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ORIGINAL ARTICLE

Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening

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► Additional appendices are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2011-301917).

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Revised 17 February 2012
Accepted 18 February 2012
Published Online First
5 April 2012

ABSTRACT

Objective The sensitivity and specificity of a single faecal immunochemical test (FIT) are limited. The performance of FIT screening can be improved by increasing the screening frequency or by providing more than one sample in each screening round. This study aimed to evaluate if two-sample FIT screening is cost-effective compared with one-sample FIT.

Design The MISCAN—colon microsimulation model was used to estimate costs and benefits of strategies with either one or two-sample FIT screening. The FIT cut-off level varied between 50 and 200 ng haemoglobin/ml, and the screening schedule was varied with respect to age range and interval. In addition, different definitions for positivity of the two-sample FIT were considered: at least one positive sample, two positive samples, or the mean of both samples being positive.

Results Within an exemplary screening strategy, biennial FIT from the age of 55—75 years, one-sample FIT provided 76.0—97.0 life-years gained (LYG) per 1000 individuals, at a cost of €259 000—264 000 (range reflects different FIT cut-off levels). Two-sample FIT screening with at least one sample being positive provided 7.3—12.4 additional LYG compared with one-sample FIT at an extra cost of €50 000—59 000. However, when all screening intervals and age ranges were considered, intensifying screening with one-sample FIT provided equal or more LYG at lower costs compared with two-sample FIT.

Conclusion If attendance to screening does not differ between strategies it is recommended to increase the number of screening rounds with one-sample FIT screening, before considering increasing the number of FIT samples provided per screening round.

Significance of this study

What is already known on this subject?

- Two-sample FIT screening with referral for colonoscopy if at least one sample is positive provides a higher detection rate for advanced neoplasia than one-sample FIT screening.
- However, this is at the expense of higher positivity rates and thus the need for more colonoscopies.

What are the new findings?

- Within a given screening age range and interval, two-sample FIT screening provides additional LYG compared with one-sample FIT screening at acceptable costs.
- Intensifying screening with one-sample FIT provides equal or more LYG at lower costs, compared with screening by means of two-sample FIT.

How might it impact on clinical practice in the foreseeable future?

- In order to improve the effectiveness of their CRC screening programme, decision-makers are recommended to increase the number of screening rounds with one-sample FIT screening, before considering increasing the number of FIT samples provided per screening round.

In industrialised countries colorectal cancer (CRC) is the third most commonly diagnosed malignancy in men and ranks second in women.[1] The majority of CRC cases are diagnosed later in life. Because life expectancy increases in many countries and the costs of CRC treatment rise rapidly, it is expected that CRC will place an increasing burden on national healthcare systems.

Screening for CRC and its premalignant lesions (ie, adenomatous polyps) can detect the disease at an earlier and more curable stage. Faecal occult blood tests (FOBT) have been developed to detect microscopic bleeding from colorectal neoplasms before there are any clinical signs or symptoms. At least three randomised controlled trials have proved the effectiveness FOBT screening, demonstrating a mortality reduction of 15—33%.[2–4] Subsequently, several screening trials have confirmed the superiority of faecal immunochemical test (FIT) screening over the more traditionally used guaiac-based FOBT (ie, non-rehydrated Hemoccult-II test) both with respect to attendance as well as the detection rate of advanced neoplasia.[5–11] Most of these trials used screening strategies with a single FIT sample.

As not all advanced neoplasia will be detected by means of one-sample FIT screening, providing two FIT samples collected on consecutive days could increase the effectiveness of a screening

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programme. On the one hand, referring a screenee for a diagnostic colonoscopy when at least one sample is positive increases sensitivity because some colorectal neoplasms bleed intermittently and can therefore be missed with one-sample FIT screening.[12] On the other hand, referring a screenee when both samples are positive can increase specificity because only colonic lesions with a more consistent bleeding pattern will be detected, which will lead to fewer false-positive test results. However, either way, providing two FIT samples within one screening round will also increase screening costs because twice the number of samples need to be analysed.

The aim of this study was to evaluate the cost-effectiveness of one-sample and two-sample FIT screening strategies with variable intervals, age ranges and cut-off levels in order to assess whether the increased performance of a second FIT sample outweighs the increased costs compared with one-sample FIT screening.

MATERIALS AND METHODS

We used the MISCAN–colon microsimulation model to estimate the additional life-years gained (LYG) and costs of two-sample FIT screening over one-sample FIT for the screening strategy of biennial FIT from the age 55 to 75 years. This screening strategy has intermediate screening intensity and was previously found to be cost-effective.[13] Additional LYG can also be achieved by increasing the intensity of one-sample FIT screening instead of adding a second sample. We therefore also compared the costs and LYG of one-sample FIT screening with that of two-sample FIT for a range of screening strategies.

MISCAN–colon microsimulation model

The MISCAN–colon model and the data sources that inform the quantifications of the model are described in detail in supplementary appendix 1, in previous publications,[14–18] and in a standardised model profile available online only.[19] In brief, the MISCAN–colon model simulates the relevant life histories of a large population of individuals from birth to death. CRC arises in this population according to the adenoma–carcinoma sequence.[20 21] More than one adenoma can occur in an individual and each adenoma can independently develop into a CRC. Adenomas progress in size from small (≤5 mm) to medium (6–9 mm) to large (≥10 mm). Although most adenomas will never turn into cancer, some will eventually become malignant, transforming to stage I CRC and some may even progress into stage IV. In every stage, there is a probability of the CRC being diagnosed due to the development of symptoms versus symptomless progressing into the next stage. If CRC has developed, the survival rate after clinical diagnosis depends on the stage in which the cancer was detected. The 5-year survival rate is on average 90% if the disease is diagnosed while still localised, 68% for regional disease, and less than 10% for disseminated disease. At any time during the development of the disease, the process may be interrupted because a person dies of other causes.

With FIT screening lesions can be detected before clinical diagnosis; a screened individual with a positive test result will be referred for a colonoscopy for the detection and removal of adenomas and early-stage cancers. In this way, CRC incidence and/or CRC-related mortality can be reduced. The LYG by screening are calculated as the difference in model-predicted life years lived in the population with and without CRC screening.

Study population

In this study we modelled the age distribution of the Dutch population in 2005[22] and all individuals were followed until death. The CRC incidence rate was based on the observed incidence rate in The Netherlands in 1999–2003, which was before the onset of opportunistic screening.[23] The observed CRC incidence in the population included cases from higher risk groups. Survival rates after clinical diagnosis of CRC was based on relative survival data from 1985 to 2004 from the south of The Netherlands,[24] since nationwide data were not available. The survival for individuals aged 75 years and older was adjusted to fit the observed age-increasing mortality/incidence ratio.[23]

Screening strategies

CRC screening was simulated in the population starting in 2010. Individuals were offered FIT screening according to different screening schedules varying by:

Age to start screening at, respectively, 45, 50, 55 and 60 years
Age to stop screening at, respectively, 70, 75 and 80 years
Screening interval with, respectively, 1, 1.5, 2 and 3 years

Separate simulations were performed in which individuals were invited for: one-sample FIT screening; two-sample FIT screening with referral if at least one sample tested positive; two-sample FIT screening with referral only if both samples tested positive; or two-sample FIT screening with referral if the mean of both samples was positive. The cut-off level for a positive test result varied between 50, 75, 100, 150 and 200 ng haemoglobin/ml. These different screening schedules with varying start and stop ages, intervals, cut-off levels and samples resulted in a total of 960 different screening strategies.

After a positive test result, individuals were referred for colonoscopy. If no adenomas were found during the procedure, the individual was assumed to be at low risk of CRC and did not return to the screening programme until after 10 years. If one or more adenomas were found, they were removed and the individual entered a surveillance programme according to the Dutch guidelines for follow-up after polypectomy,[25] ie, a colonoscopy after 6 years in the case of one or two adenomas and after 3 years in the case of three or more adenomas. We assumed that surveillance colonoscopies would be performed until the stop age for screening.

