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ARTICLE

Fecal Occult Blood Testing When Colonoscopy Capacity is Limited

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Background Fecal occult blood testing (FOBT) can be adapted to a limited colonoscopy capacity by narrowing the age range or extending the screening interval, by using a more specific test or hemoglobin cutoff level for referral to colonoscopy, and by restricting surveillance colonoscopy. Which of these options is most clinically effective and cost-effective has yet to be established.

Methods We used the validated MISCAN-Colon microsimulation model to estimate the number of colonoscopies, costs, and health effects of different screening strategies using guaiac FOBT or fecal immunochemical test (FIT) at various hemoglobin cutoff levels between 50 and 200 ng hemoglobin per mL, different surveillance strategies, and various age ranges. We optimized the allocation of a limited number of colonoscopies on the basis of incremental cost-effectiveness.

Results When colonoscopy capacity was unlimited, the optimal screening strategy was to administer an annual FIT with a 50 ng/mL hemoglobin cutoff level in individuals aged 45–80 years and to offer colonoscopy surveillance to all individuals with adenomas. When colonoscopy capacity was decreasing, the optimal screening adaptation was to first increase the FIT hemoglobin cutoff value to 200 ng hemoglobin per mL and narrow the age range to 50–75 years, to restrict colonoscopy surveillance, and finally to further decrease the number of screening rounds. FIT screening was always more cost-effective compared with guaiac FOBT. Doubling colonoscopy capacity increased the benefits of FIT screening up to 100%.

Conclusions FIT should be used at higher hemoglobin cutoff levels when colonoscopy capacity is limited compared with unlimited and is more effective in terms of health outcomes and cost compared with guaiac FOBT at all colonoscopy capacity levels. Increasing the colonoscopy capacity substantially increases the health benefits of FIT screening.

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Screening with a guaiac fecal occult blood test (gFOBT) has been proven to reduce mortality from colorectal cancer (CRC) (1–3). The ability of a screening program to have an impact at the population level depends on attendance at all screening rounds and on diagnostic yield (the proportion of individuals found with adenomas or CRC). For that reason, recent studies have raised considerable interest in screening with a fecal immunochemical test (FIT), as it has been shown to increase attendance as well as diagnostic yield compared with the conventional gFOBT (4–7). Another advantage of the quantitative FIT is that it enables the choice of a hemoglobin cutoff level for referral to colonoscopy. However, using FIT vs gFOBT in a screening program may be associated with a substantial demand for colonoscopies, especially when low hemoglobin cutoff levels are being used.

Currently, colonoscopy capacity is limited in many countries (8–10), and waiting times for a colonoscopy of up to 12 weeks have been reported (11). Colonoscopy capacity cannot be increased overnight, and screening programs should be adjusted to the available capacity, at least temporarily. The limited capacity was an important consideration in various countries such as Canada, Finland, and the United Kingdom, in which screening programs that had a relatively low impact on colonoscopy capacity were started. Most countries have limited the colonoscopy demand by using the highly specific guaiac-based FOBT (12–14), sometimes focusing on populations with narrow age restrictions such as 60–69 years (13,14), whereas both the European Union Council and the Public Health Agency of Canada recommend FOBT screening for individuals between ages 50 and 75. However, the optimal strategy to adjust to limited colonoscopy capacity is unclear.

There are several established ways to limit colonoscopy demand. One way is to screen individuals less frequently by starting screening at older ages, stopping at younger ages, or by increasing

CONTEXT AND CAVEATS

Prior knowledge

Colonoscopy capacity is limited in many countries. To alleviate the demand and decrease the waiting time, some countries have relied on the guaiac-based fecal occult blood test (gFOBT) and have narrowed the ages at which colonoscopies are recommended. However, the fecal immunochemical test (FIT) has been shown to have several advantages over the gFOBT and may offer an effective alternative to increase attendance and decrease demand in a cost-effective way without compromising clinical effectiveness.

Study design

The cost-effectiveness and sensitivity of FIT at varying hemoglobin cutoff levels under different colonoscopy capacities was compared with that of the gFOBT using the MISCAN-Colon microsimulation model. Attendance rates, costs, positivity, and detection rates from two Dutch implementation trials were analyzed.

Contribution

FIT was more effective in terms of health benefits and cost compared with gFOBT at all colonoscopy capacity levels. When the capacity is limited, FIT with a higher hemoglobin cutoff level performed better than gFOBT and was more effective if the colonoscopy capacity was expanded.

Implications

Administering FIT is a cost-effective and clinically beneficial method for the detection of colorectal cancer. Increasing colonoscopy capacity increases the effectiveness of FIT.

Limitations

The model assumes that all colorectal cancers develop from adenomas. Implementation of a population-wide screening program using FIT would be complex. Strategies needed to do so may vary from country to country and would require an expanded colonoscopy capacity.

From the Editors

the screening interval. Use of a more specific test or hemoglobin cutoff level is another strategy to limit colonoscopy demand. Finally, reduction of colonoscopy demand can be achieved by more selective referral of individuals to surveillance colonoscopy after adenoma removal. We assessed which are the most clinically effective and cost-effective FOBT screening alternatives under different colonoscopy capacity levels with the validated MISCAN-Colon microsimulation model, using attendance rates, costs, positivity, and detection rates of gFOBT and FIT at varying hemoglobin cutoff levels from two implementation trials in the Netherlands (5,6).

