Original Research Article

MDM Policy & Practice

MDM Policy & Practice
2023, Vol. 8(1) 1–13

DOI: 10.1177/23814683221145701
journals.sagepub.com/home/mpp
SAGE

Modeling the Natural History and Screening Effects of Colorectal Cancer Using Both Adenoma and Serrated Neoplasia Pathways: The Development, Calibration, and Validation of a Discrete Event Simulation Model

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Abstract

Background. Existing colorectal cancer (CRC) screening models mostly focus on the adenoma pathway of CRC development, overlooking the serrated neoplasia pathway, which might result in overly optimistic screening predictions. In addition, Bayesian inference methods have not been widely used for model calibration. We aimed to develop a CRC screening model accounting for both pathways, calibrate it with approximate Bayesian computation (ABC) methods, and validate it with large CRC screening trials. **Methods.** A discrete event simulation (DES) of the CRC natural history (DECAS) was constructed using the adenoma and serrated pathways in R software. The model simulates CRC-related events in a specific birth cohort through various natural history states. Calibration took advantage of 74 prevalence data points from the German screening colonoscopy program of 5.2 million average-risk participants using an ABC method. CRC incidence outputs from DECAS were validated with the German national cancer registry data; screening effects were validated using 17-y data from the UK Flexible Sigmoidoscopy Screening sigmoidoscopy trial and a German screening colonoscopy cohort study. **Results.** The Bayesian calibration rendered 1,000 sets of posterior parameter samples. With the calibrated parameters, the observed age- and sex-specific CRC prevalences from the German registries were within the 95% DECAS-predicted intervals. Regarding screening effects, DECAS predicted a 41% (95% intervals 30%–51%) and 62% (95% intervals 55%–68%) reduction in 17-y cumulative CRC mortality for a single screening sigmoidoscopy and colonoscopy, respectively, falling within 95% confidence intervals reported in the 2 clinical studies used for validation. **Conclusions.** We presented DECAS, the first Bayesian-calibrated DES model for CRC natural history and screening, accounting for 2 CRC tumorigenesis pathways. The validated model can serve as a valid tool to evaluate the (cost-)effectiveness of CRC screening strategies.

Highlights

- This article presents a new discrete event simulation model, DECAS, which models both adenoma-carcinoma and serrated neoplasia pathways for colorectal cancer (CRC) development and CRC screening effects.
- DECAS is calibrated based on a Bayesian inference method using the data from German screening colonoscopy program, which consists of more than 5 million first-time average-risk participants aged 55 years and older in 2003 to 2014.

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- DECAS is flexible for evaluating various CRC screening strategies and can differentiate screening effects in different parts of the colon.
- DECAS is validated with large screening sigmoidoscopy and colonoscopy clinical study data and can be further used to evaluate the (cost-)effectiveness of German colorectal cancer screening strategies.

Keywords
colorectal cancer, serrated polyps, screening, discrete event simulation, bayesian calibration

Date received: May 8, 2022; accepted: November 28, 2022

Colorectal cancer (CRC) is among the most common cancers and a leading cause of cancer mortality globally, as well as in Germany,[1,2] where 58,100 new cases and 24,048 CRC deaths are estimated in 2022.[3] Early detection through screening and removal of CRC precursors by endoscopy has been shown to be effective in reducing CRC incidence and mortality[4,5]; however, a significant proportion of postcolonoscopy (or interval) cancers occur in the proximal colon.[6] The contributing factors are not only technical (e.g., missed lesion or incomplete resection)[7] but also biological (e.g., morphology of the lesions).[8,9]

Knowledge of CRC tumorigenesis has accrued in the past 2 decades. In addition to the long-established adenoma-carcinoma pathway,[10] consensus has grown that the serrated neoplasia pathway can play an important role.[11,12] A subset of serrated lesions, sessile serrated adenomas/polyps (SSA/Ps) and traditional serrated adenomas (TSAs), are regarded as precancerous.[8,12] Moreover, certain hyperplastic polyps (HPs) are found to share the same genetic mutations as SSA/Ps and TSAs, suggesting that HPs could be their precursor.[8,12] Serrated lesions are largely flat or nonpolypoid in morphology and located in the proximal colon, contributing to 15% to 30% of CRCs[12,13] and to proximal interval cancer.[6]

Mathematical screening models help forecast effectiveness and costs of various CRC screening strategies and can inform health policy decisions, and individual-based models have played a big role.[14–16] Nevertheless, the serrated pathway of CRC tumorigenesis has not been routinely incorporated in screening models,[17] despite its growing importance in CRC formation. To our knowledge, only 2 published models, the ASCCA[18] and Policy1-Bowel[16] models, have built in both tumorigenesis pathways.

An essential part of a screening model is simulating the natural history of the disease. This poses a great challenge because the rates at which the disease progresses along the tumorigenesis pathways are not directly observable. Thus, direct estimation of the required parameters from available evidence is impossible.[19] These rates are mostly estimated through calibration, that is, the process of adjusting parameter values until a good fit between the model predictions and real-world observable data ("calibration targets") is achieved.[20,21] Among the parameter search algorithms, the downhill simplex method (also known as the Nelder-Mead method) is the most commonly used in model calibration of CRC screening microsimulation models, including ASCCA and Policy1-Bowel.[14,16,18,22] However, it renders only 1 best-fit parameter set at the end of the process, which does not capture uncertainty around fitted parameters.[19]

Given that assessing the impact of parameter uncertainty is good practice in modeling,[23] some modelers apply Bayesian methods.[24–26] Bayesian inference approaches summarize knowledge and uncertainty about parameter values in the form of probability distributions. In particular, the prior distribution of parameters is updated

