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Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests: a cost-effectiveness analysis

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Comparability of cost-effectiveness of colorectal cancer (CRC) screening strategies is limited if heterogeneous study data are combined. We analyzed prospective empirical data from a randomized-controlled trial to compare cost-effectiveness of screening with either one round of immunochemical fecal occult blood testing (I-FOBT; OC-Sensor®), one round of guaiac FOBT (G-FOBT; Hemoccult-II®) or no screening in Dutch aged 50 to 75 years, completed with cancer registry and literature data, from a third-party payer perspective in a Markov model with first- and second-order Monte Carlo simulation. Costs were measured in Euros (€), effects in life-years gained, and both were discounted with 3%. Uncertainty surrounding important parameters was analyzed. I-FOBT dominated the alternatives: after one round of I-FOBT screening, a hypothetical person would on average gain 0.003 life-years and save the health care system €27 compared with G-FOBT and 0.003 life years and €72 compared with no screening. Overall, in 4,460,265 Dutch aged 50–75 years, after one round I-FOBT screening, 13,400 life-years and €320 million would have been saved compared with no screening. I-FOBT also dominated in sensitivity analyses, varying uncertainty surrounding important effect and cost parameters. CRC screening with I-FOBT dominated G-FOBT and no screening with or without accounting for uncertainty.

Cost-effectiveness studies on colorectal cancer (CRC) screening suffer from heterogeneous data based on partially ambiguous evidence.[1] Usually, the effect of CRC screening is performed by exploring a single type of test or strategy. A literature search showed that, if data from studies with more than one type of test were available, they suffered from no random allocation of tests and limited comparability due to differences in inclusion criteria, follow-up periods and geographical regions.[1–6] Most studies are accompanied by extensive sensitivity analyses covering a broad range of outcomes, but authors seldom report on decreased precision and possible lack of generalizability.[2–7]

Besides these forms of potential biases, several cost-effectiveness studies suffered from unrealistic assumptions. For example, participation in screening can vary between populations and screening tests. Primary endoscopy screening hardly ever exceeds 30% and is consistently lower than participation in guaiac fecal occult blood test (FOBT) screening, which hardly ever exceeds 50% participation.[8–12] However, in cost-effectiveness analysis, participation is often assumed to be 100%, regardless of the population, test or strategy. When imperfect participation is taken into account, it is often assumed to be only dependent on the population and not on the test or strategy.[3,5,7] In reality, participation levels related to different types of tests can vary considerably within a population, because of test-specific aspects such as the design of the test or the number of days a test has to be performed. Also, adherence to colonoscopy to verify a positive indirect screening test like a FOBT can vary considerably, ranging

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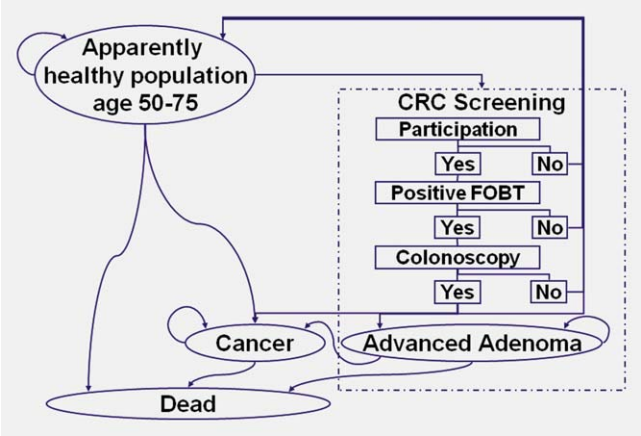

Figure 1. Markov states in the cost-effectiveness model. Average risk Dutch persons aged between 50 and 75 age make 10 cycles of 1 year. Markov States and cycle flows are given in curved boxes and lines. The implementation of a once only FOBT screening (with participation, positivity and colonoscopy steps) is illustrated with straight boxes and lines.

from 70% to almost 100%.[9,13,14] However, in cost-effectiveness studies, colonoscopy adherence is frequently assumed to be 100%.[2,7] Similar incorrect assumptions will be made for test performance aspects, such as sensitivity, specificity, detection rates or positive predictive value. Therefore, to date, still uncertainty exits about the cost-effectiveness of immunochemical FOBT (I-FOBT) in comparison with guaiac FOBT (G-FOBT) or no screening for CRC screening.

In the Netherlands, no CRC screening programs or studies were implemented, and therefore we had a unique opportunity to counter these comparability problems with a randomized-controlled trial comparing two different types of FOBT in a random selection of the general population at average risk for CRC.[9] Only direct prospective empirical evidence of this trial, completed with cancer registry data, were used as input for this cost-effectiveness study with the aim to compare I-FOBTs, traditional G-FOBTs and no screening on costs and effects.

