

Colorectal Cancer Screening with Blood-Based Biomarkers: Cost-Effectiveness of Methylated Septin 9 DNA versus Current Strategies

Uri Ladabaum^{1,2}, John Allen^{3,4}, Michael Wandell⁶, and Scott Ramsey⁵

Abstract

Background: Screening reduces colorectal cancer mortality, but many persons remain unscreened. Screening with a blood test could improve screening rates. We estimated the comparative effectiveness and cost-effectiveness of colorectal cancer screening with emerging biomarkers, illustrated by a methylated Septin 9 DNA plasma assay (^mSEPT9), versus established strategies.

Methods: We conducted a cost-utility analysis using a validated decision analytic model comparing ^mSEPT9, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), sigmoidoscopy, and colonoscopy, projecting lifetime benefits and costs.

Results: In the base case, ^mSEPT9 decreased colorectal cancer incidence by 35% to 41% and colorectal cancer mortality by 53% to 61% at costs of \$8,400 to \$11,500/quality-adjusted life year gained versus no screening. All established screening strategies were more effective than ^mSEPT9. FIT was cost saving, dominated ^mSEPT9, and was preferred among all the alternatives. Screening uptake and longitudinal adherence rates over time strongly influenced the comparisons between strategies. At the population level, ^mSEPT9 yielded incremental benefit at acceptable costs when it increased the fraction of the population screened more than it was substituted for other strategies.

Conclusions: ^mSEPT9 seems to be effective and cost-effective compared with no screening. To be cost-effective compared with established strategies, ^mSEPT9 or blood-based biomarkers with similar test performance characteristics would need to achieve substantially higher uptake and adherence rates than the alternatives. It remains to be proven whether colorectal cancer screening with a blood test can improve screening uptake or long-term adherence compared with established strategies.

Impact: Our study offers insights into the potential role of colorectal cancer screening with blood-based biomarkers. *Cancer Epidemiol Biomarkers Prev*; 22(9); 1567–76. ©2013 AACR.

Introduction

Colorectal cancer is the third most common cancer globally and the second most common cancer in industrialized countries (1–3). Screening can decrease colorectal cancer-related mortality through removal of precancerous lesions and detection of early-stage cancers (4–8). The United States Preventive Services Task Force (USPSTF)

recommends guaiac or immunochemical fecal occult blood tests (FOBT, FIT), sigmoidoscopy, or colonoscopy for colorectal cancer screening starting at age 50 years (grade A recommendation; ref. 9).

Despite the established benefits of colorectal cancer screening, approximately 40% of eligible Americans do not undergo colorectal cancer screening (10). Moreover, adherence to screening over time is suboptimal (10–19). Barriers to screening at the system, practice, and individual level can substantially reduce the effectiveness of screening programs (20). Several promising blood-based biomarkers of colorectal cancer are under investigation and development (21, 22). An easily conducted blood-based screening test might be accepted by persons not currently participating in screening and may improve adherence over time, and a highly accurate blood test could even replace current tests if it proved more acceptable to most people.

Plasma methylated Septin 9 DNA is a marker of colorectal cancer (23–25). In a recent large prospective study in average-risk persons undergoing screening colonoscopy in the United States and Germany, a 2-well plasma Septin

Authors' Affiliations: ¹Division of Gastroenterology and Hepatology; ²Department of Medicine, Stanford University School of Medicine, Stanford, California; ³University of Minnesota School of Medicine and ⁴Minnesota Gastroenterology PA, Minneapolis, Minnesota; and ⁵Divisions of Public Health Sciences and ⁶Epigenomics, Fred Hutchinson Cancer Research Center, Seattle, Washington

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

Corresponding Author: Uri Ladabaum, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 300 Pasteur Drive, Always Bldg Rm M211, Stanford, CA 94305-5187. Phone: 650-725-6511; Fax: 650-723-5488; E-mail: uri.ladabaum@stanford.edu

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9 DNA methylation assay showed an overall sensitivity of 48% for colorectal cancer and a specificity of 92%, with sensitivities of 35% for stage I colorectal cancer, 63% for stage II colorectal cancer, 46% for stage III colorectal cancer, and 11.2% for advanced adenoma (26). This sensitivity is superior to that of FOBT, but inferior to that of FIT. It cannot yet be compared with that of other promising blood-based biomarkers (21, 22) because these other markers have not yet been evaluated in large prospective studies. A commercial assay for this biomarker is available in Europe.

We used our published decision analytic model of colorectal cancer screening, which is validated against randomized controlled trials of FOBT and sigmoidoscopy (27, 28), to address key questions pertaining to the potential use of a blood-based biomarker in a screening program, illustrated by methylated Septin 9 DNA, including the appropriate screening interval, comparative effectiveness and cost-effectiveness in relation to established strategies, and the potential impact at the population level accounting for differential patterns of uptake and adherence among screening strategies over time.

