Published in final edited form as:

Gut. 2015 December ; 64(12): 1985–1997. doi:10.1136/gutjnl-2015-309316.

The value of models in informing resource allocation in colorectal cancer screening – 1 the case of the Netherlands

Frank van Hees¹, Ann G. Zauber², Harriët van Veldhuizen³, Marie-Louise A. Heijnen⁴, Corine Penning¹, Harry J. de Koning¹, Marjolein van Ballegooijen¹, and Iris Lansdorp-Vogelaar¹

¹Department of Public Health, Erasmus MC, Rotterdam, the Netherlands ²Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, United States ³Department of Quality Improvement, Erasmus MC, Rotterdam, the Netherlands from August 2014, before National Institute of Public Health and the Environment, Bilthoven, The Netherlands ⁴National Institute of Public Health and the Environment, Bilthoven, the Netherlands

Abstract

In May 2011, the Dutch government decided to implement a national programme for colorectal cancer (CRC) screening using biennial faecal immunochemical test (FIT) screening between ages 55 and 75.[1] Decision modelling played an important role in informing this decision, as well as in the planning and implementation of the programme afterwards. In this overview, we illustrate the value of models in informing resource allocation in CRC screening, using the role that decision modelling has played in the Dutch CRC screening programme as an example.

Keywords

colorectal cancer screening; decision modelling; microsimulation modelling

BACKGROUND

More than 1 million people worldwide are diagnosed with CRC each year.[2] Half of these patients die from the disease, making CRC the fourth leading cause of cancer death in the world.[2] Randomized controlled trials (RCTs) have shown that screening can prevent many of these deaths by detecting CRC in an earlier stage or by detecting and removing its precursor lesion: the adenoma.[3, 4]

Corresponding author: Frank van Hees, MSc, Department of Public Health, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, the Netherlands; phone: +31-10-7044528; fax: +31-10-7038474; f.vanhees@erasmusmc.nl.

DECLARATION OF COMPETING INTERESTS

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

AUTHOR CONTRIBUTIONS

FvH and ILV were responsible for drafting the manuscript. All authors contributed to the conception and design of the study; the generation, collection, assembly, analysis and/ or interpretation of data; and the revision of the manuscript. All authors approved of the final version of the manuscript.

Although RCTs are the gold standard for determining the effectiveness of screening, they also have their limitations. First, RCTs are expensive and time consuming. As a result, the number of RCTs that have evaluated CRC screening is limited. Until now, only guaiac faecal occult blood test (gFOBT) and sigmoidoscopy screening have been evaluated by means of a RCT. Screening modalities such as the FIT and colonoscopy, although expected to be more effective, have not. For the same reasons, so far, direct comparisons between different CRC screening modalities, as well as comparisons between different screening strategies using the same screening modality (e.g. annual versus biennial gFOBT screening), have never been made. Second, RCTs usually have a limited follow up time. As a result, they cannot be used to determine life-time health effects and costs, which is necessary to determine the (cost-)effectiveness of screening. Third, the effectiveness of screening might differ from setting to setting. For example, a sigmoidoscopy screening trial in Norway showed a 63% attendance rate,[5] while in the Netherlands an attendance rate of only 32% was observed.[6] This will impact the comparative (cost-)effectiveness of sigmoidoscopy screening compared with FIT screening, for example. Finally, country-level resource demands for a certain screening programme cannot easily be inferred from a RCT. To summarize: RCTs alone do not answer the question of which screening strategy is optimal for a certain country. This might explain the large differences between the screening programmes that are currently implemented in the European Union (Table 1).

Decision models provide a useful tool to extrapolate evidence from RCTs and address the question of which screening strategy is optimal given local conditions with respect to CRC risk, life-expectancy, resource availability and population preferences, which is the central question in the decision phase of a CRC screening programme. This is the phase in which models have been most frequently used. However, modelling is also valuable in the phases afterwards: during the planning, implementation, and evaluation of a screening programme. In this paper, we will illustrate the value of models during the whole cycle of a screening programme using the role of the MISCAN-Colon model in the Dutch CRC screening programme as an example.

MISCAN-COLON DECISION MODEL

The Dutch CRC screening programme has been co-informed by MISCAN-Colon. MISCAN-Colon is a microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Center (Rotterdam, the Netherlands). The model's structure, underlying assumptions, and calibration are described extensively in a standardized model profile (available at <http://cisnet.cancer.gov/colorectal/profiles.html>) and previous publications.[7, 8] In brief, MISCAN-Colon simulates the life histories of a large population of individuals from birth to death. CRC arises in this population according to the adenoma-carcinoma sequence.[9, 10] More than one adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas may progress in size from small (< 5 mm) to medium (6–9 mm) to large (> 10 mm) and some adenomas will eventually become malignant. Cancer can progress from a localized stage I cancer to a metastasized stage IV cancer. However, during each stage, there is a probability of the cancer being diagnosed due to symptoms. At any time during the development of the disease, the process may be interrupted because the individual dies of another cause.

Screening will alter some of the simulated life histories: Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favourable survival. However, screening can also result in serious complications and over-diagnosis and over-treatment of CRC (i.e. the detection and treatment of cancers that would not have been diagnosed without screening). By comparing all life histories with screening with the corresponding life histories without screening, MISCAN-Colon quantifies the benefits of screening, as well as the associated harms and costs.

MISCAN-Colon was calibrated to data on the age-, stage- and localization-specific incidence of CRC in the Netherlands [11] and the age-specific prevalence and multiplicity distribution of adenomas as observed in autopsy and colonoscopy studies.[12–22] Furthermore, MISCAN-Colon was calibrated to the reductions in CRC incidence and mortality observed in RCTs evaluating the effectiveness of screening with either gFOBTs or flexible sigmoidoscopy and showed good concordance with these trials results.[8, 23, 24]

THE VALUE OF MISCAN-COLON IN INFORMING THE DUTCH CRC SCREENING PROGRAMME

The run-up to the Dutch CRC screening programme is characterized by a long history of decision-making and planning by various stakeholders. Figure 1 gives an overview of the most important milestones in this process. The process and milestones as well as the role MISCAN-Colon has played in this process are described in more detail below.

