Original Article

Cost-effectiveness analysis of colorectal cancer screening in a low incidence country: The case of Saudi Arabia

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Abstract

Background: Colorectal cancer (CRC) screening is cost-effective in many Western countries, and many have successfully implemented CRC screening programs. For countries with a lower CRC incidence, like Saudi Arabia, the value of CRC screening is less evident and requires careful weighing of harms, benefits, and costs.

Methods: We used the MISCAN-Colon microsimulation model to simulate a male and female cohort with life expectancy and CRC risk as observed in Saudi Arabia. For both cohorts, we evaluated strategies without screening, with annual or biennial faecal immunochemical testing (FIT), and with 10-yearly or once-only colonoscopy. We also considered different start and end ages of screening. For both cohorts, we estimated lifetime costs and effects of each strategy. We then identified a set of potentially cost-effective strategies using incremental cost-effectiveness ratios (ICERs) defined as the additional cost per additional quality-adjusted life year (QALY).

Results: Without CRC screening, an estimated 14 per 1,000 males would develop CRC during their lifetime and 9 would die from CRC. Several strategies proved potentially cost-effective including biennial FIT at ages 55-65 (ICER of $7,400), once-only colonoscopy at age 55 (ICER of $7,700), and 10-yearly colonoscopy at ages 50–65, 45–65, and 45–75 (ICERs of $34,000, 71,000, and 375,000, respectively). For females, risk of CRC was lower and CRC screening was therefore less cost-effective, but efficient strategies were largely similar.

Conclusions: Despite low CRC incidence in Saudi Arabia, some FIT or colonoscopy screening strategies may meet reasonable thresholds of cost-effectiveness. The optimal strategy will depend on multiple factors including the willingness to pay per QALY, the colonoscopy capacity, and the accepted budget impact.

Keywords: Colon cancer, cost-effective analysis, public health, Saudi Arabia, screening

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INTRODUCTION

Colorectal cancer (CRC) is the most commonly diagnosed cancer among Saudi males, and the third most commonly diagnosed cancer among Saudi females.[1] In 2014, the age-standardized incidence ratio (ASR) was 10.6 per 100,000 for males, and 8·2 per 100,000 for females. This is significantly lower than in western countries, where the incidence has been reduced already due to widely implemented CRC screening programs. For example, in the United States (US), the ASR has dropped from 56·7 per 100,000 in 1992 to 36·7 per 100,000 in 2016.[2]

CRC screening not only enables early detection of cancer, resulting in a more favourable prognosis, but also allows for detection of adenomas, which can be removed endoscopically before developing to cancer. In western populations with high incidence of CRC, population-wide screening has proved effective and cost-effective. The most commonly used screening tests include the faecal immunochemical test (FIT), mainly used in Europe and Australia, and colonoscopy, mainly used in the US.

In Saudi Arabia, there is no national CRC screening program in place and only a small fraction of the population undergoes screening on their own or their health care provider's initiative.[3] Whether a national screening program would be cost-effective for a low incidence country like Saudi Arabia remains uncertain. In this study, we used a microsimulation model to assess the cost-effectiveness of CRC screening using either FIT or colonoscopy in the Saudi population.

METHODS

MISCAN model

The microsimulation screening analysis model for CRC (MISCAN-Colon) used for this study was developed at the Department of Public Health of Erasmus MC, University Medical Center Rotterdam, in the Netherlands. The model has been essential in informing CRC screening policies in the US,[4-6] Australia,[7] the Netherlands,[8] and other European countries.[9] It simulates the individual life histories of a large population from birth to death. Each simulated individual ages over time and may develop one or more adenomas. Adenomas may progress in size from small (≤5 mm) to medium (6–9 mm) to large (≥10 mm), and some adenomas will become malignant. Cancer can progress from a localized to a regional and distant stage. By comparing life histories in the presence and absence of screening, the model evaluates the effect of screening.

A previous publication provides an extensive discussion of the MISCAN model's structure and underlying assumptions.[10] For this project, MISCAN-colon was calibrated to replicate the population of Saudi Arabia. To do so, we used data regarding CRC incidence[11] and stage distribution[12], as well as 5-year CRC survival in Saudi Arabia[13]. We assumed that the adenoma onset differs in comparison to the current model version for the Netherlands and the US, but the progression of the disease does not.

Analysis and assumptions

Simulated population

We simulated male and female cohorts of 10 million previously unscreened 45-year-olds in Saudi Arabia, and followed them until death. Life expectancy was obtained from life tables for Saudi Arabia published by the World Health Organization.[14] Model results are presented for males and females separately, as well as for both genders combined, assuming that 46·8% of the 45-year-olds are female.[15]

Screening and surveillance

Simulated screening strategies include annual and biennial FIT, as well as once-only and 10-yearly colonoscopy screening. For both modalities, we considered different start ages (45, 50, and 55 years), and end ages (65, 70, and 75 years). To estimate the added value of these strategies, we also simulated a strategy without any CRC screening as the reference scenario.

Individuals with a positive FIT were referred for diagnostic colonoscopy. Individuals with adenomas detected at a screening or diagnostic colonoscopy were assumed to enter a surveillance scheme similar to US guidelines[16] in which those with high-risk findings have their next surveillance colonoscopy in 3 years, and those with low-risk findings in 5 years. Surveillance may be discontinued at age 85, provided that no adenomas are found at that age. In FIT-based strategies, individuals with a false-positive screening test return to their original screening schedule 10 years after their negative diagnostic colonoscopy.

International literature provided test characteristics of FIT and colonoscopy [Table 1]. As screening should be optimal for those who adhere to the guidelines, adherence with all screening, surveillance, and treatment procedures was set to 100%.

Utilities

The assumed loss in quality-adjusted life years (QALYs) due to CRC screening was 0.00028-0.00118 QALY per colonoscopy for colonoscopies without and with

Table 1: Model inputs: Test characteristics of FIT and colonoscopy

Parameter	Value	Source
FIT (cutoff of 20 μg of hemoglobin per gram of feces)		
Sensitivity (per person)		Imperiale *et al*.[17]
Small adenomas (≤5 mm)	7.6%*	
Medium-sized adenomas (6-9 mm)		
Large adenomas (≥10 mm)	23.8%†	
Colorectal cancer	73.8%	
Specificity‡	96.4%	
COLONOSCOPY§		
Sensitivity within reach (per lesion)¶		Van Rijn *et al*.[18]
Small adenomas (≤5 mm)	75%	
Medium-sized adenomas (6-9 mm)	85%	
Large adenomas (≥10 mm)	95%	
Colorectal cancer	95%	
Specificity‡	86%‖	
Reach	95% reaches the cecum; the reach of the remaining 5% is distributed uniformly over colon and rectum	
Complication rate for colonoscopy with polypectomy		
Serious gastrointestinal event**	Age-specific††	
Other gastrointestinal event‡‡	Age-specific§§	
Cardiovascular event¶¶	Age-specific‖‖	
Mortality rate		
Colonoscopy with polypectomy	0·0191 per 1,000***	Warren *et al*.[19], Gatto *et al*.[20] and Van Hees *et al*.[8]
Colonoscopy without polypectomy	0	

CRC=Colorectal cancer; FIT=fecal immunochemical test; LY=Life year; QALY=Quality-adjusted life year. *Sensitivity for persons with non-advanced adenomas. For persons with 1-5 mm adenomas, we assume that the sensitivity of the test is equal to the positivity rate in persons without adenomas (i.e., 1-specificity). The sensitivity for persons with 6-9 mm adenomas is chosen such that the weighted average sensitivity for persons with 1-5 mm and with 6-9 mm adenoma (s) is equal to that of non-advanced adenomas. †Sensitivity for persons with advanced adenomas (i.e., adenomas ≥10 mm and/or adenomas with advanced histology). Sensitivity was not reported for the subset of ≥10 mm adenomas. ‡Specificity is defined as the probability of a negative test result among persons who do not have adenomas or colorectal cancer. §We assume the same test characteristics for screening, diagnostic and surveillance colonoscopies. ¶The sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies.[18] ‖The lack of specificity reflects the detection of non-adenomatous polyps, which leads to unnecessary polypectomy or biopsy. **Serious gastrointestinal events are perforations, gastrointestinal bleeding, or transfusions. ††Formula: 1/[exp (9·27953−0·06105×Age) + 1] − 1/[exp (10·78719−0·06105×Age) + 1] ‡‡Other gastrointestinal events are paralytic ileus, nausea and vomiting, dehydration, or abdominal pain. §§Formula: 1/[exp (8·81404−0·05903×Age) + 1] − 1/[exp (9·61197−0·05903×Age) + 1] ¶¶Cardiovascular events are myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock. ‖‖Formula: 1/[exp (9·09053−0·07056×Age) + 1] − 1/[exp (9·38297−0·07056×Age) + 1] ***Risk of dying from a colonoscopy at age 65

polypectomy, respectively (20-22 hours at 0.88 utility, plus 0.033 disutility for waiting for pathology results if applicable.) and 0·0027-0·0055 QALY per complication of colonoscopy (2–4 days at 0·5 utility) [Table 2]. In the main analysis, no disutility was assumed for having a FIT. We did assume that life years (LYs) with CRC are of lower quality than those without CRC, with the amount of disutility being dependent on both the stage of the cancer and the phase of the clinical disease (*i.e.*, considering time since diagnosis and time until death) [Table 2].[21]

Costs

We included all costs from a third-party payer perspective (see Supplement I for details). The Saudi Food and Drug Authority (SFDA) website provided cost of medications.[27] Costs of FIT and colonoscopy were obtained from a large laboratory and private hospital, respectively. Treatment modalities and lines of management were based on a compilation of a number of international guidelines[28-32] as well as what is practiced in the community in Saudi Arabia.

