SUPPLEMENTARY MATERIALS

Supplementary Methods

Cost-accounting

Prospective cost-accounting was embedded in the intervention arm of the randomized controlled trial of persons aged 50-75 years who were not up-to-date with colorectal cancer (CRC) screening (NCT02613260, initiated December 2015). We reviewed published literature on CRC screening program costs and decided to use cost categories defined by the Centers for Disease Control and Prevention Colorectal Cancer Screening Demonstration Project. We selected the relevant cost categories for the current study from the CDC's project participants user guide for cost collection.[1] The program components were separated into sets of fixed or variable costs. The variable costs consisted of the various activities performed by the program manager and outreach workers. Clinical activities were considered separately from research activities. Data related to staff time and costs associated with outreach activities and materials were collected in three 2-month periods (February - March and September - October 2016 and June - July 2017) in an electronic database.

During these three time periods, we accounted for all direct patient-related activities (assembling kits, postcard and kit mailings, phone calls, data management) as well as program-related activities (budgeting, hiring, assessment of outreach workers, inventory and supplies management). Average minutes spent per patient on each activity were calculated and average costs per patient were estimated based on individual salaries and benefits of responsible staff. In addition, average costs of materials and supplies per

patient were calculated. The total average per patient cost associated with outreach was calculated as the sum of the average costs per patient of direct patient related activities, program related activities and materials per patient. One-time start-up costs to establish the program, including staff training, were ascertained separately.

For the calls preceding direct mail of FIT kits, 43% of calls connected with an individual, 33% resulted in a voicemail, 9% could not be reached, and 15% were not called (e.g., already up to date, moved, no longer active in network.). During reminder phone calls, 30% of patients answered their phones over two attempted calls, 31% were left voicemails, 9% could not be reached, and 30% were not called.

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.[2-7] 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.[2,4,6] Screening strategies are superimposed on the Natural History module.

Persons transition between health states of normal, small polyp, large polyp, localized, regional or disseminated CRC, and dead, in 1-year cycles (Figure A2). 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.[8]

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 is superimposed on the natural history module, resulting in CRC prevention or early detection as determined by screening test performance characteristics, and patient participation.[4,9,10] Screening and surveillance are offered from age 50 to 80, with persons followed until age 100 or death. If fecal immunochemical test (FIT) is positive, colonoscopy is offered, and if colonoscopy is normal, the screening test is assumed to be a false-positive and screening is resumed in 10 years with FIT. With colonoscopy, polyps are removed and CRCs are biopsied if detected. Persons with adenomas enter colonoscopic surveillance as described previously [2,4,6,7]. Colonoscopy is performed within one year of CRC diagnosis, and three years and then every five years after CRC diagnosis.[11]

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 Medicare payments rates (Appendix Table 1).

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 fecal occult blood testing (FOBT) and screening sigmoidoscopy, with the time horizon of each validation exercise determined by the time horizon of the comparator clinical trial.

FOBT

Our first validation exercise[4] was against data from the Minnesota Colon Cancer Control Study.[12,13] FOBT screening was modeled by intent-to-treat as in the trial, assuming mean age 62 years; annual FOBT offered for five years, then not for five years, and then again for six 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.[12,13]

Sigmoidoscopy

We performed three validation exercises[9] against data from the United Kingdom Flexible Sigmoidoscopy Trial,[14] the SCORE Trial,[15] and the PLCO Cancer Screening Trial.[16] For validation against the United Kingdom Flexible Sigmoidoscopy Trial,[14] 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.[14] 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.[14]

For validation against the SCORE trial,[15] 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.[15] 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.[15]

We performed a third validation exercise against data from the PLCO trial,[16] 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.[16]

Cost-effectiveness Analysis

General study design for cost-effectiveness Analysis

We adapted our validated model of CRC screening in the general U.S. population[4,9] to allow complex screening participation patterns over time and to consider the incremental cost of patient outreach for FIT-based CRC screening. First, we explored the potential effectiveness and cost-effectiveness of patient outreach to improve FIT-based screening participation rates, based on the clinical and economic results of the prospective randomized trial. Second, we performed sensitivity analyses as described below.

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, who participated at least once over two cycles of screening including late entry and dropouts; and consistent non-responders.[17,18] The population proportions in each group were derived based on the 2-year participation rates in our prospective trial. The ratios for consistent to intermittent screeners observed in the trial were 1.8:1 with the outreach intervention and 0.65:1 with usual care. Published studies suggest that, among intermittent screeners, the fraction of screening cycles completed is distributed relatively evenly from the minimum to maximum possible.[12,17-28] 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. As in our previous published work, we extrapolated these screening behavior patterns over the simulation's time horizon.