Decision phase

The discussion on population screening for CRC was initiated in the Netherlands by a report of the Dutch Health Council in 2001.[25] This report not only recommended that feasibility studies and screening trials should be conducted, but also that a simulation model should be developed in order to make well-founded judgements about screening strategies. In 2003 and 2004, more landmark reports were published stressing the need to implement a national CRC screening programme.[26–28] In response to these signals, the Netherlands Organisation for Health Research and Development and the Dutch Cancer Society joined forces and organised a consensus development meeting in February 2005 in which both public health researchers (in favour of fecal occult blood test (FOBT) screening) and clinicians (in favour of endoscopy screening) participated. During this meeting, consensus was reached to perform population screening with FOBT biennially with the specific test (FIT or gFOBT), the cut-off for referral to colonoscopy in case of a FIT, and the age range for screening to be decided within 2–3 years based upon further research.[29]

In 2006 and 2007, screening trials were conducted in the Amsterdam, Rotterdam, and Nijmegen areas to compare attendance rates and detection rates of advanced neoplasia for different FOBTs. More than 30,000 individuals aged between 50 and 74 were randomly selected from the municipal registries and randomised to receive either a gFOBT (Hemoccult II, Beckman Coulter, USA) or a FIT (OC-Sensor, Eiken, Japan). For the FIT a cut-off for referral to colonoscopy of 50ng/mL buffer (10µg/g faeces) was applied, which

allowed us to also calculate positivity and detection rates for higher cut-offs. All three regions showed higher attendance and detection rates for FIT compared with gFOBT screening.[30, 31] FIT detection rates were higher at lower cut-offs, but applying a low cut-off also required substantially more colonoscopies. What could not be estimated from the trials was whether the health benefit of detecting more advanced neoplasia justified the additional upfront costs of colonoscopies. To answer that question, MISCAN-Colon was developed and adjusted to reproduce the positivity and detection rates of gFOBT and FIT screening as observed in the Dutch screening trials. The model was subsequently used to predict the costs and effects of different screening strategies, varying the test and cut-off for referral to colonoscopy, as well as the age range and screening interval to determine the optimal FOBT screening strategy for the Dutch setting.

Figure 2 presents the outcomes of this analysis.[32] Each symbol in the graph represents a screening strategy. The higher the symbol in the graph, the more effective the strategy, the more to the right, the more expensive. The strategies lying on the top-left, which are connected by the solid line, form the efficient frontier, i.e. the economically rational subset of choices.[33] Symbols lying beneath the efficient frontier represent strategies that are not as effective for the given amount of money as a point lying on the efficient frontier. These strategies are “dominated” by (combinations of) other strategies. All gFOBT strategies clearly lie beneath the efficient frontier and hence, are dominated by FIT strategies. In other words, FIT screening is more effective than gFOBT screening at lower cost. The strategies that form the efficient frontier all consist of FIT screening with a cut-off for referral to colonoscopy of 50ng/mL (10µg/g), indicating that screening using this low cut-off does not only result in more life-years (LYs) gained, but that the higher upfront costs of colonoscopies are also more than compensated for by higher future savings on CRC treatment.

Table 2 gives an overview of the FIT strategies on the efficient frontier. The strategy with the lowest costs per LY gained was 3-yearly screening between ages 60 and 69; next came lowering the start age to 55. The age range recommended by the Council of Europe (50 to 75) was not among the cost-effective options. As said, each of these strategies is an economically rational choice. Which strategy to choose depends on the willingness-to-pay for a LY gained. Generally in the Netherlands, a threshold between €20,000 and €40,000 per quality-adjusted life-year gained is used for preventive interventions. All efficient strategies resulted in costs per LY gained well beneath that threshold, making the most intensive strategy (i.e. annual screening between ages 45 and 80) still an appropriate choice in the Dutch setting.

This MISCAN-Colon analysis was an important component of the 2009 Health Council advice on CRC screening.[34] The Health Council advised the Minister of Health to implement biennial FIT screening between ages 55 and 75 using a cut-off for referral to colonoscopy of 75ng/mL (15µg/g). Based on the outcomes of the cost-effectiveness analysis a different age range was chosen than recommended by the European Council (i.e., 55 to 75 instead of 50 to 75) and a different cut-off was chosen than recommended by the FIT manufacturer (i.e., 75ng/mL (15µg/g) instead of 100ng/mL (20µg/g)). The Health Council recognised that applying a lower cut-off for referral to colonoscopy was more cost-effective

and that the willingness-to-pay threshold allowed for more intensive FIT screening. However, their choice also reflects the anticipated lack of colonoscopy capacity in the Netherlands to implement such a colonoscopy-intensive programme.[34]

Planning phase

In January 2010, the Minister of Health responded to the Health Council advice. He acknowledged the value of a nationwide CRC screening programme, but felt forced to postpone a final decision on its implementation.[35] The financial climate at that time put the government in a situation of radical cost reductions, so there was no budget for a national CRC screening programme. In addition, the Minister considered the anticipated shortage of colonoscopy capacity [36] an important bottleneck that needed to be resolved before a national CRC screening programme could be implemented and emphasized the need for a system for quality assurance. He therefore commissioned the National Institute for Public Health and the Environment to investigate the feasibility of a national CRC screening programme in the Netherlands. The purpose of this feasibility study was to ascertain the prerequisites for a CRC screening programme and to determine how such a programme could be introduced successfully. The study should identify potential problems with implementation and suggest how to deal with them, including issues of capacity, communication, quality assurance, flexibility in the light of new technological developments, link with further diagnostics and care, as well as monitoring and evaluation. [37]

To investigate the issue of capacity, the National Institute for Public Health and the Environment requested Erasmus MC to predict the resource requirements for a national CRC screening programme using MISCAN-Colon.[38] The model was used to simulate the Dutch population from 2013 up to 2042 under the implementation of a national CRC screening programme as proposed by the Health Council, including a phased roll-out from 2013 to 2018 (Figure 3).

Assuming attendance, positivity, and detection rates for FIT screening with a cut-off of 75ng/mL (15µg/g), the model predicted the annual numbers of FIT analyses, colonoscopies, histopathological examinations, surgical procedures, as well as the numbers of CRC deaths prevented, and the costs of screening from the anticipated start of the programme in 2013 until 2042 when resource requirements and screening benefits were expected to stabilize (Figure 4).[37, 38] A comparison of required and available endoscopy capacity showed that in 2016, 2017 and 2018 there would be a shortage of endoscopy capacity (Figure 5). The professional groups proposed that increasing colonoscopy efficiency and increasing the intake to training programmes could overcome the expected shortage in these years.

Implementation phase

Based on the outcomes of the feasibility study, a new Minister of Health decided in May 2011 to implement a national CRC screening programme in accordance with the Health Council advice.[1] After two years of preparation of programme infrastructure, quality assurance protocols, and communication materials, the national programme was first piloted in the Rotterdam-Rijnmond area in the fall of 2013 and then gradually rolled out nationally

starting in January 2014. Based on the outcome of a public tender, the FOB-Gold (Sentinel, Italy) was chosen as the preferred test. The cut-off for referral to colonoscopy was set at 88ng/mL (15µg/g), which corresponds with the 75ng/mL (15µg/g) of the OC-Sensor as recommended by the Dutch Health Council. Because of the slight delay in the start of the programme (January 2014 instead of September 2013), not only individuals aged 63, 65, 67 and 75, but also individuals aged 76 were invited in 2014, thereby assuring that these individuals, originally scheduled for screening in 2013, still got a chance to participate in screening at least once.