Cost-effectiveness analysis

Cost-effectiveness analysis was carried out over the lifetime horizon from a public payer's perspective. Screening effectiveness (i.e., number of CRC deaths prevented, relative CRC mortality reduction, LYs and QALYs gained) and resources utilized (e.g. colonoscopies and costs) were computed for each screening strategy. Both (QA) LYs and costs were discounted at the conventional 3% annually. Outcomes are reported per 1,000 45-year olds.

We first ranked all strategies by the total costs and eliminated strategies that were more costly and less effective than other strategies (*i.e.*, strictly dominated strategies) and those that were less effective and less costly but provided an additional QALY at a higher incremental cost (*i.e.*, weakly dominated strategies). The remaining non-dominated strategies provide an efficient allocation of resources. For all these efficient strategies, we calculated the incremental cost-effectiveness ratio (ICER), defined as the additional cost per additional QALY gained compared

Table 2: Model inputs: Disutilities and costs associated with doing a FIT, undergoing a colonoscopy, having a colonoscopy complication, and living with CRC

Parameter	Disutilities		Costs*
	Base-case value	Source (s)	Base-case value (USD)
Per FIT†		Kirkegaard *et al*.[22]	51
without colonoscopy referral	0		
with colonoscopy referral†	0	Group Health[23]	
Per colonoscopy‡			
without polypectomy/biopsy	0·00028	Swan *et al*.[24] and Jonas *et al*. [25]	613
with polypectomy/biopsy§	0·00118	Kirkegaard *et al*.[22]	773
Per complication of colonoscopy			
Serious gastrointestinal event¶	0·0055		6,996
Other gastrointestinal event‖	0·0027		4,984
Cardiovascular event**	0·0048		5,463
Per LY with CRC care††		Ness *et al*.[21]	
Localized CRC			
Initial phase	0·12		18,045
Continuing phase	0·05		184
Terminal phase (CRC death) ‡‡	0·70		37,178
Terminal phase (death other cause) ‡‡	0·05		55,246
Regional CRC			
Initial phase	0·21		49,294
Continuing phase	0·15		2,665
Terminal phase (CRC death) ‡‡	0·70		59,654
Terminal phase (death other cause) ‡‡	0·15		90,003
Distant CRC			
Initial phase	0·70		121,182
Continuing phase	0·70		110,852
Terminal phase (CRC death) ‡‡	0·70		143,013
Terminal phase (death other cause) ‡‡	0·70		179,837

*More details on costs are provided in Supplement I. †In sensitivity analyses, taking a FIT test was assumed to be associated with a disutility of 0·024 (i.e., 20% that of colonoscopy) for a duration of one hour. We assumed a disutility of 0·0083 (25% * 0·033) for the time waiting for the result (5 days). This disutility was based on a small Danish study on how patients feel while waiting for a diagnostic colonoscopy after a positive FIT (0·033);[22] this value was multiplied with 0·25 because waiting for a FIT result is part of regular screening and is likely to be significantly less stressful compared to waiting for a diagnostic colonoscopy. In the same sensitivity analysis, for people with a positive FIT, we assumed an additional disutility of 0·033 for the time waiting for follow-up colonoscopy.[22] This disutility was assumed for the entire waiting time from a positive FIT until diagnostic colonoscopy, which was assumed to have a median duration of 84 days, based on Group Health results.[23]. ‡For colonoscopy, a disutility of 0·12 was assumed based on Swan *et al*.[24] for a duration of 20·22 hours, based on Jonas *et al*.[24]§If polyps were detected, an additional disutility of 0·033 was assumed for the time waiting for the pathology results, based on a small Danish study on how patients feel while waiting for a diagnostic colonoscopy after a positive FIT.[22] We assumed that this waiting period would take on average 10 days.¶Serious gastrointestinal events are perforations, gastrointestinal bleeding, or transfusions. These were assumed to be associated with a disutility of 0·5 for a duration of 4 days. ‖Other gastrointestinal events are paralytic ileus, nausea and vomiting, dehydration, or abdominal pain. These were assumed to be associated with a disutility of 0·5 for a duration of 2 days.**Cardiovascular events are myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock. These were assumed to be associated with a disutility of 0·5 for a duration of 3·5 days.††Care for CRC was divided in three clinically relevant phases: the initial, continuing, and terminal care phase. The initial care phase was defined as the first 6 months after diagnosis; the terminal care phase was defined as the final 12 months of life; the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between CRC patients dying from CRC and CRC patients dying from another cause. For patients surviving less than 18 months, the final 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.‡‡Costs of terminal care were calculated based on the cost difference for initial care between Saudi Arabia (Saudi Food & Drug Authority) and the US.[26] For each terminal care cost category, this difference ratio was multiplied with the US terminal costs. Given the uncertainty of these estimates, costs of terminal care (for both CRC-related death and death due to others causes) were increased and decreased with 50% in sensitivity analyses

with the next efficient strategy. These strategies are on the efficiency frontier and are potentially cost-effective, depending on the willingness-to-pay threshold.

Sensitivity analyses

We performed sensitivity analyses on the following model assumptions, for which the available data were limited;

- Disutility of FIT screening. In the main analysis we did not assume any disutility for FIT screening, because the test is non-invasive and easy to use. However, individuals may experience anxiety and stress towards the FIT result and especially towards the colonoscopy after a positive FIT result, which may reduce their quality of life. Therefore, in sensitivity analyses we assumed a QALY loss of 0·00012 for having a FIT without colonoscopy referral (*i.e.*, a disutility of 0·024 for 1 hour for having the test, and of 0·00826 for 5 days for waiting for the result), and a QALY loss of 0·00772 for having a FIT with colonoscopy referral (*i.e.*, 0·00012 plus a disutility of 0·033 for 84 days[23] for waiting for the diagnostic colonoscopy).
- Life expectancy of 45-year-olds in Saudi Arabia. In the main analysis, we used life tables from the World

Health Organisation, which may not be accurate.[14] Therefore, in sensitivity analyses, we increased and decreased the age-specific probability to die of other causes than CRC with 20%.
- Because these figures were based on US numbers, which may be different in Saudi Arabia, costs of terminal care were increased and decreased with 50%.
- Costs of FIT and colonoscopy were increased and decreased with 50%, because prices were obtained from one lab and one hospital respectively (see supplement for details), and nationwide implementation of screening will likely lead to price changes.

Budget impact analysis

Although cost-effectiveness analysis can determine which strategy provides good value for money, other restrictions such as available colonoscopy capacity and financial resources may limit the strategies feasible to implement. Therefore, we also performed a budget impact analysis to determine the impact of the identified cost-effective screening strategies on annual budget and colonoscopy capacity. For this analysis, we simulated the population of Saudi Arabia in 2020 and followed them for a lifetime under all identified cost-effective screening strategies. We assumed 50% adherence to screening, 80% to diagnostic follow-up, and 100% to surveillance colonoscopies. For each strategy, the model estimated annual colonoscopy demand, and costs for screening, diagnostic follow-up, surveillance and treatment from 2020 until 2050.

RESULTS

Main analysis

In the absence of screening, 14 per 1,000 45-year-old males would ever be diagnosed with CRC, and 9 would die from CRC [Table 3]. Biennial FIT from ages 55 to 65 would prevent 2 of those cases and 3 of those deaths, at an incremental cost of $100,000. Colonoscopy screening would prevent up to 9 cases and 6 deaths, but would also be significantly more costly (i.e., costing up to $950,000), compared to no screening. Colonoscopy strategies on the efficiency frontier include once-only colonoscopy at age 55, and 10-yearly colonoscopy screening at ages 50–65, 45–65, and 45–75 [Figure 1a].

With an estimated 11 CRC diagnoses and 6 CRC deaths per 1,000, the lifetime risk for 45-year-old females was lower than for males. Both FIT and colonoscopy screening were less effective; however, the strategies on the efficiency frontier were largely similar. Compared to the set of strategies identified as being efficient for males, only once-only colonoscopy at age 50 was added [Figure 1b]. When considering both males and females combined, this strategy again dropped from the efficiency frontier. The cheapest efficient option was biennial FIT from ages 55 to 65 with ICERs ranging from $7,450 for males to $10,525 for females. Once-only colonoscopy showed similar cost-effectiveness (ICERs ranging from $7,607 to $10,761) at slightly higher costs ($60,000 per 1,000).