Methods

MISCAN-Colon Microsimulation Model

The MISCAN-Colon microsimulation model and the data sources that inform the quantification of the model are described in detail in the Supplementary Methods (available online), in previous publications (15,16) and in a standardized model profile (17). In brief, the model simulates the relevant biographies of a large population of individuals from birth to death (n = 1 000 000 individuals per simulated strategy), first without screening and subsequently with the changes that would occur under the implementation of a screening program. In every individual, one or more adenomas may arise and some of them may develop into cancer. Adenomas can progress from small (1–5 mm) to medium (6–9 mm) and large (≥10 mm). The majority of adenomas are assumed to be nonprogressive and will never develop into cancer. The progressive adenomas have the ability to become cancer, but not all of them will because the individual may die of causes other than CRC. The adenomas that become malignant transform into stage I cancers and may successively progress to stage II, III, and IV until they are diagnosed at one of these stages. After diagnosis, the patient will or will not die of CRC, depending on the stage-specific survival, and again, may die of other causes.

The same life history is simulated by the model for the situation with screening. An individual with an adenoma or cancer has a chance of having it detected during a screening round depending on the sensitivity of that test for that lesion. After a person tests positive, he/she is referred for colonoscopy for removal of adenomas and diagnosis of cancers. In this way, CRC incidence or CRC death can be prevented. For the situations with and without screening, the life-years lived are aggregated for the total simulated population. The life-years gained by screening are calculated as the difference between these totals.

The model reproduced the Dutch population with age distribution during the year 2005 (Statistics Netherlands, www.cbs.nl), with the cancer incidence as observed in the Netherlands from January 1, 1999, to December 31, 2003 (Comprehensive Cancer Centre, Netherlands, www.ikcnet.nl). Survival after clinical diagnosis of a cancer was on the basis of relative survival data (n = 16000) from January 1, 1985, to December 31, 2004, from the South of the Netherlands (18), because national data were not available. The survival for individuals aged 75 years or older was adjusted to fit the observed age-increasing mortality/incidence ratio.

The validity of the model has successfully been tested on the results of large screening studies, such as the randomized FOBT trials in Minnesota (US), Funen (Denmark), and Nottingham (UK) (19); and the CoCap sigmoidoscopy study in the United States (15). Also, the model was validated with surveillance data from the National Polyp Study in the United States (20). Additionally, when accounting for risk factor trends, screening practice, and chemotherapy treatment in the United States (21), the model was able to reproduce observed incidence and mortality trends.

Test Characteristics

When the MISCAN-colon model was calibrated using three FOBT trials (19), the modeled sensitivity of gFOBT for CRC increased with a shorter time until the cancer would have been diagnosed by symptoms vs screening (Table 1). Other test characteristics were fitted to the positivity and detection rates as observed in the first screening round of the Dutch trials (4–7) (Tables 1 and 2). Because FIT also tests for blood in the feces, we assumed that the sensitivity of FIT for CRC depended on the time until diagnosis, similar to that of gFOBT. We assessed FIT at varying hemoglobin cutoff levels for referral to colonoscopy: 50, 75, 100, 150, and 200 ng hemoglobin per mL. Colonoscopy sensitivity was assumed to be

Table 1. Specificity and sensitivity of guaiac fecal occult blood test (gFOBT) and fecal immunochemical test (FIT) at various hemoglobin cutoff levels to detect adenomas and colorectal cancer (CRC)*

Test	Specificity per person, %	Sensitivity per lesion, %†				
		Adenoma ≤5 mm	Adenoma 6–9 mm	Adenoma ≥10 mm	CRC, all stages before diagnosis in the absence of screening	CRC, stages at diagnosis in the absence of screening
gFOBT	98.9	0	1.3	6.5	18.2	50.8
FIT 200 ng hemoglobin per mL	98.7	0	2.0	10.6	46.0	80.0
FIT 150 ng hemoglobin per mL	98.3	0	2.3	12.2	47.0	81.0
FIT 100 ng hemoglobin per mL	97.8	0	4.0	13.0	51.0	83.0
FIT 75 ng hemoglobin per mL	97.0	0	4.1	15.2	56.0	85.5
FIT 50 ng hemoglobin per mL	95.8	0	8.4	16.7	61.0	88.0

* The sensitivity for CRC is assumed to be higher in the stage at diagnosis in the absence of screening than in earlier stages. The average duration of each preclinical CRC stage is 2.5, 2.5, 3.7, and 1.5 years in stage I, II, III, and IV, respectively. The total duration accumulates with the stage progression and corresponds with the duration of a low or high sensitivity (eg, sensitivity is low during on average 5 years for a CRC diagnosed in stage III without screening).

† Excluding the probability that an adenoma or cancer is found because of a lack of specificity.

75% for adenomas 1–5 mm, 85% for adenomas 6–9 mm, and 95% for both adenomas 10 mm or more and CRC (22).

Screening, Surveillance Strategies, and Attendance Assumptions

We simulated screening in the Dutch population during a period of 30 years starting in January 1, 2005, until December 31, 2034, including 48 screening strategies per test (gFOBT or FIT at 50, 75, 100, 150, or 200 ng hemoglobin per mL). The 48 screening strategies were obtained by varying the age to start screening (45, 50, 55, and 60 years), the age to stop screening (70, 75, and 80 years), and the screening interval (1, 1.5, 2, and 3 years).