Because the IT-system especially developed for the CRC screening programme allowed for continuous monitoring of the programme, attendance, positivity, and detection rates could be tracked real-time. The programme was an immediate success. Attendance to the programme was higher than expected (68% versus 60%),[39] as was the detection rate of advanced adenomas/CRC (4.0% versus 2.7%).[34, 40] However, the positivity rate was also considerably higher than expected (13.4% versus 6.4%) and the observed positive predictive value for detecting an advanced adenoma/CRC was substantially lower than expected (30.0% vs 42.5%).[37,40] Consequently, colonoscopy capacity became an important bottle neck and waiting times for diagnostic colonoscopy increased.

Several steps were taken to address this problem. In a first step, positivity and detection rates at several cut-offs as observed in the national programme were compared to those observed in the Rotterdam screening trial. This comparison showed that applying the same cut-off level resulted in a higher positivity and a higher detection rate in the national programme than in the trial (Figures 6a and b). The correlation between the positivity rate and the detection rate, however, was strikingly similar (Figure 6c). Based on a MISCAN-Colon analysis in which we corrected for the difference in the age distribution between the individuals screened within the Rotterdam screening trial and the national programme, who were substantially older, it was concluded that the test characteristics corresponding to a cut-off level of 75ng/mL (15µg/g) as observed in the trial, could be reproduced by elevating the cut-off level in the national programme to 275ng/mL (47µg/g).

In a second step, MISCAN-Colon was used to quantify the impact of the modified roll-out, the higher than expected attendance, and the higher than expected positivity rate on the anticipated colonoscopy demand for 2014 and to determine which measure could best be taken to reduce this demand. Also screening 76 year-olds in 2014 was found to increase the anticipated colonoscopy demand for 2014 from 28,000 to 33,000 (Figure 7). The higher attendance rate further increased this demand to 38,000 colonoscopies. However, the higher positivity rate resulted in the largest increase in colonoscopy demand for 2014: up to 64,000 colonoscopies. By 2030, the higher attendance and positivity rate would result in a doubling of colonoscopy demand compared with what was anticipated based on the feasibility study.

To reduce colonoscopy demand for 2014, two measures could be taken: screening could be postponed until 2016 in one or more of the age groups scheduled for screening in 2014 or the cut-off for referral to colonoscopy could be elevated in all age groups. To determine which of these measures was best suited to reduce colonoscopy demand for 2014, MISCAN-Colon was used to estimate the associated loss in benefit from screening and the reductions

in colonoscopy demand for 2014. The best measure to reduce colonoscopy demand for 2014 was defined as the measure that resulted in the largest reduction in colonoscopy demand per CRC death not prevented.

Postponing screening in 75 and 76 year-old individuals, which implies not screening them at all, reduced colonoscopy demand by 21 and 22 per CRC death not prevented, respectively (Table 3). Postponing screening in 63, 65, and 67 year-old individuals, was somewhat more efficient, reducing colonoscopy demand by 54, 60, and 53 per CRC death not prevented, respectively. However, temporarily elevating the cut-off for referral in all age groups to 275ng/mL (47µg/g) reduced colonoscopy demand by 68 per CRC death not prevented and was most efficient. The National Institute for Public Health and the Environment therefore decided to increase the cut-off for referral to colonoscopy to 275ng/mL (47µg/g), starting on 23 July 2014.[40] MISCAN-Colon predicted that applying this higher cut-off will result in a similar number of CRC deaths prevented as anticipated based on the 2010–2011 feasibility study (Figure 8).

The increased cut-off will be sustained in 2015, but in that same year the MISCAN-Colon model will again be used to compare the increased cut-off with other measures to reduce colonoscopy requirements for the longer-term: lengthening the screening interval and narrowing the age range. In addition, when data from repeat screenings become available, the model will be updated to reflect observed positivity and detection rates for repeat screenings and will again be used to predict long-term resource requirements and benefits of the Dutch CRC screening programme. In case of substantial changes in anticipated resource requirements and benefits, the impact of changes to the programme may need to be evaluated anew.

Established programme

In an established programme that has been running for several years and in which a steady-state has been reached, the value of modelling may be less apparent than in the decision, planning, and implementation phase of a screening programme. However, modelling also has its value in a well-established programme. In the first place, modelling can be used for evaluation of the screening programme. Is the programme working as expected? What are the expected changes in the long-term impact of the programme based on differences in anticipated and observed programme indicators? Model predictions can be used as a benchmark for observed CRC incidence and mortality to determine if the programme is having the anticipated benefit. An important example of such work has been done using the MISCAN-breast model. Because screening resulted in a substantial increase in the incidence of breast cancer in women in the screen-eligible age range there was considerable debate about the amount of overdiagnosis from mammography screening. Using the model, we demonstrated that this increase in incidence could be anticipated and that it is almost completely compensated for by a sharp decrease in breast cancer incidence at older age.[41]

Secondly, in every programme, even the well-conducted programmes, there is room for improvement. There might be regional variation in performance indicators (e.g. attendance, delay in diagnostic follow-up) and modelling can be used to estimate the impact of this regional variation on long-term outcomes of the screening programme. This way the impact

of reducing regional variation can be determined for each indicator and interventions can be prioritized.

Finally, medicine in general but CRC screening in particular is a continuously developing field and therefore a moving target. New technologies for screening may become viable such as Computed Tomographic Colonography, Stool DNA testing and serum testing.[42–44] In addition, the call for precision medicine, and in that light risk-stratified screening, is increasing.[45–47] It is important to continuously follow these developments and determine their potential benefits and harms for an existing CRC screening programme. For example, for CRC screening, it is well known that test characteristics of FIT differ by gender and age [48, 49] and using differential cut-offs for men versus women and older versus younger people has therefore been proposed. Modelling can help determine whether these calls are justified and what the potential benefit of gender and age-specific FIT screening is.

DISCUSSION

This overview shows that decision modelling played an important role in the decision, planning, and implementation phase of the Dutch CRC screening programme and we believe it will continue to do so in the coming years as it has done for other programmes. On several occasions, model results have influenced the programme: in the decision phase FIT screening was chosen over gFOBT screening, a higher age to start screening was chosen than that recommended by the Council of Europe, and a lower cut-off for referral to colonoscopy was chosen than that recommended by the test's manufacturer. To remediate the higher than anticipated colonoscopy demand during the implementation phase, the cut-off for referral to colonoscopy was temporarily elevated. If modelling would not have been available or used, these choices might not have been made and the benefits and harms of the screening programme could have turned out less favourable than they will now.

