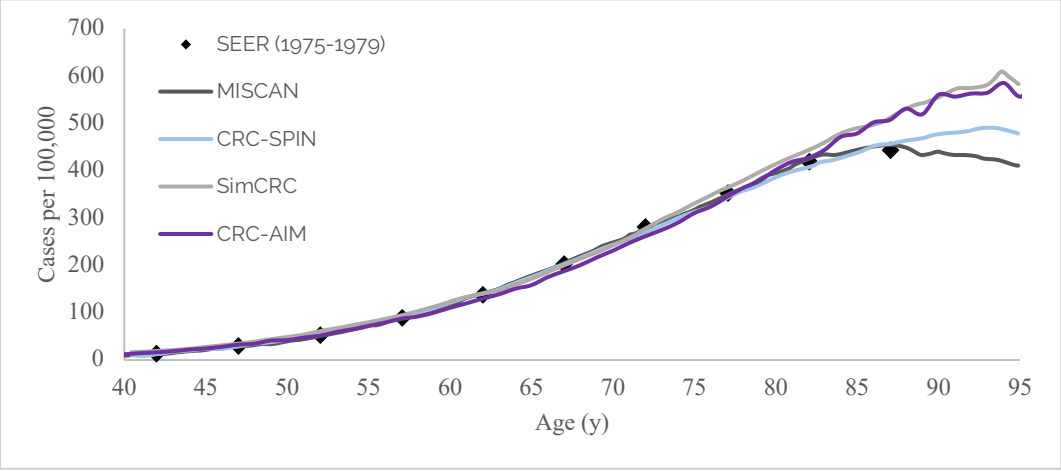
CRC-AIM natural history validation

We compared model outcomes to SEER 1975-1979 CRC incidence per 100,000 to validate the natural history of CRC. SEER includes the most comprehensive population-based nationwide CRC data before widespread CRC screening in the US, thus forming critical input for natural history model development. These data have been utilized by several other models of CRC in the US (including CISNET CRC models).[36-39] Given that American Joint Committee on Cancer (AJCC) staging was not included in SEER data before 1988, stage-specific CRC incidence was unavailable as a calibration target. Even though SEER includes important data, it does not provide necessary details (e.g., average adenoma size) that are needed to develop precise natural history for the model. Therefore, the primary targets were supplemented by data from studies by Corley et al.[28] and Pickhardt et al.[29], which reported adenoma prevalence and distribution by size based on a large sample of asymptomatic patients.[28, 29]

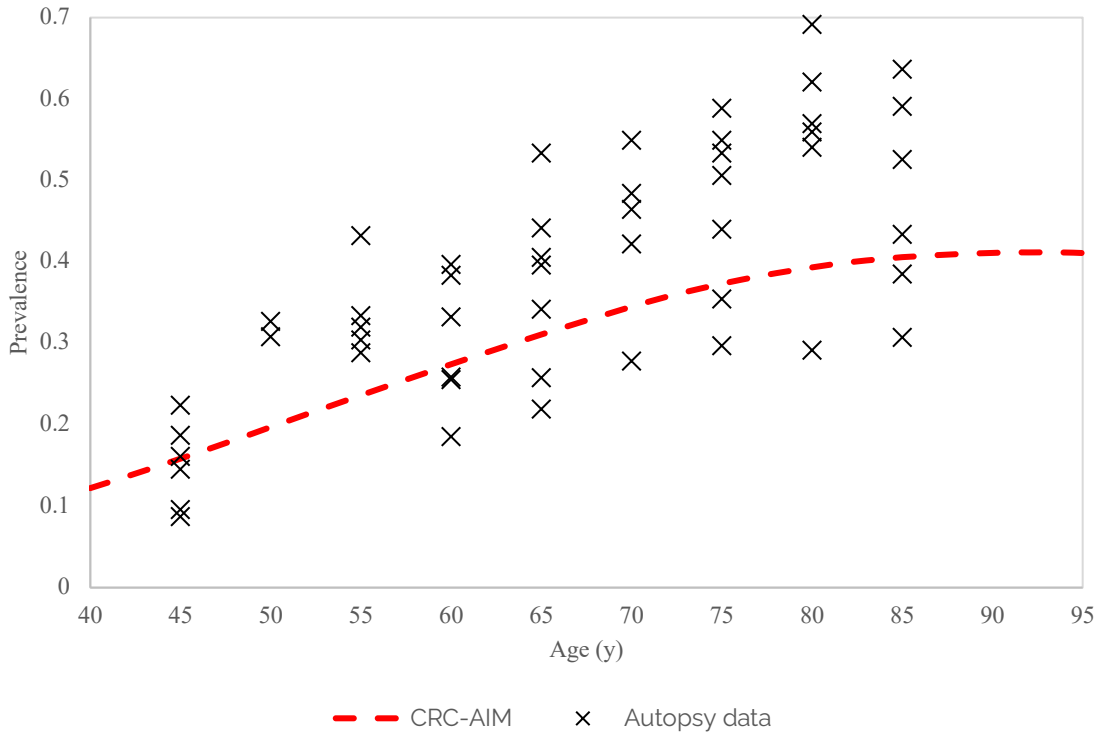
Age-specific CRC incidence as reported by SEER's 1975-1979 data was matched by CRC-AIM (Supplemental Figure 5) along with adenoma prevalence reported by the autopsy studies[35] (Supplemental Figure 6). Distributions of adenomas by location (Supplemental Figure 7), adenoma size by age group (Supplemental Figure 8), and cancer stage at diagnosis (Supplemental Figure 9) estimated by CRC-AIM were also compared to estimates from the SEER data[22] and CISNET models. The dwell time and sojourn time estimated by CRC-AIM were 20.3 years and 4.1 years, respectively, both of which fall within the estimated values from the literature[40-42] and CISNET models (Supplemental Figure 10).

