Appendix

Literature search and data sources

The sources for most inputs for our U.S. model (Appendix **Table 1**) have been described previously [1–6]. Literature searches were performed in PubMed to update model inputs by using combinations of terms *colorectal cancer*, *screening*, *detection*, *sensitivity*, *specificity*, *test performance*, *fecal occult blood*, *fecal immunohistochemistry*, *sigmoidoscopy*, *colonoscopy*, *cost*, and *cost-effectiveness*. Data for colorectal cancer (CRC) epidemiology and costs in Germany were derived from the Munich Cancer Registry [7] (Appendix **Fig. 1**), the German national mortality table 2007–2009 [8], literature review [9–11], the doctor's fee scale and procedure reimbursement (Einheitlicher Bewertungsmaßstab: EBM) catalogue 2011 for office-based physicians with a EBM point value of € 0.035 [12], the German Diagnostic Related Group (DRG) codes for hospitalizations [13], and expert consultations. The recently completed PRESEPT (PRospective Evaluation of SEPTin) study provided data on the sensitivity and specificity of methylated Septin 9 DNA assays [14].

Decision analytic model

We adapted our published, validated decision analytic model of CRC screening in the United States for the current analyses. The model, its calibration, and initial validation have been described in detail [1–6]. The model is constructed in TreeAge Pro (TreeAge Software, Inc., Williamstown, MA). The principal health states in the model are as follows (Appendix **Fig. 2**): normal; small (< 10 mm) adenomatous polyp; large (≥ 10 mm) adenomatous polyp; localized, regional, or distant CRC; and dead [3,5]. Approximately 85% of CRCs develop through a potentially identifiable adenoma. In the model, among persons in whom CRC develops by the age of 80 years, the median dwell time between large adenoma and CRC is 9.5 years, and between small adenoma and CRC it is 19.5 years. These dwell times are a result of the derived annual transition probabilities and not parameters that are programmed into the model a priori. In the natural history module, CRCs are diagnosed with colonoscopy once they lead to symptoms. Screening from ages 50 to 80 years may identify adenomas and asymptomatic CRC. Diagnosed CRCs are treated, resulting in stage-specific survival. Patients with adenomas enter surveillance. Beginning at age 50 years, average-risk persons progress through the model for 50 yearly cycles until age 100 years or death. Age-specific non-CRC mortality rates reflect U.S. life table data in the original model [15] and German life table data in the current model [8]. Model inputs are shown in Appendix **Table 1**.

The natural history module of the U.S. model reproduces the natural history and age-specific incidence and prevalence of colorectal adenomas and CRC by stage in the United States without screening [1,3,5]. For the current analysis, we adjusted the transition rates from normal to small polyp and from normal to localized CRC by a common factor to match CRC epidemiologic data from Germany [7,8], as we have previously reported [16]. Making this factor 1.25 yielded excellent calibration to data from Germany (Appendix **Fig. 1**). Screening strategies are superimposed on the natural history module, allowing for variable rates of utilization of any strategy and per-cycle adherence within a strategy.

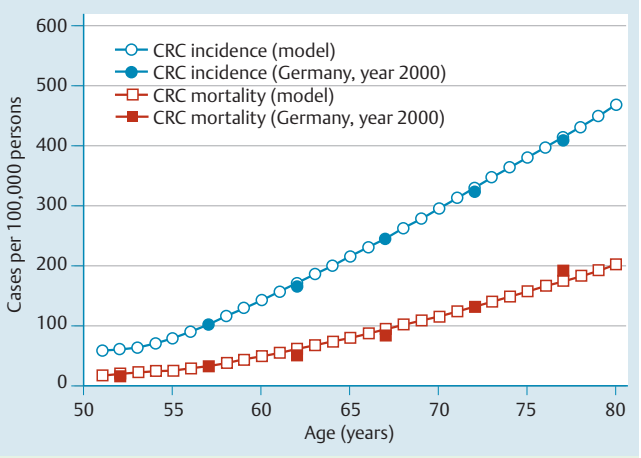

Fig. 1 Model calibration. The model reproduces colorectal cancer incidence and mortality in Germany in the year 2000, a time when screening was not expected to have affected colorectal cancer epidemiology.

