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Comparative Effectiveness and Cost Effectiveness of a Multitarget Stool DNA Test to Screen for Colorectal Neoplasia

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BACKGROUND & AIMS: We developed a model to determine whether a multitarget stool DNA (MT-sDNA) test that detects colorectal cancer (CRC) and polyps with higher sensitivity and lower specificity, but at a higher cost, than the fecal immunochemical test (FIT) can be used in screening. **METHODS:** We used a Markov model of average-risk CRC screening to compare the effectiveness and cost effectiveness of screening with the MT-sDNA test vs FIT or colonoscopy. We accounted for the complex longitudinal participation patterns observed in organized programs vs opportunistic screening, as well as organized programs' patient support costs and differential payment rates by commercial insurers vs Medicare. **RESULTS:** With optimal adherence, yearly FIT and colonoscopy every 10 years were dominant (more effective and less costly) than MT-sDNA every 3 years. Compared with successful organized FIT programs (50% consistent and 27% intermittent participation; patient support costs, $153/cycle), the patient support program for the MT-sDNA test would need 68% of subjects to participate consistently and 32% to participate intermittently every 3 years, or the MT-sDNA test would need to cost 60% less than in the base case ($260 commercial payment and $197 Medicare payment), for the MT-sDNA test to be preferred over FIT at a threshold of $100,000 per quality-adjusted life-year (QALY) gained. Compared with opportunistic yearly FIT screening (15% consistent and 30% intermittent participation), performing the MT-sDNA test every 3 years would cost less than $100,000 per QALY gained if the MT-sDNA test achieved a participation rate more than 1.7-fold that of FIT. The results were robust in sensitivity analyses. Assuming equal participation across strategies and a threshold of $100,000 per QALY gained, FIT was preferred in 99.3% of iterations in Monte Carlo simulation. **CONCLUSIONS:** In a Markov model, we found FIT and colonoscopy to be more effective and less costly than the MT-sDNA test when participation rates were equal for all strategies. For the MT-sDNA test to be cost effective, the patient support program included in its cost would need to achieve substantially higher participation rates than those of FIT, whether in organized programs or under the opportunistic screening setting that is more common in the United States than in the rest of the world.

Keywords: Colon Cancer; Prevention; Adherence; Early Detection.

Randomized controlled trials have shown that screening with guaiac-based fecal occult blood testing (gFOBT)[1] or sigmoidoscopy[2] decreases colorectal cancer (CRC) incidence and mortality. These findings appear to extend to fecal immunochemical testing (FIT)[3–6] and colonoscopy,[7–10] although randomized controlled trials of these screening modalities have not yet been completed.

A multitarget stool DNA (MT-sDNA) test including assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and hemoglobin recently was reported to have superior sensitivity for CRC (92.3% vs 73.8%; $P = .002$) and advanced precancerous lesions (42.4% vs 23.8%; $P < .001$), but inferior specificity (89.8% vs 96.4%; $P < .001$) compared with FIT in a large prospective study of persons at average risk for CRC.[11] The role of this test alongside established strategies remains to be determined.

Multiple decision analyses have estimated the potential clinical and economic impact of established and emerging CRC screening alternatives. However, previous studies have not addressed comprehensively the complex patterns of screening participation over time that now are being described (consistent screeners, late entrants, drop outs, intermittent screeners, and consistent nonresponders),[12,13] the patient support costs that are required to realize the higher participation rates that organized programs achieve compared with opportunistic screening,[14,15] the possibility that one-time test performance characteristics may overestimate the ability of tests to detect lesions that were missed in previous rounds of testing,[6,16,17] and the higher payment rates by commercial insurers compared with Medicare.[18]

Our aims were to explore the potential effectiveness and cost effectiveness of screening for colorectal neoplasia with MT-sDNA compared with the most established current strategies: FIT and colonoscopy. We performed a decision analytic health economic evaluation including scenarios with optimal patient participation or complex longitudinal

Abbreviations used in this paper: **CRC, colorectal cancer; FIT, fecal immunochemical testing; gFOBT, guaiac-based fecal occult blood testing; MT-sDNA, multitarget stool DNA; QALY, quality-adjusted life-year.**

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participation patterns as reported in the real world, allowing for differential participation rates among strategies, and incorporating the additional critical factors identified above.

Materials and Methods

General Study Design

We adapted our validated decision analytic Markov cohort model of CRC screening in the general US population[19,20] to allow complex screening participation patterns over time, test cycle-specific test performance characteristics, and differential costs for persons younger than age 65 (reflecting commercial insurance payments) vs age 65 and older (reflecting Medicare payments) (Appendix).

First, we explored the potential effectiveness and cost effectiveness of screening with MT-sDNA at 1- to 5-year intervals to select a testing interval for a MT-sDNA–based screening program (Appendix). Second, we compared screening strategies in hypothetical cohorts with optimal (100%) longitudinal participation, without patient support costs. Third, we modeled different participation patterns over time and considered patient support costs for organized FIT programs; no incremental costs were considered for MT-sDNA because its test cost include a patient support program (see Discussion section). Fourth, we performed extensive sensitivity analyses as described below.

Decision Analytic Model

Our original model, data sources, and validation against the Minnesota Colon Cancer Control Study,[21,22] United Kingdom Flexible Sigmoidoscopy Trial,[23] Screening for COlon REctum (SCORE) trial,[24] and Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial[25] have been detailed previously[19,20,26] (Appendix, Supplementary Figure 1, and Table 1). The model reproduces the natural history of CRC precursors and CRC in the general US population without screening. Persons transition between health states of normal, small polyp, large polyp, localized, regional or disseminated CRC, and dead, in 1-year cycles. Screening is superimposed on the natural history module, resulting in CRC prevention or early detection as determined by screening test performance characteristics and patient participation.[19,20,26] The model inputs are derived from autopsy data on polyp prevalence; Surveillance, Epidemiology, and End Results (SEER) data on CRC incidence and stage distribution from dates preceding widespread CRC screening; clinical studies on test performance characteristics and complication rates, outcomes after CRC treatment, and CRC-related quality of life; US Life Tables data; and commercial and Medicare payment rates (Table 1 and Appendix). Persons enter the model at age 50 and screening and surveillance are offered from ages 50 to 80, with persons followed up until age 100 or death.

Screening Participation Behavior Patterns

We created cohorts made up of subcohorts with different longitudinal screening participation patterns: consistent screeners, with participation in every screening round; intermittent screeners, including a spectrum of participation patterns including late entry, drop out, and intermittent; and consistent nonresponders.[12,13] The population proportions in each group were based on published reports of screening programs and clinical trials,[5,6,12,13,16,17,21,27–32] and these were varied to reflect different scenarios, including organized programs providing patient support. In threshold analyses, consistent and intermittent screening rates were varied in the same proportions first, and were varied separately only when specific thresholds were not achievable otherwise. Participation patterns have been described over the medium term, but not over 30 years[5,6,12,13,16,17,21,27–32]; we extrapolated these patterns over the simulation's time horizon.

Among intermittent screeners, the fraction of screening cycles completed was distributed relatively evenly from the minimum to maximum possible.[5,6,12,13,16,17,21,27–32] Thus, we modeled this subcohort as made up of 5 equal-size subsubcohorts with participation probabilities per cycle of 0.1, 0.3, 0.5, 0.7, or 0.9.

