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Development of new non-invasive tests for colorectal cancer screening: The relevance of information on adenoma detection

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Researchers are actively pursuing the development of a new non-invasive test (NIT) for colorectal cancer (CRC) screening as an alternative to fecal occult blood tests (FOBTs). The majority of pilot studies focus on the detection of invasive CRC rather than precursor lesions (*i.e.*, adenomas). We aimed to explore the relevance of adenoma detection for the viability of an NIT for CRC screening by considering a hypothetical test that does not detect adenomas beyond chance. We used the Simulation Model of Colorectal Cancer (SimCRC) to estimate the effectiveness of CRC screening and the lifetime costs (payers' perspective) for a cohort of US 50-years-old persons to whom CRC screening is offered from age 50–75. We compared annual screening with guaiac and immunochemical FOBTs (with sensitivities up to 70 and 24% for CRC and adenomas, respectively) to annual screening with a hypothetical NIT (sensitivity of 90% for CRC, no detection of adenomas beyond chance, specificity and cost similar to FOBTs). Screening with the NIT was not more effective, but was 29–44% more costly than screening with FOBTs. The findings were robust to varying the screening interval, the NIT's sensitivity for CRC, adherence rates favoring the NIT, and the NIT's unit cost. A comparative modelling approach using a model that assumes a shorter adenoma dwell time (MISCAN-COLON) confirmed the superiority of the immunochemical FOBT over an NIT with no ability to detect adenomas. Information on adenoma detection is crucial to determine whether a new NIT is a viable alternative to FOBTs for CRC screening. Current evidence thus lacks an important piece of information to identify marker candidates that hold real promise and deserve further (large-scale) evaluation.

Colorectal cancer (CRC) is the third most common cancer and cancer cause of death worldwide, with more than 1.2 million new cases and more than 600,000 deaths per year.[1] Given the slow development from precursor lesions (adenomas) that can be removed through endoscopy and the prognostic advantages of early versus late stage detection, both CRC incidence and mortality can be reduced through screening, as demonstrated by randomized controlled trials.[2–5]

Currently-available CRC screening options include fecal occult blood tests (FOBTs) as the primary non-invasive screening tools. There are two types of FOBTs—traditional guaiac-based tests and the newer fecal immunochemical tests for hemoglobin. Compared to guaiac-based FOBTs, immunochemical FOBTs (FITs) have higher rates of acceptability and diagnostic accuracy and improved analytical robustness (*e.g.*, there is no need for dietary restrictions).[6,7] Still, sensitivity of FOBTs is inherently limited because not all CRCs and adenomas bleed, and those that do only bleed intermittently.[8]

Researchers are therefore actively pursuing the development of a novel non-invasive test (NIT) for CRC screening and have proposed various biomarkers in stool and blood as promising candidates.[9] The detection of CRC is, naturally, an important aspect of pilot studies evaluating such candidate markers. However, our search of the published literature suggests that little attention is paid to the detection of adenomas. Only 15 (24%) of 62 studies evaluating the diagnostic performance of a new blood test and 13 (50%) of 26 studies evaluating the performance of a new stool test reported on sensitivity for adenomas (Fig. 1).

While there is limited information on the potential of NITs to detect adenomas, FOBTs—the benchmark against which NITs will be compared—have been shown to detect up to one quarter of advanced adenomas with a false-positive rate of about 5%.[10] We therefore sought to assess how important information on adenoma detection will be in

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What's new?

The development of new non-invasive tests (NITs) for colorectal cancer (CRC) screening has centered primarily on improving the detection of invasive disease. But according to this study, whether new NITs are viable alternatives to immunochemical fecal occult blood tests—already established screening tests for CRC—depends also on their ability to detect adenomas, the precursor lesions of CRC. Without that ability, immunochemical fecal occult blood tests retain their superiority over newer NITs, many of which attempt to detect biomarkers in stool or blood. The identification of adenoma-specific markers could be critical to the advance of NITs for CRC screening.

determining the viability of an NIT for CRC screening. Accordingly, we used a microsimulation model of CRC to assess the effectiveness and costs of CRC screening with a hypothetical NIT that does not detect adenomas in comparison to screening with FOBTs.

Methods

We used the Simulation Model of Colorectal Cancer (SimCRC)[11–14] to assess the costs and life-years gained from screening for CRC with a hypothetical NIT that does not detect precursor lesions (beyond chance detection) in comparison to screening with FOBTs. The model is part of the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) and it has been used previously to inform the CRC screening guidelines of the US Preventive Services Task Force[12] and the coverage determinations by the Centers for Medicare and Medicaid Services for stool DNA testing[13] and computed tomographic colonography.[14]

Model description

Figure 2 and the Supporting Information provide an overview of SimCRC. Its specifications have been described elsewhere.[15,16] In brief, the model simulates the life histories of a large population of individuals from birth to death for scenarios without and with CRC screening. Events (*e.g.*, screening, follow-up, and surveillance tests, CRC diagnoses, deaths) are tracked and summed across individuals to yield estimates of lifetime risks and costs, as well as life expectancy.