Material and Methods

Model overview

We designed a Markov model to evaluate the cost-effectiveness of CRC screening and no screening in a random sample of asymptomatic average risk individuals aged between 50 and 75 years invited for a randomized-controlled trial comparing two different types of FOBT (Fig. 1). Our analyses do not include productivity losses, neither in the numerator nor in the denominator, and we based our unit costs on charges and retail prices. We used a third-party payer perspective in accordance with several other cost-effectiveness studies on CRC screening.[7,15–17] The results are based on a static cohort, *i.e.*, no new individuals enter into the model. The model was based on the natural history of CRC in the general population without screening, and the time frame of the analysis considered a single round of FOBT screening and, with 1-year cycles, the estimated cost and effects over 10 years. The model incorporated all aspects of one round of screening from invitation to participation, to FOBT result, to adherence to colonoscopy in FOBT positives, to colonoscopy results and, in case of CRC, to surgery or additional treatment if necessary. In descending order of prognostic seriousness, patients with FOBT positive results who undergo a colonoscopy might have CRC, advanced adenomas or either no or less significant neoplastic lesions. Differences in prognosis are included in the model as differences in CRC incidence and survival. Also, differences in treatment are taken into account, because of differences in stage distributions as for example differences in surgery rates. The population still at risk to be diagnosed with CRC after performing one FOBT is limited to the false-negative rate of the FOBT, which equals one minus the sensitivity (1 − sensitivity). This is why, in subjects who performed the FOBT, the probability of CRC incidence during the 10 years of follow-up after the FOBT was equal to the overall incidence for CRC multiplied by one minus the sensitivity: leaving 0.74*CRC incidence for G-FOBT and 0.52*CRC incidence for I-FOBT in the years following the FOBT.

Clinical data

We used data from a single trial in the Netherlands, in which 20,623 persons at average risk for CRC aged between 50 and 75 years were invited for CRC screening. Invited individuals were randomly allocated to receive either a G-FOBT (Hemoccult-II, Beckman Coulter, Inc. Brea, CA 92822-8000 USA) or an I-FOBT (OC-Sensor, Eiken Chemical CO. Ltd., Tokyo, Japan.). Details of the study design and the performance of the FOBTs have previously been described in more detail.[9] The inputs for the model were completed with relevant data from the Dutch National Cancer Registry database and literature (Table 1).[18–20]

Only a single semiquantitative I-FOBT was performed and was considered positive when the test result was $\geq$100ng/ml. The G-FOBT was considered positive if any blue discoloration occurred in one or more of six samples over 3 consecutive days with stools.

Before CRC becomes incident by showing symptoms or complaints, the disease has been prevalent as early stage cancer and, before that, as adenoma for many years. We refer to this unknown prevalence where we address prevalence in this manuscript. A true-positive FOBT patient is, therefore, defined to be part of the population with (previously) unknown prevalence. The FOBT sensitivities were estimated by combining the data from the comparative study with the available European data on the prevalence of CRC in studies using primary colonoscopy screening.[8,21,22]

Dutch Cancer Registry data were used to calculate the average 10-year survival, according to CRC stage distributions, as derived from TNM classifications per strategy: I-FOBT

Table 1. Base-case effects

Variable	Base case	Used in sensitivity analysis[1]	Reference
Effects			
CRC Incidence[2]	0.00138	0.00051–0.00375	18, 29
CRC incidence postpolpypectomy[2]	0.00028	0.00006–0.00075	18, 20
CRC prevalence[2]	0.00815	SE 0.00033	8, 21, 22
Mortality rate overall per year[2]	0.00943	SE 0.00005	26
Mortality rate CRC per year[2]	0.00049	0.00010–0.00141	18
Mortality rate per colonoscopy	0.00001	0.0001–0.000001	20–23
Complication colonoscopy[3]			
With polypectomy	0.005	SE 0.001	20–23
Without polypectomy	0.00008	SE 0.00001	20–23
Response rate			
G-FOBT	0.469	SE 0.0049	9
I-FOBT	0.596	SE 0.0048	9
Positivity rate			
G-FOBT	0.024	SE 0.0022	9
I-FOBT	0.055	SE 0.0029	9
Adherence to colonoscopy	0.84	SE 0.017	9
Positive predictive value			
Advanced adenoma			
G-FOBT	0.447	SE 0.049	9
I-FOBT	0.432	SE 0.030	9
Colorectal cancer			
G-FOBT	0.107	SE 0.030	9
I-FOBT	0.086	SE 0.017	9
5-yr CRC survival			
No screening	0.55	SE 0.005	18
G-FOBT	0.61	SE 0.15	18, 19
I-FOBT	0.82	SE 0.07	18, 19
Endoscopic treatment of CRC			
No screening	0.03	SE 0.014	18, 19
G-FOBT	0.18	SE 0.12	18, 19
I-FOBT	0.30	SE 0.08	18, 19
Chemotherapy (Stages III and IV)			
No screening	0.51	SE 0.005	18, 19
G-FOBT	0.45	SE 0.15	18, 19
I-FOBT	0.33	SE 0.08	18, 19
Radiotherapy (Stages IIIC and IV)			
No screening	0.32	SE 0.005	18, 19
G-FOBT[4]	0.32	SE 0.14	18, 19
I-FOBT	0.1	SE 0.05	18, 19
Metastasis (Stage IV)			
No screening	0.22	SE 0.004	18, 19
G-FOBT[4]	0.22	SE 0.12	18, 19
I-FOBT[5]	0.01	SE 0.02	18, 19