Attendance rates

We modelled attendance rates in the first screening round as observed in two Dutch population-based CRC screening trials;[9 11 12] 60% for both one and two-sample FIT screening, and we assumed these rates would remain stable over time. For subsequent screening rounds, we assumed that 80% of the individuals who attended the previous screening round would attend again.[26 27] Furthermore, we assumed that 10% of the individuals never attended FIT screening[28] and that these never-attenders had a higher risk of CRC than the general population (RR 1.15).[2] Attendance at diagnostic colonoscopies following a positive FIT and subsequent surveillance colonoscopies were assumed to be 85% and 80%, respectively.[29]

Test characteristics

Test characteristics of the one-sample and two-sample FIT tests were fitted to the positivity rates and detection rates of advanced neoplasia observed in the first screening round of two Dutch randomised trials (table 1).[9–12] Advanced neoplasia included CRC and advanced adenomas, of which the latter was

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Table 1 Test characteristics of one-sample and two-sample FIT used in the model

Cut-off level (ng Hb/ml)	Specificity (per person, %)	Sensitivity (per lesion, %)* Adenoma ≤5 mm	Adenoma 6–9 mm	Adenoma ≥10 mm	CRC early preclinical†	CRC late preclinical†
One-sample FIT						
50	95.79	0.0	9.6	16.1	65.0	90.0
75	97.05	0.0	5.7	14.4	58.5	87.0
100	97.76	0.0	4.4	13.1	52.0	83.5
150	98.34	0.0	2.9	12.3	50.5	83.0
200	98.70	0.0	2.5	10.3	50.0	82.5
Two-sample FIT, at least one sample positive						
50	93.01	0.0	14.2	16.7	75.0	93.5
75	94.90	0.0	8.4	15.5	71.0	92.0
100	96.03	0.0	6.9	14.4	66.0	90.0
150	97.03	0.0	5.2	14.3	66.0	90.0
200	97.65	0.0	4.9	12.5	66.0	90.0
Two-sample FIT, mean of both samples positive						
50	95.51	0.0	12.6	17.0	67.0	90.0
75	96.90	0.0	7.5	15.1	61.0	87.5
100	97.66	0.0	5.4	13.8	54.0	84.0
150	98.31	0.0	3.3	12.8	51.0	83.0
200	98.63	0.0	2.1	10.7	49.0	81.5
Two-sample FIT, both samples positive						
50	98.40	0.0	3.8	12.0	34.0	70.0
75	98.94	0.0	1.8	10.0	29.0	65.0
100	99.21	0.0	0.9	8.8	24.0	59.0
150	99.43	0.0	0.1	7.1	20.0	53.0
200	99.49	0.0	0.0	5.2	16.0	47.5

The test characteristics used in the model were fitted to the positivity rates and detection rates of advanced neoplasia and CRC from two Dutch randomised controlled trials.[9–12] Sensitivity for adenomas smaller than 5 mm was assumed to be 0% for all tests, at any cut-off level.
*Excluding the probability that an adenoma or cancer is found due to a lack of specificity.
†It was assumed that the probability a CRC bleeds and thus the sensitivity of FIT for CRC depends on the time until clinical diagnosis, in concordance with findings for FOBT, which were based on a previous calibration of the MISCAN–colon model to three FOBT trials.[16] This result is to be expected when cancers that bleed do so increasingly over time, starting 'occultly' and ending as clinically visible. This interpretation also holds for FIT.
CRC, colorectal cancer; FIT, faecal immunochemical test; FOBT, faecal occult blood tests; Hb, haemoglobin.

defined as adenomas of 10 mm or greater in size, with 25% or greater villous component, and/or high-grade dysplasia.

To estimate the two-sample FIT test characteristics the following approach was applied; we used the average positivity rates and detection rates of the first and second test performed from the two-sample FIT group as reference and calculated the relative difference in performance when both samples were evaluated. Subsequently, we added this relative difference to the positivity rates and detection rates derived from the original one-sample FIT trials. An example of this method of calculation is presented in figure 1. The main reasons for this approach were: (1) the larger sample size of the one-sample FIT group provides more statistical power for the estimates of test sensitivity and specificity; (2) to avoid possible bias caused by the fact that the positivity rates and detection rates of the one-sample and two-sample FIT groups were calculated from different cohorts that were not 1:1 randomly assigned before invitation;[10 12] (3) in this way we used paired observations, which gives a better estimate of the additional performance of a second FIT sample.

The sensitivity of diagnostic colonoscopies was assumed to be 75% for adenomas 1–5 mm, 85% for adenomas 6–9 mm, and 95% for adenomas 10 mm or greater and CRC.[30]

Costs

The analysis was conducted from a healthcare system perspective. In the base case analyses, we included screening and treatment costs as presented in table 2. Base case organisational costs for one-sample FIT screening were based on the Dutch cervical cancer screening programme, adjusted for differences with FIT screening. Costs for the test kits were based on prices from the manufacturer. Costs for analysis of the tests included material and personnel needed during the process of registration, analysis and authorisation of returned tests.[34] The additional costs associated with two-sample FIT screening included double costs for FIT test kits and packaging material, and double costs for materials needed during the analysis of returned samples. Although double the number of FIT samples would need to be analysed, the costs of personnel needed for the analysis only increased by a factor of 1.5 because some tasks (eg, patient registration) do not require double the amount of work compared with analysing samples with one-sample FIT screening. Colonoscopy costs were based on an internal 6 months study at the Erasmus MC (data not shown). Costs for complications after colonoscopy were based on diagnosis treatment combination (DTC) rates derived from the Dutch Health Care Authority.[35]

Costs for treatment of CRC were divided into three clinically relevant phases of care: initial treatment, continuous care and terminal care. Initial treatment costs were based on DTC rates, except for oxaliplatin. The costs for oxaliplatin were derived from the Dutch Health Care Insurance Board.[36] We assumed that during the continuous care phase, individuals would follow the Dutch CRC treatment guidelines,[37] and costs for periodic control were based on DTC rates. Terminal care costs were based on a Dutch last year of life cost analysis. These were estimated at €19 700 for patients who ultimately died from CRC.[38] We assumed that these costs increased with stage at diagnosis, at a rate observed for US patients.[39 40] Dutch terminal care costs for

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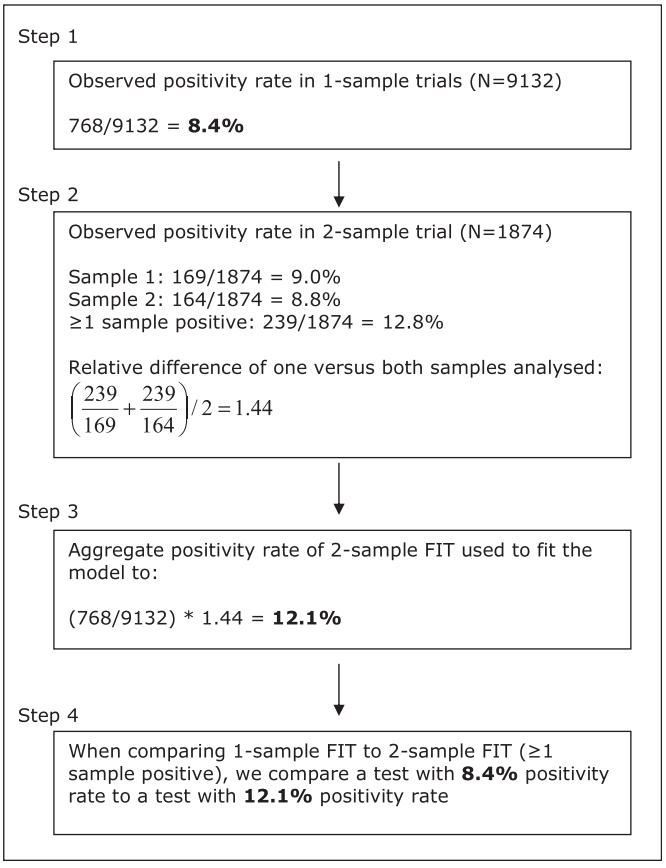

Figure 1 Example of calculation of the added performance of two-sample faecal immunochemical tests (FIT) compared with one-sample FIT screening. *This example provides the calculation of the positivity rate of two-sample FIT with at least one sample positive at a cut-off level of 50 ng haemoglobin/ml. The method of calculation is similar for both the positivity rate and detection rate, as well as for the different two-sample FIT positivity criteria (ie, at least one sample positive, both samples positive and the mean of both samples positive).

individuals who died from CRC were approximately 40% of the US costs. We assumed that terminal care costs of CRC patients who die from other causes were also 40% of the US costs.