Cost Inputs

Base-case cost inputs were derived from Medicare reimbursement rates[33–35] and estimated CRC care costs[36] for persons age 65 and older, and from commercial payment rates in persons age 50–64,[18] accounting for colonoscopy site of service,[18,36] and updated to 2015 dollars using the medical component of the consumer price index (Table 1 and Appendix). The costs for MT-sDNA were based on Medicare reimbursement rates for persons age 65 and older, and rates for commercial insurer carriers for persons age 50 to 64.[37] Based on the mean ratio of commercial to Medicare payment rates for colorectal tests,[18] we assumed CRC care and complication costs for persons ages 50–64 that were 1.35-fold those of persons age 65 and older. Patient support costs were derived from the CDC's Colorectal Cancer Screening Demonstration Program.[14,15]

Clinical and Economic Outcomes

The principal model outputs were quality-adjusted life-years (QALYs) and costs per person.[38,39] Future QALYs and costs were discounted by 3% annually.[40] Health state utilities for CRC by stage (Table 1) were used to calculate QALYs by applying these for 5 years after CRC diagnosis. We estimated CRC cases by stage and CRC deaths, and lifetime number of tests per person in cohorts of 100,000 persons.

Cost-Effectiveness Analyses

Analyses from the perspective of a third-party payer were performed in TreeAge Pro (TreeAge Software, Inc, Williamstown, MA) and Excel 2010 (Microsoft Corporation, Redmond, WA). Incremental cost-effectiveness ratios were calculated.[38,39]

Sensitivity analyses examined all model inputs, including test performance characteristics, and the possibility that test sensitivities decrease over testing cycles for a previously missed lesion. We performed threshold analyses on key variables. We performed a probabilistic Monte Carlo simulation with 10,000 trials in which we varied all model inputs simultaneously using β distributions for probabilities derived from means, standard deviations, and ranges in the literature.[41] 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.

Table 1. Model Inputs

Variable	Base case value (range)[a]	References
Clinical		
Polyp prevalence at age 50, %	15	48–50
Small polyp, %	95	49,51,52
Large polyp, %	5	49,51,52
Annual transition rate to small polyp from normal, %	Age specific, 1.1–1.9	48–52
Annual transition rate to large polyp from small polyp, %	1.5	49,51,52
Annual transition rate to cancer without polypoid precursor, %	Age specific, 0.006–0.086	48–50,53,54
Annual transition rate to cancer from large polyp, %	5	48–50,53,54
Symptomatic presentation of localized cancer, %	22/y over 2 y	54
Symptomatic presentation of regional cancer, %	40/y over 2 y	54
Mortality rate from treated localized cancer, %	1.74/y in first 5 y	54
Mortality rate from treated regional cancer, %	8.6/y in first 5 y	54
Mean survival from distant cancer, *y*	1.9	54,55–61
Mortality rate from cancer treatment, %	2	53,62
Test performance characteristics and complications		
FIT sensitivity for cancer, %	73.3 (60.3–83.9)	11
FIT sensitivity for large polyp, %	23.8 (20.8–27.0)	11
FIT sensitivity for small polyp, %	7.6 (6.7–8.6)	11
FIT specificity, %	96.4 (95.8–96.9)	11
MT-sDNA sensitivity for cancer, %	93.3 (83.8–98.2)	11
MT-sDNA sensitivity for large polyp, %	42.4 (38.9–46.0)	11
MT-sDNA sensitivity for small polyp, %	17.2 (15.9–18.6)	11
MT-sDNA specificity, %	89.8 (88.9–90.7)	11
Colonoscopy sensitivity for cancer, %	95 (90–97)	63,64
Colonoscopy sensitivity for large polyp, %	90 (85–95)	63,64
Colonoscopy sensitivity for small polyp, %	85 (80–90)	63,64
Colonoscopy major hemorrhage rate, %	0.08 (0.05–0.14)	65
Colonoscopy perforation rate, %	0.04 (0.02–0.05)	65
Mortality rate given endoscopic perforation, %	7.5 (4.5–16)	66–68
Health state utilities		
Localized colorectal cancer	0.90 (SD, 0.06)	69
Regional colorectal cancer	0.80 (SD, 0.22)	69
Distant colorectal cancer	0.76 (SD, 0.11)	69
Costs, commercial payments for persons age <65 y, $[a]		
FIT	19	18
MT-sDNA	649	37
Colonoscopy	1391	18
Colonoscopy with lesion removal	1755	18
Major hemorrhage after colonoscopy	8321	18,34,35
Perforation after colonoscopy	22,650	18,34,35
Colorectal cancer care by stage		
Localized, initial	44,431	18,36
Localized, continuing yearly	3535	18,36
Localized, colorectal cancer death	79,649	18,36
Regional, initial	74,760	18,36
Regional, continuing yearly	4710	18,36
Regional, colorectal cancer death	83,688	18,36
Distant, initial	97,624	18,36
Distant, colorectal cancer death	112,316	18,36
Costs, Medicare payments for persons age ≥65 y, $[a]		
FIT	22	33
MT-sDNA	493	33
Colonoscopy	773	35
Colonoscopy with lesion removal	975	35
Major hemorrhage after colonoscopy	6164	34,35
Perforation after colonoscopy	16,778	34,35
Colorectal cancer care by stage		
Localized, initial	32,912	36
Localized, continuing yearly	2619	36
Localized, colorectal cancer death	58,999	36
Regional, initial	55,378	36

Table 1. Continued

Variable	Base case value (range)[a]	References
Regional, continuing yearly	3489	36
Regional, colorectal cancer death	61,991	36
Distant, initial	72,314	36
Distant, colorectal cancer death	83,197	36
Costs for organized screening programs achieving high participation rates, $		
Additional patient support cost per patient per FIT testing cycle	153 (72–242)	14,15

[a]Range in Monte Carlo simulation; costs were varied within ±20% of base-case values.
SD, standard deviation.

Results

Multitarget Stool DNA Testing Interval

The incremental cost per QALY gained increased in an accelerating fashion as the frequency of MT-sDNA screening increased (Appendix): for example, $21,000 per QALY gained for screening every 5 years vs no screening, $119,000 per QALY gained for screening every 3 vs 4 years, and $4,180,000 per QALY gained for screening every 1 vs 2 years (Supplementary Figure 2). If Medicare payment rates were assumed for all ages, screening every 3 vs 4 years cost $92,000 per QALY gained (Supplementary Figure 3). Because MT-sDNA screening every 3 years cost approximately an incremental $100,000 per QALY gained, meeting a common willingness-to-pay threshold, and because FIT every 2 years dominated MT-sDNA every 4 or 5 years, and MT-sDNA every 1 or 2 years was prohibitively expensive compared with colonoscopy or FIT (Appendix, Supplementary Table 1), we selected 3 years as the base case MT-sDNA interval. This coincides with the interval approved by the Centers for Medicare and Medicaid Services (CMS).