Table 3: Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	14	14	9	19,919	19,910	1,092	Reference
Biennial FIT at ages 55-65	4,942	548	12	6	19,932	19,924	1,195	7,450
Once Only COL at age 55	0	1,302	8	5	19,932	19,932	1,254	7,607
10y COL at ages 50-65	0	2,258	6	3	19,946	19,941	1,559	33,825
10y COL at ages 45-65	0	3,100	5	3	19,951	19,946	1,929	71,332
10y COL at ages 45-75	0	3,554	5	3	19,951	19,946	2,042	467,890
Women								
No Screening	0	11	11	6	20,886	20,877	994	Reference
Biennial FIT at ages 55-65	5,023	584	9	4	20,896	20,889	1,115	10,525
Once Only COL at age 55	0	325	6	3	20,900	20,894	1,174	10,761
Once Only COL at age 50	0	344	6	3	20,902	20,896	1,257	38,070
10y COL at ages 50-65	0	2,261	4	2	20,907	20,902	1,481	40,518
10y COL at ages 45-65	0	3,123	3	1	20,911	20,907	1,847	74,418
10y COL at ages 45-75	0	3,675	3	1	20,911	20,907	1,990	2,636,617
Men+Women								
No Screening	0	13	13	7	20,389	20,380	1,044	Reference
Biennial FIT at ages 55-65	4,982	565	10	5	20,401	20,393	1,156	8,808
Once Only COL at age 55	0	1,298	7	4	20,406	20,400	1,215	8,872
10y COL at ages 50-65	0	2,259	5	3	20,413	20,408	1,521	36,503
10y COL at ages 45-65	0	3,111	4	2	20,418	20,413	1,889	72,792
10y COL at ages 45-75	0	3,613	4	2	20,418	20,413	2,017	848,977

COL=Colonoscopy; CRC=Colorectal cancer; FIT=Fecal immunochemical test; ICER=Incremental cost-effectiveness ratio; LY=Life year; QALY=Quality-adjusted life year. *(Quality-adjusted) life years and costs were discounted at an annual rate of 3%. †Colonoscopies include screening, diagnostic and surveillance colonoscopies

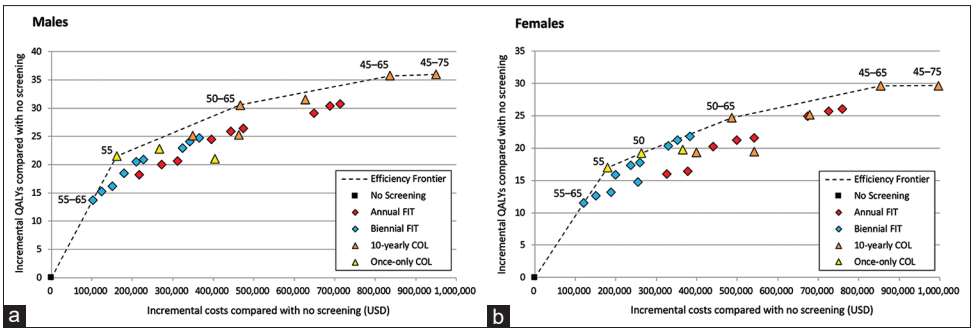

Figure 1: (a) Costs, QALYs, and efficiency frontier for FIT and colonoscopy screening of 1,000 men in Saudi Arabia. (b) Costs, QALYs, and efficiency frontier for FIT and colonoscopy screening of 1,000 women in Saudi Arabia

Sensitivity analyses

In all sensitivity analyses, the least expensive cost-effective screening option was either biennial FIT at ages 55–65 or once-only colonoscopy at age 55 [Supplementary Tables 4-12]. The ICER compared with no screening varied from $2,300 to $16,400 per QALY gained [Figure 2a and b].

We assumed a disutility for FIT screening reduced the effectiveness of FIT-based screening strategies. Consequently, biennial FIT at ages 55–65 was no longer an efficient screening option [Supplementary Table 4], and the efficiency frontier only included colonoscopy-based strategies. All FIT strategies were also dominated when a higher life expectancy was assumed [Supplementary Table 6], when costs of terminal care were increased by 50% [Supplementary Table 8], when the costs of FIT were increased by 50% [Supplementary Table 10], or when the costs of colonoscopy were decreased by 50% [Supplementary Table 11].

We assumed a lower life expectancy resulted in the same strategies being identified as efficient, but at relatively higher costs per QALY gained [Supplementary Table 5]. The same was true for assuming 50% lower costs of terminal care [Supplementary Table 7]. Foregoing screening becomes less expensive when costs of terminal care are reduced, and therefore the strategies with screening become relatively more expensive.

When costs of FIT were reduced by 50% [Supplementary Table 9] or when costs of colonoscopy were increased by 50% [Supplementary Table 12], several additional FIT strategies appeared on the efficiency frontier. Efficient colonoscopy-based strategies were on the higher end of the efficiency frontier, with ICERs of more than $90,000 per QALY.

Budget impact analysis

Nationally, in a situation without screening, costs of CRC diagnosis and treatment are relatively stable in the coming 30 years at around $305 million annually. For a strategy with biennial FIT at ages 55–65, total costs of CRC screening, surveillance, complications, and treatment would be highest in the first years after implementation, with a peak of an additional $57 million in the second

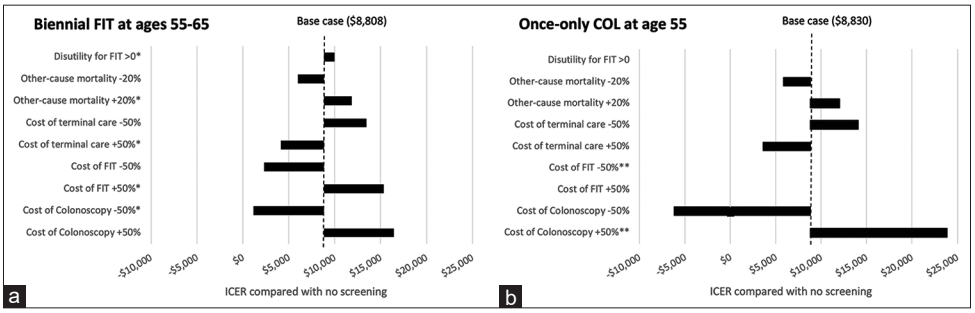

Figure 2: (a) Incremental cost-effectiveness ratio of screening the Saudi Arabian population (both males and females) with biennial FIT at ages 55 to 65 as compared to a situation without screening, for the base case and sensitivity analysis. COL = colonoscopy; FIT = fecal immunochemical testing; ICER = incremental cost-effectiveness ratio. *Biennial FIT at ages 55 to 65 was dominated by colonoscopy strategies. **Once-only colonoscopy at age 55 was dominated by FIT-based strategies. (b) Incremental cost-effectiveness ratio of screening the Saudi Arabian population (both males and females) once-only colonoscopy at age 55 as compared to a situation without screening, for the base case and sensitivity analyses. COL = colonoscopy; FIT = fecal immunochemical testing; ICER = incremental cost-effectiveness ratio. *Biennial FIT at ages 55 to 65 was dominated by colonoscopy strategies. **Once-only colonoscopy at age 55 was dominated by FIT-based strategies

year [Supplementary Figure 1a]. Costs would then decline steadily to $29 million at 30 years after implementation. A similar trend exists for once-only colonoscopy screening at age 55, albeit somewhat higher, with a peak of $82 million and long-term cost of $48 million. The colonoscopy demand was highest in the colonoscopy-based screening strategies. Compared to the situation without screening, once-only colonoscopy at age 55 would require an additional 120,000 colonoscopies in the first year to 137,000 in the 30th year [Supplementary Figure 1b]. In comparison, biennial FIT at ages 55–65 would require an additional 21,000 to 31,000 colonoscopies annually.

DISCUSSION

This cost-effectiveness analysis shows that with inputs from Saudi Arabia, implementing biennial FIT screening at ages 55–65 is likely to be the least expensive option among a set of efficient CRC screening strategies. Three CRC cases and three CRC deaths per 1,000 45-year-olds would be averted at an ICER of $8,800 per QALY. Once-only colonoscopy at age 55 showed similar cost-effectiveness (ICER of $8,900) at slightly higher total costs. In general, screening would be both more effective and cost-effective for men than for women, because men are at higher risk of developing CRC and therefore their expected benefit from screening is larger. Nevertheless, the set of efficient strategies was largely similar for both men and women.

These results indicate that CRC screening strategies may meet reasonable thresholds of cost-effectiveness in Saudi Arabia despite the generally lower risk compared to many Western countries. There are two important explanations for this. First, CRC screening can prevent CRC diagnosis and the associated treatment costs resulting in cost savings. Indeed, treatment costs for CRC in Saudi Arabia are high (*i.e.*, comparable to that of US[26]) and therefore preventing disease through screening results in considerable cost savings. Second, the cost-effective screening strategies in Saudi Arabia are less intense than those used in, for example, the US.