Natural history component. SimCRC's natural history component simulates the adenoma-carcinoma pathway in the absence of screening. Simulated individuals are at risk of developing one or more colorectal adenomas during their life, some of which may further progress to preclinical CRC. Preclinical cancer may progress from stage I through stage IV and has the chance of being diagnosed by symptoms at any stage. Survival from CRC depends on the stage at diagnosis and is based on data from the surveillance, epidemiology and end Results (SEER) program.[17] Individuals are at risk of dying from causes other than CRC based on all-cause mortality estimates from US life tables.[18] The natural history component of the model was calibrated to data on adenoma prevalence, size, and location from autopsy studies[19–28] and to SEER program data on CRC incidence for 1975–1979, which was before the introduction of CRC screening.[17] On the cost side, the natural history component tallies CRC treatment costs based on stage and phase of care.[14]

Screening component. CRC screening strategies can be superimposed on the natural history component to estimate the effectiveness of screening in terms of CRC cases and deaths prevented and life-years gained (LYG) relative to no screening. A simulated individual with an adenoma or CRC has a chance of having it detected through screening. Non-adenomatous polyps are not modeled explicitly, but their detection is reflected in the false-positive rate of the test. The model considers surveillance examinations after adenoma detection and incorporates the risk for fatal complications associated with perforation during colonoscopy. An individual with a negative follow-up colonoscopy after a positive test result (*i.e.*, an individual with a false positive test result) was assumed to undergo subsequent screening with colonoscopy with a 10-year interval (as long as the repeat colonoscopy is negative) and not to return to the initial screening schedule. In terms of required resources, the net costs of screening are estimated taking into account all expenditures related to screening (including follow-up and surveillance colonoscopies) as well as potential savings in treatment costs.

Analysis

For the present analysis, we simulated a cohort of US 50-year-old persons to whom CRC screening with a non-invasive test is offered annually from age 50 to age 75. We assumed that persons with a positive test result would be followed up by colonoscopy for diagnostic work-up. All persons with an adenoma detected and removed during the diagnostic colonoscopy were assumed to undergo colonoscopy surveillance according to the 2006 guidelines of the US Multi-Society Task Force.[29–32] We assumed that colonoscopy surveillance continues until diagnosis of CRC or death.

We compared screening with a hypothetical NIT to screening with a guaiac FOBT (Hemoccult II) and a FIT. We focused on these two FOBTs because they represent the upper and lower bounds of diagnostic performance of existing FOBTs. The effectiveness of Hemoccult II demonstrated in randomized controlled trials is considered the minimum that needs to be achieved by an NIT for it to be a viable option, while FIT is considered to be the best available FOBT.[33] The assumptions and parameters regarding test