Supplemental Figure 5. CRC-AIM and CISNET predictions of colorectal cancer cases per 100,000 people by age (adapted from Knudsen et al.[35] and Vahdat et al.[1])



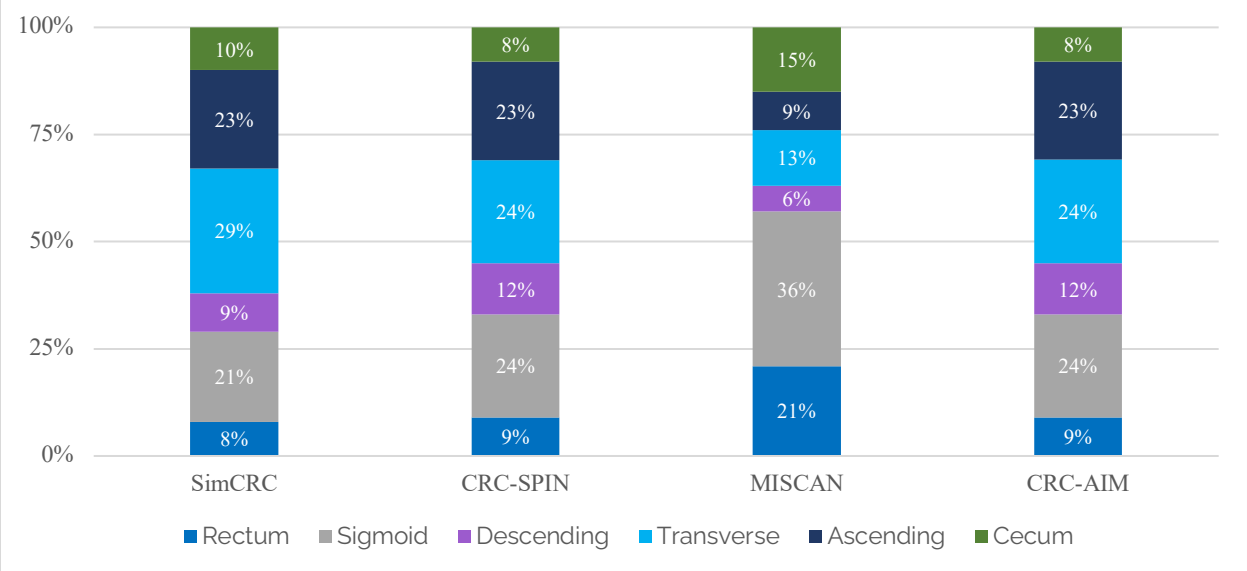
Abbreviations: CRC-AIM, Colorectal Cancer-Adenoma Incidence and Mortality model; CRC-SPIN, ColoRectal Cancer Simulated Population Incidence and Natural history model; MISCAN, MIcrosimulation SCreening Analysis; SEER, Surveillance, Epidemiology, and End Results; SimCRC, Simulation Model of Colorectal Cancer.