Effectiveness and Cost Effectiveness With Optimal Patient Participation

In cohorts of persons adhering with every recommended screening cycle, screening colonoscopy yielded the greatest reduction in CRC incidence and mortality, followed by yearly FIT, which yielded the greatest shift toward earlier stage at diagnosis (Table 2).

Yearly FIT yielded the highest mean QALYs per person, followed by screening colonoscopy, MT-sDNA every 3 years, and FIT every 2 years (Table 2 and Figure 1, and see Supplementary Figure 4 for MT-sDNA at 1- to 5-year intervals). Compared with no screening, FIT every 1 or 2 years was both more effective and less costly, whereas screening colonoscopy cost $15,000 per QALY gained and MT-sDNA every 3 years cost $29,500 per QALY gained (Table 2). In incremental comparisons between strategies, yearly FIT and screening colonoscopy were both more effective and less costly than MT-sDNA every 3 years, and MT-sDNA every 3 years cost $2,390,000 per QALY gained compared with FIT every 2 years (Table 2).

Table 2. Base-Case Clinical and Economic Outcomes for Hypothetical 100,000-Person Cohorts With Optimal Screening Participation From Age 50 to 80

	No screening	FIT every 2 years	MT-sDNA every 3 years	Colonoscopy	FIT yearly
CRC cases per 100,000 persons	5927	3083	2627	1597	2334
CRC stage, number of cases per 100,000 persons (% of all cases)					
Localized	2373 (40)	2096 (68)	1673 (64)	892 (56)	1625 (70)
Regional	2210 (37)	714 (23)	710 (27)	512 (32)	495 (21)
Distant	1345 (23)	273 (9)	244 (9)	194 (12)	214 (9)
CRC deaths per 100,000 persons	2316	694	628	445	519
QALYs/person	18.6687	18.7410	18.7423	18.7455	18.7470
Cost/person, $	3020	2211	5190	4173	2407
Incremental cost/QALY gained (column compared with row)					
No screening	-	Dominates	$29,500	$15,000	Dominates
FIT every 2 years	-	-	$2,390,000	$436,000	$33,000
MT-sDNA every 3 years	-	-	-	Dominates	Dominates
Colonoscopy	-	-	-	-	Dominates
Lifetime tests/person, mean					
Colonoscopies/person	0.1	1	1.4	3.8	1.5
Fecal tests/person	-	10.6	6.6	-	17.5

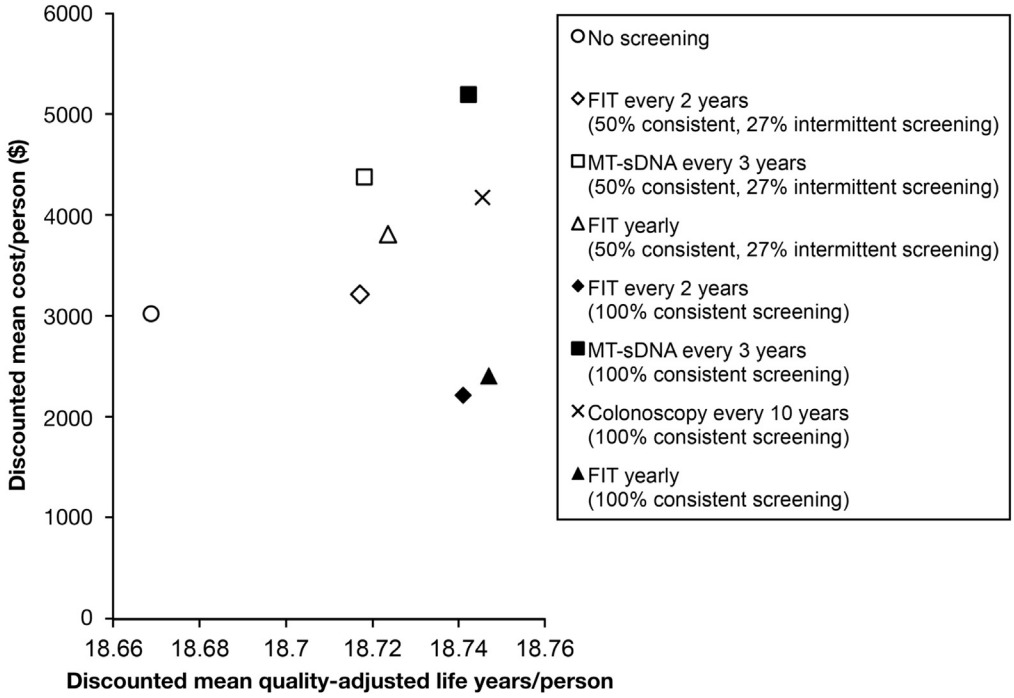

Figure 1. Effectiveness (discounted quality-adjusted life years per person) and cost (discounted dollars per person) for screening strategies. FIT with 100% consistent screening participation and without additional patient support costs was cost-saving compared with no screening. MT-sDNA achieved effectiveness similar to the other strategies given the same levels of patient participation, but it was more costly. Participation rates of 50% consistent screening and 27% intermittent screening are representative of successful organized screening programs, and the results for FIT with these participation rates include patient support costs of $153 per testing cycle.

Yearly FIT required the highest number of lifetime tests per person, and screening colonoscopy required more than 2.5-fold as many colonoscopies as the alternatives (Table 2).

Organized Programs With High Participation Rates and Patient Support Costs

When we assumed screening behaviors with FIT and MT-sDNA of 50% consistent screeners, 27% intermittent screeners, and 23% never screeners, reflecting the most successful organized FIT screening programs, the estimated effectiveness of screening decreased compared with the optimal participation scenario (Figure 1 and Table 3 compared with Table 2). With these participation patterns and an additional $153 per patient per testing cycle for patient support for FIT (MT-sDNA test cost already includes a patient support program), yearly FIT remained less costly and more effective than MT-sDNA every 3 years, but it was no longer cost-saving compared with no screening (Table 3).

Assuming 50% consistent screeners and 27% intermittent screeners for all strategies, MT-sDNA every 3 years would need to cost 60% less than in the base case ($260 commercial payment and $197 Medicare payment) for yearly FIT including patient support costs of $153 per cycle to be rendered costly (>$100,000/QALY gained) compared with MT-sDNA every 3 years. If MT-sDNA every 3 years achieved participation rates of 68% consistent screeners and 32% intermittent screeners vs 50% consistent screeners and 27% intermittent screeners with FIT, then it cost $100,000 per QALY gained vs yearly FIT assuming base-case test costs.

Opportunistic Screening With Lower Participation Rates But No Program Patient Support Costs

When we assumed screening behaviors with FIT and MT-sDNA of 15% consistent screeners, 30% intermittent screeners, and 55% never screeners, the estimated effectiveness of screening decreased further (Table 4). If the patient support program that is included in the cost of MT-sDNA yielded participation rates more than 1.7-fold relative to FIT (>26% consistent screeners and >51% intermittent screeners with MT-sDNA), then MT-sDNA every 3 years cost less than $100,000 per QALY gained compared with yearly FIT.

Sensitivity Analyses

In nearly all one-way and multiway sensitivity analyses, FIT remained dominant or preferred over MT-sDNA (Table 5). The notable exception was once-only screening (Table 5).