Model validation

Fecal occult blood test

We have reported our first validation exercise, using our U.S. model [3] against data from the Minnesota Colon Cancer Control Study [17,18]. Fecal occult blood test (FOBT) screening was modeled by intent to treat as in the trial, assuming the following: mean age of 62 years; annual FOBT offered for 5 years, then not for 5 years, and then again for 6 years; adherence rates with at least one screening of 90% and all screenings of 46%; and complete bowel examination after 83% of abnormal FOBT results. For screening compared with no screening, our model predicted relative rates of CRC incidence of 0.79 versus 0.80 (CI 0.70–0.90) in the trial, and CRC mortality of 0.64 versus 0.67 (CI 0.50–0.87) in the trial [17,18].

Sigmoidoscopy

We have performed three validation exercises [19] against data from the U.K. Flexible Sigmoidoscopy Screening Trial [20], the SCORE trial [21], and the PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial [22].

For validation against the U.K. Flexible Sigmoidoscopy Screening Trial [20], screening sigmoidoscopy was modeled by intent to treat and per protocol, assuming the following: a population mean age of 60 years, once-only sigmoidoscopy undergone by 71% of persons, colonoscopic surveillance only after detection of a large adenoma, 11-year follow-up, and 60% of lesions within reach of the sigmoidoscope. For screening compared with no screening by intent to treat, our model predicted relative rates of CRC incidence of 0.75 versus 0.77 (CI 0.70–0.84) in the trial, CRC mortality of 0.67 versus 0.69 (CI 0.59–0.82) in the trial, and all-cause mortality of 0.99 versus 0.97 (CI 0.94–1.0) in the trial [20]. For screening compared with no screening per protocol, our model predicted relative rates of CRC incidence of 0.65 versus 0.67 (CI 0.60–0.76) in the trial, CRC mortality of 0.55 versus 0.57 (CI 0.45–0.72) in the trial, and all-cause mortality of 0.99 versus 0.95 (CI 0.91–1.0) in the trial [20].

For validation against the SCORE trial [21], screening sigmoidoscopy was modeled by intent to treat and per protocol as in the trial, assuming the following: a population mean age of 60 years, once-only sigmoidoscopy undergone by 58% of persons, colonoscopic surveillance after detection of a small or a large adenoma, 11-year follow-up, and 60% of lesions within reach of the sigmoi-

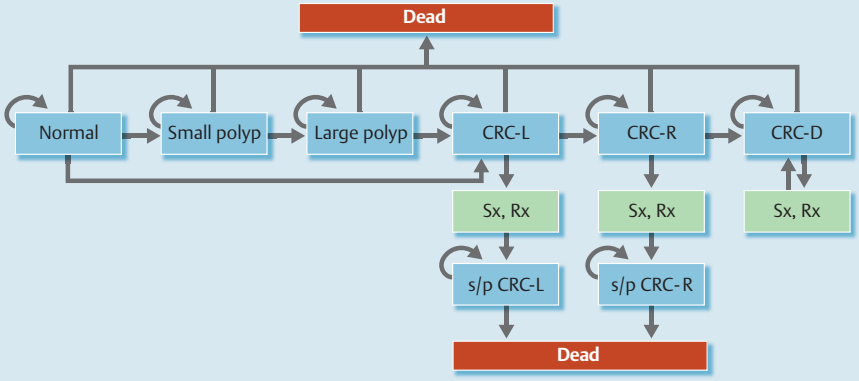

Fig. 2 Schematic of the natural history module in the decision analytic model. The principal health states in the model are normal, small polyp, large polyp, localized colorectal cancer (CRC-L), regional colorectal cancer (CRC-R), disseminated colorectal cancer (CRC-D), alive following treatment for localized colorectal cancer (s/p CRC-L), alive following treatment for regional colorectal cancer (s/p CRC-R), and dead. Without screening, colorectal cancer is diagnosed and treated after symptoms develop (Sx, Rx).

Table 1 Model inputs.

