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Article

Comparing the Cost-Effectiveness of Innovative Colorectal Cancer Screening Tests

Elisabeth F. P. Peterse, PhD,[1,2,*] Reinier G. S. Meester, PhD,[1] Lucie de Jonge, MSc,[1] Amir-Houshang Omidvari, MD,[1] Fernando Alarid-Escudero, PhD,[3] Amy B. Knudsen, PhD,[4] Ann G. Zauber, PhD,[5] Iris Lansdorp-Vogelaar, PhD[1]

[1]Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands; [2]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]Drug Policy Program, Center for Research and Teaching in Economics (CIDE)-CONACyT, Aguascalientes, AGS, Mexico; [4]Institute for Technology Assessment, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA and [5]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[*]**Correspondence to:** Elisabeth F. P. Peterse, PhD, Department of Public Health, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands (e-mail: e.peterse@erasmusmc.nl).

Abstract

Background: Colorectal cancer (CRC) screening with colonoscopy and the fecal immunochemical test (FIT) is underused. Innovative tests could increase screening acceptance. This study determined which of the available alternatives is most promising from a cost-effectiveness perspective. **Methods:** The previously validated Microsimulation Screening Analysis-Colon model was used to evaluate the cost-effectiveness of screening with capsule endoscopy every 5 or 10 years, computed tomographic colonography every 5 years, the multi-target stool DNA test every 1 or 3 years, and the methylated *SEPT9* DNA plasma assay (*mSEPT9*) every 1 or 2 years. We also compared these strategies with annual FIT screening and colonoscopy screening every 10 years. Quality-adjusted life-years gained (QALYG), number of colonoscopies, and incremental cost-effectiveness ratios were projected. We assumed a willingness-to-pay threshold of $100 000 per QALYG. **Results:** Among the alternative tests, computed tomographic colonography every 5 years, annual *mSEPT9*, and annual multi-target stool DNA screening had incremental cost-effectiveness ratios of $1092, $63 253, and $214 974 per QALYG, respectively. Other screening strategies were more costly and less effective than (a combination of) these 3. Under the assumption of perfect adherence, annual *mSEPT9* screening resulted in more QALYG, CRC cases averted, and CRC deaths averted than annual FIT screening but led to a high rate of colonoscopy referral (51% after 3 years, 69% after 5 years). The alternative tests were not cost-effective compared with FIT and colonoscopy. **Conclusions:** This study suggests that for individuals not willing to participate in FIT or colonoscopy screening, *mSEPT9* is the test of choice if the high colonoscopy referral rate is acceptable to them.

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Colorectal cancer (CRC) is a leading cause of cancer death in the United States, with an estimated 53 000 associated deaths in 2020 (1). CRC screening can prevent CRC death through earlier detection or through removal of premalignant polyps (2,3) and is recommended by the US Preventive Services Task Force from age 50 years to 75 years (4) and by the American Cancer Society (ACS) from age 45 years to 75 years (5). Despite the effectiveness of screening, almost 40% of 50- to 75-year-olds reported not having received guideline-consistent CRC screening. Important barriers for screening include fear and disgust of the screening test (6,7). Therefore, new tests that circumvent these barriers are needed to increase screening participation.

Fecal occult blood testing and colonoscopy were already proposed as CRC screening tests in the late 1960s (8,9). More recently developed US Food and Drug Administration (FDA)-approved tests are capsule endoscopy, specifically the PillCam COLON 2 (PillCam); the computed tomographic colonography (CTC); the multitarget stool DNA test (mtSDNA), also known as Cologuard (Exact Sciences Corporation, Madison, Wisconsin); and the methylated *SEPT9* DNA plasma assay (*mSEPT9*), also known as the Epi proColon (Epigenomics AG). All these tests require colonoscopy follow-up of individuals with a positive test result. Several studies have suggested that these alternative tests are not cost-effective compared with colonoscopy or fecal immunochemical test (FIT) screening (10–16). However, these

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tests have potential to attract the population not currently participating in screening. The *mSEPT9* requires a blood sample, which may be preferred for some patients over collecting a stool sample or a more invasive test. The CTC, PillCam, and mtSDNA all have better test sensitivities than FIT while being less invasive than colonoscopy. Therefore, it is important to evaluate which of these alternative tests should be offered to individuals who are not willing to participate in FIT or colonoscopy screening. No study to our knowledge has compared all of these alternative screening tests in terms of cost-effectiveness. Therefore, in this study, the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model was used to evaluate the comparative cost-effectiveness of the PillCam, the CTC, the mtSDNA, and the *mSEPT9*.

