Accepted Manuscript

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Please cite this article as: Ladabaum U, Mannalithara A, Comparative Effectiveness and Cost-Effectiveness of a Multi-target Stool DNA Test to Screen for Colorectal Neoplasia, *Gastroenterology* (2016), doi: 10.1053/j.gastro.2016.06.003.

Comparative Effectiveness and Cost-Effectiveness of a Multi-target Stool DNA Test

to Screen for Colorectal Neoplasia

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Running Title: Multitarget stool DNA for CRC screening

Word count: 5,530 (abstract, text, legends, references)   Figures: 1   Tables: 4

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Author roles: Study concept and design, UL; acquisition of data, UL, AM; analysis and interpretation of data, UL, AM; drafting of the manuscript, UL; critical revision of the manuscript for important intellectual content, UL, AM; statistical analysis, UL, AM; obtained funding, UL; technical, or material support, AM; study supervision, UL.

UL was a consultant to Exact Sciences Corporation in 2014, and currently serves as consultant to Given Imaging, and as scientific advisor to Mauna Kea Technologies. AM has no potential conflicts to report.

ABSTRACT

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 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) over 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 consistently participate and 32% to intermittently participate 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 MT-sDNA to be preferred over FIT at a threshold of $100,000/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 <$100,000/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/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 more common in the US than in the rest of the world.

Keywords: colon cancer; prevention; adherence; early detection

INTRODUCTION

Randomized controlled trials demonstrate 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 was recently reported to have superior sensitivity for CRC (92.3% vs 73.8%, P = 0.002) and advanced precancerous lesions (42.4% vs 23.8%, P<0.001), but inferior specificity (89.8% vs 96.4%, P<0.001), 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 are now being described (consistent screeners, late entrants, dropouts, intermittent screeners, consistent non-responders),[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 participation patterns as reported in the real world, allowing for differential participation rates among strategies, and incorporating the additional critical factors identified above.

METHODS

General study design

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

First, we explored the potential effectiveness and cost-effectiveness of screening with MT-sDNA at 1-5 year intervals in order 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 includes a patient support program (see Discussion). 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] SCORE Trial,[24] and PLCO Cancer Screening Trial,[25] have been detailed previously[19, 20, 26] (Appendix, Supplementary Figure 1, Table 1). The model reproduces the natural history of CRC precursors and CRC in the general U.S. 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; U.S. Life Tables data; and commercial and Medicare payments rates (Table 1 and Appendix). Persons enter the model at age 50 and screening and surveillance are offered from age 50 to 80, with persons followed until age 100 or death.

Screening participation behavior patterns

We created cohorts made up of sub-cohorts 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, dropout and intermittent; and consistent non-responders.[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 is 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 sub-subcohorts with participation probabilities/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 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 rates for commercial insurer carriers for persons age 50-64.[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 age 50-64 that were 1.35-fold those of persons age ≥65. "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 five years after CRC diagnosis. We estimated CRC cases by stage and CRC deaths, and lifetime number of tests/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 beta 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.

RESULTS

Multitarget stool DNA testing interval

The incremental cost/QALY gained increased in an accelerating fashion as the frequency of MT-sDNA screening increased (Appendix): *e.g.* $21,000/QALY gained for screening every 5 years vs no screening, $119,000/QALY gained for screening every 3 vs. 4 years, and $4,180,000/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/QALY gained (Supplementary Figure 3). Because MT-sDNA screening every 3 years cost approximately an incremental $100,000/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 & 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 towards earlier stage at diagnosis (Table 2).

Yearly FIT yielded the highest mean QALYs/person, followed by screening colonoscopy, MT-sDNA every 3 years, and FIT every 2 years (Table 2, Figure 1; see Supplementary Figure 4 for MT-sDNA at 1-5 year intervals). Compared with no screening, FIT every 1 or 2 years were both more effective and less costly, while screening colonoscopy cost $15,000/QALY gained

and MT-sDNA every 3 years cost $29,500/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/QALY gained compared with FIT every 2 years (Table 2).

Yearly FIT required the highest number of lifetime tests/person, and screening colonoscopy required >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 to the optimal participation scenario (Figure 1; Table 3 compared to Table 2). With these participation patterns and an additional $153/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/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/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 >1.7-fold relative to FIT (>26% consistent screeners and >51% intermittent screeners with MT-sDNA), then MT-sDNA every 3 years cost <$100,000/QALY gained compared with yearly FIT.