In the base case, the overall screening participation rate with outreach was 57.9% in the first cycle, with 45.3% consistent and 25.1% intermittent screeners over time; with usual care, the overall screening participation rate was 37.4% in the first cycle, with 21.2% consistent and 32.5% intermittent screeners over time. In sensitivity analyses, we covered the higher and lower ends of participation rates observed across clinics in our prospective trial.

Cost inputs

Base case cost inputs were derived from Medicare reimbursement rates[29-31] and estimated CRC care costs[32] and updated to 2018 dollars using the medical component of the consumer price index (Appendix Table A1). Base case outreach related costs were derived from our prospective cost accounting in the clinical trial. In sensitivity analysis, we explored the outreach cost threshold that would make outreach cost-saving, as well as illustrative lower end and higher end values (e.g. $50for outreach including FIT kit costs).

Colonoscopy follow-up rate after a positive FIT test

In the base case, the follow-up rate for colonoscopy was 55.6% with both outreach and usual care, based on the rate at which patients completed a colonoscopy within a year after a positive FIT in a previous retrospective cohort study conducted in the same integrated safety-net system.[33] In sensitivity analysis we considered a 20% higher follow-up rate of

colonoscopy with navigation for follow-up colonoscopy, as we have modeled previously for screening colonoscopy based on published literature on navigation.[34,35]

Clinical and economic outcomes

The principal model outputs were quality-adjusted life-years (QALYs) and costs per person.[36,37] Future QALYs and costs were discounted by 3% annually.[38] Health state utilities for CRC by stage (Appendix Table 1) were used to calculate QALYs by applying these for five years after CRC diagnosis.

Cost-effectiveness analyses

Analyses from the perspective of a third-party payer[39] were performed in TreeAge Pro (TreeAge Software, Inc., Williamstown, MA) and Excel 2010 (Microsoft Corporation, Redmond, WA). Incremental cost-effectiveness ratios were calculated.[36,37] A base case analyses and sensitivity analyses were performed as detailed above.

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Supplementary Tables

Supplementary Table 1. Model Inputs

Variable	Base Case Value (Range)*	References
Clinical		
Polyp prevalence at age 50, %	15	Vatn, et al., 1982 (40), Williams, et al., 1982(41), Clark, et al., 1985(42)
small polyp, %	95	Williams, et al., 1982(41), Arminski, et al., 1964(43), Rickert, et al., 1979(44)
large polyp, %	5	Williams, et al., 1982(41), Arminski, et al., 1964(43), Rickert, et al., 1979(44)
Annual transition rate to small polyp from normal , %	Age specific, 1.1-1.9	Vatn, et al., 1982 (40), Williams, et al., 1982(41), Clark, et al., 1985(42), Arminski, et al., 1964(43), Rickert, et al., 1979(44)
Annual transition rate to large polyp from small polyp , %	1.5	Williams, et al., 1982(41), Arminski, et al., 1964(43), Rickert, et al., 1979(44)
Annual transition rate to cancer without polypoid precursor, %	Age specific, 0.006-0.086	Vatn, et al., 1982 (40), Williams, et al., 1982(41), Clark, et al., 1985(42), Wagner, et al., 1996 (45), Ries, et al., 1997, (46)
Annual transition rate to cancer from large polyp, %	5	Vatn, et al., 1982 (40), Williams, et al., 1982(41), Clark, et al., 1985(42), Wagner, et al., 1996 (45), Ries, et al., 1997, (46)
Symptomatic presentation of localized cancer, %	22/y over 2y	Ries, et al., 1997, (46)
Symptomatic presentation of regional cancer, %	40/y over 2y	Ries, et al., 1997, (46)
Mortality rate from treated localized cancer, %	1.74/y in first 5y	Ries, et al., 1997, (46)
Mortality rate from treated regional cancer, %	8.6/y in first 5y	Ries, et al., 1997, (46)
Mean survival from distant cancer, y	1.9	Ries, et al., 1997, (46), Bernold, et al., 2006(47), Cunningham, et al., 2004(48), Goldberg, et al., 2004(49), Hurwitz, et al.,