After a positive FOBT, a diagnostic colonoscopy was offered. If no adenomas or CRC were found at the time of the colonoscopy, an individual was offered repeat FOBT screening after 10 years. If one or more adenomas were found during the colonoscopy, the adenomas were removed by polypectomy. We simulated two surveillance policies for individuals who had adenomas removed: 1) current Dutch guidelines (23), which dictate that the next colonoscopy is offered after 6 years when one or two adenomas are found and after 3 years when three or more adenomas are found, and 2) less intensive surveillance in which individuals with one or two adenomas of no more than 10 mm in diameter are returned to screening and offered FOBT after 10 years (the same strategy as for individuals with a negative colonoscopy after a positive FIT). Other individuals were referred to colonoscopy on the basis of current surveillance guidelines. We assumed that surveillance stopped at age 80 years, the oldest age at which screening is stopped in the considered strategies.

Attendance rates for gFOBT, FIT, and diagnostic colonoscopy were based on the three Dutch trials (50%, 60%, and 85%, respectively) (5,7). Attendance to surveillance colonoscopies was assumed to be 80% (24). Guided by a report on gFOBT by Mandel et al. (25), we also assumed that 10% of the individuals never attended FIT screening and that never-attendees had a higher risk for CRC than the general population (relative risk = 1.15) (1). Of the individuals who did attend in a certain screening round, 80% attended again in the subsequent screening round (26), but this imbalance was corrected by attendance of individuals who did not attend the previous screening round, so that the overall attendance rates stayed at 50% and 60% for gFOBT and FIT, respectively, in each screening round.

Costs

We included screening and treatment costs in the analysis (Table 3). Organizational costs for FOBT screening were based on current expenses in the Dutch cervical screen program and were adjusted for differences with FOBT screening. Cost assumptions for the test kits were on the basis of prices from the manufacturer. Costs for analysis of the tests included the material and personnel needed during the process of registration, analysis, and authorization of returned tests. Colonoscopy costs were based on a 6-month-long study at the Erasmus MC (Rotterdam, the Netherlands). Additional costs for polypectomy were based on additional time, polypectomy materials needed for the procedure, and costs for pathology. Complications during or after colonoscopy can occur, such as perforations or bleeding. Costs for complications were based on Diagnose Behandel Combinatie rates (Diagnosis Treatment Combination), derived from the Dutch Health Care Authority (http://dbc-tarieven.nza.nl/Nzatarieven/top.do).

Costs of CRC were divided into three clinically relevant phases of care: initial treatment, continuous care, and terminal care. Initial treatment costs were based on Diagnose Behandel Combinatie rates, except for oxaliplatin, for which the costs were derived from the Dutch Health Care Insurance Board (www.medicijnkosten.nl). We assumed that during continuous care, individuals followed the Dutch guidelines (www.oncoline.nl), and costs for periodic control were based on Diagnose Behandel Combinatie rates. Terminal care costs for patients who ultimately died of CRC were based on a last year of life analysis and were estimated at €19700 (30). We assumed that terminal care costs increase with stage, as was previously observed for patients in the United States (31,32). Dutch terminal care costs for individuals who died of CRC were approximately 40% of those in the United States. We assumed that terminal care costs of CRC patients who died of other causes were also 40% of the US costs.

Limited Colonoscopy Capacity

Colonoscopy capacity was defined as the number of colonoscopies available per year for CRC screening and diagnosis per 1000

Table 2. Modeled and observed positivity rates and detection rates per 100 screened individuals (highest grade finding per individual) for guaiac fecal occult blood test (gFOBT) and fecal immunochemical test (FIT) at various hemoglobin cutoff levels in the first screening round

Test	Positivity rate, %		Detection rate of no adenomas or CRC, %		Detection rate of non-advanced adenomas, %		Detection rate of advanced adenomas*, %		Detection rate of colorectal cancer, %	
	Modeled	Observed	Modeled	Observed	Modeled	Observed	Modeled	Observed	Modeled	Observed
gFOBT	2.5	2.5	98.5	98.5	0.35	0.33	0.98	0.97	0.20	0.24
FIT 200 ng hemoglobin per mL	3.7	3.7	97.6	97.6	0.48	0.48	1.54	1.54	0.39	0.39
FIT 150 ng hemoglobin per mL	4.4	4.4	97.2	97.2	0.59	0.58	1.78	1.82	0.40	0.40
FIT 100 ng hemoglobin per mL	5.3	5.3	96.8	96.8	0.83	0.80	1.98	2.01	0.42	0.42
FIT 75 ng hemoglobin per mL	6.4	6.4	96.3	96.3	0.99	1.02	2.30	2.27	0.45	0.45
FIT 50 ng hemoglobin per mL	8.4	8.4	95.2	95.3	1.57	1.54	2.73	2.71	0.48	0.48

* Advanced adenoma was defined as an adenoma of 10 mm or larger in diameter, or a histology showing either at least a 25% villous component or high-grade dysplasia in the trials. In the model, adenomas are classified by size only, and advanced adenomas were all assumed to be 10 mm or larger in diameter.

individuals aged between 45 and 80 years in the year 2005. The number of colonoscopies included diagnostic colonoscopies after a positive FOBT, surveillance colonoscopies, and colonoscopies that preceded the diagnosis of a cancer outside the screening program. The cost-effectiveness analysis over 30 years of screening after introduction of a screening program was first done under the assumption of an unlimited colonoscopy capacity and repeated for different colonoscopy capacity levels of on average 5, 10, 20, and 40 colonoscopies per year per 1000 individuals aged 45–80 years. The analyses at different capacity levels together were the base case.