Sensitivity analyses

In nearly all one-way and multi-way 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; Supplementary Table 1). Even at MT-sDNA test costs lower than those of FIT, yearly MT-sDNA cost >$385,000/QALY gained vs yearly FIT, due 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 $29,800 (95% CI, $24,200-$34,600) per QALY gained compared with no screening, and a median $943,000 (95% CI, 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/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/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 addresses the potential role of a novel MT-sDNA test, which is more sensitive but less specific and has a higher per-test cost compared with FIT, among the 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 could potentially achieve reductions in CRC incidence and mortality that are comparable to those with FIT or colonoscopy, depending on screening interval, it is reasonable to ask when MT-sDNA might be acceptable compared to 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 >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 non-advanced adenomas were detected in more subjects in the colonoscopy group, but the cumulative adenoma detection rate in the FIT group is expected to rise 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 in order 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/non-response.[12, 13] In four organized FIT programs and one 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% non-responders.[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% non-responders.[27] In contrast, in post-trial follow-up 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% non-responders.[28] For comparison, randomized controlled trials of gFOBT achieved participation rates of 38-60% consistent screeners, 21-29% intermittent screeners, and 11-40% non-responders over 3-6 cycles with biennial screening,[21, 29-32] and 46% consistent screeners, 44% intermittent screeners, and 10% non-responders 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 CDC's Colorectal Cancer Screening Demonstration Program averaged $153/person over approximately 1 year, with a range of $72-242.[15] This represented 7% (2-12%) of all program costs, with 32% (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/cycle to FIT only 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 (*e.g.* blood,

specific DNA changes, radiographic 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 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 U.S. Preventive Services Task Force (USPSTF) 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 two 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.

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FIGURE LEGENDS

Figure 1. Effectiveness (discounted quality-adjusted life years per person) and cost (discounted dollars per person) for screening strategies. FIT, fecal immunochemical testing. MT-sDNA, multitarget stool DNA testing. FIT with 100% consistent screening participation and without additional patient support costs was cost-saving compared with no screening. MT-sDNA achieved similar effectiveness 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.

Table 1. Model Inputs

Variable	Base Case Value (Range)*	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 2y	54
Symptomatic presentation of regional cancer, %	40/y over 2y	54
Mortality rate from treated localized cancer, %	1.74/y in first 5y	54
Mortality rate from treated regional cancer, %	8.6/y in first 5y	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 under age 65, $ *		
FIT	19	[18]
MT-sDNA	649	[37]
Colonoscopy	1,391	[18]
Colonoscopy with lesion removal	1,755	[18]
Major hemorrhage after colonoscopy	8,321	[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	3,535	[18, 36]
Localized, colorectal cancer death	79,649	[18, 36]
Regional, initial	74,760	[18, 36]
Regional, continuing yearly	4,710	[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 and older, $ *		
FIT	22	[33]
MT-sDNA	493	[33]
Colonoscopy	773	[35]
Colonoscopy with lesion removal	975	[35]
Major hemorrhage after colonoscopy	6,164	[34, 35]
Perforation after colonoscopy	16,778	[34, 35]
Colorectal cancer care by stage		
Localized, initial	32,912	[36]
Localized, continuing yearly	2,619	[36]
Localized, colorectal cancer death	58,999	[36]
Regional, initial	55,378	[36]
Regional, continuing yearly	3,489	[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]

FIT, fecal immunochemical testing; MT-sDNA, multitarget stool DNA testing; SD, standard deviation.

* Range in Monte Carlo simulation; costs were varied within ±20% of base case values.

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	5,927	3,083	2,627	1,597	2,334
CRC stage, number of cases per 100,000 persons (% of all cases)					
Localized	2,373 (40%)	2,096 (68%)	1,673 (64%)	892 (56%)	1,625 (70%)
Regional	2,210 (37%)	714 (23%)	710 (27%)	512 (32%)	495 (21%)
Distant	1,345 (23%)	273 (9%)	244 (9%)	194 (12%)	214 (9%)
CRC deaths per 100,000 persons	2,316	694	628	445	519
QALYs/person	18.6687	18.7410	18.7423	18.7455	18.7470
Cost/person	$3,020	$2,211	$5,190	$4,173	$2,407
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

Table 3. Clinical and economic outcomes for hypothetical 100,000-person cohorts in organized fecal-based screening programs achieving high participation rates* from age 50 to 80

	No Screening	FIT every 2 years	MT-sDNA every 3 years	FIT yearly
CRC cases per 100,000 persons	5,927	4,039	3,714	3,464
CRC stage, number of cases per 100,000 persons (% of all cases)				
Localized	2,373 (40%)	2,200 (54%)	1,915 (52%)	1,898 (55%)
Regional	2,210 (37%)	1,223 (30%)	1,206 (32%)	1,026 (30%)
Distant	1,345 (23%)	615 (15%)	594 (16%)	539 (16%)
CRC deaths per 100,000 persons	2,316	1,224	1,173	1,054
QALYs/person	18.6687	18.7171	18.7181	18.7236
Cost/person	$3,020	$3,212	$4,377	$3,806
Incremental cost/QALY gained (column compared with row)				
No Screening	-	$3,970	$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