[1]Range: range used in sensitivity analysis where appropriate. [2]Calculated for the 50–75 yr of age population. [3]Complication of colonoscopy (mainly perforation and bleeding) are in terms of percentage calculated into the cost of complications due to colonoscopy. [4]G-FOBT actually worse than no screening, therefore set equal to no screening. [5]Actually zero persons with metastasis in the I-FOBT group.
SE: standard error.

Table 2. Base-case costs

Variable	Base case	Range	Reference
Screening costs			
Costs independent of test and participation	€2.40	(0.3–3)*base case	Retail prices[1]
Costs independent of test, depending on participation	€3.04	(0.3–3)*base case	Retail prices[1]
Test specific invitation costs independent of participation			
G-FOBT	€2.80	(0.3–3)*base case	Retail prices[1]
I-FOBT	€1.35	(0.3–3)*base case	Retail prices[1]
Test specific costs depending on participation			
G-FOBT	€1.39	(0.3–3)*base case	Retail prices[1]
I-FOBT	€1.71	(0.3–3)*base case	Retail prices[1]
Direct health care costs			24
Colonoscopy			
Including polypectomy and pathology report[2]	€921	(0.3–3)*base case	
Complication (bleeding or perforation)	€6,532	(0.3–3)*base case	
Colorectal cancer			
Surgery	€12,366	(0.3–3)*base case	
Chemotherapy	€12,731	(0.3–3)*base case	
Surgery and chemotherapy metastasis	€23,097	(0.3–3)*base case	
Radiotherapy	€5,710	(0.3–3)*base case	

[1]Retail prices include personnel, transport, reporting time and material costs. [2]In the costs of colonoscopies, a fixed proportion for polypectomies and pathology reports is calculated.

screening, G-FOBT screening and no screening.[18] Advanced adenomas were defined as adenomas $\geq$10 mm in size, with high grade dysplasia or with >20% villous component. The presence of only $\geq$3 small adenomas without any of the other markers for advanced neoplasia was very rare.[9] Therefore, and because of the literature, it becomes clear that, mainly, the removal of large adenomas is associated with a decreased risk of CRC incidence, the presence of $\geq$3 small adenomas was not considered as a separate marker for increased CRC risk.[23] We did address this in the sensitivity analysis.

Costs

We considered direct healthcare costs only (Table 2). The costs of the FOBTs consist of costs that were independent and dependent on the type of test. Ignoring the differences in participation between the types of test, costs independent of the type of test were costs related to the invitation for screening as letters and information brochures, basic administration of tests, feedback of test results to the patient and postal charges. Costs dependent on the type of test were costs of the FOBT itself and costs for laboratory analyses. For FOBT, we used retail prices. For the analysis of FOBTs, costs were calculated for administration, laboratory work and correspondence of test results only for returned tests. Consequently, participation rates influenced the total cost of FOBT screening. For the G-FOBT, a complete test kit of Hemoccult-II includes a number of tests and the test developer solution. For the I-FOBT, OC-Sensor testing materials are made available separately and were, therefore, calculated for returned tests only. The costs of the automated analyser OC-micro, used for the analysis of the OC-Sensor, were also included into the costs of a returned I-FOBT given the assumption of 100,000 tests per year and depreciated over 3 years. All other clinical costs for the follow-up of positive FOBT results (*e.g.*, CRC surgery) were given as charges and directly derived from the Dutch Health Care Authority database (NZA).[24] The NZA is the supervisory body for all the healthcare markets in the Netherlands and supervises both healthcare providers and insurers in the curative markets and in the long-term care markets.