Variable	Base case value (range)[1]	References
Clinical		
Polyp prevalence at age 50, %	19	[24–26]
Small polyp, %	95	[25, 27, 28]
Large polyp, %	5	[25, 27, 28]
Annual transition rate to small polyp from normal, %	Age-specific, 1.4–2.4	[7, 8, 24–28]
Annual transition rate to large polyp from small polyp, %	1.5	[25, 27, 28]
Annual transition rate to cancer without polypoid precursor, %	Age-specific, 0.007–0.108	[7, 8, 24–26, 29, 30]
Annual transition rate to cancer from large polyp, %	5	[24–26, 29, 30]
Symptomatic presentation of localized cancer, %	22/y over 2 y	[30]
Symptomatic presentation of regional cancer, %	40/y over 2 y	[30]
Mortality rate from treated localized cancer, %	2.4/y in first 5 y	[7, 8, 30]
Mortality rate from treated regional cancer, %	9.4/y in first 5 y	[7, 8, 30]
Mean survival from distant cancer, y	1.9	[30, 31–37]
Mortality rate from initial cancer treatment, %	2	[7, 8, 29, 38]
Test performance characteristics and complications		
^{m}SEPT9-2well sensitivity for localized colorectal cancer, %	42 (18–66)	[14]
^{m}SEPT9-2well sensitivity for regional colorectal cancer, %	52 (22–86)	[14]
^{m}SEPT9-2well sensitivity for distant colorectal cancer, %	77 (24–100)	[14]
^{m}SEPT9-2well sensitivity for large polyp, %	11 (7–16)	[14]
^{m}SEPT9-2well sensitivity for small polyp, %	7 (4–11)	[14]
^{m}SEPT9-2well specificity, %	91 (89–93)	[14]
^{m}SEPT9-3well sensitivity for localized colorectal cancer, %	51 (26–75)	[14]
^{m}SEPT9-3well sensitivity for regional colorectal cancer, %	75 (42–100)	[14]
^{m}SEPT9-3well sensitivity for distant colorectal cancer, %	100 (55–100)	[14]
^{m}SEPT9-3well sensitivity for large polyp, %	14 (10–19)	[14]
^{m}SEPT9-3well sensitivity for small polyp, %	10 (6–15)	[14]
^{m}SEPT9-3well specificity, %	88 (85–90)	[14]
FOBT sensitivity for cancer, %	40 (25–50)	[39, 40]
FOBT sensitivity for large polyp, %	11 (9–28)	[39, 40]
FOBT sensitivity for small polyp, %	5 (5–14)	[39, 40]
FOBT specificity, %	97 (95–99)	[39, 40]
FIT sensitivity for cancer, %	70 (50–87)	[39–41]
FIT sensitivity for large polyp, %	24 (16–48)	[39–41]
FIT sensitivity for small polyp, %	10 (8–24)	[39–41]
FIT specificity, %	95 (93–98)	[39–41]
Colonoscopy sensitivity for cancer, %	95 (90–97)	[42, 43]
Colonoscopy sensitivity for large polyp, %	90 (85–95)	[42, 43]
Colonoscopy sensitivity for small polyp, %	85 (80–90)	[42, 43]
Colonoscopy major hemorrhage rate, %	0.16 (0.1–0.23)	[39, 44]
Colonoscopy perforation rate, %	0.085 (0.06–0.11)	[39, 44–47]
Mortality rate given endoscopic perforation, %	7.5 (4.5–16)	[44, 45, 47]
Health state utilities		
Localized colorectal cancer	0.90 (SD 0.06)	[48]
Regional colorectal cancer	0.80 (SD 0.22)	[48]
Distant colorectal cancer	0.76 (SD 0.11)	[48]

Table 1 (Continuation)

Variable	Base case value (range)[1]	References
Costs, euros[1]		
^{m}SEPT9	150	Current cost
FOBT	2.45	[12]
FIT	15.9	Estimate based on literature review
Colonoscopy	193	[12]
Colonoscopy with lesion removal	234	[12]
Major hemorrhage after colonoscopy	3130	[13]
Perforation after colonoscopy	4485	[13]
Colorectal cancer care by stage		
Localized, initial	3015	[9 – 13]
Localized, continuing yearly	21	[9 – 13]
Localized, colorectal cancer death	63 856	[9 – 13]
Regional, initial	29 644	[9 – 13]
Regional, continuing yearly	210	[9 – 13]
Regional, colorectal cancer death	63 857	[9 – 13]
Distant, initial	80 248	[9 – 13]
Distant, colorectal cancer death	63 698	[9 – 13]

^{m}SEPT9-2well, methylated Septin 9 DNA 2-well assay; ^{m}SEPT9-3well, methylated Septin 9 DNA 3-well assay; FOBT, fecal occult blood testing; FIT, fecal immunochemical testing; SD, standard deviation.