Validation of model results

This overview describes how modelling has influenced and changed the Dutch CRC screening programme. However, the use of a model does not necessarily imply that the right decisions are made. Policy makers considering using a model to inform their (CRC) screening programmes should be aware of the considerable variation in quality of available models. An important strength of the MISCAN-Colon model is that it has been extensively validated against available evidence from RCTs and other sources, and, where necessary, adapted to accurately predict the impact of screening on CRC incidence and mortality. The good fit with trial results builds confidence in model extrapolations to the Dutch population and other settings. However, it remains very important to closely monitor the outcomes of the screening programme and compare them with model predictions. Important outcomes to consider include detection rates during repeat screening rounds, interval cancer rates, and CRC mortality. For example, to validate the decision to increase the cut-off for a positive FIT in the programme, it is important to monitor the interval cancer rate after a negative screening in the programme. This rate should not exceed the rate predicted by the model.

An important example of how model-induced changes to a screening programme were validated by subsequent monitoring of the programme comes from the Dutch cervical cancer

screening programme. This programme originally offered women 3-yearly Pap smear testing between ages 35 and 53: a total of 7 smears. Evaluation using the MISCAN-Cervix model indicated that spreading those 7 smears over a wider age range increased the benefits of screening without increasing its costs.[50] Based on this analysis, the cervical cancer screening programme was changed to offer 5-yearly screening between ages 30 and 60. Evaluation of this change several years later showed that the 9-year incidence of cervical cancer after a negative primary smear did not increase.[51] This example clearly illustrates how modelling resulted in the *right* decision to change an existing screening programme.

Conditions for decision modelling

Decision modelling in the Dutch CRC screening programme could only be applied because several critical conditions were met. First of all, the availability of local data on adherence and yield of FIT screening from the Dutch screening trials was essential to reliably estimate the required capacity and long-term impact of FIT screening in the Netherlands. Second, involvement of monitoring and evaluation experts of the Department of Public Health in the development of quality indicators ensured that all indicators relevant for decision modelling were consistently collected in the screening programme. Third, the IT-system developed for the CRC screening programme allowed real-life tracking and thus continuous monitoring of all relevant data from the screening programme. These data timely revealed the higher than anticipated adherence to and referral rate of FIT screening and allowed for further diagnosis of the problem followed by the model analysis described above. However, perhaps the most important factor was the good collaboration between the Department of Public Health, the National Institute for Public Health and the Environment, and the Dutch Ministry of Health and the willingness of the decision makers involved to consider model results.

Other examples of applications of decision modelling in screening

The Dutch CRC screening programme is not the only screening programme that has applied modelling to inform the design, planning, and implementation of screening. Modelling has also been used to inform the Irish, Canadian and Australian CRC cancer screening programmes.[52–54] For Ireland, modelling showed that FIT-based screening would be very effective, but that colonoscopy demand could not be met instantly. A staggered age-based roll-out was therefore suggested to gain time to increase colonoscopy capacity to meet the programme demand.[54] In Canada, modelling was used to inform the National Committee on Colorectal Cancer Screening on the mortality reduction, cost-effectiveness, and resource requirements of biennial gFOBT screening.[53] The expansion of screening ages in the Australian CRC screening programme has been accelerated to occur in the coming 5 years instead of the previously proposed 17 years after a model analysis showed that this would double the number of CRC deaths prevented in the upcoming 40 years.[52] Models were also used to inform the US Preventive Services Task Force recommendations for lung, breast and colorectal cancer screening [55–57] and the Centers for Medicare and Medicaid Services coverage decisions for FIT, Stool DNA and CT Colonography screening.[58, 59] Co-informed by modelling outcomes, the USPSTF no longer recommends routine screening for breast cancer before age 50 and after age 74, nor CRC screening after age 75 in those with an adequate screening history. Interestingly, most examples relate to the use of

modelling in the decision phase of screening programmes. The potential of modelling in the planning, implementation, and established programme phase is currently underused.

Conclusion

In this overview we have shown that modelling has been very useful in the decision, planning, and implementation phase of the Dutch CRC screening programme. In the absence of a decision model, decisions concerning the programme would have to be made based on expert opinion and implicit assumptions. Decision models synthesize all relevant available data and can be used to extrapolate trial findings and generate information to support optimal resource allocation in CRC screening. When using models to inform health policy, it is important to select a well-validated model for the analysis and closely monitor outcomes of the screening programme in comparison with model predictions. We believe that the MISCAN-Colon microsimulation model has contributed and will continue to contribute to the success of the Dutch CRC screening programme.

Acknowledgments

FUNDING

This work was made possible by the Dutch National Institute for Public Health and the Environment (contract number: 3910055067) and the Health Programme of the European Union (contract number: 2013 2203). The development of MISCAN-Colon was made possible by the Netherlands Organization for Health Research and Development (contract numbers: 62200022 and 63300022) and the National Cancer Institute as part of the Cancer Intervention and Surveillance Modeling Network (contract number: U01CA152959).

Abbreviations

CRC	colorectal cancer
FIT	faecal immunochemical test
RCT	randomized controlled trial
gFOBT	guaiac faecal occult blood test
FOBT	faecal occult blood test
LY	life-year

REFERENCES

1. Schippers EI. Besluit invoering bevolkingsonderzoek naar darmkanker [Decision to implement population screening for colorectal cancer]. 2011 http://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Uitgaven/Preventie_Ziekte_Zorg/Darmkankerscreening/Brief_besluit_minister_VWS_1_juni_2011.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015; 136:E359–E386. [PubMed: 25220842]
3. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ*. 2014; 348:g2467. [PubMed: 24922745]