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

Table 4. Clinical and economic outcomes for hypothetical 100,000-person cohorts with opportunistic fecal-based screening* from age 50 to 80

	No Screening	FIT every 2 years	MT-sDNA every 3 years	FIT yearly
CRC cases per 100,000 persons	5,927	4,982	4,806	4,648
CRC stage, number of cases per 100,000 persons (% of all cases)				
Localized	2,373 (40%)	2,293 (46%)	2,147 (45%)	2,149 (46%)
Regional	2,210 (37%)	1,720 (35%)	1,702 (35%)	1,590 (34%)
Distant	1,345 (23%)	969 (19%)	957 (20%)	908 (20%)
CRC deaths per 100,000 persons	2,316	1,760	1,730	1,642
QALYs/person	18.6687	18.6932	18.6937	18.6979
Cost/person	$3,020	$2,729	$3,648	$2,741
Incremental cost/QALY gained (column compared with row)				
No Screening	-	Dominates	$25,100	Dominates
FIT every 2 years	-	-	$1,781,000	$2,500
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

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

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 [#]	Incremental QALYs/ 100,000 persons [#]	ICER
MT-sDNA sensitivity for small polyp/large polyp/CRC	0.17/0.42/ 0.93	Low range 0.16/0.39/ 0.84	$2,230	7,043	$31,662	($2,842)	790	FIT Dominates **
		High range 0.19/0.46/ 0.98	$2,127	7,542	$28,202	($2,740)	290	FIT Dominates **
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	$2,238	7,031	$31,831	($2,851)	801	FIT Dominates **
		High range 0.19/0.46/ 0.907	$2,119	7,555	$28,043	($2,731)	277	FIT Dominates **
FIT sensitivity for small polyp/large polyp/CRC	0.076/0.24 /0.733	Low range 0.067/0.21/ 0.60	$2,170	7,363	$29,473	($2,750)	225	FIT Dominates **
		High range 0.086/0.27/ 0.84	$2,170	7,363	$29,473	($2,798)	605	FIT Dominates **
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	$2,170	7,363	$29,473	($2,692)	201	FIT Dominates **
		High range 0.086/0.27/ 0.84/0.969	$2,170	7,363	$29,473	($2,849)	626	FIT Dominates **
FIT sensitivity for CRC/specificity	0.733/ 0.964	Based on FIT meta-analysis[4] 0.79/0.94	$2,170	7,363	$29,473	($2,575)	445	FIT Dominates **

		Based on FIT meta-analysis[4] Low range 0.69/0.92	$2,170	7,363	$29,473	($2,418)	269	FIT Dominates **
		Based on FIT meta-analysis[4] High range 0.86/0.95	$2,170	7,363	$29,473	($2,663)	539	FIT Dominates **
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	$2,170	7,363	$29,473	($2,774)	388	FIT Dominates **
		Decrease by 10% in round 2 and 15% in round ≥3 for a given prevalent lesion	$2,170	7,363	$29,473	($2,773)	371	FIT Dominates **
		Decrease by 15% in round 2 and 15% in round ≥3 for a given prevalent lesion	$2,170	7,363	$29,473	($2,768)	343	FIT Dominates **
		Decrease by 15% in round 2 and 20% in round ≥3 for a given prevalent lesion	$2,170	7,363	$29,473	($2,766)	324	FIT Dominates **
Colonoscopy sensitivity for small polyp/large polyp/CRC	0.85/0.90/ 0.95	Low range 0.80/0.85/ 0.90	$2,202	7,398	$29,766	($2,788)	491	FIT Dominates **

		High range 0.90/0.95/0.97	$2,128	7,439	$28,600	($2,779)	468	FIT Dominates **
Colonoscopy bleeding rate ***	0.0008	Low range 0.0005	$2,168	7,363	$29,447	($2,783)	469	FIT Dominates **
		High range 0.0014	$2,174	7,363	$29,525	($2,782)	469	FIT Dominates **
Colonoscopy perforation rate ***	0.0004	Low range 0.0002	$2,167	7,381	$29,354	($2,783)	470	FIT Dominates **
		High range 0.0005	$2,172	7,354	$29,532	($2,783)	469	FIT Dominates **
Colonoscopy bleeding/perforation rates	0.0008/ 0.0004	0.004/ 0.002 (five-fold increase)	$2,218	7,220	$30,722	($2,781)	468	FIT Dominates **
Utilities for localized/ regional/disseminated CRC	0.90/0.80/ 0.76	Low range 0.76/0.65/ 0.54	$2,170	8,202	$26,457	($2,783)	554	FIT Dominates **
		High range 0.98/0.95/ 0.93	$2,170	6,647	$32,645	($2,783)	390	FIT Dominates **
MT-sDNA cost commercial/Medicare	$649/$493	$70/50	($444)	7,363	MT-sDNA Dominates **	($169)	469	FIT Dominates **
		$140/100	($133)	7362.8	MT-sDNA Dominates **	($480)	469	FIT Dominates **
		$210/150	$178	7,363	$2,419	($791)	469	FIT Dominates **

