Comparative Effectiveness of Screening Strategies for Colorectal Cancer - Supplementary Materials

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Introduction

Some aspects of the methods used in this study require more details that are presented in the following paragraphs. Detailed results from the analyses are provided.

Some results are discussed in more details.

Supplementary Materials and Methods

The methods of this study are discussed in more depth in the following sections.

The Study Model

Supplementary Table-1 provides a comprehensive list of all assumptions used in the modeling of this study. The sources are cited.

Figure 1 and Figure 2 depict the Markov model in closed and tree formats, respectively.

This model was primarily focused on the outcomes of colorectal cancer screening and therefore aimed to match the empiric evidence documented in the literature without attempting to describe the mechanisms of pathogenesis of colorectal cancer. The benefits of screening in terms of risk reduction (or incidence reduction), and stage-shift were modeled.

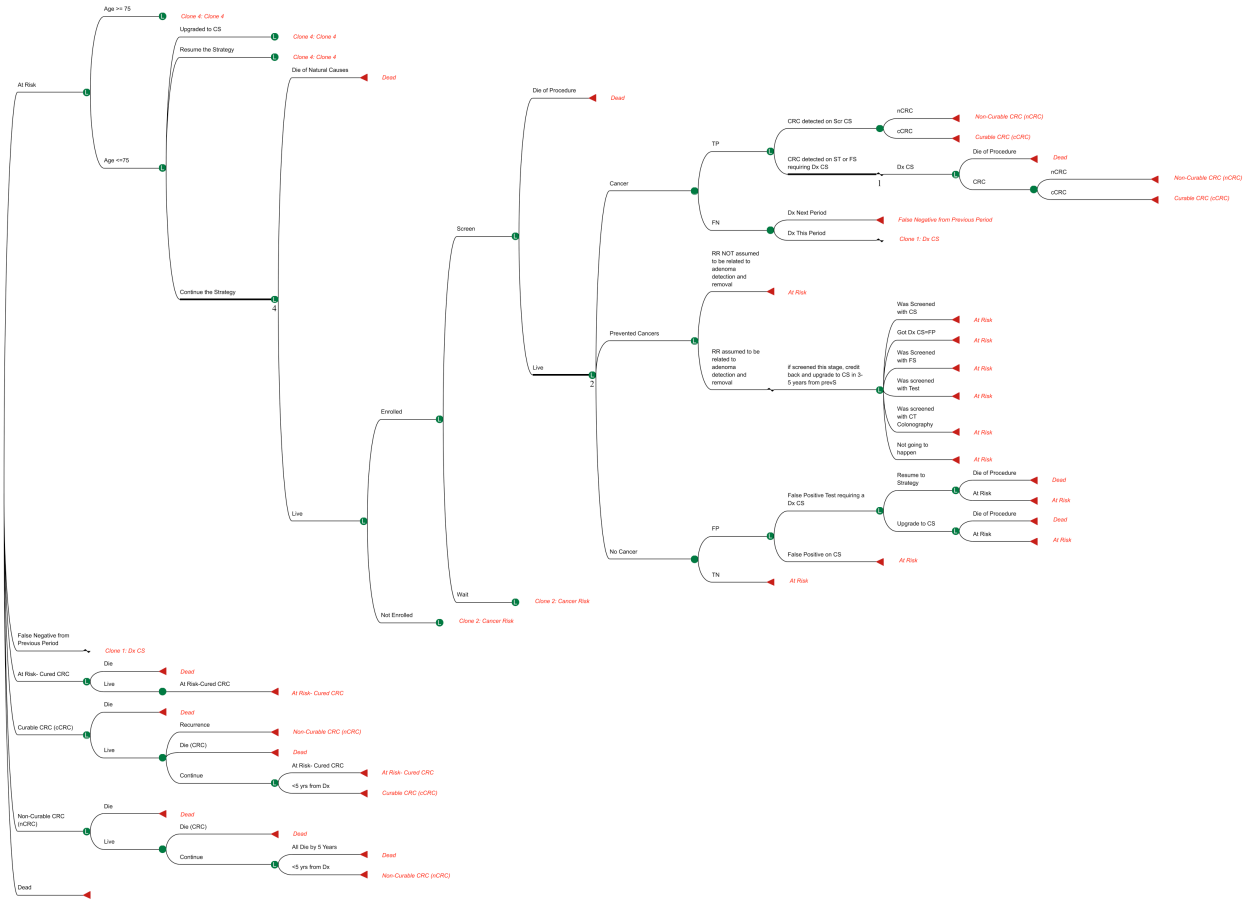
The screening strategies evaluated included:

1) ST 1: FOBT Fecal Occult Blood Testing (FOBT) annually

2)	ST 2: FIT	Fecal Immunochemical Testing (FIT) annually
3)	ST 3: FOBT + Flex Sig	FOBT annually and Flexible Sigmoidoscopy (Flex Sig) every 5 years
4)	ST 4: FIT + Flex Sig	FIT annually and Flex Sig every 5 years
5)	ST 5: Colonoscopy	Colonoscopy every 10 years (3 or 5 years, with adenoma)
6)	ST 6: Flex Sig	Flex Sig every 5 years
7)	ST 7: FOBT 2	FOBT every other year
8)	ST 8: FIT 2	FIT every other year
9)	ST 9: FOBT 2 + Flex Sig	FOBT every other year and Flex Sig every 5 years
10)	ST 10: FIT 2 + Flex Sig	FIT every other year and Flex Sig every 5 years
11)	ST 11: DNA	Stool DNA testing annually
12)	ST 12: DNA 3	Stool DNA testing every 3 years
13)	ST 13: CT Colonography	CT Colonography every 10 years

There are suggestions in the literature that DNA testing could be done every 3 years[1,2]. Therefore, it was included in this model. That is also why we have also included FOBT and FIT at two year intervals with or without sigmoidoscopy.

Supplementary Figure 1: Closed form model representing states (in ovals) and transitions (arrows).



Supplementary Figure 2: Tree form of the model with states as root nodes and transitions as branches.

Model Assumptions

Two important groups of assumptions, among others, deserve further discussion:

1) Assumptions related to the benefits of screening as exemplified by studies of outcomes with sigmoidoscopy and colonoscopy, and
2) Assumptions related to performance of all screening tests evaluated in this study, namely, sensitivity, specificity, and compliance.

Benefits of screening in terms of such outcomes as incidence reduction and mortality reduction were primarily associated with ideal screening methods such as colonoscopy and sigmoidoscopy. These are considered ideal because through these screening methods, precancerous adenomas as well as cancers could be detected and biopsied, and with respect to precancerous adenomas, treated. These benefits were modeled using a reduction of incidence and a stage-shift effect linked to colonoscopy screening. The mortality reduction benefit was not explicitly modeled and the model predicted the mortality using the natural history of colorectal cancer after incidence reduction and stage-shift for the screened population (*after* a colonoscopy or sigmoidoscopy) and without incidence reduction or stage-shift for the non-screened population. These assumptions are defined and appropriate sources cited in Supplementary Table-1, and are used in strategies as appropriate, without any calibration or adjustments to their values. For example, risk reduction and stage-shift are implemented at the same rates after a sigmoidoscopy for ST 3, ST 4, ST 6, ST 9 and ST 10. As a result, the model behavior followed the screening test rather than the strategy (which may include two different tests).

For the second groups of assumptions, the values for the performance characteristics of the screening tests were taken from the literature as cited in Supplementary Table-1. These values were used as reported in the sources and did not require any calibration or adjustment to make the model outcomes consistent with expectation or observation.

Supplementary Table 1: Detailed listing of assumptions with corresponding sources.