Cost-effectiveness analyses

For all screening strategies we used the MISCAN–colon model to estimate costs and compare the number of LYG due to screening with the situation without screening. Costs and LYG were discounted by 3% per year.[41] Strategies that were more costly and less effective than other strategies were ruled out by simple dominance. Strategies that were more costly and less effective than a mix of other strategies were ruled out by extended dominance. The remaining strategies are not dominated and are known as 'efficient'. On a plot of LYG versus costs, the line that connects the efficient strategies is called the efficient frontier, which implies that all dominated strategies lie below this line. The incremental cost-effectiveness ratio (ICER) of an efficient strategy was determined by comparing its additional costs and effects with those of the next less costly and less effective efficient strategy.

Sensitivity analyses

We performed several sensitivity analyses on different parameters, which are summarised in table 2. We started with sensitivity analyses with respect to the additional performance and costs of two-sample FIT over one-sample FIT. Furthermore, we adjusted for reduced quality of life due to screening as well as CRC treatment. Correlated FIT test results were assumed because individuals with a false-negative test result are likely to have a higher than average probability to have another false-negative test result at a successive screening round. We used the results of a population-based CRC screening programme in Italy to estimate the correlation between false-negative FIT results for cancers and advanced adenomas in subsequent screening rounds.[33] Effects of limited colonoscopy capacity were evaluated by only considering strategies in which colonoscopy demand did not exceed 40, 20, 10, or five colonoscopies per 1000 individuals per year. In order to assess the cost-effectiveness of the different strategies for individuals who adhere to the CRC screening guidelines, we simulated all screening strategies with 100% attendance to screening, diagnostic and surveillance colonoscopies. In addition, we performed sensitivity analyses on lower and higher values than the base case analysis for fatal complication rates with colonoscopy and for unit costs of FIT, colonoscopy, complications and treatment. We decided not to perform a probabilistic sensitivity analysis after having weighed the limited added value against the computational effort required (see Discussion).

RESULTS

The strategy of biennial one-sample FIT screening from age 55 to 75 years yielded 76.0–97.0 LYG per 1000 individuals aged 45 years and older, compared with no screening (the range in LYG reflects different FIT cut-off levels). The associated costs ranged from €259 000 to €264 000 per 1000 individuals, corresponding with €2690–3473 per LYG compared with no screening (figure 2). The two-sample FIT screening strategies with the mean of both test results being positive and at least one test result being positive provided, respectively, between −0.3–2.6 and 7.3–12.4 more LYG than one-sample FIT screening at additional costs of, respectively, €43 000–50 000 and €50 000–59 000 per 1000 individuals. The corresponding ICER ranged from €16 818–31 930 and €4024–8041 per additional LYG. The two-sample FIT screening strategies with two positive outcomes were less effective (ie, fewer LYG per 1000 individuals) and more costly than one-sample FIT screening, and were therefore dominated from a cost-effectiveness standpoint (see supplementary appendix 2, available online only, for detailed results on effects and costs for the different biennial FIT screening strategies with the age range of 55–75 years).

When all simulated screening strategies were considered (ie, by varying not only the cut-off level, but also the screening age range and interval), the number of LYG compared with no screening ranged between 17.5 and 153.4 per 1000 individuals, and costs ranged between €105 000 and €889 000 per 1000 individuals (figure 3). The LYG and costs of the strategies on the efficient frontier are presented in table 3. Although the ICER of biennial two-sample FIT screening between ages 55 and 75 years (mean of both samples being positive, or at least one sample being positive) compared with one-sample FIT seemed reasonable, table 3 shows that most two-sample FIT strategies are not cost-effective. When comparing the additional effect of providing two samples per screening round to the effect of providing one-sample FIT more frequently (ie, with a larger age range and/or shorter interval), the latter provided more LYG at equal or less costs than the two-sample FIT strategies. This effect is also demonstrated in figure 2, because the strategies of biennial two-sample FIT are located below the efficient frontier.

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Table 2 Summary of model assumptions of the base case and sensitivity analyses

Variable	Base case analysis				Sensitivity analyses	
Quality of life loss						
Colonoscopy	–				1 day lost per colonoscopy	
CRC from diagnosis onwards† (1-utility)	–				Initial treatment[31]: - Stage I: 0.26 during first year - Stage II: 0.3 during first year - Stage III: 0.4 during first year - Stage IV: 0.75 during first year Continuous care[32]: 0.15 in years between initial and terminal phase Terminal care death by CRC: 0.75 in last year before dying of CRC Terminal care death by other cause: 0.35 in last year before dying of other causes	
Adherence to:						
- *Screening tests*	60%				100% adherence to all tests.	
- *Diagnostic tests*	85%					
- *Surveillance tests*	80%					
Correlation of FOBT results	–				74% of the large adenomas (≥10 mm) that are not detected, will not be detected in the next screening round[33]	
Colonoscopy capacity	Not limited				Limited to either 40, 20, 10 and 5 colonoscopies per 1000 individuals per year	
					Low value	**High value**
Fatal complications after colonoscopy	1 per 10 000 colonoscopies				No fatal complications	- 1 per 1000 colonoscopies with polypectomy - 1 per 10 000 colonoscopies without polypectomy
Relative increase in test performance between 1-sample and 2-sample FIT	Average of the first and second sample used as comparator				Relative increase in test performance 50% smaller	Relative increase in test performance 50% greater
FIT costs	*1-sample FIT*		*2-sample FIT*			
Costs per invitation (organization and test kit)	€15.51		€17.76		Difference between 1- and 2-sample FIT 50% smaller	Difference between 1- and 2-sample FIT 200% greater
Costs per attendee (personnel and materials for analysis)	€4.37		€8.19			
Colonoscopy costs						
Without polypectomy	€303				50%	200%
With polypectomy	€393					
Costs complications after colonoscopy*	€1250				50%	200%
Treatment costs†	*Initial treatment*	*Continuous care*	*Terminal care death CRC*	*Terminal care death other causes*		
Stage I	€12 100	€340	€17 500	€4400	50%	200%
Stage II	€16 600	€340	€17 500	€4000		
Stage III	€20 600	€340	€18 500	€5200		
Stage IV	€24 600	€340	€25 000	€14 000		

*The assumed complication rate is 2.4 per 1000 colonoscopies.
†CRC treatments were divided into three clinically relevant phases—initial, continuous and terminal care. The initial phase was defined as the first 12 months following diagnosis, the terminal phase was defined as the final 12 months of life, and the continuous phase was defined as all months between the initial and terminal phase. For patients surviving less than 24 months, the final 12 months were allocated to the terminal phase. The remaining months of observation were allocated to the initial phase.
CRC, colorectal cancer; FIT, faecal immunochemical test; FOBT, faecal occult blood tests.

The two-sample FIT screening strategies with the mean from both test results being positive or at least one positive test outcome were therefore ruled out by extended dominance and were considered not to be cost-effective compared with one-sample FIT screening. Although figure 2 demonstrates this effect for biennial FIT screening, the principle applies to all screening intervals, including annual screening.

Sensitivity analyses

The higher cost-effectiveness of more frequent one-sample FIT screening compared with two-sample FIT strategies was robust to alterations in our model assumptions. However, decreasing the cost difference between one-sample and two-sample FIT by 50% resulted in multiple two-sample FIT strategies becoming efficient next to one-sample FIT. In addition, limited colonoscopy capacity did not affect the preference of one-sample FIT over two-sample FIT strategies, with the exception of the most stringent scenario. In case the colonoscopy demand was not allowed to exceed five colonoscopies per 1000 individuals per year, two-sample FIT strategies with both samples being positive were preferred over one-sample FIT.