		$280/200	$489	7,363	$6,643	($1,102)	469	FIT Dominates **
		$350/250	$800	7,363	$10,867	($1,413)	469	FIT Dominates **
		$420/300	$1,111	7,363	$15,091	($1,724)	469	FIT Dominates **
		$560/400	$1,733	7,363	$23,539	($2,346)	469	FIT Dominates **
Colonoscopy cost/with biopsy or polypectomy	$773/$975/$1,391/$1,755	$1,237/$1,560/$2,226/$2,808 (60% increase)	$2,806	7,363	$38,105	($2,766)	469	FIT Dominates **
		$464/$585/$835/$1,053(40% decrease)	$1,746	7,363	$23,717	($2,794)	469	FIT Dominates **
Colonoscopy bleeding/perforation costs	$6,164/$16,778/$8,321/$22,650	$12,328/$33,556/$16,643/$45,300 (two-fold increase)	$2,182	7,363	$29,637	($2,782)	469	FIT Dominates **
Colonoscopy cost/with biopsy or polypectomy/bleeding/perforation	$773/$975/$6,164/$16,778/$1,391/$1,755/$8,321/$22,650	$1,160/$1,463/$9,246/$25,167/$2,087/$2,363/$12,482/$33,975 (50% increase)	$2,706	7,363	$36,749	($2,768)	469	FIT Dominates **
CRC care costs		(50% decrease)	$3,083	7,363	$41,875	($2,710)	469	FIT Dominates **

		(40% increase)	$1,439	7,363	$19,551	($2,841)	469	FIT Dominates **
Medicare costs for all ages	Medicare rates only for ages ≥65	Medicare rates for ages 50-64 and ≥65	$1,432	7,363	$19,450	($2,223)	469	FIT Dominates **
One-time testing only (instead of programmatic testing over time)	NA	At age 50	$481	1,725	$27,862	($580)	(679)	MT-sDNA vs FIT $85,486
	NA	At age 60	$214	2,767	$7,736	($478)	(981)	MT-sDNA vs FIT $48,728
	NA	At age 70	($166)	2,689	MT-sDNA Dominates **	($222)	(795)	MT-sDNA vs FIT $27,884
MT-sDNA testing interval	3 years	1 year	$5,268	7,923	$66,483	($5,880)	(91)	MT-sDNA vs FIT $6,460,000
		2 years	$3,180	7,873	$40,393	($3,793)	(41)	MT-sDNA vs FIT $9,250,000
		4 years	$1,668	6,942	$24,029	($2,281)	891	FIT Dominates **
		5 years	$1,312	6,412	$20,459	($1,924)	1,421	FIT Dominates **
For hypothetical cohorts in organized fecal-based screening programs achieving high participation rates****								
Patient support cost per FIT testing cycle	$153	Low range $72	$1,357	4,941	$27,476	($1,239)	550	FIT Dominates **
		High range $242	$1,357	4,941	$27,476	$162	550	$29,395

* For hypothetical cohorts with optimal (100%) participation, unless stated otherwise.