Yearly MT-sDNA was more effective than yearly FIT, reflecting the net clinical benefit of better sensitivity despite worse specificity. However, yearly MT-sDNA was prohibitively costly compared with FIT (Table 5 and Supplementary Table 1). Even at MT-sDNA test costs lower than those of FIT, yearly MT-sDNA cost more than $385,000

Table 3. Clinical and Economic Outcomes for Hypothetical 100,000-Person Cohorts in Organized Fecal-Based Screening Programs Achieving High Participation Rates[a] From Age 50 to 80

	No screening	FIT every 2 years	MT-sDNA every 3 years	FIT yearly
CRC cases per 100,000 persons	5927	4039	3714	3464
CRC stage, number of cases per 100,000 persons (% of all cases)				
Localized	2373 (40)	2200 (54)	1915 (52)	1898 (55)
Regional	2210 (37)	1223 (30)	1206 (32)	1026 (30)
Distant	1345 (23)	615 (15)	594 (16)	539 (16)
CRC deaths per 100,000 persons	2316	1224	1173	1054
QALYs/person	18.6687	18.7171	18.7181	18.7236
Cost/person, $	3020	3212	4377	3806
Incremental cost/QALY gained (column compared with row)				
No screening	-	$3970	$27,500	$14,300
FIT every 2 years	-	-	$1,270,000	$92,400
MT-sDNA every 3 years	-	-	-	Dominates
Lifetime tests/person, mean				
Colonoscopies/person	0.1	0.7	1	1
Fecal tests/person	-	6.8	4.3	11.4

[a]50% consistent screeners, 27% intermittent screeners and 23% never-screeners, at an additional cost of $153/patient per FIT testing cycle for "patient support".

per QALY gained vs yearly FIT owing to its lower specificity and higher rate of colonoscopy in people with normal colons.

In the Monte Carlo simulation of cohorts with optimal participation, MT-sDNA every 3 years cost a median of $29,800 (95% confidence interval, $24,200–$34,600) per QALY gained compared with no screening, and a median of $943,000 (95% confidence interval, dominates-$19,800,000; 3.0% of iterations at <$500,000) per QALY gained compared with FIT every 2 years. Compared with MT-sDNA every 3 years, yearly FIT was more effective and less costly in 99.93% of iterations, and screening colonoscopy was more effective and less costly in 98.34% of iterations. At a willingness-to-pay threshold of $100,000 per QALY gained, the preferred strategy was yearly FIT in 99.3% of iterations, and FIT every 2 years in 0.7% of iterations. At a willingness-to-pay threshold of $50,000 per QALY gained, the preferred strategy was yearly FIT in 84.5% of iterations, and FIT every 2 years in 15.5% of iterations.

Discussion

Our study addressed the potential role of a novel MT-sDNA test that is more sensitive but less specific and has a higher per-test cost compared with FIT among the

Table 4. Clinical and Economic Outcomes for Hypothetical 100,000-Person Cohorts With Opportunistic Fecal-Based Screening[a] From Age 50 to 80

	No screening	FIT every 2 years	MT-sDNA every 3 years	FIT yearly
CRC cases per 100,000 persons	5927	4982	4806	4648
CRC stage, number of cases per 100,000 persons (% of all cases)				
Localized	2373 (40)	2293 (46)	2147 (45)	2149 (46)
Regional	2210 (37)	1720 (35)	1702 (35)	1590 (34)
Distant	1345 (23)	969 (19)	957 (20)	908 (20)
CRC deaths per 100,000 persons	2316	1760	1730	1642
QALYs/person	18.6687	18.6932	18.6937	18.6979
Cost/person, $	3020	2729	3648	2741
Incremental cost/QALY gained (column compared with row)				
No screening	-	Dominates	$25,100	Dominates
FIT every 2 years	-	-	$1,781,000	$2500
MT-sDNA every 3 years	-	-	-	Dominates
Lifetime tests/person, mean				
Colonoscopies/person	0.1	0.4	0.6	0.6
Fecal tests/person	-	3.3	2.1	5.6

[a]15% consistent screeners, 30% intermittent screeners and 55% never-screeners, without any additional cost per FIT testing cycle for "patient support".

alternatives to screen for colorectal neoplasia. Our results suggest that at comparable screening participation rates among strategies, FIT or screening colonoscopy are likely to be more effective and less costly than MT-sDNA. Because our modeling suggests that MT-sDNA potentially could achieve reductions in CRC incidence and mortality that are comparable with those with FIT or colonoscopy, depending on screening interval, it is reasonable to ask when MT-sDNA might be acceptable compared with the alternatives. Compared with an organized screening program of yearly FIT, with resources dedicated to patient support and achieving high FIT screening participation rates over time, a program of MT-sDNA testing every 3 years could be cost effective if the MT-sDNA program could achieve consistent participation by approximately two thirds of people, and intermittent participation by the rest. Alternatively, compared with opportunistic use of yearly FIT, without resources dedicated to patient support and achieving only modest FIT screening participation rates, MT-sDNA every 3 years could be cost effective at current MT-sDNA test costs if the patient support program that is included in its test cost could yield participation rates higher than 1.7-fold relative to the participation rates with FIT.

The efficacy of CRC screening strategies depends on test performance characteristics and testing interval, as well as participation rates. In the first screening cycle of a randomized controlled trial of FIT vs colonoscopy, the participation rate was higher with FIT than with colonoscopy, resulting in equal rates of CRC detection per group; advanced and nonadvanced adenomas were detected in more subjects in the colonoscopy group, but the cumulative adenoma detection rate in the FIT group is expected to increase with subsequent screening cycles.[42] In a randomized trial of once-only screening sigmoidoscopy, the contrasting reductions in CRC incidence and mortality in the per-protocol (33% and 43%) vs the intention-to-treat (23% and 31%) analyses highlight the importance of patient participation.[23] Sustained adherence over time is likely to be particularly important for tests that require short screening intervals to minimize the miss rates for treatable CRC or advanced CRC precursors.

Population-based data are accumulating that allow categorization of screening participation over time into various patterns. These patterns include consistent screening/re-participation, intermittent screening/re-participation (including delayed entry, drop out, and intermittent screening), and consistent refusal/nonresponse.[12,13] In 4 organized FIT programs and 1 organized gFOBT program in Europe and Australia, the rates of participation over 3–4 cycles have been 48%–56% consistent screeners, 14%–30% intermittent screeners, and 20%–29% nonresponders.[5,12,13,16,17] Kaiser Permanente in California has reported a 48% initial participation rate, and subsequent participation rates among those who remained eligible of 75%–86% over 4 cycles in a program of annual FIT.[6] A program in Hong Kong that includes only self-referred persons has reported participation rates over 4 FIT cycles of 70% consistent screeners, 28% intermittent screeners, and 2% nonresponders.[27] In contrast, in post-trial follow-up evaluation of a randomized controlled trial in San Francisco in which resources for continued patient navigation were no longer available, the cumulative rates of participation over 3 cycles of gFOBT were 21% consistent screeners, 58% intermittent screeners, and 21% nonresponders.[28] For comparison, randomized controlled trials of gFOBT achieved participation rates of 38%–60% consistent screeners, 21%–29% intermittent screeners, and 11%–40% nonresponders over 3–6 cycles with biennial screening,[21,29–32] and 46% consistent screeners, 44% intermittent screeners, and 10% nonresponders over 11 cycles with annual screening.[21] In our analyses, we accounted for these complex participation patterns, which is an important enhancement compared with previous cost-effectiveness analysis of CRC screening.

