A national colorectal cancer screening programme

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : presentation of advisory report *A national colorectal cancer screening programme*
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Dear Minister,

In reaction to your request for advice dated 27 November, 2008, I herewith present you the report *A national colorectal cancer screening programme*. It has been drawn up by a special committee, which has also taken advice from the Standing Committee on Public Health, the Standing Committee on Medicine, and the Health Council's Committee on the Population Screening Act.

The Committee was in a position to draw on many sources, such as the knowledge and experience gained from trials which got off to a good start after the consensus meeting in February 2005 convened by the Dutch Cancer Society and the Netherlands Organisation for Health Research and Development (ZonMw).

The Committee concludes that colorectal cancer lends itself admirably to population screening. It recommends a scheme based on the screening of men and women between 55 and 75 years old once every two years, on the basis of an immunochemical Faecal Occult Blood Test (iFOBT), a self test. At a 60 per cent participation rate, this may help to prevent 1,400 bowel cancer deaths a year. The implementation of a national screening programme is a major undertaking. Building up the necessary capacity (colonoscopy, pathology) is expected to take five years.

I endorse the conclusions and recommendations of the committee.

Yours sincerely,
(signed)
Professor J.A. Knottnerus

P.O.Box 16052
NL-2500 BB The Hague
Telephone +31 (70) 340 66 40
Telefax +31 (70) 340 75 23
E-mail: wa.van.veen@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 VX The Hague
The Netherlands
www.healthcouncil.nl

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to:

the Minister of Health, Welfare and Sport

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Contents

Executive summary

Conclusion

The Committee has concluded that there is sufficient evidence to justify starting a national bowel cancer screening programme. The most appropriate screening method is an immunochemical Faecal Occult Blood Test (iFOBT). The Committee recommends a programme based on the screening of people between fifty-five and seventy-five years old once every two years. People in the target group would be sent a faecal test sampling kit by the screening organisation. The faecal sample would have to be sent to a laboratory to be tested for invisible traces of blood. Persons with a 'positive' (i.e. abnormal) test result would be referred for colonoscopy, which would take place in an outpatient clinic under sedation and with the aid of pain management.

Recent trials in the Dutch cities of Nijmegen, Amsterdam and Rotterdam suggest that a 60 per cent participation rate may be expected. Under this assumption, modelling indicates that screening will in due course help to prevent an average of 1,428 bowel cancer deaths a year. In 2008, 4,843 people died from the disease in the Netherlands.

Bowel cancer is a serious health problem

Bowel cancer (colorectal cancer) is a common disease. In 2006, 11,231 cases were diagnosed in the Netherlands. In the general population, the lifetime risk of

bowel cancer is 4 to 5 per cent. The average five-year survival is 59 per cent, but an individual's chances of survival depend largely on how extensive the disease is when diagnosed. If the cancer is confined to the inner lining of the bowel (stage I), the five-year survival is 94 per cent; for patients wifh metastatic bowel cancer (stage IV), the five-year survival is limited to 8 per cent.

Bowel cancer is preceded by a prolonged adenomal state, which is relatively easy to detect and treat. Furthermore, a person who has bowel cancer is unlikely to notice any health problems for several years. These two facts mean that bowel cancer is an ideal 'candidate' for screening. From FOBT-based efficacy trials it has been known for some time that screening can reduce bowel cancer mortality by enabling early detection or prevention through the removal of adenomas. However, the implementation of a screening programme would be responsible only if other internationally recognised criteria are met, such as the availability of adequate manpower for diagnosis and treatment.

Research into possible screening methods

In trials held over the last few years, tens of thousands of Dutch people aged between fifty and seventy-five have been offered bowel cancer screening. Various recruitment strategies and screening methods have been used in these pilot trials, whose aim was to establish whether a national and organized population-based screening programme like those in England, Scotland and Finland would be desirable and feasible in the Netherlands.

In contrast to the situation with most other screenable diseases, there are several screening tests available for bowel cancer. The methods differ in various ways, including the participation rate and the sensitivity (in connection with which some tests need to be repeated annually, while others are needed only once every ten years). The four efficacy trials that have been conducted in other countries were all based on the guaiac (gFOBT) Haemoccult II test, which has been used with limited success for more than forty years. The test involves taking 2 samples from each of 3 consecutive stools. If blood is present, a dye (guaiac) reacts with the haem moiety in haemoglobin (the substance that gives red blood cells their colour), resulting in blue discoloration, which has to be visually assessed.

More recently, a test method has been developed, which involves the immunological analysis of faecal samples for occult blood (iFOBTs). The method has two advantages: the subject only has to provide a single faecal sample, and analysis can be automated, thus increasing quality control and reducing cost.

Another possible screening method is sigmoidoscopy: visual examination using an endoscope inserted through the anus into the distal (left-hand) portion of the large intestine. An enema is required prior to the examination.

A fourth option is colonography ('virtual colonoscopy'). This involves examination of the entire large intestine by means of CT or MRI scanning, preferably after limited bowel preparation (low-fibre diet, oral contrast agent). To achieve colonic distension carbon dioxide (CO_2) is delivered via a rectal catheter. Examinations are performed in both supine and prone position.

With all four methods described above, if any abnormalities are detected, the patient is referred for colonoscopy i.e. visual examination of the entire large intestine (Figure 1). Colonoscopy is a reliable way of detecting most abnormalities. Some screening programmes use colonoscopy as a screening method in its own right.

Finally, screening for molecular biomarkers is under development. Numerous biomarkers might theoretically be used for screening, but it is expected to be another five years before suitable ones can be identified. Even then, it will be necessary to conduct research in unselected populations to establish whether biomarker-based screening offers any advantages over the existing methods.

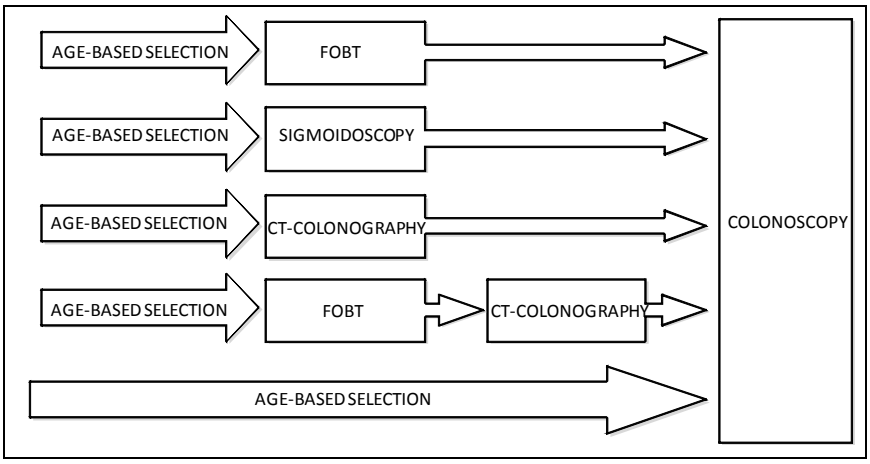


Figure 1 Colonoscopy is the final common pathway of all CRC screenng.

Careful assessment is required before introduction of a national screening programme

Assessment of the possible screening methods against the criteria for responsible screening – serious health problem, proven value, suitable screening test, acceptance, cost-effectiveness – reveals the following picture.

As indicated above, it is evident that bowel cancer is a serious health problem. However, it is less obvious which screening method best satisfies the other criteria. It has been demonstrated that gFOBT screening can reduce bowel cancer mortality by 15 per cent. On the other hand, the method is not a very sensitive means of detecting bowel cancer (less than 40 per cent of cases are picked up at first screening). Furthermore, the participation rate is low (47 per cent in the trials).

iFOBT screening is based on the same principle as gFOBT screening: the detection of blood in faecal samples. However, the randomized trials in Amsterdam, Nijmegen and Rotterdam demonstrated convincingly that iFOBT screening yielded better participation and detection rates than gFOBT screening. Furthermore, despite what is often assumed, the cost of iFOBT screening did not prove to be higher. In other words, iFOBT screening is significantly more effective and efficient as a means of reducing both the incidence of bowel cancer and the associated mortality.

The participation rate was significantly higher with iFOBT screening (60 to 62 per cent) than with gFOBT screening (47 to 50 per cent). Moreover, on an intention-to-screen basis (i.e. relative to the number of invitations sent), the number of cases of bowel cancer and advanced adenoma detected was 2.5 times as great. The higher participation and positivity rates do mean that colonoscopy is needed more often (35 cases per thousand invitations). Nevertheless, iFOBT screening is substantially more cost-effective than gFOBT screening.

Compared with a single iFOBT screening, sigmoidoscopy is roughly equally sensitive for bowel cancer, but significantly more sensitive for advanced adenomas. Some studies suggest that re-screening with this method at intervals of five years would be sufficient. However, the level of participation in the Rotterdam trial was low: only 32 per cent. No data are currently available regarding the effectiveness of sigmoidoscopy screening as a means of reducing bowel cancer mortality. It is therefore difficult to draw conclusions regarding its cost-effectiveness. Furthermore, even allowing for a low participation rate, sigmoidoscopy screening requires a great deal of endoscopy capacity (327 sigmoidoscopic

examinations plus twenty-seven coloscopic examinations per thousand invitations). The results of sigmoidoscopy trials in England and Italy are expected in 2010. If they are encouraging, they should be taken into account in modelling of the Dutch situation.

CT colonography is almost identical to colonoscopy in terms of its sensitivity for bowel cancer and polyps measuring ten millimetres or more. However, it is less unpleasant for the subject and less likely to have serious complications. Furthermore, re-screening might not be required for five or ten years. On the other hand, the participation rate associated with colonography is not known, there is no evidence that CT colonography reduces bowel cancer mortality, and it involves exposure to radiation. Colonoscopy is likely to be needed in more than twenty cases per thousand invitations (assuming a 35 per cent participation rate and a referral threshold of ten millimetres).

Colonoscopy is the most sensitive means of detecting bowel cancer (more than 97 per cent) and advanced adenomas (90 to 98 per cent). This form of testing is therefore regarded as the reference standard. Evidence for the timing of colonoscopy screening is limited, suggesting that screening would be needed only once every ten years. No data are available regarding the participation rates and detection rates associated with colonoscopy in the Netherlands. Limited evidence exists on the efficacy of colonoscopy screening on colorectal cancer incidence and mortality. Consequently, it is not possible to calculate its cost-effectiveness. In one of the Dutch pilots, the COCOS trial, the anticipated participation rate is 20 to 25 per cent. Several other factors argue against using colonoscopy as a primary screening method: it is unpleasant for the subjects, there is a risk (albeit a small one) of serious complications and considerable colonoscopy capacity would be required (even assuming a participation rate of 25 per cent, 250 examinations per thousand invitations).

iFOBT screening meets the criteria for responsible screening

A single round of iFOBT testing will pick up 65 per cent of all bowel cancer cases – about the same as five or six rounds of gFOBT testing. The (programme) sensitivity is further boosted by the fact that iFOBT screening is repeated every two years. Assuming that the participation rate associated with iFOBT screening is 60 per cent, while the rate associated with sigmoidoscopy screening is 30 per cent, the effect of iFOBT screening will be one and a half times as great. Screening based only on sigmoidoscopy is not therefore desirable in the Netherlands. In

terms of simplicity, acceptance, performance and safety, iFOBT testing is the best screening method for use in the Netherlands.

Bowel cancer screening is desirable and possible, provided that the required capacity (e.g. colonoscopy) can be realised in the years ahead

The Committee recommends iFOBT-based screening (OC-Sensor, one faecal sample) once every two years for men and women between fifty-five and seventy-five years old. Modelling indicates that a programme designed on that basis would be cost-effective. Assuming a participation rate of 60 per cent, it would be possible to prevent 1,428 bowel cancer deaths each year. This works out at 2,200 euros per life year gained. This is more advantageous than in other cancer screening programmes in the Netherlands – the cost per life year gained being 11,300 euros for cervical cancer screening. For every bowel cancer death prevented, 785 people would need to complete iFOBT tests and 40 would need to undergo follow-up colonoscopy.

If the Committee's recommended screening strategy and the proposed introduction scheme were adopted, the colonoscopic capacity required for full introduction would be no more than 78,000, not 129,000 as previously calculated. The capacity needs can be further limited by updating the surveillance guidelines soon, partly in line with the availability of a screening programme, which will result in the detection of numerous small adenomas.

Alignment of screening with curative care is vital for quality

Experience has shown that the benefits of screening-related early detection are not fully utilised, because referral does not always lead to (prompt) diagnosis and treatment. Furthermore, there are major variations in the quality of colonoscopy among endoscopists. The Committee therefore recommends direct referral by the screening organisation to colonoscopy providers, with GPs playing a supporting role and always being informed. Appropriate arrangements should be made with the health insurers. Such a system would allow for preferential referral to the centres whose colonoscopy services meet the highest quality standards, and which maintain dedicated teams of certified endoscopists and other specialists.

Staged introduction

The implementation of a national screening programme is a major undertaking. The target population would amount to 3.5 million people, who would need to be

invited for screening every two years. Phased introduction is essential; it is expected to take five years to build up the necessary endoscopic capacity. The Committee makes the following recommendations:

- A bowel cancer screening programme should be introduced in phases, with a gradually expanding invitation scheme, as described in subsection 14.8.
- An organisational structure as described in subsection 14.2 should be adopted, with a view to assuring quality and – if the iFOBT test method is used – sustainability.
- If it is decided that a screening programme is to be set up, clear arrangements should be made with the relevant professions and care providers regarding:
  - the development of integrated (multidisciplinary) guidelines covering the entire chain from screening to diagnosis, treatment, follow up and surveillance, together with updating the guidelines on surveillance;
  - ways of assuring the quality of colonoscopy, including direct referral by the screening organisation and the creation of a system for on-site audits by a national reference centre; in this context it would seem appropriate for the Centre for Population Screening, as the national supervisory body, to play a supporting role;
  - the provision of data for quality control and evaluation of the screening programme, together with regular reporting;
  - public accountability for work-up, treatment and surveillance within the *Visible Care* programme.
- From the outset, budgetary provision should be made for monitoring and evaluation, for a reference system and for the promotion of knowledge and innovation-oriented scientific research (necessary to keep the screening programme up to date).
- The introduction of service screening for bowel cancer should be accompanied by a national public information campaign.
- To enable people to make informed choices, a system of basic information and supplementary information should be developed, similar to those established in connection with screening for breast cancer and cervical cancer. In this context, particular attention should be given to the national uniformity of information provision in the various phases of the screening process.

Chapter 1

Introduction

1.1 Background to this advisory report

On 15 May 2006, the Minister for Health, Welfare and Sport concluded that serious consideration should be given to population screening for colorectal cancer (CRC, bowel cancer). He announced that it should be possible to begin phasing in nationwide population screening in 2010. Bowel cancer is a common disease with a high mortality rate. It has a long preclinical CRC duration and an easily recognisable, protracted pre-malignant stage that is relatively easy to treat. Therefore, CRC lends itself well to screening.[1,2] One of the other factors on which the Minister based his conclusion was the outcome of a 2005 consensus meeting convened by the Netherlands Organisation for Health Research and Development (ZonMw) and the Dutch Cancer Society at Zwolle.[3-6]

The recommendation from the meeting in Zwolle was that a start should be made, within two to three years, on a nationwide population screening programme based on the standard guaiac-based Faecal Occult Blood Test (gFOBT). It was also recommended that a check be made to determine whether other available screening methods might be better alternatives to gFOBT. The first part of the advisory report was not followed. Instead, it was decided to initiate a series of pilot projects to pursue additional research into alternatives to gFOBT screening and to examine the feasibility of population screening in the Netherlands.

1.2 Request for advice

On 27 November 2008, the Minister of Health asked the Health Council of the Netherlands for advice on the advisability and feasibility of introducing population screening for colorectal cancer (Annex A). The Minister asked for special consideration to be given to three points in particular. Firstly, what advances in terms of the test methods used for colorectal cancer screening can be anticipated in the medium term. This question relates to the creation of a future-proof infrastructure for the screening programmes in question. A second question was whether it would make sense for such population screening programmes to focus on groups that are at increased risk of colorectal cancer (other than on the basis of the known cancer predisposition syndromes). Any such population screening programme would be introduced in stages, given the existing capacity of the healthcare system. The Minister's third point concerned the best way to do this.

On 3 November 2008, the President of the Health Council appointed a committee to prepare the advisory report in question (Annex B).

1.3 Structure of the report

Chapter 2 deals briefly with the current situation regarding bowel screening outside the Netherlands. Chapter 3 discusses various Dutch pilot population screening programmes. In chapter 4, the Committee summarises the principles of screening that it employs in Chapters 5 to 10 in the course of its assessment of the advisability of screening for colorectal cancer. Chapter 5 explores the severity and scope of the burden of disease. Chapters 6 to 10 respectively give explanations of the following screening methods: FOBT screening, sigmoidoscopy, colonoscopy, colonography, and molecular tests. In Chapter 11, the Committee reaches a conclusion concerning the advisability of staging a population screening programme for colorectal cancer. Here too, it selects its preferred option from the various screening methods discussed and considers the extent to which the proposed screening programme is future proof. Chapter 12 contains the results of model-based calculations and a more detailed version of the preferred screening strategy. Chapter 13 deals with the public acceptance of screening, and with the anticipated uptake. Chapter 14 makes recommendations concerning the organisation, quality control and gradual introduction of a nationwide population screening programme. Chapter 15 summarises the responses to the individual points of the request for advice.