DISCUSSION

Our analysis demonstrates that given a screening schedule (ie, age range and screening interval), two-sample FIT strategies with the mean from both test results being positive or at least one positive test outcome provide more LYG at acceptable costs than one-sample FIT screening. However, when all simulated screening strategies are considered (ie, including varying age ranges and screening intervals), increasing the screening intensity of one-sample FIT testing (ie, greater age range and/or shorter screening interval) is more cost-effective than providing two FIT within one screening round.

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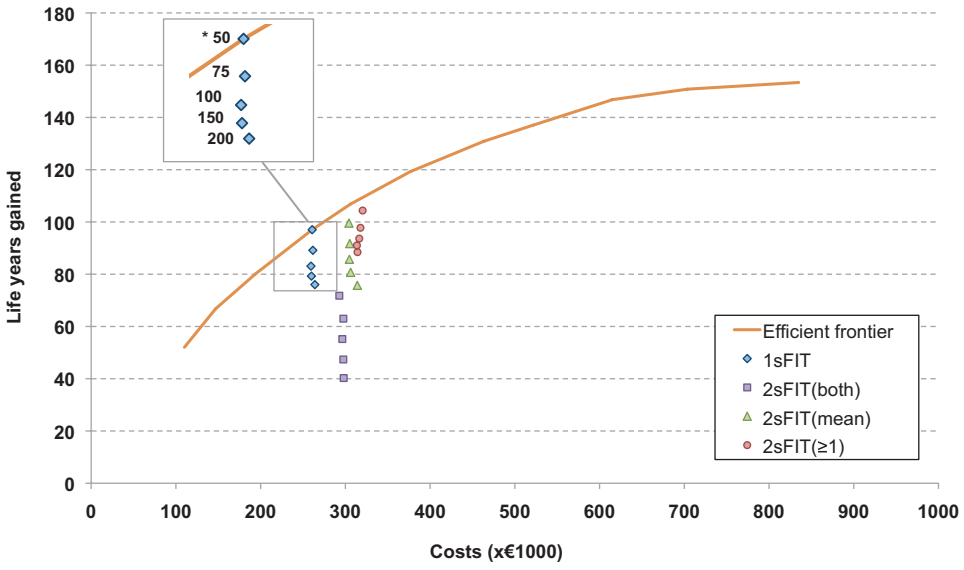

Figure 2 Costs and life-years gained (LYG) compared with no screening per 1000 individuals in 2005 (start of the programme) for one-sample and two-sample faecal immunochemical test (FIT) screening at different cut-off values. All data points represent biennial FIT screening from age 55 to 75 years. *Per screening test (ie, one or two-sample FIT), the data points represent the results at cut-off values of 50, 75, 100, 150 and 200 ng haemoglobin/ml. For each test, a higher cut-off level is associated with fewer LYG, that is the data point at the bottom represents the result at a cut-off value of 200 ng haemoglobin/ml, whereas the data point at the top represents the result at a cut-off value of 50 ng haemoglobin/ml. 1sFIT, one-sample FIT; 2sFIT(both), two-sample FIT, referral to colonoscopy restricted to subjects with both samples positive; 2sFIT(mean), two-sample FIT, referral to colonoscopy restricted to subjects for whom the mean of both samples is positive; 2sFIT(≥1), two-sample FIT, referral to colonoscopy of all subjects with at least one sample positive. The most efficient strategies, ie, those strategies which for a given amount of costs yield the largest number of life-years saved, are connected by the efficient frontier. The screening interventions were modelled from the year 2005, all individuals were invited for screening until they reached the end age for screening, and healthcare costs for each individual were calculated until death. Costs and LYG were discounted at an annual rate of 3%.

This study was based on data from a randomised trial in which the attendance and diagnostic yield of one and two-sample FIT were compared.[12] Considering only the relation between the positivity rate and the detection rate of advanced adenomas it seems that to choose FIT screening with either one or two samples based on the available colonoscopy capacity should be recommended. However, the current analysis demonstrates that including the costs for the screening and treatment of CRC over multiple screening rounds affects the relation between one and two-sample FIT. Although a number of two-sample FIT screening strategies (eg, with at least one sample, or the mean of both samples being positive) are close to the cost-efficiency frontier, increasing the number of one-sample FIT screening rounds was found to be a more cost-effective way of gaining health benefits.

Other cost-effectiveness analyses determining the optimal number of FIT samples are limited. Two Japanese studies compared the costs of FIT screening with either one, two or three FIT per cancer detected in a single screening round.[42 43] In all three sampling strategies individuals were referred for

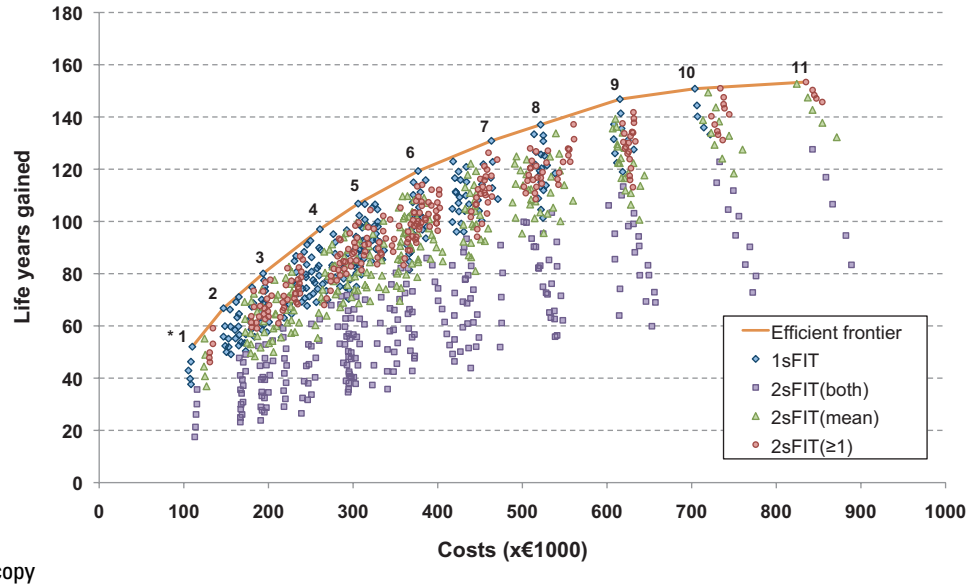

Figure 3 Costs and life years gained (LYG) compared with no screening per 1000 individuals in 2005 (start of the programme), for one-sample and two-sample faecal immunochemical test (FIT) screening at different cut-off values. The data represent all simulated screening strategies, which include various sampling strategies, cut-off levels, screening age ranges and intervals. *The numbers of the strategies on the efficient frontier correspond to the cost-efficient strategies presented in table 3. 1sFIT, one-sample FIT; 2sFIT (both), two-sample FIT, referral to colonoscopy restricted to subjects with both samples positive; 2sFIT(mean), two-sample FIT, referral to colonoscopy restricted to subjects for whom the mean of both samples is positive; 2sFIT (≥1), two-sample FIT, referral to colonoscopy of all subjects with at least one sample positive. The most efficient strategies, ie, those strategies that for a given amount of costs yield the largest number of life-years saved, are connected by the efficient frontier. Strategies with the least intensive screening schedule (ie, small age range, and long screening interval) are located at the bottom left of the graph, whereas strategies with the most intensive screening schedule (ie, large age range and short screening interval) are located at the top right of the graph. The screening interventions were modelled from the year 2005, all individuals were invited for screening until they reached the end age for that particular screening strategy, and healthcare costs for each individual were calculated until death. Costs and LYG were discounted at an annual rate of 3%.

