ORIGINAL RESEARCH—CLINICAL

Impact of the Sessile Serrated Polyp Pathway on Predicted Colorectal Cancer Outcomes

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BACKGROUND AND AIMS: Approximately 20%–30% of colorectal cancers (CRCs) arise from the serrated polyp pathway. CRC screening options have differential sensitivity to detect sessile serrated polyps (SSPs). We used the Colorectal Cancer and Adenoma Incidence and Mortality Microsimulation Model (CRC-AIM) to assess how the detection of SSPs impacts predicted life years gained (LYG), CRC incidence, and CRC mortality with multitarget stool DNA (mt-sDNA) or fecal immunochemical test (FIT) screening. **METHODS:** A simulated cohort of average-risk US individuals underwent triennial mt-sDNA or annual FIT screening between ages 45–75 years. SSP-attributed CRCs were modeled at 0% (base case), 14.3%, 20%, and 30%, in combination with 4 adherence & attendance scenarios: S1: 100% stool-screening adherence/100% follow-up colonoscopy attendance after a positive stool test; S2: reported stool-screening adherence (mt-sDNA = 71%; FIT = 43%)/100% follow-up colonoscopy attendance; S3: reported stool-screening adherence/reported follow-up colonoscopy attendance (mt-sDNA = 72%; FIT = 47%); and S4: reported stool-screening adherence/72% follow-up colonoscopy attendance. Outcomes were per 1000 individuals. Sensitivity analyses used ranges of stool-screening adherence or follow-up attendance. **RESULTS:** At S1, S2, S3, and S4, LYG with FIT at the base case (0% SSP-attributed CRC) was 346.7, 279.3, 126.6, and 196.1, respectively, and with mt-sDNA was 324.6, 311.8, 215.8, and 215.8, respectively. Among the 4 adherence/attendance scenarios, modeling SSP-attributed CRCs decreased LYG by 4.9–20.9 with FIT and 2.0–5.1 with mt-sDNA. At S3 and 30% SSP-attributable CRCs, mt-sDNA had 95.1 more LYG, 21.5% greater CRC incidence reduction, and 22.2% greater CRC mortality reduction than FIT. **CONCLUSION:** Incorporating SSPs and real-world adherence into the CRC-AIM modeling analyses yielded more practice-relevant estimates of CRC screening outcomes and should be applied in future studies to afford more appropriate assessment of comparative effectiveness estimates between guideline-endorsed screening options.

Introduction

Among individuals in the United States, colorectal cancer (CRC) is the second most common cause of cancer death with more than an estimated number of 53,000 deaths in 2021.[1] Screening has been shown to reduce the incidence of CRC and associated mortality.[2,3] Screening options recommended by US guidelines and organizations include colonoscopy and stool-based tests, such as the multitarget stool DNA (mt-sDNA) test and fecal immunochemical test (FIT).[4–6]

Colorectal carcinogenesis is heterogenous, and CRCs develop along several molecular pathways. The primary pathways of the conventional adenoma-carcinoma sequence are driven by the development of chromosomal or microsatellite instability.[7] Another important pathway is the serrated polyp pathway.[7] It is estimated that approximately 20%–30% of CRCs arise from the serrated polyp pathway, which develop mainly via the CpG island methylation pathway.[8–11] One clinical study of nearly 10,000 patients found that 14.3% of advanced precancerous lesions that were at least 10 mm in size were sessile serrated polyps (SSPs).[12] The stool-based FIT test has a low sensitivity to detect SSPs because serrated polyps are less likely to bleed than adenomas.[13] The mt-sDNA test, which detects DNA biomarkers, including several methylated genes, shed into the stool from CRCs and advanced precancerous lesions, has greater sensitivity than FIT to detect SSPs that are at least 10 mm (42.4% vs 5.1%, respectively).[12]

The Colorectal Cancer and Adenoma Incidence and Mortality Microsimulation Model (CRC-AIM) has been developed as a platform for CRC screening modeling analyses.[14] CRC screening microsimulation models are used to predict outcomes associated with various potential screening permutations, but most previous modeling analyses did not account for SSP-attributable CRC.[6,15] The lack of consideration for SSPs in CRC development is an

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acknowledged limitation of previous modeling analyses, mainly because of uncertainty around SSP biology.[15,16] One model, the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA), did incorporate the serrated polyp pathway when estimating outcomes with biennial FIT and one-time colonoscopy screening, but did not estimate outcomes with mt-sDNA.[17,18] We used the CRC-AIM model to assess how the detection of SSPs impacts predicted CRC outcomes of life-years gained (LYG), CRC incidence, and CRC mortality with mt-sDNA or FIT screening. We further aimed to assess the impact of real-world test utilization factors, specifically patient adherence with stool-based screening and attendance at follow-up colonoscopy for evaluation of positive stool-based screening tests.