Methods

MISCAN-Colon

The MISCAN-Colon model was developed by the Department of Public Health within Erasmus University Medical Center, Rotterdam, the Netherlands, and has been described in detail elsewhere (17,18). It is part of the US National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (19) and has been used to inform screening recommendations (20–22). In brief, the model generates, with random variation, a large population similar to the US population in terms of life expectancy and CRC risk. As each simulated person ages, 1 or more adenomas may develop, which can progress in size and can develop into preclinical cancer (stages I-IV). During each stage, CRC may be diagnosed because of symptoms. Screening can alter some simulated life histories, because CRC can be prevented or diagnosed at an earlier stage. Screening may also result in complications, overdiagnosis, and overtreatment, which are also taken into account by the model.

Screening Strategies

We simulated screening from age 50 years through 75 years in an average-risk population, with perfect adherence to screening, diagnostic follow-up, and surveillance recommendations (4,23). We used the same model assumptions as for the 2018 ACS guidelines, which account for recent trends in CRC incidence (21,24). The screening strategies evaluated were CTC every 5 years, mtSDNA testing every 1 or 3 years (4), PillCam every 5 or 10 years, and annual or biennial *mSEPT9* testing. These alternative screening strategies were compared with colonoscopy every 10 years and annual FIT. Positive noncolonoscopy tests were followed by a diagnostic colonoscopy, and individuals in whom adenomas were detected and removed received colonoscopy surveillance through age 85 years (23).

To compare the different screening strategies, an incremental cost-effectiveness analysis was performed, ranking strategies based on costs. Strategies that were more costly and less effective than a (combination of) other strategies were considered dominated. The remaining strategies provided good value for money (ie, were efficient). For the efficient strategies, the incremental cost-effectiveness ratios (ICERs) were obtained by dividing the additional costs by the additional quality-adjusted life-years gained (QALYG) compared with the next less costly alternative strategy. In this analysis, we assumed a willingness-to-pay threshold of $100 000 per QALYG (25,26).

Test Characteristics

mSEPT9 performance characteristics were based on Potter et al. (27) (Table 1; Supplementary Table 1, available online), which was used for the FDA approval of *mSEPT9* (33). In this study, 1544 samples were retrospectively selected from the PRospective Evaluation of SEPTin 9 (PRESEPT) trial (34). CRC sensitivity and specificity of 68.2% and 78.8% were reported, respectively, with a sensitivity for advanced adenoma of 21.6%. PillCam characteristics were based on the study of Rex et al. (30) in which 695 asymptomatic individuals were successfully screened using the PillCam, followed by colonoscopy several weeks later. This study reported a sensitivity of 92% and 91% for adenomas larger than 10 mm and 6 mm, respectively, with a specificity of 83% (30). Colonoscopy, FIT, CTC, and mtSDNA characteristics were similar to previous analyses from our group (20,21) (Table 1). All test characteristics were varied in probabilistic sensitivity analyses (see below).

Costs and Disutilities

Costs of screening, screening-related complications, and cancer care were computed from a societal perspective, obtained from various sources, and included (as relevant) payments, coinsurance, cathartic bowel preparation agents, and patient and escort time costs (Table 2; Supplementary Tables 2-6, available online). Costs were updated to 2017 US dollars using the Personal Health Care Deflator Price Index. Estimated test disutilities included those associated with the test itself and those related to fear or anxiety while waiting for the test result or a follow-up colonoscopy after a positive result (Supplementary Table 4, available online). Complication and CRC care disutilities were in line with previous analyses (16,35).