Cost-Effectiveness Analysis

We used the MISCAN-Colon microsimulation model to estimate costs and the number of life-years gained for all screening strategies and cutoff levels compared with the situation without screening. Costs and life-years gained were discounted by 3% annually. Strategies that were more costly and less effective than one or more 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 known as "efficient." On a plot of costs vs life-years gained, the line that connects the efficient strategies is called the efficient frontier, and all dominated strategies lie below this line. The incremental cost-effectiveness ratio (ICER) of an efficient strategy was determined by comparing the additional clinical benefit and costs with those of the next less costly and less effective efficient strategy.

Sensitivity Analysis

In addition to the base case analysis, we performed 13 sensitivity analyses on eight parameters (Table 3). Attendance rates were increased to 100% for FOBT and colonoscopy, representing the schedules for individuals who followed the recommendations. We adjusted for reduced quality of life because of screening as well as CRC treatment. Correlated FOBT results were assumed to account for the possibility that lesions that were difficult to detect in a screening round may be difficult to detect in the next round as well. We used the results of a population-based screening program in Italy to estimate the correlation between false-negative FIT results for cancers and advanced adenomas in subsequent screening rounds (29). We evaluated low and high values for the number of fatal complications, and for costs of FOBT, colonoscopy, complications, and treatment (Table 3). We decided not to perform a probabilistic sensitivity analysis after having weighed the limited added value against the computational effort required (see "Discussion").

Results

Cost-Effectiveness Analysis

Efficient strategies with an ICER below €20000 per life-year gained were investigated for an unlimited and for a limited colonoscopy capacity of 40, 20, 10, and 5 colonoscopies per year per 1000 45- to 80-year-olds during the year 2005 (Figure 1 and Table 4). For an unlimited capacity, it was most beneficial to screen intensively with the lowest FIT hemoglobin cutoff level for referral to colonoscopy set at 50 ng hemoglobin per mL for those aged 45–80 years with

Table 3. Model assumptions of the base case and sensitivity analyses*

Variable	Assumptions	
	Base case analysis	**Sensitivity analysis**
Attendance	FIT = 60% gFOBT = 50% Diagnostic colonoscopy = 85% Surveillance colonoscopy = 80%	FOBT = 100%; Colonoscopy = 100%
Quality of life loss		
Colonoscopy	NA	1 d lost per colonoscopy; Initial treatment(27): Stage I = 0.26 during 1 year; Stage II = 0.3 during 1 year; Stage III = 0.4 during 1 year; Stage IV = 0.75 during 1 year; Continuous care (28) = 0.15 in years in 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 the last year before dying of other causes.
CRC from diagnosis onwards† (1-utility‡)	NA	
Correlation FOBT results	NA	74% of the large adenomas (>9 mm) that are not detected will not be detected in the next screening round (29)
Fatal complications after colonoscopy	One fatal complication per 10 000 colonoscopies	Low = 0 fatal complications; high = 1 fatal complication per 1000 colonoscopies with polypectomy or 1 fatal complication per 10 000 colonoscopies without polypectomy
Costs per invitation (organizational costs and test kit)		
gFOBT	€14.05	Low = 50%; high = 200%
FIT	€14.85	
Costs per attendee (personnel and material costs for analysis)		
gFOBT	€1.90	These costs were varied to 50% and 200% in parallel with the costs per invitation.
FIT	€4.37	
Colonoscopy costs		
Without polypectomy	€303	Low = 50%; high = 200%
With polypectomy	€393	
Costs associated with complications after colonoscopy†	€1250	Low = 50%; high = 200%
Treatment costs by stage§		Low = 50%, high = 200%
Stage I		
Initial treatment	€12 500	Treatment costs of stage I, II, III, and IV were varied at the same time
Continuous care	€340	
Terminal care, death from CRC	€17 500	
Terminal care, death from other cause	€4400	
Stage II		
Initial treatment	€17 000	Treatment costs of stage I, II, III, and IV were varied at the same time
Continuous care	€340	
Terminal care, death from CRC	€17 500	
Terminal care, death from other cause	€4000	
Stage III		
Initial treatment	€21 000	Treatment costs of stage I, II, III, and IV were varied at the same time
Continuous care	€340	
Terminal care, death from CRC	€18 500	
Terminal care, death from other cause	€5200	
Stage IV		
Initial treatment	€25 000	Treatment costs of stage I, II, III, and IV were varied at the same time
Continuous care	€340	
Terminal care, death from CRC	€25 000	
Terminal care, death from other cause	€14 000	

* CRC = colorectal cancer; FIT = fecal immunochemical test; FOBT = fecal occult blood test; NA = Not Applicable.

† The assumed complication rate is 2.4 complications per 1000 colonoscopies, and 0.1 complications per 1000 colonoscopies is assumed to have a lethal complication.

‡ 1-utility describes the loss in quality of life because of the health states listed.

§ CRC treatment was divided into three clinically relevant phases—initial, continuous, and terminal care. The initial phase was defined as treatment administered during 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 phase and the beginning of the terminal phase. For patients surviving less than 24 months after diagnosis, the final 12 months of observation and costs of care were then allocated first to the last year of life phase because the content of care for patients with short survival is more similar to the last year of life phase than the initial phase. The remainder of months of observation and costs were allocated to the initial phase, with no contribution to the continuing phase.