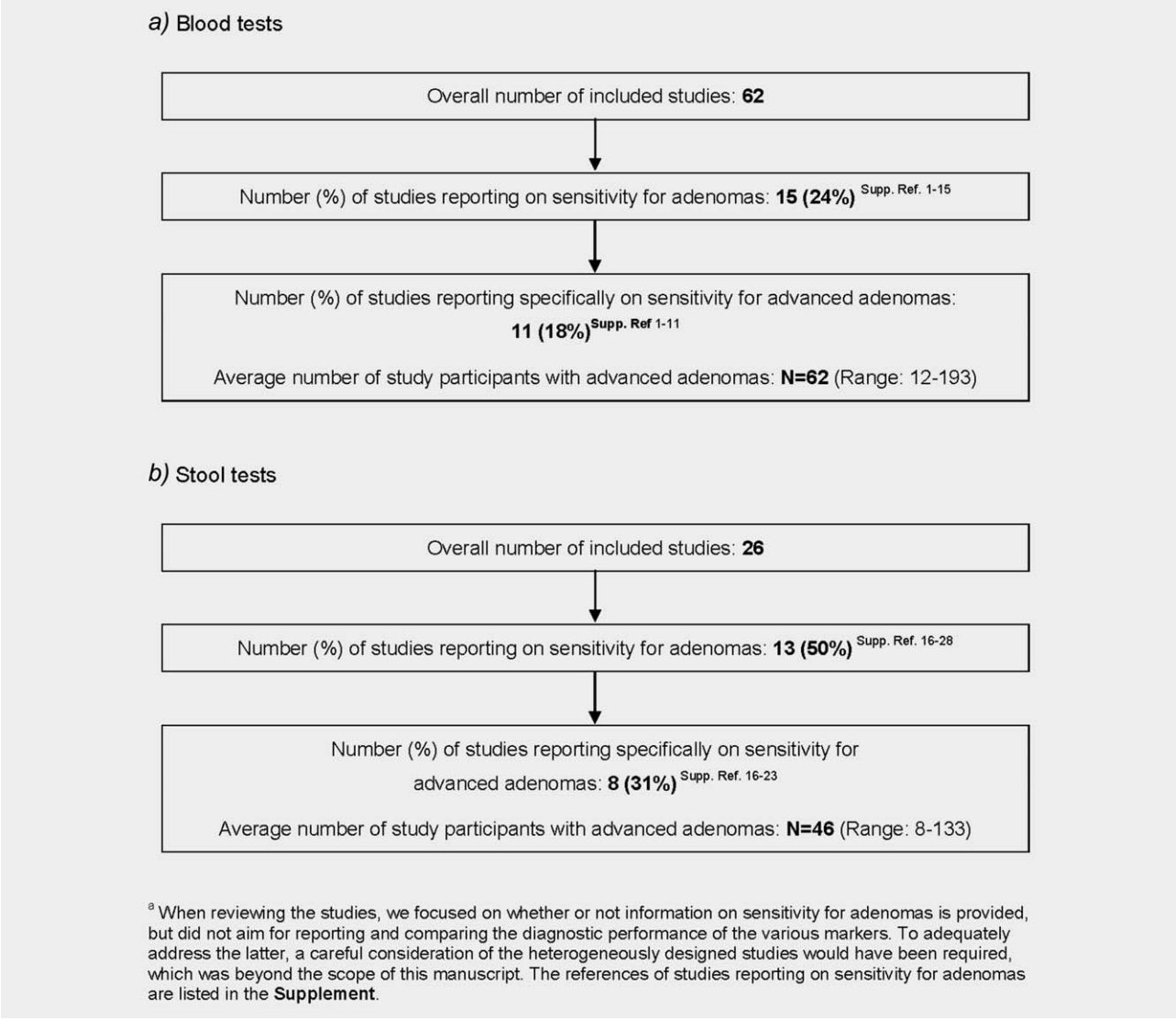

Figure 1. Results of the search of the MEDLINE database for studies published between January 2009 and March 2012 using the search terms "colorectal neoplasm" and "blood marker" (*a*) or "stool marker" (*b*).

performance characteristics, costs related to screening, and CRC treatment costs are summarized in Tables 1 and 2. For the FOBTs, we used established estimates regarding diagnostic performance and cost.[14] For the NIT we assumed a specificity similar to FIT (95%), a sensitivity of 90% for CRC, no sensitivity for adenomas of any size (*i.e.*, adenomas are only detected by chance according to the false-positive rate), and a unit cost per test similar to FIT ($24). For colonoscopy (relevant as diagnostic follow-up of persons with positive non-invasive tests and surveillance of persons with a history of adenomas in this analysis) we used established estimates regarding diagnostic performance, complication rates and costs.[14,34] We also took into account that some colonoscopies may be incomplete and need to be repeated to ensure visualization of the entire colon, which was assumed to affect 5% of colonoscopies. We considered the costs (expressed in 2012 dollars) from the payers' perspective (*i.e.*, excluding patient co-payments, time costs, and costs of lost productivity) and discounted future costs and life-years by 3% annually. Discounting is a commonly used technique that converts all benefits and costs into their value in the present to account for the fact that a dollar saved or a year of life gained today are valued more than a dollar saved or a year of life gained in the future. In the base-case analysis we assumed 100% adherence with FOBTs and the NIT as well as with recommended diagnostic and surveillance colonoscopies.

We performed sensitivity analyses in which screening was offered biennially instead of annually and we varied the sensitivities of Hemoccult II, FIT and the NIT (Table 1). We also explored the impact of overall adherence rates of 50 and 80%. For the analyses with imperfect adherence rates, we assumed that the population consists of four groups with

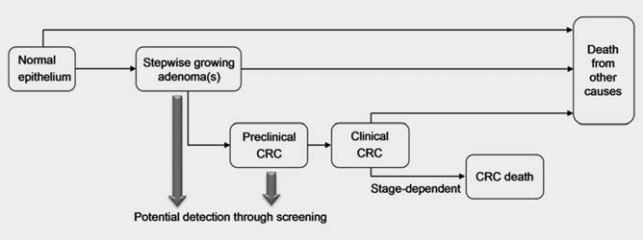

Figure 2. Illustration of the model structure: A cohort was simulated from birth to death. A certain proportion of the population develops one or more stepwise growing adenomas during life, of which a minority progresses to colorectal cancer (CRC). A certain proportion of adenomas and preclinical CRCs may be detected through screening, depending on the sensitivity of the screening test.

different screening behavior: those who are never screened and those with low, moderate, and high adherence; 10% of the population was in the never-screened group and 30% were in each of the other groups. The proportion of the population who was adherent at each screening round was randomly composed of individuals from the three groups with low, moderate and high adherence, to come up with a final overall adherence of 50 and 80%, respectively. We assumed that adherence with follow-up and surveillance was 75, 85 and 95% for those with low, moderate and high adherence, respectively, and that individuals remain in their screening behavior group. Furthermore, we performed sensitivity analysis on the cost of the NIT, lowering the unit cost of the test