Methods

CRC-AIM Model

The development and validation of the CRC-AIM model have been previously described.[14,16] Briefly, the model has 2 components, a natural history component and a screening component. The natural history component models the natural progression of adenomas to CRC if the adenomas were not removed. The assumptions in the natural history component of CRC-AIM include the risk of adenoma development based on age and sex, the rate of adenoma growth, the probability of a transition from adenoma to preclinical CRC, and CRC survival estimates, among others.[14,16] The screening component factors in assumptions related to CRC screening, such as the screening modality used, screening test sensitivity and specificity, the frequency of screening, and age at screening to determine the impact on screening compared with those who naturally progress to CRC (no screening).[14,16] The model assumes that screening will detect advanced precancerous lesions, which can be removed to prevent cancer incidence, and early-stage asymptomatic CRC, for which treatment lowers mortality. The ability to detect these screen-relevant neoplasms differs based on the sensitivity and specificity of the screening modality used.

Model Assumptions

A simulated cohort of 30 million average-risk US individuals born in 1975 without diagnosed CRC at the age of 40 years underwent triennial mt-sDNA or annual FIT screening between ages 45–75 years, in accordance with screening recommendations.[4–6] The percentage of CRCs arising from the SSP pathway was modeled at 0% (base case), 14.3%, 20%, and 30%, in combination with 4 screening adherence and attendance scenarios:

- Scenario 1 assumed theoretical (100%) adherence for initial stool-test screening and attendance for follow-up colonoscopy after a positive stool test.
- Scenario 2 assumed previously reported adherence for initial stool-test screening (mt-sDNA, 71%; FIT, 43%)[19–21] and theoretical (100%) attendance for follow-up colonoscopy.
- Scenario 3 assumed previously reported adherence for initial stool-test screening and previously reported

attendance for follow-up colonoscopy (after positive mt-sDNA, 72%; after positive FIT, 47%).[22]
- Scenario 4 assumed previously reported adherence for initial stool-test screening and equivalent rate of reported attendance for follow-up colonoscopy (after positive mt-sDNA or FIT, 72%).

Screening every 10 years with colonoscopy was modeled only for 0% SSP-attributed CRCs (base case) at theoretical adherence for screening and attendance for follow-up colonoscopy.

Assumptions for the natural history of SSPs were the same as those previously described for conventional adenomas modeled in CRC-AIM,[14,16,23–25] except for an assumption that SSPs would be localized more toward the proximal colon. When incorporating the percentage of SSP-attributed CRCs (eg, 14.3%, 20%, or 30%) into the model, 15% more of the SSPs were assumed to develop in the cecum and ascending colon, as described in a previous CRC screening model analysis.[26] Model assumptions regarding the sensitivities of mt-sDNA, FIT, and colonoscopy to detect SSPs and conventional adenomas by polyp size are in Table 1. Sensitivities of mt-sDNA and FIT to detect SSPs are derived from clinical trial results,[12] which for FIT was conservatively assumed to be the same for SSPs <10 mm and ≥10 mm because sensitivity for SSPs <10 mm was not determined. Sensitivity of mt-sDNA to detect SSPs was assumed to be the same as for conventional adenomas.[12] The sensitivity for colonoscopy to detect SSPs is assumed to be 10% less than for conventional adenomas because of poorer visibility, as previously described.[26] Sensitivity of FIT to detect conventional adenomas was derived from the study by Imperiale et al, 2014[12] after adjusting for the proportion SSPs (Table A1). Sensitivity of colonoscopy to detect conventional adenomas by size is from published reports[27,28] and is identical to those used in previous CRC-AIM and Cancer Intervention and Surveillance Modeling Network model analyses (Table 1).[15,16]

All other model assumptions for the natural history and screening components used in the current analysis are identical to those previously described for CRC-AIM.[14,16] A summary of the assumptions is in the Supplemental Materials.