4. Hewitson P, Glasziou P, Watson E, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol*. 2008; 103:1541–1549. [PubMed: 18479499]
5. Gondal G, Grotmol T, Hofstad B, et al. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50–64 years. *Scand J Gastroenterol*. 2003; 38:635–642. [PubMed: 12825872]
6. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut*. 2010; 59:62–68. [PubMed: 19671542]
7. Loeve F, Boer R, van Oortmarssen GJ, et al. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. *Computers and biomedical research, an international journal*. 1999; 32:13–33.
8. van Hees F, Habbema JD, Meester RG, et al. Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis. *Annals of internal medicine*. 2014; 160:750–759. [PubMed: 24887616]
9. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer*. 1975; 36:2251–2270. [PubMed: 1203876]
10. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. *N Engl J Med*. 1988; 319:525–532. [PubMed: 2841597]
11. Comprehensive Cancer Centre The Netherlands. Dutch Cancer Figures. 2011 <http://www.cijfersoverkanker.nl/?language=en>.
12. Arminski TC, McLean DW. Incidence and Distribution of Adenomatous Polyps of the Colon and Rectum Based on 1,000 Autopsy Examinations. *Dis Colon Rectum*. 1964; 7:249–261. [PubMed: 14176135]
13. Blatt L. Polyps of the Colon and Rectum: Incidence and Distribution. *Dis Colon Rectum*. 1961; 4:277–282.
14. Bombi JA. Polyps of the colon in Barcelona, Spain. An autopsy study. *Cancer*. 1988; 61:1472–1476. [PubMed: 3345499]
15. Chapman I. Adenomatous polypi of large intestine: incidence and distribution. *Ann Surg*. 1963; 157:223–226. [PubMed: 14020146]
16. Clark JC, Collan Y, Eide TJ, et al. Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. *Int J Cancer*. 1985; 36:179–186. [PubMed: 4018911]
17. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. *Gut*. 1992; 33:1508–1514. [PubMed: 1452076]
18. Johannsen LG, Momsen O, Jacobsen NO. Polyps of the large intestine in Aarhus, Denmark. An autopsy study. *Scand J Gastroenterol*. 1989; 24:799–806. [PubMed: 2799283]
19. Rickert RR, Auerbach O, Garfinkel L, et al. Adenomatous lesions of the large bowel: an autopsy survey. *Cancer*. 1979; 43:1847–1857. [PubMed: 445371]
20. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *The Lancet Oncology*. 2012; 13:55–64. [PubMed: 22088831]
21. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. *Cancer*. 1982; 49:819–825. [PubMed: 7055790]
22. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. *Gut*. 1982; 23:835–842. [PubMed: 7117903]
23. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*. 2010; 375:1624–1633. [PubMed: 20430429]
24. Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, et al. A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials. *Cancer*. 2009; 115:2410–2419. [PubMed: 19288570]
25. Health Council of the Netherlands. Population screening for colorectal cancer. 2001 <http://www.gr.nl/en/publications/preventie/population-screening-for-colorectal-cancer>.

26. Beleidsgroep National Programma Kankerbestrijding. Nationaal Programma Kankerbestrijding 2005–2010 [National Programme Cancer Control 2005–2010]. 2004 <http://www.iknlzuid.nl/bibliotheek/index.php?id=1460>.
27. Signalling committee Cancer of the Dutch Cancer Society. Vroege opsporing van dikkedarmkanker - Minder sterfte door bevolkingsonderzoek [Early detection of colorectal cancer - Lower mortality because of population screening]. 2004 http://repository.kwfkankebestrijding.nl/PublishingImages/vroege_opsporing_van_dikke_darmkanker.pdf.
28. Van Ballegooijen M. Screening op colorectaal kanker in Nederland: tijd om te starten [Colorectal cancer screening in the Netherlands - time to start]. 2003 Accessed:
29. de Visser M, van Ballegooijen M, Bloemers SM, et al. Report on the Dutch consensus development meeting for implementation and further development of population screening for colorectal cancer based on FOBT. Cellular oncology : the official journal of the International Society for Cellular Oncology. 2005; 27:17–29. [PubMed: 15750204]
30. Hol L, Wilschut JA, van Ballegooijen M, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. British journal of cancer. 2009; 100:1103–1110. [PubMed: 19337257]
31. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008; 135:82–90. [PubMed: 18482589]
32. Wilschut JA, Hol L, Dekker E, et al. Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. Gastroenterology. 2011; 141:1648–1655. e1. [PubMed: 21784045]
33. Mark DH. Visualizing cost-effectiveness analysis. Jama. 2002; 287:2428–2429. [PubMed: 11988064]
34. Health Council of the Netherlands. A national colorectal cancer screening programme. 2009 <http://www.gr.nl/en/publications/preventie/a-national-colorectal-cancer-screening-programme>.
35. Klink A. Minister of Health. Standpunt darmkankerscreening [Viewpoint colorectal cancer screening]. 2010 www.rijksoverheid.nl/bestanden/documenten-en-publicaties/kamerstukken/2010/02/16/standpunt-darmkankerscreening/pg-2984840.pdf.
36. Nationaal programma kankerbestrijding; werkgroep 2. Bevolkingsonderzoek dikke darmkanker: 'scenarios voor een goede invoering' [Population screening for colorectal cancer: 'scenarios for good implementation']. 2009 Accessed:
37. van Veldhuizen HMEM, Carpay J, van Delden L, Grievink B, Hoebee AJJ, Lock R. Reij Feasibility study into population screening for bowel cancer - Detection of bowel cancer screening put into practice. 2011 http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2011/juni/Uitvoeringstoets_bevolkingsonderzoek_naar_darmkanker_Opsporing_van_darmkanker_in_praktijk_gebracht.
38. Centre for Population Screening. Verdiepingsstudies bij de uitvoeringstoets bevolkingsonderzoek naar darmkanker [In-depth studies with the feasibility study into population screening for bowel cancer]. 2011 http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2011/juni/Uitvoeringstoets_bevolkingsonderzoek_naar_darmkanker_Opsporing_van_darmkanker_in_praktijk_gebracht.
39. National Monitoring and Evaluation Team Colorectal Cancer Screening. Flyer National Monitoring & Evaluation of Colorectal Cancer Screening Programme. 2014 http://www.rivm.nl/en/Documents_and_publications/Common_and_Present/Brochures/Disease_Prevention_and_Healthcare/Bowel_cancer_screening_programme/Flyer_National_Monitoring_Evaluation_of_Colorectal_Cancer_Screening_Programme.
40. van Veldhuizen H, Marie-Louise Heijnen, Iris Lansdorp-Vogelaar. Adjustment to the implementation of the colorectal cancer screening programme in 2014 and 2015. 2014 http://www.rivm.nl/dsresource?objectid=rivmp:262417&type=org&disposition=inline&ns_nc=1.
41. Boer R, Warmerdam P, de Koning H, et al. Extra incidence caused by mammographic screening. Lancet. 1994; 343:979. [PubMed: 7909035]

42. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut*. 2014; 63:317–325. [PubMed: 23408352]
43. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014; 370:1287–1297. [PubMed: 24645800]
44. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med*. 2008; 359:1207–1217. [PubMed: 18799557]
45. Leach CR, Klabunde CN, Alfano CM, et al. Physician over-recommendation of mammography for terminally ill women. *Cancer*. 2012; 118:27–37. [PubMed: 21681736]
46. Saini SD, van Hees F, Vijan S. Smarter screening for cancer: possibilities and challenges of personalization. *Jama*. 2014; 312:2211–2212. [PubMed: 25461993]
47. Saini SD, Vijan S, Schoenfeld P, et al. Role of quality measurement in inappropriate use of screening for colorectal cancer: retrospective cohort study. *BMJ*. 2014; 348:g1247. [PubMed: 24574474]
48. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. *Am J Gastroenterol*. 2010; 105:2457–2464. [PubMed: 20700114]
49. Stegeman I, de Wijkerslooth TR, Stoop EM, et al. Risk factors for false positive and for false negative test results in screening with fecal occult blood testing. *Int J Cancer*. 2013; 133:2408–2414. [PubMed: 23649826]
50. van den Akker-van Marle ME, van Ballegooijen M, van Oortmarssen GJ, et al. Cost-effectiveness of cervical cancer screening: comparison of screening policies. *Journal of the National Cancer Institute*. 2002; 94:193–204. [PubMed: 11830609]
51. Rebolj M, van Ballegooijen M, van Kemenade F, et al. No increased risk for cervical cancer after a broader definition of a negative Pap smear. *Int J Cancer*. 2008; 123:2632–2635. [PubMed: 18767046]
52. Cenin DR, St John DJ, Ledger MJ, et al. Optimising the expansion of the National Bowel Cancer Screening Program. *The Medical journal of Australia*. 2014; 201:456–461. [PubMed: 25332032]
53. Flanagan WM, Le Petit C, Berthelot JM, et al. Potential impact of population-based colorectal cancer screening in Canada. *Chronic diseases in Canada*. 2003; 24:81–88. [PubMed: 14733756]
54. Sharp L, Tilson L, Whyte S, et al. Using resource modelling to inform decision making and service planning: the case of colorectal cancer screening in Ireland. *BMC health services research*. 2013; 13:105. [PubMed: 23510135]
55. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Annals of internal medicine*. 2014; 160:311–320. [PubMed: 24379002]
56. Mandelblatt JS, Cronin KA, Bailey S, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Annals of internal medicine*. 2009; 151:738–747. [PubMed: 19920274]
57. Zuber AG, Lansdorp-Vogelaar I, Knudsen AB, et al. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. *Annals of internal medicine*. 2008; 149:659–669. [PubMed: 18838717]
58. Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, et al. Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the medicare population. *Journal of the National Cancer Institute*. 2010; 102:1238–1252. [PubMed: 20664028]
59. Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, et al. Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. *Annals of internal medicine*. 2010; 153:368–377. [PubMed: 20855801]
60. Altobelli E, Lattanzi A, Paduano R, et al. Colorectal cancer prevention in Europe: burden of disease and status of screening programs. *Prev Med*. 2014; 62:132–141. [PubMed: 24530610]

BOX 1**Key Messages**

- Decision models synthesize all relevant available data and can be used to extrapolate trial findings and generate information to support optimal resource allocation in CRC screening.
- When using models to inform health policy, it is important to select a well-validated model for the analysis and closely monitor outcomes of the screening programme in comparison with model predictions.
- On several occasions during the decision, planning, and implementation phase of the Dutch national CRC screening programme, MISCAN-Colon model results have influenced the programme. Without modelling, other choices might have been made, possibly resulting in a less favourable balance between the benefits and harms of screening.
- We believe that the MISCAN-Colon microsimulation model has contributed and will continue to contribute to the success of the Dutch national CRC screening programme.

2001	DECISION PHASE	The Dutch Health Council publishes a signalling report stressing the need for a national CRC screening programme
		More landmark reports stressing the need for a national CRC screening programme are published
2002		
2003		
2004		
2005		The Netherlands Organization for Health Research and Development and the Dutch Cancer Society organise a consensus development meeting on CRC screening
2006		Screening trials comparing FIT and gFOBT screening are conducted in the Amsterdam, Rotterdam, and Nijmegen areas. MISCAN-colon is used to determine the optimal screening strategy for the Dutch setting
2007		
2008	PLANNING PHASE	
2009		The Dutch Health Council recommends to implement a national CRC screening programme
2010		The Dutch Minister of Health postpones a final decision on implementing a national CRC screening programme. A feasibility study is performed by the National Institute for Public Health and the Environment. MISCAN-Colon is used to predict the annual resource requirement for a national CRC screening programme.
2011		The Dutch Minister of Health decides to implement a national CRC screening programme.
2012		The infrastructure, quality assurance protocols, and communication materials for the national CRC screening programme are being prepared under supervision of the National Institute for Public Health and the Environment.
2013		The screening programme is piloted in the Rotterdam-Rijnmond area.
2014		The screening programme is rolled out nationally.
	IMPLEMENTATION PHASE	Based on a MISCAN-Colon analysis, the cut-off for referral is elevated to 275ng/mL (47µg/g).

IMPLEMENTATION PHASE	2013	The screening programme is piloted in the Rotterdam-Rijnmond area.
	2014	The screening programme is rolled out nationally. Based on a MISCAN-Colon analysis, the cut-off for referral is elevated to 275ng/mL (47µg/g).
	2015	
	2016	The age range of individuals invited to the programme will be gradually expanded to 55-75.
	2017	

Figure 1.

Overview of the most important milestones in the run-up to the Dutch national colorectal cancer screening programme.

CRC = colorectal cancer

Figure 2.

The costs and life-years gained associated with FOBT-based screening programmes in the Dutch setting (MISCAN-Colon predictions).¹

FOBT = faecal occult blood test; LY = life-year; gFOBT = guaiac faecal occult blood test; FIT = faecal immunochemical test; HC = Health Council

¹Costs and LYs gained per 1,000 individuals aged 45–80 in 2005 compared with no screening (3% discounted). We simulated screening in the Dutch population between 2005 and 2034 using either a gFOBT (Hemoccult II, Biopharma, Weesp, the Netherlands) or a FIT (OC-Sensor, Eiken, Tokyo, Japan). For the FIT, we simulated cut-offs for referral to colonoscopy of 200, 150, 100, 75, and 50 ng/mL (i.e. 40, 30, 20, 15, and 10 µg/g). For each screening modality and cut-off, we simulated 48 screening strategies. We varied the age to start screening (45, 50, 55, and 60), the age to stop screening (70, 75, and 80), and the screening interval (1, 1.5, 2, and 3 years). We assumed 100% attendance to screening and diagnostic and surveillance colonoscopies. The 10 efficient strategies connected by the efficient frontier are given in Table 2. This analysis is described in detail in a paper by Wilschut and colleagues.[32]

Birth year	AGE (years)					
	Calendar year					
	2013	2014	2015	2016	2017	2018
1963	50	51	52	53	54	55
1962	51	52	53	54	55	56
1961	52	53	54	55	56	57
1960	53	54	55	56	57	58
1959	54	55	56	57	58	59
1958	55	56	57	58	59	60
1957	56	57	58	59	60	61
1956	57	58	59	60	61	62
1955	58	59	60	61	62	63
1954	59	60	61	62	63	64
1953	60	61	62	63	64	65
1952	61	62	63	64	65	66
1951	62	63	64	65	66	67
1950	63	64	65	66	67	68
1949	64	65	66	67	68	69
1948	65	66	67	68	69	70
1947	66	67	68	69	70	71
1946	67	68	69	70	71	72
1945	68	69	70	71	72	73
1944	69	70	71	72	73	74
1943	70	71	72	73	74	75
1942	71	72	73	74	75	76
1941	72	73	74	75	76	77
1940	73	74	75	76	77	78
1939	74	75	76	77	78	79
1938	75	76	77	78	79	80

Figure 3.