Materials and Methods

Decision analytic model

Our published decision analytic model, its validation (27, 28) against the Minnesota Colon Cancer Control Study (4, 5), the United Kingdom Flexible Sigmoidoscopy Trial (8), the SCORE Trial (29), and the PLCO Cancer Screening Trial (30), the data sources used, and a model schematic are presented in the Supplementary Appendix. We modeled the contemporary population in the United States at average risk for colorectal cancer, with age-specific all-cause mortality based on U.S. Life Tables from 2003.

The PRESEPT study and methylated Septin 9 DNA assays

PRESEPT, a prospective multicenter study in the United States and Germany, examined the performance for colorectal cancer detection of a polymerase chain reaction-based assay for methylated Septin 9 DNA in plasma of average risk persons undergoing screening colonoscopy (26). Two plasma aliquots per person were initially tested (2-well assay), and a third aliquot of remaining DNA was tested later *post hoc* to emulate a 3-well assay (26). Based on these results, we modeled both assays, with the 3-well assay having higher sensitivities but slightly lower specificity than the 2-well assay.

Screening strategies and surveillance

Because there is value in illustrating different sets of test performance characteristics for blood-based biomarkers, we compared screening using 2-well or 3-well methylated Septin 9 DNA assays (¹³C-SEPT9-2well and ¹³C-SEPT9-3well) with established strategies recommended by the USPSTF: annual FOBT, annual FIT, sigmoidoscopy every 5 years, and colonoscopy every 10 years (9), and the combinations

sigmoidoscopy/FOBT and sigmoidoscopy/FIT. We recognize that the 3-well assay model inputs are based on an emulation and not a prospective evaluation.

Screening was superimposed on the Natural History module. Screening and surveillance were offered to persons at average risk of colorectal cancer from ages 50 to 80 years. If a screening test was positive, then colonoscopy was offered. If colonoscopy was normal after a positive screening test, the screening test was assumed to be a false-positive and screening resumed in 10 years with the primary screening strategy. With colonoscopy, polyps were removed and colorectal cancers were biopsied if detected. In all strategies, surveillance colonoscopy was carried out on average every 5 years after adenoma detection to reflect guidelines that suggest surveillance at 3, 5, or 5 to 10 years depending on adenoma number and size (31), and within 1 year of diagnosis, 3 years, and then every 5 years after colorectal cancer diagnosis (31).

Assumptions about test performance characteristics, uptake, and adherence are crucial in our analyses. Test sensitivities and specificities are presented in the Supplementary Appendix, Supplementary Table S1. In the base case, we modeled perfect uptake and adherence, and we considered multiple levels of imperfect uptake and adherence in sensitivity analyses.

Septin 9–based screening: testing performance and interval

Our model is calibrated to SEER data on stage distribution by localized, regional, and disseminated colorectal cancer. SEER coding guidelines consider stage IIA as localized and IIB as regional disease. We used the reported population-adjusted sensitivities of ¹³C-SEPT9-2well and ¹³C-SEPT9-3well (26) to estimate the assay's sensitivities for localized, regional, and disseminated colorectal cancer.

In the PRESEPT study, only one-time screening was carried out. Before a ¹³C-SEPT9-2well or ¹³C-SEPT9-3well screening program could be compared with alternatives, a testing interval had to be selected. We examined screening with ¹³C-SEPT9-2well and ¹³C-SEPT9-3well at progressively shorter intervals, as we have described previously (32), and selected 2 years as a screening interval consistent with the common willingness to pay threshold of \$50,000/life-year gained (see Results).

Cost inputs

The derivation of cost inputs in year 2010 dollars is described in the Supplementary Appendix. The cost of ¹³C-SEPT9-2well and ¹³C-SEPT9-3well in the United States is not yet determined. We used \$150 in the base case (range \$100–200) based on anticipated costs (C. Lofton-Day, personal communication).

Clinical and economic outcomes

The principal model outputs were quality-adjusted life-years (QALY) and costs per/person (33, 34). Future QALYs and costs were discounted by 3% annually (35).

Reported health state utilities for colorectal cancer by stage were used to calculate QALYs by applying these for 5 years after colorectal cancer diagnosis. For each strategy, we estimated colorectal cancer cases by stage and deaths in a cohort of 100,000 persons. The effects on colorectal cancer mortality for ¹²⁵SEPT9-based screening are unknown. Estimates of effectiveness were produced by the model for these and all strategies based on the assumptions about natural history, uptake, adherence, and test-performance characteristics.