Scenario Analyses

We repeated analyses under several alternative scenarios. In the first scenario, we evaluated CRC screening from age 45 years instead of 50 years, in line with the most recent ACS screening guideline (5). In the second scenario, we used the version of MISCAN-Colon that was used to inform the 2016 US Preventive Services Task Force CRC screening recommendations, with CRC incidence based on 1975-1979 data (20) instead of more recent data. In the third scenario, we accounted for suboptimal adherence to diagnostic and surveillance colonoscopy and for decreasing adherence over multiple screening rounds (36). For this scenario, we assumed a 100% adherence at the first screening and that 90% of the people screened at a given age would participate again at the next recommended age (37,38). In line with current CRC participation rates (39), we assumed screening adherence would not drop below 60% at any age by assuming that 15% of the people who previously did not participate would participate at the next recommended age. We further assumed 80% adherence to diagnostic and surveillance colonoscopy (40,41). Finally, we evaluated a scenario in which 12% of the advanced adenomas and 18% of CRCs were systematically missed by the *mSEPT9* due to no methylation of the *SEPT9* gene promoter (42).

Probabilistic Sensitivity Analyses

To evaluate the model parameter uncertainty, a probabilistic sensitivity analysis was performed, varying the characteristics, costs, and disutilities of all screening tests as well as the costs

Table 1. Test characteristics

Screening test	Sensitivity, %[a]				Specificity[b]	Source[c]
	Adenomas ≤5 mm	Adenomas 6-9 mm	Adenomas ≥10 mm	CRC		
Direct visualization						
Colonoscopy[d]	75	85	95	95	100[e]	van Rijn et al., 2006 (28)
CTC	12[f]	57	84	84[g]	88[h]	Johnson et al., 2008 (29)
PillCam	17[f]	91[i]	92	92[g]	83	Rex et al., 2015 (30)
Stool based						
FIT	7.6[j]		23.8[k]	73.8	96.4	Imperiale et al., 2014 (31)
mtSDNA	17.2[j]		42.4[k]	92.3	89.8	Imperiale et al., 2014 (31)
Blood based						
mSEPT9	21.2[f]	21.2[f]	21.6[k]	68.2	78.8	Potter et al., 2014 (27)

[a]The sensitivities of CTC and colonoscopy are presented per lesion; the sensitivities of the other tests are presented per person, which were calibrated to per lesion test sensitivities that were used as Microsimulation Screening Analysis-Colon model input. CRC = colorectal cancer; CTC = computed tomographic colonography; FIT = fecal immunochemical test; mSEPT9 = methylated SEPT9 DNA plasma assay; mtSDNA = multitarget stool DNA; PillCam = PillCam COLON 2.
[b]Specificity is defined as the probability of having a negative test result for individuals without lesions (including adenomas and CRC) unless otherwise noted.
[c]Additional details about these studies (designs, sample sizes, periods, and regions) can be found in Supplementary Table 1 (available online).
[d]We assumed that 95% of colonoscopies reach the cecum.
[e]We accounted for the detection of nonadenomatous polyps, which is 14% based on Schroy et al., 2013 (32).
[f]Sensitivity equals the false-positivity rate. It is 1 – specificity.
[g]The same sensitivity for CRC as for adenomas 10 mm or larger was assumed.
[h]The lack of specificity of a CTC reflects the detection of larger than 5 mm nonadenomatous lesions, artifacts, stool, and adenomas smaller than the 6-mm threshold for referral to colonoscopy that are measured as larger than 5 mm.
[i]Value of all adenomas 6 mm or larger.
[j]Sensitivity for persons with nonadvanced adenomas. For persons with 1-5 mm, it was assumed that the sensitivity is equal to the positivity in persons without adenomas. The sensitivity for adenomas 6-9 mm was chosen such that the weighted average sensitivity is equal to that for nonadvanced adenomas.
[k]Sensitivity for persons with advanced adenomas. In Microsimulation Screening Analysis-Colon, advanced adenomas are equated to large adenomas.

Table 2. Assumptions regarding disutilities and costs of screening tests (2017$)

Screening test	Disutility when positive	Disutility when negative	Total CMS payment	Cost of bowel preparation kit	Patient and escort time costs	Total cost
Colonoscopy screening w/o polypectomy	—	0.000496	$794	$51	$434	$1279
Colonoscopy follow-up w/o polypectomy	—	0.000496	$847	$51	$434	$1332
Colonoscopy surveillance w/o polypectomy	—	0.000496	$796	$51	$434	$1281
Colonoscopy with polypectomy	0.001401	—	$1 172	$51	$434	$1656
CTC	0.001559	0.000292	$236	$51	$206	$493
PillCam	0.001692	0.000425	$939	$104	$310	$1352
FIT	0.001330	0.000063	$22	—	$18	$40
mtSDNA	0.001394	0.000127	$512	—	$18	$531
mSEPT9	0.001330	0.000063	$192	—	$18	$210

CMS = Centers for Medicare and Medicaid Services; CTC = computed tomographic colonography; FIT = fecal immunochemical test; mSEPT9 = methylated SEPT9 DNA plasma assay; mtSDNA = multitarget stool DNA; PillCam = PillCam COLON 2; w/o = without.

