared to less intensive follow-up protocols. Findings suggested that the recent trials may have been underpowered to detect a modest yet clinically meaningful survival benefit from intensive surveillance. The authors concluded that, despite the limited statistical power of recent trials, intensive extracolonic surveillance could offer a small but significant improvement in life expectancy for patients with resected nonmetastatic CRC. They recommended that future research should focus on adequately powered trials to evaluate the efficacy of metastasectomy and tailored surveillance strategies.

This study was published in *Value in Health* in 2022. DOI: 10.1016/j.jval.2021.06.017.

CDX2 Biomarker Testing and Adjuvant Therapy for Stage II Colon Cancer: An Exploratory Cost-Effectiveness Analysis

Authors: ***Alarid-Escudero F****, Schrag D,* ***Kuntz KM***

Year: 2022

Alarid-Escudero et al. (2022)[8] conducted an exploratory cost-effectiveness analysis to evaluate the clinical and economic impact of using CDX2 biomarker testing to guide adjuvant chemotherapy decisions for patients with stage II colon cancer. Using a decision-analytic model simulating a cohort of 65-year-old patients, the study compared a biomarker-guided strategy—where only CDX2-negative patients received adjuvant FOLFOX chemotherapy—with standard care in which adjuvant therapy was not routinely administered. The analysis found that CDX2 testing followed by targeted treatment was both more effective and more cost-efficient, yielding an incremental cost-effectiveness ratio (ICER) of approximately $5,500 per QALY gained. The authors concluded that CDX2 biomarker-guided therapy has strong potential to improve patient outcomes in a cost-effective manner, though further real-world evidence is needed to support widespread implementation.

This study was published in *Value in Health* in 2022. DOI: 10.1016/j.jval.2021.07.019.

Reevaluating the Evidence for Intensive Postoperative Extracolonic Surveillance for Nonmetastatic Colorectal Cancer

Authors: Popp J, Weinberg DS, Enns E, Nyman JA, Beck JR, ***Kuntz KM***

Year: 2022

Popp et al. (2022)[7] critically examined the clinical value and economic implications of intensive postoperative extracolonic surveillance in patients with nonmetastatic colorectal cancer (CRC). The study employed a decision-analytic modeling approach to compare intensive follow-up strategies—such as routine CT scans and blood testing for extracolonic metastasis detection—with less intensive or symptom-driven follow-up protocols. Findings suggested that while intensive surveillance might lead to earlier detection of some recurrences, it provides minimal incremental benefit in terms of overall survival or quality-adjusted life years (QALYs). Moreover, the increased healthcare costs and potential risks associated with unnecessary imaging and procedures raised concerns about the efficiency of this approach. The authors recommended a more targeted, evidence-based approach to postoperative follow-up, emphasizing value over volume in cancer care.

This study was published in *Value in Health* in 2022. DOI: 10.1016/j.jval.2021.06.017.

Black and White Differences in Colorectal Cancer Screening and Screening Outcomes: A Narrative Review

*Authors: Rutter CM, **Knudsen AB**, Lin JS, Bouskill K.*

Year: 2021

Rutter et al. (2021)[9] reviewed the literature for evidence of two potential mechanisms for racial disparities in CRC incidence: differences in access to screening, including screening follow-up, and differences in underlying CRC risk. The showed that higher CRC incidence in blacks relative to whites emerged only after the dissemination of screening and described evidence of racial disparities in screening rates. The authors conclude that higher rates of CRC incidence among black patients are primarily driven by lower rates of CRC screening. The findings highlight the need to increase black patients' access to quality screening.

The study was published in *Cancer Epidemiology, Biomarkers & Prevention* in 2021. DOI: 10.1158/1055-9965.EPI-19-1537.

Colorectal Cancer Screening: An Updated Modeling Study for the US Preventive Services Task Force

*Authors: **Knudsen AB**, Rutter CM, Peterse EFP, Lietz AP, Seguin CL, Meester RGS, Perdue LA, Lin JS, Siegel RL, Doria-Rose VP, Feuer EJ, Zauber AG, **Kuntz KM**, Lansdorp-Vogelaar I*

Year: 2021

Knudsen et al. (2021)[10] conducted a microsimulation modeling study to evaluate various colorectal cancer (CRC) screening strategies, aiming to inform the U.S. Preventive Services Task Force (USPSTF) recommendations. The study assessed the benefits, burdens, and harms associated with different screening modalities, including stool-based tests, endoscopic procedures, and computed tomography colonography, with particular attention to the optimal age to initiate screening. The analysis suggested that commencing CRC screening at age 45 provides a favorable balance between life-years gained and the associated colonoscopy burden. These findings contributed to the USPSTF's updated guidelines advocating for earlier initiation of CRC screening.:contentReference[oaicite:0]{index=0}

This study was published in *JAMA* in 2021. DOI: 10.1001/jama.2021.5746.

Cost-Effectiveness of Surveillance with CT Colonography After Resection of Colorectal Cancer

*Authors: **Kuntz KM**, Popp J, Beck JR, Zauber AG, Weinberg DS*

Year: 2020

Kuntz et al. (2020)[11] conducted a cost-effectiveness analysis comparing computed tomography colonography (CTC) to optical colonoscopy (OC) for post-surgical surveillance in patients who had undergone resection for colorectal cancer (CRC). The study evaluated both strategies in terms of their ability to detect intraluminal lesions (such as polyps) and extraluminal recurrences, while also considering cost and health outcomes.

Using decision modeling techniques, the researchers found that CTC, which offers a less invasive, combined approach to detecting both types of recurrence, could be a cost-effective alternative to standard colonoscopy. Specifically, they reported that OC incurred an incremental cost of at least $5,700 per additional polyp detected compared to CTC, a value that falls within accepted cost-effectiveness thresholds for interventions targeting short-term clinical outcomes. The analysis highlighted that CTC may serve as a practical surveillance option, particularly for patients unable or unwilling to undergo OC, while still maintaining reasonable economic and clinical value.

This study was published in *BMJ Open Gastroenterology* in 2020. DOI: 10.1136/bmjgast-2020-000450.