** More effective and less costly than the comparator.

*** 95% confidence intervals in systematic review performed for US Preventive Services Task Force.[65]

**** 50% consistent screeners, 27% intermittent screeners and 23% never-screeners

Negative numbers are in parentheses

CRC, colorectal cancer; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; FIT, fecal immunochemical testing; MT-sDNA, multitarget stool DNA testing.
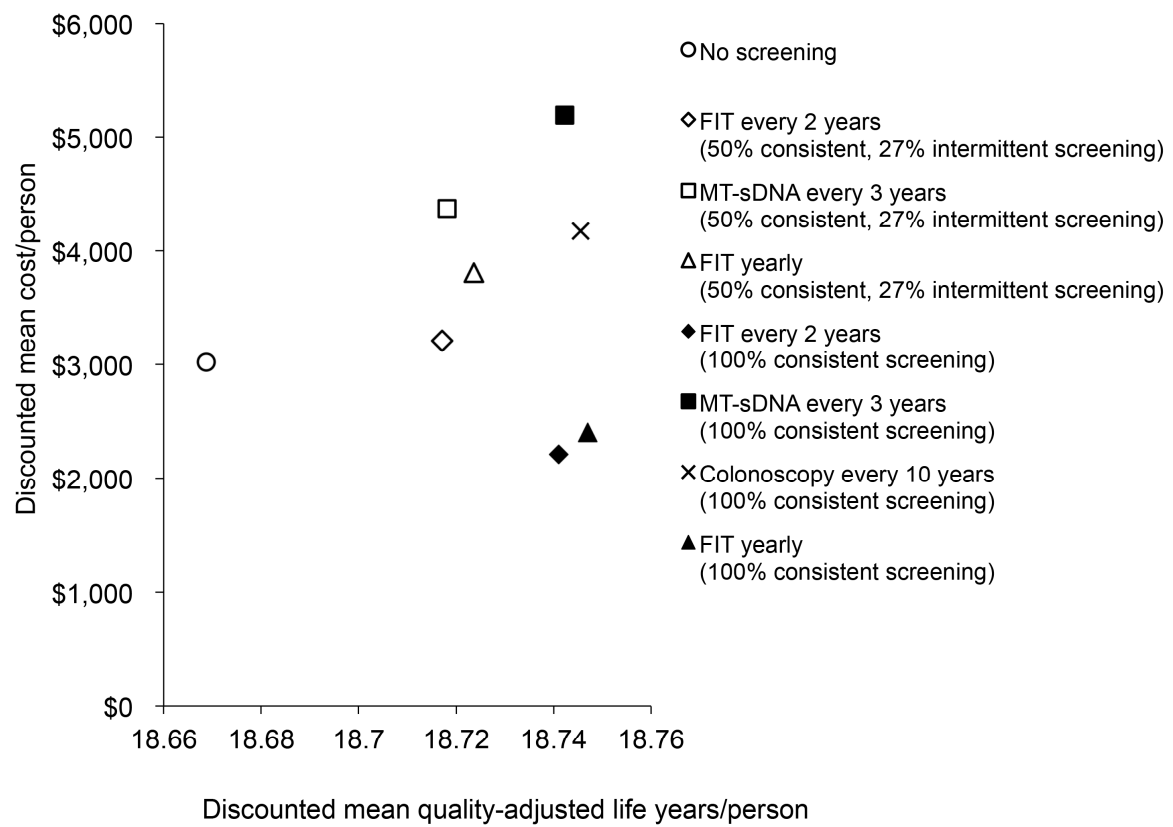
SUPPLEMENTARY APPENDIX

Decision analytic model

We adapted our published, validated decision analytic Markov cohort model of CRC

screening in the U.S for the current analyses. The original model for the general U.S. population,

its calibration and initial validation have been described in detail.[1-6] The model is constructed in

TreeAge Pro (TreeAge Software, Inc., Williamstown, MA). The Natural History module

reproduces the natural history and age-specific incidence and prevalence of colorectal adenomas

and CRC by stage in the U.S. without screening.[1, 3, 5] Screening strategies are superimposed on

the Natural History module.

The principal health states in the model are (Supplemental Figure 1): 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 50 1-year cycles, until age 100 years or death. Age-specific non-CRC mortality rates reflect

U.S. life table data.[7]

Model validation

We have performed four 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 mean age 62 years; annual FOBT offered for 5 years, then not for 5 years, and then again for 6 years; adherence rates with at least one screening of 90% and all screenings of 46%; and complete bowel exam 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 (CI 0.70-0.90) in the trial, and CRC mortality of 0.64 *vs.* 0.67 (CI 0.50-0.87) in the trial.[8, 9]

Sigmoidoscopy

We have performed three 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 of mean age 60 years, once-only sigmoidoscopy taken up by 71% of persons, colonoscopic surveillance only after detection of a large adenoma, 11 year follow-up, 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 (CI 0.70-0.84) in the trial, CRC mortality of 0.67 *vs.* 0.69 (CI 0.59-0.82) in the trial, and all-cause mortality of 0.99 *vs.* 0.97 (CI 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 (CI 0.60-0.76) in the trial, CRC

mortality of 0.55 *vs.* 0.57 (CI 0.45-0.72) in the trial, and all-cause mortality of 0.99 *vs.* 0.95 (CI

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 of mean age 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, 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 to 0.96) in the trial, and CRC

mortality 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 to 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 due to 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 of mean age 63 years, colonoscopic

surveillance after detection of a small or large adenoma, 11 year follow-up, 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 to usual care, our model predicted relative rates of CRC incidence of 0.83 *vs.* 0.79 (0.72 to 0.85) in the trial, and CRC mortality of 0.72 *vs.* 0.74 (0.63 to 0.87)) in the trial.[13]

Multitarget stool DNA (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/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 paper, we were aware of the practical considerations that CMS 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 U.S. at present.