Our study identified biennial FIT at ages 55–65 and once-only colonoscopy at age 55 as promising strategies for Saudi Arabia. Their comparative cost-effectiveness varied with assumptions for the disutility due to FIT screening, remaining life expectancy of 45-year-olds in Saudi Arabia, and the costs of FIT, colonoscopy, and terminal care. However, the least expensive cost-effective strategy was consistently one of these two strategies and the ICER compared to a situation without screening did not increase beyond $16,500. Even though Saudi Arabia does not have a fixed willingness-to-pay threshold, the World Health Organization would identify such an intervention as very cost-effective, given that the ICER is well below the Saudi Arabian gross domestic product per capita of $23,000.

An important strength of this study is that it was conducted using the MISCAN microsimulation model, which has been validated and used in other countries. We calibrated the model using Saudi Arabian demographic and CRC epidemiology data. As to its limitations, uncertainty exists regarding our cost-effectiveness estimates due to the lack of local data on health utilities and costs of cancer care. Although some parameter values are unknown for the Saudi Arabian setting and were therefore based on estimates from other countries, we did investigate the local costs of different procedures. Moreover, sensitivity analyses showed that varying costs and utilities does not change our conclusion that CRC screening is likely cost-effective. Second, we did not conduct a probabilistic sensitivity analysis, which could have provided insight into the probability of specific strategies to be cost-effective. However, distributions for parameters including health utilities and costs would have been chosen arbitrarily, and therefore performing a probabilistic sensitivity analysis would have had limited value.

The decision to implement a specific screening strategy will not depend exclusively on its cost-effectiveness. Other factors that decision-makers should consider include the budget impact, adherence to different test modalities, and organizational feasibility of the program. For example, FIT may be preferred in settings where colonoscopy capacity is limited. A program's effectiveness is also largely affected by the adherence of the eligible population to the guidelines. To reach sufficiently high adherence levels, it is important to consider patient preferences for different types of screening modalities. Further research is warranted to explore such preferences and to identify any potential organizational barriers for implementation of CRC screening in the Saudi Arabian population.

An alternative we did not consider is screening implemented in the context of individualized shared decision making, an approach suggested in a recent CRC practice guideline.[33] A low-risk setting like Saudi Arabia may be particularly suitable for this because many low-risk individuals might not need any type of CRC screening. However, successful implementation of such risk-based screening would require detailed data on risk factors, which is generally not available. Thus, our analyses did not consider this approach.

In conclusion, despite low CRC incidence in Saudi Arabia, some FIT-or colonoscopy-based screening strategies may

meet reasonable thresholds of cost-effectiveness. Biennial FIT screening from ages 55 to 65 appears to be the cheapest option, but its cost-effectiveness is dependent on several model assumptions. Once-only colonoscopy screening at age 55 seems a more robust alternative at similar cost-effectiveness. The optimal strategy will ultimately depend on multiple factors including the willingness to pay per QALY, the colonoscopy capacity, and the accepted budget impact.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENT I. DESCRIPTION OF COSTS

This supplement describes the derivation of cost estimates from several different sources. All cost estimates were based on a third-party payer perspective.

Unit costs for screening

The cost of the screening tests including FIT and colonoscopy as well as the cost associated with investigations associated with the screening procedure (e.g., performing a polypectomy and histopathological examination of a resected polyp) were based on prices from private healthcare institutions in Riyadh, Saudi Arabia [Supplementary Table 1] as there is no current national registry that captures such information equivalent to the National Inpatient Sample in the USA.

Unit costs for diagnosis and treatment procedures

The costs associated with the evaluation of an individual diagnosed with colorectal cancer, including complete blood count, chemistry profile, carcinoembryonic antigen (CEA) and other blood investigations were adopted from prices obtained from a large commercial medical laboratory network in the region.[1] Also, special histopathological tests for those diagnosed with colon cancer including; RAS tests (including KRAS and NRAS gene mutations), and BRAF V600E mutation tests were obtained from the same source. Also the costs of imaging procedures performed including computerized tomography (CT) with and without contrast of the chest, abdomen and pelvis (based on the stage of disease), as well as the costs of surgeries that would be performed (laparoscopic colectomy with primary anastmosis) were obtained from a private healthcare institution in Riyadh, Saudi Arabia.

Unit costs for medication

The costs of the individual chemotherapy medications used to treat colorectal cancer, namely, Bevasuzomab, Capecitabine, Cetuximab, 5-Fluorouracil, Folinic Acid, Irinotecan**,** and Oxaliplatin were obtained from the official website of the Saudi Food and Drug Authority (SFDA), where the list of registered medications and their costs are posted and updated [Supplementary Table 2].[2]

Calculation of total costs per cancer stage

The National Comprehensive Cancer Network (NCCN) guidelines (1.2017) were used for calculating the cost of investigating and treating each stage of colorectal cancer which included: investigations recommended (e.g., laboratory, imaging, and endoscopy), surgery, or chemotherapy as well as the frequency of these interventions.[3] For details see Supplementary Table 3.

When calculating the cost of each infusion/cycle of chemotherapy we presumed that the average body surface area of patients was 1.79 m^2 for the combination of chemotherapy agents that would be used to treat each stage of colorectal cancer.

We did not take into account the costs of magnetic resonance imaging (MRI) with contrast or positron emission testing (PET) CT scans as these are only used in some cases. Radiation and ablation therapy is not often used to treat colon cancer in Saudi Arabia and thus were not calculated. Also the costs of steroids and antiemetic were not included in the analysis. In addition, the cost of day-infusion units and potential adverse events that might result from the administration of the medications was not accounted for.

Supplementary Table 1: The costs of the screening tests

	Cost (SAR)	Source
Colonoscopy without polypectomy or biopsy	2300	Private Hospital
Colonoscopy with polypectomy or biopsy	2900	Private Hospital
FIT test	190	Large Private Lab

FIT=Fecal immunochemical test; SAR=Saudi Arabian Riyals (1 USD=3.75 SAR)

Supplementary Table 2: The costs of the drugs

	Cost (SAR)
Capecitabine (150 mg)	273
Capecitabine (500 mg)	1,632
Fluorouracil, 5-FU (50 mg/ml, 10 ml)	63
Oxaliplatin (100 mg)	2,402
Irinotecan (20 mg/ml, 25 ml)	2,609
Folinic Acid (leucovorin) (10/mg/ml, 3 ml)	91
Bevasuzomab (25 mg/ml, 16 ml)	5,956

SAR=Saudi Arabian Riyals (1 USD=3.75 SAR)

Supplementary Table 3: The costs of treatment for each stage for the initial 6 months and the years thereafter

	Cost (SAR)	Source
LOCALIZED CANCER		
Initial 6 months		
Colonoscopy with polypectomy and or biopsy	2,900	Private Hospital
Complete Blood Count	120	Large Private Lab
Creatinine in Serum	60	Large Private Lab
Na and K	144	Large Private Lab
Bicarbonate	150	Large Private Lab
Urea	60	Large Private Lab
CT chest plane and post contrast	1,800	Private Hospital
CT abdomen and pelvis plane and post contrast	2,600	Private Hospital
Colectomy+lymphadenectomy (Laparoscopic)	26,000	Private Hospital
Total	33,834 (9,022 USD)	
Continuous costs		
Colonoscopy surveillance (3 times in first 10 years)	2,300*3=6,900	Private Hospital
Total	6,900 (1,840 USD)	
REGIONAL CANCER		
Initial 6 months		
Colonoscopy with Histology	2,900	Private Hospital
Complete Blood Count	120	Large Private Lab
Creatinine in Serum	60	Large Private Lab
Na and K	144	Large Private Lab
Bicarbonate	150	Large Private Lab
Urea	60	Large Private Lab
CEA	180	Large Private Lab
CT chest plane and post contrast	1,800	Private Hospital
CT abdomen and pelvis plane and post contrast	2,600	Private Hospital
CAPEOX (CAPE=capecitabine+OX=oxaliplatin)* (8 cycles)	63,740 (based on a 79 Kg person)	SFDA pricing
CT chest plane and post contrast after 4th cycle	1,800	Private Hospital
CT abdomen and pelvis plane and post contrast after 4th cycle	2,600	Private Hospital
Chair time costs (MD costs, IV kits, Nursing) (8 cycles)	1,500*8=12,000	University Hospital fees at King Khalid University Hospital
Complete Blood Count (8 cycles)	120*8=960	Large Private Lab
Creatinine in Serum (8 cycles)	60*8=480	Large Private Lab
Na and K (8 cycles)	144*8=1,152	Large Private Lab
Bicarbonate (8 cycles)	150*8=1,200	Large Private Lab
Urea (8 cycles)	60*8=480	Large Private Lab
Total	92,426 (24,647 USD)	
Continuous costs		
CEA (Every 3 months for 2 years, then every 6 months for 3 years)	180* 14=2,520	Large Private Lab
CT chest plane and post contrast (Every 6 months for up to 5 years)	1,800 * 10= 18,000	Private Hospital
CT abdomen and pelvis plane and post contrast (Every 6 months for up to 5 years)	2,600* 10=26,000	Private Hospital
Colonoscopy surveillance (3 times in first 10 years)	2,300*3=6,900	Private Hospital
Total	53,420 (14,245 USD)	
DISTANT CANCER		
Initial 6 months		
Colonoscopy	2,300	Private Hospital
Histology	480	Large Private Lab
RAS test (KRAS and NRAS gene mutations)	2871	Large Private Lab
BRAF V600E mutation test	2871	Large Private Lab
Complete Blood Count	120	Large Private Lab
Creatinine in Serum	60	Large Private Lab
Na and K	144	Large Private Lab
Bicarbonate	150	Large Private Lab
Urea	60	Large Private Lab
CEA	180	Large Private Lab
CT chest plane and post contrast	1,800	Private Hospital
CT abdomen and pelvis plane and post contrast	2,600	Private Hospital
Capecitabine**	6,093	SFDA pricing
Bevasuzomab** (Twice a month for 6 months)	14,890* 12= 178,680	SFDA pricing
CT chest plane and post contrast after 4th cycle	1,800	Private Hospital
CT abdomen and pelvis plane and post contrast after 4th cycle	2,600	Private Hospital

Contd...