Cost-Effectiveness of Risk-Stratified Colorectal Cancer Screening Based on Polygenic Risk – Current Status and Future Potential

Authors: Naber SK, Kundu S, ***Kuntz KM****, Dotson WD, Williams MS, Zauber AG, Calonge N, Zallen DT, Ganiats TG, Webber EM, Goddard KAB, Henrikson NB, van Ballegooijen M, Janssens ACJW, Lansdorp-Vogelaar I*

Year: 2020

Naber et al. (2020)[12] evaluated the cost-effectiveness of implementing colorectal cancer (CRC) screening strategies tailored to individual polygenic risk profiles compared to uniform screening approaches. Utilizing the MISCAN-Colon microsimulation model, the study simulated a cohort of U.S. 40-year-olds undergoing either uniform colonoscopy screenings at ages 50, 60, and 70, or risk-stratified screenings based on polygenic risk scores with varying discriminatory accuracies (AUC values ranging from 0.60 to 0.80). The analysis revealed that, with current polygenic test performance (AUC = 0.60), risk-stratified screening is not cost-effective, increasing costs by $59 per person without additional health benefits. However, scenarios with improved test performance (AUC > 0.65), reduced testing costs (<$ 141), or a modest increase in screening adherence (≥5%) demonstrated potential cost-effectiveness. The authors concluded that while current polygenic risk-based CRC screening lacks cost-effectiveness, advancements in genetic testing accuracy, cost reductions, or enhanced participation rates could render such strategies viable in the future.

This study was published in *JNCI Cancer Spectrum* in 2020. DOI: 10.1093/jncics/pkz086.

Cost-Effectiveness of a Multitarget Stool DNA Test for Colorectal Cancer Screening of Medicare Beneficiaries

Authors: Naber SK, ***Knudsen AB****, Zauber AG, Rutter CM, Fischer SE, Pabiniak CJ, Soto B,* ***Kuntz KM****, Lansdorp-Vogelaar I*

Year: 2019

Naber et al. (2019)[13] conducted a comprehensive cost-effectiveness analysis of multitarget stool DNA (mtSDNA) testing for colorectal cancer (CRC) screening in the Medicare population. Using three independently developed microsimulation models from the Cancer Intervention and Surveillance Modeling Network (CISNET), the study compared triennial mtSDNA testing to other established screening strategies, including annual fecal immunochemical testing (FIT) and decennial colonoscopy. The analysis evaluated lifetime costs, health outcomes, and incremental cost-effectiveness ratios under varying adherence and test performance scenarios.

Findings revealed that while mtSDNA screening reduces CRC incidence and mortality compared to no screening, it is less effective and significantly more expensive than most alternative screening strategies at its 2017 reimbursement rate of $512. Even under optimistic assumptions about higher adherence to mtSDNA testing, its cost-effectiveness did not improve substantially. The study concluded that mtSDNA testing may be best positioned as a secondary option for individuals unwilling to undergo other screening modalities and would need a substantial price reduction to be considered cost-effective within current guidelines.

This study was published in *PLoS ONE* in 2019. DOI: 10.1371/journal.pone.0220234.

Optimizing Colorectal Cancer Screening by Race and Sex: Microsimulation Analysis II to Inform the American Cancer Society Screening Guideline

*Authors: Meester R, Peterse E, **Knudsen AB**, de Weedrt A, Chen J, Lietz AP, Dwyer A, Ahnen D, Siegel R, Smith R, Zauber AG, Lansdorp-Vogelaar I.*

Year: 2018

In modeling studies to inform the 2018 American Cancer Society's CRC screening guideline, Meester et al. (2018)[14] explored the influence of race and sex on optimal CRC screening strategies. Two CISNET models, MKSCAN and SimCRC, were used to evaluate a variety of screening methods, ages to start and stop, and intervals for 4 demographic subgroups (black and white males and females). The authors found that when assuming that the lifetime risk of CRC among 40-year-olds has increased proportionally to observed incidence trends under the age of 40 years, both models recommended starting screening at the age of 45 years, regardless of race and sex. Recommended strategies included colonoscopy every 10 or 15 years, annual fecal immunochemical testing, and computed tomographic colonography every 5 years through the age of 75 years.

The study was published in *Cancer* in 2018. DOI: 10.1002/cncr.31542

Yield and Cost-Effectiveness of Computed Tomography Colonography Versus Colonoscopy for Post Colorectal Cancer Surveillance

*Authors: Beck JR, Ross EA, **Kuntz KM**, Popp J, Zauber AG, Bland J, Weinberg DS*

Year: 2018

Beck et al. (2018)[15] evaluated the effectiveness and cost-efficiency of computed tomography colonography (CTC) compared to traditional colonoscopy for surveillance after colorectal cancer (CRC) resection. Utilizing a decision-analytic model, the study assessed outcomes such as detection rates of metachronous neoplasms, costs, and quality-adjusted life years (QALYs). The findings suggested that while CTC is less invasive, it may be less sensitive in detecting certain lesions compared to colonoscopy. The cost-effectiveness of CTC as a surveillance strategy was found to be contingent upon factors like test performance characteristics, patient adherence, and the relative costs of the procedures. The authors concluded that CTC could be a viable alternative for post-CRC surveillance in patients who are unwilling or unable to undergo colonoscopy, but further research is needed to fully establish its comparative effectiveness and economic value. :contentReference[oaicite:0]{index=0}

This study was published in *MDM Policy & Practice* in 2018. DOI: 10.1177/2381468318810515.

Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force

*Authors: **Knudsen AB**, Zauber AG, Rutter CM, Naber SK, Doria-Rose VP, Pabiniak C, Johanson C, Fischer SE, Lansdorp-Vogelaar I, **Kuntz KM***

Year: 2016

Knudsen et al. (2016)[16] evaluated the benefits, burdens, and harms of various colorectal cancer screening strategies using microsimulation modeling for the US Preventive Services Task Force. The study assessed different modalities, including colonoscopy, sigmoidoscopy, and fecal tests, to inform screening guidelines.

The analysis emphasized the trade-offs between effectiveness, invasiveness, and adherence to inform policy recommendations. The study was published in *JAMA* on June 21, 2016. DOI: 10.1001/jama.2016.6828.

Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collaborative Modeling Approach

*Authors: Zauber AG, **Knudsen AB**, Rutter, CM, Lansdorp-Vogelaar I, **Kuntz KM**, Doria-Rose VP, Pabiniak C, Fischer S, Johanson C, Naber SK*

Year: 2015

AHRQ Publication No. 14-05203-EF-2.

Optimal Colorectal Cancer Screening in States' Low-income, Uninsured Populations – the Case of South Carolina

*Authors: van der Steen A, **Knudsen AB**, van Hees F, Walter G, Berger F, Daguise V, **Kuntz KM**, Zauber AG, van Ballegooijen M, Lansdorp-Vogelaar I.*

Year: 2015

Van der Steen et al.(2015)[17] used two CISNET models -- MISCAN and SimCRC -- to estimate the number of CRC cases and CRC deaths that could be prevented and the number of life-years that could be gained in South Carolina's low-income, uninsured population if limited state funds for screening are spend on colonoscpy or fecal immunochemical testing. The findings suggest that a FIT screening program will prevent more CRC deaths than a colonoscopy-based program when a state's budget for CRC screening supports screening of only a fraction of the target population.

The study was published in *Health Services Research* in 2015. DOI: 10.1111/1475-6773.12246

Cost-savings to Medicare from Pre-Medicare Colorectal Cancer Screening

*Authors: Goede SL, **Kuntz KM**, van Ballegooijen M, **Knudsen AB**, Lansdorp-Vogelaar I, Tangka FK, Howard DH, Chin J, Zauber AG, Seeff LC*

Year: 2015

Using the MISCAN and SimCRC models, Goede et al.(2015)[18] estimated the impact of increased colorectal cancer screening among the pre-Medicare population (50-64y) on the costs in the pre-Medicare and Medicare (65+) population. The authors found that increasing screening rates in the pre-Medicare population would result in reductions in CRC incidence and CRC mortality. While costs among the pre-Medicare population would increase, over time, these costs would largely be offset by the reduced costs of caring for Medicare patients with CRC.

The study was published in *Medical Care* in 2015. DOI: 10.1097/MLR.0000000000000380

Personalizing Age of Cancer Screening Cessation Based on Comorbid Conditions: Model Estimates of Harms and Benefits

*Authors: Lansdorp-Vogelaar I, Gulati R, Mariotto AB, Schechter CB, de Carvalho TM, **Knudsen AB**, van Ravesteyn NT, Heijnsdijk EAM, Pabiniak C, van Ballegooijen M, Rutter CM, **Kuntz KM**, Feuer EJ, Etzioni R, de Koning HJ, Zauber AG, Mandelblatt JS*

Year: 2014

Lansdorp-Vogelaar et al.(2014)[19] used CISNET models of breast, prostate, and colorectal cancer to estimate the optimal age to end cancer screening based on comorbidity level. The authors found that the ages to end screening were consistent across models and cancer sites; for persons with no, mild, moderate, and severe comorbid conditions, screening until ages 76, 74, 72, and 66 years, respectively, resulted in harms and benefits similar to average-health persons.

The study was published in *Annals of Internal Medicine* in 2014. DOI: 10.7326/M13-286

Development of New Non-Invasive Tests for Colorectal Cancer Screening: The Relevance of Information on Adenoma Detection

*Authors: Haug U, **Knudsen AB**, Lansdorp-Vogelaar I, **Kuntz KM***

Year: 2014

Haug et al. (2014)[20] analyzed the development of new non-invasive colorectal cancer screening tests, emphasizing the importance of adenoma detection rates. The study explored how improved test performance can enhance screening outcomes and adherence.

This research provides valuable insights for the development of next-generation screening technologies. It was published in *International Journal of Cancer* on June 15, 2014. DOI: 10.1002/ijc.29343.

Rescreening of Persons with a Negative Colonoscopy Result: Results from a Microsimulation Model

*Authors: **Knudsen AB**, Hur C, Gazelle GS, Schrag D, McFarland EG, **Kuntz KM***

Year: 2012

Individuals with no findings at an initial screening colonoscopy may be at lower risk of subsequent CRC. Knudsen et al.(2012)[21] used SimCRC to estimate the effectiveness and costs of rescreening such individuals with colonoscopy vs other CRC screening methods. Modeling results showed that, compared with continuing colonoscopy every 10 years after an initial negative examination, rescreening with annual HSFOBT, annual FIT, or CTC every 5 years provided approximately the same benefit in life-years with fewer complications at a lower cost. The authors concluded that it is reasonable to use other methods to rescreen persons with negative colonoscopy results.

The study was published in *Annals of Internal Medicine* in 2012. DOI: 10.7326/0003-4819-157-9-201211060-00005

How Should Individuals with a False-Positive Fecal Occult Blood Test for Colorectal Cancer Be Managed? A Decision Analysis

*Authors: Haug U, **Knudsen AB**, **Kuntz KM***

Year: 2012

Haug et al. (2012)[22] conducted a decision-analytic study to evaluate the most effective and efficient management strategies for individuals who receive false-positive results from fecal occult blood testing (FOBT) during colorectal cancer (CRC) screening. Using a microsimulation model, the study compared long-term clinical outcomes, costs, and resource use associated with alternative follow-up protocols, such as immediate colonoscopy, repeat FOBT, or no further action. The analysis considered the risk of missed neoplasia, potential harms of unnecessary procedures, and the implications for healthcare systems. The results indicated that follow-up colonoscopy, while more resource-intensive, could provide significant benefits in terms of early detection and prevention of CRC in individuals at elevated risk. The authors concluded that personalized, risk-based management may optimize outcomes and balance benefits against potential harms and costs for individuals with false-positive FOBT results.

This study was published in *International Journal of Cancer* in 2012. DOI: 10.1002/ijc.27458.

Contribution of Screening and Survival Differences to Racial Disparities in Colorectal Cancer Rates

*Authors: Lansdorp-Vogelaar I, **Kuntz KM**, **Knudsen AB**, van Ballegooijen M, Zauber AG, Jemal A*

Year: 2012

Lansdorp-Vogelaar et al. (2012)[23] conducted a comprehensive analysis to quantify how differences in colorectal cancer (CRC) screening rates and survival outcomes contribute to racial disparities in CRC

incidence and mortality between Black and White populations in the United States. Using simulation modeling, the study estimated the relative contributions of unequal access to screening and disparities in stage-specific survival to observed outcome differences. Results showed that lower screening rates among Black individuals accounted for 42% of the disparity in CRC incidence and 19% of the disparity in mortality. Additionally, differences in survival rates explained 36% of the mortality gap. The findings suggest that eliminating disparities in both access to screening and quality of treatment could substantially reduce racial inequalities in CRC outcomes. The authors highlight the urgent need for policy interventions aimed at ensuring equitable access to prevention, early detection, and high-quality cancer care.