		2004(50), Kabbinavar, et al., 2003(51), Meyerhardt, et al., 2005(52), Saltz, et al., 2004(53)
Mortality rate from cancer treatment, %	2	Wagner, et al., 1996 (45), Winawer, et al., 1997(54)
Test performance characteristics and complications		
FIT sensitivity for cancer, %	73.3 (60.3-83.9)	Imperiale, et al., 2014(55)
FIT sensitivity for large polyp, %	23.8 (20.8-27.0)	Imperiale, et al., 2014(55)
FIT sensitivity for small polyp, %	7.6 (6.7-8.6)	Imperiale, et al., 2014(55)
FIT specificity, %	96.4 (95.8-96.9)	Imperiale, et al., 2014(55)
Colonoscopy sensitivity for cancer, %	95 (90-97)	van Rijn, et al., 2006(56), Pickhardt, et al., 2003(57)
Colonoscopy sensitivity for large polyp, %	90 (85-95)	van Rijn, et al., 2006(56), Pickhardt, et al., 2003(57)
Colonoscopy sensitivity for small polyp, %	85 (80-90)	van Rijn, et al., 2006(56), Pickhardt, et al., 2003(57)
Colonoscopy major hemorrhage rate, %	0.08 (0.05-0.14)	Lin, et al., 2015(58)
Colonoscopy perforation rate, %	0.04 (0.02-0.05)	Lin, et al., 2015(58)
Mortality rate given endoscopic perforation, %	7.5 (4.5-16)	Rabeneck, et al., 2008(59), Gatto, et al., 2003(60), Anderson, et al., 2000(61)
Health state utilities		
Localized colorectal cancer	0.90 (SD 0.06)	Ramsey, et al., 2000(62)
Regional colorectal cancer	0.80 (SD 0.22)	Ramsey, et al., 2000(62)
Distant colorectal cancer	0.76 (SD 0.11)	Ramsey, et al., 2000(62)
Costs, $		
FIT	19.64	Centers for Medicare & Medicaid Services, 2018(29)
Colonoscopy	710	Centers for Medicare & Medicaid Services, 2018(30)
Colonoscopy with lesion removal	1,013	Centers for Medicare & Medicaid Services, 2018(30)

Major hemorrhage after colonoscopy	6,096	Centers for Medicare & Medicaid Services, 2018(30), Centers for Medicare & Medicaid Services, 2018(31)
Perforation after colonoscopy	16,599	Centers for Medicare & Medicaid Services, 2018(30), Centers for Medicare & Medicaid Services, 2018(31)
Colorectal cancer care by stage		
Localized, initial	35,888	Zauber, et al., 2007(32)
Localized, continuing yearly	2,856	Zauber, et al., 2007(32)
Localized, colorectal cancer death	64,335	Zauber, et al., 2007(32)
Regional, initial	60,387	Zauber, et al., 2007(32)
Regional, continuing yearly	3,805	Zauber, et al., 2007(32)
Regional, colorectal cancer death	67,598	Zauber, et al., 2007(32)
Distant, initial	78,854	Zauber, et al., 2007(32)
Distant, colorectal cancer death	90,721	Zauber, et al., 2007(32)
FIT outreach related costs		
FIT kit	4.50	Current study
FIT kit processing cost	15.14	Current study
FIT outreach (not including the cost of FIT kit)	18.47	Current study
Implementation and training cost once every 10 years	2.97	Current study
Navigation cost for colonoscopy after a positive FIT test		
Completer cost	28.83	Jandorf, et al., 2013(34), Ladabaum, et al., 2015(35)
Non-completer cost	21.4	Jandorf, et al., 2013(34), Ladabaum, et al., 2015(35)

*FIT, fecal immunochemical testing; SD, standard deviation; y, year.

Supplementary Table 2. Colonoscopy follow-up rates after abnormal FIT tests among those assigned to usual care and outreach intervention

Clinic	Outreach			Usual Care		
	No. of FIT Positive	No. of Colonoscopies	Follow-up, %	No. of FIT Positive	No. of Colonoscopies	Follow-up, %
1	52	36	69.2	23	16	69.6
2	13	9	69.2	6	3	50.0
3	21	8	38.1	7	5	71.4
4	29	12	41.4	12	6	50.0
5	20	11	55.0	25	12	48.0
6	44	12	27.3	19	8	42.1
7	13	9	69.2	5	2	40.0
8	16	9	56.3	14	5	35.7
Total	208	106	51.0	111	57	51.4