Assumption	Value (Range)	Varied in Sensitivity Analysis	Source
Test Characteristic			
Sensitivity of FOBT	0.643 (0.356, 0.86)	No	3,4
Sensitivity of FIT	0.818 (0.478, 0.968)	No	3,4
Sensitivity of Colonoscopy	0.95 (0.92, 0.99)	No	4-6
Sensitivity of Diagnostic Colonoscopy	0.95 (0.92, 0.99)	No	4,5
Sensitivity of Flex Sig	0.75 (0.72, 0.85)	No	4,7
Sensitivity of DNA	0.923 (0.83, 0.975)	No	4,8,9
Sensitivity of CT Colonography	0.922 (0.84, .93)	No	4,10,11
Sensitivity of Test X (Set to match DNA)	0.923 (0.83, 0.975)	No	
Sensitivity of DNA Testing for Adenoma	0.424 (0.389-0.46)	No	4,8,9
Sensitivity of CT Colonography for Adenoma	0.8 (0.076-1)	No	4,11
Sensitivity of Test X for Adenoma (relative to colonoscopy)	0.5 (0.5-1)	No	
Specificity of FOBT	0.901 (0.893, 0.908)	No	3,4
Specificity of FIT	0.969 (0.964, 0.974)	No	3,4
Specificity of Colonoscopy	0.9 (0.9, 1)	No	4,5
Specificity of Diagnostic Colonoscopy	0.9 (0.9, 1)	No	4,5
Specificity of Flex Sig	0.92 (0.92, 1)	No	4,5,7,12
Specificity of DNA	0.866 (0.859, 0.872)	No	4,8,9
Specificity of CT Colonography	0.82 (0.796, 0.88)	No	4,10,11
Specificity of Test X (Set to match DNA)	0.866 (0.859, 0.872)	No	
Test Costs			
Societal Cost of FOBT	$21.54	No	13
Societal Cost of FIT	$39.22	No	13
Societal Cost of Colonoscopy	$835.08	No	13
Societal Cost of Diagnostic Colonoscopy	$874.07	No	13
Societal Cost of Flex Sig	$276.01	No	13
Societal Cost of DNA	$599	No	14
Societal Cost of Test X	$599	Yes	
Societal Cost of CT Colonography	$646.64	No	10,15
Cost of FOBT	$4.54	No	13
Cost of FIT	$22.22	No	13

Assumption	Value (Range)	Varied in Sensitivity Analysis	Source
Cost of Colonoscopy	$522.71	No	[13]
Cost of Diagnostic Colonoscopy	$547.12	No	[13]
Cost of Flex Sig	$164.17	No	[13]
Cost of DNA	$502	No	[14]
Cost of Test X	$502	Yes	
Cost of CT Colonography	$488.29	No	[10,15]
Test Compliance			
Compliance Referent	1		
Compliance with FOBT	0.462 (0.462, 1)	Yes	[16]
Compliance with FIT- extrapolated using FOBT	0.462 (0.462, 1)	Yes	[16]
Compliance with FOBT + Flex Sig- extrapolated using Flex Sig	0.63 (0.63, 1)	Yes	[16]
Compliance with FIT + Flex Sig- extrapolated using Flex Sig	0.63 (0.63, 1)	Yes	[16]
Compliance with Colonoscopy- extrapolated using Flex Sig	0.63 (0.63, 1)	Yes	[17,18]
Compliance with Flex Sig	0.63 (0.63, 1)	Yes	[18]
Compliance with FOBT 2	0.597 (0.597, 1)	Yes	[16,19]
Compliance with FIT 2	0.597 (0.597, 1)	Yes	[16,19]
Compliance with FOBT 2 + Flex Sig	0.63 (0.63, 1)	Yes	[16,19]
Compliance with FIT 2 + Flex Sig	0.63 (0.63, 1)	Yes	[16,19]
Compliance with DNA 1- extrapolated using FOBT	0.462 (0.462, 1)	Yes	[16,19]
Compliance with DNA 3- extrapolated using FOBT 2	0.597 (0.597, 1)	Yes	[16,19]
Compliance with Test X - extrapolated using FOBT	0.462 (0.462, 1)	Yes	[16,19]
Compliance with Test X 3 - extrapolated using FOBT 2	0.597 (0.597, 1)	Yes	[16,19]
Compliance with Test X 5- extrapolated using Flex Sig	0.63 (0.63, 1)	Yes	[18]
Compliance with CT Colonography- extrapolated using Flex Sig	0.63 (0.63, 1)	Yes	[18]
Procedure Related Complications and Associated Management Costs			
Probability of Death with Colonoscopy	0.00002	No	[10]
Probability of Perforation Colonoscopy	0.00070	No	[13]
Probability of Bleeding Colonoscopy	0.00045	No	[13]
Cost of Perforation Colonoscopy	$12,446	No	[13]
Cost of Bleeding Colonoscopy	$5,208	No	[13]
Probability of Death with Sigmoidoscopy	0.00002	No	[20]
Probability of Perforation with Sigmoidoscopy	0.00003	No	[13, 20]
Probability of Bleeding with Sigmoidoscopy	0.00023	No	[13, 20]
Cost of Perforation with Sigmoidoscopy	$12,446	No	[13]
Cost of Bleeding with Sigmoidoscopy	$5,208	No	[13]
Non Colorectal Cancer Causes of Mortality			
Probability of Death, non Colorectal Cancer Related	Period Life Table, 2010	No	[21]
Colorectal Cancer			
CRC Risk After Colonoscopy, Observed/Expected			[22]
Year 1, 2, 3	0.35 (0.28-0.45)	No	
Year 4, 5	0.4 (0.31-0.52)	No	
Year 6-10	0.52 (0.38-0.70)	No	
CRC Risk After Flex Sig, Observed/Expected			[20]

Assumption	Value (Range)	Varied in Sensitivity Analysis	Source
Year 1-5	0.79 (0.72-0.85)	No	
Risk Reduction After Stool Testing			[23]
Year 1-2	0	No	
CRC Risk After CT Colonography, Observed/Expected	Extrapolated at 0.8 of Colonoscopy	No	[24]
Year 1, 2, 3	0.48 (0.42-0.56)	No	
Year 4, 5	0.52 (0.45-0.62)	No	
Year 6-10	0.62 (0.5-0.76)	No	
Probability of curable CRC with screening	0.91 (0.8)	Yes	[16,25,26]
Probability of incurable CRC with screening	0.09 (0.2)	Yes	[16,25,26]
Probability of curable CRC with no screening	0.84 (0.8)	Yes	[16,25,26]
Probability of incurable CRC with no screening	0.16 (0.2)	Yes	[16,25,26]
Probability of Recurrence			
Stage 1			[27]
Year 1	0.01	No	
Year 2	0.04	No	
Year 3	0.01	No	
Year 4	0.01	No	
Year 5	0	No	
Stage 2			[28]
Year 1	0.05	No	
Year 2	0.065	No	
Year 3	0.065	No	
Year 4	0.045	No	
Year 5	0.028	No	
Stage 3			[28]
Year 1	0.2	No	
Year 2	0.21	No	
Year 3	0.1	No	
Year 4	0.05	No	
Year 5	0.04	No	
Probability of Survival (cause and period specific)			[26]
Stage 1			
Year 1	0.95	No	
Year 2	0.96	No	
Year 3	0.97	No	
Year 4	0.98	No	
Year 5	0.98	No	
Stage 2			
Year 1	0.85	No	
Year 2	0.88	No	
Year 3	0.91	No	
Year 4	0.93	No	
Year 5	0.95	No	

Assumption	Value (Range)	Varied in Sensitivity Analysis	Source
Stage 3			
Year 1	0.63	No	
Year 2	0.70	No	
Year 3	0.76	No	
Year 4	0.82	No	
Year 5	0.87	No	
Stage 4 (Incurable)			
Year 1	0.09	No	
Year 2	0.15	No	
Year 3	0.24	No	
Year 4	0.35	No	
Year 5	0.48	No	
Stage Distribution			[26]
Stage 1	0.18 (S), 0.17 (NS), 0.16 (N)	Yes*	
Stage 2	0.40 (S), 0.37 (NS), 0.35 (N)	Yes	
Stage 3	0.32 (S), 0.30 (NS), 0.28 (N)	Yes	
Stage 4	0.09 (S), 0.16 (NS), 0.21 (N)	Yes	
Costs of Treatment			
Curable CRC (adjusted for stage distribution)			[1,13,29,30]
Year 1	$36,069	No	
Continuing	$2,257	No	
Societal, Year 1	$44,965	No	
Societal, Continuing	$3,015	No	
Year of Death	$46,598	No	
Societal, Year of Death	$57,731	No	
Incurable CRC			[1,13,29,30]
Year 1	$93,731	No	
Continuing	$103,188	No	
Societal, Year 1	$115,244	No	
Societal, Continuing	$132,364	No	
Year of Death	$64,428	No	
Societal, Year of Death	$78,227	No	
Age Distribution of Simulated Individuals			[31]
50-54 Age Group	27%	No	
55-59 Age Group	24%	No	

* SEER data shows a stage distribution of 16, 35, 28, and 21 percent for stages 1, through 4 in most recent years, respectively, designated (N) in the table, as this number has been stable over time, it does not reflect a stage-shift as a result of screening- this assumption is simulated under sensitivity analysis. Assuming there exists a screening shift effect as a result of screening (S) vs. no screening (NS), with stage 4 cancer probability at 9, and16percent, respectively, stage distribution for stage 1, 2 and 3 were adjusted.