Cost-effectiveness analyses

Analyses from the perspective of an insurer such as Medicare were conducted in TreeAge Pro (TreeAge Software, Inc.) and in Excel 2003 (Microsoft Corporation). Incremental cost-effectiveness ratios were calculated (33, 34).

One-way sensitivity analyses were conducted on all model inputs. Threshold analyses were conducted on influential variables. To estimate the uncertainty of our projections, a Monte Carlo simulation with 1,000 trials was carried out. We used beta distributions for probabilities derived from means, SD, and ranges in the literature (36). Costs of screening were varied by a common factor within a range of 20% of the base case value, and costs of care by a different common factor within the same range.

We conducted analyses reflecting persons who take up and adhere with screening and follow-up colonoscopy after abnormal screening (maximum efficacy), as well as scenarios reflecting imperfect uptake, per-cycle adherence, and follow-up (potential effectiveness). We addressed the potential impact of ¹²⁵SEPT9 at the population level by contrasting scenarios with increased overall uptake of screening as a consequence of acceptance of ¹²⁵SEPT9 by some of those currently unscreened, versus partial substitution by ¹²⁵SEPT9 for current strategies (10–19).

Results

Testing interval for strategies based on ¹²⁵SEPT9

The incremental cost/QALY gained with ¹²⁵SEPT9-3well increased from \$5,900 to \$16,400 as the testing interval decreased from every 5 years to every 2 years, and rose sharply to \$49,200 for annual testing, assuming a test cost of \$150. This accelerating cost/QALY gained as the testing interval moved to yearly was also observed with ¹²⁵SEPT9-2well, and at ¹²⁵SEPT9 costs of \$100 and \$200. Annual testing at a test cost of \$200 had incremental costs/QALY gained of \$64,600 for ¹²⁵SEPT9-3well and \$52,500 for ¹²⁵SEPT9-2well. ¹²⁵SEPT9-3well and ¹²⁵SEPT9-2well with annual testing were less effective and more costly than annual FIT. Thus, a base case testing interval of 2 years was selected for ¹²⁵SEPT9-based screening.

Base case: effectiveness and cost-effectiveness with perfect uptake, adherence, and follow-up

Assuming perfect uptake, adherence, and follow-up after abnormal screening, the greatest reductions in colo-

rectal cancer incidence and mortality compared with no screening were observed with sigmoidoscopy/FIT, and the reductions with ¹²⁵SEPT9-3well and ¹²⁵SEPT9-2well were lower than with the alternatives (Table 1).

All strategies yielded substantial gains in life expectancy, and some but not all were cost-saving (Fig. 1, Table 1). ¹²⁵SEPT9-3well and ¹²⁵SEPT9-2well gained fewer QALYs than the other strategies, and incurred the highest costs (Fig. 1, Table 1).

Compared with no screening, ¹²⁵SEPT9-2well and ¹²⁵SEPT9-3well yielded costs/QALY gained of \$11,500 and \$8,400, respectively (Table 1). In comparison, sigmoidoscopy/FIT, sigmoidoscopy/FOBT, and colonoscopy yielded costs/QALY gained under \$3,000, and FOBT, sigmoidoscopy, and FIT were more effective and less costly (i.e., cost-saving) compared with no screening (Table 1).

While all strategies yielded substantial gains in life expectancy compared with no screening, and the differences in effectiveness between strategies were comparatively small, annual FIT was preferred in incremental comparisons between strategies. It was more effective and less costly than ¹²⁵SEPT9-2well, ¹²⁵SEPT9-3well, FOBT, sigmoidoscopy, and colonoscopy (Table 1).

Sensitivity analyses assuming perfect uptake, adherence, and follow-up

Comparisons between strategies were affected by key attributes of the screening tests. Assuming a best-case scenario for ¹²⁵SEPT9 based on the CIs for reported sensitivities and specificities, ¹²⁵SEPT9-2well and ¹²⁵SEPT9-3well became more effective than FOBT but not FIT. With these assumptions, ¹²⁵SEPT9-3well would have to be carried out yearly at a test cost of less than \$10 to approximate but still not match the effectiveness and costs with FIT. At the lower bound of reported sensitivities for FIT, ¹²⁵SEPT9-3well with base case assumptions carried out yearly was nearly as effective as FIT, but ¹²⁵SEPT9-3well cost would have to be less than \$5 in order for costs to be similar with the 2 strategies. Compared with no screening, ¹²⁵SEPT9-2well and ¹²⁵SEPT9-3well every 2 years were cost-saving at a cost of \$50.