SUPPLEMENTARY FIGURE LEGENDS

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 following treatment for localized colorectal cancer (s/p CRC-L), alive following 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 quality-adjusted life years per person) and cost (discounted dollars per person) for screening with MT-sDNA at progressively higher frequencies. Each arrow points to a line segment whose slope is the incremental cost per quality-adjusted life-year (QALY) gained of the shorter *vs.* the longer screening interval that are represented by the two points joined by the line segment.

Supplementary Figure 3. Effectiveness (discounted quality-adjusted life years per person) and cost (discounted dollars per 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 quality-adjusted life-year (QALY) gained of the shorter *vs.* the longer screening interval that are represented by the two points joined by the line segment.
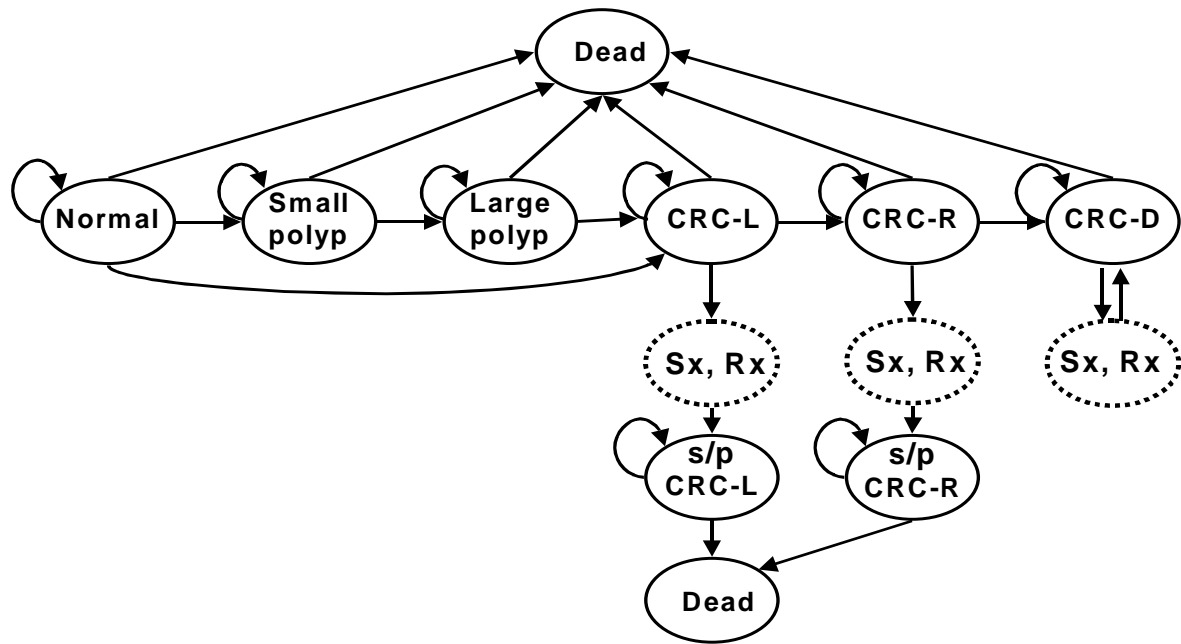
Supplementary Figure 4. Effectiveness (discounted quality-adjusted life years per person) and

cost (discounted dollars per person) for screening strategies. FIT, fecal immunochemical testing.