Table 4. Most effective fecal immunochemical test (FIT) strategy with an incremental cost-effectiveness ratio (ICER) below €20 000 per life-year gained per colonoscopy restriction*

Maximum no. of colonoscopies†	FIT hemoglobin cutoff, ng/mL	Surveillance strategy*	No. of years between beginning and final age, y	Screening interval, y	No. of screening rounds	Costs†	No. of life-years gained†	ICER	Average number of colonoscopies per year (undiscounted)
Unlimited	50	GS	45–80 (35)	1	36	€493	109	€16 200	49
40	75	GS	50–80 (30)	1	31	€415	99	€17 700	36
20	200	LS	50–75 (25)	1	26	€360	78	€17 900	20
10	200	LS	60–80 (20)	2	11	€175	48	€8600	10
5	200	LS	60–69 (9)	3	4	€73	24	€3000	5

* GS = surveillance after polypectomy following established guidelines; LS = less intensive surveillance and no surveillance for individuals with one or two adenomas <10 mm.

† Maximum number of colonoscopies, costs, and life-years gained are per 1000 individuals aged 45–80 years during the year 2005. The number of colonoscopies is undiscounted, although the costs and life-years gained are discounted by 3% annually.

an annual screening interval and offering colonoscopy surveillance to all individuals with adenomas. The colonoscopy demand with this strategy was 49 colonoscopies per 1000 individuals. To optimally adapt screening when capacity was limited to 40 colonoscopies per 1000 individuals, individuals with a FIT hemoglobin measurement between 50 and 75 ng hemoglobin per mL were no longer referred to colonoscopy and individuals between ages 45 and 50 years were no longer invited. This decreased the demand to 36 colonoscopies per 1000 individuals. If capacity was limited to 20 colonoscopies per 1000 individuals, the next step was to further increase the FIT hemoglobin cutoff to 200 ng/mL and to stop screening 5 years earlier at age 75. Also surveillance colonoscopies in individuals with only one or two non-advanced adenomas were cancelled. If colonoscopy demand had to decrease even further, it became efficient to greatly reduce the number of screening rounds by first narrowing the age range to 60–80 years and lengthening the screening interval to 2 years (11 rounds) to reach a demand of 10 colonoscopies per 1000 individuals, and then to narrow the age range to 60–69 years every 3 years (four rounds) for a final capacity of five colonoscopies per 1000 individuals. Efficient screening with limited colonoscopy capacity had fewer health benefits and was less cost-effective compared with screening with a higher colonoscopy capacity: With more colonoscopies, there are strategies with the same costs but more

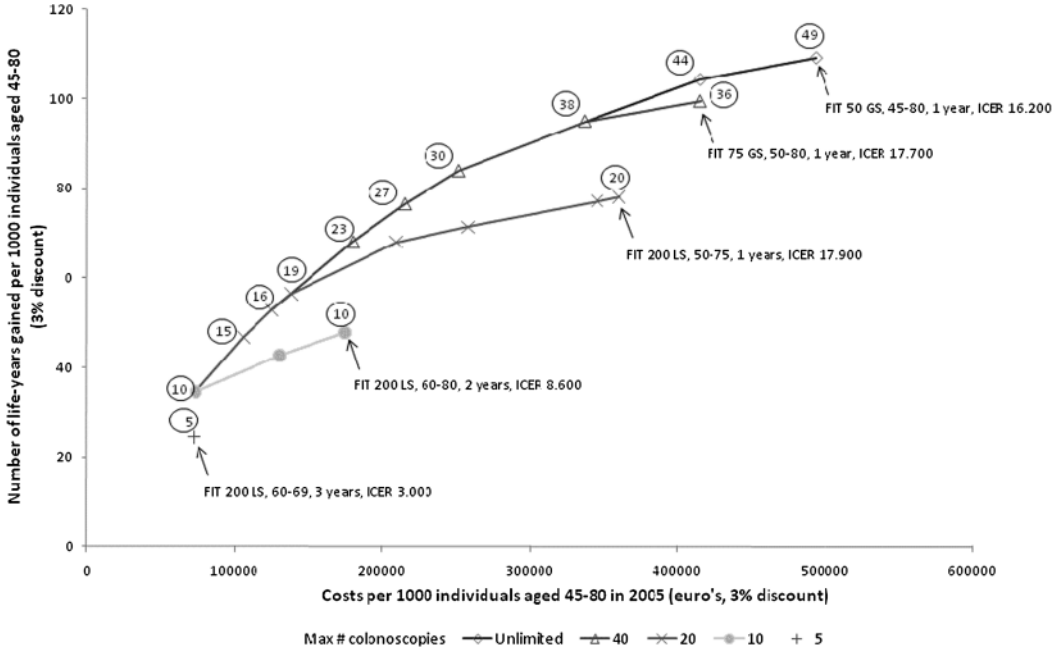

Figure 1. Efficient strategies per colonoscopy capacity restriction. The strategies vary by age to begin and end screening, screening interval, screening test, and surveillance strategy. Screening tests included guaiac fecal occult blood test or fecal immunochemical testing (FIT) with hemoglobin cutoff levels of 50, 75, 100, 150, or 200 ng/mL. The number of life-years gained and costs of 30 years of screening were calculated per 1000 individuals (age 45–80 years) in 2005 and discounted by 3% annually. Colonoscopy capacity was unlimited (**diamonds**) or set to a maximum of 40 (**triangles**), 20 (**times symbol**), 10 (**circles**), or 5 (**plus**) colonoscopies per 1000 individuals. For every colonoscopy capacity level, a **line** connects the corresponding efficient strategies. The most effective strategies are given, and list the FIT hemoglobin cutoff level (ng/mL) with either less intensive surveillance with no surveillance for individuals with one or two adenomas smaller than 10 mm in diameter (LS) or surveillance after polypectomy following guidelines (GS), the beginning and ending screen age, the screening interval, and the incremental cost-effectiveness ratio (ICER, in euros). For each strategy, the number of colonoscopies needed is displayed by a **circled number**.

life-years gained that had an ICER below €20 000 per life-year gained (Figure 1).