Chapter 2

Colorectal cancer screening abroad

On 2 December 2003, the Council of the European Union put forward recommendations concerning screening for breast, cervical and colorectal cancer in the European Union. FOBT screening for colorectal cancer was recommended for men and women between the ages of 50 and 74.*[7] The situation was evaluated in 2007.[8] In that year, there were 136 million people in this target group.

The evaluation[8] – together with other sources, such as the International Colorectal Cancer Screening Network (ICRCSN)[9] – showed that a great deal of screening is already taking place, but rarely in the form of well-organised, population-based, nationwide screening programmes like those for breast and cervical cancer in Finland and the Netherlands. Only Finland, England and Scotland are currently working on the phased introduction of nationwide population-based screening programmes.[8,10-14] Nationwide population-based programmes are at the preparatory stage in five other countries, while France, Spain, Italy and Sweden already have population screening programmes in place at regional level.[8,15-17] Indeed, Italy already has a national body for the evaluation of its 72 regional screening programmes for colorectal cancer.[18] (www.osservatorionazionale-screening.it/eng-programmes.php). In total, the population-based programmes that are either in preparation or already under way cover 43 per cent of the target population in the EU.

* The indicated age ranges are to be understood as maximum ranges; subject to national epidemiological evidence and prioritisation, smaller age ranges may be appropriate.

Many countries have a variety of obstacles to a nationwide population-based programme, such as a decentralised health care policy. For example, Germany, Austria and the Czech Republic have established non-population-base programmes. Screening in those countries is carried out on an individual basis (27 per cent of the target group). This is referred to as opportunistic screening. The participation rates involved are low.

Eight of the twenty-seven member states have yet to start preparing screening programmes of their own. In 2007, 12 million people actually underwent screening for colorectal cancer.[8] On the basis of a biennial screening, this represents 18 per cent of the target group. In almost every case, member states opted for gFOBT screening. Italy selected iFOBT screening[18], and the UK is considering a switch to that system in the near future. The primary screening test in Poland is colonoscopy. In six countries, endoscopic screening is used in combination with – or as an alternative to – FOBT screening. Five of these states (including Germany) use colonoscopy while Italy uses sigmoidoscopy.

Outside the EU, countries like Australia and three of the ten Canadian provinces have commenced the phased introduction of population screening based on gFOBT, iFOBT or sigmoidoscopy.[13,19] In the US, Japan and Taiwan, screening takes place on an individual basis.[20] Colonoscopy is the most widely used technique in the US. In 2002, fourteen million colonoscopies were carried out in the US, approximately 40 per cent of which involved primary screening. Over 20 per cent were performed as part of the surveillance of high-risk groups.[21] The limitations of colonoscopy have recently come under the spotlight. As a result, there is increasing interest in the use of iFOBT screening.[22] Since 1992, Japanese citizens who are over 40 years of age and who have health insurance cover have been offered iFOBT screening.[20] Only 17 per cent of the target group made use of this facility in 2002. There is no provision for the evaluation of the screening programme.[20,23]

In conclusion, the sum total of current programmes throughout the world represents a considerable amount of screening activity. Many such programmes have been under way for many years, as in Japan, Italy and Germany. Nevertheless, only a few countries have well-organised nationwide, population-based screening programmes. Although the Netherlands was relatively late in starting to make preparations, it has quickly gained a great deal of experience and expertise (see Chapter 3).

Chapter 3

Feasibility of population screening for colorectal cancer in the Netherlands

Since the consensus meeting at Zwolle (in 2005), various pilot projects have been launched to test the uptake and diagnostic yield of bowel screening in the Netherlands. The programmes themselves are briefly described below, and the results obtained are discussed in Chapters 6 to 10.

3.1 Maastricht

The aim of the first pilot project, by the Maastricht University Medical Centre, is to investigate the yields and costs of various screening methods.[24,25] A second goal is to investigate whether stools or blood contain tumour-derived DNA or other biomarkers which might be useful for CRC screening. This investigation would take place within the context of a major collaborative project (DeCoDe, see section 3.5). Over a period of several years, 3,500 employees (all over 50 years of age) of large companies in the province of South Limburg are invited to undergo a colonoscopy, and to submit blood and stool samples for testing.

3.2 FOCUS, Nijmegen-Amsterdam

FOCUS (Faecal OCcUlt blood Screening) was a trial conducted jointly by the Radboud University Nijmegen Medical Centre, the Academic Medical Center (AMC) in Amsterdam and the East and Amsterdam Comprehensive Cancer Centers (IKO, IKA). In the first round of screening, a prerandomisation design was

used to compare gFOBT and iFOBT screening. Never before had a randomised controlled trial (RCT) been conducted on such a large scale in the general population. A total of 20 623 individuals aged between 50 and 75 were invited to take part in this pilot project. The pivotal questions concerned the level of uptake and the magnitude of the yield.[26,27]

The Amsterdam branch of FOCUS began the second round in September 2008, using only iFOBT$_{50}$ screening (OC-Sensor, referral threshold 50 nanograms of haemoglobin per millilitre of sample solution). The central study question was how large the uptake would be for a second round of screening, two years after the first. The Nijmegen branch will begin the second round in 2010.

3.3 CORERO, Groot-Rijnmond

Erasmus Medical Center (MC) of Rotterdam is conducting feasibility studies in Groot-Rijnmond, in collaboration with the Rotterdam Comprehensive Cancer Center and the regional screening organisation. In an initial project, prerandomisation was used to compare the screening methods of sigmoidoscopy, iFOBT and gFOBT (CORERO-I, 2006-2007; Pilot population screening programme for COloREctal cancer ROtterdam). This RCT anticipated the forthcoming results of trials in other countries on the effectiveness of sigmoidoscopy as a screening method.[28-30] Each of the three branches of this study involved 5,000 subjects between the ages of 50 and 75.[31,32]

Using 2,500 new subjects and 5000 individuals who had been invited to participate in CORERO-I, CORERO-II (2008-2010) will focus on the optimal time interval for screening. This will involve comparing uptake and yield in a second round of screening, one, two or three years after the first. In addition, the first round results obtained from the above-mentioned 2,500 new subjects will be compared to those of another 3,200 new subjects who will be asked to send in two stool samples for iFOBT screening.

3.4 COCOS (Amsterdam-Rotterdam), NordICC

In June 2009, AMC and Erasmus MC launched a RCT by the name of COCOS (COlonoscopy or COlonography for Screening). Here, the use of CT colonography and colonoscopy as screening methods was compared on the basis of the primary outcome measure, which is uptake. Two and a half thousand subjects aged from 50 to 75 will be invited to undergo CT colonography. Prior to colonoscopy, one group of 2,500 subjects will have an interview in the outpatients department, while another 2,500 subjects will have a telephone interview.

The colonoscopy parts of the study, together with a control group of 10,000 subjects, are also part of an international screening RCT, called NordICC.[33] To measure the impact of screening capacity on mortality from colorectal cancer after a 10-year follow-up period, NordICC will compare one-off colonoscopy screening to the usual care.

3.5 DeCoDe

DeCoDe (Decrease Colorectal cancer Death) is a Center for Translational Molecular Medicine project. The Center is a public-private initiative that subsidises research into new methods of diagnosing and treating common diseases. The aim of DeCoDe is to develop molecular screening tests and molecular diagnostics for customised therapy. The main thrust of their approach is to translate recent discoveries about the molecular biology of colorectal cancer into new laboratory tests and new applications for diagnostic imaging. Existing biomarker tests are validated in a screening population (participants in the Maastricht pilot project and in the colonoscopy study arms of the COCOS trial). All of these subjects undergo colonoscopy, enabling the yield of the molecular tests to be compared to the reference standard.

DeCoDe also focuses on the integration of molecular imaging and colonography, in this case molecular MRI colonography. DeCoDe also includes the development of a research infrastructure, in fields such as IT and biobanking. This project is being coordinated by VUmc. The participants include medical institutions (MUMC, LUMC, AMC, and Erasmus MC) and industrial companies (Oncomethylome Sciences, Philips, MRC Holland, NIPED, Percuros, ServiceXS, BV Cyclotron and Dionex).

3.6 SCRIPT

The NDDO (New Drug Development Organisation) Institute for Prevention and Early Diagnostics (NIPED) in Amsterdam is conducting tests of colorectal cancer screening with colonoscopy on the basis of integrated risk profiling. This is a form of tiered screening involving preselection for various disorders that have certain risk factors in common. The project, which is called SCRIPT, is linked to NIPED's existing range of screening, in which Prevention Compass risk profiles are developed for such conditions as cardiovascular diseases and mental disorders. Within the SCRIPT framework, participants aged between 50 and 75 can also obtain a personal risk profile for colorectal cancer. This is done on an experimental basis.[34]

The Prevention Compass is based on three modules: an Internet questionnaire which is completed at home, a physical examination, and tests of blood, urine and stool samples (an iFOBT, OC-Sensor). On the basis of their risk profile, subjects with an elevated risk of colorectal cancer are invited to undergo a colonoscopy. The results are expected early in 2011.

Chapter 4

Criteria for sound population screening

A key difference between curative medicine and screening is that the former is demand oriented (from the patient's point of view) while the latter is largely supply oriented (generally offered to healthy individuals). In 2008, the Health Council drafted a normative framework as an aid to decision making about whether or not to introduce a population screening programme.[35] This framework is based on the ten principles of screening that were formulated by Wilson and Jungner[36] in 1968 at the behest of the World Health Organization. These criteria have subsequently been further developed and adapted by various authors and agencies. This normative framework is summarised as follows:

- Screening is directed at important health problems.
- Screening results in health gains or other benefits for the test subjects in question.
- The screening method is reliable and valid.
- Participation in screening and follow-up examinations is based on an informed and voluntary choice.
- Efficient use is made of resources.

On the basis of this normative framework, the advisory process pertaining to the feasibility and desirability of conducting a bowel screening programme requires that the following questions be answered.

Screening must be directed at major health problems

1 To what extent, and for whom, is colorectal cancer a major health problem? Can specific high-risk groups be identified? *These questions are explored in greater detail in Chapter 5.*

Screening must result in health gains for test subjects

It is not enough that screening results in the early detection of disease, it is all about the actual health gains that can be achieved by this means. While there are always some disadvantages attached to screening, the relationship between beneficial and adverse health effects must always be a favourable one.

2 To what extent can screening for colorectal cancer help to reduce the disease burden in terms of mortality, incidence, or quality of life? *This question is explored in greater detail in Chapters 6 to 10.*
The optimum outcome measure for screening trials is disease-specific mortality, taking all-cause mortality into account. What is the situation when new tests emerge, while a screening test that has been proven to be effective (such as gFOBT) is already available? Guidelines for such situations have been drawn up on the basis of a systematic review of the literature together with a consensus approach involving experts.[37-39] Studies to determine whether a new test is as good or better than existing ones do not need to use disease-specific mortality as an end point again, provided that randomised screening trials have demonstrated that the existing test reduces disease-specific mortality. The evaluation must involve a direct comparison of the old and new tests, on the basis of 'intention to screen', in terms of uptake and yield, conducted among the general population, and followed by a cost-effectiveness analysis.[37]

3 What are the disadvantages of screening in terms of false positive test results, false negative test results, complications, overdiagnosis and loss of quality of life? Can specific groups be identified for whom the population screening programme is not intended, and others for whom it is? *These questions are raised in Chapters 5 to 10.*

4 How do the benefits of colorectal cancer screening weigh up against the drawbacks involved? Are there groups which, on balance, stand to benefit from such screening? *These questions are explored in greater detail in Chapter 12.*

The screening strategy used must be both reliable and valid

The testing strategy used must be both reliable and valid. In this context, 'reliability' is taken to mean that repeating the test consistently produces the same results. 'Validity' means that the test measures exactly what it is intended to measure. The test characteristics that determine its validity are sensitivity and specificity. The usefulness of a test in practice is particularly dependent on the predictive value of a positive test (Positive Predictive Value or PPV). The PPV depends on the validity of the test and the prevalence of the disease. In addition, it is only possible to determine the reliability and validity of a screening programme if the programme in question has been systematically designed, implemented and evaluated.

5 What is the PPV of the various screening methods for colorectal cancer? *This question is explored in greater detail in Chapters 6 to 10.*

6 How can the organisation of a screening programme safeguard high quality? *This is the principle issue addressed in Chapter 14.*

Participation in screening and follow-up tests must be based on an informed and voluntary choice

Screening involves the use of risk-assessing tests. This places exacting demands on education and counselling.

7 How can the screening programme best be structured to provide potential participants with sufficient information to make well informed choices in this regard? *This question is explored in greater detail in Chapters 13 to 14.*

Efficient use must be made of resources

There are few screening programmes in which the savings exceed the costs. The net cost of financing such programmes should be specifically justified in terms of cost-effectiveness and equity. The costs involved in screening must be justified in relation to total health service expenditure. This means that the question of opportunity costs should also be examined.

8 How cost-effective is colorectal cancer screening in the Netherlands? These costs can be expressed per life year gained, preferably after being adjusted for quality of life (QALY). *This question is answered in Chapter 12.*

9 How significant is the introduction of screening for colorectal cancer in terms of health service costs as a whole? *This question is explored in greater detail in section 14.7.*

Conclusion

In Chapter 11, the Committee reaches a conclusion concerning the advisability of staging a population screening programme for colorectal cancer, and selects its preferred option from the various screening methods discussed.

Chapter 5

Severity and scope of the burden of disease

5.1 Colorectal cancer, adenomas and early detection

Colorectal cancer arises in epithelial cells lining the interior of the large intestine. It takes many years for colorectal cancer to develop.[40,41] Cancer is caused by changes in gene function – usually acquired during life rather than being inherited – which tend to disrupt the normal functions of the cells in question. During the process of neoplasia, these cells acquire cancer cell characteristics, such as the potential for unregulated growth, the invasion and destruction of surrounding tissues, and metastasis. In the course of this process there is a protracted phase during which the cells exhibit autonomous growth but are – as yet – incapable of invasive growth and metastasis. This results in a benign tumour known as an adenoma.

Usually, when an adenoma is completely removed (a procedure that can often be performed endoscopically), no tumour cells will remain behind, as neither invasive growth nor metastasis have yet taken place. Ideally, therefore, intestinal tumours should be removed at the adenoma stage. However, surgery is sometimes required (in the case of sessile adenomas, for example).

Autopsy studies have shown that adenomas of the colon are quite common, occurring in about 30 per cent of those over 60 years of age. Those adenomas that do go on to become malignant generally take many years to do so. As with precancerous cervical cancer, there is usually no progression, indeed regression may even occur (see also section 9.4). Unlike cervical cancer, regression does

not play a particularly significant role in this case. This is because cervical cancer is caused by an infection. Such infections usually clear up, after which the pre-cancerous histological changes exhibit regression.

It is estimated that only five per cent of all adenomas actually become malignant.[42] Theoretically, the removal of this five per cent of adenomas is sufficient to prevent colorectal cancer. The problem is that it is impossible to know which adenomas will become malignant and which will not. This inevitably results in a degree of overdiagnosis. In practice, *advanced adenomas* are defined as adenomas ≥ 10 millimetres in size, adenomas with high grade dysplasia, or adenomas containing > 25 per cent of villous tissue. The latter two characteristics are determined by tissue examination.

The optimum outcome measure for screening trials is disease-specific mortality, taking all-cause mortality into account.[43] Where follow-up is too short or the number of events is too limited, it is often necessary to use intermediate end points.[44] In the case of colorectal cancer screening, these would be advanced adenomas and colorectal cancer. These two measures of outcome are often combined, and referred to as 'advanced neoplasia'. That is not always wise, as by no means all advanced adenomas become malignant. In the case of most adenomas, removing them would have no effect on the survival of the individual concerned. Including all advanced adenomas as relevant screening yield causes the effect of screening to be overestimated. At the other end of the disease spectrum, late stage cancer is also included as relevant yield, while only a small number of such cases can be cured. This too tends to overestimate the effect of screening.

Accordingly, in this advisory report, the figures for advanced adenomas and those for colorectal cancer are listed separately. In addition, the figures for colorectal cancer are also broken down by stage, where possible. After all, the goal of screening is not simply to detect abnormalities, it is to reduce people's risk of developing colorectal cancer and of dying from this disease.

5.2 Incidence

Colorectal cancer is common in western countries. In terms of age-standardised incidence rates, there is little difference from one European country to another, nor is there a clear geographic pattern. In 2006, the Netherlands ranked eighth in Europe.[45] In that year, 11,231 cases of colorectal cancer were diagnosed in the Netherlands (www.ikcnet.nl). After prostate cancer and lung cancer in men and breast cancer in women, this disease is the most common type of malignant

tumour. Rather more than 90 per cent of all new colorectal cancer patients are above 55 years of age (www.ikcnet.nl).