The costs of colonoscopy and colorectal cancer care, and the underlying risk of colorectal cancer in the population affected the results for all strategies (Table 2). For instance, if colonoscopy costs increased by 70% to \$1,097 and \$1,722 with biopsy, to illustrate costs for commercial insurance instead of Medicare, then FIT was no longer cost-saving, but it was still dominant over the ¹²⁵SEPT9 strategies. Other variables did not significantly affect the results, ranking of strategies, or conclusions (Table 2).

Monte Carlo simulation assuming perfect uptake, adherence, and follow-up

FIT remained more effective and less costly than ¹²⁵SEPT9-2well and ¹²⁵SEPT9-3well in all iterations. Cost-effectiveness acceptability curves are shown Fig. 2. Compared with no screening, the strategies' median

Table 1. Base case clinical and economic results assuming perfect screening uptake, adherence, and follow-up

	Natural history	"SEPT9-2well"	"SEPT9-3well"	FOBT	Sigmoidoscopy	Colonoscopy	FIT	FOBT	Sigmoidoscopy/FIT
Colorectal cancer cases per 100,000 persons from age 50 to 100 years	5,927	3,871	3,468	3,140	1,883	1,584	2,243	1,716	1,618
Colorectal cancer stage									
Localized	40%	57%	60%	64%	53%	56%	68%	63%	65%
Regional	37%	31%	31%	26%	33%	32%	23%	27%	25%
Distant	23%	12%	10%	10%	14%	12%	10%	10%	10%
Deaths attributable to colorectal cancer	2.4%	1.1%	1.0%	0.8%	0.6%	0.5%	0.6%	0.5%	0.4%
QALYs/person ^a	18,6686	18,7225	18,7305	18,7352	18,7372	18,7443	18,7456	18,7477	18,7498
Cost/person ^a	\$2,364	\$2,983	\$2,884	\$1,953	\$2,160	\$2,564	\$1,866	\$2,408	\$2,411
Increment cost/QALY gained compared with:									
Natural history	—	\$11,500	\$8,400	Dominates	Dominates	\$2,600	Dominates	\$550	\$580
"SEPT9-2well"	—	—	Dominates	Dominates	Dominates	Dominates	Dominates	Dominates	Dominates
"SEPT9-3well"	—	—	—	Dominates	Dominates	Dominates	Dominates	Dominates	Dominates
FOBT	—	—	—	—	\$105,000	\$67,300	Dominates	\$36,500	\$31,500
Sigmoidoscopy	—	—	—	—	—	\$56,800	Dominates	\$23,600	\$20,000
Colonoscopy	—	—	—	—	—	—	Dominates	Dominates	Dominates
FIT	—	—	—	—	—	—	—	\$258,000	\$130,000
Sigmoidoscopy/FOBT	—	—	—	—	—	—	—	—	\$1,600

NOTE: "Dominates" denotes a strategy that is more effective and less costly than its comparator and "Dominated" denotes a strategy that is less effective and more costly than its comparator.

^aDiscounted 3%/year.

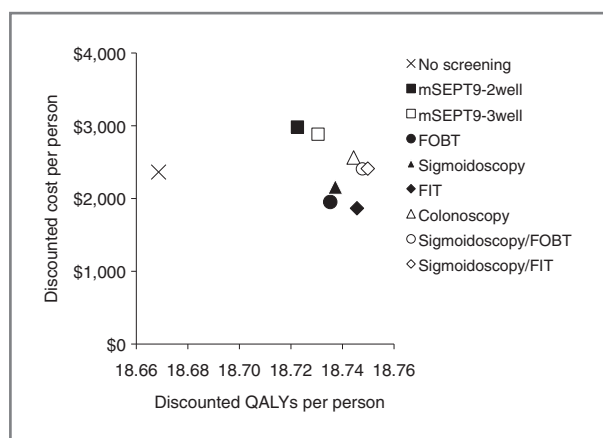


Figure 1. Discounted mean QALYs/person and costs/person for the screening strategies in the base case. Sigmoidoscopy/FIT, sigmoidoscopy/FOBT, FIT, and colonoscopy yielded the greatest gains in life expectancy, whereas FOBT, sigmoidoscopy, and FIT were cost saving compared with no screening. ¹²⁵SEPT9-3well and ¹²⁵SEPT9-2well gained fewer QALYs than the other strategies and incurred the highest costs.

costs/QALY gained and the 95% CIs were \$11,600 (\$8,200–\$16,300) for ¹²⁵SEPT9-2well, and \$8,500 (\$5,800–\$11,600) for ¹²⁵SEPT9-3well. By comparison, the values were \$600 (cost saving to \$2,900) for sigmoidoscopy/FIT; \$570 (cost saving to \$2,900) for sigmoidoscopy/FOBT; \$2,700 (\$300–\$5,300) for colonoscopy; and cost-saving in all iterations for FIT, FOBT, and sigmoidoscopy.