Screening with gFOBT never became a cost-effective alternative. The gFOBT strategy with the lowest colonoscopy demand (gFOBT, individuals aged 60–69 years, screened every 3 years, with less intensive surveillance) required three colonoscopies per 1000 individuals. However, setting a FIT hemoglobin cutoff of 200 ng hemoglobin per mL for 63- and 66-year-olds with less intensive surveillance required the same number of colonoscopies at lower costs (€37 000 vs €53 000 per 1000 individuals for FIT and gFOBT, respectively) and resulted in more life-years gained (14 vs 12 life-years gained per 1000 individuals for FIT and gFOBT, respectively) (data not shown).

The relationship between the life-years gained and the colonoscopy demand was also investigated (Figure 2 and Table 4). At the lower end, doubling the number of colonoscopies required from 5 to 10 colonoscopies per 1000 individuals doubled the number of life-years gained from 24 to 48. At the high end, increasing colonoscopy demand by more than 25% increased the life-years gained by 10%.

Sensitivity Analyses

The most effective strategies with an ICER below €20 000 per life-year gained for the base case and the sensitivity analyses per level of colonoscopy capacity restriction were investigated (Table 5). Halving the costs for FOBT, colonoscopy or complications, or doubling the costs for complications found the most beneficial strategies were the same as the base case at all capacity levels (Table 5). In the other sensitivity analyses, at least at one capacity level there was a change in which strategies were most beneficial because the base case strategy became more costly than €20 000 per life-year gained, or because the base case strategy was now dominated by alternative strategies. None of the cost and the fatal complication rate variables were of influence if capacity was 10 or 5 colonoscopies per 1000 individuals aged 45–80 years.

In all sensitivity analyses, the FIT hemoglobin cutoff value for referral to colonoscopy increased with a decreasing colonoscopy capacity, except for the analysis with an assumed 100% attendance (Table 5). The optimal hemoglobin cutoff value increased more slowly compared with that of the base case when we used quality-adjusted life-years and when FOBT costs were doubled. Under these conditions, there was an extra penalty on quality of life or costs, for primary screening, which was in favor of less frequent screening with a lower FIT hemoglobin cutoff relative to more frequent screening with a higher cutoff. When we assumed a correlation between repeated false-negative FOBT results for individuals with large adenomas, it was only cost-effective to offer less surveillance to individuals with adenomas less than 10 mm in diameter for less than five colonoscopies per 1000 individuals (Table 5). Under this assumption, FOBT missed large adenomas more often and offering individuals in whom any other adenoma had been detected surveillance was therefore more important. Screening intervals were longer when we assumed 100% attendance and when we adjusted for quality of life. If 100% attendance was