Outcomes

The key outcomes were LYG, CRC incidence, and CRC mortality compared with no screening. All outcomes are per 1000 individuals.

Sensitivity Analyses

Because of the rapid evolution of CRC screening guidelines with respect to recommended screening initiation age, all primary analyses were repeated for individuals aged 50–75 years. In addition, analyses were repeated using initial stool-test screening adherence rates of 40%–70%, in 10% increments, instead of the specific previously reported adherence rates of 71% for mt-sDNA and 43% for FIT. The attendance to follow-up colonoscopy was assumed to be 100%. Alternatively, analyses were repeated assuming adherence to the initial stool-test screening was fixed at 71% for mt-sDNA and 43% for FIT and using follow-up colonoscopy attendance rates of 40%–90%, in 10% increments.

Table 1. Sensitivity and Specificity Model Inputs for mt-sDNA, FIT, and Colonoscopy in the Detection of Conventional Adenomas or SSPs

Screening modality	Adenoma type	Sensitivity				
		Adenomas, mm			Cancer	Specificity
		<6[c]	6–9[c]	≥10[d]		
Colonoscopy[a]	Conventional	75.0%[28]	85.0%[28]	95.0%[28]	95.0%[b]	86.0%[27]
	SSP	65.0%[26]	75.0%[26]	85.0%[26]		
mt-sDNA	Conventional	17.2%[12]	17.2%[12]	42.4%[12]	92.3%[12]	89.8%[12]
	SSP	17.2%[12]	17.2%[12]	42.4%[12]		
FIT	Conventional[e]	8.0%[12]	8.0%[12]	26.6%[12]	73.8%[12]	96.4%[12]
	SSP	5.1%[12]	5.1%[12]	5.1%[12]		

[a]It was assumed that the same sensitivity and specificity for screening colonoscopies applied to follow-up colonoscopies.
[b]By assumption.
[c]Sensitivity for mt-sDNA and FIT in persons with nonadvanced adenomas.
[d]Sensitivity for mt-sDNA and FIT in persons with advanced adenomas (ie, adenomas ≥10 mm or adenomas with advanced histology).
[e]Sensitivity of FIT for conventional adenomas was derived from the study by Imperiale et al, 2014,[12] after adjusting for the proportion of SSPs (Table A1).

Results

SSPs With Adherence/Attendance Scenario 1

At scenario 1 and 0% SSP-attributed CRCs (base case), the LYG were highest with colonoscopy (381.7), followed by FIT (346.7) and then mt-sDNA (324.6; Figure 1A and Table 2). Incorporating 14.3%, 20%, or 30% SSP-attributed CRCs into the model had the largest impact on FIT, resulting in a decrease from the base case of 7.3–14.5 LYG with FIT, 3.0–5.1 LYG with mt-sDNA, and 2.3–4.6 LYG with colonoscopy. The difference in LYG between mt-sDNA and FIT changed from −22.1 LYG at the base case to −12.3 LYG when assuming 30% SSP-attributed CRCs (Table 2). Similar patterns were observed with CRC incidence reduction and CRC mortality reduction (Table 2). The difference in CRC incidence reduction between mt-sDNA and FIT changed from −5.3% at the base case to −0.6% when assuming 30% SSP-attributed CRCs; the difference in CRC mortality reduction changed from −4.9% to −2.3% (Table 2).

SSPs With Adherence/Attendance Scenario 2

At scenario 2 and 0% SSP-attributed CRCs (base case), the LYG were higher with mt-sDNA (311.8) than those with FIT (279.3; Figure 1B and Table 2). Incorporating 14.3%, 20%, or 30% SSP-attributed CRCs into the model resulted in a decrease from the base case of 10.6–20.9 LYG with FIT and 2.6–4.4 LYG with mt-sDNA. The difference in LYG between mt-sDNA and FIT changed from +32.5 LYG at the base case to +49.1 LYG when assuming 30% SSP-attributed CRCs (Table 2). Similar patterns were observed with CRC incidence reduction and CRC mortality reduction (Table 2). The difference in CRC incidence reduction between mt-sDNA and FIT changed from +8.7% at the base case to +14.5% when assuming 30% SSP-attributed CRCs; the difference in CRC mortality reduction changed from +7.7% to +12.1% (Table 2).