Supplementary Table 3. Patient responses to reminder calls

Barrier	Responses, n (%)	Up-to-date after call, %
Forgot/Not a priority/Busy	330 (26.4)	62.7
Returned test already/completed test but not mailed	300 (24.0)	90.7
Did not receive/lost test/did not check the mail/test damaged	191 (15.3)	61.8
Did not understand how to complete test	133 (10.7)	77.4
Other health problems/stool/bowel movement	115 (9.2)	54.8
Not in residence for extended period	66 (5.3)	54.5
Doesn't want the test/wants colonoscopy/ doesn't see need	46 (3.7)	23.9
Other	38 (3.0)	50.0
Too embarrassing or unpleasant/fearful of results	30 (2.4)	50.0
Total	1249 (100.0)	67.6

Supplementary Table 4. Startup Costs

Itemized Cost	Units	Unit cost	Total cost
Audio Processor	2	$68.87	$137.74
Headset	2	$99.45	$198.90
Docking station	3	$130.89	$392.67
Computers	2	$1,359.20	$2,718.40
Computer	1	$1,653.58	$1,653.58
Printer	1	$685.34	$685.34
Keyboard Trays	2	$289.90	$579.80
Furniture	1	$3,705.65	$3,705.65
Keyboards	3	$15.39	$46.17
Mouse	3	$16.93	$50.79
Warranty	3	$129.99	$389.97
Phones	3	$246.67	$740.00
Health Coaching Training	3	$500.00	$1,500.00
UCSF/SFGH Startup	--	--	$885.42
Training	--	--	$2,312.28
Total	--	--	$15,997

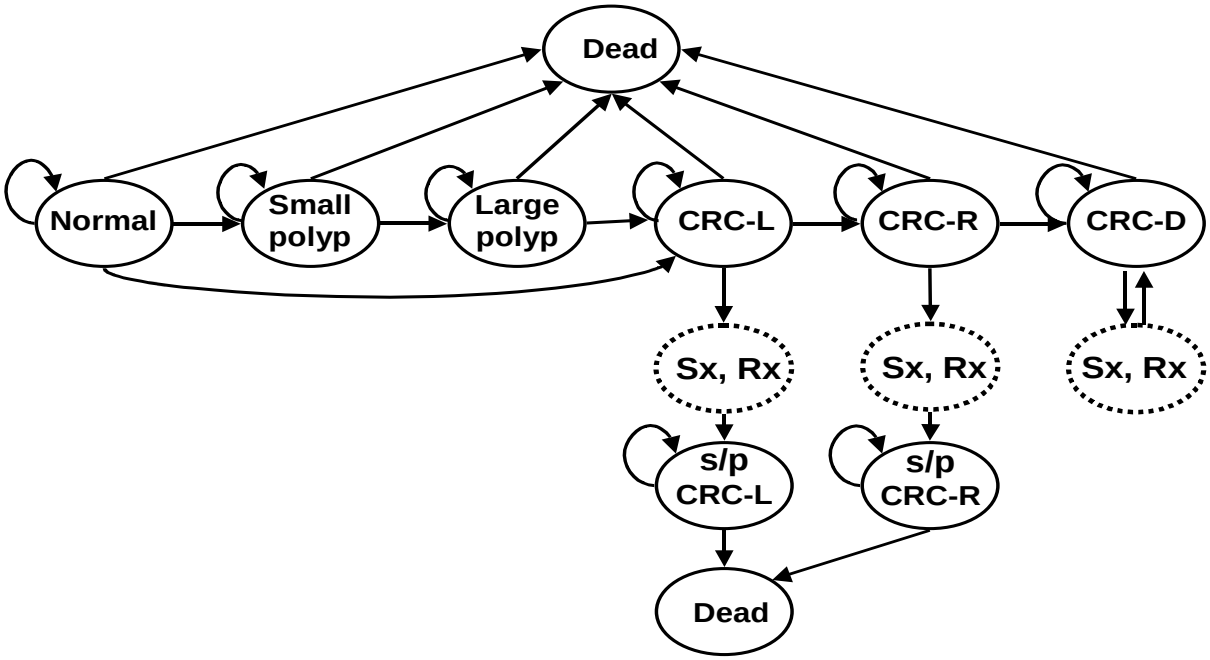
Supplementary Table 5. Effectiveness and cost effectiveness of organized outreach versus usual care*