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and disutilities of CRC treatment and colonoscopy complications (Supplementary Tables 7 and 8, available online). For every evaluated screening strategy, we performed 1000 simulation runs of 10 million persons in which we sampled parameters values from distributions that reflect the parameter's current level of evidence (Supplementary Tables 7 and 8, available online). The results of the probabilistic sensitivity analysis were displayed with cost-effectiveness acceptability curves and a frontier representing the proportion that each strategy is cost-effective and the strategy with the highest expected net monetary benefit at each cost-effectiveness threshold, respectively (43). Results were analyzed using R with the package BCEA (44,45).

Results

Projected Outcomes

Without screening, the model predicted 108 CRC cases and 45 CRC deaths per 1000 50-year-olds (Figure 1). The number of CRC cases and deaths ranged from 37 to 59 and from 8 to 15, respectively, for the different screening strategies. The strategy that prevented the most CRC deaths was colonoscopy screening every 10 years, whereas screening with the PillCam every 10 years prevented the fewest.

In the absence of screening, the model predicted lifetime CRC-related costs of $7.286 million per 1000 50-year-olds

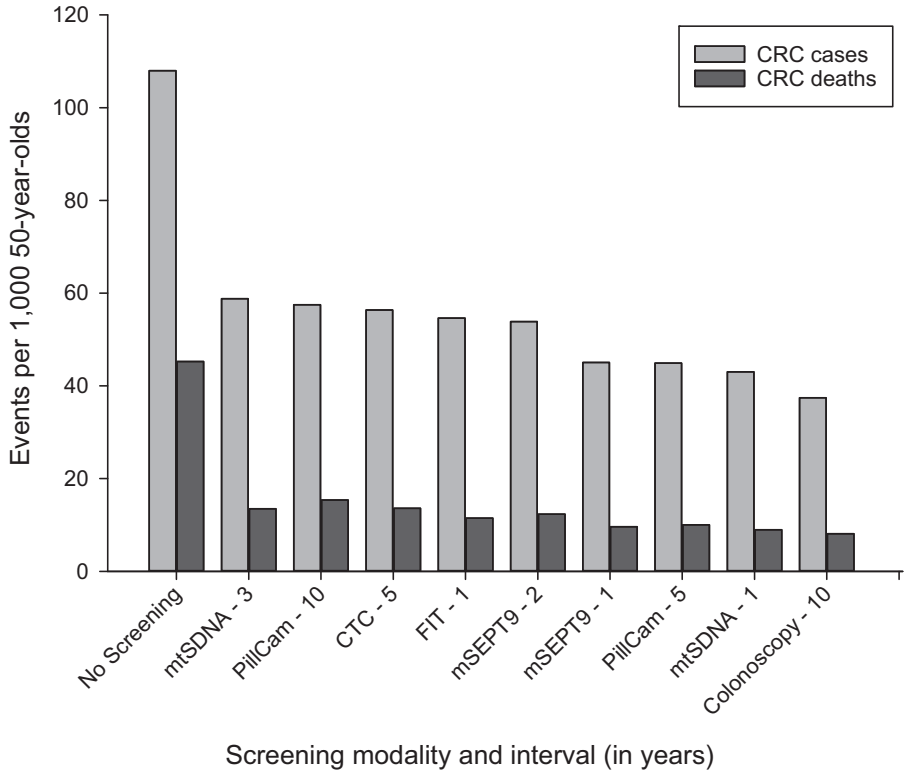

Figure 1. Colorectal cancer (CRC) cases and deaths with the different screening strategies. CTC = computed tomographic colonography; FIT = fecal immunochemical test; m*SEPT9*= methylated *SEPT9* DNA plasma assay; mtSDNA = multitarget stool DNA; PillCam = PillCam COLON 2.