Analysis

Analyses were performed in accordance with intention to screen, meaning that both costs and effects were analyzed per person invited. Costs and effects were calculated in respectively Euros (€) and life-years gained. Both costs and effects were discounted at a 3% rate, according to the recommendations by the U.S. panel on cost-effectiveness.[25] The baseline results from our model were translated to population level. We analyzed the model using probabilistic sensitivity analysis simulating 1,000 first and 5,000 second-order draws to account for the fact that CRC is relatively rare in population-based screening as approximately 8 per 1000 individuals will have CRC.[8,21,26] Deterministic one-way sensitivity analyses were performed on all the model parameters and especially on the incidence of CRC and

Table 3. Cost-effectiveness according to intention to screen of once only immunochemical FOBT screening compared with guaiac FOBT screening or no screening

Strategy	Cost (€) per person	Incremental cost[1]	Life-years per person[2]	Incremental life-years[3]	Incremental cost per life year
I-FOBT	€301		9.0496		
G-FOBT	€327	€27	9.0472	−0.003	Dominated[4]
No Screening	€373	€72	9.0471	−0.003	Dominated[4]

[1]Differences in costs compared with I-FOBT. [2]Average life-years per person invited to participate in once only screening with FOBT. [3]Life-years gained compared with I-FOBT (1 d is 1/365.25 = 0.0027 yr). [4]Dominated means both costs (€) and effects (life years) are favorable for I-FOBT.

major cost drivers such as the costs of colonoscopy and on the discount rates of costs and effects.

In Table 1, the base case for effects is presented. Standard errors were given if available, and for these, we used probabilistic sensitivity analysis to come up with 95% confidence intervals surrounding the Incremental cost effectiveness ratio (ICER). If distributions were not available, ranges of extremes are given in Table 1. For CRC incidence (and mortality), we applied deterministic sensitivity analysis with a range of extremes where the lower range corresponded with the incidence of 50-year-old females and the highest range with the incidence of 75-year-old males. The frequency of mortality as a complication of colonoscopy differs extensively in the literature.[21,26–28] Therefore, we used a wide range from one fatality per thousand to one fatality per million colonoscopies. The costs in Table 2 are the unit costs—retail prices and charges for interventions—and for these in sensitivity analysis, we applied one third of the base case as the lower limit and triple the base-case costs as the upper limit for all cost items in the sensitivity analysis—(0.3–3)*base case. The software we used for building the model and analyzing the data was TreeAge Pro Suite 2008 Release 1.6, TreeAge Software (www.TreeAge.com).

Results

The participation-independent costs of the FOBTs were: €5.20 for G-FOBT and €4.39 for I-FOBT. Compared with the manually operated and evaluated G-FOBT, the automated analyser (OC-Sensor micro) reduced operation and evaluation time for the I-FOBT with more than 90%. When assuming 100% participation, one G-FOBT overall cost €9.63 and one I-FOBT cost €8.50. The actual participation was 47% for G-FOBT and 60% for I-FOBT.[9] Therefore, the overall cost according to intention to screen for one G-FOBT was €7.06 and for one I-FOBT €6.22.

Table 3, the base-case analysis, discounted with 3% for costs and effects, shows that I-FOBT dominated both G-FOBT and no screening, *i.e.*, I-FOBT saved both life-years and money. Over a period of 10 years, an average person aged between 50 and 75 years would cost the healthcare system CRC-related costs in the amount of €372 without screening, €327 with G-FOBT and €301 with I-FOBT screening. Considering a period of 10 years, an average invited person would live 9.0471 years without screening, 9.0472 years with G-FOBT and 9.0496 years with I-FOBT screening (Table 3 and Fig. 4). An average invited person for I-FOBT screening can expect to gain 0.003 life years or 1.1 days compared with both G-FOBT and no screening. Moreover, an average invited person for I-FOBT screening would save the healthcare system €27 compared with G-FOBT and €72 compared with no screening (Table 3). Therefore, I-FOBT dominated both G-FOBT and no screening. Considering the entire screening population in the Netherlands between 50 and 75 years (n = 4,460,265)[29], a single round of I-FOBT screening compared with no screening would result in 13,400 life-years gained and €320 million saved over a period of 10 years.

Figure 2 represents two acceptability curves presenting the probability of cost-effectiveness as a function of the willingness to pay for a life-year gained. The figure shows that both FOBTs had a favorable probability of cost-effectiveness compared with no screening. I-FOBT had a higher probability of cost-effectiveness compared with no screening over a wide range of willingness to pay for a life-year gained, whereas G-FOBT compared with no screening had a higher probability of being cost-effective compared with no screening only up to ~€30.000.