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Table 3 Costs per LYG compared with no screening and ICER of the cost-effective screening strategies, in a population with realistic attendance* at the screening programme

Strategy†	Test (cut-off)	Start age (y)	Stop age (y)	Interval (y)	LYG (y)	Costs (€)	Costs/LYG (€)	ICER‡ (€)
1	1s FIT (50)	60	69	3	52	110 000	2115	2115
2	1s FIT (50)	60	70	2	67	147 000	2200	2500
3	1s FIT (50)	60	74	2	80	194 000	2420	3524
4	1s FIT (50)	55	75	2	97	261 000	2688	3956
5	1s FIT (50)	55	74.5	1.5	107	306 000	2865	4613
6	1s FIT (50)	55	79	1.5	119	377 000	3159	5678
7	1s FIT (50)	50	80	1.5	131	463 000	3541	7480
8	1s FIT (50)	55	80	1	137	522 000	3806	9427
9	1s FIT (50)	50	80	1	147	615 000	4191	9590
10	1s FIT (50)	45	80	1	151	704 000	4667	22 099
11	2s FIT ≥1s pos. (50)	45	80	1	153	835 000	5444	51 336

Costs and LYG are expressed per 1000 individuals aged 45 years and older in 2005.
The strategies are in ascending order from least to most costly.
The screening interventions were modelled from the year 2005, all individuals were invited for screening until they reached the end age for that particular screening strategy, and healthcare costs for each individual were calculated until death. Costs and LYG were discounted at an annual rate of 3%.
*Attendance rate was 60% for screening, 85% for diagnostic colonoscopies, and 80% for surveillance colonoscopies.
†The strategy number corresponds to the strategies on the efficient frontier in figure 3.
‡The ICER of an efficient strategy is determined by comparing its additional costs and effects with those of the next less costly and less effective efficient strategy.
FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio; LYG, life-years gained.

diagnostic colonoscopy if at least one sample was positive. In both studies it was concluded that two-sample FIT screening with at least one test being positive would be the most desirable strategy from a diagnostic accuracy and cost-effectiveness stand point. A more recent French study did include multiple screening rounds in their cost-effectiveness model and also evaluated the effect of different cut-off levels.[44] The authors concluded that three-sample FIT screening with a cut-off level of 50 ng haemoglobin/ml was the most cost-effective strategy to be preferred. The results of our current analysis do agree with these studies about the added value of multiple FIT sampling within a given screening schedule. More than one FIT sample can provide additional health benefits at acceptable costs. Unfortunately, these studies do not provide information comparing the added effect of multiple FIT samples per screening round with the effect of increasing screening intensity with one-sample FIT.

Several limitations need to be acknowledged. First, we based our analysis on data from one screening round. Therefore, we could not estimate the correlation of test outcomes between successive screening rounds. Individuals with a false-negative test result (eg, because the lesion did not bleed) in one screening round may have a higher than average probability to have another false-negative test result at a successive screening round. Therefore, we performed a sensitivity analysis based on Italian results,[31] in which correlation of systematic false-negative test outcomes was assumed for advanced adenomas and CRC. The analysis showed that the cost-effectiveness of two-sample FIT decreased less than the cost-effectiveness of one-sample FIT strategies, but one-sample FIT screening remained dominant. Nevertheless, we need further data from repeat screening rounds in The Netherlands to get a good estimate of systematic false-negative rates in the population we modelled. Second, we assumed the screening attendance rate to be independent of screening intensity and the number of FIT samples performed. In the first screening round of one of the Dutch trials,[10–12] the screening attendance rate was not significantly different between the two-sample FIT and one-sample FIT study arm (61.3% vs 61.5%; p=0.837). However, it could be hypothesised that, for example, adherence in the case of a more intense screening schedule with one-sample FIT would decrease compared with less intense screening schedules with two-sample screening. This would negatively affect the cost-effectiveness of more intensive screening strategies relative to two-sample testing and might alter our conclusions. Third, we based our analyses on a screening-naive population. Depending on the amount of previous screening, CRC incidence in the population and the resulting cost-effectiveness could be lower. However, this would affect the strategies we compared in a similar way. If anything, the effect of previous screening would make one-sample FIT screening more preferable, because a lower CRC incidence would reduce the added value of a second FIT sample. Finally, we did not perform a probabilistic sensitivity analysis. Given the large number of strategies that has to be evaluated for each draw, such an analysis would require a huge computational effort. We believe that simulating the range of varying strategies is one of the strengths of this analysis, because we were primarily interested in the comparison of different FIT screening strategies with varying numbers of samples provided, FIT cut-off levels, screening intervals and age ranges. Regardless of this, data on the probability distributions of most of the parameter values are lacking, which makes the interpretation of a probabilistic sensitivity analysis difficult and the outcome of limited added value. One of the most uncertain assumptions of the model is that all CRC arise from adenoma precursors. For FIT screening, this assumption will have limited impact because FIT has a low sensitivity for adenomas. In addition, the assumption of non-bleeding (and therefore for FIT undetectable) adenomas was evaluated in the sensitivity analysis by assuming correlation between false-negative results.

In conclusion, our analysis provides new insights for decision-makers; in a situation in which attendance to screening does not differ between strategies, intensifying screening with one-sample FIT was found to be more cost-effective than providing two FIT samples within one screening round. It is therefore recommended to increase the number of screening rounds with one-sample FIT screening, before considering increasing the number of FIT samples provided per screening round.

Contributors EJK, JDFH, MvB, and MEvL conceived the idea for the study; MvB and ILV supervised the model simulations and data analysis; SLG drafted the report; AHCvR provided critical review of the report. All co-authors listed above were given an opportunity to comment on the paper.

Funding This trial was funded by the Dutch Cancer Society (EMCR 2006-3673), the Dutch Ministry of Health, Health Care Prevention Program—Implementation (ZonMw 63300022 and ZonMw 120720011), Olympus Medical Systems Europe GmbH,

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Hamburg, Germany, the Jacoba Foundation and Eiken Chemical Co., Tokyo, Japan. The funding sources had no influence on study design, data collection, monitoring, analysis and interpretation of results or the decision to submit the manuscript for publication.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1: The MISCAN-Colon microsimulation model

OUTLINE

MODEL OVERVIEW

The MISCAN-Colon model is a semi-Markov micro-simulation model. The population is simulated individual by individual, and each person can evolve through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the MISCAN-Colon model generates durations in states. This improves model performance. With the assumption of exponential distribution of the duration in each state, this way of simulating leads to the same results as a Markov model with yearly transition probabilities. The advantage of the MISCAN approach is that durations in a certain state need not necessarily be a discrete value but can be continuous. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, adenoma incidence and transitions from one state of disease to another.

The basic structure of MISCAN-Colon is illustrated in Figure A1.1. Figure A1.1 clearly demonstrates that MISCAN-Colon consists of three parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is useful to consider them separately.