Clinical Scenarios	Comparison Groups	Key variable	QALY/ person	Cost/ person	Cost/QALY gained by annual FIT-outreach vs. usual care
FIT uptake: 57.9% with outreach (participation 45.3% consistent, 25.1% intermittent, 29.6% never) *vs.* 37.4% with usual care (participation 21.2% consistent, 32.5% intermittent and 46.3% never) – Base case (55.6% Follow-up Colonoscopy)	Usual Care Intervention	-- --	19.6103 19.6259	$2,816 $2,960	$9,200/ QALY
FIT uptake: 66.1% with outreach (participation 51.8% consistent, 28.6% intermittent, 19.6% never) *vs.* 36.1% with usual care (participation 20.4% consistent, 31.4% intermittent and 48.2% never) – SA1 (Participation rates – largest effect)	Usual Care Intervention	-- --	19.6090 19.6330	$2,832 $2,854	$900/ QALY
FIT uptake: 52.4% with outreach (participation 41.1% consistent, 22.7% intermittent, 36.2% never) *vs.* 38.7% with usual care (participation 21.9% consistent, 33.6% intermittent and 44.5% never) – SA2 (Participation rates – smallest effect)	Usual Care Intervention	-- --	19.6114 19.6212	$2,800 $3,029	$23,400/ QALY
FIT uptake: 57.9% with outreach (participation 45.3% consistent, 25.1% intermittent, 29.6% never) *vs.* 37.4% with usual care (participation 21.2% consistent, 32.5% intermittent and 46.3% never) – SA3 (Cost of FIT outreach-including FIT Kit cost: $10)	Usual Care Intervention	-- --	19.6103 19.6259	$2,816 $2,749	FIT outreach dominates
FIT uptake: 57.9% with outreach (participation 45.3% consistent, 25.1% intermittent, 29.6% never) *vs.* 37.4% with usual care (participation 21.2% consistent, 32.5% intermittent and 46.3% never) – SA4 (Cost of FIT outreach-including FIT Kit cost: $50)	Usual Care Intervention	-- --	19.6103 19.6259	$2,816 $3,399	$37,400/ QALY

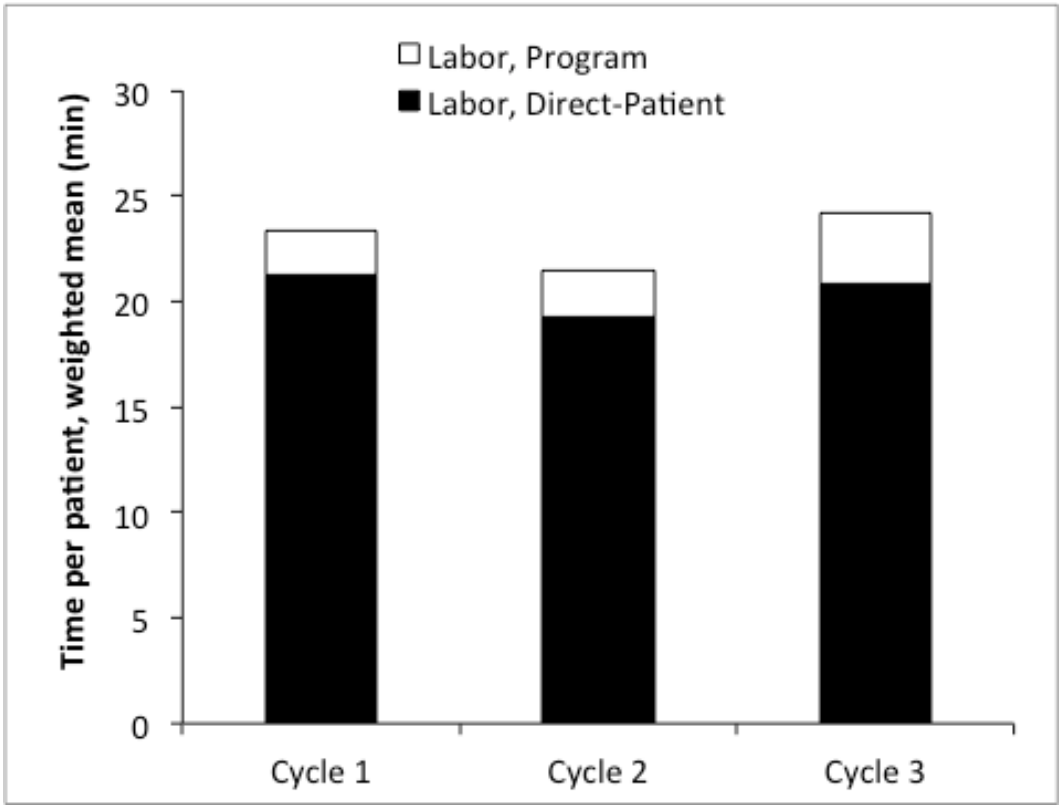
FIT uptake: 57.9% with outreach (participation 45.3% consistent, 25.1% intermittent, 29.6% never) *vs.* 37.4% with usual care (participation 21.2% consistent, 32.5% intermittent and 46.3% never) – SA5 (varied rate of follow-up colonoscopy after abnormal FIT)	Usual care Intervention	Follow-up colonoscopy rate: 55% Follow-up colonoscopy rate: 75%	19.6101 19.6312	$2,818 $2,872	$2,500/ QALY
FIT uptake: 57.9% with outreach (participation 45.3% consistent, 25.1% intermittent, 29.6% never) *vs.* 37.4% with usual care (participation 21.2% consistent, 32.5% intermittent and 46.3% never) – SA6 (varied rate of follow-up colonoscopy after abnormal FIT with added cost of navigation for follow-up colonoscopy in FIT outreach group)	Usual Care Intervention + colonoscopy navigation	Follow-up colonoscopy rate: 55% Follow-up colonoscopy rate: 75% + Cost of navigation for colonoscopy	19.6101 19.6312	$2,818 $2,882	$3,000/ QALY