Assumption	Value (Range)	Varied in Sensitivity Analysis	Source
60-64 Age Group	21%	No	
65-69 Age Group	16%	No	
70-74 Age Group	12%	No	

Colorectal Cancer Incidence in Non-Screened Individuals

The incidence and mortality of colorectal cancer has been declining since the early 1980s. Although the earlier declines was slower and was more likely to be attributable to risk factor modification and improved treatments, the accelerated rate of decline especially in the 2000s is most likely attributable to the increased rates of screening[32-34]. While it may not be possible to separate the net benefit of screening and risk factor modifications and treatment advances completely, we used the SEER data on incidence between 1990-1995 to include some of the benefits of risk factor modifications and treatment improvements without the benefits of accelerated adoption of screening. The incidence rates represent probabilities of developing colorectal cancer in an age group and are shown in Supplementary Table-2.

Age Group	Rate	Count	Population Size
50-54 years	48.9	3,494	7,148,667
55-59 years	87.3	5,161	5,908,669
60-64 years	139.2	7,795	5,600,026
65-69 years	207.5	11,049	5,325,008
70-74 years	279.4	12,626	4,518,886
75-79 years	360.2	12,355	3,430,152
80-84 years	449.7	10,021	2,228,471
85+ years	466.8	8,588	1,839,631

Supplementary Table 2: Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard.
SEER*Stat Query[21]:
{Race, Sex, Year Dx, Registry, County.Year of diagnosis} = '1990','1991','1992','1993','1994','1995'
{Site and Morphology.Site recode ICD-O-3/WHO 2008} = ' Colon and Rectum'

Sequential Repetition of a Screening Test

The screening tests are used repeatedly in some instances, for example, FOBT and FIT may be used for years before a positive screening test occurs. This raises the question whether it is possible that sequential screening using the same test may influence the overall sensitivity or specificity of the test.

It stands to reason that at the population level the performance of a test (sensitivity and specificity) will remain independent of the results of a prior application of the same test. In the case of FOBT, for instance, it is possible that by redirecting the positive tests to undergo a colonoscopy we might potentially "thin" the cancer cases in the population for a future FOBT. However, the incidence of cancer is applied based on age at an individual level during the simulation and each year the "thinned" segment of the population is replenished by new cases of cancer. In this study, those who will have a positive test will undergo a colonoscopy and depending on the results of the colonoscopy will be diagnosed with cancer or return to screening which can be either continuing with FOBT starting with the next recommended time frame for colonoscopy (i.e., 3, 5, or 10 years) or continue screening with colonoscopy. The risk of cancer after a negative screening test is expected to return to baseline after the recommended screening interval, for FOBT 1 year and for colonoscopy depending on the results with respect to adenomas, 3, 5 or 10 years.

Based on the above, we concluded that using the same performance parameters for all screening tests at the recommended screening intervals was the best approach, compared to changing the sensitivity/specificity parameters arbitrarily. The CISNET

investigators have also argued in favor of the independence of the sequential testing results[13].

While we acknowledge that the conditional independence assumption discussed above may not necessarily hold true for DNA testing, we chose to use the same sensitivity and specificity for DNA testing, as well, to remain consistent in our approach. With an appropriately wide repertoire of cancer signatures, the probability of conditional independence for DNA testing is expected to approaches 1.

Compliance with Screening

Our methods for selecting the base case compliance relied on validation studies for the respective screening modalities. In the case of CT colonography and colonoscopy we extrapolated from sigmoidoscopy compliance rates as invasive tests. When using extrapolation for colonoscopy and CT colonography, the compliance rates were considered in a relative fashion. For instance, CT colonography, and colonoscopy were assumed to have compliance rates that were at least as high as that reported for sigmoidoscopy. In a recent study of self-reported compliance with colorectal cancer screening rates in the US, the average "up-to-date status" with screening, which was related to compliance with screening, was 54-75 percent[35].

During the sensitivity analysis, we used the average self-reported compliance rate as the lower end at 60% and increased the compliance for all strategies to 100%. We did not observe a non-proportional change in effectiveness for any strategy and therefore, we found no indication that a certain compliance range would favor using one strategy and a different range would favor using a different strategy.

Cancer Risk Reduction and Strategies Based on Stool Testing

Stool testing alone, whether FOBT, FIT or DNA, has not been shown to reduce the incidence of colorectal cancer. However, when subjects with a positive screening tests undergo further studies such as diagnostic colonoscopy, evidence suggests that there may be a reduction in the incidence of cancer[23].

In this Markov model it was assumed that screening was associated with a reduction in the risk of colorectal cancer for the screened individuals. The source of the reduction was assumed to be the removal of precancerous lesions as a result of a positive screening test[22,36-39].

A positive stool test could be cancer, normal, or a polyp, all of which would prompt a diagnostic colonoscopy. If the polyp were to be removed, the individual screened would be expected to have a lower risk of colorectal cancer.

It also stands to reason that *negative* screening results do not change the inherent risk of colorectal cancer for this population; rather, with continued screening a portion of patients who would otherwise develop colorectal cancer are detected in precancerous polyp states and with appropriate intervention, i.e. colonoscopy, are prevented from developing invasive cancer. This would result in fewer cases of invasive cancer in this population and therefore explains the observed cancer risk reduction.

Evidence from studies in polyps supports this mechanism[5]. The model in this study was designed to simulate screening benefits in a manner consistent with this mechanism.

A consequence of subscribing to this mechanism as the explanation of risk reduction is that a positive non-invasive screening study must be further worked up with a diagnostic colonoscopy to examine the entire colon to diagnose a cancer or remove suspicious and potentially precancerous lesions. Without this, screening is incomplete and the maximum risk reduction cannot be expected.

Therefore, in this model, after a positive screening test with modalities other than screening colonoscopy, a diagnostic colonoscopy was performed. The costs of this procedure were categorized as diagnostic work up. In cases where a cancer was not diagnosed, these were added to the costs of screening. If a cancer was diagnosed, these costs were added to the management costs of cancer.

Strategies that can independently of a colonoscopy identify a polyp, such as sigmoidoscopy, CT colonography, or the hypothetical "Test X" were modeled to confer a risk reduction to the screened population. The individuals in whom the cancer was prevented as a result of a reduction in cancer risk were assumed to have had a precancerous polyp removed, in keeping with the mechanisms described above, and the cost of a diagnostic colonoscopy were added to the screening cost.

Stage-Shift for Colorectal Cancer as a Result of Screening

There is a hint of a reduction in the probability of metastatic colorectal cancer as a result of screening[26,38]- see Supplementary Table-1. However, in our review of the data from SEER registry using data from 1973-2012 and *SEER historic stage A* variable, we found that this rate has been stable around 21% in periods prior to and after the population-wide adoption of screening[25]- see Supplementary Table-3. Even when considering the unstaged population to be mainly metastatic, we could not

account for the stage-shift through SEER data. The average unstaged proportion between 1973- and 2012 was 4%, the same as the unstaged percentage in 2012. As seen in Supplementary Table-2, the rates were higher in 1973, 1974 and 1975. Whether this was related to the quality of data or in fact significantly more patients were unstaged and likely metastatic, was unclear and in the subsequent years these percentages decreased, significantly. In fact since 1980, the percentage of stage IV disease and unstaged disease as well as the sum of the two shows minimal change. However, to examine the role of stage-shift, we performed a sensitivity analysis around this assumption, accepting a stage-shift, and also rejecting a stage-shift role for screening.