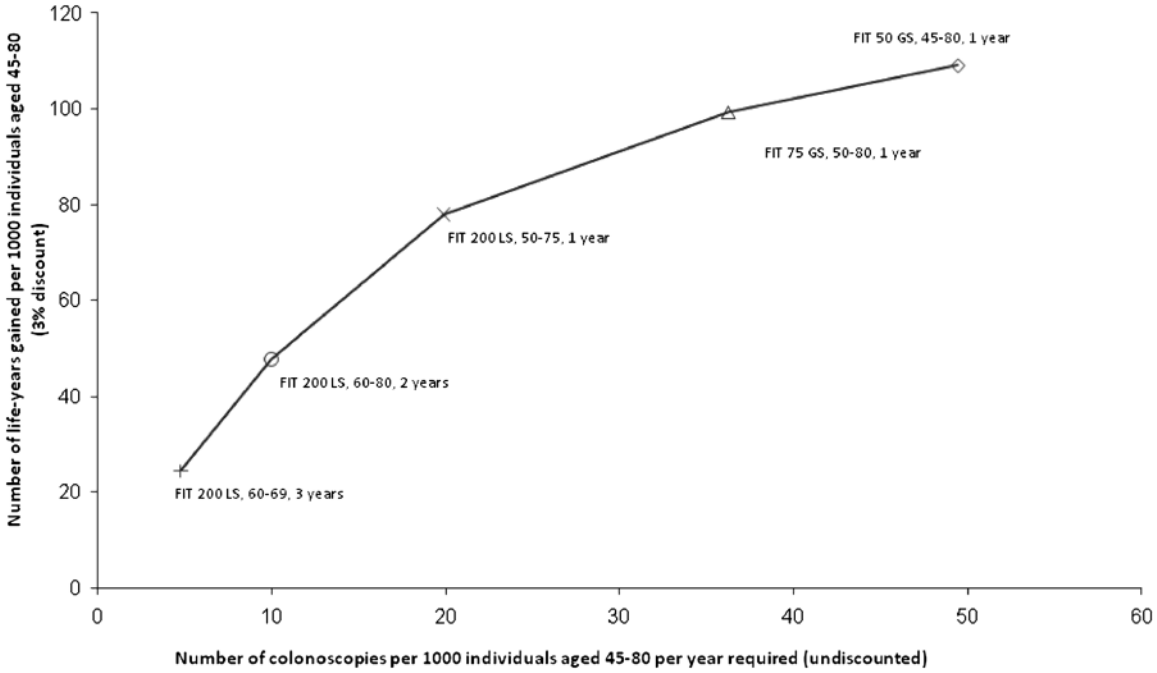

Figure 2. The maximum number of life-years gained by colonoscopy demand with an incremental cost-effectiveness ratio below €20 000 per life-year gained. The efficient frontier (**line**) connecting efficient strategies to adapt fecal immunochemical testing (FIT) by altering the hemoglobin cutoff levels (200, 75, and 50 ng/mL) and the surveillance strategy, the beginning and ending screen age, the screening interval, and the incremental cost-effectiveness ratio (euros) is shown. The surveillance strategy was either less intensive surveillance with no surveillance for individuals with one or two adenomas smaller than 10 mm in diameter (LS) or surveillance after polypectomy following guidelines (GS). Data is shown for when colonoscopy capacity was unlimited (**diamonds**) or set to a maximum of 40 (**triangles**), 20 (**times symbol**), 10 (**circles**), or 5 (**plus**) colonoscopies per 1000 individuals. The number of life-years gained per 1000 individuals aged 45–80 is discounted by 3%, whereas the number of colonoscopies per year are undiscounted.

Table 5. Sensitivity analyses of the most effective strategies with an incremental cost-effectiveness ratio below €20 000 per life-year gained per colonoscopy restriction*

		Assumptions for sensitivity analyses												
Maximum No. of colonoscopies	**Base case**	**Attendance 100%**	**Quality-adjusted life-years**	**Correlated FOBT results**	**Fatal complications (low)**	**Fatal complications (high)**	**1/2 FOBT costs**	**2 × FOBT costs**	**1/2 Colonscopy costs**	**2 × Colonoscopy costs**	**1/2 complication costs**	**2 × complication costs**	**1/2 tx costs**	**2 × tx costs**
Unlimited														
FIT	FIT 50	B	B	FIT 50	B	FIT 50	B	FIT 50	B	FIT 50	B	B	B	B
Surveillance	GS			GS†		GS†		GS†		GS†				
Age group, y	45–80			50–80		50–80		50–80		50–80				
Frequency, y	1			1		1		1		1				
40														
FIT	FIT 75	FIT 100	FIT 50	FIT 50	B	B	B	FIT 50	B	B	B	B	B	FIT 50
Surveillance	GS	GS	GS†	GS				GS†						GS†
Age group, y	50–80	45–79.5	55–80	50–75				55–80						55–80
Frequency, y	1	1.5	1	1				1						1
20														
FIT	FIT 200	FIT 200	FIT 75	FIT 200	FIT 200	B	B	FIT 75	B	FIT 200	B	B	FIT 200	B
Surveillance	LS	GS	LS†	GS	LS†			GS†		LS†			LS†	
Age group, y	50–75	55–79	55–74.5	50–80	55–80			55–79		55–80			55–80	
Frequency, y	1	2	1.5	1	1			2		1			1	
10														
FIT	FIT 200	FIT 150	FIT 200	FIT 200	B	B	B	B	B	B	B	B	B	B
Surveillance	LS	LS	GS	GS										
Age group, y	60–80	60–69	55–74	55–75										
Frequency, y	2	3	3	2										
5														
FIT	FIT 200	N	B	B	B	B	B	B	B	B	B	B	B	B
Surveillance	LS													
Age group, y	60–69													
Frequency, y	3													

* B = the same strategy was used as was used in the base case analysis; FIT = fecal immunochemical test; FOBT = fecal occult blood test; GS = surveillance after polypectomy following guidelines; LS = less intensive surveillance with no surveillance for individuals with one or two adenomas <10 mm; N = no strategies met the requirement of fewer than five colonoscopies per year per 1000 individuals aged 45–80 years during the year 2005, tx = treatment. FIT 200, FIT 150, FIT 100, FIT 75, and FIT 50 indicate a FIT hemoglobin cutoff of 200, 150, 100, 75, or 50 ng hemoglobin per mL.

† These strategies replaced the base case strategies because the base case strategies were on the efficient frontier (Figure 1), but with an incremental cost-effectiveness ratio of less than €20000 per life-year gained. All other strategies replaced the base case strategies because the base case strategies were not on the efficient frontier.

reached, the longer screening intervals compensated for the fact that individuals were participating in all screening rounds.

Discussion

There are several ways to adjust an FOBT screening program to a limited colonoscopy capacity. After assessing the most effective and cost-effective FOBT screening alternatives under different colonoscopy capacity levels, we found that a FIT hemoglobin cutoff level of 50 ng/mL for referral to colonoscopy was most effective at all cost levels when colonoscopy capacity is unlimited, and higher cutoff levels are most effective when there is a limited colonoscopy capacity. Excluding individuals with one or two adenomas less than 10 mm in diameter from surveillance colonoscopy and reducing the number of screening rounds are the next most effective strategies to reduce the colonoscopy demand. For all levels of colonoscopy capacity, FIT screening was more effective clinically and in terms of cost compared with gFOBT screening. The same patterns were found in the sensitivity analyses.

Increasing the FIT hemoglobin cutoff level—which was efficient when there was a decrease in colonoscopy capacity—resulted in higher-risk individuals being referred to colonoscopy. The health benefit per colonoscopy in terms of life-years gained as well as cost savings from treatment is greater in higher-risk individuals; so these individuals should be given the highest priority to receive a colonoscopy in a situation of limited capacity.