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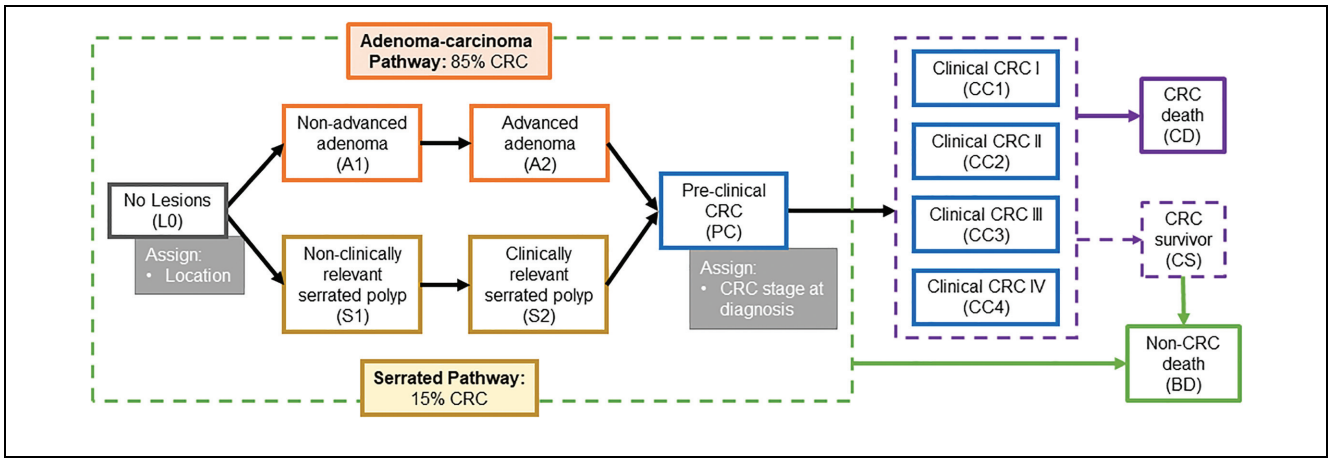

Figure 1 DECAS schematic model structure. CRC, colorectal cancer.

according to the data evidence, generating a joint posterior distribution of parameters conditional on the data, reflecting residual parameter uncertainty and correlation.[27,28] Approximate Bayesian computation (ABC) methods, which are among the popular Bayesian approaches, have been widely applied to high-dimension dynamic models in various fields.[29] ABC methods bypass the challenge of calculating likelihood functions in complex models, and they take advantage of modern computational capability to compare the simulated and observed data to approximate the posterior distribution.[29]

In Germany, stool-based and colonoscopy CRC screening tests have been offered to the population for more than 20 years,[30] and the screening programs have shown significant benefits in reducing CRC mortality.[31] Nevertheless, with changes like the introduction of novel tests for CRC screening[32] and increased incidence of CRC in younger populations,[33] it is unknown if the current CRC screening program requires adjustments. Before any definitive evidence can be obtained from clinical studies, simulation studies using CRC screening models are most commonly used to inform policy makers about the benefits and costs of different hypothetical screening policies. To date, there are 2 cohort-based CRC screening models designed for the German setting, which, however, consider only the adenoma pathway.[34,35] Hence, there is still a need to develop an individual-based model accounting for both CRC carcinogenesis pathways for the German setting.

In this article, we present a discrete event simulation (DES) of the natural history of colorectal cancer that accounts for both adenoma-carcinoma and serrated neoplasia pathways (DECAS). This model was calibrated using an ABC method with large data sets from the German screening colonoscopy program. The model was then applied to population screening and validated with data from 1 of the largest sigmoidoscopy trials from the United Kingdom and a long-term screening colonoscopy cohort study from Germany.

Methods

Given that the time-to-event approach provides a more efficient solution than state-transition models for the problems needed to be followed up for longer term (e.g., screening models with lifetime follow-up), as one can avoid checking periodically when none of the events happen in most of the cycles,[27] a DES model, DECAS, was developed. DECAS simulates the natural history of colorectal cancer from age 20 years until 90 years, or death. The occurrence of events (lesion initiation, progression, and death) is conditioned to the state occupation, ensuring that patients progress through the randomly assigned pathway.[36] The recommendations of ISPOR-SMDM Modeling Good Research Practice Task Force were followed.[37,38] See Appendix A for the DECAS pseudocode.

CRC Natural History

DECAS simulates 2 CRC tumorigenesis pathways: the adenoma-carcinoma pathway and the serrated neoplasia pathway (see Figure 1). The precancer lesions progress from nonadvanced to advanced stages, to preclinical (asymptomatic), and then to clinical (symptomatic) cancers. Each simulated individual may develop up to 20 adenomas or serrated polyps throughout the simulated time horizon.[18] DECAS does not consider lesion regression. Advanced adenoma (AA) is defined as adenomas