Age-adjusted incidence rates are increasing slightly, especially in men. This rise is probably due to changes in lifestyle.[46] Absolute incidence is expected to increase by three per cent per year, mainly due to the aging population. It is projected to reach 14,000 by 2015.[47]

In the Netherlands, people's risk of acquiring colorectal cancer at some stage during their lifetime (the cumulative risk from birth up to the age of 80) is four to five per cent (www.ikcnet.nl, calculated by the life table method, on the basis of figures from the Dutch Cancer Registry for the period from 1999 to 2003). About 95 per cent of people have no direct benefit from screening. So, even if such screening were to completely eliminate colorectal cancer, it is still necessary to carefully weigh up the pros and cons of any such programme.

5.3 Prevalence

The known prevalence of colorectal cancer can be expressed as the number of people who have (or who have ever had) colorectal cancer and who are still alive at a given point in time. In 2005, the known prevalence was 66,000 individuals. By 2015, an aging population and improved survival will push this up to approximately 102,000.[47] The majority of these individuals are currently disease-free.

The unknown prevalence is the number of people who have already developed colorectal cancer but in whom this disease has not yet been diagnosed. However, given that there is no significant difference in incidence between European countries, data from five European population screening programmes can be used to estimate the numbers involved. A total of 52,346 individuals were examined using colonoscopy. Of this group, 0.8 per cent were found to have colorectal cancer, while 6.7 per cent had advanced adenomas.[48-52] The Rotterdam pilot trial CORERO-I (which used sigmoidoscopy) detected colorectal cancer in 0.6 per cent of the participants.[32] Because sigmoidoscopy misses approximately 40 per cent of the total number of tumours present in the colon (see section 7.2) this study supports the suggestion that, in the Netherlands, at least 0.8 per cent of the population has colorectal cancer.

In 2009, there are 3.47 million individuals between 55 and 75 years of age in the Netherlands. Accordingly, in this group alone, 28,000 individuals would be expected to have colorectal cancer. This is five times the detected annual incidence of approximately 5,770 cases in this age group. This also indicates that

early stage colorectal cancer usually grows slowly[41], which provides ample opportunity for screening.

5.4 High-risk groups

An individual's risk of being diagnosed with colorectal cancer within a given period of time is shown in Table 1. This risk relates to the general population of the Netherlands, in the absence of a screening programme. In theory, population screening is not for those in high-risk groups. These individuals are covered by existing guidelines, which involve more intensive monitoring by means of colonoscopy (surveillance).[53,54] It is difficult to determine how many cases involve a familial predisposition for colorectal cancer, as this depends on the individual's knowledge of the occurrence of the disease within the family. The Swedish cancer registry shows that about thirteen per cent of colorectal cancer patients have a first-degree relative (FDR) with colorectal cancer.[55,56] When asked, eleven per cent of Dutch adults without colorectal cancer reported that an FDR had had the disease.[57]

Most colorectal cancer patients (approximately 80 per cent) have no close relatives who have suffered from this disease. Such cases are described as 'sporadic colorectal cancer'.[58] Fifteen to twenty per cent of patients with colorectal cancer have a positive family history. This mainly involves a form that does not match the major hereditary forms of colorectal cancer, i.e. Lynch syndrome (until recently referred to as hereditary non-polyposis colorectal carcinoma, or HNPCC) and the various forms of polyposis. The extent to which close relatives are at increased risk of colorectal cancer depends on the number of relatives with this cancer, their degree of kinship, and the age at which colorectal cancer was diagnosed.

Table 1 The risk of colorectal cancer by age and sex, for the Netherlands. Percentages (www.ikc-net.nl).

Sex	Period of time	Age (years)		
		40	55	75
Male	Within 20 yrs.	0.9	3.6	4.1
	Till the age of 80	5.9	4.8	1.9
Female	Within 20 yrs.	1.3	2.7	3.5
	Till the age of 80	4.0	3.7	1.3

Individuals with one FDR who suffered from colorectal cancer have more than twice the normal risk of developing this disease.[59,60] The more FDRs suffering from the disease, the greater the risk. The same is true where one FDR was diagnosed with colorectal cancer before the age of fifty (see Table 2).[59-61] The term ‘familial cancer’ is only used when the risk of colorectal cancer for an FDR is at least three times as high as that pertaining to the general population, and where hereditary colorectal cancer has been excluded.[55] This applies to individuals having two FDRs with colorectal cancer and to those with one FDR diagnosed with colorectal cancer before the 50th year of life.

A diagnosis of ‘hereditary colorectal cancer’ can only be made with certainty on the basis of a known germ-line mutation. According to the Dutch Institute for Healthcare Improvement (CBO) guideline[53], patients with this cancer must be referred to a genetic centre if they meet certain criteria (revised Bethesda criteria). A hospital-based study involving 154 patients with colorectal cancer showed that one quarter of these individuals met the criteria, but that only 15 per cent were referred.[62] However, no details were provided on the number of referred patients who actually visited the genetic centre. According to a study conducted in seventeen hospitals, only 30 per cent of patients with an indication for referral for genetic testing were in fact referred, while only 70 per cent of the referred patients actually visited a genetic centre.[63]

Approximately five per cent of all cases of colorectal cancer are genetically determined.[64,65] Individuals with Lynch syndrome are, by definition, germ-line mutation carriers. They have a 25 to 70 per cent lifetime risk of colorectal cancer.[66] In familial adenomatous polyposis (FAP), that risk is virtually 100 per cent.[53,67]

Table 2 Absolute risk of colorectal cancer by number of FDRs with CRC and age of onset.

Number of FDRs	Age of onset (years)	Cumulative risk of CRC for persons aged 50-70 (%)	Cumulative risk >10%
1	50-70	5- 8	*No*
1	< 50	9-13	Yes
≥ 2	50-70	12-18	Yes
≥ 2	< 50	21-29	Yes

The Dutch Institute for Healthcare Improvement (CBO) guideline[53] recommends that where familial colorectal cancer increases the risk of developing this disease by more than 10 per cent, the individuals in question should have a colonoscopy every six years from the age of 45 onwards. This recommendation applies particularly to individuals below the age of 70.

The risk that germ-line mutation carriers will actually go on to develop CRC is almost always in excess of 10 per cent. Accordingly, they are given a specific, risk-adjusted surveillance recommendation.

The Committee notes that the CBO guideline[53] was drawn up for situations in which there are no well-organised population screening programmes with a sensitive test for colorectal cancer. In Section 14.3, the Committee addresses the issue of how to deal with individuals with a family history.

5.5 Selective screening

One of the many ways in which screening can be conducted is tiered screening (selective screening, risk profiling). Initially a questionnaire and, possibly, some further tests are used to make a preselection of individuals with an increased risk of disease, such as colorectal cancer. These individuals are subsequently offered tests that involve a degree of discomfort, in this case colonoscopy. Preselection can either be disease-specific or it can focus on a range of different disorders that have some risk factors in common (integrated risk profiling, section 3.6).

Selective screening sounds like an attractive alternative to traditional, disease-specific population screening, which is only offered on the basis of age. If the final screening group can simply be limited to a high risk group, then fewer people will ultimately be exposed to the (more embarrassing or invasive) screening test, and there will be a greater chance of detecting disease. Furthermore, there will be a more favourable relationship between the intended and unintended effects of screening, while the staff costs and material costs involved will be less than in the case of universal screening. In addition, according to those offering screening on the basis of risk profiles, more people are willing to participate than is the case with traditional population screening.[68] It is also claimed that, following a positive screening result, more people are prepared to participate in follow-up testing. Moreover, integrated risk profiling is said to have a greater PPV than classical population screening. If integrated risk profiling does not lead to more false positive results, then it could be said to be more effective than traditional population screening. Finally, integrated risk profiling is claimed to be more efficient than traditional population screening.

From the outset, the option of selective screening has featured in the decision-making process with regard to the introduction of screening programmes. So far without success, however.[69-75] Apparently, the situation is not as straightforward as it seems. For instance, women with no known risk factors can nevertheless develop breast cancer. This would not be picked up by selective screening. Traditional population screening does not suffer from this drawback. Age and gender are the only effective risk factors in risk profiling. Neither separately nor in combination do any other risk factors appear able to improve risk profiling. The aim is not to curtail the final screening group to such an extent that the benefits outweigh the disadvantages of not offering screening to those outside the high risk group.

The research literature contains reports of various attempts to develop a model for risk profiling. As yet, however, there are no usable, validated examples.[68,76] Despite this scientifically shaky basis, a wide range of tiered screening services are being touted on the basis of risk profiles, especially on the Internet.[77]

5.6 Exclusion criteria

Population screening for colorectal cancer is intended for individuals with average risk of developing this disease. It makes little sense to screen people who have had an adequate colonoscopy in the previous ten years, which found either no abnormalities or only ‘small’ adenomas that were removed completely. Their risk is too small to justify the burden and cost of a second screening within the space of ten years (section 14.6).

In the event of symptoms that are suggestive of colorectal cancer – such as bloody stools or weight loss – then diagnosis rather than screening is indicated. Nor is population screening intended for individuals with a personal case history of colorectal cancer or large adenomatous polyps (section 14.6). According to the current guidelines (see section 14.3) this also applies to:

- individuals with hereditary colorectal cancer
- individuals with one FDR below the age of 50 who has had colorectal cancer
- individuals with two FDRs below the age of 70 who have had colorectal cancer.

A questionnaire study coupled with an FOBT screening programme indicated that 23 per cent of the participants in that programme were not appropriate candidates for population screening.[78] In another study – which also took place in

Australia – 19 per cent of the participants in a screening programme had undergone colonoscopy in the preceding ten-year period.[79]

5.7 Prognosis and mortality

The prognosis for colorectal cancer patients depends on the extent of the disease when the diagnosis is made. The average five-year survival rate in the Netherlands is 59 per cent.[80] If tumour growth is still limited to the mucosa (stage I), then the five-year survival rate is 94 per cent, but if the tumour has metastasised (stage IV), then it is just eight per cent (www.ikcnet.nl). In 45 per cent of cases, the disease is diagnosed in stages III (metastases in regional lymph nodes) or IV.[81]

This last percentage has hardly changed since 1980.[81] Despite this, from 1987-1991 to 2002-2006, the five-year survival rate for stage III increased from 45 to 61 per cent and for stage IV from 3 to 8 per cent. This is attributed to improved therapy, such as adjuvant chemotherapy, pre-operative radiotherapy, and improved surgical techniques.[47,82]

Surgery is an option for over 90 per cent of patients.[81] Compared to other Western countries, the Netherlands has a good colorectal cancer survival rate.[5] For this reason, mortality is lower than the incidence would suggest.[45]

For those above the age of 55, the risk of dying from colorectal cancer (the cumulative risk up to the age of 80) is 2 per cent for men and 1.5 per cent for women (www.ikcnet.nl). In 2008, well over 4800 patients died of colorectal cancer (www.cbs.nl).

Age-adjusted colorectal cancer mortality exhibits a declining trend (www.rivm.nl/vtv). This is primarily due to earlier diagnosis, which may be the result of increasing opportunistic screening[83], combined with better treatment.[46]

5.8 Prevention

Aside from genetic factors, it is likely that lifestyle factors are also primarily responsible for the development of colorectal cancer. While American studies showed that the consumption of red meat and meat products was a risk factor, this has not been demonstrated in the Netherlands. There does not seem to be a strong correlation between fat intake and the development of colorectal cancer. For men, however, there is a relationship with obesity. Smoking increases the risk of colorectal cancer.[84] Fruit and vegetables seem to have a protective effect, at least for non-smokers and ex-smokers.[85] Physical activity has been shown to have a protective effect against colon cancer.[86]

5.9 Conclusion

Colorectal cancer is a serious disease and a major health problem. In practice, further preventive measures (not smoking, taking more exercise, chemoprevention) cannot be expected to have a significant effect on the incidence of colorectal cancer. Improved treatment options increase the five year survival rate for patients with metastatised colorectal cancer, however this is accompanied by an exponential increase in the cost of medication. Although there have been significant scientific advances in the field of genetic predisposition to colorectal cancer, this contributes little to prevention or treatment. There are no effective selective screening methods. Well-organised population screening is certainly one way of substantially reducing the disease burden and mortality from colorectal cancer.

Nine out of ten new cases occur in individuals over 55 years of age. When determining the target group for a population screening programme, this age group should be the first to be considered. Population screening is basically aimed at people with an average risk of disease. Those at increased risk of colorectal cancer have recourse to surveillance programmes.

Chapter 6

FOBT screening

Intestinal tumours can cause blood loss. Accordingly, bloody stools indicate the presence of colorectal cancer. Tests have been developed to detect the presence of occult blood in stools, these involve chemical and immunological FOBTs.

Chemical FOBTs have been used for more than forty years. Most make use of guaiac gum, which is extracted from the hardwood tree *guaiacum officinale* (gFOBTs). Guaiac oxidises when in contact with hydrogen peroxide, resulting in an unstable colour change. This reaction is catalysed by haem, a component of haemoglobin common to all species. The test is not specific for human blood and can generate false positive and false negative results due to peroxidase reactions (and their inhibitors) in food products, such as red meat. This complicating factor is prevented by dietary measures. Population screening outside the Netherlands mainly involves the use of gFOBTs, but this situation is changing rapidly.

In recent years, tests have been developed which detect occult blood by immunological means (iFOBTs). These use antibodies against the species specific globin component of human haemoglobin, which means that they are specific for human blood. These tests do not require the use of dietary measures. It is not necessary to take account of medication use. According to an Israeli study, the use of painkillers or anticoagulant therapy does not increase the number of false positive results.[87]

Another advantage of iFOBTs is that some of these are quantitative in nature. With iFOBTs which provide a numeric result, it is possible to adjust the thresh-

old to be shifted, enabling screening to be more focused and cost-effective.The threshold value for iFOBTs (usually 20 micrograms (µg)/g faeces, corresponding to 100 nanograms (ng)/ml sample solution) is lower than that for gFOBTs (200 µg/g faeces), which means that iFOBTs are more sensitive than gFOBTs.

Individuals with a positive FOBT are given further tests to determine whether the abnormal test results were produced by advanced neoplasia. Colonoscopy is the most appropriate technique for this purpose. This is because it enables tissue samples to be taken, which means that less advanced cancers and almost all advanced adenomas can be removed completely.

6.1 gFOBT screening

6.1.1 Effectiveness

Four RCTs demonstrated that offering biennial gFOBT screening can cut colorectal cancer mortality by 11 to 18 per cent.[88-93] These trials were conducted from 1975 to 2002 in Minnesota (USA), Nottingham (UK), Funen (Denmark) and Gothenburg (Sweden). They involved a total of over 320,000 participants aged from 45 to 80, with follow-up ranging from 8-18 years. A systematic review concluded that there was a 15 per cent relative risk reduction in colorectal cancer mortality: odds ratio 0.85 (95% confidence interval 0.78-0.92).[94,95] A large non-randomised trial,[96] several case-control studies[97-104] and a comparison with regions having a 15-20 year time lag before screening was initiated[105] showed that similar results can be achieved outside a scientific setting. Eighteen years after the Minnesota trial, it emerged that the incidence of colorectal cancer had also decreased, by 17 per cent.[106] This was probably achieved by the removal of 'large' adenomas (≥ 10 mm in diameter).[107]

Does this represent a genuine reduction in mortality or were the benefits negated by an increase in mortality from such things as stress, anxiety, or the complications of colonoscopy, following a positive FOBT?[108] Colonoscopy involves a minor risk of serious complications such as perforation and bleeding (section 8.3). The survey study showed no reduction in overall mortality. This is not surprising, as deaths from colorectal cancer account for only a few per cent of all deaths. On the other hand, there was no increase in mortality from causes other than colorectal cancer.[94] 'Blinded', standardised assessment was performed for the purpose of classifying causes of death.

6.1.2 *Test performance*

Hemoccult II (HCII) – the most commonly used gFOBT in Europe – was also used in the four screening trials. Its sensitivity can be determined by giving the test to individuals who then undergo colonoscopy as a reference test. This shows that HCII detects between 13 and 38 per cent of cases of colorectal cancer.[109,110] In the case of biennial screening, the programme sensitivity is 50 to 60 per cent.[111-117]

Accordingly, gFOBT screening has only limited sensitivity, but a relatively high specificity (about 99 per cent).[118] About two per cent of participants have positive test results. In the course of the subsequent colonoscopy, advanced neoplasia was found in half of all 'positive' participants. Of these, 10 to 20 per cent had colorectal cancer and another 22 to 40 per cent had advanced adenomas.[17,90,93,117] In other words, the predictive value of a positive result (PPV) for advanced neoplasia was approximately 50 per cent. Accordingly, the other half of the approximately two per cent with positive results were false positives for advanced neoplasia.[12,90,93,119]

This is in keeping with the results of the Dutch pilots. Using the combined data from FOCUS and CORERO-I, 15 305 individuals were invited to undergo gFOBT screening. In total, 47 per cent returned test samples. Two and a half per cent of the returned tests were found to be positive. Ninety-one per cent of the participants with a positive gFOBT underwent colonoscopy, with a PPV of 10 per cent for cancer and 33 per cent for advanced adenomas.[27,32]

gFOBT screening makes it possible to detect colorectal cancer at an earlier stage (74 per cent at stages I or II[12,15,90,93,118,120,121]) than would be possible without any screening at all (55 per cent). Early treatment improves survival.

