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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

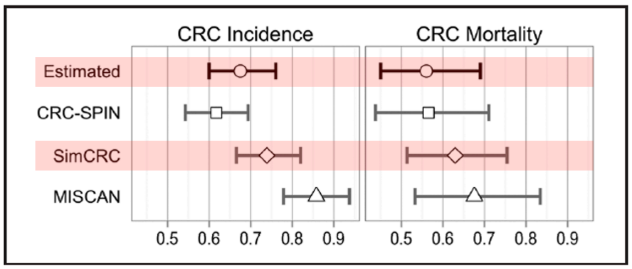

Figure 2 Hazard ratios: study-estimated and model-predicted intervention effects, with 95% percentile intervals for model predictions and 95% confidence intervals for estimates. Both estimated and predicted hazard ratios compare screening-adherent intervention participants to control participants who 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

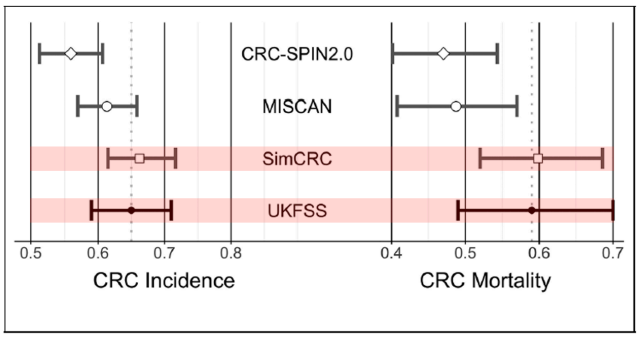

Figure 1 Hazard ratios. The United Kingdom Flexible Sigmoidoscopy Screening (UKFSS) Trial–estimated and model-predicted hazard ratios for intervention effects. Point estimates as well as 95% confidence or credible intervals for model predictions and 95% confidence intervals for estimates are displayed. 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

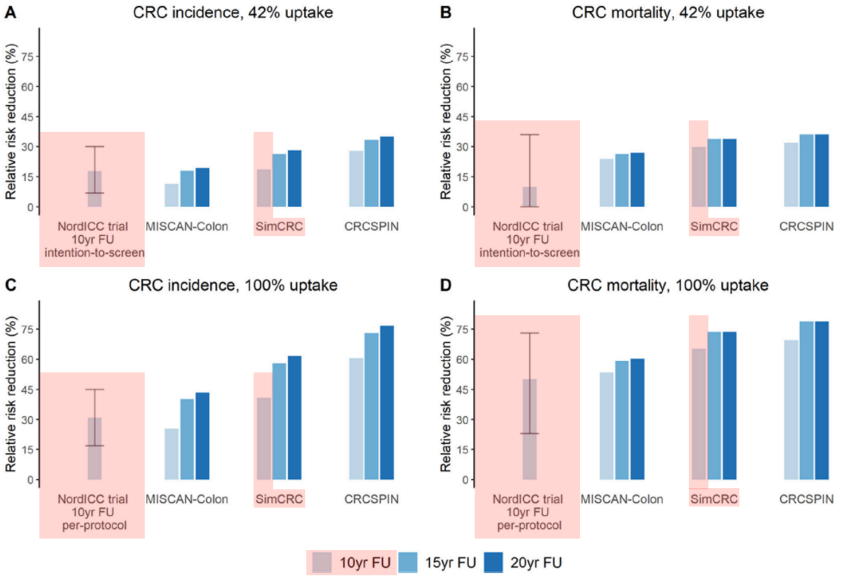

Figure 1. Relative risk reductions in CRC incidence (*A*, *C*) and CRC mortality (*B*, *D*) compared to no screening for 2 different uptake scenarios (42% and 100% uptake) and 3 different follow-up durations (10, 15, and 20 years). CRCSPIN, Colorectal Cancer Simulated Population Model for Incidence and 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.

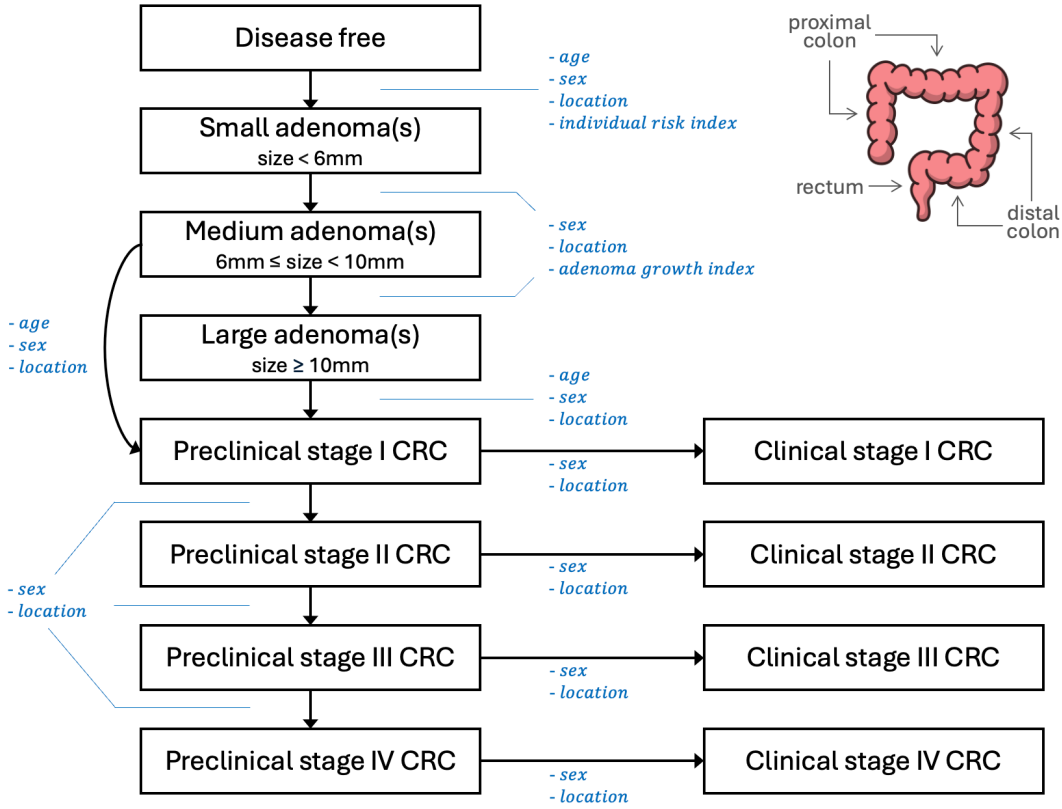
We are currently updating the model to incorporate the sessile-serrated polyp pathway.

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].

References

1. Rutter CM, Johnson EA, Feuer EJ, Knudsen AB, Kuntz KM, Schrag D. Secular trends in colon and rectal cancer relative survival. Journal of the National Cancer Institute. 2013;105(23):1806–1813.

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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

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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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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