We performed deterministic sensitivity analysis on all the relevant model parameters. A Tornado diagram (Fig. 3) graphically displays the results of single-factor sensitivity analysis of the six parameters with the largest impact on the result. The uncertainty in the parameter associated with the largest bar—at the top of the chart—having the maximum impact on the result and each successive lower bar having a lesser impact. The variables with the highest impact in descending order were the discount rate for effects, CRC incidence and costs of surgery, chemotherapy, colonoscopy and chemotherapy for metastasis. The discount rate of effects had by far the largest impact on the result. However, sensitivity analysis with the discount rate of effects (and costs) over a range between 0% and 6% never resulted in a relevant impact on the incremental cost-effectiveness of I-FOBT screening compared with both G-FOBT and no screening. The most relevant factor in the sensitivity analysis was the CRC incidence. In the lowest extremes of the CRC incidence in the sensitivity analysis, the screening with I-FOBT with the usual cutoff value of 100ng/ml was less cost-effective compared with no screening. In I-FOBT screening, cost-effectiveness sharply increased from 51 to 85 per 100,000 and became

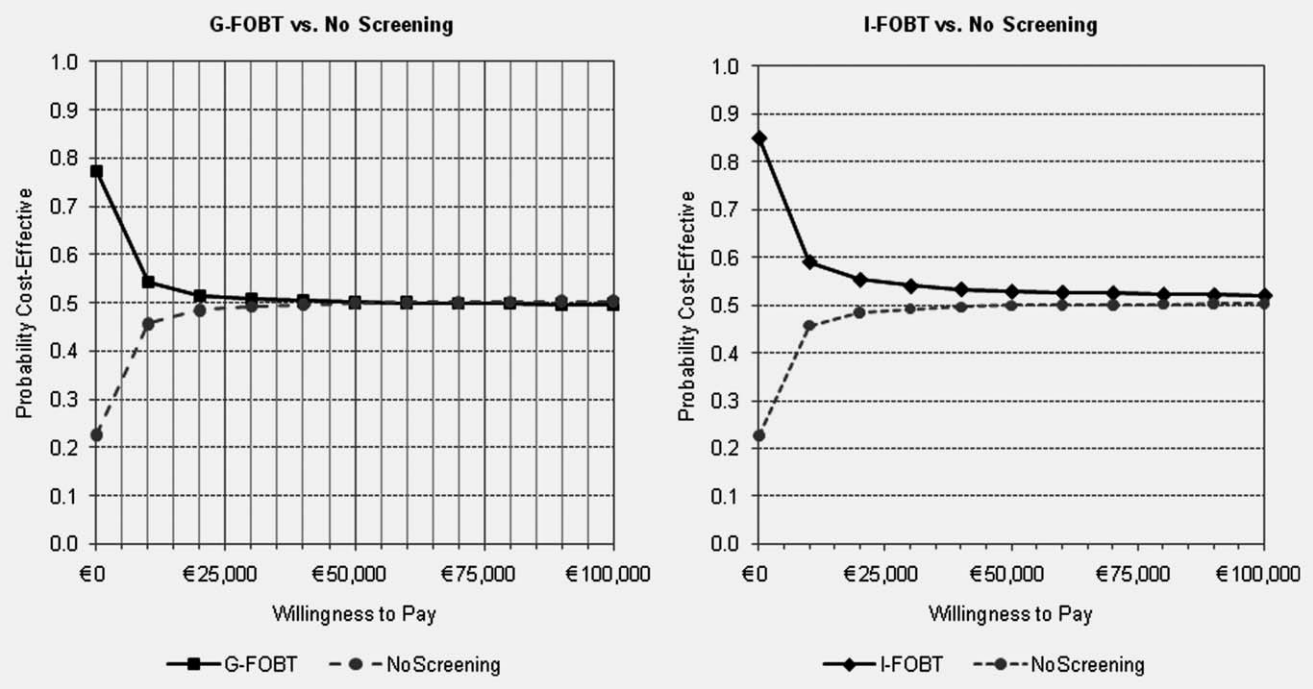

Figure 2. Acceptability curves for I-FOBT and G-FOBT *vs*. no screening, representing the probability of cost-effectiveness as a function of the willingness to pay for a life-year gained.