6.1.3 *Acceptance*

In addition to its limited sensitivity, a second shortcoming of gFOBT screening is the low uptake involved (around 50 per cent).[17,27,32,91,96,122] This is because gFOBT screening is laborious and not particularly user-friendly. Its poor test sensitivity, means that two samples must be collected from each of three consecutive stools.

In the European trials, only 59 to 67 per cent took part at least once in the six to nine biennial screening rounds. The relative risk reduction for this subgroup

was 25 per cent: RR = 0.75 (0.66-0.84).[94] In the Funen trial, this rose to 43 per cent for those who had participated in all nine rounds.[123]

The available data indicates that there is a steady uptake at repeat screening (to which those who did not take part in the first round were also invited). In Burgundy, the uptake for the first screening round was 53 per cent. In five subsequent rounds it varied from 54 to 58 per cent.[96] In England and Finland there was a slight decrease in the uptake for subsequent rounds.[119,124] In Scotland, after three rounds, uptake remained stable at a level of 55 per cent.[125]

6.1.4 Efficiency and cost-effectiveness

The results of model-based calculations indicate that biennial gFOBT screening may produce health gains at a cost which is currently considered acceptable.[126,127] Based on data from the Danish and UK trials, the cost per year of life gained as a result of biennial HCII screening is calculated to be GBP 1,584.[127,128] A review conducted on behalf of the United States Preventive Services Task Force showed that the cost-effectiveness of annual or biennial gFOBT screening ranges from USD 5,691 to USD 17,805.[126] The results of subsequent analyses were usually below USD 10,000. The results of a model-based calculation based on twenty years of screening in Burgundy gave a figure of EUR 3,357 per year of life gained.[129]

6.1.5 Conclusion

gFOBT screening has only a limited sensitivity for colorectal cancer, and the uptake is low. Nevertheless, it has been shown that the provision of biennial gFOBT screening decreases mortality from colorectal cancer by fifteen per cent. It is worth noting that this could have been better if the age threshold used had been higher than 45.

6.2 iFOBT screening

6.2.1 Effectiveness

Only one iFOBT screening trial has been conducted with colorectal cancer mortality as the outcome measure.[130] In this Chinese study, which was based on cluster randomisation, 94,423 individuals were offered a one-off iFOBT. Eighty per cent of these subjects took up this offer. However, those participants with a posi-

tive iFOBT were generally given sigmoidoscopy rather than colonoscopy. After eight years, the mortality from rectal cancer decreased by 32 per cent, but there was no effect on colon cancer mortality. The interpretation of the results was further complicated by the use of risk profiling.

Numerous observational studies have been carried out, especially in Italy and Japan [110,131-140] with favourable outcomes from case-control studies, pointing to a significant reduction in mortality from colorectal cancer.[141,142]

6.2.2 *Test performance*

Some iFOBTs are qualitative in nature, others are quantitative.

Qualitative iFOBTs show widely varying test performances.[143]

Quantitative iFOBTs (OC-Sensor, Magstream-HT, FOB gold) are preferred because they allow referral thresholds (cut-off value for a positive test) to be changed, such that the best possible (in terms of test performance) threshold value to be selected. In addition, the results are not affected by subjective perception.

The results of many studies of test performance are difficult to place, as they involve high-risk groups[138,139,144,145], non-western populations[146-148], or case-control studies.[149] iFOBTs too are often compared to gFOBTs other than HCII, such as the more sensitive but less specific Hemoccult Sensa test.[131,144,147,150-153] Such studies are difficult to use in support of value judgments about mortality reduction through iFOBT screening as against gFOBT screening (with HCII, which was used in the four efficacy trials).[154]

More usable Dutch data on the sensitivity of OC-Sensor indicate that, at a threshold value of 75 ng/ml, it was possible to detect 75 per cent of early colorectal cancers (TNM stages I or II).[155] This study involved patients who were referred for colonoscopy, but whose results corresponded with those from studies into the sensitivity of the iFOBT when used in the general population.[110,139,156-159] In the largest of these studies,[158] which involved 21,805 subjects, the Magstream-1,000 test was performed prior to colonoscopy. 1,231 of the returned tests (5.6 per cent) were found to be positive. As a single test, Magstream was found to have a sensitivity of 66 per cent for cancer and 27 per cent for advanced adenomas. In the other iFOBT studies, the sensitivity for cancer lay between 55 and 90 per cent. These results are significantly better than those for gFOBTs (13 to 38 per cent for cancer).

In a Taiwanese study well over 7400 individuals underwent colonoscopy as well as gFOBT and iFOBT screening (OC-Sensor), which allowed a direct comparison to be made.[110] OC-Sensor exhibited a greater sensitivity for cancer (88

per cent) and advanced adenomas (40 per cent) than gFOBT (38 per cent versus 33 per cent). In a smaller study with the same design, iFOBT (33 per cent) was also shown to be more sensitive than gFOBT (24 per cent) for large adenomas.[157]

A longitudinal study in which sensitivity was calculated on the basis of the number of colorectal cancer cases detected through screening and the number of interval carcinomas (colorectal cancer diagnosed within two years following a negative screening test) indicated a sensitivity for colorectal cancer of between 69 and 87 per cent.[112,136,160,161] A study carried out in the Florence region, which was based on the more accurate proportional interval cancer incidence method, gave a sensitivity for colorectal cancer of 72 per cent.[162]

Data is also available on an iFOBT (Monohaem) that was repeated on successive days.[159] This Japanese study involved 4,611 subjects, who also underwent colonoscopy. As a result, colorectal cancer was detected in 18 participants (0.4 per cent). Monohaem's sensitivity for cancer was 56 per cent after one test, rising to 83 per cent after two tests, and 89 per cent after three tests, while the specificity fell successively (97, 96 and 94 per cent).[159] In an Israeli study with the same design, which included 1,221 patients (1.4 per cent colorectal cancer), the sensitivity of $iFOBT_{75}$ (OC-Sensor) increased from 64 per cent to 94 per cent for colorectal cancer and from 38 per cent to 55 per cent for advanced adenomas.[145,163] Accordingly, the Committee anticipates that the sensitivity achieved in the programme will be significantly higher than the value of around 65 per cent achieved in a single test.

The progress reports on population screening in Italy provide data on test performance in the case of $iFOBT_{100}$ screening that is repeated at regular intervals (http://win.osservatorionazionalescreening.it/eng-programmes.php). In 2006, OC-Sensor gave a positive result for 5.3 per cent of the subjects who were participating for the first time. The PPV was 6.8 per cent for colorectal cancer, and 32 per cent for advanced adenomas. In a follow-up screening, 3.8 per cent had a positive test, with a PPV of 4.0 per cent for colorectal cancer, and 23 per cent for advanced adenomas.[164] Similar figures have been presented for the 2007 reporting year.[18] A screening programme involving this $iFOBT_{100}$ has been taking place in Florence since 1995. There, over a period of nine years, the PPV for colorectal cancer was 7.3 per cent and that for advanced adenomas was 26 per cent.[165]

In one study, which was linked to a population screening programme in the French department of Calvados, nearly 11,000 participants completed both a standard gFOBT and an iFOBT (Magstream, two faecal samples, threshold value 20 ng/ml). Three times as many advanced neoplasias were found using iFOBT

than with gFOBT.[140] At a referral threshold of 75 ng/ml, MagStream was positive just as often as gFOBT (2.4 per cent), but it detected twice as many individuals with advanced neoplasia.[140] Another study of the same design (a paired-sample design), which was linked to the population screening programme in Burgundy, included well over 17,000 participants. Using the iFOBT, colorectal cancer was detected 2.6 times more often and advanced adenomas 3.5 times more often.[166] A smaller Australian study revealed that another iFOBT (!nform, two faecal samples) detected more than twice as many advanced neoplasias as gFOBT (3.6 per cent versus 1.6 per cent).[167] In terms of sensitivity, the benefit of iFOBT relative to gFOBT lies primarily in the detection of early colorectal cancers and advanced adenomas, which involve less bleeding than later stage colorectal cancer.[140] This means that iFOBT screening can be expected to have a greater effect on cancer incidence and mortality than gFOBT screening.

An Italian study showed that, at a high referral threshold for OC-Sensor (200 ng/ml), specificity is 98.5 per cent, while the sensitivity for colorectal cancer declines by 13 per cent (10 instead of 12 cases of colorectal cancer detected).[133] Other researchers reported similar results.[136,160] This means that, at equal specificity, iFOBT is more sensitive than HCII.[160]

In FOCUS and CORERO-I, a total of 30,634 people between the ages of 50 and 75 (registered with the local authority) were invited to attend for screening.[27,32] In random order, 15,329 were sent an iFOBT (OC-Sensor) and 15,305 individuals received a gFOBT (HCII). Table 3 shows that the iFOBT was positive significantly more often (6.4 per cent at a referral threshold of 75 ng/ml) than HCII (2.5 per cent). In the subsequent colonoscopy, abnormalities were found almost as often as with the gFOBT. The PPV was 8.2 per cent versus 10.3 per cent for colorectal cancer and 52 per cent versus 55 per cent for advanced neoplasia. On the basis of an intention-to-screen analysis, $iFOBT_{75}$ detected colorectal cancer and advanced adenomas 2.5 times more often than gFOBT screening.

Some researchers suggest that abnormalities in the distal part of the colon bleed more easily, due to the mechanical action of stools, than do abnormalities in the wider, proximal part. Indeed, for subjects with distal adenomas that had been detected during a population screening programme in Florence, OC-Sensor gave higher average values than for proximal adenomas. In the case of colorectal cancer, the difference was not statistically significant.[165] Other researchers found no significant difference.[140,163] Is FOBT screening less effective at detecting proximal tumours than distal ones? In FOCUS, slightly more proximal colorectal cancers were detected in a control group of symptomatic patients than in the

iFOBT$_{50}$ screening group. This difference was not statistically significant, however.[168] That was also the outcome of a Japanese study involving 21,805 individuals who underwent both Magstream 1,000 and colonoscopy.[158] A study in the province of North-Holland did reveal a difference, however.[511] This iFOBT$_{100}$ study involved 1,808 patients who were referred for colonoscopy. All in all, there is no convincing evidence to suggest that iFOBT screening is less effective in detecting proximal tumours.

iFOBT screening makes it possible to detect colorectal cancer at an earlier stage (approximately 74 per cent at stages I or II) than would be the case without a screening programme.[18,133,139,158,159,169]

In total, 47 cases of colorectal cancer were detected by iFOBT[50] screening in FOCUS and CORERO. For these cases, the TNM staging was determined in order to predict five-year survival on that basis. In 71 per cent (33 of the 47 cases) colorectal cancer was detected at an early stage (62 per cent at stage I and 9 per cent at stage IIA). In a control group of 144 patients in the Nijmegen region (whose colorectal cancer had been detected following the appearance of symptoms) 49 per cent involved early-stage disease.[168] With iFOBT screening, predicted five-year survival was 85 per cent, which is significantly better than for the clinical control group (59 per cent).

Table 3 Test performance of gFOBT, iFOBT by referral threshold, and sigmoidoscopy. Numbers (and percentages), FOCUS and CORERO-I.

	gFOBT	iFOBT	(Nt=9136)		sigmoidoscopy
	(Nt=7211)	50	*75*	100	(Nt=1,386)
Test positives:Np (%)	182 (2.5)	767 (8.4)	*581 (6.4)*	482 (5.3)	142 (10.2)
Colonoscopy: Nc (%)	165 (2.3)	654 (7.2)	*498 (5.5)*	417 (4.6)	141 (10.2)
Detection rate CRC: n (%)	17 (0.24)	44 (0.48)	*41 (0.45)*	38 (0.42)	8 (0.6)
Detection rate: CRC +advanced adenomas: n (%)	91 (1.3)	300 (3.3)	*257 (2.8)*	232 (2.5)	111 (8.0)
PVV CRC: n/Nc	10.3%	6.7%	*8.2%*	9.1%	5.7%
PVV CRC + advanced adenomas: n/Nc	55.2%	45.9%	*51.6%*	55.6%	78.7%
Number Needed To Scope (Nc/n)					
NNScope darmkanker	9.7	14.9	*12.2*	11.0	17.6
NNScope CRC + advaced adenomas	1.8	2.2	*1.9*	1.8	1.3
CRC missed against iFOBT$_{50}$	NA	NA	*6.8%*	14.3%	n.v.t.

Nt=number of participants; Np=number of test postives; Nc=number of test positives who underwent colonoscopy.
Detection rate = percentage of true positives among all participants.
PVV = positive predictive value = percentage of true positives among test positives who underwent colonoscopy (n/Nc).
NNScope = Number Needed to Scope to find an extra person with advanced adenomas or CRC (Nc/n); NA=not applicable.

6.2.3 Acceptance

For the participants in a screening programme, iFOBT is significantly easier to perform than gFOBT. There is evidence from studies conducted outside the Netherlands that the participation rate for iFOBT screening is greater than that for gFOBT screening.[131,152,161,167,170] As iFOBT is able to detect smaller amounts of blood in stools than gFOBT, participants need only take a single stool sample rather than six. Moreover, more user friendly designs have been used, such as tubes with a brush attached to the inside of the screw cap, instead of test cards and spatulas. As a result, sampling is easier, more user friendly, more hygienic and more reliable. Italy and Japan have already gained considerable experience with OC-Sensor. The uptake there was higher than in previous years, when gFOBT had been used.[131]

The results obtained from the Dutch Pilots, which involved the use of randomisation, convincingly demonstrated that uptake is boosted when iFOBT is used. In FOCUS and CORERO-I, the iFOBT groups scored nearly 13 percentage points higher than the gFOBT groups (the respective uptakes were 60 per cent versus 47 per cent, and 62 per cent versus 50 per cent).[27,32]

There is no clear evidence of adverse risk selection[90] (in which fewer individuals from high-risk groups participate) as is the case with cervical cancer screening (see also 13.4).

In $iFOBT_{75}$ screening, 6.4 per cent of the participants had a positive test result (Table 3) and further examination by means of colonoscopy was recommended. Colonoscopy is a procedure that involves a degree of discomfort, and which carries a risk (albeit a small one) of serious complications (see 8.3). In half of all cases colonoscopy fails to detect any advanced neoplasia, indicating that the screening result was a false positive. However, this should be weighed against the fact that no further screening will be needed for another ten years (given that the colonoscopy is performed adequately).

In conclusion, the uptake for iFOBT screening is significantly higher (about 12 percentage points in the first round screening) than is the case for gFOBT screening. Furthermore, in none of the subgroups was the percentage of non-participants less than 50 per cent. As yet, little is known concerning the uptake associated with regularly repeated iFOBT screening. In one Italian region, four

rounds of screening involved a stable uptake of around 60 per cent.* At national level too, there is a stable uptake.[18]

In 2010, uptake data will be published for the second rounds of CORERO and FOCUS (in the Amsterdam region).

6.2.4 *Efficiency and cost-effectiveness*

Screening reveals many advanced adenomas, which can be removed endoscopically. In the long term, this reduces the incidence of colorectal cancer (after ten years, in the case of the gradual introduction of a population screening programme in the Netherlands; section 14.8). In some cases, stage I tumours can also be removed endoscopically or by means of minimally invasive surgery. This was the case in FOCUS and CORERO-I for 21 per cent of the 47 colorectal cancer patients detected using iFOBT, compared to 3 per cent of the 144 patients in a clinical control group.[168] This means that some patients – approximately 500 per year in the Netherlands – are spared major abdominal surgery, which would otherwise involve a twelve-day period of hospital admission.

The greater sensitivity of iFOBT and the increased uptake associated with its use suggest that, in terms of cost-effectiveness, iFOBT screening is superior to gFOBT screening[151,161], unless iFOBT is more expensive than gFOBT, as is often assumed.[14] In reality, however, there is little difference in the screening costs incurred by these techniques.[171,172] Accordingly, it is not surprising that iFOBT screening is indeed the more cost-effective of the two, as shown by an economic evaluation of the screening programme in Calvados.[171] An analysis carried out on behalf of the US Agency for Healthcare Research and Quality found that iFOBT could cost USD 12 more than gFOBT and still be just as cost-effective, while more years of life would be gained.[173] These researchers found that iFOBT screening achieves greater savings than no screening at all.[173] A model-based calculation based on FOCUS data also indicated that iFOBT screening produces net savings.[172] The data in question was only first round data, however. Model-based calculations for the US Preventive Services Task Force showed that, based on a 100 per cent uptake, annual iFOBT screening was just as effective as colonoscopy screening once every ten years. With a 50 per cent uptake, annual iFOBT screening was more effective.[174]

* Crotta S.Screening for colorectal cancer by immunochemical fecal occult blood: results of four rounds in two municipalities of Aosta Valley (Italy). Digestive Disease Week, May 30-June 4, 2009 Chicago, Illinois.

The treatment costs for highly advanced stages of colorectal cancer (i.e. the very cases that screening can often prevent) are expected to rise sharply when the latest generation of chemotherapy agents (which are extremely expensive) is deployed. This increase in costs makes the screening programme for colorectal cancer even more cost-effective (see also section 12.1).