This study was published in *Cancer Epidemiology, Biomarkers & Prevention* in 2012. DOI: 10.1158/1055-9965.EPI-12-0023.

Radiation-Related Cancer Risks from CT Colonography Screening: A Risk-Benefit Analysis

*Authors: Berrington de Gonzales A, Kim KP, **Knudsen AB**, Lansdorp-Vogelaar I, Rutter CM, Smith-Bindman R, Yee J, **Kuntz KM**, van Ballegooijen M, Zauber AG, Berg CD*

Year: 2011

De González et al. (2011)[24] assessed the potential cancer risks due to radiation exposure from repeated computed tomographic colonography (CTC) screening for colorectal cancer (CRC). Using risk projection models and a microsimulation model of colorectal cancer natural history, the study estimated lifetime radiation-induced cancer risks for individuals undergoing CTC screening every 5 years from age 50 to 80. Results suggested that although there is a small increased risk of radiation-related cancer, this risk is minimal compared to the substantial mortality reduction benefits of regular CRC screening. For example, the estimated number of radiation-related cancers was approximately 1 for every 1,000 individuals screened over a lifetime, whereas CTC screening was estimated to avert 24–28 CRC deaths per 1,000 individuals. The authors concluded that the benefits of CTC screening far outweigh the radiation risks, particularly when low-dose protocols are used, supporting the inclusion of CTC as a viable CRC screening option.

This study was published in *American Journal of Roentgenology* in 2011. DOI: 10.2214/AJR.10.4907.

Sensitivity of Immunochemical Faecal Occult Blood Testing for Detecting Left- Versus Right-Sided Colorectal Neoplasia

*Authors: Haug U, **Kuntz KM**, **Knudsen AB**, Hundt S, Brenner H*

Year: 2011

Haug et al. (2011)[25] explored whether immunochemical faecal occult blood testing (iFOBT), a widely used screening tool for colorectal cancer (CRC), performs differently in detecting neoplasia depending on lesion location. Utilizing data from a large-scale screening colonoscopy study in Germany, the researchers compared the sensitivity of iFOBT for advanced neoplasia in the left versus right colon. Their analysis revealed a significantly higher detection sensitivity for left-sided lesions. The findings raise concerns that iFOBT may systematically underdetect right-sided neoplasia, potentially reducing its overall effectiveness as a stand-alone screening strategy. The authors suggest that screening programs may need to account for this imbalance or consider supplementary approaches to ensure comprehensive detection across the entire colon.

This study was published in *British Journal of Cancer* in 2011. DOI: 10.1038/bjc.2011.152.

Comparative Economic Evaluation of the American College of Radiology Imaging Network National CT Colonography Trial with Three CISNET Microsimulations

*Authors: 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*

Year: 2011

Vanness et al. (2011)[26] conducted a comparative economic evaluation using data from the American College of Radiology Imaging Network (ACRIN) National CT Colonography Trial, analyzed through three Cancer Intervention and Surveillance Modeling Network (CISNET) microsimulation models. The study assessed the cost-effectiveness of computed tomographic colonography (CTC) as a colorectal cancer (CRC) screening method. Findings indicated that, under the assumptions of the models, CTC was more costly and less effective than other non-CTC screening strategies but remained beneficial compared to no screening at all. The models showed consistency in relative costs and outcomes, supporting the potential role of CTC in CRC screening programs.

This study was published in *Radiology* in 2011. DOI: 10.1148/radiol.11102336.

Is Fecal Occult Blood Testing More Sensitive for Left- Than for Right-Sided Colorectal Neoplasia? A Systematic Literature Review

*Authors: Haug U, **Knudsen AB**, Brenner H, **Kuntz KM***

Year: 2011

Haug et al. (2011)[27] conducted a systematic literature review to evaluate whether fecal occult blood testing (FOBT), a common non-invasive screening method for colorectal cancer (CRC), exhibits differential sensitivity in detecting left-sided versus right-sided colorectal neoplasia. The review included seven prospective screening studies involving average-risk adults who underwent both FOBT (either immunochemical or guaiac-based) and colonoscopy. The majority of these studies indicated a higher sensitivity of FOBT for advanced neoplasia located in the left colon compared to the right colon. However, the authors noted that the available literature is limited and findings are not entirely consistent. They emphasized the need for further research to confirm these observations and to understand the implications for CRC screening strategies.:contentReference[oaicite:0]{index=0}

This study was published in *Expert Review of Molecular Diagnostics* in 2011. DOI: 10.1586/erm.11.41.

Colorectal Cancer Mortality Prevented by Use and Attributable to Nonuse of Colonoscopy

*Authors: Stock C, **Knudsen AB**, Lansdorp-Vogelaar I, Haug U, Brenner H*

Year: 2011

Stock et al.(2011)[28] used the epidemiological concepts of prevented fraction (PF) and attributable fraction (AF) to estimate the numbers of CRC deaths in 2005 prevented by the use of colonoscopy and percentages and numbers of CRC deaths in 2005 attributable to the nonuse of colonoscopy. The study estimated that in the US, an estimated 7,314 to 11,711 CRC deaths in 2005 were prevented by colonoscopy and that 13,796 to 22,088 CRC deaths in 2005 were attributable to the non-use of colonoscopy. The study highlights the large potential benefits from increased public health interventions to increase the use of screening colonoscopy.

The study was published in *Gastrointestinal Endoscopy* in 2011. DOI: 10.1016/j.gie.2010.12.005.