Table 1. Test characteristics used in the analyses

		Sensitivity analyses	
	Base-case analysis	Best-case value	Worst-case value
Hemoccult II			
Sensitivity for adenomas ≤5 mm	2.0[1]	1.0[1]	5.0[1]
Sensitivity for adenomas 6–9 mm, %	5.0	13.7	5.0
Sensitivity for adenomas ≥10 mm, %	12.0	27.5	8.9
Sensitivity for cancer, %	40.0	50.0	25.0
Specificity, %	98.0	99.0	95.0
Fecal immunochemical test (FIT)			
Sensitivity for adenomas ≤5 mm	5.0[1]	2.0[1]	7.5[1]
Sensitivity for adenomas 6–9 mm, %	10.1	24.0	7.5
Sensitivity for adenomas ≥10 mm, %	22.0	48.0	16.0
Sensitivity for cancer, %	70.0	87.0	50.0
Specificity, %	95.0	98.0	92.5
Hypothetical new test (NIT)			
Sensitivity for adenomas of any size, %	5.0 [2]	Not varied	Not varied
Sensitivity for cancer, %	90.0	100.0	80.0
Specificity, %	95.0	Not varied	Not varied
Colonoscopy[3]			
Sensitivity for adenomas ≤5 mm, %	75.0	Not varied	Not varied
Sensitivity for adenomas 6–9 mm, %	85.0	Not varied	Not varied
Sensitivity for adenomas ≥10 mm, %	95.0	Not varied	Not varied
Sensitivity for cancer, %	95.0	Not varied	Not varied
Specificity, %	90.0	Not varied	Not varied
Complications:			
Rate of perforation	0.7 per 1000	Not varied	Not varied
Rate of serosal burn	0.3 per 1000	Not varied	Not varied
Rate of bleeding with transfusion	0.4 per 1000	Not varied	Not varied
Rate of bleeding without transfusion	1.1 per 1000	Not varied	Not varied
Mortality rate	1 per 10,000	Not varied	Not varied

[1]We assumed that adenomas ≤ 5 mm do not bleed and cannot be detected by fecal occult blood testing, that is, adenomas ≤ 5 mm can only be detected by chance according to the false-positive rate (*i.e.*, 1-specificity).
[2]We assumed that adenomas of any size cannot be detected by the new test, that is, adenomas can only be detected by chance according to the false-positive rate (i.e., 1-specificity).
[3]Relevant as follow-up and surveillance examination in this analysis.

Table 2. Cost estimates used in the analyses (expressed in 2012 dollars)

Costs of screening tests (unit cost), $				
Hemoccult II	6			
Fecal immunochemical test	24			
Hypothetical new test	24			
Costs of colonoscopy [1], $				
Without polypectomy	552			
With polypectomy	719			
Annual costs of colorectal cancer (CRC) treatment (by stage and phase of care), $				
	Initial phase	Continuing phase	Terminal phase, death from CRC	Terminal phase, death from other causes
UICC stage I	28,225	2,246	50,597	12,466
UICC stage II	38,951	2,093	50,454	10,904
UICC stage III	47,492	2,992	53,163	14,425
UICC stage IV	62,016	9,275	71,349	38,732

UICC = Union for International Cancer Control.
Relevant as follow-up and surveillance examination in this analysis.

from $24 to $0, which yields the total costs of the NIT strategy without the costs attributable to the screening test itself.

We used a comparative modeling approach as a sensitivity analysis on the underlying structural assumptions regarding the natural history of CRC—in particular regarding adenoma dwell time (*i.e.*, the time from adenoma formation to malignant transformation). For that purpose, we repeated the analyses with the MISCAN-COLON model, which is a microsimulation model that has been developed independently of SimCRC and assumes a considerably shorter adenoma dwell time as compared to SimCRC. In SimCRC the mean adenoma dwell time is assumed to be 21 years and in the MISCAN-COLON model it is about half of it. Further details are described elsewhere.[12–16]

Results

Table 3 gives an overview of the results of the base-case and sensitivity analyses. The model predicts that 67 CRC cases and 28 CRC deaths per 1,000 50-years-old persons would occur in the absence of screening.

Base-case analyses

Compared to no screening, annual screening from age 50 to 75 with FIT yielded a 75% reduction in the number of CRC cases and an 84% reduction in the number of CRC deaths. Hemoccult II reduced the number of CRC cases by 60% and the number of CRC deaths by 73%. The NIT reduced the number of CRC cases by 46% and the number of CRC deaths by 71%.

Figure 3 displays the discounted LYG compared with no screening (a measure of the effectiveness of screening) and the discounted lifetime costs for the three screening strategies. All three strategies showed a gain in life-years compared with no screening, ranging between 98 and 113 years per 1,000 50-years-old persons screened. The NIT strategy was less effective than the FIT strategy and equally as effective as the Hemoccult II strategy. On the cost side, the Hemoccult II and FIT strategies were cost saving compared with no screening, while the NIT strategy had considerably higher cost than no screening. The NIT strategy was thus not more effective but more costly than the Hemoccult II and the FIT strategy (*i.e.*, it was dominated by the other strategies).