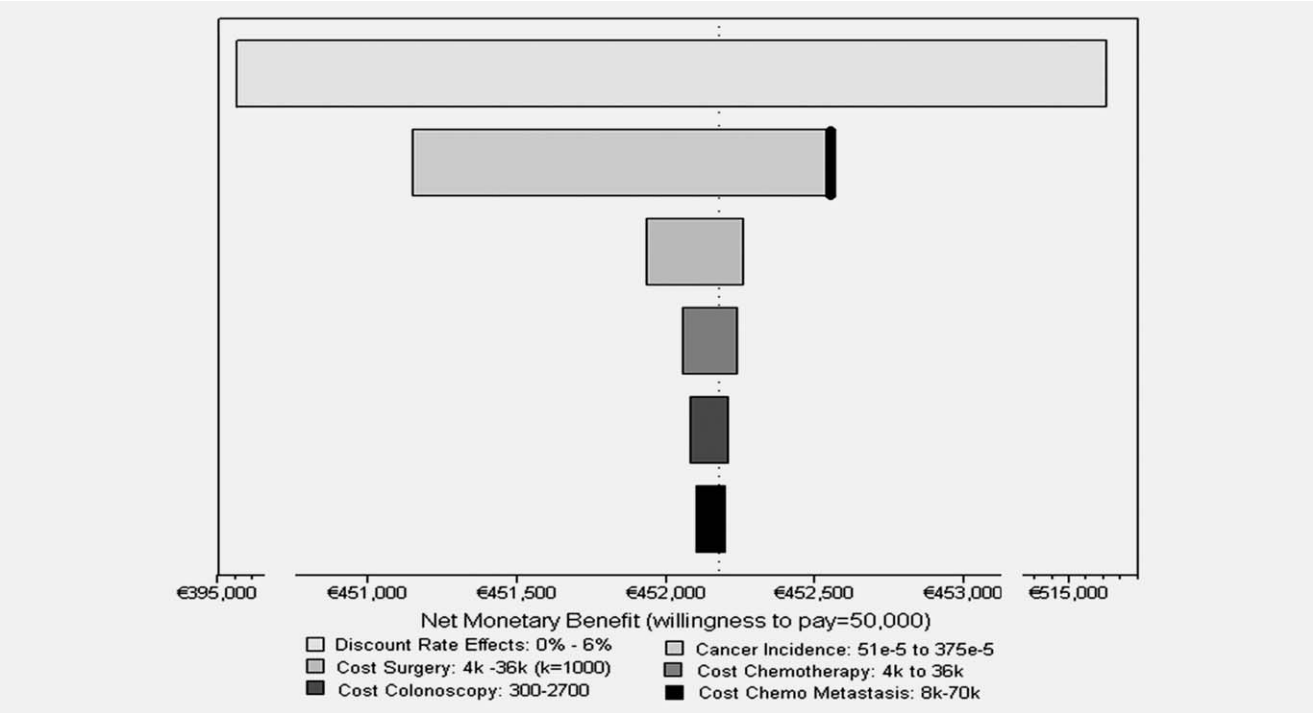

Figure 3. Tornado diagram of the results of the single-factor sensitivity analysis of all the relevant model parameters, graphically displaying the six parameters with the largest impact on the result. The horizontal axis represents the Net Monetary Benefit. The uncertainty in the parameter associated with the largest bar—at the top of the chart (the discount rate for effects)—has the maximum impact on the result, with each successive lower bar having a lesser impact. Note: The top bar (the discount rate for effects) had much more impact compared with the other bars. Therefore, the horizontal axis was presented with break offs in both extremes to be able to show the contrast between the parameters with lesser impact.

dominant above 85 per 100,000. If the cost of colonoscopy increased over €2,000 (about twice the current rate), then I-FOBT remained dominant over no screening but lost dominance over G-FOBT. Combining CRC incidence and the cost of colonoscopy in two-way sensitivity analysis increased the negative effect on cost-effectiveness. None of the other parameters had a significant negative effect on the cost-effectiveness of I-FOBT compared with G-FOBT and no screening.

According to the current CRC stage distribution at diagnosis in the Netherlands, CRC treatment with surgery and chemotherapy on average costs €37,000 without screening and would be €22,000 with the more favorable CRC stage distribution with I-FOBT screening. Therefore, we performed deterministic one-way sensitivity analysis on the stage distribution observed with I-FOBT. We observed that I-FOBT screening remained dominant even if the stage distribution in the screened patients would shift to 20% more later stages.

For a fair comparison between the two types of FOBT, we used a fixed cutoff value for the I-FOBT at the most usual level of 100 ng/ml. In sensitivity analysis, we did address the effect of the cutoff value of the I-FOBT on cost-effectiveness. At the lowest reliable cutoff level of 50 ng/ml the cost-effectiveness of the I-FOBT was higher than at 100 ng/ml, however, at the expense of many more colonoscopies that have to be performed: both in total number and in relative, *i.e.*, the number to find CRC or advanced adenomas. Increasing the cutoff value above 100 ng/ml decreased the number of colonoscopies needed, both absolute and relative without missing many CRC patients, but cost-effectiveness was always lower than at the lowest cutoff values.[30] Although cost-effectiveness was highest at the 50-ng/ml arguably, the 75-ng/ml cutoff resulted in a far more balanced absolute and relative number of colonoscopies needed per screening round. At all cutoff values, I-FOBT dominated G-FOBT screening. We do not have any experimental data for more successive stool samples with the I-FOBT, but the sensitivity of more consecutive samples is higher.[31–33] Higher sensitivity (as with the lower cutoff values) means higher cost-effectiveness, but only if the participation remained constant. Although direct data are lacking for the I-FOBT, the comparison between G-FOBT (a 3-day test) with the I-FOBT as a 1-day test[9] shows that the participation would probably drop and maybe even dramatically. Because of this uncertainty, we did not model these scenarios extensively, but our sensitivity analysis shows that probably lowering the cutoff value to 50 ng/ml is more cost-effective than adding an extra sample with a higher cutoff value.