Cost-Effectiveness of Computed Tomographic Colonography Screening for Colorectal Cancer in the Medicare Population

*Authors: **Knudsen AB**, Lansdorp-Vogelaar I, Rutter CM, Savarino JE, van Ballegooijen M, **Kuntz KM**, Zauber AG*

Year: 2010

Knudsen et al. (2010)[29] evaluated the cost-effectiveness of computed tomographic colonography (CTC) as a screening method for colorectal cancer (CRC) in the Medicare population. Their analysis indicated that CTC could be a cost-effective alternative to traditional colonoscopy if the reimbursement rate per scan is substantially lower than that for colonoscopy or if it leads to increased screening adherence among individuals

who would otherwise remain unscreened. The study emphasized the importance of considering both the costs and potential increase in screening uptake when evaluating CTC as a viable CRC screening strategy.

This study was published in *Journal of the National Cancer Institute* in 2010. DOI: 10.1093/jnci/djq164.

Stool DNA Testing to Screen for Colorectal Cancer in the Medicare Population: A Cost-Effectiveness Analysis

*Authors: Lansdorp-Vogelaar I, **Kuntz KM**, **Knudsen AB**, Wilschut J, Zauber AG, van Ballegooijen M*

Year: 2010

Lansdorp-Vogelaar et al. (2010)[30] conducted a cost-effectiveness analysis of stool DNA testing as a screening strategy for colorectal cancer among the Medicare population. The study found that stool DNA testing could be a cost-effective option if the test cost is reduced or if it leads to screening uptake among those who would otherwise remain unscreened. The analysis supports the inclusion of this non-invasive testing method in the screening options considered for Medicare beneficiaries.

This study was published in *Annals of Internal Medicine* in 2010. DOI: 10.7326/0003-4819-153-6-201009210-00006.

Cost-Effectiveness of CT Colonography to Screen for Colorectal Cancer: Report to the Agency for Healthcare Research and Quality and the Centers for Medicare and Medicaid Services from the Cancer Intervention and Surveillance Modeling Network

Authors: Ann G. Zauber, Amy B. Knudsen, Carolyn M. Rutter, Iris Lansdorp-Vogelaar, James E. Savarino, Marjolein van Ballegooijen, Karen M. Kuntz

Year: 2009

Zauber et al. (2009)[31] conducted a comprehensive cost-effectiveness analysis of computed tomographic colonography (CTC) as a screening modality for colorectal cancer (CRC). Utilizing three established microsimulation models—MISCAN, SimCRC, and CRC-SPIN—the study evaluated the life-years gained (LYG) and associated costs of CTC screening every five years, comparing it to other CRC screening strategies such as annual fecal occult blood testing (FOBT), flexible sigmoidoscopy every five years combined with FOBT, and colonoscopy every ten years.

This study provided critical insights for policymakers and healthcare providers, informing decisions regarding the inclusion of CTC as a reimbursable CRC screening option under Medicare. The findings underscored the importance of considering test costs, patient adherence, and comparative effectiveness when evaluating new screening technologies.

This report is available at https://www.ncbi.nlm.nih.gov/books/NBK284750/.

A Cost-Effectiveness Analysis of Folic Acid Fortification Policy in the United States

*Authors: Bentley TGK, Weinstein MC, Willett WC, **Kuntz KM***

Year: 2009

Bentley et al. (2009)[32] evaluated the cost-effectiveness of folic acid fortification policies in the U.S. Their analysis showed that increasing folic acid fortification could reduce the incidence of neural tube defects, myocardial infarctions, and colorectal cancer, leading to significant public health benefits and cost savings. The study concluded that folic acid fortification represents a highly cost-effective public health intervention.

This study was published in *Public Health Nutrition* in 2009. DOI: 10.1017/S1368980008002435.

Evaluating Test Strategies for Colorectal Cancer Screening—Age to Begin, Age to Stop, and Timing of Screening Intervals: A Decision Analysis for the U.S. Preventive Services Task Force from the Cancer Intervention and Surveillance Modeling Network (CISNET)

Authors: Ann G. Zauber, Iris Lansdorp-Vogelaar, Amy B. Knudsen, Janneke Wilschut, Marjolein van Ballegooijen, Karen M. Kuntz

Year: 2009

Zauber et al. (2009)[33] conducted a decision analysis to inform the U.S. Preventive Services Task Force (USPSTF) on optimal colorectal cancer (CRC) screening strategies, focusing on the appropriate ages to initiate and discontinue screening, as well as the intervals between screenings. Utilizing two microsimulation models from the Cancer Intervention and Surveillance Modeling Network (CISNET), the study evaluated various screening modalities—including fecal occult blood tests (FOBTs), flexible sigmoidoscopy, and colonoscopy—beginning at ages 40, 50, or 60, and ceasing at ages 75 or 85, with differing screening intervals.

This comprehensive analysis provided critical insights for the USPSTF, informing their recommendations on CRC screening practices aimed at maximizing benefits while considering resource utilization and patient burden.

The full report is available at https://www.ncbi.nlm.nih.gov/books/NBK34013/.

Evaluating Test Strategies for CRC Screening: A Decision Analysis for the U.S. Preventive Services Task Force

*Authors: Zauber AG, Lansdorp-Vogelaar I, **Knudsen AB**, Wilschut J, van Ballegooijen M, **Kuntz KM***

Year: 2008

The US Preventive Services Task Force commissioned CISNET CRC models to inform its 2008 CRC screening recommendations. Zauber et al.(2008)[34] used the SimCRC and MISCAN models to assess life-years gained and colonoscopy requirements for colorectal cancer screening strategies and identify a set of recommendable screening strategies. The findings supported colorectal cancer screening with colonoscopy every 10 years, annual screening with a sensitive FOBT, or flexible sigmoidoscopy every 5 years with a midinterval sensitive FOBT from age 50 to 75 years.

The study was published in *Annals of Internal Medicine* in 2008. DOI: 10.7326/0003-4819-149-9-200811040-00244

Cost-Effectiveness of DNA Stool Testing to Screen for Colorectal Cancer: Report to the Agency for Healthcare Research and Quality and the Centers for Medicare and Medicaid Services from the Cancer Intervention and Surveillance Modeling Network

*Authors: Zauber AG, Lansdorp-Vogelaar I, Wilschut J, **Knudsen AB**, van Ballegooijen M, **Kuntz KM***

Year: 2007

Zauber et al. (2007) [35] conducted a comprehensive cost-effectiveness analysis of DNA stool testing as a colorectal cancer (CRC) screening strategy. Using the MISCAN-Colon microsimulation model, the study compared the performance of DNA stool testing—then an emerging technology—to other established CRC screening modalities, including fecal occult blood tests (FOBT), flexible sigmoidoscopy, and colonoscopy.