Period	Localized	Regional	Distant	Unstaged
1973-2012	21 (39%)	19.4 (36%)	10.4 (19%)	3.7 (7%)
1973	17 (29%)	17.6 (30%)	11.8 (20%)	11.5 (20%)
1974	19.4 (32%)	20.1 (34%)	13.3 (22%)	6.9 (12%)
1975	18.9 (32%)	20.5 (34%)	13.1 (22%)	7.1 (12%)
1976	20.2 (33%)	22 (36%)	12.9 (21%)	6.2 (10%)
1977	20.4 (33%)	22.5 (36%)	13.3 (21%)	6.2 (10%)
1978	21.5 (35%)	22.2 (36%)	12.6 (20%)	5.7 (9%)
1979	21.8 (35%)	22.2 (36%)	12.7 (20%)	5.6 (9%)
1980	22.1 (35%)	23.1 (36%)	13.1 (21%)	5.5 (9%)
1981	22.1 (34%)	24.3 (38%)	12.5 (19%)	5.4 (8%)
1982	21.2 (34%)	23.9 (38%)	12.4 (20%)	5.2 (8%)
1983	22.1 (35%)	24.6 (39%)	12 (19%)	5 (8%)
1984	22.8 (35%)	25 (39%)	12.3 (19%)	4.7 (7%)
1985	24.8 (37%)	24.8 (37%)	11.8 (18%)	4.9 (7%)
1986	24.5 (38%)	23.7 (37%)	11.1 (17%)	4.9 (8%)
1987	23.7 (38%)	23.7 (38%)	10.8 (17%)	4.5 (7%)
1988	23.9 (39%)	21.4 (35%)	11.6 (19%)	4.3 (7%)
1989	23.8 (39%)	21.2 (34%)	12 (19%)	4.7 (8%)
1990	23 (38%)	21.9 (36%)	11.6 (19%)	4.2 (7%)
1991	22.4 (38%)	21.7 (36%)	11 (18%)	4.4 (7%)
1992	21.9 (38%)	21.3 (37%)	10.9 (19%)	4 (7%)
1993	21.6 (38%)	20.4 (36%)	10.8 (19%)	4 (7%)
1994	20.9 (38%)	20.6 (37%)	10.4 (19%)	3.8 (7%)
1995	20.4 (38%)	20 (37%)	10.1 (19%)	3.6 (7%)
1996	21.4 (39%)	19.9 (36%)	10.1 (18%)	3.3 (6%)
1997	21.8 (39%)	20.3 (36%)	10.6 (19%)	3.6 (6%)
1998	22.6 (40%)	20.7 (36%)	9.9 (17%)	3.7 (7%)
1999	22.6 (41%)	20.4 (37%)	9.5 (17%)	3 (5%)
2000	21.9 (40%)	19.9 (37%)	9.5 (18%)	2.8 (5%)
2001	21.8 (41%)	19.8 (37%)	9.4 (18%)	2.6 (5%)
2002	22.1 (42%)	18.7 (35%)	9.7 (18%)	2.7 (5%)
2003	21.3 (42%)	17.6 (35%)	9.3 (18%)	2.5 (5%)
2004	21 (42%)	17.3 (35%)	9.1 (18%)	2.5 (5%)
2005	20 (42%)	16.5 (35%)	9.1 (19%)	2.2 (5%)
2006	19.9 (42%)	15.6 (33%)	9.1 (19%)	2.3 (5%)
2007	19.6 (42%)	15.9 (34%)	8.7 (19%)	2.2 (5%)
2008	19.6 (43%)	14.8 (33%)	8.7 (19%)	2.1 (5%)
2009	18.3 (42%)	14.3 (33%)	8.5 (20%)	2.1 (5%)
2010	16.8 (41%)	13.7 (33%)	8.4 (21%)	2 (5%)
2011	16.2 (41%)	12.9 (33%)	8.5 (21%)	2 (5%)
2012	15.8 (41%)	12.6 (33%)	8 (21%)	2.1 (5%)

Supplementary Table 3: Stage distribution for colorectal cancer between 1973-2012.
Numbers reflect incidence rates per 100,000 US population, and the relative frequency in percentage in parentheses. Based on SEER historic stage A variable.
From Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2014 Sub (1973-2012) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2013 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission.

Explicit vs. Implicit Modeling for Adenomas

A successful model that has set the standard for colorectal cancer modeling is MISCAN. In this semi-Markov model, extensive details of the natural history of adenoma development, implications of size, sensitivity and specificity of various screening tests for their detection, and finally progression to invasive cancers and stage at diagnosis over time is modeled based on our current understanding of the pathogenesis of colorectal cancer. This is an example of explicit modeling.

In our approach, we chose to model the risk reduction in the incidence and advanced stages at diagnosis for colorectal cancer, implicitly. As such, individuals would face the same risk for development of colorectal cancer.

It is assumed that in this model all positive screening tests are followed with a diagnostic colonoscopy during which adenomas, if found, can be removed. Populations screened with sigmoidoscopy and colonoscopy were shown to have a reduction in the incidence and mortality of colorectal cancers[20,22]. The CRC risk (incidence) reduction is modeled, implicitly, as follows:

- Individuals in strategies 5 and 6 who are compliant with screening recommendations and undergo screening using colonoscopy or sigmoidoscopy as the only screening test will be subject to this reduction. The age based risk for CRC in the non-screened population as reflected by SEER data (see Supplementary Table-2) is adjusted by the risk reduction demonstrated in the cited studies in Supplementary Table-1. All individuals who are screened, regardless of detection of adenomas enjoy this risk reduction.

- Individuals in strategies 1, 2, 7, 8, 11, and 12 are screened with non-invasive stool testing that by themselves are not thought to confer a risk reduction. As a result, those who are compliant and are screened are not subjected to a risk reduction. However, in the case of a positive screen, all individuals undergo a diagnostic colonoscopy. Those who are not diagnosed with colorectal cancer, i.e. false negatives, are assumed to incur the same risk reduction benefits as those who are primarily screened with colonoscopy. The net effect is a risk reduction for the population in these strategies that is smaller in size compared to colonoscopy strategy.
- Individuals in strategies 3, 4, 9, and 10 are screened with non-invasive stool tests and at fixed intervals, if the prior tests have been negative, will undergo sigmoidoscopy for screening. As described in previous paragraph, the non-invasive testing will not result in a reduced risk. However, if a screening sigmoidoscopy if performed, the individuals will be subjected to the appropriate risk reduction consistent with that of screening primarily with sigmoidoscopy. Furthermore, a positive non-invasive stool screen will result in colonoscopy and risk reduction conferred as described in the previous paragraph. The net effect is a risk reduction for the population in these strategies that is smaller in size compared to colonoscopy strategy.
- Strategy 13 is CT colonography. Given the ability of CT colonography to identify polyps which in turn can be removed by colonoscopy, it is assumed to confer a risk reduction onto the screened population. Since the performance of CT colonography in detection of polyps is close to

colonoscopy[24], conservatively, we extrapolated 80% of the incidence reduction for colonoscopy could be conferred onto individuals screened by CT colonography.

- Strategies 11, and 12 are based on DNA testing (Cologuard) that has a reported sensitivity of 42.4%[9]. As with strategies 1 and 2, no risk reduction is conferred onto the individuals screened by DNA testing unless a positive screen is followed up with colonoscopy and no cancer is found (false positive). However, given the modest reported sensitivity for adenoma detection, during sensitivity analysis, a risk reduction benefit is extrapolated based on colonoscopy as gold standard for detection of adenomas- See Sensitivity of Detection of Adenoma and Cancer Risk Reduction.
- Those who are spared the diagnosis of cancer due to risk reduction are considered to be individuals in whom cancer was prevented as a result of removal of precancerous adenomas. In a retrospective manner, the costs of a colonoscopy and polyp removal are added to the overall costs the strategy. As such, this model *infers* that a polyp was detected based on incidence reduction as modeled based on screening studies.
- Mortality risk reduction is thought to be mainly a function of incidence reduction[40] and therefore no adjustments are made to cancer mortality risk for individuals based on their compliance for screening, or screening strategy. Cancer mortality is modeled based on age and stage for all simulated individuals based on SEER data[41].

The benefit of taking this implicit modeling approach is that the empiric risk reduction is modeled as observed and the effect is attributed to the cause of adenoma removal. The effect is modeled independently of the presumed cause, and the association is implemented *ex post facto*. As long as the effect is inline with empiric observation, changes in causality would not affect the accuracy of the model in predicting cancer cases in the simulated population. Therefore, this also provides another means of independent verification of predictions made by other models.

There are other competing factors influencing the effectiveness of a given strategy in this model, e.g. sensitivity and specificity of the screening test, compliance with screening associated with the screening test, stage-shift associated with screening, and screening intervals associated with a test to name a few.

Sensitivity of Detection of Adenoma and Cancer Risk Reduction

Let's assume the following about colorectal cancer risk reduction associated with colonoscopy:

- It is related to adenoma detection and removal
- Colonoscopy is the gold standard for detection of adenomas
- Adenomas detected by Test X will be removed

Then it can be shown that:

$$\frac{Sen_{Test\ X}}{Sen_{Colonoscopy}} = \frac{RR_{Test\ X}}{RR_{Colonoscopy}}$$

And as a result:

$$\Rightarrow RR_{Test\ X} = \frac{Sen_{Test\ X} \cdot RR_{Colonoscopy}}{Sen_{Colonoscopy}}$$

Assuming that colonoscopy is the gold standard for detection of precancerous adenomas, its sensitivity for detection of adenoma is set at 1 (this is different from it's sensitivity for detection of colorectal cancer). Therefore:

$$\Rightarrow RR_{Test\ X} = Sen_{Test\ X} \cdot RR_{Colonoscopy}$$

Equation 1: Risk Reduction as a result of adenoma detection is directly proportional to the sensitivity of a test for adenoma detection.