Patient support, which can include navigation,[43,44] has emerged as an important component of many CRC screening efforts. We and others have estimated that patient navigation for CRC screening is likely to be cost effective.[45,46] The total costs of planning and implementing a CRC screening program can be substantial.[14,15] Patient support costs in the Centers for Disease Control and Prevention's Colorectal Cancer Screening Demonstration Program averaged $153 per person over approximately 1 year, with a range of $72–$242.[15] This represented 7% (range, 2%–12%) of all program costs, with 32% (range, 23%–47%) of total costs related to clinical service delivery, and the rest related to program management, outreach, data collection, and other functions.[15] We did not include all of these other costs in our simulation because our focus was on incremental comparisons between screening strategies, and we reasoned that these other costs would approximately cancel out in these comparisons. MT-sDNA is unique among screening tests in that its cost covers a customer support center that calls patients to confirm test shipment information and review the collection process, ships kits, and works to ensure sample collection. Adding support costs of $153 per cycle only to FIT may be biased in favor of MT-sDNA, but FIT with these additional costs still dominated MT-sDNA when participation rates were equal. It remains to be determined what impact the MT-sDNA program has on one-time and sustained screening participation rates vs programmatic or opportunistic FIT screening.

Most information on screening test performance characteristics reflects one-time testing.[3,4,11] It is unclear whether the same sensitivities apply in subsequent screening cycles after a lesion has been missed. It is conceivable that a fraction of CRCs or advanced CRC precursors may be persistently silent with respect to the signals detected by a particular test (eg, blood, specific DNA changes, radiographic features, or endoscopic features). The available evidence suggests that subsequent cycles of FIT screening retain a reasonable yield, even if the initial screening has slightly higher sensitivity.[6,16,17] Previous modeling studies have not taken into account a possible degradation in test sensitivity for prevalent lesions from screening cycle to cycle. Our results were not affected substantially when FIT sensitivity was assumed to degrade with subsequent cycles within plausible ranges.[6] Future

Table 5. Sensitivity Analyses

Variable	Base-case value	Value in sensitivity analysis	MT-sDNA every 3 years vs no screening			FIT yearly vs MT-sDNA every 3 years		
			Incremental cost/person	Incremental QALYs/100,000 persons	ICER	Incremental cost/person[a]	Incremental QALYs/100,000 persons[a]	ICER
MT-sDNA sensitivity for small polyp/large polyp/CRC	0.17/0.42/0.93	Low range, 0.16/0.39/0.84	$2230	7043	$31,662	($2842)	790	FIT dominates[b]
		High range, 0.19/0.46/0.98	$2127	7542	$28,202	($2740)	290	FIT dominates[b]
MT-sDNA sensitivity for small polyp/large polyp/CRC/specificity	0.17/0.42/0.93/0.898	Low range, 0.16/0.39/0.84/0.889	$2238	7031	$31,831	($2851)	801	FIT dominates[b]
		High range, 0.19/0.46/0.98/0.907	$2119	7555	$28,043	($2731)	277	FIT dominates[b]
FIT sensitivity for small polyp/large polyp/CRC	0.076/0.24/0.733	Low range, 0.067/0.21/0.60	$2170	7363	$29,473	($2750)	225	FIT dominates[b]
		High range, 0.086/0.27/0.84	$2170	7363	$29,473	($2798)	605	FIT dominates[b]
FIT sensitivity for small polyp/large polyp/CRC/specificity	0.076/0.24/0.733/0.964	Low range, 0.067/0.21/0.60/0.958	$2170	7363	$29,473	($2692)	201	FIT dominates[b]
		High range, 0.086/0.27/0.84/0.969	$2170	7363	$29,473	($2849)	626	FIT dominates[b]
FIT sensitivity for CRC/specificity	0.733/0.964	Based on FIT meta-analysis,[4] 0.79/0.94	$2170	7363	$29,473	($2575)	445	FIT dominates[b]
		Based on FIT meta-analysis,[4] low range, 0.69/0.92	$2170	7363	$29,473	($2418)	269	FIT dominates[b]
		Based on FIT meta-analysis[4] High range 0.86/0.95	$2170	7363	$29,473	($2663)	539	FIT dominates[b]
FIT sensitivity for small polyp/large polyp/CRC	0.076/0.24/0.733	Decrease by 10% in round 2 and 10% in round ≥3 for a given prevalent lesion	$2170	7363	$29,473	($2774)	388	FIT dominates[b]
		Decrease by 10% in round 2 and 15% in round ≥3 for a given prevalent lesion	$2170	7363	$29,473	($2773)	371	FIT dominates[b]
		Decrease by 15% in round 2 and 15% in round ≥3 for a given prevalent lesion	$2170	7363	$29,473	($2768)	343	FIT dominates[b]
		Decrease by 15% in round 2 and 20% in round ≥3 for a given prevalent lesion	$2170	7363	$29,473	($2766)	324	FIT dominates[b]
Colonoscopy sensitivity for small polyp/large polyp/CRC	0.85/0.90/0.95	Low range, 0.80/0.85/0.90	$2202	7398	$29,766	($2788)	491	FIT dominates[b]
		High range, 0.90/0.95/0.97	$2128	7439	$28,600	($2779)	468	FIT dominates[b]