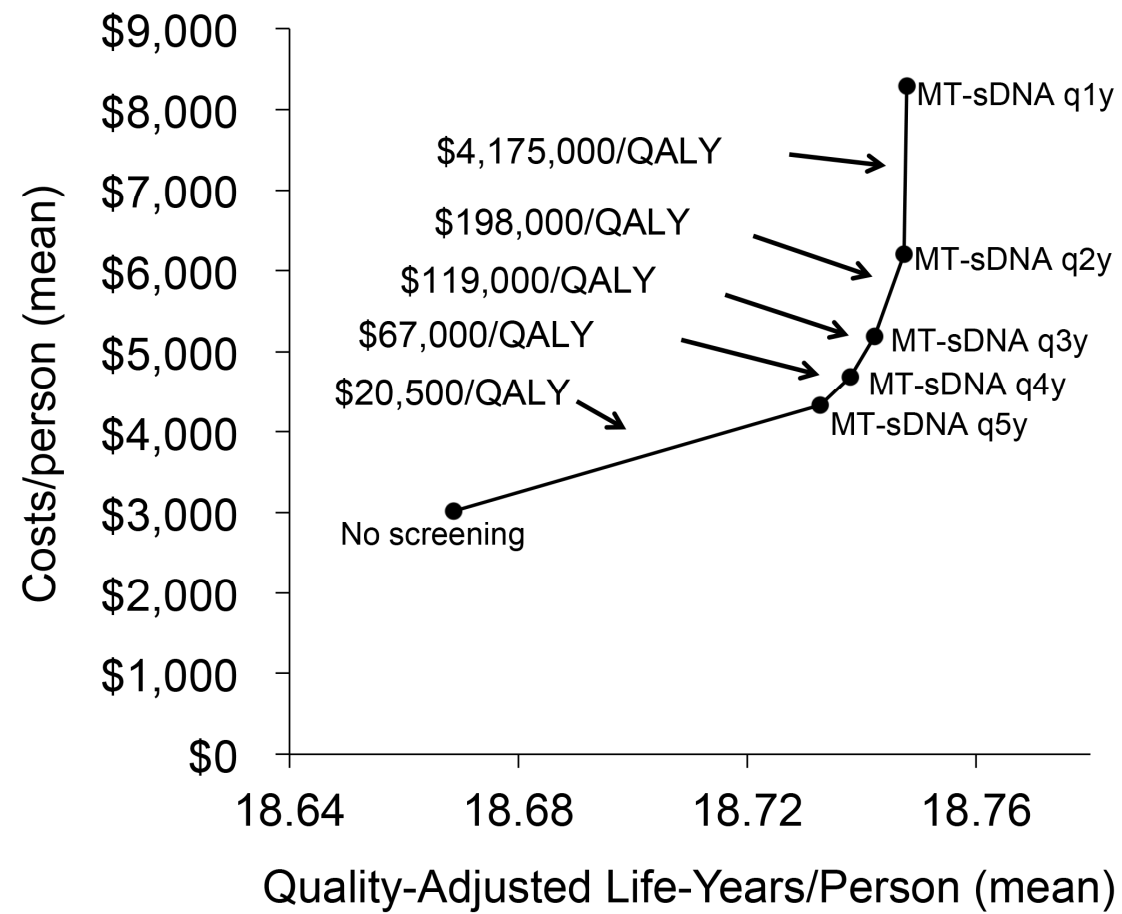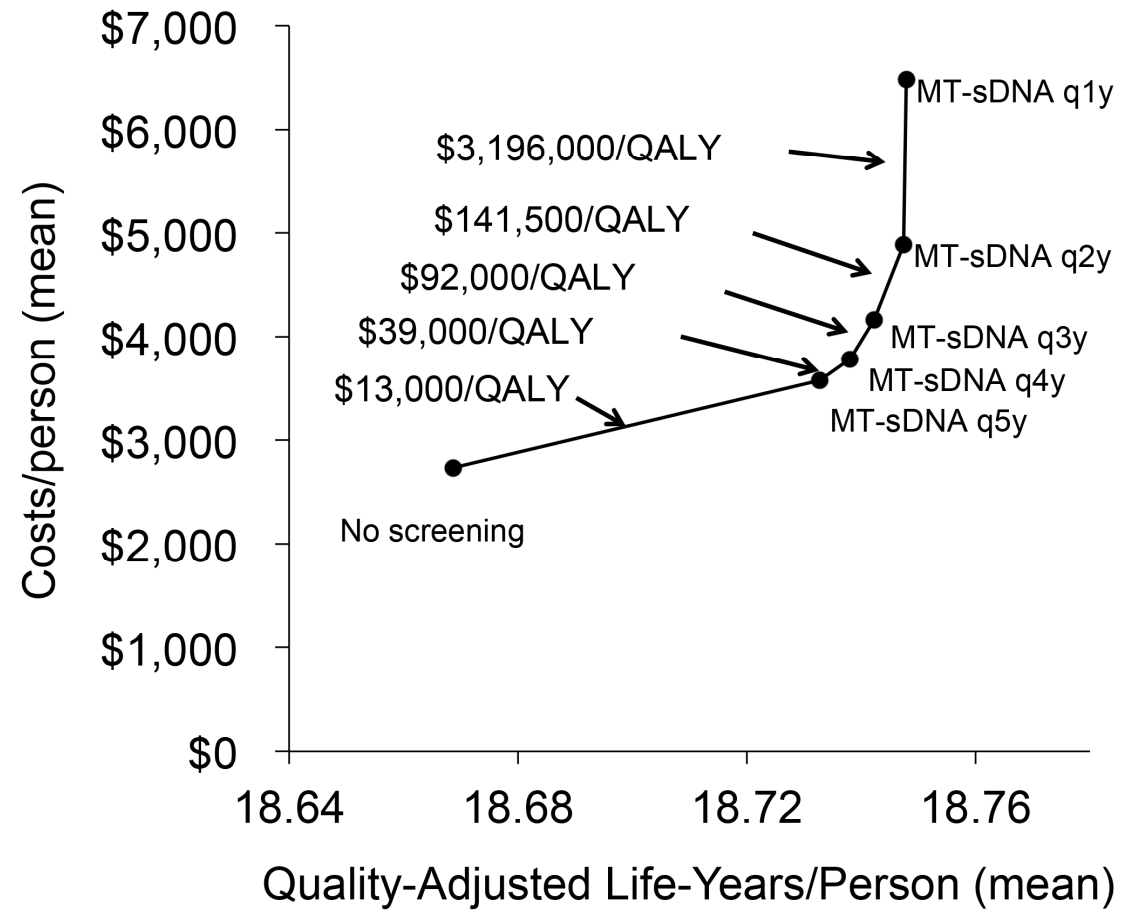MT-sDNA, multitarget stool DNA testing.