6.3 Conclusion

Data from the Dutch Pilots and from screening programmes in other countries shows that iFOBT is clearly superior to gFOBT. In addition to being much more convenient for the participants (which also boosts uptake), it is also more amenable to laboratory quality control procedures, and is superior in terms of its yield. Accordingly, the use of $iFOBT_{75}$ enables colorectal cancer to be detected 2.5 times more often – and advanced adenomas 2.6 times more often – than would be the case with gFOBT screening. This means that a greater reduction in cancer deaths can be achieved than with gFOBT. Furthermore, a reduction in the incidence of colorectal cancer is a realistic objective. However, it should be noted that the greater sensitivity of iFOBT means that more participants have positive test results and that, in absolute terms, there are more false positive test results. The latter is a disadvantage, given the anxiety engendered and the limited capacity for colonoscopy. However, this should be weighed against the fact that no further iFOBT screening will be needed for another ten years (given that the colonoscopy is performed adequately). The Committee recommends that the issue of false negative findings (obtained by tracing interval cancers via the cancer registry) be routinely raised during external reviews, as is presently the case with the population screening programme for breast cancer.

In this context, the Committee notes that little data is available on regularly repeated iFOBT screening. However, it points out that this will enable 80 per cent to 90 per cent of colorectal cancer cases to be detected, at the cost of only a relatively slight increase in the percentage of false positive results.

Furthermore, the Committee concludes that iFOBT screening detects colorectal cancer at a more prognostically favourable stage than is currently the case, in the absence of screening. With iFOBT screening, fewer patients ultimately require surgery and the predicted five-year survival increases with 22 percentage points, as compared to the current policy.

Chapter 7

Sigmoidoscopy

Sigmoidoscopy allows the distal portion of the colorectum (from the *flexura lienalis* to the anus) to be examined. For bowel preparation, the patient is given an enema (120 to 150 ml of lukewarm water). CORERO-I showed that 86 per cent of the participants preferred to administer the enema themselves, at home. As a result, well over 80 per cent were adequately prepared for endoscopy. Where this was not the case, a second enema was administered in the endoscopy room. Ultimately, nine per cent of the participants still had excessive faecal contamination and had to make a new appointment for sigmoidoscopy.[32,175] The procedure itself takes about seven minutes.[176] In CORERO-I, individual appointments were scheduled at 10-minute intervals. Sigmoidoscopies can be performed by a nurse endoscopist.[176] A survey of all registered gastroenterologists (and gastroenterology residents) in the Netherlands (response 62 per cent) showed that 89 per cent of them considered sigmoidoscopy for CRC screening as appropriate procedure to be performed by nurse endoscopists.[177]

In the case of some abnormalities, the results of sigmoidoscopy are considered to be positive and colonoscopy is recommended. In general, the following referral criteria apply: the presence of an advanced adenoma, of 3 adenomas, of 20 hyperplastic polyps, or of colorectal cancer. However, the Norwegian Colorectal Cancer Prevention (NORCCAP) trial, for example, defined a positive screening test as any polyp ≥ 10 mm, any adenoma irrespective of size, or carcinoma.[178] No data is available concerning an optimum referral threshold.

7.1 Effectiveness

From 1993 to 1998, in the US, Italy, the UK and Norway, four randomised trials were launched into the effectiveness of a single sigmoidoscopy screening, with colorectal cancer mortality as an endpoint.[28-30,179] The first results of the NORCCAP trial (which had a 65 per cent uptake and a follow-up period of six years) produced no statistically significant reduction in colorectal cancer mortality.[178] However, further mortality follow-up may well provide evidence of benefit.[180] The results of the British and Italian studies are expected in 2010.

7.2 Test performance

There is a considerable body of evidence to support the view that sigmoidoscopy can be an effective screening test. Among the participants, 0.3 to 0.6 per cent were found to have colorectal cancer, while 3 to 7 per cent had advanced adenomas.[29,30,32,181] The results of observational studies and model-based calculations indicate that individuals can at least halve their risk of dying of colorectal cancer by *participating* in a sigmoidoscopy screening programme.[182-192]

Estimates of the sensitivity of sigmoidoscopy are based mainly on the results of studies in average-risk populations who undergo colonoscopy.[193-198] Here, 'sigmoidoscopy' is taken to mean the results of colonoscopy from the *flexura lienalis* to the anus (which would also involve full colonoscopy if any abnormalities were found in this region). The estimates range from a sensitivity (for the entire large intestine) of 58 to 75 per cent for colorectal cancer and 72 to 86 per cent for advanced neoplasia. For a variety of reasons, however, this approach led to overestimates of sensitivity. This is because it was assumed that any anomalies revealed by colonoscopy between the *flexura lienalis* and the anus would also have been detected using true sigmoidoscopy screening, while this 'pseudo-sigmoidoscopy' benefits from more extensive bowel preparation and probably also from the greater experience of the endoscopist. Furthermore, the depth of insertion using true sigmoidoscopy does not always reach as far as the *flexura lienalis*.[199] Moreover, these studies assumed a very low referral threshold for colonoscopy, involving the detection of any adenoma, regardless of size and histology.[193-198]

A case-control study (a type of study that is equally prone to potential bias[200]) arrived at a sensitivity of 53 per cent for colorectal cancer, again based on the location of the tumour and assuming that sigmoidoscopy extended to the *flexura*

lienalis, and that the detection of adenomas (regardless of their characteristics) would result in referral for colonoscopy.[201] Using the same assumptions, a study of 783 patients who had undergone colonoscopy in a Rotterdam hospital derived a value for maximum achievable sensitivity of 69 per cent.[175]

As yet, little data is available concerning the sensitivity of population screening by means of sigmoidoscopy. In the NORCCAP trial, sigmoidoscopy was found to have a sensitivity for colorectal cancer of 47 per cent (calculated on the basis of interval cancers, with a seven-year follow up).[178] It is not clear whether sigmoidoscopy screening needs to be repeated every five or ten years.

In CORERO-I, 5,000 individuals were invited to attend for sigmoidoscopy screening.[32] Thirty-two per cent of the group took advantage of this offer (n=1,522). Ten per cent of the participants in complete sigmoidoscopy screening (n=142) were referred for colonoscopy (referral criterion: advanced neoplasia). Of these, 141 actually underwent the procedure. Among those participating in the screening programme, 7.4 per cent were found to have advanced adenomas, while 0.6 per cent had colorectal cancer (Table 3).[32] Despite the lower participation rate, sigmoidoscopy detected more individuals with advanced adenomas than a single $iFOBT_{75}$ screening (21 per 1000 invitees for the former, and 14 for the latter). However, the number of cases of colorectal cancer detected were about the same (two per 1000 invitees for the former, three for the latter).[32,202]

The test characteristics of sigmoidoscopy screening depend on the referral threshold. The lower this threshold the higher the sensitivity, but the higher the number of participants who have to be referred for colonoscopy.

The screening yield is heavily dependent on the endoscopist. Efficacy trials show significant differences in yields, even though the endoscopists were expected to work in accordance with a common protocol.[203-206] This serves to underline the importance of effective quality assurance.

More than seventy five per cent of screen-detected colorectal cancer cases involve TNM stages I or II.[28,182,183,207,208] This is a considerable improvement over the current situation, in which there is no screening, particularly for distal tumours.[209] The NORCCAP trial, however, gave a lower value (64 per cent).[178]

7.3 Acceptance

Uptake

In a study of 200 patients between 50 and 60 years of age who were attending an internal medicine outpatients clinic in the Maastricht region of the Netherlands, 45 per cent took up a written invitation to participate in sigmoidoscopy screening.[210] The uptake figures reported in literature from other countries range from 10 to 40 per cent.[14,50,182,211] Uptake in the British and Italian efficacy trials was 39 per cent and 24 per cent respectively.[29,30] In the Italian regions of Piedmont and Veneto, 29 per cent of invitees took up the offer of service screening.[164] Only in the Norwegian trials was uptake significantly higher, at 68 to 81 per cent.[179,190] Population screening programmes in northern Europe often have remarkably high uptakes.[124] CORERO-I, however, had an uptake of only 32 per cent.[32]

Discomfort

Sigmoidoscopy usually involves less extensive bowel preparation than colonoscopy. 9-20 per cent of participants, however, have to make a new appointment for sigmoidoscopy due to inadequate bowel preparation.[32,181,199] Studies of the practical experiences of the select group of people who have undergone sigmoidoscopy show favourable outcomes.[30,212,213]

Depending on the referral threshold, 5 to 21 per cent of the participants are referred for colonoscopy.[29,32,181,199]

Complications

The risk of perforation during sigmoidoscopy screening is 0.002 to 0.003 per cent.[29,30,181,184,190,214-217]

Individuals who undergo colonoscopy following a positive screening result (FOBT, sigmoidoscopy, colonography) run a 0.1 per cent risk of perforation and a 0.14 per cent risk of bleeding that necessitates hospital admission.[29,30,88,181,184,218]

7.4 Efficiency and cost-effectiveness

In CORERO-I, 625 invitations, 207 sigmoidoscopies and 18 colonoscopies were needed to detect colorectal cancer in just a single individual. Finding a single

individual with advanced adenomas requires 48 invitations, 16 sigmoidoscopies and 1-2 colonoscopies.[32]

Model-based calculations for the US Preventive Services Task Force showed sigmoidoscopy screening to be less effective than colonoscopy or iFOBT screening.[174]

7.5 Conclusion

Sigmoidoscopy can be an effective screening method, provided that the forthcoming trial results are favourable and that the uptake is significantly higher than 30 per cent. The ongoing trials involve a single screening, so there is no data on regular sigmoidoscopy screening. The outcome of CORERO-I demonstrated the feasibility of high-volume testing, using experienced endoscopists (> 200 colonoscopies) in selected centres.

The uptake for sigmoidoscopy screening was significantly lower than for iFOBT screening. Accordingly, population screening in the Netherlands should not be restricted to sigmoidoscopy alone.

Chapter 8

Colonoscopy

In this chapter, the role of colonoscopy as a primary screening test (Figure 1 lower arrow) is discussed. In colonoscopy, a video-endoscope is used to examine the entire length of the colon. The examination is preceded by extensive bowel preparation at home, on the preceding day. Subjects drink two litres of a laxative solution. This should have a laxative effect on the intestine, such that only virtually clear fluid is eliminated via the anus. Colonoscopy is considered the reference standard for detecting colorectal cancer and adenomas. The test takes about twenty minutes. In the Netherlands, colonoscopy is usually performed with the subject under conscious sedation (fentanyl, midazolam). Where technically possible, polyps are removed immediately (polypectomy). If this is not possible, biopsies are taken (see 14.5). All retrieved lesions are evaluated histologically.

8.1 Effectiveness

Results on colorectal cancer mortality and incidence are not yet available from RCTs. One such efficacy trial is currently in progress, however. This is the NordICC trial (Nordic Initiative on Colorectal Cancer), to which the Netherlands has contributed since June 2009, as part of the COCOS trial (section 3.4).[33,219] The results will be reviewed after ten years.

8.2 Test performance

Observational studies are mainly performed on patients. The results support the view that colonoscopy can be an effective screening test. One example is an American study of 1,400 high-risk patients who were referred for colonoscopy after developing symptoms, *and* who had one or more adenomas removed. In the subsequent six years, 75 to 90 per cent fewer cases of colorectal cancer were found in this group than in same-sex peers.[220] This National Polyp Study was subjected to considerable criticism for a variety of reasons, one of which was the failure to incorporate randomisation into the study design. The results of later studies indicate that the preventive effect is actually smaller than was reported by the National Polyp Study.[190,201,221-223]

Colonoscopy is the most sensitive method for advanced neoplasia, accordingly it is seen as the 'gold standard'.[157,193,194] Following a negative test outcome, the risk of colorectal cancer is substantially reduced for at least ten years.[221,223] Systematic reviews show that the test performs well. Its sensitivity for cancer is virtually 100 per cent. When measured using tandem or back-to-back colonoscopy – in which subjects undergo two colonoscopy examinations performed by different, experienced endoscopists – the test has a sensitivity of 90 to 98 per cent for 'large' adenomas (diameter ≥ 10 mm) as against 87 per cent for 'small' adenomas (6-9 mm).[224,225] When colonoscopy findings were combined with those of CT colonography (segmental unblinding), the sensitivity for adenomas ≥ 6 millimetres in size ranged from 88 to 99 per cent.[157,226-228]

For various reasons, tumours in the right (proximal) colon are harder to detect using colonoscopy. One reason is that the proximal surfaces of haustral folds are notorious blind spots.[226,229] Moreover, inadequate bowel preparation mainly affects the right-hand section of the colon. These two effects can make it particularly difficult to detect sessile adenomas. A third reason is that – in the case of incomplete colonoscopy (i.e. which does not penetrate as far as the appendix) – this section is only partially inspected.

Canadian studies, however, project an excessively gloomy picture. A study conducted in the province of Ontario investigated how many of the 31 000 new colorectal cancer patients had undergone colonoscopy in the 6 to 36 months prior to diagnosis.[230] The researchers concluded that 3.4 per cent of patients either should have been diagnosed with 'colorectal cancer' (but that this had been missed) or had a rapidly growing cancer. A second study by the same research group generated considerable commotion because colonoscopy was found to be

associated with lower mortality from colorectal cancer in the left (distal) colon, but not with lower mortality from colorectal cancer in the right colon.[231]

These studies engendered considerable criticism. The researchers themselves indicated that they were unable to distinguish between screening and colonoscopy on medical indication. Moreover, these studies were based on claim codes, which – without verification from detailed endoscopy reports – is a cruder approach. Accordingly, the investigators were unaware how many of the procedures declared by the individuals in question as 'colonoscopies' were actually incomplete colonoscopies. Furthermore, only 31 per cent of the procedures that were declared as colonoscopies were carried out by gastroenterologists, and even these gastroenterologists often failed to meet generally accepted standards. These results serve to emphasise the fact that colonoscopy procedures have to meet high quality standards.

Five European studies have provided information on the yields of population screening using colonoscopy. In all, 52,346 individuals between the ages of 50 and 75 were examined. Of this group, 0.8 per cent were found to have colorectal cancer, while 6.7 per cent had advanced adenomas.[48-52] From 2003 to 2006, opportunistic colonoscopy screening in Germany (which involved 1,875,708 participants aged 55 and above) gave similar detection rates. Advanced adenomas or colorectal cancer was found in 4.9 per cent of the women and 8.6 per cent of the men.[232] In an Italian experiment, the participants were offered iFOBT, sigmoidoscopy or colonoscopy.[182] While the uptake for colonoscopy was the lowest, it still found the highest number of advanced neoplasias (per invitation) in the first round of screening. However, this situation may change if colonoscopy is compared to regularly repeated iFOBT screening or sigmoidoscopy screening.

In one German study[157], both colonoscopy and CT colonography detected significantly more advanced adenomas than did a single iFOBT. As with sigmoidoscopy, test performance is dependent on the individual endoscopist. When it comes to finding adenomas, there are substantial differences in performance from one endoscopist to another (see section 14.4). A US study found that colonoscopy's sensitivity for colorectal cancer was 97 per cent for gastroenterologists versus 87 per cent for non-gastroenterologists.[233]

When colorectal cancer is identified by means of screening colonoscopy, 77 per cent of the cases involved early-stage disease (TNM stage I or II).[51,109,159,193,234-236]

8.3 Acceptance

Uptake

An attitude survey conducted among colonoscopy-naive individuals showed that, once they had been fully informed about the techniques in question, most people preferred FOBT screening to colonoscopy.[237] The initial data on screening by means of colonoscopy indicate uptake rates of 20 to 40 per cent[50,79,122], with individual peaks of up to 60 to 70 per cent.[79,238] An American study showed that 59 per cent of those who had been verbally advised by their physician to undergo screening, actually followed this advice. That proportion climbed to 71 per cent when, following advice from the physician, a brochure was sent to the patient's home address.[239] Preliminary data from the pilot project in Maastricht indicate an uptake of 41 per cent, even though the target group is not representative of the general population.[25]

In the US, colonoscopy has emerged as the primary screening test for CRC. A nationwide telephone survey showed that more than half (56 per cent) of Americans over the age of 50 had undergone an endoscopic examination (sigmoidoscopy, colonoscopy) in the ten years preceding the survey.[240] However, these examinations were by no means only in the context of screening. Data from the Clinical Outcomes Research Initiative showed that 51 per cent of all colonoscopies are performed for screening.[241] In Germany, from October 2002 until January 2005, less than six per cent of the target group made use of colonoscopy.[241] In Poland, around 50,000 individuals took part in opportunistic screening between October 2000 and December 2004.[49] In terms of colonoscopy, organised population screening seems to do no better than opportunistic screening. The Italian AMOD feasibility study had a compliance of only eleven per cent.[241]

Many people opted out of screening due to the invasive nature of colonoscopy and the extensive bowel preparation that is required.[242] On the other hand, it does have the advantage that screening does not have to be repeated frequently. It could be carried out just once every ten years, or indeed once-only.