Table 5. Continued

Variable	Base-case value	Value in sensitivity analysis	MT-sDNA every 3 years vs no screening			FIT yearly vs MT-sDNA every 3 years		
			Incremental cost/person	Incremental QALYs/100,000 persons	ICER	Incremental cost/person[a]	Incremental QALYs/100,000 persons[a]	ICER
Colonoscopy bleeding rate[c]	0.0008	Low range, 0.0005	$2168	7363	$29,447	($2783)	469	FIT dominates[b]
		High range, 0.0014	$2174	7363	$29,525	($2782)	469	FIT dominates[b]
Colonoscopy perforation rate[c]	0.0004	Low range, 0.0002	$2167	7381	$29,354	($2783)	470	FIT dominates[b]
		High range, 0.0005	$2172	7354	$29,532	($2783)	469	FIT dominates[b]
Colonoscopy bleeding/perforation rates	0.0008/0.0004	0.004/0.002 (5-fold increase)	$2218	7220	$30,722	($2781)	468	FIT dominates[b]
Utilities for localized/regional/disseminated CRC	0.90/0.80/0.76	Low range, 0.76/0.65/0.54	$2170	8202	$26,457	($2783)	554	FIT dominates[b]
		High range, 0.98/0.95/0.93	$2170	6647	$32,645	($2783)	390	FIT dominates[b]
MT-sDNA cost commercial/Medicare	$649/$493	$70/$50	($444)	7363	MT-sDNA Dominates[b]	($169)	469	FIT dominates[b]
		$140/$100	($133)	7362.8	MT-sDNA Dominates[b]	($480)	469	FIT dominates[b]
		$210/$150	$178	7363	$2419	($791)	469	FIT dominates[b]
		$280/$200	$489	7363	$6643	($1102)	469	FIT dominates[b]
		$350/$250	$800	7363	$10,867	($1413)	469	FIT dominates[b]
		$420/$300	$1111	7363	$15,091	($1724)	469	FIT dominates[b]
		$560/$400	$1733	7363	$23,539	($2346)	469	FIT dominates[b]
Colonoscopy cost/with biopsy or polypectomy	$773/$975/$1391/$1755	$1237/$1560/$2226/$2808 (60% increase)	$2806	7363	$38,105	($2766)	469	FIT dominates[b]
		$464/$585/$835/$1053 (40% decrease)	$1746	7363	$23,717	($2794)	469	FIT dominates[b]
Colonoscopy bleeding/perforation costs	$6164/$16,778/$8321/$22,650	$12,328/$33,556/$16,643/$45,300 (2-fold increase)	$2182	7363	$29,637	($2782)	469	FIT dominates[b]
Colonoscopy cost/with biopsy or polypectomy/bleeding/perforation	$773/$975/$6164/$16,778/$1391/$1755/$8321/$22,650	$1160/$1463/$9246/$25,167/$2087/$2363/$12,482/$33,975 (50% increase)	$2706	7363	$36,749	($2768)	469	FIT dominates[b]
CRC care costs		(50% decrease)	$3083	7363	$41,875	($2710)	469	FIT dominates[b]
		(40% increase)	$1439	7363	$19,551	($2841)	469	FIT dominates[b]
Medicare costs for all ages	Medicare rates only for ages ≥65	Medicare rates for ages 50–64 and ≥65	$1432	7363	$19,450	($2223)	469	FIT dominates[b]

Table 5. Continued

Variable	Base-case value	Value in sensitivity analysis	MT-sDNA every 3 years vs no screening			FIT yearly vs MT-sDNA every 3 years		
			Incremental cost/person	Incremental QALYs/100,000 persons	ICER	Incremental cost/person[a]	Incremental QALYs/100,000 persons[a]	ICER
One-time testing only (instead of programmatic testing over time)	NA	At age 50	$481	1725	$27,862	($580)	(679)	MT-sDNA vs FIT $85,486
	NA	At age 60	$214	2767	$7736	($478)	(981)	MT-sDNA vs FIT $48,728
	NA	At age 70	($166)	2689	MT-sDNA dominates[b]	($222)	(795)	MT-sDNA vs FIT $27,884
MT-sDNA testing interval	3 years	1 year	$5268	7923	$66,483	($5880)	(91)	MT-sDNA vs FIT $6,460,000
		2 years	$3180	7873	$40,393	($3793)	(41)	MT-sDNA vs FIT $9,250,000
		4 years	$1668	6942	$24,029	($2281)	891	FIT dominates[b]
		5 years	$1312	6412	$20,459	($1924)	1421	FIT dominates[b]
For hypothetical cohorts in organized fecal-based screening programs achieving high participation rates[d]								
Patient support cost per FIT testing cycle	$153	Low range, $72	$1357	4941	$27,476	($1239)	550	FIT dominates[b]
		High range, $242	$1357	4941	$27,476	$162	550	$29,395

NOTE. For hypothetical cohorts with optimal (100%) participation, unless stated otherwise.
ICER, incremental cost-effectiveness ratio.
[a]Negative numbers are in parentheses.
[b]More effective and less costly than the comparator.
[c]95% confidence intervals in systematic review performed for US Preventive Services Task Force.[65]
[d]50% consistent screeners, 27% intermittent screeners, and 23% never-screeners.

studies should incorporate any emerging information on test performance characteristics of MT-sDNA or other tests from cycle to cycle.

A recent modeling study for the US Preventive Services Task Force examined the potential clinical impact of various screening strategies, including MT-sDNA, but it did not consider cost or imperfect participation.[47] That study's estimated clinical outcomes were similar to ours: MT-sDNA every 3 years yielded similar but slightly lower gains in life expectancy than yearly FIT or colonoscopy every 10 years; yearly MT-sDNA yielded greater gains in life expectancy than yearly FIT; and colonoscopy volume, which was used as a proxy for harm, was higher with yearly MT-sDNA than with yearly FIT. Our current analysis extends these observations by considering costs, including the economic costs of performing colonoscopy after false-positive stool tests, and by exploring the important dimension of screening participation patterns.

In our current analysis, yearly FIT yielded greater gains in discounted quality-adjusted life expectancy than colonoscopy every 10 years when optimal participation was assumed, despite the greater reductions in CRC incidence and CRC-related deaths with colonoscopy. This reflects the age-dependent distributions of CRC stages at diagnosis with the 2 strategies and the ages at which CRC cases and CRC-related deaths occur under each strategy, as well as the effects of quality-of-life adjustment and of discounting. These results point out the greater nuance incorporated into the outcome of QALYs gained in contrast with the outcomes of prevented CRC cases and CRC-related deaths.

In conclusion, at comparable levels of screening participation, a program of screening for colorectal neoplasia with MT-sDNA is likely to be dominated by programs based on FIT or colonoscopy. MT-sDNA may be a cost-effective alternative if it can achieve patient participation rates that are high enough compared with those of FIT that paying for its higher test cost can be justified.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.06.003.

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Conflicts of interest
This author discloses the following: Uri Ladabaum was a consultant to Exact Sciences Corporation in 2014, and currently serves as a consultant to Given Imaging and as a scientific advisor to Mauna Kea Technologies. The remaining author discloses no conflicts.

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Supplementary Appendix

Decision Analytic Model

We adapted our published, validated, decision analytic Markov cohort model of CRC screening in the United States for the current analyses. The original model for the general US population, its calibration, and initial validation have been described in detail.[1–6] The model was constructed in TreeAge Pro. The Natural History module reproduces the natural history and age-specific incidence and prevalence of colorectal adenomas and CRC by stage in the United States without screening.[1,3,5] Screening strategies are superimposed on the Natural History module.

The principal health states in the model are (Supplementary Figure 1) as follows: normal; small (<10 mm) adenomatous polyp; large (≥10 mm) adenomatous polyp; localized, regional, or distant CRC; and dead.[3,5] Approximately 85% of CRCs develop through a potentially identifiable precursor. In the Natural History module, CRCs are diagnosed with colonoscopy once they lead to symptoms. Screening from ages 50 to 80 years may identify adenomas and asymptomatic CRC. Diagnosed CRCs are treated, resulting in stage-specific survival. Patients with adenomas enter surveillance. Beginning at age 50 years, average-risk persons progress through the model for fifty 1-year cycles, until age 100 years or death. Age-specific non-CRC mortality rates reflect US life-table data.[7]

Model Validation

We have performed 4 validation exercises for the outcomes of CRC incidence and CRC mortality (and overall mortality when reported in the comparator clinical trial) predicted by our model, compared against the results of randomized controlled trials of FOBT and screening sigmoidoscopy, with the time horizon of each validation exercise determined by the time horizon of the comparator clinical trial.