Table 1 Summary of DECAS Parameters

Model Parameters	Prior Distribution	Posterior Estimates		Reference
		Mean	95% CrI	
Precancerous lesion initiation (L0 to A1 or S1)				
Adenoma				
Baseline log-risk, mean	~ U(−9, −4.6)	−7.240	(−8.899, −4.970)	Rutter,[25] US Preventive Services Task Force,[32] and Robert Koch Institute[48]
Baseline log-risk, standard deviation	~ U(0.8, 5.4)	2.723	(1.693, 4.096)	
Sex effect	~ U(−0.65, 0)	−0.373	(−0.628, −0.078)	
Age effect, 20 ≤ age < 50 years	~ U(−0.06, 0.1)	0.023	(−0.035, 0.072)	
Age effect, 50 ≤ age < 70 years	~ U(−0.1, 0.15)	0.035	(−0.083, 0.137)	
Age effect, age ≥ 70 years	~ U(−0.1, 0.2)	0.036	(−0.091, 0.181)	
Serrated polyp				
Baseline log-risk, mean	~ U(−9.8, −5.4)	−8.648	(−9.744, −6.696)	Assumption based on Vanness[20] and Rutter[25]
Baseline log-risk, standard deviation	Same as in adenoma			
Sex effect	~ U(−0.65, 0.25)	−0.265	(−0.606, 0.142)	
Age effect, 20 ≤ age < 50 years	~ U(−0.12, 0.06)	0.018	(−0.033, 0.055)	
Age effect, 50 ≤ age < 70 y	~ U(−0.12, 0.15)	−0.005	(−0.111, 0.118)	
Age effect, age ≥ 70 years	~ U(−0.12, 0.2)	0.026	(−0.112, 0.185)	
Progression to the advanced stage of precancerous lesion (A1 to A2 or S1 to S2)				
Hazard of non-AA progressing to AA	~ U(0.002, 0.3)	0.004	(0.002, 0.012)	Assumption based on Vanness,[20] Rutter,[25] and Brenner[49]
Hazard of non-crSP progressing to crSP	~ U(0.002, 0.6)	0.014	(0.005, 0.040)	
Progression to preclinical cancer (A2 or S2 to PC)				
Adenoma				
Base risk of colonic lesion progressing to pre-clinical cancer, male at age 20 years	~ U(0.002, 0.3)	0.005	(0.002, 0.014)	Assumption based on Rutter,[25] US Preventive Services Task Force,[32] and Brenner[49]
Location effect, rectum	~ U(2, 30)	5.871	(2.192, 23.252)	
Age effect, 50 ≤ age < 70 years	~ U(1, 5)	1.923	(1.040, 4.384)	
Age effect, age ≥ 70 years	~ U(1.2, 10)	4.004	(1.439, 9.395)	
Serrated polyp				
Base risk of colonic lesion progressing to pre-clinical cancer, male at age 20 years	~ U(0.002, 0.6)	0.004	(0.002, 0.008)	Assumption based on Vanness[20] and Rutter[25]
Location effect, rectum	~ U(4, 50)	18.897	(6.133, 47.341)	
Age effect, 50 ≤ age < 70 years	~ U(1, 5)	1.651	(1.022, 3.624)	
Age effect, age ≥ 70 years	~ U(1.2, 10)	3.761	(1.404, 9.123)	

A1, nonadvanced adenoma; A2, advanced adenoma; CrI, credible interval; ~ U(a, b) denotes the uniform distribution bounded by (a, b); L0, no lesions; PC, preclinical cancer; S1, nonclinically relevant serrated polyp; S2, clinically relevant serrated polyp.

>10 mm, with villous components or high-grade dysplasia[31]; clinically relevant serrated polyps (crSP) such as those ≥10 mm or >5 mm if located proximally to the splenic flexure.[39,40] DECAS takes 21 inputs specifying the progression-related parameters to randomly generate times to events (see Table 1). All parameter priors were assumed to be uniformly distributed (as required by the calibration algorithm[41]). The model was programed in R software (version 4.0.4).

Precancerous lesion initiation (state L0 to A1 or S1). The risk of developing adenomas or serrated polyps varies among individuals. This was modeled using a nonhomogeneous Poisson process.[42] The baseline individual risk of developing precancerous lesions was assumed to be lesion specific and lognormally distributed. This allows the majority to remain free from precancerous lesions, with a minority prone to developing 1 or more lesions, as seen in the literature.[43] The risks over time of developing an adenoma or serrated polyp were assumed to be a function of the baseline individual risk, sex, and piecewise age effects.[44] Piece was specified for 3 intervals: age 20 to 49 years, 50 to 69 years, and 70 yeats and older. The mathematical formulation of the risk of precancerous lesion is given in Equation B1, Appendix B. The prior ranges for adenoma-related parameters were informed by Rutter et al.[42]; for serrated polyp parameters, analogous ranges were assumed.[16,18]

Progression to the advanced stage of precancerous lesion (state A1 to A2 or S1 to S2). Once a lesion, either

adenoma or non-crSP, appeared in the model, its location (proximal, distal colon or rectum) was assigned based on the proportions reported.[18,40] A constant risk for adenoma progressing to AA[45] and for non-crSP to crSP was assumed. The prior ranges of the parameters were informed by the annual transition probability estimated by Brenner et al.[46] and Policy1-Bowel.[16]

Progression to preclinical cancer (A2 or S2 to PC). In DECAS, only AA and crSP can progress to preclinical CRC, based on a nonhomogeneous Poisson process. For each pathway, the risk to progression is a function of location and a piecewise constant with change points at the age 50 and 70 years (see Equation B2 in Appendix B).[45] The prior ranges were informed as by Brenner et al.[44,46] and Policy1-Bowel.[16]

Cancer detection (PC to CC). The first lesion becoming preclinical cancer determined the cancer stage at detection and the respective stage-specific 10-y survival, which were input directly based on the CRC stage distribution and survival data from the literature.[47–49] When preclinical cancers became symptomatic, they are detected as clinical cancers. The time from the start of being a preclinical cancer until clinical cancer detection, defined as sojourn time, was randomly drawn from a Weibull distribution[25] with shape and scale parameters equal to 5.4 and 5.1, respectively. This yields a mean of 4.7 years with a standard deviation of 1, covering the reported sojourn time range.[45]

Death (any to BD or CC to CD). Individuals could die from noncancer causes at any time, whereas only patients with a clinical cancer were subject to cancer-specific death. Cancer patients surviving beyond 10 years suffered only noncancer mortality thereafter.[18]