Supplemental Figure 6. CRC-AIM predicted adenoma prevalence by age against autopsy data (adapted from Knudsen et al.[35])



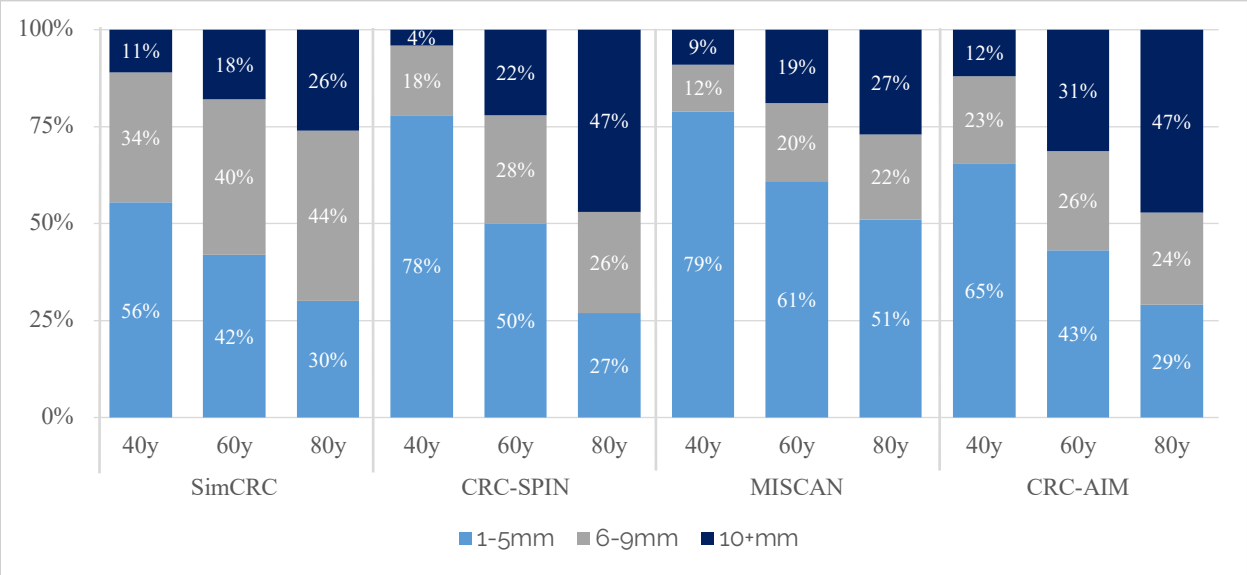
Abbreviations: CRC-AIM, Colorectal Cancer-Adenoma Incidence and Mortality model; y, year.

Supplemental Figure 7. CRC-AIM and CISNET adenoma distribution by location (adapted from Knudsen et al.[35])