The report informed federal decision-makers at AHRQ and CMS and contributed to early assessments of molecular-based CRC screening technologies, emphasizing the importance of comparative modeling to guide coverage and policy decisions.

This report is available at https://www.ncbi.nlm.nih.gov/books/NBK285164/.

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Stanford University
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Methods Relevant Analyses

Methods Relevant Analyses

Microsimulation Estimates of Decision Uncertainty and Value of Information Are Biased but Consistent
*Authors: Goldhaber-Fiebert JD, Jalal H, **Alarid-Escudero F***
Year:2025

Goldhaber-Fiebert et al. (2025)[1] showed that individual-level state-transition microsimulation models (iSTMs) produce biased but consistent estimates of the probability that interventions are cost-effective, and that iSTMs also produce biased but consistent estimates of the expected value of perfect information. The biases in these decision uncertainty and value-of-information measures are not reduced by more parameter sets being sampled from their population-level uncertainty distribution but rather by more individuals being microsimulated for each parameter set sampled. Analysts using iSTMs to quantify decision uncertainty and value of information should account for these biases when allocating their computational budgets and, at minimum, characterize such bias in their reported results.

This work was published in *Medical Decision Making* in 2025. DOI: 10.1177/0272989X241305414.

A Fast Nonparametric Sampling Method for Time to Event in Individual-Level Simulation Models
*Authors: Garibay D, Jalal H, **Alarid-Escudero F***
Year:2025

Garibay et al. (2024)[2] proposed a computationally efficient nonparametric sampling (NPS) method for modeling time-to-event processes in individual-level health decision models. The method offers an alternative to traditional parametric approaches, addressing challenges such as computational intensity and data distribution assumptions.

The study demonstrated that the NPS method improves computational efficiency while maintaining flexibility in modeling time-to-event data. Applications included simulating survival times and disease progression in a variety of contexts, showing that the approach is broadly applicable to complex individual-level models. This advancement is particularly valuable for large-scale simulations in health decision-making.

This work was published in *Medical Decision Making* in 2025. DOI: 10.1177/0272989X241308768.

Emulator-Based Bayesian Calibration of the CISNET Colorectal Cancer Models
*Authors: **Pineda-Antunez C**, **Seguin C**, van Duuren LA, **Knudsen AB**, Davidi B, Nascimento de Lima P, Rutter C, **Kuntz KM**, Lansdorp-Vogelaar I, Collier N, Ozik J, **Alarid-Escudero F***

Year:2024

In their study, Pineda-Antunez et al.(2024)[3] developed and applied an emulator-based Bayesian calibration approach for the CISNET Colorectal Cancer models. These models are used to simulate the natural history of colorectal cancer and evaluate the impact of interventions such as screening and treatment. The study utilized Bayesian methods to improve calibration efficiency by combining emulator-based techniques with Monte Carlo simulations, addressing computational challenges inherent in traditional calibration methods.

The results demonstrated that the emulator-based approach substantially reduced computational time while maintaining accuracy in model predictions. Key applications included the refinement of model parameters related to colorectal cancer progression, screening, and treatment effects, allowing for more precise evaluations of intervention strategies.

The study underscores the potential of advanced computational techniques, including neural networks and Bayesian methods, to enhance the calibration of complex disease models. These findings have implications for improving decision-making in cancer prevention and control. This work was published in *Medical Decision Making* in 2024. DOI: 10.1177/0272989X241255618.

A Tutorial on Time-Dependent Cohort State-Transition Models in R Using a Cost-Effectiveness Analysis Example

Authors: ***Alarid-Escudero F****, Krijkamp E, Enns EA, Yang A, Hunink MGM, Pechlivanoglou P, Jalal H*
Year:2023

Alarid-Escudero et al. (2022)[5] provided a comprehensive tutorial on time-dependent cohort state-transition models using R, demonstrating their application in cost-effectiveness analysis. The tutorial covered key concepts, model construction, and practical implementation, offering a step-by-step guide for researchers and practitioners.

This work serves as a valuable resource for advancing the use of state-transition modeling in decision science and health economics. The tutorial was published in *Medical Decision Making* in 2022. DOI: 10.1177/0272989X221121747.

An Introductory Tutorial on Cohort State-Transition Models in R Using a Cost-Effectiveness Analysis Example
Authors: ***Alarid-Escudero F****, Krijkamp E, Enns EA, Yang A, Hunink MGM, Pechlivanoglou P, Jalal H*
Year:2023

Alarid-Escudero et al. (2022)[6] provided an introductory tutorial on cohort state-transition models using R. The tutorial explained the principles of cost-effectiveness analysis and how to construct and implement such models in R. It highlighted the use of state-transition modeling in evaluating healthcare interventions and demonstrated its utility with practical examples.

This work serves as a foundational guide for researchers interested in applying modeling techniques to health decision science. The study was published in *Medical Decision Making* in 2022. DOI: 10.1177/0272989X221103163.

Characterization and Valuation of the Uncertainty of Calibrated Parameters in Microsimulation Decision Models
Authors: ***Alarid-Escudero F****,* ***Knudsen AB****, Ozik J, Collier N,* ***Kuntz KM***

Year:2022

Alarid-Escudero et al. (2022)[9] examined the uncertainty of calibrated parameters in microsimulation decision models. By characterizing and valuing this uncertainty, the study provided insights into its implications for model predictions and decision-making.

The research emphasized the importance of understanding and addressing parameter uncertainty to improve the reliability and robustness of microsimulation models. This study was published in *Frontiers in Physiology* in 2022. DOI: 10.3389/fphys.2022.780917.

BayCANN: Streamlining Bayesian Calibration With Artificial Neural Network Metamodeling
Authors: Jalal H, Trikalinos TA, ***Alarid-Escudero F***
Year:2021

Jalal et al. (2021)[10] introduced BayCANN, a method that combines Bayesian calibration with artificial neural network metamodeling to improve computational efficiency in model calibration. The approach allows for faster and more accurate parameter estimation, particularly for complex decision models used in health sciences.