SSPs With Adherence/Attendance Scenario 3

At scenario 3 and 0% SSP-attributed CRCs (base case), the LYG were higher with mt-sDNA (215.8) than those with FIT (126.6; Figure 1C and Table 2). Incorporating 14.3%, 20%, or 30% SSP-attributed CRCs into the model resulted in a decrease from the base case of 4.9–10.1 LYG with FIT and 2.0–4.2 LYG with mt-sDNA. The difference in LYG between mt-sDNA and FIT changed from +89.2 LYG at the base case to +95.1 LYG when assuming 30% SSP-attributed CRCs (Table 2). Similar patterns were observed with CRC incidence reduction and CRC mortality reduction (Table 2). The difference in CRC incidence reduction between mt-sDNA and FIT changed from +19.4% at the base case to +21.5% when assuming 30% SSP-attributed CRCs; the difference in CRC mortality reduction changed from +20.6% to +22.2% (Table 2).
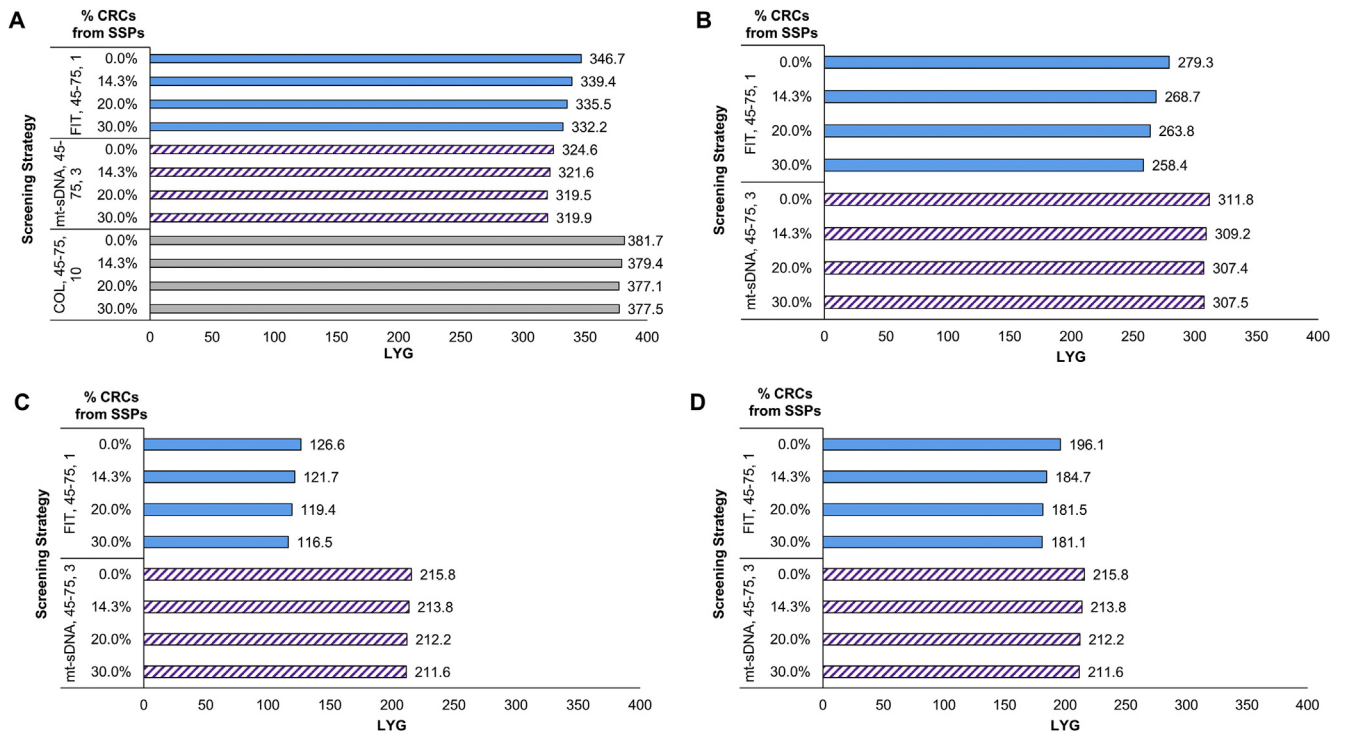
SSPs With Adherence/Attendance Scenario 4