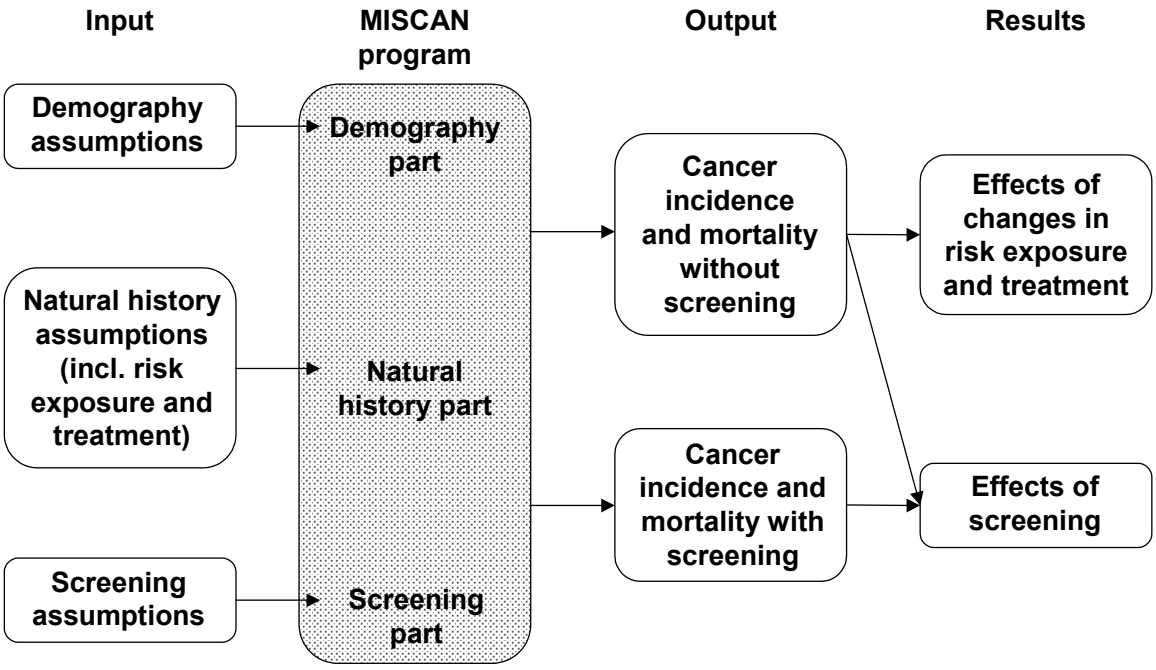

Figure A1.1: Structure of MISCAN-Colon

DEMOGRAPHY PART
The demography part of the model simulates individual life histories without colorectal cancer to form a population. For each person, a date of birth and a date of death of other causes than colorectal cancer are simulated. The distribution of births and deaths can be adjusted to represent the population simulated. For example, a population of Caucasian females will have higher death ages than a population of African American males.

NATURAL HISTORY PART
The Natural History part of MISCAN-Colon simulates the development of colorectal cancer in the population. We assume all colorectal cancers develop according to the adenoma-carcinoma sequence of Morson[1] and Vogelstein[2] (Figure A1.2). For each individual in the simulated population a personal risk index is generated. Subsequently, adenomas are generated in the population according to this personal risk index and an age specific incidence rate of adenomas. This results in no adenomas for most persons and one or more adenomas for others. The distribution of adenomas over the colorectum is simulated according to the observed distribution of colorectal cancer incidence. Each of the adenomas can independently develop into colorectal cancer. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (10+ mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. The survival after clinical diagnosis depends on the stage of the cancer.

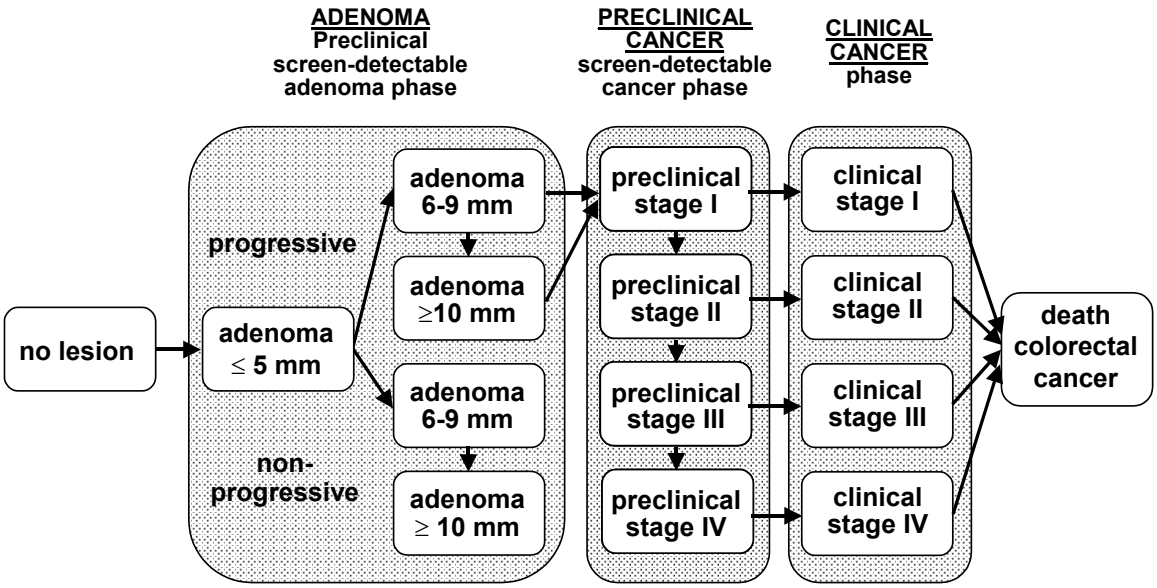

Figure A1.2: Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for colorectal cancer. Adenomas are categorized by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age.

SCREENING PART
Screening interrupts the development of CRC. With screening, adenomas may be detected and removed and cancers may be found, usually in an earlier stage than with clinical diagnosis. In this way screening prevents CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening. The effects of different screening policies can be compared by applying them to identical natural histories.

INTEGRATION OF THE THREE MODEL COMPONENTS
For each individual, the demography part of the model simulates a time of birth and a time of death of other causes than colorectal cancer, creating a life history without colorectal cancer (top line in Figure A1.3a). Subsequently adenomas are simulated for that individual. For most individuals no adenomas are generated, for other multiple. In the example in Figure A1.3, the person gets two adenomas (2nd and 3rd line in Figure A1.3a). The first adenoma arises at a certain age, grows into 6-9 mm and eventually becomes larger than 10 mm. However, this adenoma does not become cancer before the death of the person. The second adenoma is a progressive adenoma. After having grown to 6-9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and diagnosis and eventually resulting in an earlier death from CRC. The life history without CRC and the development of the two adenomas in Figure A1.3 together lead to the combined life history with CRC depicted in the bottom line. Because this person dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly.

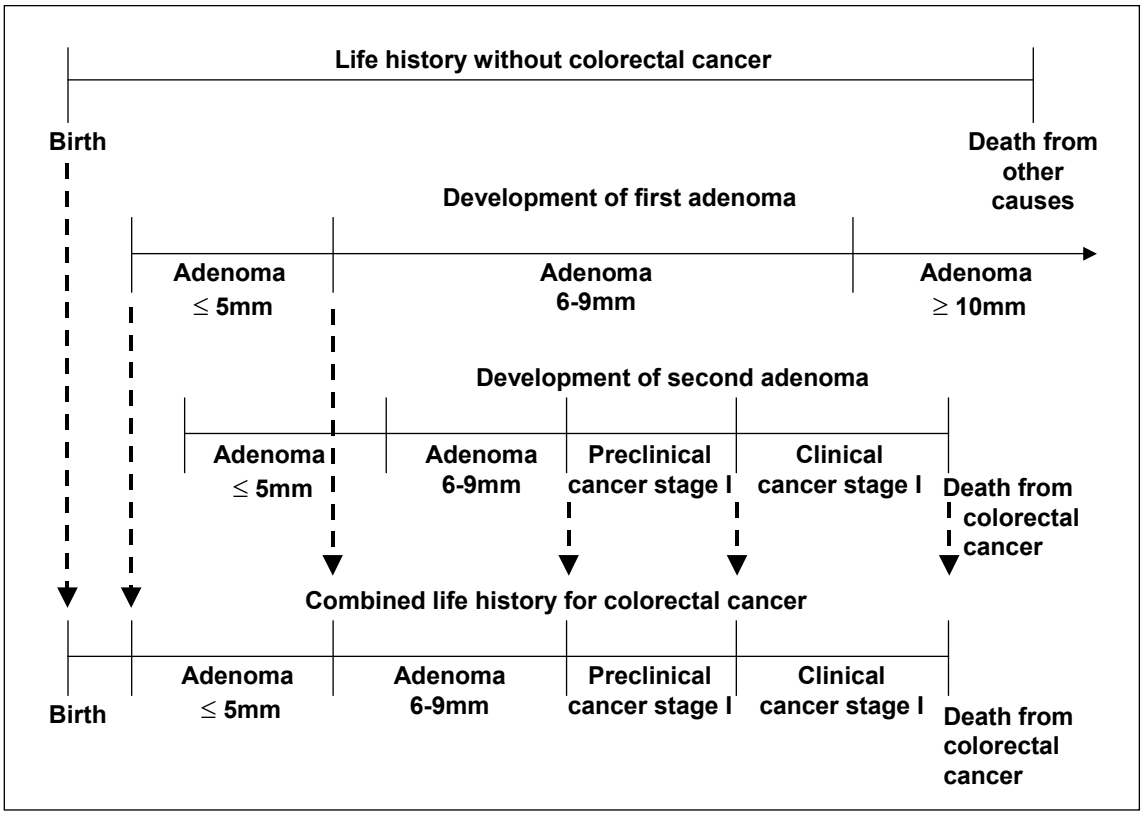

Figure A1.3a: Modeling natural history into life history

After the life history of a person is adjusted for colorectal cancer, the history will now be adjusted for the effects of screening. The effect of screening on life history is explained in Figure A1.3b.The top line in this figure is the combined life history for colorectal cancer from Figure A1.3a. The development of the separate adenomas is repeated in the second and third line. In this picture there is one screening intervention. During the screening both prevalent adenomas are detected and removed. This results in a combined life history for colorectal cancer and screening (bottom line). From the moment of screening the adenomas are removed and this individual becomes adenoma and carcinoma free. He does not develop cancer because the precursor lesion has been removed. Therefore the person dies at the moment of death from other causes and the effect of screening is the difference in life-years in the situation without screening and the situation with screening. Of course many other possibilities could have occurred: a person could have developed new adenomas after the screening moment, or an adenoma could have been missed by the screening test, but in this case this individual really benefited from the screening intervention.