Model Calibration: An ABC Approach

Let θ be the parameter set to be estimated, $\pi(\theta)$ be its prior distribution, and $f(s|\theta)$ be the likelihood function of θ for a set of summary statistics s, representing a reduction of the data y to a lower dimensional set. ABC aims to approximate the posterior distribution, $\pi(\theta|s) \propto f(s|\theta)\pi(\theta)$, while avoiding direct computation of the likelihood $f(s|\theta)$.[35] This is accomplished by repeatedly drawing samples θ^* from the prior, simulating summary statistics s according to the model $f(s|\theta^*)$, and retaining the proposed samples if the simulated output s and the observed data summary statistics s_y have distance $d(s_y, s) < \epsilon$, for a prespecified distance measure d and tolerance ϵ (see Appendix C for the generic algorithm).[50] After a suitable number of iterations, N samples of the parameter set θ are obtained from the distribution $\pi(\theta|d(s_y, s) \leq \epsilon)$, which should be a good approximation for the posterior distribution $\pi(\theta|s_y)$ if ϵ is small enough.[50]

For DECAS calibration, we chose the adaptive population Monte Carlo (APMC) algorithm,[51] which has been demonstrated to converge to the target distribution faster than some other well-known ABC algorithms while maintaining the quality of posterior approximation for complex models.[51,52] APMC is a multistep procedure that starts from an initial sample set $\theta_i^*, \ldots \theta_N^*$ from the prior distribution $\pi(\theta)$ with a related initial tolerance ϵ_1. It involves sequential importance sampling[53] of a prespecified proportion α of the samples while automatically downward adjusting ϵ in each step, and it stops when reaching the predefined threshold of the proposed sample acceptance rate $p_{acc_{min}}$.[51] See Appendix D for more details of the APMC algorithm.

During calibration, a population of 30,000 was simulated, similar in size to each 5-y age group in the screening registry.[43] After confirming sensible prior ranges from test runs, a pilot run sampled 50,000 parameter sets using Latin Hypercube[19] to explore the prior spaces efficiently (Table 1). Given the pilot results, the ABC rejection sampler was used to select 1,000 samples with the smallest standard deviation–weighted Euclidean distance. According to the selected samples, the prior ranges were adjusted.[54] The APMC algorithm was then applied via the R package EasyABC[41] using $\alpha = 0.1$ and $p_{acc_{min}} = 0.05$ (as suggested in Lenormand et al.[51]) with 10,000 simulations in each cycle. Parallel computing used a 60-core cluster.

Data Sources

Some parameters were not calibrated but directly input to the model: the location of the adenoma and serrated polyp in the colon and rectum were informed by screening colonoscopy studies[18,40] (see Appendix E Table E1). Clinical cancer stage distribution and stage-specific CRC mortality were input from the Bavarian Cancer Registry data[47,55] (see Appendix E Table E2). The background mortality was taken from the German life table 2010–2014,[48] and it was adjusted by removing CRC-specific mortality from the German Centre for Cancer Registry Data (ZfKD) in the same period[49] (see Appendix E Table E3). The mean sojourn time was taken as 4.7 years (95% confidence interval [CI] 4.5, 4.9) from a study using German screening colonoscopy registry data.[45]

To calibrate the model (see Appendix F), 74 CRC epidemiological data points were used as targets based on the data from the German screening colonoscopy registry.[43] Adenoma prevalence was obtained from the registry data on 3.3 million first-time average-risk participants aged 55 years and older in the period 2007 to 2014. For CRC prevalence, the period 2003 to 2006, when the effect of screening colonoscopy on CRC incidence was still minimal, was used. The serrated polyp prevalence and the proportion of multiple lesions were calibrated using a study that included 4,161 screening colonoscopies among average-risk individuals aged 50 years and older in North Rhine–Westphalia, Germany, during 2012 to 2016.[40] The prevalence for 40 to 49 years old was derived by applying the proportion from a meta-analysis of screening colonoscopy studies,[56] and all target prevalences were upward corrected considering a colonoscopy miss rate from a meta-analysis.[57]

Approximately 15% to 30% of CRCs arise via the serrated pathway.[8,12] In DECAS, 15% was assumed for easier comparison with other studies.[16,18] These proportions were applied to the calibration target prevalence to derive the prevalence of CRCs developing from adenoma or serrated polyps, respectively.

Natural History Model Validation

DECAS was validated according to good practice guidelines to assess the prediction credibility.[38] Concerning the external validity of the natural history model, the DECAS-predicted age- and sex-specific CRC incidences were compared with the data from ZfKD in 2003 to 2006[49] (see Appendix G).

Screening Model Validation

The screening module with the flexibility accommodating various screening tests is superimposed on the natural history model, with the time-to-screening or time-to-surveillance competing with time-to-events in CRC natural history. Before any lesion reaches the clinical cancer state, all lesions in an individual are subject to detection by screening or surveillance tests and will be removed upon detection by screening, follow-up, or surveillance colonoscopy. Screening detected cancer stage distribution was applied based on the German screening colonoscopy registry data[43] (see Appendix E Table E2). More details on the setting of the DECAS screening model are in Appendix H.