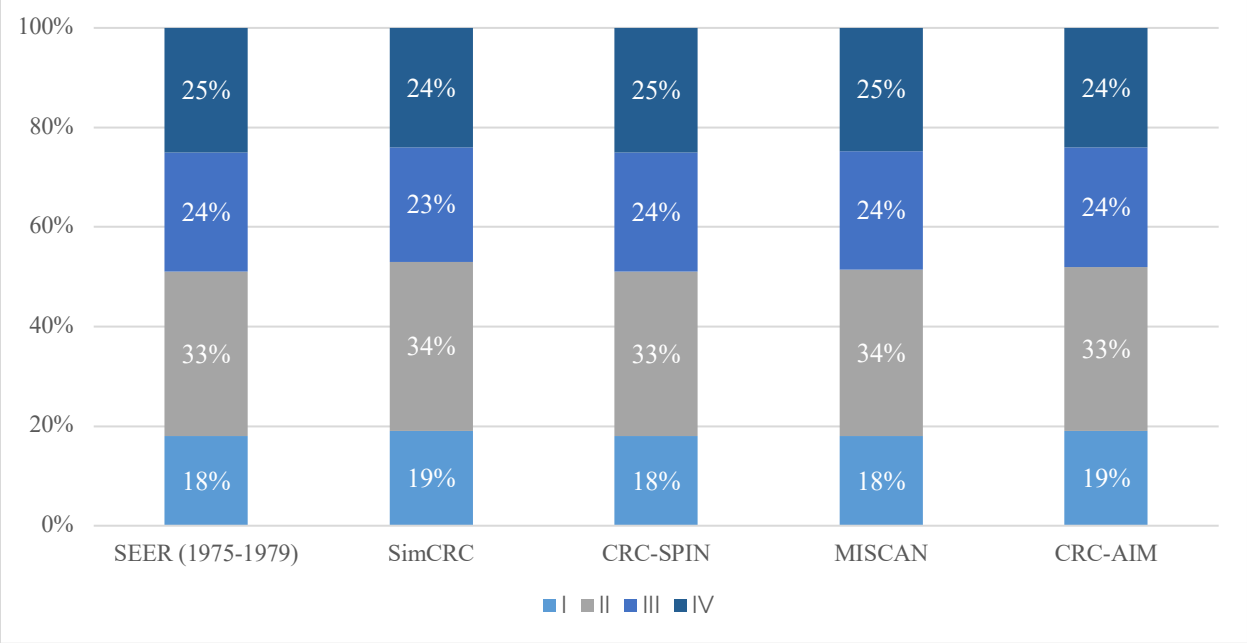
Abbreviations: CRC-AIM, Colorectal Cancer-Adenoma Incidence and Mortality model; CRC-SPIN, ColoRectal Cancer Simulated Population Incidence and Natural history model; MISCAN, MIcrosimulation SCreening Analysis; SimCRC, Simulation Model of Colorectal Cancer.

Supplemental Figure 8. CRC-AIM and CISNET adenoma size distribution by age group (adapted from Knudsen et al.[35])



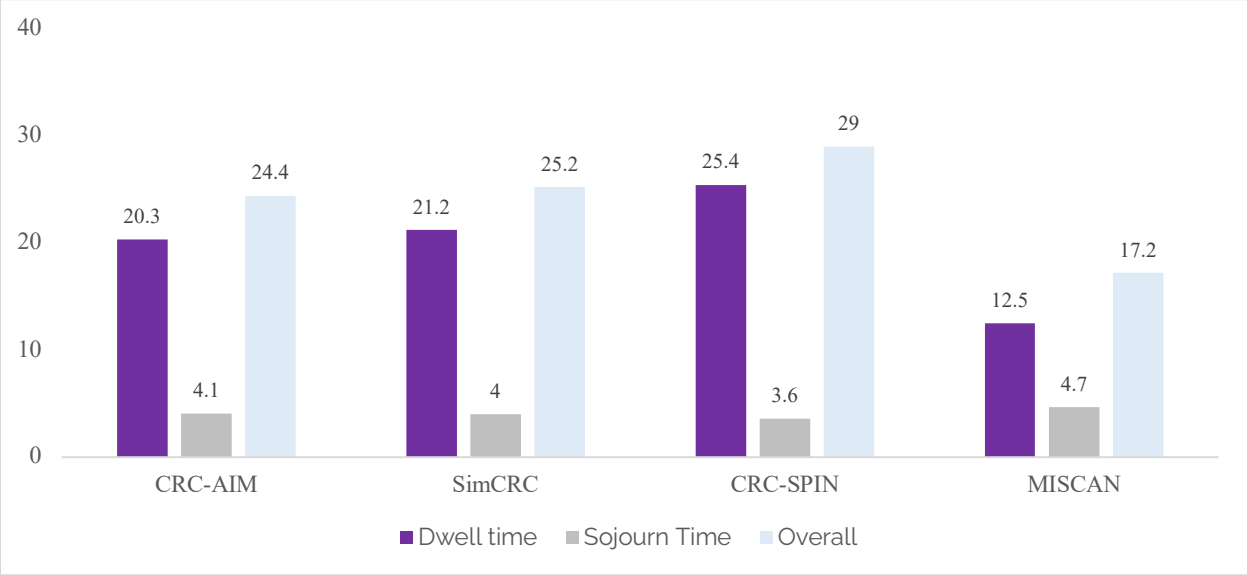
Abbreviations: CRC-AIM, Colorectal Cancer-Adenoma Incidence and Mortality model; CRC-SPIN, ColoRectal Cancer Simulated Population Incidence and Natural history model; MISCAN, MIcrosimulation SCreening Analysis; mm, millimeter; SimCRC, Simulation Model of Colorectal Cancer; y, year.