The phased roll-out of the Dutch national colorectal cancer screening programme as recommended by the Dutch Health Council.

Figure 4.

The resource demands (A–D), health effects (E), and costs (F) of the Dutch national colorectal cancer screening programme between 2013 and 2042 (MISCAN-Colon predictions).¹

FIT = faecal immunochemical test; CRC = colorectal cancer

¹We simulated the Dutch population on January 1st 2013. In this population, we simulated screening as recommended by the Dutch Health Council (i.e. biennial FIT screening [OC-Sensor, Eiken, Tokyo, Japan] between ages 55 and 75 with a cut-off for referral to colonoscopy of 75ng/mL [i.e. 15µg/g]) and applied the roll-out scheme shown in Figure 3. We assumed that no opportunistic screening took place before 2013 and that no such screening would take place after 2013, neither in a scenario with, nor in a scenario without a screening programme. We assumed that the age-specific risks for CRC, the age-specific risks for other cause mortality, and the age-, stage-, and localization-specific CRC survival probabilities remained constant over time.

²We assumed that 10% of the target population will never participate in screening. In the remainder of the population, we assumed a 67% attendance rate at first invitation to arrive at a 60% overall attendance rate as observed in the Rotterdam pilot study. In those attending, we assumed an 80% attendance rate in the subsequent screening round; in those not attending, we assumed a 40% attendance rate, again arriving at an average attendance rate of

60% in the total target population. We assumed that all returned FITs could be analyzed and that no one had to return multiple FITs.

³We considered 3 categories of colonoscopies: 1) diagnostic colonoscopies after a positive FIT; 2) surveillance colonoscopies after the detection and removal of adenomas; and 3) colonoscopies during which CRC is clinically detected. We assumed that 85% of those with a positive FIT underwent a diagnostic colonoscopy, as was observed in the Rotterdam pilot study. Moreover, we assumed that 80% of those referred for a surveillance colonoscopy – according to a slightly de-intensified version of the 2002 Dutch surveillance guidelines – underwent this colonoscopy. Finally, we took into account that screening reduces the number of clinically detected cancers and corresponding colonoscopies.

⁴We considered 3 categories of histopathological examinations: 1) examinations of adenomas, cancers, and hyperplastic polyps detected during a diagnostic or surveillance colonoscopy; 2) examinations of surgically removed adenomas and cancers, and 3) examinations of clinically detected cancers. We assumed that each hyperplastic polyp, adenoma, and cancer detected during a diagnostic or surveillance colonoscopy resulted in one histopathological examination. Moreover, we assumed that each surgically removed adenoma and cancer resulted in one additional examination. We assumed that all cancers, except 58% of all stage I cancers, and 3.9% of all large adenomas (≥ 10mm) required surgery. Finally, we took into account that screening reduces the number of clinically detected cancers and corresponding histopathological examinations.

⁵We assumed that all adenomas and cancers that had to be surgically removed required one surgical procedure. Since screening eventually prevents cancers, the screening programme results in a reduction in surgical procedures from year 2023 onward.

⁶We calculated costs from a third party payer perspective and took into account the costs of 1) FITs (i.e. the costs of the test kit, analysis, organization of the programme, and telephonic consultations by primary care physicians in case of a positive FIT), 2) all colonoscopies (see footnote 3), 3) all histopathological examinations (see footnote 4), 4) complications of colonoscopy, 5) surgical removal of adenomas and 6) short and long term CRC care. Since screening eventually prevents cancers, the costs of the screening programme decrease over time.

Figure 5.

The endoscopy demand and supply (A) and resulting endoscopy shortage (B) in the Netherlands between 2013 and 2020.¹

CRC = colorectal cancer

¹We simulated the Dutch national CRC screening programme applying the phased roll-out scheme shown in Figure 3 to estimate the endoscopy demand for the Dutch national CRC screening programme (see also Figure 4). The endoscopy demand outside the programme and the endoscopy supply were determined by independent management consulting firm Berenschot (<http://www.berenschot.com/>). See van Veldhuizen et al., 2011 [37] for more details.

Figure 6.

The differences in the associations between the cut-off for referral to colonoscopy and the positivity rate (A); the cut-off for referral to colonoscopy and the detection rate of advanced neoplasia¹ (B); and the positivity rate and the detection rate of advanced neoplasia (C) between the Rotterdam pilot study and the first half year of the Dutch national colorectal cancer screening programme.²

¹The detection rate of advanced neoplasia was defined as the proportion of individuals with an analysable FIT that were diagnosed with CRC or an advanced adenoma (i.e., an adenoma with a diameter ≥ 10 mm, and/or with a $\geq 25\%$ villous component, and/or high-grade dysplasia).

²In the Rotterdam pilot study, individuals aged between 50 and 74 were included, whereas the Dutch national CRC screening programme data are largely based on individuals aged 75 and 76. This is likely to explain part of the observed differences.

Figure 7.

The cumulative effects of modifying the roll-out of the Dutch national colorectal cancer screening programme, the higher than expected attendance, and the higher than expected positivity and detection rates on colonoscopy demand (MISCAN-Colon predictions).¹ FIT88 = FIT screening with a cut-off for referral to colonoscopy of 88ng/mL (15µg/g)

¹The original estimates were based on adherence, positivity, and detection rates as observed in the Dutch screening trials and the original phased roll-out scheme (see Figure 3). See also Figure 4.

²Because the Dutch national colorectal cancer screening programme started in 2014 instead of 2013, the roll-out of the programme was modified. In 2014, not only individuals aged 63, 65, 67, and 75, but also individuals aged 76 were invited for screening.

³In the first half of 2014, the attendance rate to screening was higher than expected based on the screening trials: 68% instead of 60%.