Taking the posterior parameters from the calibration, the DECAS screening model was validated against 2 clinical studies: the UK Flexible Sigmoidoscopy Screening (UKFSS) trial[58] and a large German colonoscopy cohort study (ESTHER).[59] The UKFSS trial is one of the largest randomized control trials (RCTs) evaluating one-time flexible sigmoidoscopy, in which 170,432 participants aged between 55 and 64 years were recruited across the United Kingdom from 1990 to 1994 and followed up for a median of 17 years.[58] The trial is well suited for screening model validation, as it was a one-off flexible sigmoidoscopy screening in the era when CRC screening was yet in place, which avoids the "contamination" in the control group.[60]

Moreover, given that DECAS screening model will eventually be used to evaluate the screening program in Germany where colonoscopy screening is implemented, an additional validation against the ESTHER study was conducted to evaluate the effect of a single colonoscopy screening. The ESTHER study is an ongoing prospective population-based cohort study conducted in Saarland, Germany, in which 9,949 male and female aged 50 to 75 years were recruited in 2000 to 2002 and followed up for 17 years.[59] The detailed setup of the 2 validation studies, including cohort demographics, test sensitivities, and screening management algorithm, is contained in Appendix H. The primary outputs for comparison were the hazard ratios (HRs) for CRC incidence and mortality rates between the screening group and no-screening group over 17 years. DECAS predictions will be deemed accurate if the mean HRs are within the 95% CIs of the estimates from the clinical studies.

Funding Statement

CYC was supported by a 3-year PhD studentship from the Helmholtz International Graduate School for Cancer Research. The funder had no role in the study.

Results

Calibration Results

After the pilot run, the APMC algorithm took 11 cycles to reach the threshold $p_{acc_{min}} \leq 0.05$. The final 1,000 parameter sets were taken from the $\alpha = 0.1$ portion of the 10,000 simulations in the last cycle. The calibration took 10 days.

In general, the APMC algorithm converged well for the parameters determining the rates (e.g., baseline risks, progression to advanced-stage precancer lesions, and base risk for progressing to cancer), as can be seen when comparing parameter distributions between the first and final cycles of APMC (Appendix I). Table 1 shows the

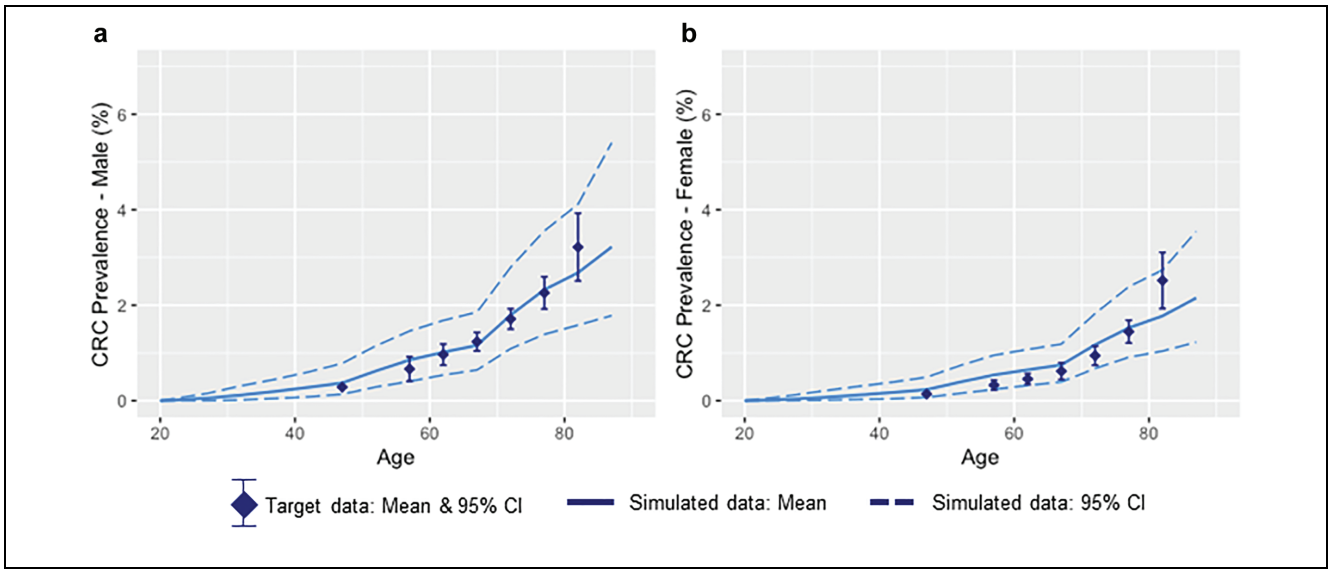

Figure 2 Model-predicted colorectal cancer (CRC) prevalence (a) in men and (b) in women compared with calibration targets. Target data references: Leshno et al.[56] and the German screening colonoscopy registry.[43]

summary statistics of the posterior samples of each parameter. We plotted DECAS outputs derived from the final posterior parameter samples against the calibration targets (Figure 2 and Appendix I), and the 95% credible intervals of the simulated results captured all calibration targets, with less ideal fit for the male and female's crSP prevalence in their 80's (Appendix I).

Natural History Validation Results

A gastroenterologist experienced in colonoscopy and an epidemiologist specialized in CRC screening felt that, upon their evaluation, DECAS had strong face validity of the structure, parameters, and data sources. The implementation of DECAS was validated by an experienced modeler outside of the project team. A systematic approach was taken to perform stepwise parameter alteration and observe the corresponding output change to ensure that DECAS produced reasonable outputs consistently. Comparison of the age- and sex-specific CRC incidence with ZfKD data demonstrated the predictive power of DECAS (Figure 3).

Screening Model Validation Results

In the validation against the UKFSS trial, DECAS predicted 36% (95% predicted intervals of the HR 0.52–0.77) and 41% (95% predicted intervals of the HR 0.49–0.70) reductions in the 17-y CRC incidence and mortality rates between the screening group and control group. The mean and 95% predicted intervals corresponded well with the estimates from the UKFSS trial (Table 2 and Figure 4). As for the validation with the ESTHER study, DECAS estimated that the 17-y CRC incidence and mortality rates were reduced by 63% (95% predicted intervals of the HR 0.31–0.44) and 62% (95% predicted intervals of the HR 0.32–0.45), respectively, in the screening colonoscopy cohort. The predictions from DECAS also reached the predefined accuracy (Table 2 and Figure 4).