FOBT. We reported our first validation exercise[3] against data from the Minnesota Colon Cancer Control Study.[8,9] FOBT screening was modeled by intent-to-treat as in the trial, assuming a mean age of 62 years; annual FOBT offered for 5 years, then not for 5 years, and then again for 6 years; adherence rates with at least 1 screening of 90% and all screenings of 46%; and complete bowel examination after 83% of abnormal FOBTs. For screening compared with no screening, our model predicted relative rates of CRC incidence of 0.79 vs 0.80 (confidence interval, 0.70–0.90) in the trial, and CRC mortality of 0.64 vs 0.67 (confidence interval, 0.50–0.87) in the trial.[8,9]

Sigmoidoscopy. We performed 3 validation exercises[10] against data from the United Kingdom Flexible Sigmoidoscopy Trial,[11] the SCORE Trial,[12] and the PLCO Cancer Screening Trial.[13]

For validation against the United Kingdom Flexible Sigmoidoscopy Trial,[11] screening sigmoidoscopy was modeled by intent-to-treat and per-protocol, assuming a population with a mean age of 60 years, once-only sigmoidoscopy taken up by 71% of persons, colonoscopic surveillance only after detection of a large adenoma, 11-year follow-up evaluation, and 60% of lesions within reach of the sigmoidoscope. For screening compared with no screening by intent-to-treat, our model predicted relative rates of CRC incidence of 0.75 vs 0.77 (confidence interval, 0.70–0.84) in the trial, CRC mortality rate of 0.67 vs 0.69 (confidence interval, 0.59–0.82) in the trial, and all-cause mortality rate of 0.99 vs 0.97 (confidence interval, 0.94–1.0) in the trial.[11] For screening compared with no screening per-protocol, our model predicted relative rates of CRC incidence of 0.65 vs 0.67 (confidence interval, 0.60–0.76) in the trial, CRC mortality rates of 0.55 vs 0.57 (confidence interval, 0.45–0.72) in the trial, and all-cause mortality rates of 0.99 vs 0.95 (confidence interval, 0.91–1.0) in the trial.[11]

For validation against the SCORE trial,[12] screening sigmoidoscopy was modeled by intent-to-treat and per-protocol as in the trial, assuming a population with a mean age of 60 years, once-only sigmoidoscopy taken up by 58% of persons, colonoscopic surveillance after detection of a small or large adenoma, 11-year follow-up evaluation, and 60% of lesions within reach of the sigmoidoscope. For screening compared with no screening by intent-to-treat, our model predicted relative rates of CRC incidence of 0.80 vs 0.82 (0.69–0.96) in the trial, and CRC mortality rate of 0.72 vs 0.78 (0.56–1.08) in the trial.[12] For screening compared with no screening per-protocol, our model predicted relative rates of CRC incidence of 0.65 vs 0.69 (0.56–0.86) in the trial, and CRC mortality of 0.55 vs 0.62 (0.40–0.96) in the trial.[12]

We performed a third validation exercise against data from the PLCO trial,[13] which was more complicated because of the variability in screening and endoscopic contamination in both the intervention and usual care control arms. Screening sigmoidoscopy was modeled as it was actually performed in the trial, assuming a population with a mean age of 63 years, colonoscopic surveillance after detection of a small or large adenoma, 11-year follow-up evaluation, and 60% of lesions within reach of the sigmoidoscope. Based on the actual reported rates of endoscopic testing in the intervention arm, we modeled 36% of persons undergoing sigmoidoscopy only once, 51% undergoing repeat sigmoidoscopy, and 6% undergoing colonoscopy during the screening period. Similarly, for the control arm we modeled 47% of persons undergoing screening by colonoscopy (34%) or sigmoidoscopy once (13%) during the screening period. For the intervention arm compared with usual care, our model predicted relative rates of CRC incidence of 0.83 vs 0.79 (0.72–0.85) in the trial, and CRC mortality of 0.72 vs 0.74 (0.63–0.87) in the trial.[13]

MT-sDNA Testing Interval

Screening with MT-sDNA yielded increasingly longer mean life expectancy, but also incurred higher costs, as screening frequency increased from every 5 years to every year (Supplementary Figure 2). In a sensitivity analysis in which Medicare payment rates were assumed for all ages, screening every 3 vs 4 years cost $92,000 per QALY gained (Supplementary Figure 3).

MT-sDNA every 4 or 5 years were both dominated by FIT every 2 years, and MT-sDNA every 1 or 2 years were both

prohibitively expensive compared with colonoscopy or yearly FIT (Supplementary Table 1 and Supplementary Figure 4).

In addition to the comparative cost-effectiveness results detailed above and in the body of the article, we were aware of the practical considerations that the Centers for Medicare and Medicaid Services has decided to cover MT-sDNA every 3 years. The sum of these findings and considerations justified focusing on MT-sDNA every 3 years in the subsequent primary analyses.

Principal FIT Comparator

We modeled FIT every 2 or 1 years because these are both clinically relevant strategies at present. In sensitivity analyses, we chose annual FIT as the primary comparator for MT-sDNA based on the same reasoning that we used to select the MT-sDNA interval. Yearly FIT was cost effective vs FIT every 2 years ($33,000/QALY gained), and yearly FIT is the most relevant clinical scenario in the United States at present.

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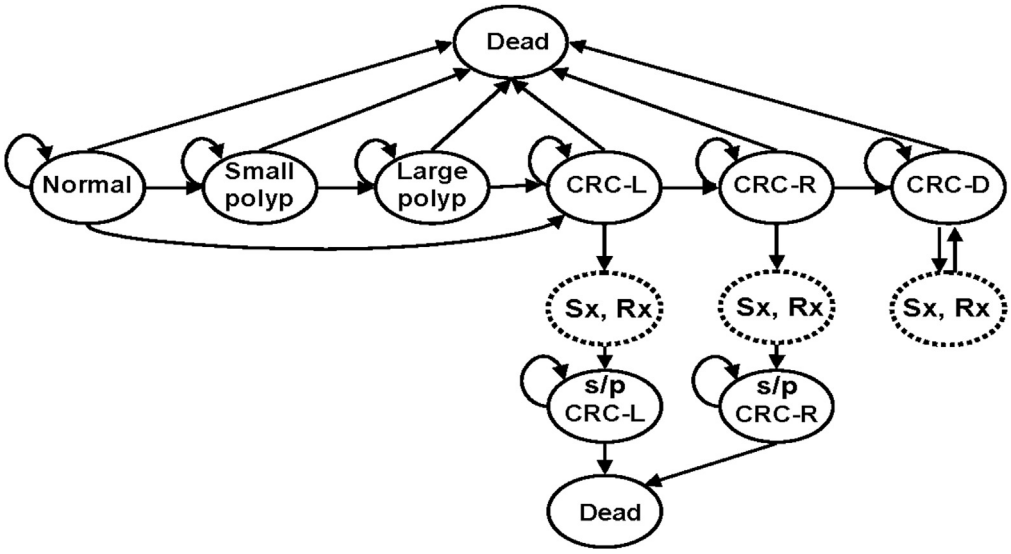
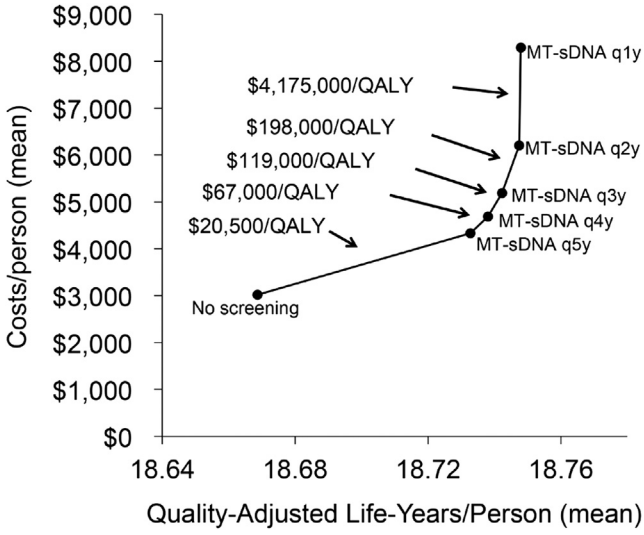
Supplementary Table 1. Base-Case Outcomes for Hypothetical 100,000-Person Cohorts With Optimal Screening Participation From Age 50 to 80, Including Various MT-sDNA Screening Intervals