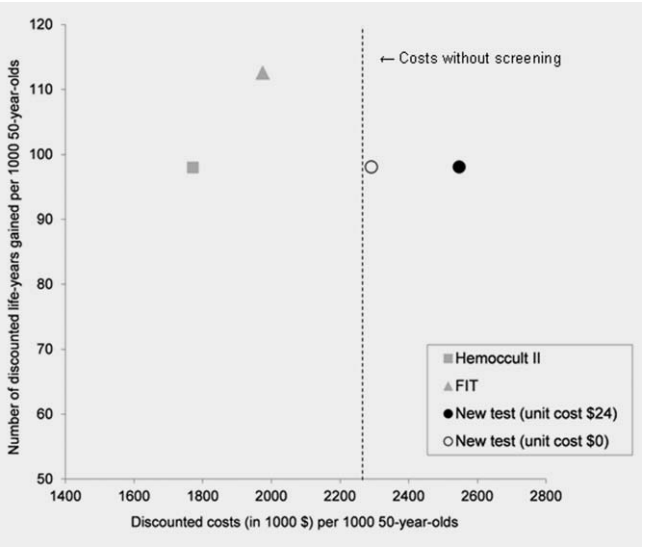

Figure 3. Discounted life-years gained compared with no screening and discounted lifetime costs for the Hemoccult II strategy, the fecal immunochemical test (FIT) strategy and the new test strategy: Results of the base-case analysis and results of the sensitivity analysis for this scenario lowering the new test's unit cost to zero.

Sensitivity analyses

When we varied the screening interval (biennial instead of annual screening), test performance characteristics (using

Table 3. Results of the base-case and the sensitivity analyses for the Hemocult II strategy, the fecal immunochemical test (FIT) strategy and the new test strategy (the results are expressed per 1000 50-years-old persons)

Strategy	No. of CRC cases	Proportion of early stage CRC cases (UICC I and II), %	Reduction in CRC cases, %	No. of CRC deaths	Reduction in CRC deaths, %	Discounted LYG	Discounted total costs, 1000 $
No screening	66.6	53	–	27.6	–	–	2,276
Base-case analyses							
Hemoccult II	26.6	79	60	7.3	74	98	1,772
FIT	16.9	82	75	4.5	84	113	1,975
New test	35.7	87	46	8.0	71	98	2,548 (2,292)[1]
Sensitivity analyses							
Test characteristics: Best case values (see Table 1)							
Hemoccult II	15.9	78	76	4.5	84	113	1,395
FIT	12.0	79	82	3.4	88	120	1,638
New test	35.7	87	46	7.9	71	99	2,550 (2,294)[1]
Test characteristics: Worst case values (see Table 1)							
Hemoccult II	28.5	75	57	8.8	68	86	2,097
FIT	20.1	82	70	5.5	80	105	2,186
New test	35.6	86	46	8.2	70	97	2,545 (2,289)[1]
Biennial screening interval							
Hemoccult II	38.3	72	42	11.9	57	76	1,891
FIT	26.0	80	61	7.1	74	100	1,913
New test	48.0	83	28	11.7	58	84	2,520 (2,356)[1]
80% adherence with screening							
Hemoccult II	35.5	71	47	11.2	59	79	1,868
FIT	25.8	73	61	8.0	71	95	1,991
New test	44.2	79	34	11.7	58	81	2,527 (2,301)[1]
50% adherence with screening							
Hemoccult II	43.5	67	35	14.7	47	62	1,952
FIT	33.9	70	49	10.9	61	80	1,975
New test	52.0	75	22	15.1	45	65	2,472 (2,314)[1]

CRC = colorectal cancer; FIT = fecal immunochemical test; LYG = life-years gained compared with no screening.
[1]Number in parentheses represents the result of the sensitivity analyses for the respective scenario when the unit cost of the new test was lowered from $24 to $0 (*i.e.*, these are the total costs of the new test strategy when subtracting the costs attributable to the screening test itself).

best case and worst case values as described in Table 1), and adherence rates (considering 80 and 50% adherence rates), the FIT strategy was more effective in terms of discounted life-years gained than the NIT strategy in all scenarios (Table 3). The Hemoccult II strategy was more effective than the NIT strategy when best case values were used for test performance, but in all other scenarios it was less effective than the NIT strategy, with the difference in discounted LYG ranging between 2 and 12 years per 1,000 50-years-old persons.

The costs of the NIT strategy changed very little across the various scenarios. The costs of the Hemoccult II and the FIT strategy were sensitive to variation in test performance. Compared to the base-case scenario, the costs of the Hemoccult II and the FIT strategy were 21 and 17% lower when best case values were used for test performance, and 18 and 11% higher when worst case values were used. In the other sensitivity analyses, the changes in the costs of the Hemoccult II and the FIT strategy were below 10% compared to the base-case analyses. Across all scenarios, the NIT strategy was the most costly strategy. It was between 21 and 83% more costly compared to the Hemoccult II strategy and between 16 and 56% more costly compared to the FIT strategy. The NIT remained the most costly strategy across all scenarios, even when the unit cost of the NIT was lowered to zero in sensitivity analyses.