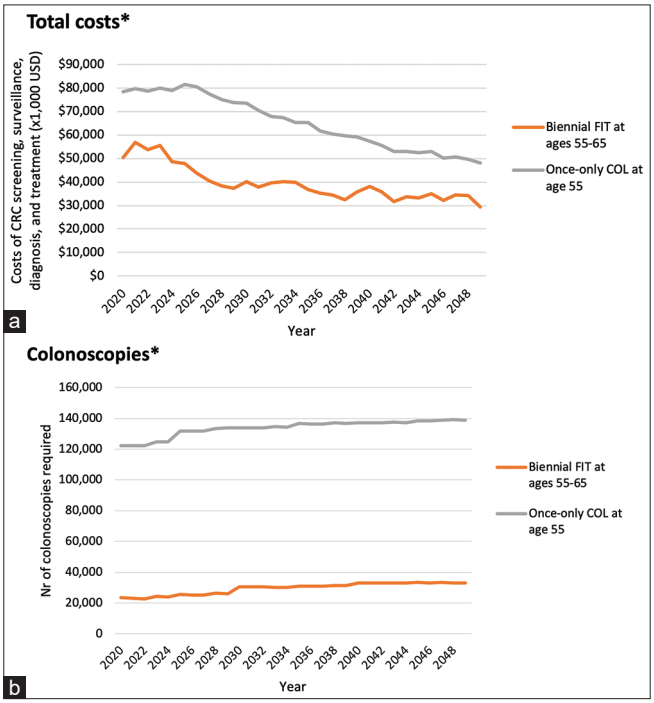
Supplementary Table 3: Contd...

	Cost (SAR)	Source
Chair time costs (MD costs, IV kits, Nursing) (Twice a month for 6 months)	1,500*12=18,000	University Hospital fees at King Khalid University Hospital
Complete Blood Count (Twice a month for 6 months)	120*12=1,440	Large Private Lab
Creatinine in Serum (Twice a month for 6 months)	60*12=720	Large Private Lab
Na and K (Twice a month for 6 months)	144*12=1,728	Large Private Lab
Bicarbonate (Twice a month for 6 months)	150*12=1,800	Large Private Lab
Urea (Twice a month for 6 months)	60*12=720	Large Private Lab
Total	227,217 (60,591 USD)	
Continuous costs		
CEA (Every 3 months for 5 years)	180*20=3,600	Large Private Lab
Bevasuzomab** (Twice a month for 5 years)	14,890*120=1,786,800	SFDA pricing
CT chest plane and post contrast (Every 6 months for 5 years)	1,800*10=18,000	Private Hospital
CT abdomen and pelvis plane and post contrast (Every 6 months for 5 years)	2,600*10=26,000	Private Hospital
Complete Blood Count (Twice a month for 5 years)	120*120=14,400	Large Private Lab
Creatinine in Serum (Twice a month for 5 years)	60*120=7,200	Large Private Lab
Na and K (Twice a month for 5 years)	144*120=17,280	Large Private Lab
Bicarbonate (Twice a month for 5 years)	150*120=18,000	Large Private Lab
Urea (Twice a month for 5 years)	60*120=7,200	Large Private Lab
Chair time costs (MD costs, IV kits, Nursing) (Twice a month for 5 years)	1,500*120=180,000	University Hospital fees at King Khalid University Hospital
Total	2,078,480 (554,261 USD)	

CEA=Carcinoembryonic antigen; CT=Computerized tomography; IV=Intravenous; MD=Medical doctor, SAR=Saudi Arabian Riyals (1 USD=3.75 SAR), SFDA=Saudi Food and Drug Authority * CAPEOX is the most frequently used treatment regimen used in Saudi Arabia. On day 1, patients get Oxaliplatin 130mg/m² IV infusion for 2 hours (7,206 SAR), and on days 1-14 patients get Capecitabine 1000mg/m2 orally twice a day (761 SAR). Treatment is administered every 21 days, usually for up to 8 cycles, and the patient is assessed radiologically after the 4th cycle. The other treatment regimen in the guidelines would be FOLFIRI (FOL=leucovorin+F = fluorouracil+IRI=irinotecan). This treatment also consists of 8 cycles and has a total cost of 35,152 SAR. All other variables would be constant. ** On days 1-14, patients get Capecitabine 1250mg/m2 PO twice daily, followed by 7 days rest (i.e., 21-day cycle) usually for up to 8 cycles. In addition, patients get Bevasuzomab 7.5 mg/kg twice a month. The patient is assessed radiologically after the 4th cycle

SUPPLEMENT II. ADDITIONAL RESULTS

The following pages provide tables with additional results for each of the sensitivity analyses and a figure with the results of the budget impact analysis.



Supplementary Figure 1: (a) Results of the Budget Impact Analysis- Annual costs of CRC screening, surveillance, diagnosis, and treatment for the two least expensive efficient screening strategies. Supplementary (b) Colonoscopy demand for the two least expensive efficient screening strategies

Supplementary Table 4: Sensitivity analysis assuming a disutility for FIT screening. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	14	14	9	19,919	19,910	1,092	Reference
Once Only COL at age 55	0	1302	8	5	19,932	19,932	1,254	7,607
10y COL at ages 50-65	0	2258	6	3	19,946	19,941	1,559	33,825
10y COL at ages 45-65	0	3100	5	3	19,951	19,946	1,929	71,332
10y COL at ages 45-75	0	3554	5	3	19,951	19,946	2,042	467,890
Women								
No Screening	0	11	11	6	20,886	20,877	994	Reference
Once Only COL at age 55	0	325	6	3	20,900	20,894	1,174	10,761
Once Only COL at age 50	0	344	6	3	20,902	20,896	1,257	38,070
10y COL at ages 50-65	0	2261	4	2	20,907	20,902	1,481	40,518
10y COL at ages 45-65	0	3123	3	1	20,911	20,907	1,847	74,418
10y COL at ages 45-75	0	3675	3	1	20,911	20,907	1,990	2,636,617
Men+Women								
No Screening	0	13	13	7	20,389	20,380	1,044	Reference
Once Only COL at age 55	0	1298	7	4	20,406	20,400	1,215	8,872
10y COL at ages 50-65	0	2259	5	3	20,413	20,408	1,521	36,503
10y COL at ages 45-65	0	3111	4	2	20,418	20,413	1,889	72,792
10y COL at ages 45-75	0	3613	4	2	20,418	20,413	2,017	848,977

Supplementary Table 5: Sensitivity analysis assuming a 20% lower life expectancy. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	13	13	8	19,257	19,429	1,014	Reference
Biennial FIT at ages 55-65	4,864	515	11	6	19,268	19,260	1,137	10,401
Once Only COL at age 55	0	1,275	8	4	19,273	19,267	1,210	10,733
10y COL at ages 50-65	0	2,218	6	3	19,281	19,275	1,524	39,098
10y COL at ages 45- 65	0	3,045	5	3	19,285	19,280	1,895	77,424
10y COL at ages 45-75	0	3,449	5	2	19,285	19,280	1,997	755,338
Women								
No Screening	0	10	10	5	20,244	20,236	935	Reference
Biennial FIT at ages 55-65	4,959	555	8	3	20,253	20,246	1,072	13,626
Once Only COL at age 55	0	1,273	6	3	20,257	20,251	1,144	14,755
Once Only COL at age 50	0	1,316	6	3	20,259	20,253	1,224	34,771
Biennial FIT at ages 45-70	9,614	1,112	7	2	20,261	20,255	1,309	46,244
10y COL at ages 50-65	0	2,227	4	2	20,263	20,258	1,458	51,855
10y COL at ages 45- 65	0	3,079	3	1	20,267	20,263	1,824	79,116
10y COL at ages 45-75	0	3,587	3	1	20,267	20,263	1,957	9,063,312
Men+Women	0	12	12	7	19,737	19,729	975	Reference
No Screening	4,910	534	9	5	19,747	19,740	1,105	11,842
Biennial FIT at ages 55-65	0	1,274	7	4	19,752	19,746	1,178	12,359
Once Only COL at age 55	0	2,222	5	2	19,758	19,753	1,492	41,567
10y COL at ages 50-65	0	3,062	4	2	19,763	19,758	1,860	78,233
10y COL at ages 45- 65	0	3,516	4	2	19,763	19,758	1,978	1,525,617
10y COL at ages 45-75								