At scenario 4 and 0% SSP-attributed CRCs (base case), the LYG were higher with mt-sDNA (215.8) than those with FIT (196.1; Figure 1D and Table 2). Incorporating 14.3%, 20%, or 30% SSP-attributed CRCs into the model resulted in a decrease from the base case of 11.4–15.0 LYG with FIT and 2.0–4.2 LYG with mt-sDNA. The difference in LYG between mt-sDNA and FIT changed from +19.7 LYG at the base case to +30.5 LYG when assuming 30% SSP-attributed CRCs (Table 2). Similar patterns were observed with CRC incidence reduction and CRC mortality reduction (Table 2). The difference in CRC incidence reduction between mt-sDNA

Table 2. CRC Outcomes for Triennial mt-sDNA and Annual FIT After Assuming 0%, 14.3%, 20%, or 30% SSP-attributed CRCs at 4 Different Adherence/Attendance Scenarios

Scenario	Screening adherence rates	Follow-up COL attendance rates	% CRCs from SSPs	Triennial mt-sDNA			Annual FIT			Difference between mt-sDNA and FIT		
				LYG	CRC incidence reduction, %	CRC mortality reduction, %	LYG	CRC incidence reduction, %	CRC mortality reduction, %	LYG	CRC incidence reduction, %	CRC mortality reduction, %
#1	100%	100%	0%	324.6	67.5%	74.7%	346.7	72.8%	79.6%	−22.1	−5.3%	−4.9%
			14.3%	321.6	67.0%	74.2%	339.4	70.1%	77.9%	−17.8	−3.1%	−3.7%
			20%	319.5	66.6%	73.9%	335.5	68.8%	77.0%	−16.0	−2.2%	−3.1%
			30%	319.9	66.3%	73.6%	332.2	66.9%	75.9%	−12.3	−0.6%	−2.3%
#2	mt-sDNA, 71%; FIT, 43%	100%	0%	311.8	64.7%	71.9%	279.3	56.0%	64.2%	+32.5	+8.7%	+7.7%
			14.3%	309.2	64.1%	71.5%	268.7	52.7%	61.7%	+40.5	+11.4%	+9.8%
			20%	307.4	63.8%	71.2%	263.8	51.3%	60.7%	+43.6	+12.5%	+10.5%
			30%	307.5	63.5%	71.0%	258.4	49.0%	58.9%	+49.1	+14.5%	+12.1%
#3	mt-sDNA, 71%; FIT, 43%	mt-sDNA, 72%; FIT, 47%	0%	215.8	44.3%	49.1%	126.6	24.9%	28.5%	+89.2	+19.4%	+20.6%
			14.3%	213.8	43.8%	48.8%	121.7	23.5%	27.4%	+92.1	+20.3%	+21.4%
			20%	212.2	43.6%	48.6%	119.4	22.8%	26.9%	+92.8	+20.8%	+21.7%
			30%	211.6	43.3%	48.3%	116.5	21.8%	26.1%	+95.1	+21.5%	+22.2%
#4	mt-sDNA, 71%; FIT, 43%	mt-sDNA, 72%; FIT, 72%	0%	215.8	44.3%	49.1%	196.1	39.1%	44.8%	+19.7	+5.2%	+4.3%
			14.3%	213.8	43.8%	48.8%	184.7	35.5%	41.6%	+29.1	+8.3%	+7.2%
			20%	212.2	43.6%	48.6%	181.5	34.5%	41.0%	+30.7	+9.1%	+7.6%
			30%	211.6	43.3%	48.3%	181.1	34.2%	41.0%	+30.5	+9.1%	+7.3%

Data are per 1000 individuals.
COL, colonoscopy.

Figure 1. LYG with triennial mt-sDNA and annual FIT after assuming 0%, 14.3%, 20%, or 30% SSP-attributed CRCs and assuming (A) adherence/attendance scenario 1, (B) adherence/attendance scenario 2, (C) adherence/attendance scenario 3, and (D) adherence/attendance scenario 4. Data are per 1000 individuals.

and FIT changed from +5.2% at the base case to +9.1% when assuming 30% SSP-attributed CRCs; the difference in CRC mortality reduction changed from +4.3% to +7.3% (Table 2).

Sensitivity Analyses

Results from the sensitivity analyses in patients aged 50–75 years were similar to those of patients aged 45–75 years (Table A2).