In the sensitivity analysis, a risk reduction benefit proportional to the sensitivity for detection of adenoma was given to the stool DNA test, and the risk reduction benefit for Test X was varied according to a hypothetical value for the sensitivity of Test X for detection of precancerous adenomas.

As discussed before, CT colonography, by virtue of detecting adenomas, is also given a risk reduction benefit proportional to its sensitivity for detection of adenomas.

Validation of the Model

It is expected that predictions of a model should correspond to observations from empiric studies. Therefore, we tested the validity of our predictions by looking effectiveness outcomes as defined in Methods section of the manuscript and compared them to the empiric observations published in the literature.

Conformity to Empiric Data

Since this model does not attempt to incorporate the mechanisms of pathogenesis of colorectal cancer, there are no assumptions in the model that require calibration to

"fit" empiric observations. The simplicity of this model allowed for the expectation that the predictions of the model would be close to empiric data and the slight observed difference would be accounted for by random events in the model such as deaths due to natural causes. And, indeed, what this model produced was very close to empiric data. For instance, we used the risk reduction values for sigmoidoscopy from Schoen, et al[20] that reported a compliance of over 83% for screening. The observed incidence reduction and mortality reduction reported by Schoen, et al[20] were 21% (95% CI 15%-28%) and 26% (95% CI of 13%-37%), respectively. Schoen study provided a slightly lower number for proximal colon risk reduction. In our simulations, when compliance was set at 80%, the percentage of cancer cases prevented (incidence reduction) increased to 27%, within the 95% confidence interval of Schoen, et al, and the mortality risk was reduced by 38%, marginally higher than Schoen, et al- Supplementary Table-4.

It is important to note that the purpose of modeling is to apply the estimates from the clinical trials to a representative and realistic sample of the US general population to evaluate screening programs effectiveness (and not efficacy) from a public health and societal perspective. Therefore, given the inevitable difference between a representative sample of the population and the conditions of a clinical trial, there would be difference, but these differences would be small and could be explained by differences in age, comorbidities, follow up duration, baseline risk, and compliance.

Strategy	Screening Compliance 60%					Screening Compliance 80%					Screening Compliance 100%				
	Comparative Effectiveness		Cost Effectiveness			Comparative Effectiveness		Cost Effectiveness			Comparative Effectiveness		Cost Effectiveness		
	LY	CRC Prevented (%Δ)	CRC Deaths (%Δ)	Total Costs	ICER	Status (Rank)	LYG	CRC Prevented (%Δ)	CRC Deaths (%Δ)	Total Costs	ICER	Status (Rank)	LYG	CRC Prevented (%Δ)	CRC Deaths (%Δ)	Total Costs	ICER	Status (Rank)
No Screening (Referent Strategy)	15.183	0 (0%)	1404 (0%)	$ 3,613	(-)	AD	15.163	0 (0%)	1392 (0%)	$ 3,595	(-)	AD	15.179	0 (0%)	1427 (0%)	$ 3,629	$ (-)	AD
ST 1: FOBT	15.197	694 (15%)	1099 (22%)	$ 3,240	$ (-)	AD	15.181	927 (20%)	977 (30%)	$ 3,078	$ (-)	AD	15.205	1196 (26%)	845 (41%)	$ 2,898	$ (-)	AD
ST 2: FIT	15.192	339 (7%)	1183 (16%)	$ 3,442	$ (-)	AD	15.176	455 (10%)	1071 (23%)	$ 3,320	$ (-)	AD	15.198	572 (13%)	998 (30%)	$ 3,238	$ (-)	AD
ST 3: FOBT + Flex Sig	15.197	700 (15%)	1095 (22%)	$ 3,289	$ (-)	AD	15.181	932 (20%)	973 (30%)	$ 3,152	$ (-)	AD	15.205	1204 (26%)	843 (41%)	$ 3,000	$ (-)	AD
ST 4: FIT + Flex Sig	15.193	411 (9%)	1165 (17%)	$ 3,502	$ (-)	AD	15.177	549 (12%)	1047 (25%)	$ 3,399	$ (-)	AD	15.200	703 (15%)	963 (33%)	$ 3,323	$ (-)	AD
ST 5: Colonoscopy	15.204	975 (21%)	968 (31%)	$ 3,107	$ 0	UD (1)	15.189	1259 (27%)	858 (38%)	$ 3,010	$ 0	UD (1)	15.216	1654 (36%)	679 (52%)	$ 2,737	$ 0	UD (1)
ST 6: Flex Sig	15.196	437 (10%)	1112 (21%)	$ 3,293	$ (-)	AD	15.180	554 (12%)	1049 (25%)	$ 3,259	$ (-)	AD	15.203	740 (16%)	964 (32%)	$ 3,153	$ (-)	AD
ST 7: FOBT 2	15.196	497 (11%)	1125 (20%)	$ 3,232	$ (-)	AD	15.180	671 (15%)	1019 (27%)	$ 3,087	$ (-)	AD	15.203	859 (19%)	906 (37%)	$ 2,933	$ (-)	AD
ST 8: FIT 2	15.191	214 (5%)	1221 (13%)	$ 3,366	$ (-)	AD	15.174	262 (6%)	1161 (17%)	$ 3,311	$ (-)	AD	15.196	345 (8%)	1073 (25%)	$ 3,205	$ (-)	AD
ST 9: FOBT 2 + Flex Sig	15.197	559 (12%)	1078 (23%)	$ 3,244	$ (-)	AD	15.182	728 (16%)	991 (29%)	$ 3,173	$ (-)	AD	15.206	959 (21%)	866 (39%)	$ 3,052	$ (-)	AD
ST 10: FIT 2 + Flex Sig	15.193	343 (8%)	1159 (17%)	$ 3,400	$ (-)	AD	15.177	408 (9%)	1087 (22%)	$ 3,390	$ (-)	AD	15.200	550 (12%)	991 (31%)	$ 3,328	$ (-)	AD
ST 11: DNA	15.199	790 (17%)	1059 (25%)	$ 4,701	$ (-)	AD	15.184	1048 (23%)	918 (34%)	$ 5,026	$ (-)	AD	15.208	1347 (30%)	790 (45%)	$ 5,360	$ (-)	AD
ST 12: DNA 3	15.197	597 (13%)	1086 (23%)	$ 4,333	$ (-)	AD	15.182	800 (17%)	976 (30%)	$ 4,566	$ (-)	AD	15.205	1036 (23%)	835 (41%)	$ 4,764	$ (-)	AD
ST 13: CT Colonography*	15.203	841 (19%)	1005 (28%)	$ 3,246	$ (-)	AD	15.187	1085 (24%)	897 (36%)	$ 3,174	$ (-)	AD	15.213	1411 (31%)	745 (48%)	$ 3,041	$ (-)	AD
ST 11: DNA (Ad Sen=0.424)†	15.202	945 (21%)	1009 (28%)	$ 4,546	$ (-)	AD	15.188	1242 (27%)	855 (39%)	$ 4,847	$ (-)	AD	15.213	1587 (35%)	714 (50%)	$ 5,131	$ (-)	AD
ST 12: DNA 3 (Ad Sen=0.424)†	15.199	831 (18%)	1051 (25%)	$ 3,929	$ (-)	AD	15.185	1075 (23%)	905 (35%)	$ 4,005	$ (-)	AD	15.211	1395 (31%)	744 (48%)	$ 4,054	$ (-)	AD

Supplementary Table 4: One-way sensitivity analysis for evaluation of the effect increasing compliance on effectiveness, costs and cost effectiveness of screening strategies.
LY: Life Years. CRC: Colorectal Cancer. ICER: Incremental Cost Effectiveness Ratio. (-) negative value. AD: Absolute Dominance. UD: Undominated. Ad Sen: Adenoma sensitivity.
* CT colonography had a reported sensitivity of 80% for detection of adenomas. Therefore, a proportional CRC risk reduction was given to this strategy.
† A sensitivity of 42.4% for detection of adenomas and a proportionate CRC risk reduction was given to DNA test. Results shown for comparison.

Conformity to MISCAN and Survival Benefit for Screening

The measure of Life Years Gained (LYG) is one of the standard measures of effectiveness used in most models. Any increase in incidence reduction would naturally result in a measureable increase in the overall survival of the simulated individuals in the model. These improvements in LYG should be interpreted with caution.

