Screening test sensitivity and specificity inputs used in cross-model validation

The sensitivity and specificity inputs are based on the USPSTF modeling approach[35] and presented in Supplemental Table 9. For stool-based tests, because Lin et al.[45] did not report the sensitivity for adenomas 1 to <6 mm and for adenomas 6 to <10 mm separately, the three CISNET models calibrated these inputs such that modeled outcomes matched the sensitivity for adenomas 1 to <10 mm from Lin and colleagues. The sensitivities in SimCRC and MISCAN were per lesion whereas both CRC-SPIN and CRC-AIM applied per-person sensitivities. Our cross-model validation experiments followed the same approach to calibrate stool-test performance based on size (Supplemental Table 10). As a comparison of the per-person sensitivities used in CRC-SPIN and CRC-AIM, the sensitivities for adenomas 1 to <6 mm between the two models differ slightly due to different assumptions used (i.e., CRC-SPIN assumed that the overall sensitivity for adenomas 1 to <6 mm was 2 percentage points higher than the false-positive rate of the screening test[35] whereas CRC-AIM, consistent with SimCRC and MISCAN, only considered the false-positive rate). The calibrated sensitivities for adenomas 6 to <10 mm between the CRC-AIM and CRC-SPIN models are similar.

Supplemental Table 9. Screening test characteristics used cross-model validation (reproduced from Knudsen et al.[35])

Test characteristics	Base-case value	Source
FIT (per person)		Lin et al.[45]
Specificity	0.97	
Sensitivity for adenomas 1 to <6 mm	0.07*	
Sensitivity for adenomas 6 to <10 mm		
Sensitivity for adenomas ≥10 mm	0.22‡	
Sensitivity for colorectal cancer	0.74	
mt-sDNA (per person)±		Lin et al.[45]
Specificity	0.91	
Sensitivity for adenomas 1 to <6 mm	0.15*	
Sensitivity for adenomas 6 to <10 mm		
Sensitivity for adenomas ≥10 mm	0.42‡	
Sensitivity for colorectal cancer	0.94	
Colonoscopy (within reach, per lesion)‡		
Specificity	0.86±	Schroy et al.[46]
Sensitivity for adenomas 1 to <6 mm	0.75	van Rijn et al.[47]
Sensitivity for adenomas 6 to <10 mm	0.85	
Sensitivity for adenomas ≥10 mm	0.95	
Sensitivity for colorectal cancer	0.95	By assumption

FIT – fecal immunochemical test with a cutoff for positivity of 20 µg of hemoglobin per g of feces; mt-sDNA – multi-target stool DNA test (stool DNA test with a fecal immunochemical test)

* Sensitivity for persons with nonadvanced adenomas. For persons with 1 to < 6 mm adenomas, we assume that the sensitivity is equal to the positivity rate in persons without adenomas. The sensitivity for persons with 6 to <10 mm adenomas was chosen such that the weighted average sensitivity for persons with 1 to < 6 mm and with 6 to <10 mm adenoma(s) is equal to the sensitivity for non-advanced adenomas.

‡ Sensitivity for persons with advanced adenomas (i.e., adenomas ≥10 mm and/or adenomas with advanced histology). Sensitivity was not reported for the subset of ≥10 mm adenomas.

‡ We assume the same test characteristics for screening, diagnostic follow-up, surveillance colonoscopies. We assume no correlation in findings between CTC or SIG and subsequent diagnostic colonoscopy.

[±] The lack of specificity with endoscopy reflects the detection of non-adenomatous polyps, which, in the case of sigmoidoscopy, may lead to unnecessary diagnostic colonoscopy, and in the case of colonoscopy, leads to unnecessary polypectomy, which is associated with an increased risk of complications.

Supplemental Table 10. Sensitivity (per-person) for stool tests used in the CRC-AIM and CRC-SPIN models

Model	Stool test	Per-person sensitivity[*]			
		Adenomas 1 to <6 mm[†]	Adenomas 6 to <10 mm	Adenomas ≥10 mm	Preclinical CRC
CRC-AIM	FIT	0.03	0.14	0.22	0.74
	mt-sDNA	0.09	0.33	0.42	0.94
CRC-SPIN	FIT	0.05	0.15	0.22	0.74
	mt-sDNA	0.11	0.31	0.42	0.94

FIT – fecal immunochemical test with a cutoff for positivity of 20 μg of hemoglobin per g of feces; mt-sDNA – multi-target stool DNA test (stool DNA test with a fecal immunochemical test); CRC – colorectal cancer

[*] Estimates were derived by calibrating model outcomes to the per-person sensitivities given in Supplemental.

[†] Consistent with SimCRC and MISCAN, CRC-AIM assumes that adenomas 1 to <6 mm do not bleed and the overall sensitivity for detecting those adenomas is equal to the false positive rate**.** CRC-SPIN assumes that the overall sensitivity for detecting adenomas 1 to <6 mm is 2 percentage points higher than the false-positive rate for FIT and mt-sDNA.