The LYG when assuming 30% SSP-attributed CRCs in sensitivity analyses with stool-test screening adherence ranging from 40% to 70% are shown in Figure 2 and with fixed reported initial screening stool-test adherence rates and follow-up colonoscopy attendance ranging from 40% to 90% are shown in Figure 3. At all the equivalent adherence or attendance rates (ie, mt-sDNA = 40%, FIT = 40%, etc.),

mt-sDNA has higher LYG than FIT. The LYG for these sensitivity analyses when assuming 0%, 14.3%, and 20% SSP-attributed CRCs are shown in Figures A1 and A2. The LYG when assuming 30% SSP-attributed CRCs for these sensitivity analyses in patients aged 50–75 years are shown in Figures A3 and A4.

Discussion

Most CRC screening modeling analyses do not consider the molecular heterogeneity of CRC development or imperfect adherence to initial screening or follow-up colonoscopy. The present study analyzed the impact of incorporating the SSP pathway into the CRC-AIM model across 4 SSP pathway scenarios and 4 adherence and attendance scenarios. The results demonstrate that

Figure 2. Difference in LYG with triennial mt-sDNA and annual FIT after assuming 30% SSP-attributed CRCs at initial screening adherence rates ranging from 40% to 70% and 100% follow-up colonoscopy attendance rates. Data are per 1000 individuals.

		Triennial mt-sDNA, 30% SSPs				
Annual FIT, 30% SSPs	Screening Adherence Rate	40%	50%	60%	70%	LYG
	40%	+24.41	+38.38	+48.20	+55.40	251.2
	50%	+0.67	+14.65	+24.46	+31.66	275.0
	60%	-17.46	-3.48	+6.33	+13.54	293.1
	70%	-30.79	-16.81	-7.00	+0.20	306.4
	LYG	275.6	289.6	299.4	306.6	

■ mt-sDNA better
▨ FIT better

Annual FIT, 30% SSPs	Triennial mt-sDNA, 30% SSPs						
Follow-up attendance rate	40%	50%	60%	70%	80%	90%	LYG
40%	+14.12	+44.88	+75.69	+107.38	+139.28	+173.01	100.1
50%	-10.71	+20.04	+50.86	+82.55	+114.44	+148.18	125.0
60%	-36.23	-5.47	+25.34	+57.03	+88.92	+122.66	150.5
70%	-62.85	-32.09	-1.27	+30.42	+62.31	+96.05	177.1
80%	-89.60	-58.84	-28.03	+3.66	+35.56	+69.29	203.8
90%	-116.40	-85.64	-54.83	-23.14	+8.75	+42.49	230.7
LYG	114.2	145.0	175.8	207.5	239.4	273.1	

■ mt-sDNA better
▢ FIT better

Figure 3. Difference in LYG with triennial mt-sDNA and annual FIT after assuming 30% SSP-attributed CRCs at fixed reported initial screening adherence rates of 71% for mt-sDNA and 43% for FIT and follow-up colonoscopy attendance rates of 40%–90%. Data are per 1000 individuals.

incorporating the SSP pathway into the CRC-AIM model reduced the predicted effectiveness with stool-test screening, regardless of which test was used. However, in all the SSP scenarios, the mt-sDNA strategy was disrupted to a lesser degree than the FIT strategy, in agreement with the lower sensitivity of FIT than mt-sDNA to detect SSPs. Compared with no SSP pathway, the decrease in LYG was between 1.1% and 11.2% more with FIT than mt-sDNA once SSPs were incorporated into the model, depending on the scenario. The impact was greater when the SSP pathway was assumed to be more common and when reported, rather than idealized, adherence rates were used. The analysis reiterates previous research with CRC-AIM that realistic, imperfect assumptions for adherence to initial screening and attendance to follow-up colonoscopy after a positive stool test have an impact on the comparative effectiveness of stool-test screening.[16,29] Together, these data provide more realistic estimates of comparative effectiveness between the most commonly utilized options for stool-based CRC screening. As incorporation of SSP contributions to CRCs and realistic adherence rates were shown to be key levers to the outcomes of the models, they should be included in any CRC screening modeling strategy for the results to be clinically relevant.