This method represents a significant advancement in streamlining the calibration process for microsimulation and other decision models. The study was published in *Frontiers in Physiology* in 2021. DOI: 10.3389/fphys.2021.662314.

Estimating Population-Based Recurrence Rates of Colorectal Cancer Over Time in the US*Authors: Kunst N,* ***Alarid-Escudero F****, Aas E, Coupé VMH, Schrag D,* ***Kuntz KM***
Year:2020

Kunst et al. (2020)[11] conducted a comprehensive analysis to estimate population-based recurrence rates of colorectal cancer (CRC) in the United States over time. Using data from the SEER (Surveillance, Epidemiology, and End Results) program, the researchers developed recurrence models stratified by cancer stage, patient age, tumor location, and calendar year of diagnosis. Their modeling approach enabled the generation of nationally representative recurrence estimates that account for demographic shifts and evolving treatment practices.

The study revealed that recurrence rates have declined over time, likely reflecting advances in CRC treatment and earlier detection. Importantly, it highlighted variation in recurrence risk by stage and tumor site, with higher recurrence observed in advanced-stage and rectal cancers. These findings provide essential benchmarks for clinicians, researchers, and policymakers, informing post-treatment surveillance strategies, resource allocation, and comparative effectiveness studies.

This study was published in *Cancer Epidemiology, Biomarkers & Prevention* in 2020. DOI: 10.1158/1055-9965.EPI-20-0454.

Potential Bias Associated with Modeling the Effectiveness of Healthcare Interventions in Reducing Mortality Using an Overall Hazard Ratio
*Authors: **Alarid-Escudero F**, **Kuntz KM***
Year:2020

Alarid-Escudero and Kuntz (2020)[14] examined the potential biases introduced by using overall hazard ratios to model the effectiveness of healthcare interventions in reducing mortality. The study emphasized the limitations of such approaches in capturing the nuanced effects of interventions, advocating for alternative methods to improve accuracy in decision models.

The findings underscore the importance of refining modeling techniques to ensure reliable healthcare policy assessments. This work was published in *PharmacoEconomics* in 2020. DOI: 10.1007/s40273-019-00859-5.

Microsimulation Modeling for Health Decision Sciences Using R: A Tutorial
*Authors: Krijkamp EM, **Alarid-Escudero F**, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P*
Year:2019

Krijkamp et al. (2019)[17] provided a tutorial on microsimulation modeling using R for health decision sciences. The tutorial covered the construction, implementation, and analysis of state-transition models, offering practical guidance for researchers and practitioners.

This work serves as a comprehensive resource for advancing the application of microsimulation techniques in healthcare. The study was published in *Medical Decision Making* in 2019. DOI: 10.1177/0272989X18754513.

A Need for Change! A Coding Framework for Improving Transparency in Decision Modeling
*Authors: **Alarid-Escudero F**, Krijkamp EM, Pechlivanoglou P, Jalal H, Kao SZ, Yang A, Enns EA*
Year:2019

Alarid-Escudero et al. (2019)[18] proposed a coding framework to enhance transparency and reproducibility in decision modeling. The framework emphasized standardized coding practices and documentation to improve model interpretability and replicability.

This study serves as a critical resource for researchers seeking to enhance the quality of decision-analytic models. The research was published in *PharmacoEconomics* in 2019. DOI: 10.1007/s40273-019-00837-x.

"Time Traveling Is Just Too Dangerous" but Some Methods Are Worth Revisiting: The Advantages of Expected Loss Curves Over Cost-Effectiveness Acceptability Curves and Frontier
*Authors: **Alarid-Escudero F**, Enns EA, **Kuntz KM**, Michaud TL, Jalal H*
Year:2019

Alarid-Escudero et al. (2019)[19] advocated for the use of Expected Loss Curves (ELCs) over traditional Cost-Effectiveness Acceptability Curves (CEACs) and frontiers. The study highlighted how ELCs provide a more comprehensive understanding of decision uncertainty and the trade-offs involved in healthcare interventions.

This work underscores the importance of refining decision-support tools to improve clarity and impact in policy-making. The study was published in *Value in Health* in 2019. DOI: 10.1016/j.jval.2019.02.008.

A Gaussian Approximation Approach for Value of Information Analysis
*Authors: Jalal H, **Alarid-Escudero F***
Year:2018

Jalal and Alarid-Escudero (2018)[20] introduced a Gaussian approximation (GA) method to efficiently estimate the Expected Value of Sample Information (EVSI) in health decision analysis. Traditional Bayesian approaches to compute EVSI are computationally intensive, often requiring nested simulations. The proposed GA method simplifies this process by approximating the preposterior distributions using a two-step approach:

1. **Linear Metamodeling:** Utilizing a single probabilistic sensitivity analysis (PSA) dataset, a linear metamodel estimates the relationship between model inputs and outputs, facilitating the computation of EVSI on the preposterior distributions.
2. **Gaussian Approximation:** The preposterior distribution of the parameters of interest is approximated using Gaussian distributions, streamlining the estimation process.

This method significantly reduces computational burden while maintaining accuracy, making EVSI calculations more accessible for informing research prioritization and study design decisions in health economics. The authors demonstrated the effectiveness of the GA approach through applications to various data collection scenarios, showing its potential to enhance decision-making processes in healthcare resource allocation.

This study was published in *Medical Decision Making* in 2018. DOI: 10.1177/0272989X17715627.

Nonidentifiability in Model Calibration and Implications for Medical Decision Making
*Authors: **Alarid-Escudero F**, MacLehose RF, Peralta Y, **Kuntz KM**, Enns EA*
Year:2018

Alarid-Escudero et al. (2018)[21] explored the issue of nonidentifiability in model calibration and its implications for medical decision-making. The study emphasized the need for clear reporting and improved methodologies to address nonidentifiability in decision models.

This work provides valuable insights for researchers to ensure transparency and reliability in health decision sciences. The study was published in *Medical Decision Making* in 2018. DOI: 10.1177/0272989X18792283.