Supplementary Table 6: Sensitivity analysis assuming a 20% higher life expectancy. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	16	16	10	20,709	20,700	1,189	Reference
Once Only COL at age 55	0	1,332	9	5	20,732	20,725	1,306	4,632
10y COL at ages 50-65	0	2,304	7	4	20,741	20,735	1,601	28,634
10y COL at ages 45- 65	0	3,161	6	3	20,746	20,741	1,968	64,150
10y COL at ages 45-75	0	3,671	5	3	20,747	20,741	2,091	301,354
Women								
No Screening	0	12	12	6	21,637	21,627	1,062	Reference
Once Only COL at age 55	0	1,318	6	3	21,653	21,647	1,210	7,549
10y COL at ages 50-65	0	2,297	4	2	21,661	21,655	1,506	34,563
10y COL at ages 45- 65	0	3,169	4	1	21,665	21,660	1,871	69,141
10y COL at ages 45-75	0	3,768	3	1	21,665	21,661	2,025	1,349,064
Men+Women								
No Screening	0	14	14	8	21,160	21,151	1,127	Reference
Once Only COL at age 55	0	1,325	8	4	21,180	21,173	1,259	5,861
10y COL at ages 50-65	0	2,301	6	3	21,188	21,182	1,555	31,248
10y COL at ages 45- 65	0	3,165	5	2	21,193	21,188	1,921	66,477
10y COL at ages 45-75	0	3,718	4	2	21,193	21,188	2,059	520,664

COL=Colonoscopy; CRC=Colorectal cancer; FIT=Fecal immunochemical test; ICER=Incremental cost-effectiveness ratio; LY=Life year; QALY=Quality-adjusted life year. *(Quality-adjusted) life years and costs were discounted at an annual rate of 3%. †Colonoscopies include screening, diagnostic and surveillance colonoscopies

Supplementary Table 7: Sensitivity analysis assuming 50% lower costs of terminal care. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	14	14	9	19,919	19,910	835	Reference
Biennial FIT at ages 55-65	4942	548	12	6	19,932	19,924	1,001	12,019
Once Only COL at age 55	0	1302	8	5	19,932	19,932	1,106	13,594
10y COL at ages 50-65	0	2258	6	3	19,946	19,941	1,450	38,096
10y COL at ages 45-65	0	3100	5	3	19,951	19,946	1,838	74,838
10y COL at ages 45-75	0	3554	5	3	19,951	19,946	1,954	480,760
Women								
No Screening	0	11	11	6	20,886	20,877	790	Reference
Biennial FIT at ages 55-65	5,023	584	9	4	20,896	20,889	966	15,282
Once Only COL at age 55	0	325	6	3	20,900	20,894	1,062	17,592
Once Only COL at age 50	0	344	6	3	20,902	20,896	1,145	37,526
Biennial FIT at ages 45-70	9,711	1,172	7	3	20,905	20,898	1,234	43,608
10y COL at ages 50-65	0	2261	4	2	20,907	20,902	1,404	49,025
10y COL at ages 45-65	0	3123	3	1	20,911	20,907	1,787	77,777
10y COL at ages 45-75	0	3675	3	1	20,911	20,907	1,931	2,667,223
Men+Women								
No Screening	0	13	13	7	20,389	20,380	813	Reference
Biennial FIT at ages 55-65	4982	565	10	5	20,401	20,393	984	13,460
Once Only COL at age 55	0	1298	7	4	20,406	20,400	1,085	15,198
10y COL at ages 50-65	0	2259	5	3	20,413	20,408	1,428	40,869
10y COL at ages 45-65	0	3111	4	2	20,418	20,413	1,813	76,228
10y COL at ages 45-75	0	3613	4	2	20,418	20,413	1,943	864,964

COL=Colonoscopy; CRC=Colorectal cancer; FIT=Faecal immunochemical test; ICER=Incremental cost-effectiveness ratio; LY=Life year; QALY=Quality-adjusted life year. *(Quality-adjusted) life years and costs were discounted at an annual rate of 3%. †Colonoscopies include screening, diagnostic and surveillance colonoscopies

Supplementary Table 8: Sensitivity analysis assuming 50% higher costs of terminal care. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	14	14	9	19,919	19,910	1,349	Reference
Once Only COL at age 55	0	1,302	8	5	19,932	19,932	1,402	2,426
10y COL at ages 50-65	0	2,258	6	3	19,946	19,941	1,668	29,553
10y COL at ages 45- 65	0	3,100	5	3	19,951	19,946	2,020	67,826
10y COL at ages 45-75	0	3,554	5	3	19,951	19,946	2,130	455,020
Women								
No Screening	0	11	11	6	20,886	20,877	1,197	Reference
Once Only COL at age 55	0	325	6	3	20,900	20,894	1,285	5,174
10y COL at ages 50-65	0	2,261	4	2	20,907	20,902	1,557	35,335
10y COL at ages 45- 65	0	3,123	3	1	20,911	20,907	1,907	71,060
10y COL at ages 45-75	0	3,675	3	1	20,911	20,907	2,048	2,606,011
Men + Women								
No Screening	0	13	13	7	20,389	20,380	1,275	Reference
Once Only COL at age 55	0	1,298	7	4	20,406	20,400	1,345	3,601
10y COL at ages 50-65	0	2,259	5	3	20,413	20,408	1,614	32,136
10y COL at ages 45- 65	0	3,111	4	2	20,418	20,413	1,965	69,355
10y COL at ages 45-75	0	3,613	4	2	20,418	20,413	2,090	832,990

COL = Colonoscopy; CRC = Colorectal cancer; FIT = Faecal immunochemical test; ICER = Incremental cost-effectiveness ratio; LY = Life year; QALY = Quality-adjusted life year. *(Quality-adjusted) life years and costs were discounted at an annual rate of 3%. †Colonoscopies include screening, diagnostic and surveillance colonoscopies

Supplementary Table 9: Sensitivity analysis assuming 50% lower costs of FIT. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	14	14	9	19,919	19,910	1,092	Reference
Biennial FIT at ages 55-65	4,942	548	12	6	19,932	19,924	1,113	1,506
Biennial FIT at ages 55-70	6,111	636	11	6	19,933	19,925	1,120	4,794
Biennial FIT at ages 50-70	8,130	875	10	5	19,938	19,930	1,162	8,077
Biennial FIT at ages 50-75	8,897	925	10	5	19,938	19,931	1,171	17,242
Biennial FIT at ages 45-75	10,625	1,172	10	4	19,942	19,935	1,262	23,889
Annual FIT at ages 50-75	14,372	1,430	8	4	19,943	19,936	1,324	38,108
Annual FIT at ages 45-75	16,473	1,772	8	4	19,947	19,941	1,495	39,450
10y COL at ages 45-65	0	3,100	5	3	19,951	19,946	1,929	86,924
10y COL at ages 45-75	0	3,554	5	3	19,951	19,946	2,042	467,890
Women								
No Screening	0	11	11	6	20,886	20,877	994	Reference
Biennial FIT at ages 55-65	5,023	584	9	4	20,896	20,889	1,032	3,306
Biennial FIT at ages 50-65	6,599	803	8	3	20,900	20,893	1,072	9,061
Biennial FIT at ages 50-70	8,304	932	8	3	20,901	20,894	1,088	11,129
Biennial FIT at ages 45-70	9,711	1,172	7	3	20,905	20,898	1,161	18,804
Biennial FIT at ages 45-75	10,913	1,250	7	2	20,905	20,899	1,179	35,875
Annual FIT at ages 45-70	15,643	1,814	6	2	20,908	20,903	1,417	59,363
Annual FIT at ages 45-75	16,824	1,885	5	2	20,908	20,903	1,438	75,281
10y COL at ages 45-65	0	3123	3	1	20,911	20,907	1,847	114,088
10y COL at ages 45-75	0	3675	3	1	20,911	20,907	1,990	2,636,617
Men+Women								
No Screening	0	13	13	7	20,389	20,380	1,044	Reference
Biennial FIT at ages 55-65	4,982	565	10	5	20,401	20,393	1,073	2,301
Biennial FIT at ages 55-70	6,190	658	10	5	20,402	20,394	1,084	8,082
Biennial FIT at ages 50-70	8,215	903	9	4	20,406	20,399	1,126	8,434
Biennial FIT at ages 45-70	9,641	1,137	8	4	20,409	20,403	1,207	21,598
Biennial FIT at ages 45-75	10,765	1,210	8	3	20,410	20,404	1,222	24,346
Annual FIT at ages 45-70	15,540	1,762	7	3	20,414	20,408	1,449	47,410
Annual FIT at ages 45-75	16,644	1,827	7	3	20,414	20,409	1,467	52,043
10y COL at ages 45-65	0	3111	4	2	20,418	20,413	1,889	97,913
10y COL at ages 45-75	0	3613	4	2	20,418	20,413	2,017	848,977

COL=Colonoscopy; CRC=Colorectal cancer; FIT=Faecal immunochemical test; ICER=Incremental cost-effectiveness ratio; LY=Life year; QALY=Quality-adjusted life year.