*Abbreviations: FIT, fecal immunochemical test; QALY, quality adjusted life years; SA, sensitivity analysis

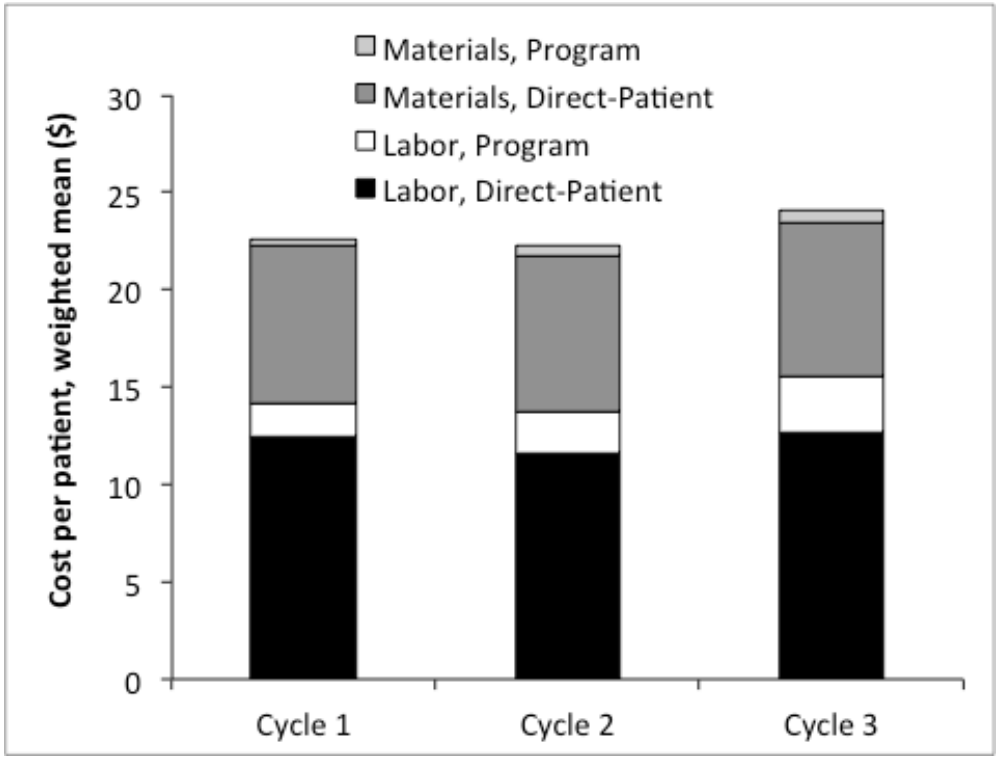
Supplementary Figures



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. Average time spent per patient during three cycles of organized outreach.



Supplementary Figure 3. Average cost per patient during three cycles of organized outreach.