Figures 4*a* and 4*b* display the discounted LYG compared with no screening and the discounted lifetime costs for the

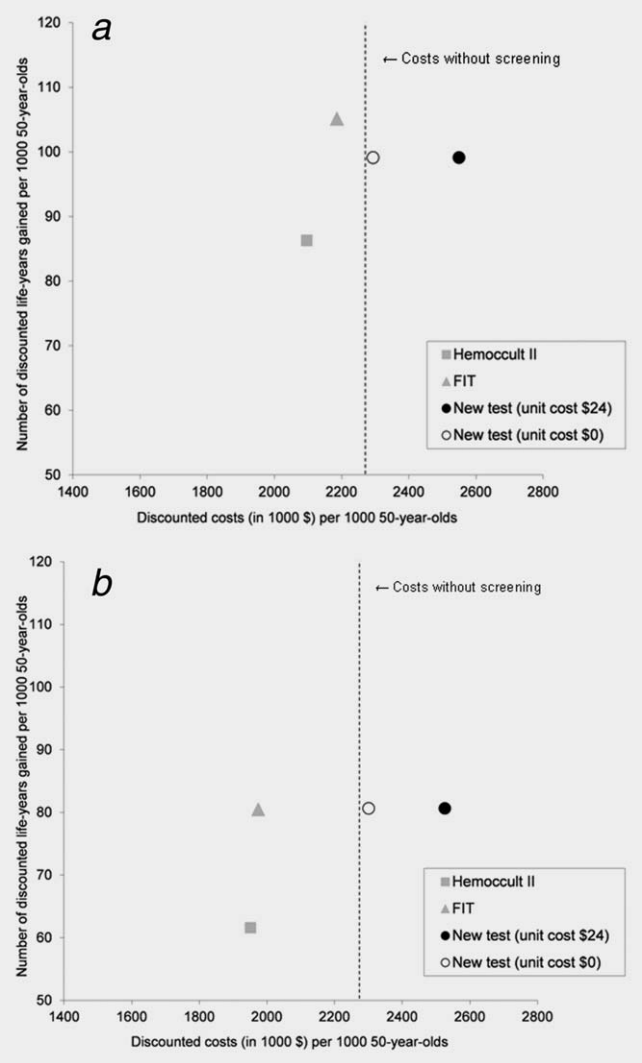

Figure 4. Discounted life-years gained compared with no screening and discounted lifetime costs for the Hemoccult II strategy, the fecal immunochemical test (FIT) strategy and the new test strategy: (*a*) Results of the sensitivity analysis using best case test performance estimates for the new test and worst case test performance estimates for Hemoccult II and FIT, and results of the sensitivity analysis for this scenario lowering the new test's unit cost to zero. (*b*) Results of the sensitivity analysis assuming an adherence rate of 80% for the new test strategy and an adherence rate of 50% for the Hemoccult II and the FIT strategy, and results of the sensitivity analysis for this scenario lowering the new test's unit cost to zero.

three strategies, combining optimistic assumptions for the NIT strategy and pessimistic assumptions for the Hemoccult II and the FIT strategy. In Figure 4*a*, the best-case test performance estimates were used for the NIT strategy and the worst-case test performance estimates were used for the Hemoccult II and the FIT strategy. In this scenario, the NIT strategy remained more costly and less effective than the FIT strategy, even when the unit cost of the NIT was lowered to zero. Compared to the Hemoccult II strategy, the NIT strategy was more effective but also more costly, with an incremental cost of $34,800 per additional LYG.

In Figure 4*b*, it was assumed that the NIT strategy results in a higher adherence than the other strategies, *i.e.*, differential adherence assumptions were used for the NIT strategy (80% adherence), and for the Hemoccult II and the FIT strategy (50% adherence). In this scenario, the NIT strategy and the FIT strategy showed almost the same effectiveness, but the NIT strategy was 28% more costly. The NIT strategy was still 17% more costly than the FIT strategy when the unit cost of the NIT was assumed to be $0. Compared to the Hemoccult II strategy, the NIT strategy was more effective but also more costly, with an incremental cost of $30,300 per additional LYG.

The above-described patterns did not change when reduction in CRC mortality (*i.e.*, reduction in the number of CRC deaths) was used as a measure of the effectiveness instead of LYG (Table 3).

When repeating the base-case analysis using the MISCAN model, the NIT strategy was more effective than the Hemoccult II strategy but less effective than the FIT strategy. The discounted lifetime costs for all three screening strategies were higher as compared to SimCRC and none of them was cost saving, but the NIT strategy was still the most costly strategy, even when the unit cost of the NIT was lowered to zero. Similarly, the FIT strategy was superior over the NIT strategy when we repeated the sensitivity analyses regarding the screening interval, test performance characteristics and adherence rates with the MISCAN model (Table 4).

The Supporting Information provides information on costs for different categories (cost of screening tests, cost of follow-up and surveillance colonoscopies, cost of treating early stage cancer, cost of treating late stage cancer) for both models and each scenario.

Discussion

The development of a new NIT to screen for CRC is the focus of intense research in both industry and academia. The primary motivation is to improve the diagnostic performance compared to FOBTs, but the studies published on new tests are often restricted to the detection of CRC, while evidence regarding the detection of adenomas is rather limited, particularly for blood tests (Fig. 1). As an attempt to guide research in the field, we addressed for the first time the basic question how important information on adenoma detection will be in determining the viability of an NIT for CRC screening. Our results suggest that the detection of adenomas is crucial for NITs to be competitive with FOBTs in terms of effectiveness and costs. Studies that aim at developing alternatives to FOBTs for optimizing CRC screening should therefore include the detection of adenomas in addition to the detection of CRC. Otherwise, an essential piece of information is missing. Our results also illustrate that the bar has been set higher for NITs since FOBTs with improved test performance are available as alternatives to Hemoccult II.