By virtue of reducing the incidence, some cancer cases and cancer deaths are prevented, and these can be viewed as additional measures of effectiveness. Colorectal cancer models, including this model, predict a fairly small LYG as the benefit of screening. Under near perfect conditions including enrolling individuals at 50 years of age, and screening them with adherence of 100% till age 75, MISCAN predicted 230 LYG per 1,000 screened individual, an incidence risk reduction of 51.9% and a mortality reduction of 64.6%, respectively[5,42]. These numbers as predicted by this model were 137 LYG per 1,000 screened individuals, 39% and 46%, respectively. MISCAN investigators in discussing their results pointed out that their model might overestimate the benefits of screening based on the set up of their assumptions[13]. A more recent published study reporting simulation results using MISCAN, shows a smaller benefit size for colonoscopy of 151.6 LYG per 1,000 screened 65-year-olds[43].

Cost Assumptions

Management of colorectal cancer has changed significantly over the past several years. With the introduction of modern chemotherapy agents such as oxaliplatin and targeted therapy such as bevacizumab, cetuximab, and panitumumab,

treatment regimens have changed significantly, costs of care have increased[30] and in many instances, patients live longer. Prior studies have not included these costs into their model and therefore their estimates of the incremental costs of screening over no intervention are expected to be different. It is expected that as costs of care increase and cancer patients live longer and therefore undergo more treatment, the costs of care will increase significantly and may quickly exceed the savings assumed to be associated with no intervention. Prior simulations using MISCAN, based on the traditional cost structure and survival expectation for colorectal cancer, have shown that screening with colonoscopy may come at an additional societal cost over no screening, although, the same studies also report simulation results using other models such as SimCRC and CRC-SPIN that show screening with colonoscopy would lower the total costs compared with no screening[1,43].

Clearly, a significant increase in the costs of cancer care could close this gap, as projected by MISCAN, and may in fact result in no screening becoming more expensive than screening[44-46]. More recent analyses have used an updated and more realistic cost structure that is also used in this study[29].

Supplementary Results

Additional Supplementary Tables summarizing results are listed here.

- Supplementary Table-5: One-way sensitivity analysis around sensitivity of Test X for adenoma detection. Includes stage-shift effect.

- Supplementary Table-6: One-way sensitivity analysis around sensitivity of Test X for adenoma detection. Excludes stage-shift effect.
- Supplementary Table-7: Cost analysis for DNA testing every year or every 3 years, with and without the benefit of adenoma detection.
- Supplementary Table-8: Further analysis on the observation that at times Test X with longer screening intervals outperforms Test X with shorter screening intervals- Also see Supplementary Discussion below.

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Assumptions	Sensitivity for Adenoma Detection	Strategy	Comparative Effectiveness			Costs		Cost Effectiveness			
			LY	CRC Diagnosed	CRC Prevented	Cancer Management	Total	Incremental Costs	Incremental Effect	ICER	Status (Rank)
Base Case Cost Model A	50%	ST 5: Colonoscopy	15.235	3,521	1,032	$ 2,477	$ 3,001	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.231	3,787	760	$ 2,891	$ 4,150	$ 1,149	-0.004	$ (-)	AD
		ST 15: Test X 3	15.232	3,643	903	$ 2,771	$ 3,770	$ 768	-0.003	$ (-)	AD
		ST 16: Test X 5	15.231	3,757	790	$ 2,810	$ 3,554	$ 552	-0.004	$ (-)	AD
	60%	ST 5: Colonoscopy	15.218	3,492	1,068	$ 2,624	$ 3,149	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.211	3,747	807	$ 3,027	$ 4,287	$ 1,137	-0.007	$ (-)	AD
		ST 15: Test X 3	15.215	3,555	1,003	$ 2,808	$ 3,807	$ 658	-0.003	$ (-)	AD
		ST 16: Test X 5	15.215	3,647	910	$ 2,828	$ 3,572	$ 423	-0.002	$ (-)	AD
	70%	ST 5: Colonoscopy	15.218	3,470	1,024	$ 2,385	$ 2,910	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.211	3,680	801	$ 2,823	$ 4,077	$ 1,166	-0.007	$ (-)	AD
		ST 15: Test X 3	15.216	3,461	1,024	$ 2,594	$ 3,591	$ 681	-0.002	$ (-)	AD
		ST 16: Test X 5	15.216	3,547	942	$ 2,601	$ 3,345	$ 434	-0.002	$ (-)	AD
	80%	ST 5: Colonoscopy	15.199	3,576	1,027	$ 2,549	$ 3,073	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.192	3,803	788	$ 3,016	$ 4,275	$ 1,201	-0.007	$ (-)	AD
		ST 15: Test X 3	15.199	3,506	1,093	$ 2,678	$ 3,678	$ 605	-0.001	$ (-)	AD
		ST 16: Test X 5	15.198	3,578	1,023	$ 2,682	$ 3,425	$ 351	-0.001	$ (-)	AD
	90%	ST 5: Colonoscopy	15.225	3,591	1,007	$ 2,531	$ 3,057	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.222	3,742	852	$ 2,793	$ 4,046	$ 753	-0.004	$ (-)	AD
		ST 15: Test X 3	15.225	3,427	1,169	$ 2,549	$ 3,549	$ 255	-0.001	$ (-)	AD
		ST 16: Test X 5	15.225	3,490	1,110	$ 2,549	$ 3,294	$ 237	0.000	$ 760,852	UD (2)
	100%	ST 5: Colonoscopy	15.198	3,536	1,030	$ 2,508	$ 3,032	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.193	3,681	890	$ 2,857	$ 4,116	$ 949	-0.008	$ (-)	AD
		ST 15: Test X 3	15.201	3,278	1,293	$ 2,462	$ 3,460	$ 292	0.000	$ (-)	AD
		ST 16: Test X 5	15.201	3,333	1,238	$ 2,424	$ 3,168	$ 136	0.004	$ 37,271	UD (2)
Alternate Case Cost Model A	50%	ST 5: Colonoscopy	15.199	3,503	989	$ 2,496	$ 3,021	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.191	3,835	644	$ 3,029	$ 4,494	$ 1,473	-0.008	$ (-)	AD