Discomfort

Bowel preparation, which involves the use of a strong laxative or intestinal lavage, is the most onerous aspect of colonoscopy. Individuals opting for colonoscopy have to reserve two days for the entire procedure, including bowel

preparation (at home) and aftercare (recovery room, transport home). People generally find that the degree of discomfort involved is less than they had anticipated.[243] An Australian study of people's experience of undergoing colonoscopy for screening or surveillance purposes (under conscious sedation with propofol) showed that 75 per cent of the participants found the process to be 'comfortable', 23 per cent rated it as 'tolerable' and 2 per cent thought that it was 'uncomfortable'. Nobody ticked the box marked 'unbearable'. In many regions, experienced endoscopists carry out colonoscopy without administering any form of sedation. For seventy eight per cent of the participants, the most onerous part of the whole procedure was bowel preparation.[212] Eighty per cent of the first participants in the Maastricht pilot project rated bowel preparation as 'somewhat' or 'very' unpleasant.[25]

The discomfort involved in the examination is counterbalanced by the fact that nearly half of all colorectal cancers detected can be removed endoscopically, which means that the patient does not have to undergo abdominal surgery.[51]

Complications

When colonoscopy is used as a screening test, there is a slight risk of perforation (0.05 per cent) or of bleeding that requires hospitalisation (0.06 per cent).[109,193,229,234] Later publications on large scale screening reported even lower rates (0.01 or 0.02 to 0.05 per cent).[49,235,236,244] The results of a Japanese survey showed that there were no serious complications after 21,805 colonoscopies in which no polypectomies were performed.[158] This study involved highly experienced endoscopists, each of whom had carried out more than 3,000 colonoscopies.

Individuals who undergo colonoscopy as a result of a positive screening result (FOBT, sigmoidoscopy, colonography) run a 0.1 per cent risk of perforation and a 0.14 per cent risk of bleeding.[29,30,88,140,181,184,218]

Most screening studies indicate no fatal outcomes of colonoscopy.[14,29,30,49,51,88,109,140,181,184,193,218,229,234-236,245-248] In Germany, of the 1.14 million individuals who have undergone colonoscopy screening, four (0.0004 per cent) have died as a direct result of the procedure.[241] This risk is lower than for patients who undergo colonoscopy in connection with a medical indication. This is because the latter group are usually older than those who participate in screening programmes, and have more intestinal problems and other diseases. Even for this group, the risk of a fatal complication as a result of colonoscopy is very low, in the order of 0.004 per cent.[249-253] In a study in Ontario, which drew no distinc-

tion between screening and colonoscopy in connection with a medical indication, three deaths were colonoscopy related, and two deaths were possibly colonoscopy related. Five deaths in a group of 67,632 patients represents a risk of 0.0074 per cent.[249]

8.4 Efficiency and cost-effectiveness

On the basis of the prevalence figures cited in section 5.2 (0.8 per cent colorectal cancer and 6.7 per cent advanced adenomas) for every thirteen people who undergo colonoscopy in the context of screening, just one will be found to have colorectal cancer or advanced adenomas. This value is known as the Number Needed to Scope (or NNScope). In the case of colorectal cancer alone, the NNScope is 125.

Nevertheless, the results of modeling indicate that colonoscopy screening (every ten years or once-only) has a favourable cost-effectiveness ratio.[126,254-256] This outcome is uncertain, however, as there is insufficient evidence to support the magnitude of the effect of colonoscopy screening on colorectal cancer mortality.

8.5 New developments in endoscopy

More adenomas can be detected using chromoscopy (colonoscopy in which the intestinal wall is stained), but this technique is very time consuming and does not appear to be suitable for use as a screening method. This same is true of high-definition endoscopes, autofluorescence and narrow-band imaging.[257,258]

Capsule endoscopy is a technique in which the subject swallows a capsule (current price approximately EUR 950) that takes photographs at regular intervals while it travels through your large bowel. These images are transferred wirelessly to an external receiver, which is worn by the individual being examined. After twenty-four hours, the data accumulated by the receiver is downloaded, and the images are examined on a monitor. At the end of the examination period, the capsule is ejected from the body with the faeces. A study of 320 patients gave a value of 64 per cent for the sensitivity of capsule endoscopy for ‘large’ adenomas. The corresponding value for colorectal cancer was 74 per cent.[259]

Capsule endoscopy has been widely used for several years, to analyse pathologies of the small intestine. Battery life limits the use of this technique as a screening method for colorectal cancer. This can be remedied by using capsules with delayed activation, reduced energy consumption, and increased battery capacity. A second drawback is the time required to download the video record-

ing (which has a playback time of approximately two hours). A third point is the need for an extensive bowel preparation; capsule endoscopy using white light requires that the colon be completely clean. Studies aimed at avoiding this problem are already underway. The use of radiation with wavelengths beyond the range of visible light makes it possible to trace the contours of the intestinal mucosa. Within the upcoming seven years, these and other techniques are expected to make capsule endoscopy suitable for use as a method of bowel screening. Randomised studies, involving comparisons with existing screening methods, will then have to be carried out to determine whether capsule endoscopy can actually improve the efficacy or efficiency of screening.[37]

In recent years, numerous developments have resulted in colonoscopes with variable flexibility, high resolution, wide-angle vision, staining, and external tracking of the intra-abdominal position of the endoscope. The methods are aimed at facilitating the use of the endoscope and increasing the diagnostic yield. In this context, researchers are examining the possibility of varying the shape of the endoscope itself. 'Easy scopes' can be passed through the colon with a minimum of pressure.

8.6 Conclusion

Colonoscopy enables the entire colon to be examined. It is the most sensitive test for detecting advanced neoplasia. The discomfort involved for participants and the risk of complications are greater than in the case of sigmoidoscopy. Participation in colonoscopy screening is significantly lower than for iFOBT-screening. On this basis (according to the intention-to-screen analysis) the detection rate of colonoscopy screening for colorectal cancer is lower than that of iFOBT screening, and this difference increases still further in subsequent rounds.

In the Committee's view, colonoscopy screening is not (or not yet) suitable for use as a screening method outside a scientific research setting. As yet, there are no results from RCTs on the effect of colonoscopy screening on colorectal cancer mortality. It will take more than another ten years before the outcome of the NordICC trial is known.

Chapter 9

Colonography

Colonography (virtual colonoscopy) is a minimally invasive imaging technique that enables the entire colon to be examined. This preferably requires limited bowel preparation, involving one day on a low-fibre diet (no fibre-rich vegetables or fruit) and the ingestion of an oral contrast agent for the uniform staining of stool residue and moisture (tagging). Prior to the examination, bowel distension is performed with a thin, flexible cannula, which is placed in the rectum. Room air or carbon dioxide (CO_2) can be used. Pneumocolon is achieved by automated gas delivery, using a dedicated insufflation device. This device electronically controls the intracolonic pressure (which is limited). Optimal bowel distension is a fundamental prerequisite and makes it easier to spot polyps and to select them on the basis of size. Bowel distension and patient acceptance are further improved by the intravenous administration of a muscle relaxant. Sedation is not required. Subjects are scanned in prone and supine position. The examination is performed by a radiographer, and takes about fifteen minutes, although the actual CT examination is completed in less than thirty seconds.

Image interpretation (2-D and 3-D images) is performed by a radiologist, who may or may not make use of computer aided detection. The time required for the assessment depends on the expertise of the radiologist, the methodology used, and the prevalence of abnormalities, although an experienced reader in a population screening programme will probably take less than ten minutes per subject. Research shows that trained radiographers are also competent in the evaluation of CT colonographic images.[260,261]

The examination also involves an evaluation of structures outside the colon itself.[262] This might be an advantage, in the case of serious, treatable disorders, but it can also be a disadvantage. Among the target group for population screening, the chance that a serious, treatable disease will be found is quite small. Moreover, screening may reveal disorders such as an aneurysm of the aorta, for which the usefulness of early detection is by no means a foregone conclusion.[263] What is clear, however, is that the reporting of extracolonic abnormalities can double the number of referrals for diagnosis.[247,262] The use of a low radiation dosage reduces image quality outside the colon, and is expected to significantly reduce the number of referrals.

If polyps are found, however, colonoscopy is still needed to investigate and remove them. The referral threshold is usually ≥ 6 mm. As yet, however, there is no agreement with regard to the best referral threshold.[264,265]

Colonography can be carried out in conjunction with computer tomography (CT) or magnetic resonance imaging (MRI). Most research data involve CT colonography. To date, only one study has been performed using MRI colonoscopy in a screening population. This involved a cohort of 315 German participants (and limited bowel preparation), which had a sensitivity for 'large' polyps of 70 per cent.[266]

9.1 Effectiveness

No efficacy trials have yet been conducted to evaluate CRC incidence or mortality reduction from colonography screening.

9.2 Test performance

CT colonography was principally investigated in connection with patients with intestinal symptoms and people with a familial predisposition. Systematic reviews show that the test performs well under these conditions. In comparison with colonoscopy, CT colonography has a 96 per cent sensitivity for colorectal cancer.[267] For 'large' polyps, the (per person) sensitivity is around 90 per cent, at a specificity of 95 to 97 per cent.[267-269] It should be pointed out that this study also involved rather dated technology.

The limited amount of data that is available concerning the performance of this test in population screening programmes is at least equal to the results of studies in patient groups.[157,248,264,270] In one of these studies, CT colonography and colonoscopy had similar detection rates for advanced neoplasia (3.2 vs. 3.4 per cent).[247] In a German study, 307 participants underwent both CT colonogra-

phy and colonoscopy, and the segmental unblinding comparison procedure was used.[157] This meant that, during colonoscopy, after each segment of the colon had been inspected the CT colonography results for that segment were checked immediately. This highly accurate comparison boosted the sensitivity of CT colonography for advanced neoplasia to nearly 97 per cent.[157]

CT colonography is less sensitive for 'small' adenomas. In the ACRIN trial, the per-person sensitivity for adenomas ≥ 6 mm was 78 per cent. For adenomas ≥ 10 mm, it was 90 per cent.[248] In the German study that employed segmental unblinding, these rates were virtually the same (91 per cent and 92 per cent respectively).[157] CT colonography may be superior to colonoscopy for detecting proximal colorectal cancer.[247,271]

The specificity for 'large' polyps is greater than 95 per cent.[157,229] A referral threshold of ≥ 6 mm means that approximately 15 per cent of the participants have to undergo colonoscopy. This inevitably means that screening will have many false positive results. When a referral threshold of ≥ 10 mm is used, 6.8 per cent of the participants have to undergo colonoscopy and there are fewer false positive screening results. According to one American study, the PPV for advanced adenoma was 41 per cent at a referral threshold of ≥ 6 mm and 67 per cent at a threshold size of ≥ 10 mm.[264] Another study gave a PPV of 52 per cent at a cut-off point of ≥10 mm.[229]

9.3 Acceptance

Uptake

In Australian studies, only 16-28 per cent participated in a screening programme using CT colonography.[270,122] However, the uptake for other screening methods was also much lower than usual.

Discomfort

Conscious sedation, analgesia and extensive bowel preparation, which are used for colonoscopy, do not appear to be necessary for colonography.[272,273] CT colonography is preferably carried out with limited bowel preparation.[272,274-276] The use of an iodinated contrast agent can induce an allergic reaction.[277] However, the risk involved is minimal. In subjects with a known allergy to iodinated contrast agents, a different contrast agent (barium) can be used. The radiation exposure also is radically reduced.[272,278,279]

This would seem to eliminate the major concerns regarding CT colonography. Studies of subjects' experience and preference in people who have undergone both CT colonography and colonoscopy, show a clear preference for CT colonography.[272,274,280]

Complications

Colonography is minimally invasive. While perforations can occur during CT colonography (at least in patients with intestinal symptoms), the risk involved is between 0.059 and 0.005 per cent.[281-283] However, these perforations were not associated with screening nor was the current standard used (thin, flexible rectal cannula; automatic insufflator with control of intracolonic pressure, experienced operator). As yet, CT colonography is in limited use as a screening method, however no perforations have been reported in over 17,500 examinations.[229,247,264,270,281]

9.4 Efficiency and cost-effectiveness

The risk of cancer depends to a great extent on polyp size.[284] It is the size of any abnormalities found during colonography that determines whether it will be recommended that the patient be referred for colonoscopy. There is a general consensus that 'large' polyps should be removed. In patient groups, there is a 10 to 15 per cent probability that such polyps are either malignant or will become so.[285] Abnormalities < 6 mm in size (80 per cent of all polyps) are regarded as irrelevant.[286,287]

However, there is no consensus regarding 'small' polyps.[264,265] In view of the low PPV of 'small' polyps, the Working Group on Virtual Colonoscopy recommended that CT colonography be repeated after three years, rather than immediate colonoscopy.[287] This policy has attracted come criticism on the grounds that it is indefensible from the standpoint of good care.[288] However, this criticism was based on the results of hospital-based studies that are not necessarily applicable to screening programmes. It is uncertain what health gains might result from performing a colonoscopy straight away. A new US guideline recommends an immediate colonoscopy, but this is based on consensus rather than evidence.[286] On the basis of data on the natural course of small polyps, there is no reason why a wait-and-see policy should not be adopted.[289] For instance, a study involving the annual endoscopic surveillance of 'small' polyps found that, after three years, their average diameter even tended to decline slightly.[290]

In patients with ‘small’ adenomas there is only a slight risk (between 0.15 and 0.7 per cent) that cancer will be present[285,291-295] In screening populations, this risk is between 0.03 and 0.2 per cent.[284,285,296-298] In one US study into the yield of CT colonography, all cases of colorectal cancer and 94 per cent of the advanced adenomas were ≥ 10 mm in diameter.[247] In the ACRIN trial too, all colorectal cancers were ≥ 10 mm.[248]

In patients with ‘small’ polyps who underwent colonoscopy, advanced neoplasia was found in 3 to 7 per cent of those involved.[193,294,295,299] In large screening studies, the PPV was virtually identical, at between 3 and 9 per cent.[157,246,247,284,298]

A recent cost-effectiveness analysis[300] showed a referral threshold of 6 millimetres to be preferable to one of 10 millimetres, but this took no account of improvements in the sensitivity of CT colonography since 2005.[157,247,264]

9.5 New developments

CT colonography involves the use of ionising radiation. The original CT colonography protocols, which were designed with the clinical setting in mind, involved an average radiation dose of 9 to 10 milliSievert (mSv).[301,302] According to an international survey, the dose involved in screening is approximately 6 mSv.[302] It has been shown that the radiation dose can be reduced even further without affecting test performance.[272,278,279] Radiation exposure in the COCOS trial is 2.2 mSv, which is equivalent to the annual dose received from background radiation in the Netherlands. According to conservative estimates, for people of the same age as the target group for population screening, the risk that this ionising radiation exposure will cause cancer later in life is in the order of 1 in 12,500, and probably even lower.[303]

Another development that has no adverse impact on test performance either, is limited bowel preparation (oral contrast agent, low-fibre diet not required).[272,273,304-307]

The use of CT colonography is not restricted to screening. It can be used as a triage technique after a positive FOBT, for instance. About half of the positive results obtained in FOBT screening are false positives; no advanced neoplasia was found using colonoscopy. This could either mean that colonoscopy had missed an abnormality, which could be the case in 2 to 10 per cent of ‘large’ adenomas and about one per cent of cancers (section 8.2), or that, in hindsight, colonoscopy was not necessary.

Can the number of unnecessary colonoscopies be reduced by first performing a CT colonography? In order to verify this, over 300 participants in Dutch trial population screening programmes who had had a positive iFOBT, were examined by CT colonography prior to colonoscopy.[308] Triage with CT colonography (Figure 1, fourth arrow) did not appear to be worthwhile, as the yield for advanced neoplasia was higher than expected. Studies carried out in Italy and Belgium led to the same conclusion.[309]

This may not be the case in subsequent rounds, as fewer abnormalities will be found (due to the previous prevalence screening) which, in turn, means that the PPV will be lower.[119,164]

CT colonography could also play a part in surveillance following polypectomy or in relation to familial colorectal cancer.[309] However, these groups appear to have more sessile (flat) abnormalities that are difficult to detect using CT colonography than the much more common pedunculated (spherical) polyps.[273,310-312]

New research is under way into the development of MRI colonography that is specifically aimed at detecting adenomas with a high risk of becoming malignant. In this context, researchers are focusing both on the detection of appropriate molecular markers and on MRI technology.

9.6 Conclusion

CT colonography is almost as sensitive to colorectal cancer and ‘large’ adenomas as colonoscopy, but it involves less discomfort for participants and a smaller risk of serious complications.

If that is the case, then why has CT colonography still not been recommended for use as a screening method? There are several reasons for this. No data are available from randomised trials into the effects of colonography screening on colorectal cancer mortality. In many cases, colonoscopy will be carried out anyway, depending on the reference criterion used. There is no agreement about whether screening should also focus on ‘small’ polyps. No details are available concerning the participation rate, although this is currently being investigated within the context of the COCOS trial. The issue of how to deal with extra-colonic abnormalities is, as yet, unresolved.

Chapter 10

Molecular tests

The basis of colorectal cancer is a disturbance of the biological processes in the intestinal epithelial cells, particularly resulting from (generally non-hereditary) changes in the way that certain oncogenes and tumour suppressor genes function. This disturbance is accompanied by changes in the molecular structure or quantity of substances such as DNA, RNA and protein. By means of laboratory tests, it is possible to measure molecules of these substances – referred to in this context as 'biomarkers' – in samples of tumour tissue, blood or faeces. Research in this field is aimed at the identification and large-scale validation of biomarkers with better test characteristics, and optimisation of the relevant test methodologies. In addition, progress is being made with efforts to render tumour markers visible using imaging techniques, such as PET and MR.