Imperfect screening uptake and adherence

Differential screening uptake affected the comparisons between strategies. FIT was no longer more effective than ¹²⁵SEPT9-2well when the FIT uptake rate fell below 70% relative to that of ¹²⁵SEPT9-2well, and it was no longer more effective than ¹²⁵SEPT9-3well when the FIT uptake rate fell below 85% relative to that of ¹²⁵SEPT9-3well. For FOBT, the analogous thresholds were 85% and 95%, respectively. The thresholds at which ¹²⁵SEPT9-3well yielded incremental costs/QALY gained less than \$50,000 compared with FIT and FOBT were relative uptake rates of 60% with FIT and 70% with FOBT (Fig. 3).

Differential rates of per-cycle adherence among persons taking up screening also affected the comparisons between strategies. To illustrate, assuming 75% per-cycle adherence with ¹²⁵SEPT9-based screening, ¹²⁵SEPT9-3well yielded incremental costs/QALY gained of less than \$50,000 compared with FIT when the per-cycle adherence with FIT was less than 20% (Fig. 4), and compared with FOBT when the per-cycle adherence rate with FOBT was less than 40%.

Projected impact at the population level with imperfect uptake, adherence, and follow-up

Table 2 shows the estimated reductions in colorectal cancer incidence and mortality in a population cohort reflecting current rates of screening uptake and adher-

ence for the currently accepted tests, and colonoscopy follow-up after an abnormal screening test in the United States. If the ¹²⁵SEPT9 blood test were then introduced into the population and it induced some of those who are currently not screened to undergo screening, then this yielded incremental reductions in colorectal cancer incidence and mortality at very reasonable costs/QALY gained (Table 3). However, when ¹²⁵SEPT9-based screening was substituted for other alternatives among some of those currently screened, effectiveness decreased and costs increased, as illustrated for FIT, FOBT, and colonoscopy (Table 3). For every 10 persons switching from the current strategies (in proportion to current use; Table 3) to ¹²⁵SEPT9-3well, more than 6 additional persons would need to switch from no screening to ¹²⁵SEPT9-3well to effect a net gain in QALYs, and a total of more than 13 additional persons would need to switch from no screening to ¹²⁵SEPT9-3well in order for this gain to incur costs of less than \$50,000/QALY gained. This shows how the net impact of an emerging screening test at the population level is likely to depend on the degree to which it induces nonscreened persons to undergo screening, and the degree to which it changes the fractions of the population taking up each specific strategy.

Discussion

Our health economic evaluation of ¹²⁵SEPT9-based colorectal cancer screening compared with established screening strategies offer insights into the potential role of screening with a blood-based biomarker at the population level, and highlights principles applicable to colorectal cancer screening in general. In our analyses, ¹²⁵SEPT9-based screening was effective and cost-effective by traditional standards compared with no screening. However, with current test performance characteristics, screening every 2 years with ¹²⁵SEPT9 was estimated to be less effective and more costly than existing alternatives. At the most favorable extremes of the reported CIs for ¹²⁵SEPT9-3well test performance characteristics (26), which serves to illustrate any emerging blood-based biomarker, ¹²⁵SEPT9-3well screening would need to be carried out yearly at a cost less than \$10 to be preferred over FIT by traditional standards, assuming comparable levels of uptake and adherence.

The potential role of screening based on ¹²⁵SEPT9 or comparable biomarkers depends on the setting in which it is offered, and population rates of screening uptake, adherence per screening cycle, and follow-up colonoscopy after an abnormal screening test. From the point of view of a health care system seeking to choose a single testing strategy, FIT emerged as the preferred alternative assuming perfect uptake, adherence and follow-up. Population studies suggest, however, that uptake, adherence and follow-up rates for fecal-based tests are disappointing (10–19). In organized programs, uptake rates have been up to 60% to 80% (37, 38). It is hypothesized that a blood-based test could lead to improved colorectal cancer