		ST 15: Test X 3	15.196	3,674	805	$ 2,751	$ 3,796	$ 775	-0.002	$ (-)	AD
		ST 16: Test X 5	15.194	3,773	706	$ 2,822	$ 3,576	$ 555	-0.005	$ (-)	AD
	60%	ST 5: Colonoscopy	15.209	3,529	1,041	$ 2,492	$ 3,016	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.200	3,837	729	$ 3,084	$ 4,544	$ 1,528	-0.009	$ (-)	AD
		ST 15: Test X 3	15.205	3,649	923	$ 2,808	$ 3,854	$ 838	-0.004	$ (-)	AD
		ST 16: Test X 5	15.204	3,744	826	$ 2,825	$ 3,579	$ 563	-0.004	$ (-)	AD
	70%	ST 5: Colonoscopy	15.211	3,543	1,020	$ 2,453	$ 2,978	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.205	3,758	800	$ 2,879	$ 4,343	$ 1,365	-0.005	$ (-)	AD
		ST 15: Test X 3	15.207	3,558	1,003	$ 2,688	$ 3,736	$ 757	-0.004	$ (-)	AD
		ST 16: Test X 5	15.207	3,641	922	$ 2,692	$ 3,449	$ 471	-0.004	$ (-)	AD
	80%	ST 5: Colonoscopy	15.200	3,491	1,046	$ 2,447	$ 2,972	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.193	3,678	858	$ 2,901	$ 4,365	$ 1,393	-0.007	$ (-)	AD
		ST 15: Test X 3	15.197	3,402	1,136	$ 2,586	$ 3,634	$ 662	-0.002	$ (-)	AD
		ST 16: Test X 5	15.197	3,486	1,057	$ 2,611	$ 3,368	$ 396	-0.003	$ (-)	AD
	90%	ST 5: Colonoscopy	15.202	3,490	1,053	$ 2,498	$ 3,025	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.195	3,626	916	$ 2,907	$ 4,380	$ 828	-0.008	$ (-)	AD
		ST 15: Test X 3	15.203	3,302	1,242	$ 2,502	$ 3,551	$ 526	0.001	$ 493,876	UD (2)
		ST 16: Test X 5	15.202	3,381	1,163	$ 2,507	$ 3,264	$ 239	0.000	$ 20,846,524	ED
	100%	ST 5: Colonoscopy	15.207	3,477	1,060	$ 2,529	$ 3,053	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.206	3,527	1,005	$ 2,802	$ 4,268	$ 1,133	-0.006	$ (-)	AD
		ST 15: Test X 3	15.210	3,149	1,393	$ 2,444	$ 3,490	$ 354	-0.002	$ (-)	AD
		ST 16: Test X 5	15.212	3,235	1,309	$ 2,382	$ 3,136	$ 83	0.005	$ 17,602	UD (2)
Base Case Cost Model B	50%	ST 5: Colonoscopy	15.186	3,492	1,028	$ 3,086	$ 3,923	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.178	3,784	726	$ 3,788	$ 5,324	$ 1,401	-0.008	$ (-)	AD
		ST 15: Test X 3	15.183	3,620	888	$ 3,496	$ 4,714	$ 792	-0.003	$ (-)	AD
		ST 16: Test X 5	15.182	3,736	771	$ 3,472	$ 4,375	$ 453	-0.004	$ (-)	AD
	60%	ST 5: Colonoscopy	15.216	3,498	1,023	$ 3,044	$ 3,883	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.210	3,717	799	$ 3,628	$ 5,171	$ 1,288	-0.006	$ (-)	AD
		ST 15: Test X 3	15.211	3,552	967	$ 3,405	$ 4,621	$ 738	-0.004	$ (-)	AD
		ST 16: Test X 5	15.212	3,654	868	$ 3,428	$ 4,334	$ 451	-0.004	$ (-)	AD
	70%	ST 5: Colonoscopy	15.200	3,598	994	$ 3,111	$ 3,950	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.194	3,801	782	$ 3,646	$ 5,185	$ 1,235	-0.006	$ (-)	AD
		ST 15: Test X 3	15.198	3,595	994	$ 3,395	$ 4,610	$ 661	-0.002	$ (-)	AD
		ST 16: Test X 5	15.197	3,673	917	$ 3,376	$ 4,281	$ 331	-0.002	$ (-)	AD
	80%	ST 5: Colonoscopy	15.208	3,514	1,052	$ 3,167	$ 4,005	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.200	3,736	817	$ 3,797	$ 5,326	$ 1,322	-0.008	$ (-)	AD
		ST 15: Test X 3	15.206	3,430	1,135	$ 3,385	$ 4,600	$ 595	-0.002	$ (-)	AD
		ST 16: Test X 5	15.207	3,472	1,093	$ 3,308	$ 4,212	$ 207	0.000	$ (-)	AD
	90%	ST 5: Colonoscopy	15.197	3,540	1,031	$ 3,199	$ 4,039	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.195	3,701	866	$ 3,618	$ 5,160	$ 1,046	-0.005	$ (-)	AD
		ST 15: Test X 3	15.198	3,360	1,212	$ 3,259	$ 4,480	$ 366	-0.002	$ (-)	AD
		ST 16: Test X 5	15.200	3,418	1,153	$ 3,207	$ 4,114	$ 75	0.003	$ 21,605	UD (2)
	100%	ST 5: Colonoscopy	15.206	3,542	1,038	$ 3,299	$ 4,138	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.201	3,643	932	$ 3,773	$ 5,320	$ 1,179	-0.008	$ (-)	AD
		ST 15: Test X 3	15.207	3,278	1,308	$ 3,245	$ 4,468	$ 328	-0.002	$ (-)	AD
		ST 16: Test X 5	15.209	3,346	1,239	$ 3,233	$ 4,141	$ 3	0.003	$ 995	UD (2)
Alternate Case Cost Model B	50%	ST 5: Colonoscopy	15.228	3,527	1,068	$ 3,070	$ 3,910	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.217	3,832	748	$ 3,961	$ 5,722	$ 1,812	-0.011	$ (-)	AD
		ST 15: Test X 3	15.222	3,733	856	$ 3,640	$ 4,895	$ 985	-0.006	$ (-)	AD
		ST 16: Test X 5	15.222	3,840	748	$ 3,603	$ 4,508	$ 597	-0.006	$ (-)	AD
	60%	ST 5: Colonoscopy	15.219	3,477	1,050	$ 3,014	$ 3,853	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.211	3,755	762	$ 3,713	$ 5,467	$ 1,613	-0.008	$ (-)	AD
		ST 15: Test X 3	15.214	3,608	914	$ 3,429	$ 4,678	$ 825	-0.005	$ (-)	AD
		ST 16: Test X 5	15.213	3,689	835	$ 3,453	$ 4,354	$ 501	-0.006	$ (-)	AD
	70%	ST 5: Colonoscopy	15.205	3,590	959	$ 3,165	$ 4,005	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.198	3,774	767	$ 3,782	$ 5,546	$ 1,540	-0.007	$ (-)	AD
		ST 15: Test X 3	15.203	3,569	977	$ 3,517	$ 4,772	$ 767	-0.002	$ (-)	AD
		ST 16: Test X 5	15.203	3,661	884	$ 3,442	$ 4,346	$ 341	-0.002	$ (-)	AD
	80%	ST 5: Colonoscopy	15.236	3,573	1,025	$ 3,253	$ 4,089	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.231	3,733	858	$ 3,822	$ 5,561	$ 911	-0.006	$ (-)	AD
		ST 15: Test X 3	15.237	3,416	1,176	$ 3,400	$ 4,650	$ 561	0.000	$ 1,946,170	UD (2)
		ST 16: Test X 5	15.236	3,551	1,045	$ 3,416	$ 4,317	$ 228	-0.001	$ (-)	AD
	90%	ST 5: Colonoscopy	15.207	3,518	1,038	$ 3,109	$ 3,949	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.202	3,644	907	$ 3,714	$ 5,478	$ 1,423	-0.007	$ (-)	AD
		ST 15: Test X 3	15.208	3,326	1,231	$ 3,225	$ 4,482	$ 427	-0.002	$ (-)	AD
		ST 16: Test X 5	15.210	3,389	1,168	$ 3,150	$ 4,055	$ 106	0.002	$ 42,607	UD (2)
	100%	ST 5: Colonoscopy	15.203	3,530	1,096	$ 3,178	$ 4,018	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.197	3,627	997	$ 3,754	$ 5,506	$ 1,424	-0.008	$ (-)	AD
		ST 15: Test X 3	15.204	3,254	1,379	$ 3,248	$ 4,497	$ 416	-0.001	$ (-)	AD
		ST 16: Test X 5	15.205	3,328	1,307	$ 3,177	$ 4,082	$ 64	0.001	$ 43,272	UD (2)