Discussion

I-FOBT screening dominated both G-FOBT and no screening. Acceptability curves confirmed that the cost-effectiveness of population-based screening with I-FOBT was more pronounced in the numerator (costs) than in the denominator (life-years gained), because the difference in the probability of cost-effectiveness between the screening alternatives became less pronounced as the willingness to pay per life-years gained increased. The probability of cost-effectiveness of I-FOBT was higher compared with no screening over a wide range of willingness to pay for a life-year gained (up to €100,000). The sensitivity analysis showed that the results of I-FOBT screening were robust over the complete set of varied parameters in the model.

Only when CRC incidence was very low or colonoscopy cost very high, I-FOBT screening could become less cost-effective. In the Netherlands, in the age group between 50 and 55 years, the incidence is so low that I-FOBT screening did not dominate no screening but was still cost-effective even if the cost for a colonoscopy would be double the current rate.[18] In countries with low CRC incidence in combination with high colonoscopy costs, I-FOBT screening might be less cost-effective.[34]

Overall, our findings are in accordance with other authors, although the size of the incremental effect differs.[3,5–7] Differences in size of effect might be explained by several facts. We considered only one round of FOBT screening. But, another explanation is the major advantage of our study that, for both FOBTs, effect parameters such as participation rates, FOBT positivity rates, adherence to follow-up with colonoscopy and positive predictive values were prospectively measured.[9] We did not have to make assumptions concerning differences in the effect parameters between FOBTs, and we showed that these have a considerable impact on the overall effect of a screening test or strategy. Studies in which FOBT participation and colonoscopy adherence rates are assumed 100%, overestimate the effect of screening.[2,35]

We did not use quality of life in our analysis, but in screening, the difference in utility between the two FOBT tests measured with the usual methods (EQ-5D, TTO or SG) will be in favor of the I-FOBT. Although both are FOBTs, the I-FOBT is performed on 1 day and the G-FOBT on 3 days, which is obviously more convenient. Anxiety about outcome after testing is equal for both tests. Earlier detection of advanced adenomas and especially CRC might increase quality of life and the detection of CRC and advanced adenomas is almost three times higher in I-FOBT screening compared with G-FOBT screening. After diagnosis, combining treatment and survival outcomes with utilities would also be in favor of I-FOBT, because it leads to the least burden of disease.

In consecutive rounds of FOBT screening, the cumulative detection of CRC and advanced adenomas would increase, and the positive predictive value would decrease only slightly.[36] We did not extrapolate our findings of the first screening round to consecutive rounds, because participation and detection rates usually are not stable during consecutive screening rounds. Furthermore, differences in populations and cultural backgrounds would lead to too much uncertainty with data from other studies[36,37] The corresponding errors in the assumptions would be magnified over

consecutive screening rounds. In a few recent studies considering annual G-FOBT and I-FOBT screening strategies, in agreement with our study, the authors observed that FOBT screening can result in cost savings for the healthcare system over several rounds of screening.[7,38]

The full set of scenarios for I-FOBT screening is comprised by several parameters: different screening intervals, cutoff values the number of consecutive samples and, *e.g.*, age and gender. In comparison with either G-FOBT screening or no screening, every scenario with I-FOBT was more cost-effective. The most cost-effective scenario is probably annual I-FOBT screening with the lowest reliable cutoff value of 50 ng/ml.[30,39] However, when, *e.g.*, also colonoscopy capacity and investment costs are considered, higher cutoff values and biennial screening could be preferable.

As only returned tests have to be handled and analyzed, costs of FOBTs are affected by participation rates. Although participation rates of I-FOBT screening are substantially higher than G-FOBT screening,[9] the overall costs according to intention to screen of I-FOBT were lower than the overall G-FOBT costs. In contrast to G-FOBT, where the test kit is all inclusive, I-FOBT analyzing materials are sold separately, relatively reducing overall costs. Most importantly, however, the automated I-FOBT reduced the time for handling and analyzing to only ~10% compared with G-FOBT. In addition, the possibilities for quality control of the I-FOBT are extensive compared with the G-FOBT, and no specific training of laboratory personnel is necessary, which will also increase the efficiency and reduce cost.