Supplemental Figure 9. Distribution of cancer stage at diagnosis: Modeled versus SEER 1975-1979 data (adapted from Knudsen et al.[35])



Abbreviations: CRC-AIM, Colorectal Cancer-Adenoma Incidence and Mortality model; CRC-SPIN, ColoRectal Cancer Simulated Population Incidence and Natural history model; MISCAN, MIcrosimulation SCreening Analysis; SEER, Surveillance, Epidemiology, and End Results; SimCRC, Simulation Model of Colorectal Cancer.

Supplemental Figure 10. CRC-AIM and CISNET predictions of dwell and sojourn times(adapted from Knudsen et al.[35])



Abbreviations: CRC-AIM, Colorectal Cancer-Adenoma Incidence and Mortality model; CRC-SPIN, ColoRectal Cancer Simulated Population Incidence and Natural history model; MISCAN, MIcrosimulation SCreening Analysis; SimCRC, Simulation Model of Colorectal Cancer.

Three studies were used to verify preclinical cancer prevalence and size distribution.[30-32] These studies were unique in that participants without a history of screening were identified, because preclinical cancer prevalence is highly attributed with prior screening history and removal of adenomas. The likelihood of detecting pre-cancerous lesions is low, so we generated a tolerance interval based on confidence intervals to determine whether CRC-AIM predictions fall within the reported values for each of the secondary targets.

To calculate the primary and secondary targets from published studies, similar settings to each study were simulated, including population age and sex distribution, screening modalities, and screening performance, if applicable (Supplemental Figure 7). In this section, we provide a brief description on each study.

Supplemental Table 7. Age and sex distribution of the studies that are used as calibration targets for CRC-AIM

Study	Gender	Age (Mean±SD [Range])	Percentage
Corley et al.[28]	Female	50-54	15.4%
		55-59	12.5%
		60-64	13.1%
		65-69	8.0%
		70-74	5.1%
		75+	3.7%
	Male	50-54	11.5%
		55-59	9.1%
		60-64	9.0%
		65-69	6.0%

		70-74	3.6%
		75+	3.0%
Pickhardt et al.[29]	--	57.8 ± 9.75¶ [40–79]	59%†
Imperiale et al.[30]	--	59.8 ± 8.3 [50–85]	58.9%†
Lieberman et al.[31]‡	--	<50	7.7%
		50-59	48.4%
		60-69	27.7%
		70-79	13.5%
		80+	2.8%
Church[32]	--	65 ± 5 [20–90]	50%†

Abbreviations: SD, standard deviation; NA: Not applicable

¶ Standard deviation estimated based on the range rule.

† Percentage of male population.

‡ Consistent with the study, 52.9% of simulated population is considered to be male.

1. *Size distribution of detected adenomas as sourced from Pickhardt et al.*[29]

The study population consisted of adults aged 50 to 79 years at average risk of colorectal cancer as well as adults aged 40 to 79 years who had a family history of colorectal cancer.[29] Computed tomography colonography (CTC) and colonoscopy screening (728 men and 505 women with a mean age of 57.8 years) were completed in 1233 individuals on the same day. To simulate the effect of screening with colonoscopy, sensitivity was set to be 75%, 85%, 95%, and 95% for ≤ 5 mm, 6-9 mm, ≥ 10 mm adenoma, and CRC, respectively, consistent with the inputs used in the 2021 modeling study for USPSTF (**Error! Reference source not found.**).[43] Next, to incorporate the effect of screening with CTC in addition to colonoscopy, we adopted the approach used in Rutter et al.[8] and assumed that the probability of missing an adenoma when screening with CTC, given that it was missed when screening with colonoscopy, is $P(miss|size = s)^{0.25}$. 611 of the 1233 patients had no polyps, and of those with polyps, 554 adenomatous polyps were found. 344, 159, and 51 adenomatous polyps were ≤5 mm, 5 to 10 mm, and ≥10 mm.