[1] Range in Monte Carlo simulation; costs were varied within ± 20 % of base case values.

doscope. For screening compared with no screening by intent to treat, our model predicted relative rates of CRC incidence of 0.80 versus 0.82 (0.69 – 0.96) in the trial and CRC mortality of 0.72 versus 0.78 (0.56 – 1.08) in the trial [21]. For screening compared with no screening per protocol, our model predicted relative rates of CRC incidence of 0.65 versus 0.69 (0.56 – 0.86) in the trial and CRC mortality of 0.55 versus 0.62 (0.40 – 0.96) in the trial [21].

We performed a third validation exercise against data from the PLCO trial [22], which was more complicated because of the variability in screening and "endoscopic contamination" in both the intervention and usual care control arms. Screening sigmoidoscopy was modeled as it was actually performed in the trial, assuming the following: a population mean age of 63 years, colonoscopic surveillance after detection of a small or a large adenoma, 11-year follow-up, and 60 % of lesions within reach of the sigmoidoscope. Based on the actual reported rates of endoscopic testing in the intervention arm, we modeled 36 % of persons undergoing sigmoidoscopy only once, 51 % undergoing additional sigmoidoscopy, and 6 % undergoing colonoscopy during the screening period. Similarly, for the control arm, we modeled 47 % of persons undergoing screening by colonoscopy (34 %) or sigmoidoscopy once (13 %) during the screening period. For the intervention arm compared with usual care, our model predicted relative rates of CRC incidence of 0.83 versus 0.79 (0.72 – 0.85) in the trial and CRC mortality of 0.72 versus 0.74 (0.63 – 0.87) in the trial [22].

Conditional independence of repeated testing

Whether repeated rounds of testing are conditionally independent is a key issue in CRC screening decision analytic modeling. Previous studies have tended to assume conditional independence. Our above validation to the Minnesota Colon Cancer Control Study [17, 18], which includes the assumption of conditional independence of repeated FOBT rounds, suggests that making this assumption in the case of FOBT may be reasonable in the context of the model, even if uncertainties remain about the degree of conditional independence of FOBT rounds.

Data are beginning to accumulate that may allow a more sophisticated approach to modeling this question for fecal immunochemical testing (FIT) [23]. Modelers are only beginning to grapple with this issue. We interpret the similar yields at second round of FIT at 1, 2, or 3 years in the study by van Roon and colleagues as informative about dwell times (i.e., advanced adenomas tended not to progress to CRC, and new advanced adenomas tended not to develop at notably different rates at 1 vs. 3 years). The yield at the second round is informative with respect to the assumption about conditional independence (1.6 % for advanced adenoma and 0.2 % for CRC, compared with first-screening yields of 2.8 % and 0.5 %).

We performed a simulation to explore the assumption of conditional independence of FIT rounds in our model. We first back-calculated the "true" prevalence of advanced adenoma and CRC that would be needed in a population undergoing FIT with our base case assumptions about sensitivity in order to yield the first-round results of van Roon and colleagues (2.8 % advanced adenoma and 0.5 % CRC) [23]. In our model, the rates of new advanced adenoma or new CRC after the first round's "partial clearing" of the colon do not substantially affect the "true" prevalence of these lesions at second round in 1 to 3 years, which is consistent with the findings of van Roon and colleagues. At this second round of testing, we predicted a yield of approximately 2.1 % advanced adenoma, 0.15 % CRC, and 2.25 % advanced neoplasia – compared with 1.6 % advanced adenoma, 0.18 % CRC, and 1.8 % (95 %CI 1.4 – 2.3 %) advanced neoplasia in the data of van Roon and colleagues. This suggests that assuming conditional independence may not be correct with respect to advanced adenomas (second-round yield of 2.1 % predicted with our assumptions vs. 1.6 % observed), but this may be less of an issue for CRC (second-round yield of 0.15 % predicted with our assumptions vs. 0.18 % observed).

At this time, it is difficult to know how data on two FIT rounds can inform a model of testing over decades. For now, we have retained the assumption of conditional independence and have explored a range of *program* sensitivities for FIT by varying the per-cycle sensitivities of FIT.

Cost inputs

Cost inputs were derived from literature review [9 – 11], the doctor's fee scale and procedure reimbursement (Einheitlicher Bewertungsmaßstab: EBM) catalogue 2011 for office-based physicians with a EBM point value of € 0.035 [12], and German Diagnostic Related Group (DRG) codes for hospitalizations [13]. Expert consultation by practicing oncologists guided estimates based on microcosting, such as the cost of CRC treatment.

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