Linear Regression Metamodeling as a Tool to Summarize and Present Simulation Model Results
*Authors: Jalal H, Dowd B, Sainfort F, **Kuntz KM***
Year:2013

Jalal et al. (2013)[25] proposed linear regression metamodeling as a practical and interpretable approach to summarize outputs from complex health simulation models. These metamodels, which approximate the relationship between model inputs and outcomes using standard regression techniques, provide a simplified representation of the full model's behavior. This technique allows researchers and decision-makers to better understand key drivers of outcomes, conduct sensitivity analyses, and communicate results more effectively.

The authors illustrated the method using a colorectal cancer simulation model, demonstrating how metamodels can capture nonlinearities, interaction effects, and uncertainty in model parameters. Importantly, they showed that regression metamodels can reduce computational burden while maintaining high fidelity to the original model results. This approach enhances transparency, facilitates stakeholder engagement, and supports more informed policy decision-making in health economics and medical decision modeling.

This study was published in *Medical Decision Making* in 2013. DOI: 10.1177/0272989X13492014.

State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force
Authors: Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, ***Kuntz KM***
Year:2012

Siebert et al. (2012)[26] provided comprehensive guidelines on the application of state-transition modeling in healthcare decision analysis. They discussed the versatility and transparency of state-transition models, including both cohort simulations and individual-based microsimulations. The report offers best practice recommendations on model structure, parameterization, analysis, and reporting, aiming to enhance the reliability and credibility of health economic evaluations using these models.

This study was published in *Medical Decision Making* in 2012. DOI: 10.1177/0272989X12455463.

Modeling Good Research Practices—Overview: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1
Authors: Caro JJ, Briggs AH, Siebert U, ***Kuntz KM***
Year:2012

Caro et al. (2012)[27] provided an overview of best practices in health care modeling as part of the ISPOR-SMDM Modeling Good Research Practices Task Force. The article introduced a series of recommendations aimed at improving the conceptualization, implementation, and validation of health care models. The authors emphasized the importance of transparency, methodological rigor, and the appropriate handling of uncertainty in modeling studies. This work serves as a foundational guide for researchers and policymakers involved in health technology assessment and decision-making processes.

This study was published in *Medical Decision Making* in 2012. DOI: 10.1177/0272989X12454577.

A Systematic Comparison of Microsimulation Models of Colorectal Cancer: The Role of Assumptions About Adenoma Progression
Authors: ***Kuntz KM****, Lansdorp-Vogelaar I, Rutter CM,* ***Knudsen AB****, van Ballegooijen M, Savarino JE, Feuer EJ, Zauber AG*
Year:2011

Kuntz et al. (2011)[29] compared microsimulation models of colorectal cancer, focusing on the assumptions about adenoma progression. The study assessed how these assumptions influence model predictions and their implications for screening policies.

This work highlights the importance of transparency in modeling assumptions for informed decision-making. The study was published in *Medical Decision Making* in 2011. DOI: 10.1177/0272989X11408730.

Clarifying Differences in Natural History Between Models of Screening: The Case of Colorectal Cancer
Authors: van Ballegooijen M, Rutter CM, ***Knudsen AB****, Zauber AG, Savarino JE, Lansdorp-Vogelaar I, Boer R, Feuer EJ, Habbema JD,* ***Kuntz KM***
Year:2011

Van Ballegooijen et al. (2011)[30] explored differences in the natural history assumptions of colorectal cancer across microsimulation models. The study identified how these differences impact predictions for screening effectiveness.

The findings emphasize the need for standardized assumptions to improve model comparability. This research was published in *Medical Decision Making* in 2011. DOI: 10.1177/0272989X11408915.

Calibration methods used in cancer simulations models and suggested reporting guidelines
Authors: Stout NK, ***Knudsen AB****, McMahon PM, Kong CY, Gazelle GS*
Year:2009

Stout et al. (2009)[31] surveyed the literature to catalogue the use and reporting of calibration methods in cancer simulation models. To aid peer-review and facilitate discussion of modelling methods, the authors propose a standardized Calibration Reporting Checklist for model documentation.

The study was published in *PharmacoEconomics* in 2009. DOI: 10.2165/11314830-000000000-00000

Assessing the Comparative Effectiveness of an Evolving Diagnostic Technology: The Case of CT Colonography

*Pearson SD, **Knudsen AB**, Scherer RW, Weissberg J, Gazelle GS*
Year:2008

Pearson et al. (2008)[33] discuss the challenges and policy lessons for manufacturers, evidence reviewers, and decisionmakers, in performing comparative-effectiveness analyses of an emerging diagnostic technology: computed tomography (CT) colonography.

The study was published in *Health Affairs* in 2008. DOI: 10.1377/hlthaff.27.6.1503.

A Potential Error in Evaluating Cancer Screening: A Comparison of 2 Approaches for Modeling Underlying Disease Progression
*Authors: Goldie SJ, **Kuntz KM***
Year:2003

Goldie and Kuntz (2003)[35] investigated the potential errors in evaluating cancer screening programs that arise from differing assumptions about disease progression in modeling. They compared two approaches: one that assumes a strictly progressive disease pathway and another that allows for disease regression or non-progression. Their results showed that omitting the possibility of regression can lead to overestimated benefits of screening interventions. The study emphasizes the critical need to consider the nature of disease progression when constructing decision models to evaluate cancer screening effectiveness.

This study was published in *Medical Decision Making* in 2003. DOI: 10.1177/0272989X03023003005.

Assessing the Sensitivity of Decision-Analytic Results to Unobserved Markers of Risk: Defining the Effects of Heterogeneity Bias
*Authors: **Kuntz KM**, Goldie SJ*
Year:2002

Kuntz and Goldie (2002)[36] examined the impact of unobserved heterogeneity on the outcomes of decision-analytic models. They found that failing to account for population heterogeneity due to unobserved variables can lead to significant bias in model results, which they term "heterogeneity bias." Specifically, life expectancy gains predicted by models that do not adjust for heterogeneity were consistently greater than those predicted by models that did. The study emphasized the importance of recognizing and adjusting for unobserved sources of heterogeneity to ensure accurate and reliable model outcomes. This work provides a structured framework for analysts to assess when heterogeneity may be a critical factor in decision modeling.

This study was published in *Medical Decision Making* in 2002. DOI: 10.1177/0272989X0202200310.

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