Discussion

DECAS, a CRC natural history and screening model, considers both adenoma-carcinoma and serrated neoplasia pathways. The natural history model was calibrated by using an ABC algorithm, APMC, which allowed estimation of 21 input parameters and their uncertainties. The calibration made use of years of nationwide data from the German screening colonoscopy program containing information on millions of participants. Through the validation exercises, DECAS demonstrated the ability to reproduce real-world CRC incidence in Germany as well as the screening benefits shown in a sigmoidoscopy trial and a screening colonoscopy cohort study.

DECAS is one of the few CRC natural history and screening models that incorporate both adenoma-carcinoma and serrated neoplasia pathways for CRC

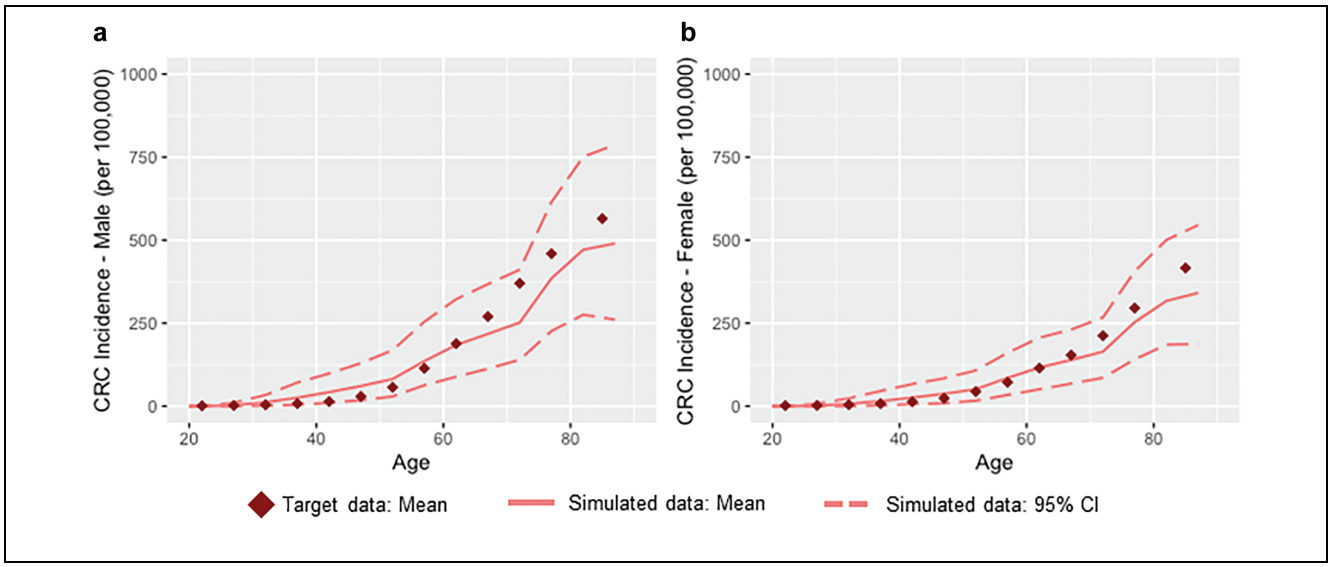

Figure 3 Model-predicted colorectal cancer incidence (a) in men and (b) in women compared with data from the German national cancer registry. Target data references: the German Centre for Cancer Registry Data (ZfKD).[49]

Table 2 Comparison of Hazard Ratios Between Screening and No Screening and 17-year Rates of CRC Incidence and Mortality Estimated by Clinical Studies and DECAS

			17-year rate per 100,000 person-years	
Output	**Source**	**Hazard ratio (Mean, 95% CI) CrI**	**Control (Mean, 95% CI) CrI**	**Screening (Mean, 95% CI) CrI**
UKFSS trial[58] compared with DECAS				
CRC incidence	UKFSS	0.65 (0.59–0.71)	184 (178–191)	120 (112–128)
	DECAS	0.64 (0.52–0.77)	183 (106–283)	116 (64–188)
CRC mortality	UKFSS	0.59 (0.49–0.70)	56 (53–59)	33 (29–38)
	DECAS	0.59 (0.49–0.70)	86 (47–138)	51 (27–83)
ESTHER study[59] compared with DECAS				
CRC incidence	ESTHER	0.44 (0.33–0.57)	248	122
	DECAS	0.37 (0.31–0.44)	189 (112–292)	71 (41–114)
CRC mortality	ESTHER	0.34 (0.21–0.53)	95	37
	DECAS	0.38 (0.32–0.45)	88 (48–141)	34 (18–57)

CI, confidence interval; CrI, credible interval; CRC, colorectal cancer.

tumorigenesis during the model development (the others are the ASCCA model[18]; its variant, Policy1-Bowel[16]; and a work-in-progress UK MiMiC-Bowel model[61]). Some models did not build in the serrated pathway, but they have attempted to assess the impact of including it (e.g., CRC-AIM).[62] Other existing models do not specifically model the serrated neoplasia pathway, although some incorporate de novo cancers that arise directly from normal epithelium, representing alternative pathways.[17,22] However, recent literature has pointed out that fecal immunochemical testing appears to have a lower sensitivity for serrated polyps,[63,64] and the colonoscopy miss rate for serrated lesions is also higher,[57] likely due to the flat or sessile morphology, similar color to the epithelium, and camouflage by a mucus cap.[65] Therefore, without the explicit inclusion of the serrated pathway and adjusting the sensitivities of the screening intervention, the modeled estimation of screening effectiveness might be overoptimistic.[18]