Table 2. One-way sensitivity analyses

Variable	Base case value	Value in sensitivity analysis	^m SEPT9-3well vs. natural history		^m SEPT9-3well vs. FIT	
			Incremental QALYs	Incremental cost/QALY gained	Incremental QALYs	Incremental cost/QALY gained
^m SEPT9-3well sensitivity for small polyp/large polyp/localized colorectal cancer/regional colorectal cancer	0.10/0.14/0.51/0.75	0.06/0.10/0.26/0.42	0.0441	\$17,000	-0.0329	Dominated
^m SEPT9-3well specificity	0.88	0.15/0.19/0.75/1.0	0.0723	\$5,100	-0.0047	Dominated
^m SEPT9-3well cost	\$150	0.85	0.0614	\$8,900	-0.0155	Dominated
^m SEPT9-3well interval	2 years	0.90	0.0622	\$8,100	-0.0148	Dominated
FIT sensitivity for small polyp/large polyp/colorectal cancer	0.10/0.24/0.70	\$50	0.0619	Dominates	-0.0151	Dominated
Cost of tests	See Supplementary Table S1	\$200	0.0619	\$13,600	-0.0151	Dominated
Colonoscopy sensitivity for small polyp/large polyp/colorectal cancer	0.85/0.90/0.95	1 year	0.0709	\$13,600	-0.0060	Dominated
Colonoscopy costs for diagnostic/with biopsy or polypectomy	\$645/\$1,013	3 years	0.0517	\$6,900	-0.0253	Dominated
Colonoscopy bleeding/perforation rates	0.0016/0.00085	0.075/0.16/0.50	0.0619	\$8,400	-0.0097	Dominated
Colonoscopy bleeding/perforation costs	\$5,882/\$14,258	All increased 1.5-fold	0.0619	\$21,800	-0.0151	Dominated
Colorectal cancer risk	See Methods for model calibration	0.75/0.85/0.92	0.0609	\$9,100	-0.0152	Dominated
Colorectal cancer care costs	See Supplementary Table S1	\$903/\$1,418 (40% increase)	0.0619	\$12,900	-0.0151	Dominated
Utility for localized/regional/disseminated colorectal cancer	0.76/0.80/0.90	\$1,097/\$1,722 (70% increase)	0.0619	\$16,300	-0.0151	Dominated
		0.008/0.00425 (5-fold increase)	0.0584	\$10,300	-0.0149	Dominated
		\$11,764/\$28,516 (2-fold increase)	0.0619	\$8,800	-0.0151	Dominated
		50% decrease	0.0297	\$34,700	-0.0075	Dominated
		50% increase	0.0960	\$130	-0.0230	Dominated
		2-fold increase	0.1378	Dominates	-0.0324	Dominated
		40% decrease	0.0619	\$15,900	-0.0151	Dominated
		50% increase	0.0619	Dominates	-0.0151	Dominated
		0.54/0.65/0.76	0.0676	\$7,700	-0.0189	Dominated
		0.93/0.95/0.98	0.0567	\$9,200	-0.0122	Dominated

NOTE: "Dominates" denotes a strategy that is more effective and less costly than its comparator and "Dominated" denotes a strategy that is less effective and more costly than its comparator.

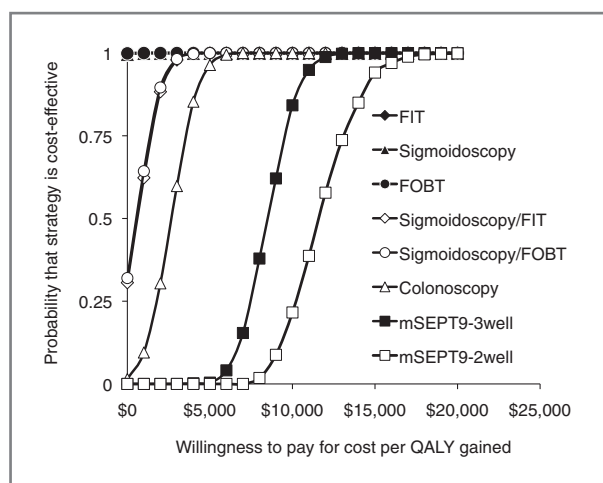


Figure 2. Cost-effectiveness acceptability curves for the screening strategies compared with no screening. The curves show the probability that a strategy would be considered cost-effective at a given willingness to pay per QALY gained.

screening uptake or adherence rates, but this remains to be proven in clinical studies.

In a health care system that accepts multiple colorectal cancer screening strategies, the potential effect of screening based on ¹²⁵SEPT9 or comparable biomarkers depends on the extent to which it increases overall screening uptake as opposed to being substituted for current alternatives, and the relative rates of adherence and follow-up compared with current alternatives. For example, if ¹²⁵SEPT9-based screening were taken up only by persons who are currently not screened at all, then net clinical benefits would be realized at acceptable costs. Alternatively, if a test such as ¹²⁵SEPT9-3well with current test performance characteristics were simply substituted for current alternatives without improvements in adherence