*(Quality-adjusted) life years and costs were discounted at an annual rate of 3%.

†Colonoscopies include screening, diagnostic and surveillance colonoscopies

Supplementary Table 10: Sensitivity analysis assuming 50% higher costs of FIT. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	14	14	9	19,919	19,910	1,092	Reference
Once Only COL at age 55	0	1302	8	5	19,932	19,932	1,254	7,507
10y COL at ages 50-65	0	2258	6	3	19,946	19,941	1,559	33,825
10y COL at ages 45-65	0	3100	5	3	19,951	19,946	1,929	71,332
10y COL at ages 45-75	0	3554	5	3	19,951	19,946	2,042	467,890
Women								
No Screening	0	11	11	6	20,886	20,877	994	Reference
Once Only COL at age 55	0	325	6	3	20,900	20,894	1,174	10,601
Once Only COL at age 50	0	344	6	3	20,902	20,896	1,257	38,070
10y COL at ages 50-65	0	2261	4	2	20,907	20,902	1,481	40,518
10y COL at ages 45-65	0	3123	3	1	20,911	20,907	1,847	74,418
10y COL at ages 45-75	0	3675	3	1	20,911	20,907	1,990	2,636,617
Men+Women								
No Screening	0	13	13	7	20,389	20,380	1,044	Reference
Once Only COL at age 55	0	1298	7	4	20,406	20,400	1,215	8,830
10y COL at ages 50-65	0	2259	5	3	20,413	20,408	1,521	36,503
10y COL at ages 45-65	0	3111	4	2	20,418	20,413	1,889	72,792
10y COL at ages 45-75	0	3613	4	2	20,418	20,413	2,017	848,977

COL=Colonoscopy; CRC=Colorectal cancer; FIT=Faecal immunochemical test; ICER=Incremental cost-effectiveness ratio; LY=Life year; QALY=Quality-adjusted life year. *(Quality-adjusted) life years and costs were discounted at an annual rate of 3%. †Colonoscopies include screening, diagnostic and surveillance colonoscopies

Supplementary Table 11: Sensitivity analysis assuming 50% lower costs of colonoscopy. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
Once Only COL at age 55	0	1302	8	5	19,932	19,932	959	Reference
10y COL at ages 50-65	0	2258	6	3	19,946	19,941	1,029	7,742
10y COL at ages 45-65	0	3100	5	3	19,951	19,946	1,169	27,023
10y COL at ages 45-75	0	3554	5	3	19,951	19,946	1,222	220,252
Women								
Once Only COL at age 55	0	325	6	3	20,900	20,894	882	Reference
10y COL at ages 50-65	0	2261	4	2	20,907	20,902	952	9,090
10y COL at ages 45-65	0	3123	3	1	20,911	20,907	1,085	26,949
10y COL at ages 45-75	0	3675	3	1	20,911	20,907	1,155	1,302,406
Men+Women								
Once Only COL at age 55	0	1298	7	4	20,406	20,400	922	Reference
10y COL at ages 50-65	0	2259	5	3	20,413	20,408	992	8,344
10y COL at ages 45-65	0	3111	4	2	20,418	20,413	1,128	26,988
10y COL at ages 45-75	0	3613	4	2	20,418	20,413	1,190	410,407

COL=Colonoscopy; CRC=colorectal cancer; FIT=Faecal immunochemical test; ICER=Incremental cost-effectiveness ratio; LY=Life year; QALY=Quality-adjusted life year. *(Quality-adjusted) life years and costs were discounted at an annual rate of 3%. †Colonoscopies include screening, diagnostic and surveillance colonoscopies

Supplementary Table 12: Sensitivity analysis assuming 50% higher costs of colonoscopy. Efficient strategies for men, women, and both genders, and their lifetime results and cost-effectiveness per 1,000 45-year-olds

Strategy	Events, no.				Cost-effectiveness*			
	FIT	COL†	CRC cases	CRC deaths	LYs	QALYs	Costs (*1,000 USD)	ICER
Men								
No Screening	0	14	14	9	19,919	19,910	1,095	Reference
Biennial FIT at ages 55-65	4,942	548	12	6	19,932	19,924	1,292	14,312
Biennial FIT at ages 55-70	6,111	636	11	6	19,933	19,925	1,327	24,010
Biennial FIT at ages 50-70	8,130	875	10	5	19,938	19,930	1,463	25,921
Biennial FIT at ages 50-75	8,897	925	10	5	19,938	19,931	1,487	47,729
Biennial FIT at ages 45-75	10,625	1,172	10	4	19,942	19,935	1,682	50,909
10y COL at ages 50-65	0	2,258	6	3	19,946	19,941	2,089	70,730
10y COL at ages 45-65	0	3,100	5	3	19,951	19,946	2,689	115,641
10y COL at ages 45-75	0	3,554	5	3	19,951	19,946	2,862	715,529
Women								
No Screening	0	11	11	6	20,886	20,877	996	Reference
Biennial FIT at ages 55-65	5,023	584	9	4	20,896	20,889	1,216	19,125
Biennial FIT at ages 50-65	6,599	803	8	3	20,900	20,893	1,340	28,209
Biennial FIT at ages 50-70	8,304	932	8	3	20,901	20,894	1,397	39,184
Biennial FIT at ages 45-70	9,711	1,172	7	3	20,905	20,898	1,569	44,365
Biennial FIT at ages 45-75	10,913	1,250	7	2	20,905	20,899	1,611	82,140
Annual FIT at ages 45-70	15,643	1,814	6	2	20,908	20,903	2,068	114,013
10y COL at ages 45-65	0	3123	3	1	20,911	20,907	2,609	139,965
10y COL at ages 45-75	0	3675	3	1	20,911	20,907	2,824	3,970,828
Men+Women								
No Screening	0	13	13	7	20,389	20,380	1,047	Reference
Biennial FIT at ages 55-65	4,982	565	10	5	20,401	20,393	1,255	16,438
Biennial FIT at ages 50-65	6,567	780	9	5	20,405	20,397	1,379	27,061
Biennial FIT at ages 50-70	8,215	903	9	4	20,406	20,399	1,431	30,353
Biennial FIT at ages 45-70	9,641	1,137	8	4	20,409	20,403	1,611	47,920
Biennial FIT at ages 45-75	10,765	1,210	8	3	20,410	20,404	1,647	60,356
10y COL at ages50-65	0	2,259	5	3	20,413	20,408	2,050	91,665
Annual FIT at ages 45-70	15,540	1,762	7	3	20,414	20,408	2,093	104,994
Annual FIT at ages 45-75	16,644	1,827	7	3	20,414	20,409	2,132	112,141
10y COL at ages 45-65	0	3,111	4	2	20,418	20,413	2,650	120,390
10y COL at ages 45-75	0	3,613	4	2	20,418	20,413	2,843	1,287,547

COL=Colonoscopy; CRC=Colorectal cancer; FIT=Faecal immunochemical test; ICER=Incremental cost-effectiveness ratio; LY=Life year; QALY=Quality-adjusted life year. *(Quality-adjusted) life years and costs were discounted at an annual rate of 3%. †Colonoscopies include screening, diagnostic and surveillance colonoscopies

SUPPLEMENT III: MISCAN-COLON MODEL DESCRIPTION

General Model Structure

MISCAN-Colon is a stochastic microsimulation model for CRC useful to explain and predict trends in CRC incidence and mortality rates and to assess the effects and costs of primary prevention and screening for CRC.[4]

The model simulates the life history of each person at individual level, rather than as proportions of a cohort. For that reason, the model allows the time dependence between future and past state transitions. However, in contrast to most traditional Markov models, MISCAN-Colon does not use yearly transition probabilities but it generates durations in states. This solution increases the model flexibility and the computational performance. In addition, the model simulates sequences of events by drawing from distribution of probability or durations, rather than using fixed values. Hence, the results of the model are subject to random variation.