Table 3. Outcomes per 1000 50-year-olds for different screening strategies

			Undiscounted			3% Discounted				
Screening test	Interval, y	Screening tests, No.	Diagnostic colonoscopies,[a] No.	Surveillance colonoscopies, No.	Colonoscopies, total No.	LYG	QALYG	Total costs, million $	ICER, $ per QALYG	ICER w/o FIT and colonoscopy, $ per QALYG
No screening	—	0	108	0	108	0	0	7.286	—	—
FIT	1	15 044	791	1558	2349	162	189	6.793	Cost saving	—
CTC	5	4292	628	1196	1824	151	177	7.479	D	1092
Colonoscopy	10	1995	15	2725	4735	174	209	7.751	48 155	—
m*SEPT9*	2	5802	1269	1932	3201	151	175	8.298	D	D
m*SEPT9*	1	7159	1548	2279	3827	165	194	8.574	D	63 253
mtSDNA	3	5583	785	1494	2279	151	175	8.887	D	D
PillCam	10	2383	671	1502	2173	141	165	8.951	D	D
PillCam	5	3710	899	1837	2736	166	196	9.940	D	D
mtSDNA	1	10 185	1233	2101	3334	173	205	10.798	D	214 974

[a]Includes both diagnostic follow-up colonoscopies and colonoscopies for clinical detection of colorectal cancer. CTC = computed tomographic colonography; D = dominated; FIT = fecal immunochemical test; ICER = incremental cost-effectiveness ratio; LYG = life-years gained; m*SEPT9* = methylated *SEPT9* DNA plasma assay; mtSDNA = multitarget stool DNA; PillCam = PillCam COLON 2; QALYG = quality-adjusted life-years gained; w/o = without.

(Table 3). None of the alternative screening strategies were cost-saving compared with no screening. Of the alternative strategies, CTC screening every 5 years had the lowest costs ($7.479 million), whereas annual mtSDNA screening was the most expensive ($10.798 million). The number of QALYG compared with no screening ranged from 165 for PillCam screening every 10 years to 205 for annual mtSDNA screening; the number of total colonoscopies required ranged from 1824 per 1000 50-year-olds for CTC every 5 years to 3827 for annual *mSEPT9* screening (Table 3).

Cost-Effectiveness Analysis

For individuals who are not willing to undergo FIT or colonoscopy screening (ie, those for whom FIT and colonoscopy are not considered acceptable alternatives), CTC every 5 years and annual *mSEPT9* were efficient strategies, with ICERs of $1092 and $63 253 per QALYG, respectively (Figure 2; Table 3). Annual screening with the *mSEPT9* resulted in a high number of individuals referred to colonoscopy: 51% after 3 years and 69% after

5 years. PillCam strategies were dominated by other strategies, and annual mtSDNA screening had an ICER of $214 974 per QALYG, which is above the willingness-to-pay threshold.

When considering all screening strategies, including FIT and colonoscopy, colonoscopy every 10 years resulted in an ICER of $48 155 per QALYG compared with annual FIT screening and was therefore the cost-effective strategy in this analysis (Table 3; Figure 2). Annual FIT screening was cost saving compared with no screening. All alternative strategies were dominated by FIT and colonoscopy screening. The number of QALYG, CRC cases prevented, and CRC deaths prevented for annual *mSEPT9* were higher than for annual FIT screening (Figure 1; Table 3). However, the test burden in terms of number of diagnostic colonoscopies was 63% higher, and the total costs were 26% higher compared with annual screening with FIT (Table 3).

Scenario Analyses

In all our scenario analyses, the same 3 strategies were efficient for individuals not willing to undergo FIT or colonoscopy screening: CTC screening every 5 years, annual *mSEPT9*, and annual mtSDNA. Our results were robust for alternative assumptions regarding starting age of screening, screening adherence, and systematically missing adenomas or cancers, which resulted in ICERs for annual *mSEPT9* of $66 372, $41 041, and $68 682 per QALYG compared with the next-best alternative, respectively (Table 4; Supplementary Table 9, available online).