Biomarkers in the DNA of the germ-line (reproductive cells) are of particular interest, since they determine hereditary predisposition towards colorectal cancer. The influence of these cells is not confined to 'hereditary colorectal cancer'. In the general population, there is significant diversity in hereditary predisposition towards colorectal cancer. This diversity is associated with variations in the coding sequence within certain genes and in the number of copies of certain genes that individuals possess per cell. Germ-line biomarkers could in principle be used to refine the process of defining the target group for screening. However, individual germ-line biomarkers are poor predictors of colorectal cancer risk; it is only in combination that they may be regarded as determinants of risk. Among

the factors that hamper research in this field is the degree of genome variation between individuals.

10.1 Testing for biomarkers in stool

DNA markers in stool

When faeces pass a tumour during progression through the bowel, tumour cells or cell remnants are entrained. The excreted faeces therefore contain tumour DNA, which can be detected by testing. A faecal test method for the detection of mutated *K-RAS* was reported as long ago as 1992.[313] Tests for mutations of *p53* and *APC* [314-316] and of MSI followed later.[317,318] Most of the reported studies involved combination testing, with colorectal cancer sensitivities of between 20 and 73 per cent at specificities of 96 to 98 per cent.[319-321] Better test characteristics have so far been reported only on the basis of relatively small series.[322]

An alternative technique involves testing for a particular type of change in DNA methylation: the development of promoter hypermethylation. Such testing is technically more straightforward than the DNA test techniques referred to above. Numerous genes are known to frequently exhibit promoter hypermethylation in colorectal cancer patients.[323] Various of these genes have been tried as individual faecal DNA test markers. In these trials, sensitivities of 42 to 94 per cent for colorectal cancer and 31 to 100 per cent for advanced adenomas have been recorded, with a specificity of 86 to 100 per cent.[324-329] Combination tests achieved sensitivities of 75 to 96 per cent for colorectal cancer and 55 to 74 per cent for adenomas, with a specificity of 63 to 96 per cent.[330-332]

In the Netherlands, a number of studies are in progress. With individual markers, sensitivities of 67 to 97 per cent have been recorded for colorectal cancer, at a specificity of 87 to 94 per cent.[333,334 335-338] A combination test had a sensitivity of 12 per cent for advanced adenomas and 86 per cent for colorectal cancer, at a specificity of 96 per cent.[339] These findings are being validated in the context of DeCoDe (see subsection 3.5).

RNA markers in faeces

Faecal RNA has also been investigated as a possible colorectal cancer biomarker. The sensitivity and specificity reported were within the range recorded in the DNA tests.[332,340-343] In addition, when microarrays were used to study marker combinations in small series, the sensitivity recorded for stage I-III tumours was 78 per cent at a specificity of 100 per cent.[344-346]

Protein markers in faeces

iFOBT is in fact a test for the presence of a protein (globin) in stool. Using the same principle, it should be possible to test for tumour-specific proteins. Although the performance of trial tests has generally been unsatisfactory,[347] a sensitivity of 93 per cent was achieved with MCM2, at a specificity of 100 per cent.[348] In another study, the sensitivity was between 82 and 88 per cent and the specificity 95 to 98 per cent.[349] These values are higher than those recorded for a single iFOBT, but were not derived from screening populations.

10.2 Testing for biomarkers in blood

DNA markers in blood

For many people, giving a blood sample is less inconvenient than providing a faecal sample. Furthermore, DNA is not broken down as quickly in blood as in faeces, and blood contains less PCR inhibitory factors. However, studies that used mutated DNA or *APC* in plasma as a biomarker recorded sensitivities of 50 per cent or less for colorectal cancer and found no evidence that the combination of markers improved sensitivity.[322]

Researchers have also investigated hypermethylation markers. With individual markers, a sensitivity of 69 to 93 per cent was recorded,[350,351] while the sensitivity of marker combinations was between 57 and 67 per cent, at a specificity of 90 to 99 per cent.[352,353]

RNA markers in blood

A lot of work has been done on the use of mRNA markers in blood, both for diagnostic purposes and for monitoring the course of the disease following treatment. The most commonly used method – reverse transcriptase PCR – is capable of detecting a single cancer cell amongst ten million other cells.[354] As free mRNA was thought to be unstable in blood, many studies focused on the isolation of mRNA from circulating tumour cells in whole blood, often in combination with enrichment methods.[355,356]

The sensitivity of mRNA markers for CEA, CK19 and CK20 varies considerably; the figures recorded for marker combinations are between 60 and 89 per cent.[357,358] The specificity was found to range from 78 to 100 per cent. However, when IBD patients were used as control subjects, the specificity was much lower.[357] The analysis of mRNA from various genes in blood has led to the iden-

tification of new gene combinations that can be used as colorectal cancer markers.[359-362] However, there is no overlap between the various gene combinations and further validation is required.

Protein markers in blood

Carcino-embryonic antigen (CEA) and carbohydrate antigens (CAs, in particular CA19-9) are not recommended for screening because of the low sensitivity of these markers. Values in excess of 50 per cent have been achieved only in CRC patients with metastases.[363] Better results have been obtained with other single protein markers, such as sCD26 (90 per cent sensitive and specific),[364] α-defensin (69 per cent sensitive, 100 per cent specific),[365] laminin (89 per cent sensitive and specific),[366] and TIMP-1 (60 per cent sensitive, 98 per cent specific).[367] Further validation is awaited. TIMP-1 is currently being validated in a prospective study including five thousand people who underwent colonoscopy.[368]

Sensitivity and specificity figures of more than 90 per cent have been reported for mass spectrometer protein profiling (proteomics).[369-372] For people with or without 'large' adenomas, this technique has been shown to have a sensitivity of 78 per cent at a specificity of 53 per cent.[373]

10.3 Conclusion

Encouraging progress is being made with the development of molecular biomarkers, but they do not yet constitute a realistic alternative to iFOBT. There are numerous candidate biomarkers. The development of practical tests will require the involvement of companies capable of marketing the tests. In practice this means that further development work will focus exclusively on markers over which intellectual property rights have been secured.

It is reasonable to believe that, in the long term, a screening programme could be enhanced by the use of molecular markers. Before that can happen, however, large-scale validation studies are required, in order to compare candidate tests directly with iFOBT.[37] Such studies can be undertaken efficiently in the context of ongoing screening activities.

Chapter 11

Desirability of screening for colorectal cancer and selection of a screening method

11.1 Desirability of screening

In sections 5 to 10, the Committee considered whether screening for colorectal cancer satisfied the criteria for justifiable screening. The outcome of the Committee's deliberations is as follows. Colorectal cancer is a serious disease and an important health problem. If the disease is detected early, a person's chances of survival are much greater than if it is detected at a later stage (section 5). Colorectal cancer is preceded by a prolonged precancerous condition, called adenoma, which is relatively easy to detect and treat. If an adenoma has progressed to carcinoma, it is an average of nearly seven years before the disease becomes symptomatic.[41] These two facts mean that colorectal cancer is a good 'candidate' for screening. There is good evidence that gFOBT screening can reduce colorectal cancer mortality. There are various early detection methods for colorectal cancer, each of which has its own advantages and disadvantages. Pilot trials have shown that screening for colorectal cancer screening (particularly iFOBT screening) is acceptable to the Dutch population. The natural history of the disease is adequately understood and there is an agreed policy on whom to treat as patients. Furthermore, FOBT screening is demonstrably cost-effective. On the other hand, the manpower and facilities for diagnosis and treatment are not currently sufficiently well developed to cope with the volume of referrals that a national screening programme would generate.

The Committee has therefore concluded that screening is desirable, provided that the necessary follow-up care capacity can be built up in the years ahead (see subsection 14.8).

11.2 Screening test selection

It is important to ascertain which screening test would yield the greatest benefit, in terms of life years gained. Table 4 summarises the forecast performance and outcomes of five test methods, in the context of a single screening round. The forecasts are based on the following assumptions (the bases of which are described in sections 6 to 8):

- prevalence of advanced adenomas: 6.7 per cent
- prevalence of bowel cancer: 0.77 per cent
- referral compliance 90 per cent.

Colonoscopy is the most sensitive means of detecting colorectal cancer, but is not regarded by the Committee as currently suitable for use as a screening method outside a scientific setting. It will take many years of research to quantify the effect of colonoscopy screening on colorectal cancer mortality and the added value of the technique relative to iFOBT. Uncertainty regarding the participation rate (which is not expected to exceed 30 per cent), the complication rate and the capacity implications also argues against using colonoscopy as a primary screening method.

CT colography is almost as sensitive for colorectal cancer and ‘large’ polyps as colonoscopy, but it is less burdensome for the subject and entails considerably less risk of serious complications. On the other hand, nothing is known about the associated participation rate, there is no evidence of its effectiveness as a screening method and it implies the subject’s exposure to radiation.

gFOBT testing is the only screening method whose effectiveness has been demonstrated. However, the sensitivity of the test and the associated participation rates are somewhat discouraging.

The results of randomised Pilot trials in Nijmegen, Amsterdam and Rotterdam showed convincingly that participation and yields were substantially higher with iFOBT screening than with gFOBT screening. The Committee consequently expects that iFOBT screening would be significantly more effective as a means of both preventing colorectal cancer and reducing the mortality associated with it. Although there is no direct evidence to support this expectation, the two test methods are based on the same principle (the detection of blood traces in faeces) and have been directly compared in the context of RCTs. Furthermore,

the costs of the two forms of screening are very similar. Although iFOBT screening requires more follow-up colonoscopies than gFOBT screening, the former is more cost-effective (subsection 12.1).

As an alternative to iFOBT screening, the Committee considered the merits of sigmoidoscopy screening once every five or ten years. Sigmoidoscopy screening is practicable if sufficient capacity is available,[32] is likely to have a favourable cost-effectiveness ratio and can serve as an adequate means of early detection, assuming that the results of screening trials in England and Italy are as positive as expected and that the participation rate is significantly higher than 30 per cent. The difference between the rates of participation associated with iFOBT and sigmoidoscopy screening is such that screening based solely on sigmoidoscopy is not an desirable option in the Netherlands.

The data in Table 4 take no account of differences in screening interval and therefore underestimate the effect of biennial iFOBT screening, relative to that of sigmoidoscopy performed every five or ten years. iFOBT screening every two years will of course lead to the detection of more cases of cancer and advanced adenoma than would be picked up in a single round, thus increasing the (programme) sensitivity. After two or three rounds, the sensitivity for colorectal cancer is likely to be 80 to 90 per cent (subsection 6.2.2). This means that the programme sensitivity of biennial iFOBT screening would be greater than that of five or ten-yearly sigmoidoscopy. Modelling suggests that, given a participation rate of 60 per cent (scenario 4 in Table 12), biennial $iFOBT_{75}$ screening would prevent 1428 colorectal cancer deaths a year (thirty-year average). For every colorectal cancer death prevented, 785 people would need to complete an iFOBT and forty would need to undergo colonoscopy.

Table 4 The forecast performance and outcomes of five test methods, in the context of a single round of screening. Percentages.

Screening method	Sensitivity for advanced adenomas	Sensitivity for CRC	PVV for advanced adenomas	PVV for CRC	Complication rate without colonoscopy	Complication rate incl. colonoscopy	Pick up rate
Colonoscopy	>90	97	6,7	0,8	0.1	n.v.t.	20-25?
CT colonography	>90	97	40-67, depending of referral size	5-9, depending of referral size	very low (< 0.00005)	0.02	35?
gFOBT	12	20	41	10		0.006	47
$iFOBT_{75}$	27	65	40	8		0.017	60
Sigmoidoscopy	55	60	79	6	0.002	0.026	30

One drawback of screening for cancer is overdiagnosis. Although the overdiagnosis risk associated with breast and colorectal cancer screening is substantially smaller than that associated with, for example, prostate cancer and neuroblastoma screening,[43,374] the introduction of colorectal cancer screening would result in more cases of colorectal cancer being detected the first ten years than would otherwise have come to light. A peak of +25 per cent would be reached in years 4 and 5, but modelling indicates that the increase will be entirely offset by a reduction in incidence in the next two decades (Table 14). It is nevertheless the case that screening will inevitably lead to colorectal cancer being detected in some people who, without screening, would have died of something else before their colorectal cancer became symptomatic. However, adenoma removal following positive iFOBT test results is liable to entail significantly higher rates of overdiagnosis and overtreatment, because by no means all adenomas are malignant. On the other hand, it should be noted that – unlike, say, prostate cancer treatment – adenoma removal is a fairly minor intervention, which involves comparatively little risk of complications.

Furthermore, it appears that iFOBT screening is more selective than colonoscopy or sigmoidoscopy in terms of picking up precursers with a high malignancy risk. There is evidence to suggest that the removal of large adenomas has a particularly marked impact on the incidence of colorectal cancer.[107] Roughly 60 per cent of people with adenomas detected through iFOBT screening have large adenomas,[27,165] compared with about 25 per cent of those picked up through endoscopy screening.[49,51,145,157,158,163,193,199]

The rates of overdiagnosis liable to result from colorectal cancer screening cannot currently be quantified accurately. However, the scale of any such problems is likely to be small in comparison with the benefits of screening, provided that the surveillance guidelines (see subsection 14.6) promote an appropriate level of caution.

Tabel 5 The relative merit of the six screening methods.

	gFOBT	$iFOBT_{75}$	Sigmoidoscopie	Colonoscopy	CT colonography	Molecular markers
Attendance	+	++	-	?	?	?
Evidence	++	+	±	±	±	±
Test performance	±	++	++±	++	++	+
Less burdensome	+	++			±	+
Less risk	++	++	+		+	++
Cost-effective	+	++	+?	+?	?	?
Less colonoscopy capacity needs	++	+				?

Table 5 shows, by means of plus and minus signs, the relative merit that the Committee attaches to the various screening methods. Taking simplicity, acceptance, test characteristics and safety into account, the Committee considers iFOBT testing to be the most appropriate method of screening for colorectal cancer.

11.3 Susceptibility to foreseeable developments

The Minister asked which new methods were likely to be suitable for use in a national bowel screening programme within five to seven years. This is a pertinent question, because it is important to have an idea of how any screening infrastructure is liable to be affected by foreseeable developments.

The Committee does not expect colonoscopy or colonography screening trials to yield significant insight into the effectiveness of these methods within ten years. Even if promising candidate molecular test methods are available within five years, it will take at least another five years before any advantage that they may have over iFOBT can be demonstrated. It would not be appropriate to introduce a new screening test until its superiority to the existing test had been demonstrated in randomised trials,[37] which could be organised in the context of the screening programme.[10,124,375] Furthermore, modelling would need to show that the new test was more efficient than iFOBT screening.

If the conditions described above were met, a new test could be introduced within the existing infrastructure, since various key elements of a colorectal cancer screening programme – such as a call/recall system and colonoscopy capacity – would be test-independent. The Committee does not anticipate that the colonoscopy capacity requirement would diminish significantly (resulting in overcapacity) following the initial rise brought about by the introduction of screening.

If the results of the sigmoidoscopy screening trials in England and Italy[29,30] (expected in 2010) confirm the mortality reductions simulated by MISCAN-Colon (as was the case with the provisional NORCCAP data[178] on incidence and colorectal cancer mortality), consideration could be given to investigating the feasibility of combining sigmoidoscopy screening with iFOBT screening and offering people the choice between the two methods. If the results of the feasibility study were positive, if a two-option programme appeared to be more effective and efficient than iFOBT screening on its own (see also subsection 12.1) and if the decision were taken to introduce a two-option programme, it would be neces-

sary to add screening centres to the existing infrastructure. Such a scenario does not imply any waste of capital expenditure, but changing over from the one approach to the other would be a major undertaking, given that the target group consists of 3.5 million people.

11.4 Conclusion

The Committee regards iFOBT testing as the most appropriate screening method and believes that an iFOBT screening programme would not be unduly susceptible to foreseeable developments. The Committee recommends designing the screening programme so that trials of potentially preferable test methods could be performed as flanking studies within the context of the operational programme.

In the following section, the Committee examines the cost-effectiveness of FOBT screening and puts forward more detailed proposals regarding the screening strategy.

Chapter 12

Cost-effectiveness and screening strategy selection

12.1 Cost-effectiveness

The cost and effects of screening for colorectal cancer in the Netherlands have been calculated using the MISCAN-Colon computer model. MISCAN-Colon was developed by the ErasmusMC in collaboration with the US National Cancer Institute.[376,377] It is a micro-simulation model for the simulation of individual life histories from birth to death, including, where relevant, the development of colorectal cancer. A life history is simulated first assuming that no screening system is in place, and again assuming that there is such a system. The economic impact of screening is ascertained by comparing the costs associated with each situation.

Cost-effectiveness analyses have been performed for gFOBT (HCII) and iFOBT (OC-Sensor); the cost-effectiveness of iFOBT screening was calculated assuming various positivity thresholds: 50, 75, 100, 150 and 200 ng/ml. Provisional calculations have also been made for sigmoidoscopy screening.

Model assumptions

The simulated screening strategies are all assumed to run for thirty years, but to differ in terms of programme entry age (45, 50, 55 and 60 years), programme exit age (70, 75 and 80 years) and screening interval (one, one and a half, two and three years). The year 2005 is used as the basis for simulation of the no-screening

Tabel 6 Model assumptions in MISCAN-Colon.