We presented the average number of colonoscopies over 30 years of screening. The number of colonoscopies varied over time because of an increasing number of individuals in the screen-eligible population, an increasing number of individuals in surveillance, and a lower positivity rate in subsequent screening rounds compared with the first screening round. Other reports previously estimated the annual number of colonoscopies for gFOBT screening as ranging from three to eight colonoscopies per 1000 individuals aged 50–74 years (34–37) for biennial screening, depending on the age range considered (smallest 60–69 years and widest 50–74 years of age). Our estimates of 5.7 and 10.8 colonoscopies per 1000 individuals aged 50–74 (corresponding to 4.4 and 8.1 colonoscopies per 1000 individuals aged 45–80 years) for biennial screening between ages 60 and 69 and between 50 and 74, respectively, are somewhat higher, possibly because of the longer screening horizon [30 years compared with 15 years (36) and 10 years (35)] or because of differences in surveillance strategies (37).

Our study is not without limitations. We performed one-way sensitivity analyses to evaluate the impact of other assumptions for some of the parameters. 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 all of the varying strategies is one of the strengths of this analysis because we were primarily interested in the comparison of a different cutoff level with different screening frequencies and ages, and different surveillance strategies. Regardless, 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 CRCs arise from adenoma precursors. For FOBT screening, this assumption will have limited impact because FOBT has a low sensitivity for adenomas, and the assumption of non-bleeding and therefore for FOBT undetectable adenomas was evaluated in the sensitivity analysis by assuming correlation between false-negative results.

There is uncertainty about the effects of changing the surveillance policy regarding small adenomas. The validity of our model was tested on the National Polyp Study (20), where individuals received several surveillance colonoscopies. A substantial proportion of the individuals had only one or two small adenomas. Nonetheless, the evidence on the effectiveness of surveillance colonoscopy, especially in individuals with one or two small adenomas (<10 mm diameter), is limited. Therefore, we also looked at our results when not varying the surveillance strategy. This had no impact on which FIT hemoglobin cutoff level was most beneficial and still cost-effective at the various colonoscopy capacity levels. Only for the lowest level of colonoscopy capacity (five colonoscopies per 1000 individuals), with surveillance according to guidelines (also surveillance in individuals with small adenomas), there were no FIT strategies with fewer than five colonoscopies per 1000 individuals. We considered strategies with an ICER value less than €20 000 per life-year gained. This was hardly restrictive because only one of the efficient strategies for the base case had a higher ICER value (€53 000 per life-year gained). We did not include more intensive screening strategies (eg, age ranges wider than 45–80 years or screening intervals of <1 year) because data are not available to validate the model predictions.

Several other tests are currently being used for CRC screening. Hemoccult Sensa is a guaiac-based FOBT with a similar sensitivity as FIT; however, the lack of specificity is three times higher than that of FIT (33). The test costs, laboratory requirements, and procedures for the two FOBTs are similar; however, the higher specificity makes FIT the preferred test. Flexible sigmoidoscopy has recently been shown to be highly effective in detecting distal lesions (38). The results for proximal lesions, however, were disappointing. Regardless, attendance to flexible sigmoidoscopy is substantially lower than that of FIT (4). Flexible sigmoidoscopy should therefore only be advocated in combination with FIT. Offering all individuals colonoscopy for primary CRC screening when there is a limited colonoscopy capacity is not supported by our results that only individuals with an increased risk for adenomas and CRC shown by a high level of hemoglobin in their stool should be selected to get colonoscopy.

Estimates of the current colonoscopy capacity differ between countries (8,10,39–42), and even within countries (39,41,42). How much of the available capacity can or is being used for screening is often unclear. Usually, introduction of a population-wide screening program requires expansion of the colonoscopy capacity. Because this takes time, a screening program needs to be introduced stepwise. Our results show that from a cost-effectiveness perspective, this can best be done by increasing the referral threshold for FIT. Besides cost-effectiveness, other aspects such as organizational aspects should be considered. Fortunately, starting with a higher cutoff level, and subsequently lowering it stepwise, is probably the easiest way to implement a screening program. Adding age groups by beginning screening earlier and stopping later in life is also feasible. However, changing

surveillance guidelines may be confusing for individuals in whom adenomas have been detected under the old regime. Also, changing the screening interval could result in nonattendance because people might think that they have erroneously received their screening invitation too early.

In some countries, organized FOBT screening has already started. Although a stepwise approach was used to implement these programs, no country considered using a FIT with a higher hemoglobin cutoff, the most (cost-) effective way according to our study. England and Finland started cautiously by using a gFOBT and inviting individuals biennially between ages 60 and 69. In England, the end age will be increased to 74 years during the year 2010. In some regions in Italy, individuals have been invited biennially between ages 50 and 70 with a FIT hemoglobin cutoff of 100 ng/mL. In Australia, FIT screening has started for individuals aged 55 and 65, with the intention to extend to biennial screening between ages 55 and 74 (43). Individuals are referred to colonoscopy if at least one of two tests determines that the amount of hemoglobin in the stool is more than 100 ng hemoglobin per mL. With the stepwise introduction of a screening program, it is important to also extend the colonoscopy capacity, to be able to screen more effectively in the future.

In conclusion, FIT is more cost-effective than gFOBT both with and without a limitation of the colonoscopy capacity but should be used in combination with a higher hemoglobin cutoff level for referral to colonoscopy when capacity is limited. It should be noted that FOBT screening can become considerably more effective if colonoscopy capacity is expanded. Efforts should therefore be undertaken to achieve an increased colonoscopy capacity.

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