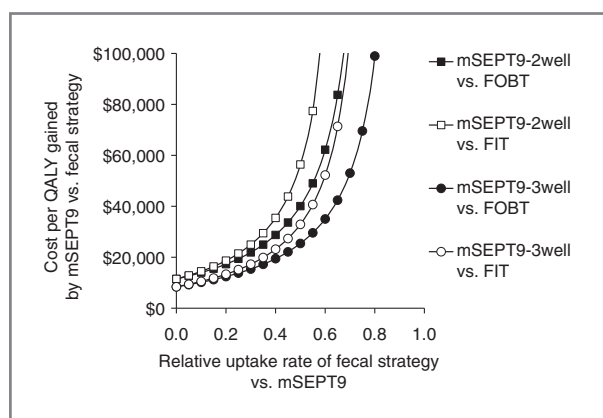


Figure 3. Incremental costs/QALY gained by ¹²⁵SEPT9-based screening strategies compared with FIT and FOBT at different rates of relative screening uptake. The incremental cost-effectiveness of ¹²⁵SEPT9-based screening improved as the relative uptake rate of the fecal strategies decreased. For example, at a per-cycle adherence of 40% for FIT, SEPT9-3well with 75% per-cycle adherence cost \$55,700/QALY gained compared with FIT.

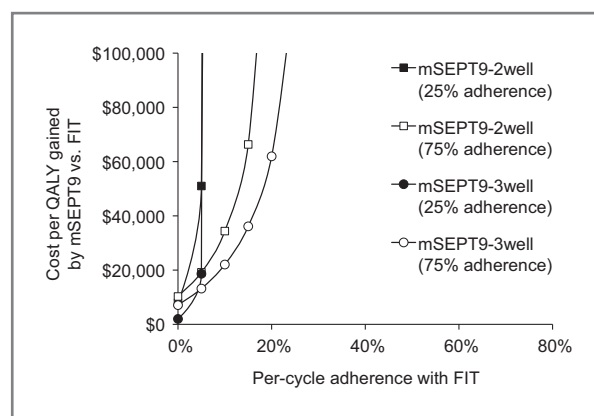


Figure 4. Incremental costs/QALY gained by ¹²⁵SEPT9-based screening strategies compared with FIT at different rates of per-cycle adherence with each strategy. The incremental cost-effectiveness of ¹²⁵SEPT9-based screening improved as the per-cycle adherence rate with FIT decreased relative to the per-cycle adherence rate with the ¹²⁵SEPT9-based strategies. For example, at a per-cycle adherence of 20% for FIT, SEPT9-3well with 75% per-cycle adherence cost \$54,900/QALY gained compared with FIT.

or follow-up, then overall effectiveness would decrease and costs would increase. The real effect of screening with ¹²⁵SEPT9 or comparable biomarkers is likely to lie between these extremes.

In most previous modeling studies by us (27, 32) and others (39), colorectal cancer screening strategies have been estimated to be highly cost-effective, but usually not cost-saving. As the cost of colorectal cancer treatment continues to rise (40, 41), certain strategies may actually be cost-saving (42–44). In recent years in the United States, the costs of colorectal cancer care have been increasing (40, 41, 45), whereas Medicare reimbursement rates for screening tests including colonoscopy have been decreasing (46). These opposing trends in colorectal cancer care costs and screening costs are the principal factors behind our and other recent study results that FIT, FOBT, and sigmoidoscopy may be cost-saving in the United States. With this in mind, it is possible that screening with a relatively inexpensive blood-based biomarker could be cost-saving compared with no screening, but its cost-effectiveness against other screening alternatives will depend on the relative test performance characteristics, uptake, adherence, and cost.

Our study has several strengths. Our model is validated against prospective, randomized clinical trials of screening with FOBT (4, 5) and sigmoidoscopy (8, 29, 30), which provides us with some confidence in our model's predictions. The test performance characteristics for ¹²⁵SEPT9-based screening were obtained from a prospective study, and the CIs serve to illustrate a range of potential performance by emerging biomarkers. We examined in detail the effects of imperfect screening uptake, adherence, and follow-up, factors that others have also emphasized recently (47). Our results with perfect uptake, adherence and follow-up represent estimated efficacy under ideal circumstances, whereas our results with imperfect uptake,

Table 3. Population level impact with a mixture of strategies and imperfect uptake, adherence, and follow-up