⁴In the first half of 2014, when a cut-off of 88 ng/mL (15µg/g) was used, the positivity rate and detection rate of advanced adenomas/CRC were higher than expected based on the screening trials: 13.4% instead of 6.4% and 4.0 % instead of 2.7%, respectively. The

positive predictive value for detecting an advanced adenoma/CRC was substantially lower than expected: 30.0% instead of 42.5%.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 8.

The effects of applying a cut-off for referral to colonoscopy of 275ng/mL (47µg/g) rather than 88ng/mL (15µg/g) from the second half of 2014 onward on the colonoscopy demand (A) and health effects (B) of the Dutch national colorectal cancer screening programme (MISCAN-Colon predictions).¹

FIT88 = FIT screening with a cut-off for referral to colonoscopy of 88ng/mL (15µg/g),
 FIT275 = FIT screening with a cut-off for referral to colonoscopy of 275ng/mL (47µg/g),
 CRC = colorectal cancer

¹The original estimates were based on adherence, positivity, and detection rates as observed in the Dutch screening trials and the original phased roll-out scheme (see Figure 3). See also Figure 4.

²In the first half of 2014, the roll-out of the screening programme was modified and attendance, positivity, and detection rates for advanced adenomas/CRC were higher than expected. For details on model assumptions see the Figure 7 legend.

³In this scenario, we maintained the modified roll-out and higher attendance rate; however, we simulated screening using a cut-off for referral to colonoscopy of 275ng/mL (47 µg/g). At this cut-off level, the positivity rate during the first half of 2014 would have been 7.9%,

the detection rate of advanced adenomas/CRC would have been 3.0%, and the positive predictive value for the detection of advanced adenomas/CRC would have been 38.3%.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Colorectal cancer screening programmes in the European Union.

Country	Programme number	Test	Screening interval (yrs)	Start age (yrs)	Stop age (yrs)
Belgium	1	gFOBT	nd	50	74
Croatia	1	gFOBT	2	50	74
Czech Republic ^I	1	gFOBT	1	50	54
		gFOBT	2	55	nd
	2	gFOBT	1	50	54
		COL	10	55	nd
Denmark	1	gFOBT	2	50	74
Estonia	1	FOBT	2	50	74
Finland	1	gFOBT	2	60	69
France	1	gFOBT	2	50	74
Germany ^I	1	gFOBT	1	50	54
		gFOBT	2	55	nd
	2	gFOBT	1	50	54
		COL	10	55	nd
Hungary	1	FIT	2	50	70
Ireland	1	FIT	2	55	74
Italy ^I	1	FIT	2	50	70
	2	SIG	once only	58–60	58–60
Latvia	1	gFOBT	1	50	nd
Malta	1	FIT	2	60	64

Country	Programme number	Test	Screening interval (yrs)	Start age (yrs)	Stop age (yrs)
Netherlands	1	FIT	2	55	75
Poland	1	COL	10	50	66
Portugal	1	FOBT	2	50	70
Slovenia	1	FIT	2	50	69
Spain	1	FIT	2	50	69
Sweden	1	gFOBT	2	60	69
UK	1	gFOBT	2	50	74

FOBT = fecal occult blood test; gFOBT = guaiac fecal occult blood test; FIT = fecal immunochemical test; SIG = sigmoidoscopy; COL = colonoscopy; nd = no data

¹In the Czech Republic and Germany 2 screening programmes are offered from age 55 onwards: 2-yearly gFOBT and 10-yearly colonoscopy screening. In Italy 2 screening programmes are offered: 2-yearly FIT screening and once only sigmoidoscopy screening. This table is based on data obtained from a paper by Altobelli and colleagues.[60]

Table 2

The efficient FOBT-based screening programmes in the Dutch setting (see also the efficient frontier in Figure 2) (MISCAN-Colon predictions).¹

Nr	Screening test	Cut-off for referral to colonoscopy (ng/mL) ²	Screening interval (yrs)	Start age (yrs)	Stop age (yrs)	Number of screens (n)	Costs (€)	LYs gained (n)	Incremental costs per LY gained (€ LY gained)
1	FIT	50	3	60	69	4	91,000	57	1,600
2	FIT	50	3	55	70	6	131,000	75	2,200
3	FIT	50	3	55	73	7	149,000	82	2,800
4	FIT	50	2	55	75	11	201,000	95	3,900
5	FIT	50	1.5	55	74.5	14	237,000	103	4,300
6	FIT	50	1.5	55	79	17	273,000	110	5,300
7	FIT	50	2	50	80	16	293,000	114	5,800
8	FIT	50	1.5	50	80	21	344,000	119	8,900
9	FIT	50	1.5	45	79.5	24	397,000	125	9,400
10	FIT	50	1	45	80	36	515,000	133	14,900

FOBT = faecal occult blood test; LY = life-year; FIT = faecal immunochemical test

¹ Costs and LYs gained per 1,000 individuals aged 45–80 in 2005 compared with no screening (3% discounted). Results for all simulated screening programmes are shown in Figure 2. This analysis is described in detail in a paper by Wilschut and colleagues.[32]

² 50ng/mL corresponds with 10µg/g.

Table 3

The efficiency of measures to reduce colonoscopy demand in 2014 (MISCAN-Colon predictions).¹

Measure	Colonoscopy demand (*1,000)	Reduction in colonoscopy demand (*1,000)	CRC deaths prevented (*1,000)	Reduction in CRC deaths prevented (*1,000)	Reduction in colonoscopy demand per CRC death not prevented
no measure (see also Figure 7)	64	-	7.71	-	-
postpone screening 63 year-olds	49	14	7.44	0.26	54
postpone screening 65 year-olds	49	15	7.46	0.25	60
postpone screening 67 year-olds	48	16	7.41	0.30	53
postpone screening 75 year-olds ²	54	9	7.26	0.45	21
postpone screening 76 year-olds ²	55	9	7.30	0.41	22
elevate the FIT cut-off to 275ng/mL (47µg/g) in 2014	36	28	7.30	0.40	68

CRC = colorectal cancer; FIT = faecal immunochemical test

¹We modelled the cohort of screen-eligible individuals in the Netherlands in 2014 (i.e. those aged 63, 65, 67, 75, and 76) and applied the observed attendance rate in the first half of 2014 and FIT test characteristics that were calibrated to the observed positivity and detection rates in the first half of 2014 (see also the Figure 7 legend). We modelled a scenario without measures, 5 scenarios in which screening was postponed in 1 of the age-groups, and a scenario in which the cut-off for referral to colonoscopy was elevated to 275ng/mL (47 µg/g). For each scenario, we determined the colonoscopy demand for 2014 as well as the life-time number of CRC deaths prevented.

²Postponing screening in 75 and 76 year-olds implies not screening them at all.