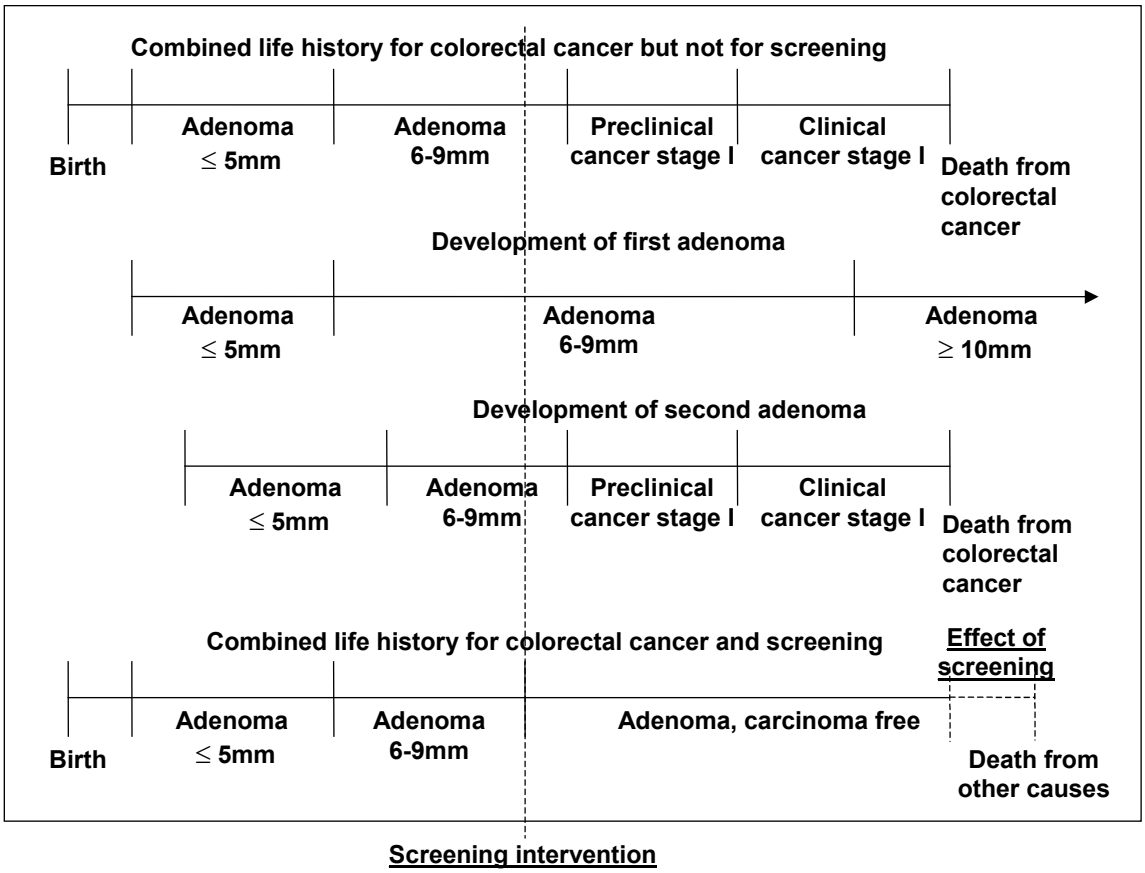

Figure A1.3b: Modeling screening into life history

MODEL QUANTIFICATION
For this analysis we simulated the Dutch population in 2005.

DEMOGRAPHY PARAMETERS
There are two types of demography parameters: birth tables and life tables. Birth tables were constructed such that the age distribution of the Dutch population in 2005 was simulated. Age distribution and life tables were derived from Statistics Netherlands (www.cbs.nl). These life tables include colorectal cancer mortality and the demography part simulates mortality from other causes than colorectal cancer. Therefore, mortality from colorectal cancer was derived from Comprehensive Cancer Centres (CCC, www.ikcnet.nl), and excluded from the life tables.

NATURAL HISTORY PARAMETERS
The parameters for natural history model that could not be directly estimated from data or fit to reference data, were established based on expert opinion. At two expert meetings at the NCI on June 5–7, 1996, and May 12–13, 1997, a model structure was devised in agreement with the currently accepted model of the adenoma–carcinoma sequence. It was assumed that all cancers are preceded by adenomas.

The average duration between onset of a progressive adenoma and the transition to preclinical cancer was assumed 20 years based on expert opinion. The duration of

cancer in preclinical stages was estimated based on the results of three large randomized controlled screening trials [3]. This resulted in an average duration of 2.5 years, 2.5 year, 3.7 years, and 1.5 year, for stages I-IV respectively, with a total average duration of 6.7 years because not every cancer reaches stage IV before clinical diagnosis. All durations were governed by an exponential probability distribution. Durations in each of the invasive cancer stages as well as durations in the stages of the noninvasive adenomas were assumed to be 100% associated with each other, but the durations in invasive stages as a whole were independent of durations in noninvasive adenoma stages that precede cancer. These assumptions resulted in an exponential distribution of the total duration of progressive noninvasive adenomas and of the total duration of preclinical cancer, which has also been used in other cancer screening models [4, 5].

It was assumed that 30% of the cancers arise from adenomas of 6–9 mm and that 70% arise from larger adenomas. Initially, the preclinical incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localization in the Netherlands in 1999-2003 (CCC). The size distribution of adenomas over all ages was assumed to be 56% for stages less than or equal to 5 mm, 24% for stages 6–9 mm, and 20% for stages greater than or equal to 10 mm [6-15]. The preclinical incidence of non-progressive adenomas that will never grow into cancer was varied until the simulated prevalence of all adenomas was in agreement with data from autopsy studies [6-15].

The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of colorectal cancers in the Netherlands in 1999-2003 (CCC). The stage-specific survival after the clinical diagnosis of colorectal cancer before age 75 is taken from the Comprehensive Cancer Centre South from 1989 through 2003, because national data were not available (CCCS, V. Lemmens 2010). The stage-specific survival after age 75 was fitted on the CRC mortality derived from the Comprehensive Cancer Centre from 1999-2003 (CCC). Table A1.1 contains a summary of the model input values and its data-sources.