Our findings were robust in sensitivity analyses that incorporated optimistic assumptions in favor of the NIT. For

Table 4. MISCAN-Colon model: Results of the base-case and the sensitivity analyses for the Hemocult II strategy, the fecal immunochemical test (FIT) strategy and the new test strategy (the results are expressed per 1000 50-years-old persons).

Strategy	No. of CRC cases	Proportion of early stage CRC cases (UICC I and II), %	Reduction in CRC cases, %	No. of CRC deaths	Reduction in CRC deaths, %	Discounted LYG	Discounted total costs, 1000 $
No screening	64.7	51	--	27.1	--	--	2,404
Base-case analyses							
Hemoccult II	41.0	74	37	9.7	64	81	2,445
FIT	31.8	80	51	6.6	76	96	2,667
New test	42.2	83	35	7.9	71	91	2,979 (2,728)[1]
Sensitivity analyses							
Test characteristics: Best case values (see Table 1)							
Hemoccult II	33.8	75	48	7.9	71	93	2,072
FIT	28.0	79	57	6.0	78	103	2,246
New test	42.2	83	35	7.7	71	93	2,979 (2,727)[1]
Test characteristics: Worst case values (see Table 1)							
Hemoccult II	37.9	71	41	9.8	64	75	2,672
FIT	31.8	78	51	7.0	74	90	2,813
New test	42.1	82	35	8.1	70	90	2,979 (2,728)[1]
Biennial screening interval							
Hemoccult II	49.4	68	24	13.8	49	62	2,469
FIT	40.6	76	37	9.3	66	84	2,590
New test	52.1	78	19	11.3	58	78	2,895 (2,734)[1]
80% adherence with screening							
Hemoccult II	47.8	68	26	13.5	50	64	2,448
FIT	40.1	72	38	10.3	62	79	2,614
New test	49.7	76	23	11.8	57	74	2,896 (2,674)[1]
50% adherence with screening							
Hemoccult II	52.3	64	19	16.2	40	50	2,456
FIT	45.4	70	30	12.5	54	67	2,571
New test	54.8	72	15	14.3	47	62	2,825 (2,667)[1]

CRC = colorectal cancer; FIT = fecal immunochemical test; LYG = life-years gained compared with no screening.
[1]Number in parentheses represents the result of the sensitivity analyses for the respective scenario when the unit cost of the new test was lowered from $24 to $0 (*i.e.*, these are the total costs of the new test strategy when subtracting the costs attributable to the screening test itself.

instance, we considered a 30% higher adherence rate for screening with the NIT, because individuals eligible for screening may prefer an NIT that is based on blood sampling over a stool test. However, even a clear advantage in terms of adherence in combination with the high sensitivity of the NIT to detect CRC did not result in the NIT strategy being superior to the FIT strategy in terms of costs or effectiveness, that is, these favorable assumptions did not compensate for the non-detection of adenomas.

The importance of adenoma detection may be influenced by assumptions on adenoma dwell time (*i.e.*, the time from adenoma formation to malignant transformation). While the dwell time is believed to be long, this parameter is uncertain and cannot be directly estimated from empirical data given that adenomas are typically removed once they are detected. To address this uncertainty, we used a comparative modeling approach. The results of the MISCAN model, which assumes a considerably shorter adenoma dwell time as compared to SimCRC,[15] showed overall similar results regarding the ranking of the strategies with respect to effectiveness and costs, but only the FIT and not the Hemoccult II strategy was superior to the NIT strategy. This was consistent with our expectations. The shorter the adenoma dwell time is, the higher the impact of sensitivity for CRC relative to sensitivity for advanced adenomas on the effectiveness, but this inverse association is weakened by surveillance. An in-depth discussion of the role of assumptions about adenoma progression in microsimulation models of CRC is provided by Kuntz et al.[15]

To explore and understand reasons for the importance of adenoma detection on the effectiveness of CRC screening, it

is important to note that the detection and removal of adenomas can lead to the prevention of CRC, while the detection and treatment of invasive CRC at an earlier *vs*. more advanced stage has an advantage in 5-year relative survival of about 20–80%.[35] The potential gain in life-years through screening is thus higher when screening allows—at least to a certain extent—for the neoplastic process to be stopped at the adenoma stage rather than when screening only allows the early detection of invasive CRC. We considered in our analysis that the higher number of colonoscopies resulting from adenoma detection goes along with a higher risk of losing life-years due to fatal complications, but adenoma detection was still advantageous.