In addition to the inclusion of serrated pathway, DECAS is one of the very few calibrated with a Bayesian inference method.[51] The majority of other models[14,17,22]

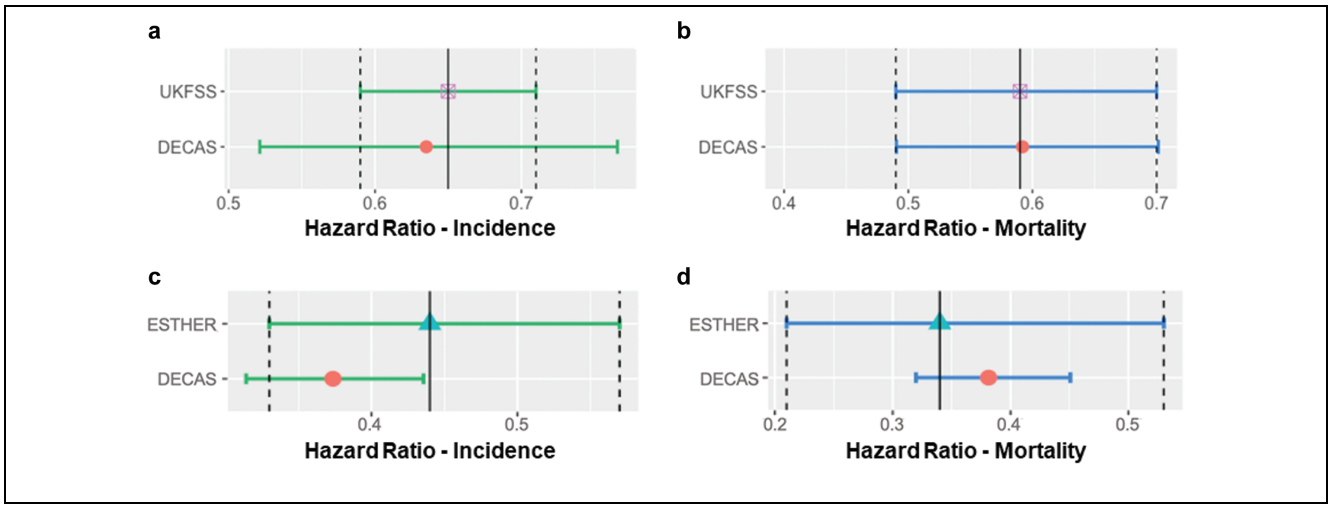

Figure 4 Hazard ratios (HRs) of colorectal cancer (CRC) incidence and mortality between screening and no-screening groups: comparison between the estimation of (a) HR of CRC incidence between the UKFSS trial and DECAS, (b) HR of CRC mortality between the UKFSS trial and DECAS, (c) HR of CRC incidence between the ESTHER study and DECAS, and (d) HR of CRC mortality between the ESTHER study and DECAS. Point estimates (mean) and 95% confidence intervals or credible intervals (horizontal bars) of hazard ratios are from the UKFSS Trial,[58] the ESTHER study,[59] and DECAS. The vertical solid lines and dashed lines signify the point estimates and 95% confidence intervals of the UKFSS trial and the ESTHER study.

(including the ASCCA models[16,18]) took the optimization approach, specifically the Nelder-Mead algorithm. The latter output only one set of "optimal" parameters, which do not inform parameter uncertainty.[66] Although some models mitigated this drawback by keeping multiple sets of best-fit parameters to capture the uncertainty using confidence intervals,[16,18] it is of concern that the frequentist methods might have unsatisfactory performance in the face of large parameter spaces and highly nonlinear models.[66]

Bayesian inference methods, on the other hand, naturally encapsulate the uncertainty as well as interdependencies in the joint posterior parameter distributions. Among them, the ABC methods are especially useful to approximate the "true" posterior distribution for complex models with high-dimension parameter spaces[66] (e.g., DECAS), where the likelihood function (which describes the relationship between model parameters and the observed data) is computationally intractable.[29] In this study, we demonstrated that, with the calibrated posterior parameter samples from one of the well-tested ABC algorithms, APMC, DECAS can reproduce the real-world CRC incidence and screening benefits from clinical studies well while naturally capturing the magnitude of uncertainty. This adds to the literature that the R-package enabled APMC algorithm[51] can be well suited to calibrate complex disease natural history models used in economic evaluation.

The validation with the data from the UKFSS trial confirmed the ability of DECAS to project the clinical benefits from sigmoidoscopy screening. In addition, it provided an opportunity for an indirect cross-model comparison with the 3 existing CRC models from the Cancer Intervention and Surveillance Modelling Network (CISNET),[14] which are also validated against the UKFSS trial and are used extensively to inform the CRC screening recommendations in the United States.[32] In their validation against the UKFSS trial, the CISNET models estimated a mean HR of 0.56 to 0.66 of CRC incidence reduction and a mean HR of 0.47 to 0.6 of CRC mortality reduction.[67] Having similar setups for the validation, they demonstrated that the validity of DECAS in predicting the screening benefits from a single sigmoidoscopy screening is on par with the CISNET models. Given that sigmoidoscopy provides more protective effects for distal cancers,[58] we further looked into the benefits of reducing the incidence of proximal and distal CRC. The results from DECAS successfully showed the differentiated protective effects in distal cancers and remained very similar to the results found in the UKFSS trial and the CISNET models (see Appendix J).