However, when we simulated a lower CRC incidence, annual *mSEPT9* resulted in an ICER of $119 336 per QALYG. Hence, CTC screening every 5 years was the cost-effective strategy for these individuals with an ICER of $9397 per QALYG (Supplementary Table 9, available online). Although efficient, annual mtSDNA screening was never cost-effective using a willingness-to-pay threshold of $100 000 per QALYG. When FIT and colonoscopy were also considered, colonoscopy screening every 10 years was the cost-effective strategy in all our scenario analyses (Supplementary Table 9, available online).

Probabilistic Sensitivity Analyses

For individuals who are not willing to undergo FIT or colonoscopy screening, annual screening with *mSEPT9* was the cost-effective strategy in 54% of the 1000 simulations evaluated in the probabilistic sensitivity analyses at a willingness-to-pay threshold of $100 000 per QALYG (Figure 3). In 20% and 17% of the simulations, annual mtSDNA screening and CTC screening every 5 years were cost-effective strategies, respectively. At higher willingness-to-pay thresholds, the probability increased that annual mtSDNA screening was the cost-effective strategy, whereas the probability that CTC screening every 5 years was cost-effective decreased. At a willingness-to-pay threshold of $200 000 per QALYG, the probabilities were 48%, 47%, and 1% for mtSDNA, *mSEPT9*, and CTC, respectively (Figure 3).

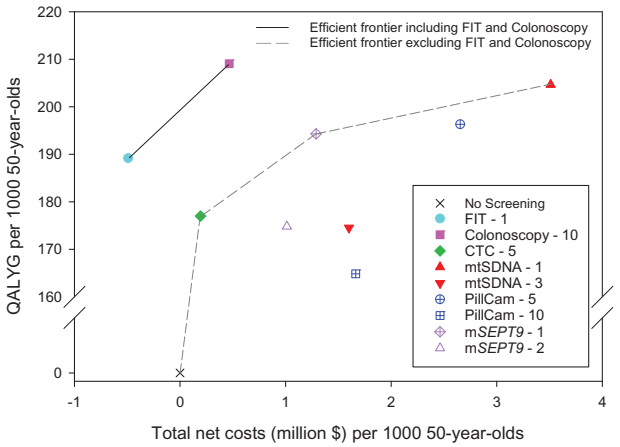

Figure 2. Efficient frontier . Lifetime costs and quality-adjusted life-years of the evaluated screening strategies. CTC = computed tomographic colonography; FIT = fecal immunochemical test; m*SEPT9* = methylated *SEPT9* DNA plasma assay; mtSDNA = multitarget stool DNA; PillCam = PillCam COLON 2; QALYG = quality-adjusted life-years gained.

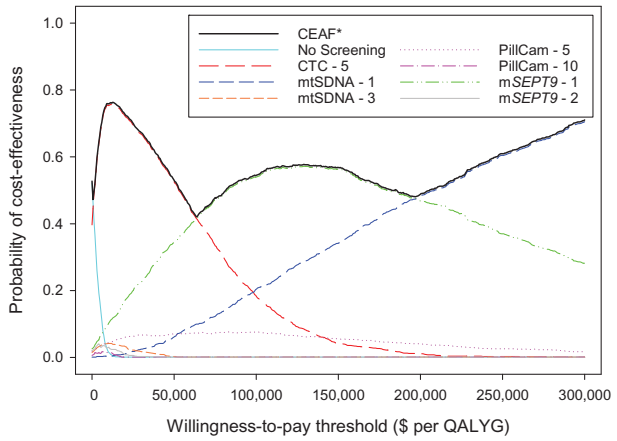

Figure 3. Cost-effectiveness acceptability curve and frontier. CTC = computed tomographic colonography; m*SEPT9* = methylated *SEPT9* DNA plasma assay; mtSDNA = multitarget stool DNA; PillCam = PillCam COLON 2; QALYG = quality-adjusted life-years gained. *The cost-effectiveness acceptability frontier (CEAF) plots the probability that the optimal screening strategy is cost-effective over a range of cost-effectiveness thresholds.