Although costs of the FOBTs have to be calculated for all invited subjects with an additional sum for participants, in total, these costs were negligible compared with colonoscopy costs to verify positive FOBTs and costs of treatment of (metastasized) CRC. Implementation of FOBT screening will result in a considerable increase in the number of colonoscopies performed each year, requiring extensive investments in personnel and facilities.[40]

The set of screening options was limited to FOBT testing, which can be considered a limitation. However, economic evaluation is based on the opportunity cost principle meaning that, at least, the comparator representing the first best alternative should be part of the evaluation. In a recent cost-effectiveness study, the cost-effectiveness of annual G-FOBT or I-FOBT, sigmoidoscopy every 5 years, colonoscopy every 10 years and a combination of sigmoidoscopy every 5 years and annual G-FOBT were studied under the realistic assumption that new expensive strategies for chemotherapy will become more widespread.[38] The colonoscopy strategy was the only strategy that did not become cost saving, even without considering the relatively low uptake of colonoscopy screening, especially if compared with I-FOBT screening uptake.[7] Furthermore, because of capacity constraints, primary endoscopy and virtual colonoscopy are not considered a realistic screening strategy for CRC in the Netherlands and most other European countries. Depending on the referral indication—only patients with large polyps or also patients with only minor polyps—the referral rates for colonoscopy can increase from 7% to 30% increasing the costs substantially.[41] Extracolonic findings can cause a further considerable increase of costs with a low return.[42] Finally, the uptake of virtual colonoscopy is not expected to be very high.[41] The opportunity costs (cost associated with the first best alternative) of I-FOBT is G-FOBT and possibly doing nothing. Therefore, at present, we did not consider virtual and actual endoscopy as realistic alternatives in our cost-effectiveness study.

Even when a sensitivity analysis with a wide range of possible colonoscopy costs of €300 to €2700 was applied, I-FOBT screening remained dominant over no screening. I-FOBT only lost dominance over G-FOBT above €1200 per colonoscopy. Colonoscopy costs have a relatively high impact in the total screening costs as the FOBTs hardly cost anything compared with the costs of a colonoscopy. Moreover, the positive predictive value of one FOBT is 10% for CRC, and therefore 10 times more subjects will have a colonoscopy than any kind of CRC treatment. Even a relatively limited increase in colonoscopy costs could have a substantial effect on the nominator.

Overall, CRC cancer treatment costs will decrease as CRC is detected at earlier stages by screening, saving costs for metastasized CRC. On the other hand, because of the results of recent studies, adjuvant chemotherapy might be recommended in selected Stage II CRC patients.[43,44] It is still uncertain if this recommendation will become common practice. However, in sensitivity analyses, I-FOBT screening remained dominant, even if costly adjuvant chemotherapy would become indicated in all CRC stages, which was also confirmed by another recent study.[38]

In the randomized-controlled trial that we used for the input of our model, we excluded all institutionalized individuals.[9] In the data from the Dutch Cancer Registry database we used to complete the data, we could not exclude institutionalized individuals.[18] We assume that selection bias is negligible, because only 232 (1%) of the random sample of the general population was institutionalized and excluded. A second source of selection bias is the use of indirect unknown prevalence data of CRC in our model. Before CRC becomes incident by showing symptoms or complaints, the disease has been unknown but prevalent as early stage cancer and, before that, as adenoma for many years. In the Netherlands, the level of this unknown prevalence of CRC is largely undetermined. We used data from studies in other European countries (Germany, Poland and Italy) where prevalence of CRC was approximately 0.8% in the age cohort of interest for screening.[8,21,26] Except for Italy, these countries use opportunistic CRC screening programs, and, therefore, although the prevalence of the German and Polish populations do not differ much from the Italian population, selection bias cannot be ruled out completely. However, opportunistic screening would mean more high-risk screening participants, resulting

in an overestimation of the prevalence in the general population from these studies. Therefore, in this case selection bias would strengthen the overall conclusion.

Finally, based on the findings in this study, we compiled the following conclusions and propositions. I-FOBT is cost-effective in CRC screening and dominates no screening and G-FOBT screening, *i.e.*, costs are saved, and life-years are gained. The cost-effectiveness of I-FOBT screening is robust for the uncertainty surrounding important parameters and more specifically CRC incidence and major cost drivers. For CRC screening, I-FOBT screening should be preferred over G-FOBT screening. The results of this study can be generalized to most European countries, even if the costs would be much higher or the incidence much lower than in the Netherlands. However, cost-effectiveness should be evaluated per country, as incidence rates and costs vary per country.

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