	No screening	Current screening uptake ^a , adherence, and follow-up	Substitution of ^m SEPT9-3well for 1/3 of current tests	Additional screening uptake of 10% with ^m SEPT9-3well	Additional screening uptake of 20% with ^m SEPT9-3well	Additional screening uptake of 20% with ^m SEPT9-3well, and shift of 50% of fecal tests to mSep9-3well	Additional screening uptake of 20% with ^m SEPT9-3well, and shift of 50% of colonoscopies to mSep9-3well
Uptake of any screening in cohort	0%	60%	60%	70%	80%	80%	80%
Per-cycle adherence among those who take up screening	0%	Test-specific ^b	Test-specific ^b	Test-specific ^b	Test-specific ^b	Test-specific ^b	Test-specific ^b
Rate of follow-up colonoscopy after abnormal screen	0%	60%	60%	60%	60%	60%	60%
QALYs/person	18,6686	18,7036	18,6991	18,7072	18,7108	18,7104	18,7048
Cost/person	\$2,364	\$2,326	\$2,441	\$2,377	\$2,428	\$2,480	\$2,520
Cost/QALY gained vs. No Screening	NA	Dominates	\$2,531	\$335	\$1,526	\$2,774	\$4,301
Cost/QALY gained vs. current screening	NA	NA	Dominated	\$14,368	\$14,368	\$22,848	\$160,448
Total colorectal cancer cases/100,000	5,927	3,971	4,352	3,836	3,700	3,722	4,201
Localized	40%	45%	45%	46%	47%	47%	47%
Regional	37%	36%	36%	35%	35%	35%	35%
Disseminated	23%	20%	19%	19%	18%	18%	18%
Reduction in colorectal cancer incidence compared with No Screening	NA	33%	27%	35%	38%	37%	29%
Fraction of all deaths attributable to colorectal cancer	2.44%	1.51%	1.64%	1.42%	1.33%	1.34%	1.51%
Reduction in colorectal cancer mortality compared with No Screening	NA	38%	33%	42%	45%	45%	38%

Abbreviations: QALY, quality-adjusted life-year; FOBT, fecal occult blood testing; FIT, fecal immunochemical testing.

^aFOBT, 6%; FIT, 6%; sigmoidoscopy, 6%; FOBT/sigmoidoscopy, 1.5%; FIT/sigmoidoscopy, 1.5%; colonoscopy, 39%; and unscreened, 40%.

^bFOBT and FIT, 50%; sigmoidoscopy, 55%; colonoscopy, 80%; ^mSEPT9-3well, 70%.

adherence, and follow-up represent estimated effectiveness under current clinical realities.

Our study has some limitations. The degree of independence between individual tests in a given strategy is not known, and our model assumes independence. For instance, although improvements in ¹⁴C-SEPT9 test-performance with 3 wells compared with 2 wells suggest that additional testing provides incremental yield, the true degree of independence between tests from year to year is not known. However, the effect of assuming independence is likely to be most pronounced for strategies with yearly testing, including FOBT, which was the subject of one of our encouraging validation exercises (Supplementary Appendix). We did not model adenoma multiplicity or location, and the number of people with adenomas and colorectal cancer detected by size and stage were not validated in the same way that colorectal cancer incidence and mortality reduction were validated (Supplementary Appendix). Disutilities associated with screening are not included; considering modest disutilities for 1 to 2 days every 1 to 10 years does not affect the results substantially (results not shown). In the real world, screening uptake, adherence, and follow-up are complex at the population and individual level. Instead of pure subpopulations, there is likely a distribution of screening behaviors that may vary over time. The data to inform a model with such complex attributes are not currently available.

In conclusion, colorectal cancer screening with a blood-based biomarker such as ¹⁴C-SEPT9 is likely to be cost-effective compared with no screening, but with test performance characteristics and costs such as those of the current ¹⁴C-SEPT9 tests, established alternatives are likely to be preferred under idealized circumstances of uptake and adherence. Screening uptake, adherence, and follow-up are as influential determinants of the real-world effectiveness and cost-effectiveness of colorectal cancer screening strategies as are the performance characteristics and costs

of screening tests themselves. Colorectal cancer screening with blood-based biomarkers offers potential benefits over current methods, but to realize their full potential, blood-based biomarkers will need to achieve a level of performance that is acceptable to clinicians and patients relative to current technologies. As blood-based biomarkers become available clinically, the decision over whether to adopt them will require weighing their costs and possibly lower performance but higher adherence rates, against the alternative of investing in efforts to improve uptake of current strategies.

Disclosure of Potential Conflicts of Interest

U. Ladabaum has a commercial research grant from Epigenomics. S.D. Ramsey has expert testimony in Epigenomics. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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Authors' Contributions

Conception and design: U. Ladabaum, M. Wandell, S.D. Ramsey
Development of methodology: U. Ladabaum, M. Wandell, S.D. Ramsey
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): U. Ladabaum, M. Wandell
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): U. Ladabaum, M. Wandell, S.D. Ramsey
Writing, review, and/or revision of the manuscript: U. Ladabaum, J. Allen, S.D. Ramsey
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): U. Ladabaum
Study supervision: U. Ladabaum, M. Wandell

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