In the absence of the results from colonoscopy screening RCTs until the late 2020s,[68] we chose to validate the coloscopy screening effect with the ESTHER study, which further ensured that DECAS is capable of reproducing the colonoscopy screening benefits observed in the German context. Furthermore, the predicted benefits

of colonoscopy screening from DECAS are also close to the findings from a meta-analysis, which showed that colonoscopy screening could reduce CRC incidence by 69% (95% CI 23%–88%) and mortality by 68% (95% CI 57%–77%).[5] Another German-specific Markov model, which predicted the effect of a single screening colonoscopy, showed the incidence reduction by 60% to 65% and mortality reduction by 75% to 80%.[35] On the other hand, CISNET models predicted up to 88% in incidence reduction and up to 90% in mortality reduction.[14] Taken together, the prediction of colonoscopy screening effect from DECAS falls on the conservative side compared with other simulation studies, while lying within the confidence intervals of clinical studies.

The strengths of DECAS include the consideration of adenoma and serrated polyp pathways, being calibrated with a long-term and large real-world screening registry data, naturally capturing the parameter uncertainty based on a Bayesian calibration, the validity gained from various validation exercises, and its flexibility to evaluate various screening test and show the benefits breaking down to proximal and distal colon level.

Despite the strengths, there are some limitations. The first pertains to parameter estimation during DECAS calibration. Using a Bayesian calibration method, we aimed to capture parameter uncertainty. Some posterior parameter distributions concentrated a relatively high probability mass close to the prior boundaries, indicating that better fits were generally achieved when the parameter in question was close to the boundary. We did not further extend the prior ranges because 1) some parameters should be strictly positive (e.g., risk of progressing to advanced lesions or cancers) and the lower range already corresponds to very low risks and 2) some were already given a very generous range compared with the data informing our priors (e.g., the age factors and location factors).

The second limitation is related to structural uncertainty.[23] Although DECAS predictions captured the general trend of calibration targets well, the targets did not appear to randomly spread around the predicted means (namely, residual correlation with age might be present). This might indicate the need for a more precise algorithm to better estimate such parameters or that a tradeoff between the current model form and parameter constraints, and the accuracy of the fit, is present. For instance, a more granular piecewise age effect or alternative change points in the initiation and cancer progression might mitigate the problem. However, one must balance between the prediction accuracy and the demanded resources (both data and computational resources). Given that we could capture the main trends with good overall accuracy, we kept the current model formulation and settings.

Third, DECAS did not capture the trend of age-specific crSP prevalence well, unlike the other target data. The limitation most likely arose from the fact that the available mean crSP prevalence data showed no positive correlation between prevalence and age,[39,40] unlike in advanced adenomas and CRC prevalence. When the APMC calibration algorithm considered a global fit, it was more likely to accept higher simulated older-age crSP prevalence to yield higher older-age CRC prevalence, which contributed to the mismatch we observed. We mitigated this gap by assigning age factors in the transition from advanced precancerous lesions (AA and crSP) to CRC. The age factors reflected the fact that a higher grade of dysplasia in crSP is more likely to happen in older age.[69,70] However, there remained a slight discrepancy between the simulated and target crSP prevalence over the age of 80 y. Such a discrepancy in trend was also observed in the SSA/P prevalence in the ASCCA model.[18] Another explanation could be the broad variability of crSP prevalence data in old age due to data scarcity,[39,40] which requires future epidemiological research on crSP to understand better.

Furthermore, the computation time is a nonnegligible limiting factor for ABC calibration, and we faced a tradeoff between computational costs and posterior sample quality. According to the authors,[51] the quality of the approximation in APMC can be improved with a smaller α and $p_{acc_{min}}$. However, this also means that more simulation steps and thus a much longer computation time are required during the calibration. With the current settings, it already took 10 d even with parallel computing on a 60-core cluster computer. Given that the fitting to the calibration targets and external validation yielded satisfactory results for our posterior samples, we believe we struck a good balance between the quality of approximation and the computational time.

Lastly, a few choices of deterministic parameter inputs and the data source might lead to some limitations. For example, the CRC cancer stages were deterministically assigned to the lesion becoming a CRC, and this makes the model unable to account for the uncertainty around the data of cancer stages. Also, only 1 assumption (15%) was tested for the proportion of CRC developing from the serrated pathway in the current version of the model. This requires future work to explore other assumptions given a relatively wide range of estimates for the serrated pathway in the literature.[12,13] Moreover, a few of the data points (e.g., the prevalence for age 40–49 years)

come from an international data source, in which the population or the colonoscopy screening practice might not be fully comparable with the German context.

In conclusion, we developed DECAS, the first DES model for CRC screening, which accounts for both the adenoma-carcinoma and the serrated neoplasia CRC tumorigenesis pathways and is flexible for evaluating various screening modalities as well as differentiating the screening effects in different parts of the colon. It successfully reproduced the CRC epidemiological data as well as the CRC screening benefits from sigmoidoscopy and colonoscopy. Being the first of its kind designed for the German setting, DECAS will be further developed to evaluate the effectiveness and cost-effectiveness of various CRC screening strategies in Germany.

Acknowledgments

We appreciate the expertise and extensive support from Dr. Jaime Caro, who advised on the conceptualization of the modeling method and critically reviewed the manuscript. We are grateful to Dr. Benjamin Misselwitz and Dr. Jie-Bin Lew, the main author of the CMOST model and Policy1-Bowel model, respectively. They provided valuable information on their experience with developing microsimulation models. We thank Dr. Bernd Hagen for granting access to the annual reports of the German screening colonoscopy program, Dr. Tao Ran for providing ideas at the early stage of model construction, Dr. Michael Hoffmeister and Dr. Peter Kolominsky-Rabas for their advice on this project, and Anett Molnar for helping with model validation. We also appreciate the kind offer to use the cluster computer from the Division of Biostatistics at DKFZ.

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Supplemental Material

Supplementary material for this article is available on the *MDM Policy & Practice* Web site at https://journals.sagepub.com/home/mpp.

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