Furthermore, screening strategies that allow interruption of the development of CRC at the adenoma stage may be less prone to interval cancers compared to strategies that only focus on the detection of early CRC stages, given that the progression from adenoma to cancer is generally assumed to take longer than the progression from early to advanced CRC.[15] This aspect is particularly relevant for real-life scenarios where longitudinal adherence patterns are not perfect and where actual intervals between screening tests are often longer than recommended.[36]

On the cost side, the prevention of CRC through adenoma detection saves CRC treatment costs, while the early detection of CRC only saves the excess costs of treating advanced versus earlier CRC stages. On the other hand, adenoma detection can lead to costs due to overdiagnosis given that adenomas are rather prevalent in the population and only a small proportion of them develop into CRC. Thus, there is unnecessary spending on diagnostic work-up, polypectomy (the costs of which are very modest as compared to CRC treatment costs) and long-term surveillance due to adenomas that would not have progressed to cancer. However, our analysis considered all these aspects and still showed that screening with an NIT that does not allow adenoma detection was the most costly one. This finding did not change when we reduced the already conservative estimate for the unit cost of the NIT from $24 (corresponding to the unit cost of FIT) to $0 in sensitivity analysis. In view of the analytical complexity of new technologies, it is likely that in reality the unit cost of NITs would be higher than FIT. The excess costs of the NIT strategy compared to the Hemoccult II and the FIT strategy would then be even more pronounced than estimated in our analysis.

In our analysis, we focused on an NIT with a specificity of 95% and did not vary this parameter. However, as a certain proportion of adenomas are detected by chance according to the false-positive rate of the screening test, adenoma detection of an NIT could also be enhanced merely by lowering its specificity, that is, lowering its positivity threshold. However, the same could also be done with quantitative FIT and the effect would even be higher as it has been shown that lowering the positivity threshold of FIT increases its sensitivity beyond what is explained by the higher false-positive rate.[37,38] Thus, it does not appear plausible that consideration of NITs at other levels of specificity would have provided any further insights that are relevant for assessing the importance of information on adenoma detection.

We used US data to inform the model, which raises the question whether our conclusions can be generalized to other—typically industrialized—countries that offer CRC screening. Demographic patterns and trends in CRC incidence and mortality have been reported to be comparable in industrialized countries.[39,40] Also, comparable CRC treatment costs have been reported for other industrialized countries.[41–43] With respect to FOBTs and colonoscopy, lower but also higher costs have been reported from other countries, although most estimates are roughly comparable.[41,42]

It may seem inconsistent that our analysis simulating screening with unrehydrated Hemoccult II suggested a reduction in CRC incidence also for scenarios with imperfect adherence, while the two randomized controlled trials (RCTs) that investigated unrehydrated Hemoccult II did not show such an effect.[44,45] However, the direct comparison between the results of the RCTs and ours is hampered in many regards. First, the overall exposure to screening, specifically the number of screening rounds and the proportion of never-screened subjects differs. Second, the approaches differ regarding the distribution of the age at first screen. In our analysis all subjects were offered screening starting from age 50. The age of subjects recruited for the RCTs ranged from 45 to 75 years, *i.e*. a certain proportion of subjects was already at an older age when screening was first offered.[44,45] Given that the chance of interrupting the carcinogenetic process already at a precancerous stage (*i.e*., before an adenoma progresses to preclinical cancer) is higher when screening starts earlier, the potential of screening in terms of incidence reduction is expected to be higher for those who start screening at a younger age as compared to those who start at an older age. Third, the management of individuals with a false-positive test result differs between the RCTs and the models (see Methods section), which could also be relevant in terms of incidence reduction. Fourth, we only considered imperfect adherence regarding the screening test itself, but other factors that may have compromised the effectiveness of screening in RCTs have not been considered, such as imperfect adherence to follow-up colonoscopy (after a positive test result) and surveillance colonoscopy or variation in the quality of colonoscopy.

In the interpretation of our results, there are several limitations that need to be taken into account. First, although Hemoccult II is no longer recommended in the US,[31,32] we included it in our analyses because its effectiveness demonstrated in randomized controlled trials is considered the minimum that needs to be achieved by a new test.[33] Furthermore, it allowed illustration of how the benchmark for new tests has changed with the availability of FOBTs with improved sensitivity compared to Hemoccult II. Additional analyses done for Hemoccult SENSA lead to similar conclusions (results

available from the corresponding author). Second, we only considered one FIT rather than the range of test characteristics when using different positivity thresholds for FIT. For reasons as mentioned above, we do not expect different conclusions regarding the comparison between the FIT and the NIT strategy when the positivity threshold is altered.

Third, our modeling approach aimed at drawing basic conclusions regarding the information that should be available to select promising marker candidates for further empirical large-scale evaluation, but it did not aim at specifying the optimal characteristics of such a test. Attempting to do the latter would require consideration of various scenarios and uncertainties including issues concerning the biology of adenomas, which was beyond the scope of this project. Fourth, we used sensitivity across all CRC stages both for the FOBTs and for the NIT in this analysis, while the empirical comparison of these tests should focus on sensitivity for early stages. Fifth, our analysis focused on the relevance of detecting (any kind of) adenomas. New tests may differ from FOBTs regarding the types of lesions being detected which should be considered when the tests are compared empirically. It would be relevant to consider such subgroup analyses in the design of diagnostic studies that compare new tests to FOBTs.

In conclusion, our results suggest that information on adenoma detection is crucial to determine whether a new NIT is a viable alternative to FOBTs for CRC screening. Studies that aim at developing alternatives to FOBTs for optimizing CRC screening should therefore pay special attention to the detection of adenomas in addition to the detection of CRC.

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