Preclinical CRCs per 1000 lesions by size as sourced from Church[32]

Church performed a prospective study that included the pathology reports of 5,722 polyps detected during colonoscopy between 1995 to 2002.[32] 1 and 21 cancers were found in 418 and 496 neoplastic polyps with sizes between 6 to 10 mm and > 10mm, respectively (Supplemental Table 8). Because the study did not report the age, sex, or any other patient characteristics, we assumed an equal probability of sex (50% male and 50% female), with an average age of 65 and no older than 90 years old, consistent with the assumption used by Rutter et al.[8]

Preclinical CRCs per 1000 lesions by size as sourced from Lieberman et al.[31]

The analysis included 6360 asymptomatic adults with one or more polyps found at screening colonoscopy in 2005 from 17 practice sites that provided both colonoscopy and pathology reports to the Clinical Outcomes Research Initiative repository.[31] Among 811 and 778 neoplastic polyps for the size groups of 6-9 mm and ≥10mm, 2 and 25 cancers were reported, respectively (Supplemental Table 8). Similar age and sex (shown in Supplemental Table 7) were used as reported in the study, and the performance of colonoscopy was consistent with the inputs used in the 2021 modeling study USPSTF (Supplemental Table 9).[43]

Adenoma prevalence by sex and age as sourced from Corley et al.[28]

Kaiser Permanente Northern California members aged ≥50 years who had a screening colonoscopy from 1/1/2006 to 12/31/2008 (n=20,792) were included in this study.[28] Adenoma prevalence (including both detected adenomas and adenocarcinomas) at screening colonoscopy by sex for each 5-year age group starting at age 50 to ≥75 was reported. The observed adenoma prevalence may be lower than expected because despite the effort to exclude the study subjects with prior screening, the study was conducted after the widespread of CRC screening and thus subjects with prior screening colonoscopies may have been included in the estimation of the target. Similar to other clinical studies, we assumed colonoscopy performance based on the USPSTF (Supplemental Table 9).[43]

Detected preclinical cancers per 1000 people as sourced from Imperiale et al.[30]

The probability of detecting preclinical cancer was found from 1994 asymptomatic adults (50 years or older, 58.9 percent male with a mean age of 59.8 years) who underwent screening colonoscopy for the first time between 1995 and 1998.[30] Among these individuals, a total of 12 cancers were detected (Supplemental Table 8). The effect of screening colonoscopy was simulated consistent with other studies.

Supplemental Table 8 presents the point estimates along with their tolerance intervals within which the outcomes from a plausible model must fall. The tolerance intervals were derived from exact confidence intervals for binomial proportions.[44]

Abbreviations: CRC, colorectal cancer; mm, millimeter; SEER, Surveillance, Epidemiology, and End Results.

Supplemental Table 8. Secondary calibration targets point estimates, tolerance intervals, and CRC-AIM estimates

Study	Target	Point estimate	Lower bound	Upper bound	CRC-AIM
Imperiale et al.[30]	Detected preclinical cancers per 1000 people	6.0	1.5	15.9	4.97
Lieberman et al.[31]	Preclinical CRCs per 1000 lesions, 6–9 mm	2.5	0.0	18.0	5.92
	Preclinical CRCs per 1000 lesions, ≥ 10 mm	32.1	13.0	64.1	23.21
Church[32]	Preclinical CRCs per 1000 lesions, [6, 10) mm	2.4	0.0	29.5	9.35
	Preclinical CRCs per 1000 lesions, ≥ 10 mm	42.3	15.6	88.7	45.37

* Upper and lower bounds were based on the exact confidence interval. 99.99% confidence interval was used due to high level of uncertainty.

Abbreviations: CRC, colorectal cancer; CRC-AIM, Colorectal Cancer-Adenoma Incidence and Mortality model.