Table 4. Most effective strategy with an ICER <$100 000 per QALYG by scenario analysis and inclusion of FIT and colonoscopy

Analysis	Most effective strategy excluding FIT and colonoscopy	Most effective strategy including FIT and colonoscopy
Base case	Annual m*SEPT9*	Colonoscopy every 10 y
Screening from age 45 y	Annual m*SEPT9*	Colonoscopy every 10 y
USPSTF model; lower CRC incidence	CTC every 5 y[a]	Colonoscopy every 10 y
Adjusted adherence	Annual m*SEPT9*	Colonoscopy every 10 y
Systematic false-negativity m*SEPT9*	Annual m*SEPT9*	Colonoscopy every 10 y

[a]In this scenario, the ICER for annual m*SEPT9* was $119 336 per QALYG, just above the willingness-to-pay threshold. CRC = colorectal cancer; CTC = computed tomographic olonography; FIT = fecal immunochemical test; ICER = incremental cost-effectiveness ratio; m*SEPT9* = methylated *SEPT9* DNA plasma assay; QALYG = quality-adjusted life-years gained; USPSTF = United States Preventative Services Task Force.

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Discussion

New strategies are needed to increase CRC screening participation in the United States given rates reached a plateau of approximately 60% (39). By comparing the incremental cost-effectiveness of CTC, PillCam, mtSDNA, and *mSEPT9* from a societal perspective, this study revealed that of these alternatives, annual screening with *mSEPT9* is cost-effective. Annual screening with the *mSEPT9* had an ICER of $63 253 per QALYG. Other efficient strategies were CTC screening every 5 years (ICER = $1092 per QALYG) and annual mtSDNA screening (ICER = $214 974 per QALYG), which were not optimal given the willingness-to-pay threshold ($100 000 per QALYG).

The uncertainty of our conclusion is reflected in our probabilistic sensitivity analyses in which the *mSEPT9* was the cost-effective strategy in 54% of our analyses. Test accuracy of the *mSEPT9* is not as well established as for some of the other tests evaluated in this study. In line with requirements of the FDA, a prospective trial including 4500 participants is currently being performed that will provide essential additional information about test characteristics of the *mSEPT9* and adherence to multiple rounds of testing and follow-up (46).

Among the tests evaluated in this analysis, the *mSEPT9* has the lowest sensitivity for both adenomas and CRC. Therefore, an important driver of its cost-effectiveness compared with CTC, PillCam, and mtSDNA is the substantially lower cost of the test. Similar as for FIT screening, the effectiveness of the *mSEPT9* depends on annual repetition of the test and, similar to any other noncolonoscopy-based screening strategy, receipt of diagnostic follow-up colonoscopy. Due to the relatively low specificity of the *mSEPT9* (79%) compared with the other tests, a high number of individuals are referred to a diagnostic follow-up colonoscopy regardless of disease status (51% after 3 years and 69% after 5 years with annual repetition of the test). Consequently, 21% of simulated individuals with a nonadvanced adenoma received a colonoscopy when screened with *mSEPT9* in contrast with 7.6% when screened with FIT. Although nonadvanced adenomas generally confer low risk, they are more common than advanced adenomas and some may have aggressive biology. The detection of nonadvanced adenomas in these colonoscopies contributed to the slightly higher QALYG, CRC cases averted, and CRC deaths averted for *mSEPT9* screening vs FIT screening despite its lower test sensitivity for advanced adenomas and cancers.

To our knowledge, this is the first study that simultaneously evaluated the PillCam, CTC, *mSEPT9*, and mtSDNA in a single cost-effectiveness analysis. In addition, it is the first cost-effectiveness analysis of these tests that uses updated test characteristics, CRC treatment costs, and CRC incidence. As expected, updated test characteristics, costs, and incidence levels have a substantial impact on cost-effectiveness outcomes. One cost-effectiveness analysis reported that *mSEPT9* is less effective and more costly than FIT screening (14), with costs of $8400 to $11 500 per QALYG compared with no screening. This study based the test characteristics of the *mSEPT9* on the study by Church et al. (34), which used an earlier version of the test. Changes that were made to the *mSEPT9* as part of the development process for its premarket approval by the FDA resulted in the version used for the Potter et al. study (27), which has an increased sensitivity but a decreased specificity compared with the version used by Church et al. (47). Our analyses suggest that with the current version of the *mSEPT9*, annual *mSEPT9* screening is not less effective than annual FIT screening but is still more costly and requires considerably more colonoscopies. One previous study found a cost-effectiveness ratio of $29 244 per QALYG of 10-yearly PillCam screening vs no screening (15) compared with approximately $10 000 in our study with updated assumptions. Previous analyses that evaluated the cost-effectiveness of mtSDNA described that the mtSDNA is too expensive to be cost-effective compared with FIT and colonoscopy screening (10,11,16). This study suggests that even when FIT and colonoscopy screening are not considered, the costs of mtSDNA screening are still too high compared with other alternative tests. Finally, our group's previous analyses on CTC suggested that CTC is not an efficient strategy compared with FIT and colonoscopy (12,13). This study suggests that for individuals unwilling to undergo FIT and colonoscopy, CTC is an efficient strategy. However, annual screening with the *mSEPT9* had an ICER of $63 253 per QALYG compared with 5-yearly CTC and is therefore preferred from a cost-effectiveness perspective.