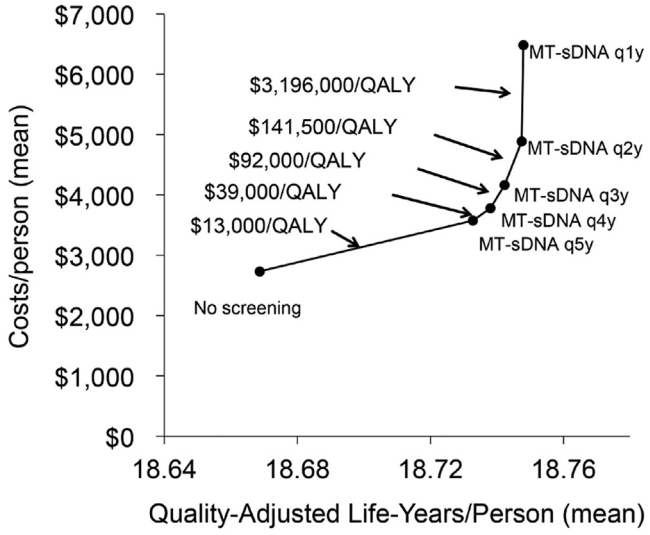
	No screening	MT-sDNA every 5 years	MT-sDNA every 4 years	FIT every 2 years	MT-sDNA every 3 years	Colonoscopy	FIT yearly	MT-sDNA every 2 years	MT-sDNA yearly
QALYs/person	18.6687	18.7328	18.7381	18.741	18.7423	18.7455	18.747	18.7474	18.7479
Cost/person, $	3020	4332	4688	2211	5190	4173	2407	6200	8287
Incremental cost-effectiveness ratios (column vs row)									
No Screening		$20,500	$24,000	Dominates	$29,500	$15,000	Dominates	$40,400	$66,500
MT-sDNA every 5 years			$67,200	Dominates	$90,400	Dominates	Dominates	$128,000	$262,000
MT-sDNA every 4 years				Dominates	$119,000	Dominates	Dominates	$163,000	$367,000
FIT every 2 years					$2,290,000	$436,000	$32,700	$623,000	$881,000
MT-sDNA every 3 years						Dominates	Dominates	$198,000	$553,000
Colonoscopy							Dominates	$1,070,000	$1,710,000
FIT yearly								$9,480,000	$6,530,000
MT-sDNA every 2 years									$4,170,000



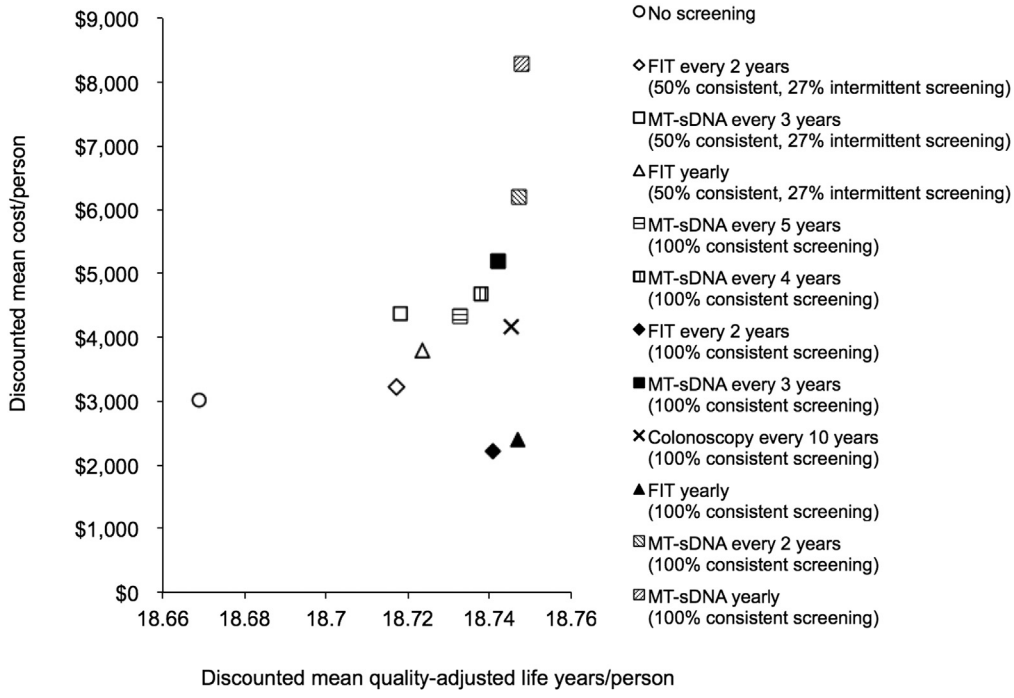
Supplementary Figure 1. Schematic of the natural history module in the decision analytic model. The principal health states in the model are normal, small adenomatous polyp, large adenomatous polyp, localized colorectal cancer (CRC-L), regional colorectal cancer (CRC-R), disseminated colorectal cancer (CRC-D), alive after treatment for localized colorectal cancer (s/p CRC-L), alive after treatment for regional colorectal cancer (s/p CRC-R), and dead. Without screening, colorectal cancer is diagnosed and treated (Rx) only after symptoms (Sx) develop.



Supplementary Figure 2. Effectiveness (discounted QALYs/person) and cost (discounted dollars/person) for screening with MT-sDNA at progressively higher frequencies. Each *arrow* points to a *line segment* whose slope is the incremental cost per QALY gained of the shorter vs the longer screening interval that are represented by the 2 points joined by the *line segment*.



Supplementary Figure 3. Effectiveness (discounted QALYs/person) and cost (discounted dollars/person) for screening with MT-sDNA at progressively higher frequencies (sensitivity analysis with Medicare costs assumed for all ages). Each *arrow* points to a *line segment* whose slope is the incremental cost per QALY gained of the shorter vs the longer screening interval that are represented by the 2 points joined by the *line segment*.



Supplementary Figure 4. Effectiveness (discounted QALYs/person) and cost (discounted dollars/person) for screening strategies.