The ASCCA model is one of the few models that have included the serrated polyp pathway.[17] Similar to the current analysis, the ASCCA model demonstrated that including the serrated pathway impacted the effectiveness of FIT and colonoscopy screening.[17,18] Over a 30-year screening period, assuming a 100% biennial FIT participation rate and a 96% follow-up colonoscopy rate, the reduction in CRC incidence decreased from 53% with 0% SSP-attributed CRCs to 47% with 30% SSP-attributed CRCs, and the reduction in CRC mortality decreased from 70% to 66%.[18] Also similar to the current analysis, the ASCCA model demonstrated an additional impact of screening adherence on outcomes.[18] When the FIT participation rate was assumed to be 40%, the reduction in CRC incidence decreased from 27% with 0% SSP-attributed CRCs to 25% with 30% SSP-attributed CRCs, and the reduction in CRC mortality decreased from 37% to 35%.

Predicted outcomes with mt-sDNA, which has greater sensitivity to detect SSPs than FIT, were not evaluated in the ASCCA model.

Estimates of SSPs in the population are influenced by self-reported colonoscopy data, and there is variation by the endoscopist in identifying SSPs.[30] Likely, the prevalence of SSPs is underestimated. However, there is overall general consensus in the published literature that the sessile polyp pathway contributes to approximately 20%–30% of CRCs.[10,11,31–33] Thus, a 20% and 30% proportion of CRCs arising from SSPs was a reasonable assumption for the current analyses. Along with the 14.3% proportion of SSP CRCs specifically identified in a clinical trial, the analysis accounts for a broad range of potential SSP-attributed CRCs. A 14% proportion of SSP CRCs is likely low because the clinical trial that provided this percentage used standard of care colonoscopy as the reference method, which has lower sensitivity for SSPs, skewing the prevalence.[12]

The current analyses focused primarily on stool-based screening tests, for which sensitivity to detect SSPs has been characterized. Several studies have found that FIT detects SSPs with less sensitivity than conventional adenomas, with reported sensitivity to detect large SSPs ($\geq$10 mm) ranging from 0% to 16.7%.[12,13,34,35] The sensitivities of mt-sDNA and FIT to detect large SSPs used in the current analyses (42.4% and 5.1%, respectively) were from the results of a head-to-head clinical trial of mt-sDNA vs FIT conducted in approximately 10,000 patients.[12] The sensitivity of mt-sDNA to detect large SSPs ($\geq$10 mm) has only been evaluated in one other study and was determined to be 55%.[34] The reduced sensitivity of 10% for colonoscopy to detect SSPs than conventional adenomas was used previously in a sensitivity analysis for cost-effectiveness using a CISNET model. A weakness of this assumption for colonoscopy is that adenomas and SSPs are found at a higher rate with colonoscopy when the endoscopist knows that the patient had a positive stool test.[36] Thus, the assumption in the current analysis of equal colonoscopy performance for screening and follow-up colonoscopy may be unrealistic and underestimates the predicted outcomes for stool-based screening.[25]

In addition to incorporating SSPs, shifting from the theoretical 100% adherence that was used in the models that informed United States Preventive Services Task Force CRC screening guidelines[15] to more realistic screening adherence and follow-up colonoscopy attendance in the current analysis caused a substantial change in the comparative effectiveness between mt-sDNA and FIT. The impact, justifications, and limitations of the real-world adherence or attendance rates for initial screening and follow-up colonoscopy used in CRC-AIM analyses have been thoroughly discussed elsewhere.[16,29] However, the results of the sensitivity analysis demonstrate that when assuming 30% SSP-attributed CRCs, mt-sDNA provided greater LYG than FIT over a broad range of equivalent adherence or attendance rates. Therefore, although the adherence and attendance rates may vary over different settings and populations, use of realistic rates should be part of any CRC screening modeling analyses.

Aside from the incorporation of realistic SSP and adherence/attendance rates, a strength of this modeling analysis was a screening starting age of 45 years, which is now a priority for average-risk individuals in CRC screening recommendations.[4–6] The results show that screening is beneficial to start in younger patients. However, a limitation of the analysis is that the prevalence of SSPs in patients aged 45–50 years is unknown and may differ from older populations. The analysis is also limited to a general US population and may not be generalizable to other populations.

Incorporating SSPs, as represented by previously reported estimates of SSP case mix, provided more practice-relevant comparative effectiveness estimates between mt-sDNA and FIT. Predicted outcomes with mt-sDNA neared those of FIT at 100% screening adherence rates and surpassed FIT at more realistic reported adherence rates. Furthermore, the use of realistic data, such as the contribution of the sessile pathway to CRCs and real-world adherence, should be applied to future CRC screening model studies to afford more appropriate assessment of comparative effectiveness estimates between guideline-endorsed screening options.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2021.10.007.

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