Several limitations of our study are noteworthy. First, we assumed that no adenomas and cancers were systematically missed over time by a particular screening test. This assumption may not hold for the stool-based tests, because bleeding of a lesion is not necessarily a random event (48). Furthermore, it may not hold for the *mSEPT9* because approximately 18% of the tumors do not have methylation of the *SEPT9* gene promoter (42) and will remain undetected at every subsequent *mSEPT9* screening until their *SEPT9* gene promoter is methylated. The systematic miss rates for the different screening tests are unknown. We performed a scenario analysis in which we assumed that 12% of advanced adenomas and 18% of CRCs are systematically missed by the *mSEPT9*, which minimally affected our results. This is in line with a previous study that suggested that incorporating systematically missing adenomas with a stool-based test has minimal impact on the effectiveness of FIT screening (48).

Second, we assumed perfect adherence to screening, diagnostic follow-up, and surveillance in our base case analysis. This implies that the model predicted the maximum achievable benefit for all screening tests. Unfortunately, there are limited data on test-specific adherence to every step in the screening process (getting screening, diagnostic follow-up, treatment and/or surveillance) over multiple rounds of screening (eg, from ages 50 years to 75 years), making it impossible to inform our analyses with empirical evidence. We performed a scenario analysis that accounted for suboptimal adherence to follow-up and surveillance colonoscopies and for decreasing adherence over multiple screening rounds. Although the effectiveness of all screening modalities decreased with a lower adherence, the impact on ICERs was limited.

Third, the current lifetime risk of developing CRC in the absence of screening is uncertain. Our assumed CRC incidence is in line with previous analyses for the ACS and the observation that the increased CRC incidence in young adults is a cohort effect (21,24). We explored the effect of a lower CRC incidence in a scenario analysis, which suggested that when CRC incidence resembles 1975-1979 data, CTC screening every 5 years is the cost-effective strategy because the ICER of annual screening with the *mSEPT9* is approximately $120 000, just above the willingness-to-pay threshold.

Our study can be used to inform clinicians because it ranks the different CRC screening tests from a cost-effectiveness perspective. Individuals who are not willing to be screened with FIT or colonoscopy should be advised to undergo *mSEPT9* screening if the high colonoscopy referral rate is acceptable to them. CTC should be the next test of choice. Ultimately, the best test is the "one that gets done." Although lack of participation

may have various reasons, such as lack of resources in rural areas or more general reluctance against screening, previous studies suggest that the *mSEPT9* has the potential to attract the population that currently does not participate in screening (49,50). A recent study found substantially higher uptake of a blood-based test compared with a FIT in individuals who were overdue for screening (49), and another study found that there was a 25% uptake of a blood-based test among people who declined stool-based tests (50). This suggests that the *mSEPT9* might be a suitable test to increase current CRC screening participation.

In conclusion, a well-established microsimulation model demonstrates that for people who are unwilling to be screened with FIT or colonoscopy, annual screening with the *mSEPT9* is the test of choice given its cost-effectiveness profile compared with CTC, PillCam, and mtSDNA. The number of CRC cases and deaths averted and the number of QALYG from annual *mSEPT9* screening are even higher than from annual FIT screening. However, the number of colonoscopies required for the *mSEPT9* is 63% higher, and the total costs are 26% higher compared with annual FIT screening. Therefore, physicians should first offer individuals to participate in CRC screening using FIT or colonoscopy.

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