Supplementary Table 1

|	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	$3,020	$4,332	$4,688	$2,211	$5,190	$4,173	$2,407	$6,200	$8,287
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

Supplementary Figure 2

Supplementary Figure 3

Supplementary Figure 4
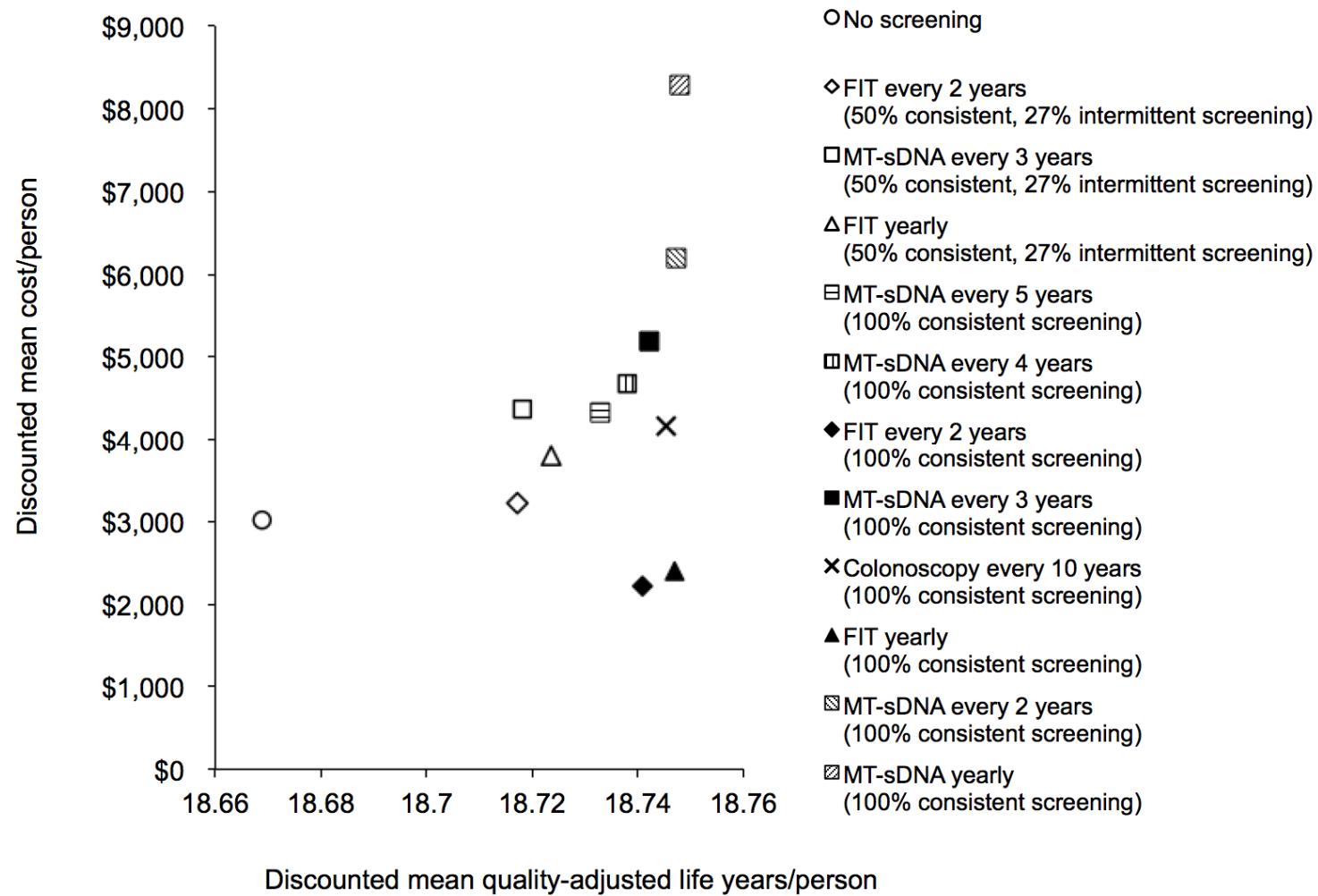
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