Table A1.1: Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2.1	Fit to multiplicity distribution of adenomas in autopsy studies [6-13, 15]
Adenoma incidence in general population	Age dependent: 0-19 years: 0.2% per year 20-24 years: 0.4% per year 25-29 years: 0.4% per year 30-34 years: 0.6% per year 35-39 years: 0.6% per year 40-44 years: 2.4% per year 45-49 years: 2.9% per year 50-54 years: 3.0% per year 55-59 years: 3.4% per year 60-64 years: 4.1% per year 65-69 years: 4.7% per year 70-74 years: 5.7% per year 75-79 years: 3.8% per year 80-84 years: 3.6% per year 85-100 years: 1.0% per year	Fit to adenoma prevalence in autopsy studies [6-15] and to cancer incidence in 1999-2003 per 100,000 (CCC) <20 years 0.2 20-24 years 0.5 25-29 years 1.3 30-34 years 2.6 35-39 years 5.6 40-44 years 11.0 45-49 years 23.9 50-54 years 50.7 55-59 years 85.4 60-64 years 142.3 65-69 years 201.4 70-74 years 275.5 75-79 years 347.7 80-84 years 389.3 85+ years 332.4
Probability that a new adenoma is progressive	Dependent on age at onset: 0–45 years: linearly increasing from 0 to 5% 45–65 years: linearly increasing from 5% to 15% 65–100 years: linearly increasing from 15% to 23%	Fit to adenoma prevalence in autopsy studies, [6-15] cancer incidence in 1999-2003 (CCC).
Regression of adenomas	No significant regression of adenomas	Expert opinion
Mean duration of development of progressive adenomas to preclinical cancer	20 years	Expert opinion*
Mean duration of preclinical cancer	6.7 years	Estimated from FOBT trials [3].
Percent of non-progressive adenomas that stay 6-9mm	50%	Fit to size distribution of adenomas in autopsy studies: [6-15] 1-5mm: 56% 6-9 mm: 24% 10+ mm: 20%

Model parameter	Value	Source
Percent of non-progressive adenoma that become 10mm or larger	50%	Fit to size distribution of adenomas in autopsy studies: [6-15] 1-5mm: 56% 6-9 mm: 24% 10+ mm: 20%
Percent of cancers that develops from 6-9mm adenoma and from 10+mm adenoma	30% of cancer develops from 6-9 mm, 70% from 10+mm	Expert opinion
Localization distribution of adenomas and cancer	Rectum: 26% Distal colon: 42% Proximal colon: 32%	Directly estimated from CCC 1999-2003.
10-year survival after clinical diagnosis of CRC	Dependent on age, stage and localization	Directly estimated from CCC South 1989-2003 for diagnosis before age 75 and fitted on mortality from CCC 1999-2003.

* To be estimated from randomized controlled endoscopy trials, data not yet available.

SCREEN PARAMETERS

We assumed a cecal intubation rate of 95% [16-18]. The sensitivity of colonoscopy for each lesion within realized reach was based on back-to-back colonoscopy studies: 75% in adenomas less than or equal to 5 mm, 85% in adenomas 6–9 mm, and 95% in adenomas greater than or equal to 10 mm and cancers (table A1.2)[19]. After a positive test, all lesions are removed within a short time. The percentage of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after colonoscopy has been estimated from Kaiser data:[20] 10%. This percentage was assumed to be independent of the screening round.

The stage-specific survival of patients with screen-detected cancer was based on a previous analysis calibrating on three large randomized FOBT-trials[3], and was more favorable than the survival after diagnosis in the same stage without screen-detecting. Removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma. Risks of complications reported in organized screening programs [21-23] are lower than those reported for general practice colonoscopies [24, 25]. The major complications of colonoscopy are perforations (which can occur with or without polypectomy), serosal burns, bleeds requiring transfusion and bleeds not requiring transfusion [21-25]. We estimated a rate of death of 0.1 per 1,000 colonoscopies [26, 27].

Table A1.2: Colonoscopy characteristics

Parameter	Value	Source
Sensitivity colonoscopy	Dependent on stage of disease Adenoma 1-5mm: 75% Adenoma 6-9mm: 85% Adenoma 10+ mm: 95% Preclinical cancer: 95%	Back-to-back colonoscopy studies [19]
Cecal intubation rate	95%	General practice [16, 17] and guidelines [18]
Complication rate with colonoscopy	2.4 per 1,000 colonoscopies	Organized screening programs[21-23] and general practice [24, 25]
Perforation	0.7 per 1,000	
Serosal burn	0.3 per 1,000	
Bleed with transfusion	0.4 per 1,000	
Bleed without transfusion	1.1 per 1,000	
Fatal complication rate with colonoscopy	0.1 per 1,000 colonoscopies	Prospective endoscopy study [28]
Probability to develop cancer from removed adenoma	0%	Expert opinion
Survival after screen detection of cancer	Same as after clinical diagnosis in the next stage	FOBT trial [3]

MODEL OUTPUTS
The model generates the following output, both undiscounted and discounted:

Demography

1. Life-years lived in the population by calendar year and age
2. Deaths from other causes than colorectal cancer by calendar year and age

Natural history

1. Colorectal cancer cases by calendar year, stage and age
2. Colorectal cancer deaths by calendar year and age
3. Life-years lived with colorectal cancer by calendar year, stage and age
4. Total number of life years with surveillance for adenoma patients
5. Total number of life years with initial therapy after screen-detected or clinical invasive cancer by stage
6. Total number of life years with continuing therapy after screen-detected or clinical invasive cancer by stage
7. Total number of life years with terminal care before death from other causes by stage
8. Total number of life years with terminal care before death from colorectal cancer by stage

Screening

1. Number of invitations for screen-tests, screen-tests, diagnostic tests, surveillance and opportunistic screen tests by calendar year
2. Number of positive and negative test results per preclinical state and per year
3. Total number of life years lived, life years lost due to cancer, number of specific deaths and non specific deaths
4. Number of screenings that prevented cancer by year of screening
5. Number of screenings that detected cancer early by year of screening
6. Number of surveillance tests that prevented cancer by year of surveillance
7. Number of surveillance tests that detected cancer early by year of surveillance
8. Number of life years gained due to screening by year of screening

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Appendix 2 – Summary results of biennial 1- and 2-sample FIT screening strategies with the age range of 55-75 years.

Screen test and cut-off level*	Incidence reduction (0% discount)	Mortality reduction (0% discount)	Life years gained (3% discount)	Costs per 1,000 individuals (x1,000 €) (3% discount)						
				Total	FIT	Diagnostic colonoscopy after positive FIT	Surveillance colonoscopy	Clinical diagnostic colonoscopy	Complications after colonoscopy	Treatment of CRC
1sFIT										
50	12.83%	28.34%	97.0	261	186	143	71	-10.4	1.7	-130
75	10.39%	25.98%	89.2	262	191	114	58	-9.8	1.4	-93
100	9.08%	24.22%	83.1	259	193	98	51	-9.3	1.2	-74
150	7.74%	22.92%	79.3	260	196	83	45	-9.0	1.0	-55
200	6.47%	21.94%	76.0	264	197	72	39	-8.7	0.9	-36
2sFIT (both)										
50	8.58%	21.38%	71.8	293	244	83	46	-8.3	1.0	-73
75	6.47%	18.60%	63.0	298	248	64	36	-7.4	0.8	-43
100	5.29%	16.39%	55.2	296	250	53	30	-6.6	0.6	-30
150	3.90%	13.92%	47.4	298	252	41	23	-5.8	0.5	-13
200	2.88%	11.71%	40.3	298	253	34	18	-5.1	0.4	-2
2sFIT (mean)										
50	13.95%	29.27%	99.5	304	230	153	77	-10.7	1.9	-147
75	11.35%	26.81%	91.7	305	237	121	63	-10.0	1.5	-107
100	9.78%	24.92%	85.7	305	240	103	55	-9.5	1.2	-85
150	8.11%	23.36%	80.7	306	244	86	46	-9.1	1.0	-62
200	6.48%	21.78%	75.7	314	246	73	39	-8.6	0.9	-36
2sFIT (≥1)										
50	15.25%	30.62%	104.4	320	223	188	85	-11.0	2.2	-166
75	12.69%	28.65%	97.8	318	230	153	71	-10.6	1.8	-127
100	11.29%	27.29%	93.6	316	234	132	64	-10.2	1.6	-105
150	10.00%	26.36%	91.0	314	238	113	57	-9.9	1.4	-87
200	8.93%	25.59%	88.4	314	241	100	52	-9.8	1.2	-70

* 1sFIT = 1-sample FIT; 2sFIT(both) = 2-sample FIT, both samples positive; 2sFIT(mean) = 2-sample FIT, mean of both samples positive; 2sFIT(≥1) = 2-sample FIT, at least one sample positive.