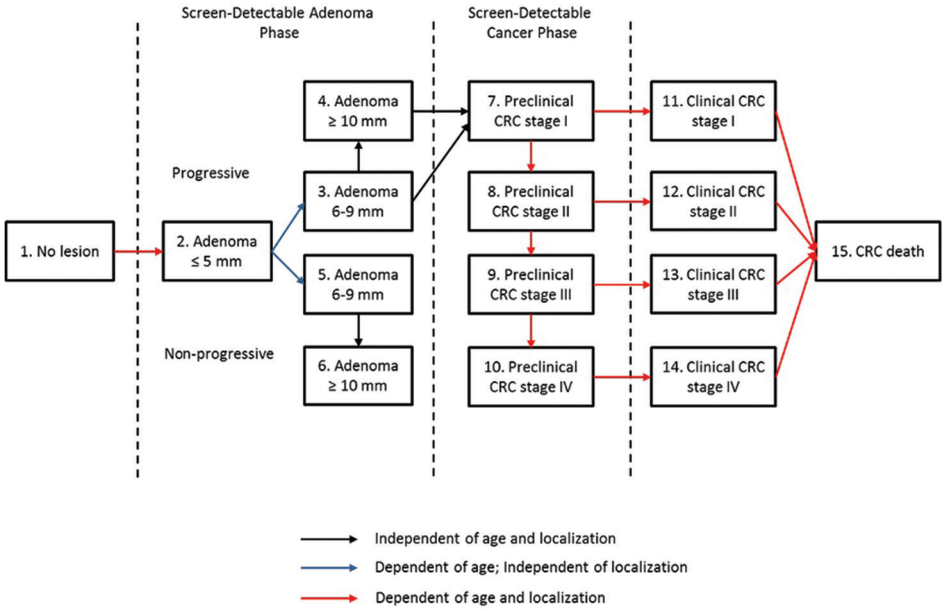
MISCAN-Colon consists of 3 modules: a demography module, natural history module, and screening module.

The Demography Module

MISCAN-Colon model draws a date of birth and a date of non-CRC death for each individual simulated, using birth and life tables (representative of the population under consideration). The model restricts the maximum age a person can achieve to 100 years.

The Natural History Module

As each simulated person ages, 1 or more adenomas may develop [Supplementary Figure 2]. These adenomas can be either progressive or non-progressive and both can grow in size from small (<5 mm) to medium (6-9 mm) and then to large (> 10 mm). Only progressive adenomas can develop into preclinical cancer, which may progress through stage I to IV. However, during each stage, CRC may be diagnosed because of symptoms. After CRC diagnosis, survival time is simulated using age-, stage-, and localization-specific survival estimates for clinically



Supplementary Figure 2: The general model structure of MISCAN-Colon model

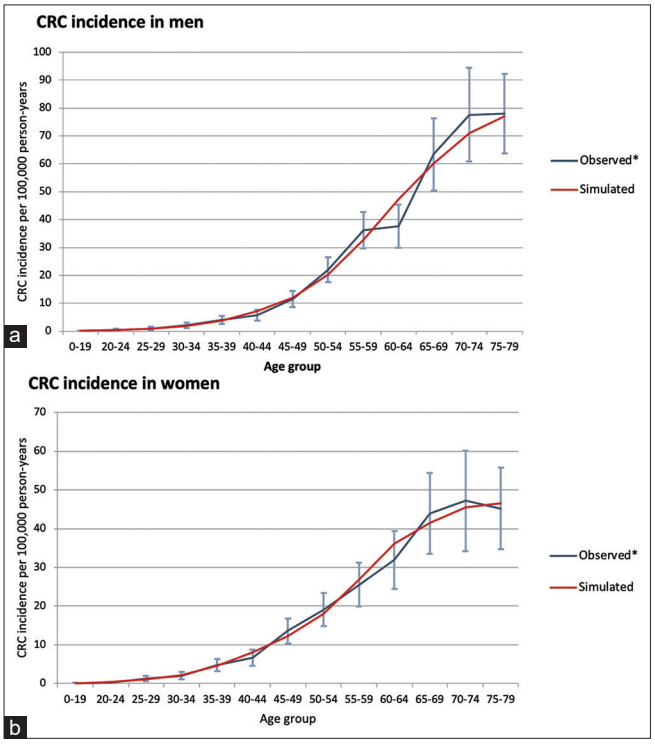
diagnosed CRC based on a study published by Rutter and colleagues.[5] For synchronous CRCs, the survival is based on the most advanced cancer. The date of death from CRC patients is the earliest simulated date of death (due to CRC or another cause).

The probability of adenoma onset differs among the individuals and it depends on the person's age and risk index. For that reason, most persons do not develop adenomas while some others develop many. The distribution of adenomas over the colon and rectum was assumed equal to the distribution of cancer cases seen in the Saudi Cancer Registry data in years 2000-2006. The age-specific onset of adenomas was calibrated to cancer incidence data from 2014 [Supplementary Figure 3].[6] The age-specific probability of adenoma progressivity and the age- and localization-specific transition between preclinical and clinical cancer stages were calibrated to SEER data on age-, stage- and localization-specific incidence of CRC in pre-screening years (i.e., 1975-1979).[7] The average duration of the preclinical cancer stages were calibrated according to data obtained from randomized, controlled trials (RCTs) evaluating screening using guaiac fecal occult blood tests.[8-10] The average duration between the adenoma onset and the progression into preclinical cancer (adenoma dwell time) was calibrated to interval cancer data from a sigmoidoscopy screening RCT.[11] Furthermore, we assumed: an equal overall dwell time for adenoma developing into cancer from medium (30% of all CRCs) and from large size adenomas (70% of all CRCs); exponential distribution for all durations in the adenoma and preclinical cancer phases; perfect correlation for the durations within adenoma and preclinical cancer (quicker growing from small adenoma and medium-sized adenoma, quicker developing into preclinical CRC); absence of correlation between durations in the adenoma phase and duration in the preclinical cancer phase.

The Screening Module

Screening will modify some of the simulated life histories: Some cancer cases will be prevented by the detection and removal of adenomas or by detection in an earlier stage

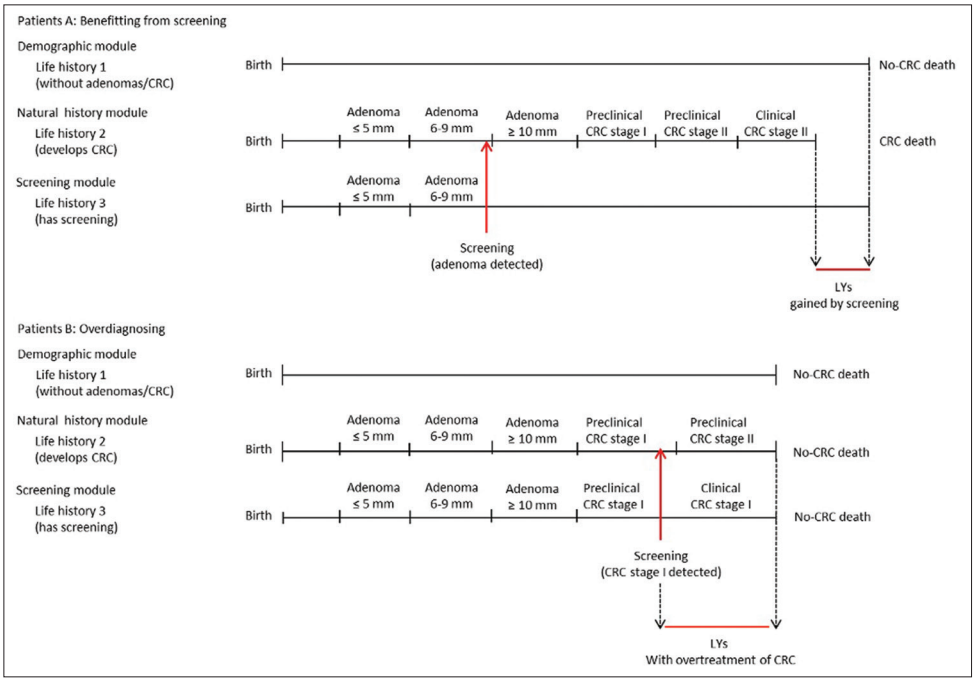
(favourable survival). As seen in RCTs on guaiac fecal occult blood testing, the stage-specific survival of screen-detected CRC was more favourable compared to clinically detected CRC, even after the lead-time bias correction.[12] Hence, we assigned those screen-detected cancer cases - that without screening would have been clinically detected in the same stage – a survival corresponding to a cancer that is 1 stage less progressive. The only exceptions were screen-detected distant cancer cases: we assigned the survival of a clinically diagnosed distant cancer. Furthermore, together with the positive effects of screening, we also modelled over-diagnosis, overtreatment, and colonoscopy-related complications.[13]



Supplementary Figure 3: (a) Model fit of CRC incidence for Saudi Arabian Males. (b) Model fit of CRC incidence for Saudi Arabian Females.jpg

Integrating Modules

For each person simulated, a date of birth and a date of no-CRC death (a lifetime history without adenoma or CRC) are generated from the demography module. In patient A in Supplementary Figure 4, the natural history module generates an adenoma. This adenoma progress into preclinical cancer (diagnosed as stage II CRC due to symptoms) and results in CRC death before non-CRC death would have occurred. However, in the screening module, a screening examination is introduced: the adenoma is detected; removed; and the CRC death prevented. The positive effect of the screening intervention is indicated by the red line and represents the increased life years gained for this patient due to screening. Another example is the patient B. He develops an adenoma and it would never have been diagnosed in a no screening scenario. However, during the screening examination, CRC is screen-detected in stage I and - for this patient - screening results in over diagnosis and overtreatment of CRC (no LYs gained, but only additional LYs with CRC care).



Supplementary Figure 4: Integrating modules with two examples

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