Supplementary Table 5: Sensitivity analysis around the adenoma detection for "Test X." Stage shift effect w as included. The cost of "Test X" w as set equal to Cologuard DNA test. The sensitivity of "Test X" for adenoma detection is increased in increments of 10%. As sensitivity increases, the effectiveness of Test X increases and surpasses colonoscopy in effectiveness, given it is performed at higher frequency than colonoscopy. How ever, it fails to dominate colonoscopy in terms of cost effectiveness, except w hen Test X has a sensitivity of >90% for adenoma detection. Highlighting show s the dominant strategy w ith the highest ICER under a w illingness to pay of $50,000.

AD: Absolute Dominance. ED: Extended Dominance. UD: Undominated. ICER: Incremental Cost Effectiveness Ratio.

Assumptions	Sensitivity for Adenoma Detection	Strategy	Comparative Effectiveness			Costs		Cost Effectiveness			
			LYG	CRC Diagnosed	CRC Prevented	Cancer Management	Total	Incremental Costs	Incremental Effect	ICER	Status (Rank)
Base Case Cost Model A	50%	ST 5: Colonoscopy	15.187	3,501	1,012	$ 2,840	$ 3,362	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.180	3,759	752	$ 3,303	$ 4,551	$ 1,189	-0.007	$ (-)	AD
		ST 15: Test X 3	15.182	3,670	843	$ 3,185	$ 4,175	$ 813	-0.005	$ (-)	AD
		ST 16: Test X 5	15.181	3,763	745	$ 3,191	$ 3,930	$ 568	-0.006	$ (-)	AD
	100%	ST 5: Colonoscopy	15.194	3,518	1,030	$ 2,796	$ 3,322	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.190	3,608	939	$ 3,067	$ 4,325	$ 913	-0.007	$ (-)	AD
		ST 15: Test X 3	15.195	3,276	1,273	$ 2,750	$ 3,753	$ 341	-0.001	$ (-)	AD
		ST 16: Test X 5	15.197	3,321	1,230	$ 2,665	$ 3,412	$ 89	0.003	$ 29,886	UD (2)
Alternate Case Cost Model A	50%	ST 5: Colonoscopy	15.220	3,523	1,048	$ 2,806	$ 3,333	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.212	3,837	724	$ 3,325	$ 4,787	$ 1,454	-0.008	$ (-)	AD
		ST 15: Test X 3	15.214	3,708	856	$ 3,153	$ 4,201	$ 868	-0.006	$ (-)	AD
		ST 16: Test X 5	15.214	3,810	755	$ 3,164	$ 3,921	$ 589	-0.007	$ (-)	AD
	100%	ST 5: Colonoscopy	15.205	3,490	1,040	$ 2,679	$ 3,201	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.199	3,558	971	$ 3,005	$ 4,474	$ 1,115	-0.010	$ (-)	AD
		ST 15: Test X 3	15.207	3,198	1,340	$ 2,630	$ 3,675	$ 315	-0.003	$ (-)	AD
		ST 16: Test X 5	15.209	3,279	1,259	$ 2,606	$ 3,359	$ 158	0.005	$ 35,046	UD (2)
Base Case Cost Model B	50%	ST 5: Colonoscopy	15.221	3,464	1,040	$ 3,416	$ 4,255	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.215	3,734	766	$ 4,029	$ 5,561	$ 1,306	-0.005	$ (-)	AD
		ST 15: Test X 3	15.218	3,587	914	$ 3,822	$ 5,035	$ 780	-0.002	$ (-)	AD
		ST 16: Test X 5	15.216	3,675	824	$ 3,847	$ 4,752	$ 497	-0.004	$ (-)	AD
	100%	ST 5: Colonoscopy	15.197	3,556	1,057	$ 3,540	$ 4,377	$ 20	-0.005	$ (-)	AD
		ST 14: Test X	15.193	3,693	921	$ 3,997	$ 5,523	$ 1,167	-0.009	$ (-)	AD
		ST 15: Test X 3	15.201	3,332	1,284	$ 3,511	$ 4,723	$ 366	-0.001	$ (-)	AD
		ST 16: Test X 5	15.202	3,399	1,221	$ 3,454	$ 4,357	$ -	0.000	$ 0	UD (1)
Alternate Case Cost Model B	50%	ST 5: Colonoscopy	15.196	3,508	1,059	$ 3,468	$ 4,310	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.188	3,848	712	$ 4,224	$ 5,989	$ 1,679	-0.008	$ (-)	AD
		ST 15: Test X 3	15.188	3,733	830	$ 4,024	$ 5,282	$ 972	-0.008	$ (-)	AD
		ST 16: Test X 5	15.188	3,830	730	$ 4,054	$ 4,961	$ 651	-0.008	$ (-)	AD
	100%	ST 5: Colonoscopy	15.227	3,458	1,039	$ 3,296	$ 4,133	$ -	0.000	$ 0	UD (1)
		ST 14: Test X	15.222	3,551	940	$ 3,847	$ 5,589	$ 1,062	-0.008	$ (-)	AD
		ST 15: Test X 3	15.230	3,184	1,317	$ 3,280	$ 4,527	$ 311	0.002	$ 165,877	UD (3)
		ST 16: Test X 5	15.228	3,266	1,235	$ 3,314	$ 4,216	$ 83	0.001	$ 63,855	UD (2)

Supplementary Table 6: Sensitivity analysis around the adenoma detection for "Test X." Stage shift effect was excluded. The cost of "Test X" was set equal to Cologuard DNA test. The sensitivity of "Test X" for adenoma detection was set at 50% and 100%.
Highlightings mark the dominant strategy with the highest ICER under a willingness to pay of $50,000.
AD: Absolute Dominance. ED: Extended Dominance. UD: Undominated. ICER: Incremental Cost Effectiveness Ratio.

Strategy	Effectiveness Gap		Costs				Cost Effectiveness	
	LY	CRC Prevented	Cancer Management	Total Costs	Break-Even DNA Cost	Total Costs at DNA Cost of $1	Colonoscopy ICER at DNA Costs of $1	DNA Costs When Colonoscopy ICER = $50,000
Colonoscopy	15.22	1,035	$ 2,492	$ 3,018				
DNA Testing Annually	-0.009	-433	$ 3,050	$ 4,305	$ (14)	$ 3,141	$ (-)	$ (248)
Not Used for Adenoma								
DNA Testing Every 3 Years	-0.009	-461	$ 3,056	$ 4,282	$ (17)	$ 3,137	$ (-)	$ (252)
Not Used for Adenoma								
DNA Testing Annually	-0.008	-312	$ 2,950	$ 4,205	$ 29	$ 3,041	$ (-)	$ (171)
42.4% Sensitivity for Adenoma								
DNA Testing Every 3 Years	-0.004	-218	$ 2,799	$ 3,796	$ 118	$ 2,862	$ 36,545	$ (30)
42.4% Sensitivity for Adenoma								

Supplementary Table 7. Comparison of DNA testing every 1 and 3 years, with and without the benefit of adenoma detection to colonoscopy, under Base assumptions, Cost Model A.

If the costs of DNA testing were $1 per test, colonoscopy would dominate the DNA testing strategies in all 4 rows with ICERs of < $50,000. For DNA testing to dominate colonoscopy with a willingness to pay of $50,000 per life year gained the costs of DNA testing would have to be negative- shown in (), see last column.

Assumptions	Statistic	Test X	Test X 3	Cancer in Test X AND Test X 3	Cancer in Test X NOT Test X 3	Cancer in Test X 3 NOT Test X
Base Case, Universal Screening, Adenoma Sensitivity of 100%, Cost Model A	Cancer Cases	2636	2449	2319	317	130
	Screening Time to Cancer Diagnosis	8.3	7.4	7.6	10.8	10.4
	Test X Time Since Last Screening	8.3	8.3	8.0	10.8	5.2
	Test X 3 Time Since Last Screening	7.4	7.4	7.2	2.0	10.4
	Test X RR at Year of Diagnosis	67%	N/A	66%	76%	49%
	Test X 3 RR at Year of Diagnosis	N/A	62%	62%	48%	74%
	Test X Colonoscopy as Last Screening Test	79%	54%	76%	100%	80%
	Test X 3 Colonoscopy as Last Screening Test	54%	79%	52%	37%	96%
Alternate Case, Universal Screening, Adenoma Sensitivity of 100%, Cost Model A	Cancer Cases	2449	2302	1245	518	327
	Screening Time to Cancer Diagnosis	7.4	6.7	6.3	9.1	7.3
	Test X Time Since Last Screening	7.4	7.4	6.9	9.1	3.8
	Test X 3 Time Since Last Screening	6.7	6.7	5.7	2.0	7.3
	Test X RR at Year of Diagnosis	63%	N/A	61%	68%	43%
	Test X 3 RR at Year of Diagnosis	N/A	60%	56%	40%	59%
	Test X Colonoscopy as Last Screening Test	63%	39%	75%	79%	72%
	Test X 3 Colonoscopy as Last Screening Test	39%	63%	38%	23%	44%

Supplementary Table 8. The results of comparison of Test X and Test X 3. Test X 3, somewhat unexpecedly prevented more cancers, 187 and 191 under Base and Alternate assumptions, respectively.
This was traced back to a 24% and 23% increase in the use of colonoscopy and longer periods of 'no need for screening' under Base and Alternate assumptions.
As a result, the average relative risk of cancer in screened individulas is lower by 5% and 3% for Test X Strategy under Base and Alternatie assumptions, respectively.
RR: Relative Risk.

Supplementary Discussion

The following provide supplemental discussion of some of the results.

The Performance Paradox of FOBT over FIT

FIT is a more sensitive screening test compared to FOBT and therefore, one might expect better effectiveness outcomes for FIT when compared to FOBT. However, as seen in the results in primary analysis and sensitivity analyses, FOBT seems to outperform FIT. As discussed in the article, this is really not a paradox and is explained by the number of false positives produced by FOBT and FIT. FOBT produces more false positives who would undergo colonoscopy. This in turn results in detection of precancerous adenomas in a larger portion of the population compared to FIT. As a result of increased number of colonoscopies performed in FOBT group, the benefits in terms of effectiveness outcomes would be higher.

The Unexpected Better Performance of Test X 5 or Text X 3 over Test X

The sensitivity analysis results show that ST 16: Test X 5, with a compliance of 100% and adenoma detection power equal to colonoscopy, outperforms ST 15: Test X 3 which in turn outperforms ST 14: Test X across all measures. This intriguing finding was traced to a reduction in the number of colonoscopies in ST 15: Test X 3 (and Test X 5 where this phenomenon was observed) as a result of fewer false positives. After a negative colonoscopy the next screening was recommended at 10 years, but in ST 15: Test X 3, the next screening was recommended at 5 years. This

resulted in a net increase in the risk of colorectal cancer in for subjects in ST 14: Test X in years 3-10 and ultimately increased cancer incidence in this group.

This effect is present in all simulations but was maximized at higher compliance rates and when the sensitivity of adenoma detection for Test X was set at levels similar to that of colonoscopy.

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