Variable	Baseline conditions	Sensitivity analysis	
Discount rate	3 per cent, for costs and health effects	4 per cent for costs and 1,5 per cent for years of life gained	
Burden of screening	No	2 hours for FOBT en 2 days for colonoscopy	
Sensitivity correlated	No	74 per cent of advanced adenomas does not bleed and is not detectable by FOBT	
		low	high
Fatal complication rate of colonoscopy	1 per 10,000)	0	1 per 1,000 with lesion, 1 per 10,000 with no lesion
FOBT costs	See table 8	50%	200%
Colonoscopy costs	€303 with no polypectomy €393 with polypectomy	50%	200%
Costs of complications after colonoscopy	1,250 euro (2,4 euro per 1,000 colonoscopies)	50%	200%
Treatment costs	See table 9	50%	200%

scenario, which is assumed to change subsequently only under the influence of demographic developments. In the no-screening scenario, no allowance is made for possible trends in, for example, incidence and treatment. The differences in costs and effects are projected forwards over a period of a hundred years; hence almost the entire 2005 population is followed until death.

Each overall cost figure (Tables 7 to 9) is the sum of the costs associated with the following: organisation, screening, diagnosis (colonoscopy, pathology) and treatment for colorectal cancer. The organisational costs (Table 8) comprise overhead costs and call-up costs, as extrapolated from the existing cervical cancer screening programme, following correction for the characteristics of FOBT screening. The cost of screening incorporates the cost of the test itself (including analysis) and the cost of colonoscopy following a positive FOBT result. The basic analysis does not take account of the benefits of scale likely to accrue from expansion of the programme into a nationwide operation. Allowance has been made, however, for colonoscopies that, according to the existing guidelines[54], are required for the surveillance of people diagnosed with adenomas. Wherever possible, the screening cost figures are based on the actual costs recorded in COR-ERO-I. The treatment costs (Table 9) have been calculated from diagnosis-treatment combination tariffs. An annual discount rate of 3 per cent has been applied to both costs and effects.

The sensitivity of gFOBT for colorectal cancer (Table 7) has been calculated using a model calibrated against the screening trials in Funen, Nottingham and Minnesota.[41] The other test characteristics of gFOBT and iFOBT associated with various positivity thresholds have been defined in line with published data and the findings of the Dutch Pilots (Table 10). More specifically, the average sensitivity of $iFOBT_{100}$ for colorectal cancer is put at 70 per cent, while that of HCII is assumed to be 40 per cent (optimistically reflecting the published figures).[118] The overall sensitivity of a test method is broken down into a low-sensitivity figure (expressing the sensitivity for early preclinical cancer) and a higher-sensitivity figure (expressing the sensitivity for colorectal cancer in the final phase before it becomes clinically manifest). The ratio between the two is assumed to be as estimated for HCII (i.e. 18:51).[41] Table 10 shows that the yields predicted by the model on the basis of these sensitivity assumptions are consistent with the yields observed in the three Dutch Pilots. In addition to the basic analysis, a sensitivity analysis was performed to establish how sensitive the cost-effectiveness calculations are to the influence of certain assumptions.

Years of life saved are not corrected for quality of life, because almost no relevant research data are available.[379] It is important to recognise that the prevention of colorectal cancer mortality and the prevention of colorectal cancer metastasis go hand in hand. In view of the seriousness of metastasised disease, a reduction in colorectal cancer mortality implies a major positive effect on quality of life.

Tabel 7 Assumed values for sensitivity and specificity of gFOBT and iFOBT with various referral thresholds (ng/ml). Percentages.

Test	Specificity (per person)	Sensitivity (per lesion)				
		CRC long before becoming clinical	CRC short before becoming clinical	Adenoma $\geq$ 10 mm	Adenoma 6-9 mm	Adenoma $\leq$ 5 mm
gFOBT	98.9	18.2	50.8	6.5	1.3	0
$iFOBT_{200}$	98.7	46.0	80.0	10.6	2.0	0
$iFOBT_{150}$	98.3	47.0	81.0	12.2	2.3	0
$iFOBT_{100}$	97.8	51.0	83.0	13.0	4.0	0
$iFOBT_{75}$	97.0	56.0	85.5	15.2	4.1	0
$iFOBT_{50}$	95.8	61.0	88.0	16.7	8.4	0

Tabel 8 Costs of screening. Euros.

Test	Per invitation		Per participant	Total costs per invitation (with realistic pick up)
	Test	Organisation[a]	Analysis	
gFOBT (HCII)	2.82	11.23	1.90	15.19[b]
iFOBT (OC-Sensor)	1.24	13.61	4.37	17.48[b]

[a] The difference between iFOBT en gFOBTare caused by higher postage costs for iFOBT.
[b] Total costs are lower than the aggregate of the items, taking into account a realistic pick up rate.

Tabel 9 Treatment costs. Euros.

Stage	Initial costs	Continuous (per year)	Terminal care, cause of death CRC	Terminal care, other cause of death	Total average treatment costs per diagnosis[a]
I	12,500	340	17,500	4,400	20,700
II	17,000	340	17,500	4,000	23,300
III	21,000	340	18,500	5,200	27,000
IV	25,000	340	25,000	14,000	24,000

[a] corrected for survival,by age

Tabel 10 Modelled (observed) values for test positivity and detection rates per 100 screened individuals for gFOBT en iFOBT with various cut-off values (ng/ml).

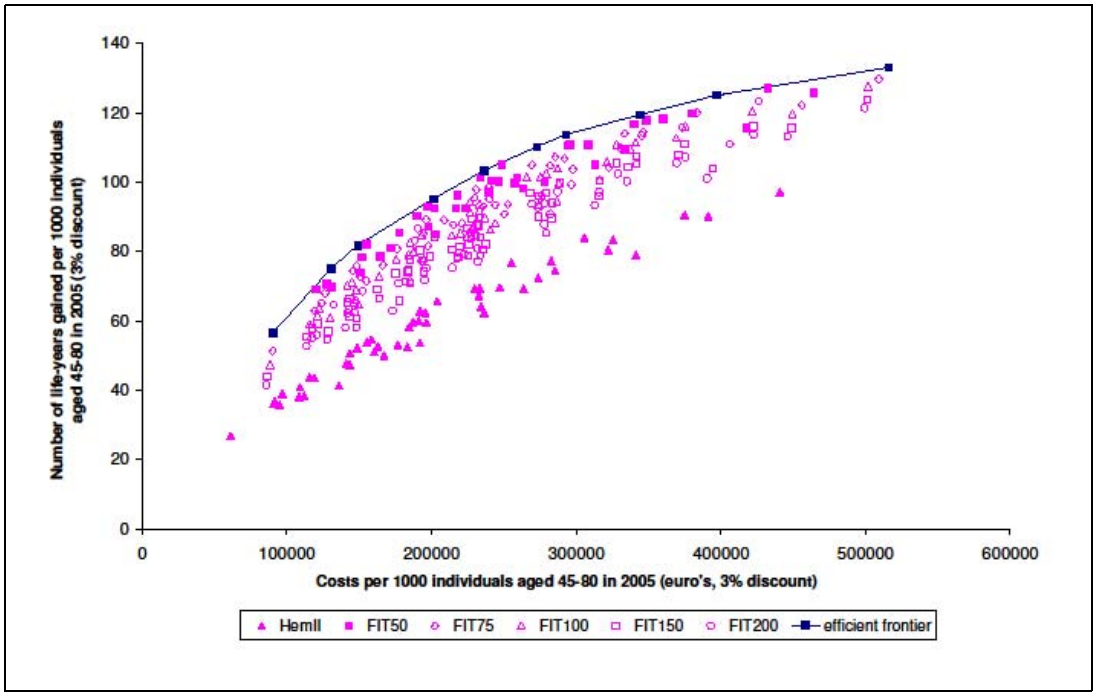
Test	Positivity rate	No adenomas or CRCr	Detection rate for CRC	Detection rate for advanced adenomas	Detection rate for non-advanced adenomas
gFOBT	2.5 (2.5)	98.5 (98.5)	0.20 (0.24)	0.98 (0.97)	0.35 (0.33)
$iFOBT_{200}$	3.7 (3.7)	97.6 (97.6)	0.39 (0.39)	1.54 (1.54)	0.48 (0.48)
$iFOBT_{150}$	4.4 (4.4)	97.2 (97.2)	0.40 (0.40)	1.78 (1.82)	0.59 (0.58)
$iFOBT_{100}$	5.3 (5.3)	96.8 (96.8)	0.42 (0.42)	1.98 (2.01)	0.83 (0.80)
$iFOBT_{75}$	6.4 (6.4)	96.3 (96.3)	0.45 (0.45)	2.30 (2.27)	0.99 (1.02)
$iFOBT_{50}$	8.4 (8.4)	95.2 (95.3)	0.48 (0.48)	2.73 (2.71)	1.57 (1.54)

Results

From Figure 2 it will be apparent that, in all the simulated scenarios, iFOBT dominates (is well ahead of) gFOBT. In other words, iFOBT screening is more effective than gFOBT screening at a similar or lower cost. Screening did not prove to be a cost-saving activity in any of the scenarios examined (based on treatment costs in 2005). In all the simulated iFOBT scenarios, a positivity threshold of 50ng/ml proved to be more cost-effective than any higher threshold (Figure 2). $iFOBT_{50}$ is more cost-effective than a strategy based on a wider age range (than sixty to sixty-nine) or a test interval of less than three years. As one might expect, each further intensification (each widening of the age range or each reduction of the screening interval) reduces cost-effectiveness, because the 'effect gain' is progressively smaller. Table 11 shows the various screening intensification options in order of cost-effectiveness. The option with the lowest cost per life year saved is screening people aged between sixty and seventy (Table 11, scenario 1); next comes lowering the programme entry age to fifty-five (scenario 2); then raising the exit age to seventy-five (scenario 4). It is therefore more cost-effective to screen people between the ages of seventy and seventy-five than people aged fifty to fifty-five. The number of life years saved by screening fifty to fifty-five-year-olds is smaller than the number saved by screening seventy to seventy-five-year-olds. The age range recommended by the Council of Europe (fifty to seventy-five) is not the most cost-effective option.

If the participation rate per screening round is 60 per cent, the programme will be about as cost-effective as if the rate were 100 per cent (results not shown). This is because the screening costs associated with non-participants are offset by the saving associated with a longer average screening interval (which results from people sometimes skipping a round). In consequence, strategies based on relatively short intervals are advantageous. The fact that not everyone adheres to the recommended schedule does not justify recommending a suboptimal schedule for the target group as a whole. When defining the optimal strategy, it is therefore better to work on the assumption that people *do* present for screening at the recommended interval (Table 11).

The cost-effectiveness of each schedule is expressed in terms of the extra cost per additional life year saved, relative to the 'previous step' in screening intensity: the incremental or marginal cost-effectiveness ratio (ICER). For the biennial screening of people aged fifty-five and seventy-five (Table 11, scenario 4) the ICER – relative to scenario 3 – is EUR 3900. If the age range is widened to fifty to eighty, the ICER is EUR 5,800; a further intensification (scenario 10) increases it to EUR 14,900.



HemII = Hemoccult II; FIT50 = $iFOBT_{50}$; FIT75 = $iFOBT_{75}$; FIT100 = $iFOBT_{100}$; FIT150 = $iFOBT_{150}$; FIT200 = $iFOBT_{200}$.

Figure 2 Costs and effects per 1,000 individuals aged 45-80 in 2005.

When the efficiency of preventive programmes is assessed in the Netherlands, an ICER ceiling of EUR 20 000 is usually applied. In other words, the figures cited in the last paragraph are within the generally accepted limits.

The Committee has reservations about a positivity threshold of 50 ng/ml, certainly in the introductory phase (see 12.2). If $iFOBT_{50}$ is excluded from the cost-effectiveness analysis, the optimum schedules are almost the same, but based on $iFOBT_{75}$ testing (Table 12).

Table 11 Results of efficient FOBT-programmes (100 per cent attendance). All ten scenarios are with $iFOBT_{50}$ (gFOBT and iFOBT with higher cut-off values than 50 ng/ml are dominated).

Nr	Age range, interval (years), # screens	Costs per thousand individuals aged 45-80 in 2005 (euros)*	Years of life gained per thousand individuals aged 45-80 in 2005[a]	ICER* (euro per life year gained)	Total costs per year in the Netherlands (million euros)[b]	#deaths saved per year in the Netherlands	Average cost effectiveness[c] (euros per per life year gained)
1	60-69, 3, 4	91,000	57	1,600	6.5	1,420	1,600
2	55-70, 3, 6	131,000	75	2,200	11.7	1,780	1,700
3	55-73, 3, 7	149,000	82	2,800	15.1	2,040	1,800
4	*55-75, 2, 11*	*201,000*	*95*	*3,900*	*23.9*	*2,420*	*2,100*
5	55-74,5, 1.5, 14	237,000	103	4,300	31.5	2,580	2,300
6	55-79, 1.5, 17	273,000	110	5,300	39.9	2,890	2,500
7	50-80, 2, 16	293,000	114	5,800	45.2	2,900	2,600
8	50-80, 1.5, 21	344,000	119	8,900	55.4	3,030	2,900
9	45-79.5, 1,5, 24	397,000	125	9,400	67.3	3,040	3,200
10	45-80, 1, 36	516,000	133	14,900	96.7	3,230	3,900

[a] discount rate 3%; ICER: incremental cost-effectiveness ratio
[b] discount rate 0%
[c] compared to no screening

Table 12 Results of efficient FOBT-based programmes, omitting $iFOBT_{50}$ (100 per cent attendance). All ten scenarios are $iFOBT_{75}$-based.

Nr	Age range, interval (years), # screens	Costs per thousand individuals aged 45-80 in 2005 (euros)*	Years of life gained per thousand individuals aged 45-80 in 2005[a]	ICER* (euro per life year gained)	Total costs per year in the Netherlands (million euros)[b]	#deaths saved per year in the Netherlands	Average cost effectiveness[c] (euros per per life year gained)
1	60-69, 3, 4	90,000	51	1,800	10	1,290	1,800
2	55-70, 3, 6	126,000	68	2,200	15	1,600	1,900
3	55-69, 2, 8	148,000	76	2,800	17	1,750	1,900
4	*55-75, 2, 11*	*196,000*	*89*	*3,600*	*27*	*2,270*	*2,200*
5	55-74,5; 1,5; 14	231,000	98	4,000	35	2,450	2,400
6	55-79, 1,5, 17	270,000	105	5,400	44	2,770	2,600
7	50-80, 2, 16	285,000	107	6,900	48	2,760	2,700
8	50-80, 1,5; 21	333,000	114	7,200	57	2,930	2,900
9	45-79,5; 1,5; 24	384,000	120	8,200	68	2,940	3,200
10	45-80, 1, 36	509,000	130	13,000	100	3,170	3,900

[a] discount rate 3%; ICER: incremental cost-effectiveness ratio
[b] discount rate 0%
[c] compared to no screening

Sensitivity analysis

First of all, the sensitivity analysis took account of the inconvenience of screening and the correlation between test results in successive screening rounds (if an advanced adenoma is missed once, the risk of it being missed again next time is greater). In addition, different assumptions were made regarding the cost and the risk of complications following colonoscopy (Table 6).

A positivity threshold of 50 ng/ml remains attractive, regardless of the alternative assumptions made. If the cost of colonoscopy is twice as high as assumed in the basic scenario, the programme is cost-effective not only using a positivity threshold of 50 ng/ml, but also with a threshold of 75 or even 100 ng/ml.

The EUR 20,000 ceiling is not broken until the frequency of screening is raised to once a year *and* a number of revised assumptions are made, particularly that each colonoscopy will mean two lost life days and each iFOBT two lost hours, or that the cost per iFOBT or per colonoscopy is double that assumed for the basic analysis. Even when the discount rates are set at 1.5 and 4 per cent and the screening interval is one year, the ICER associated with these assumptions is less than EUR 20,000.

Reducing the assumed initial cost of treating a patient with stage I cancer by 25 per cent has no effect on which strategies work out the most cost-effective. The cost falls – because the patients in question can be treated endoscopically and the ICER becomes more favourable: for biennial screening, EUR 3,500 if the age range is fifty-five to seventy-five and EUR 5,100 if it is fifty to eighty. With more intensive schedules, the influence on the ICER reduces. Hence, the cost-effectiveness of annual screening between the ages of forty-five and eighty remains the same.

The treatment costs (2005, Table 9) have been estimated conservatively: it is assumed that the cost of treating a stage III-IV patient is only EUR 3,000 to EUR 7,000 higher than the cost of treating a stage I patient, even though the use of chemotherapy to treat metastasised colon cancer is increasing sharply. In the south-east of the Netherlands, chemotherapy use for patients under the age of seventy rose from 24 per cent in the period 1990 to 1994, to 58 per cent in the period 2000 to 2004; its use for older patients went up from 2 to 23 per cent.[82] A French study of the direct medical costs of treating 384 colorectal cancer patients in 2004 put the initial cost at EUR 17,596 for stage I and EUR 35,059 for stage IV.[380] Furthermore, treatment costs for stage III and IV patients have risen enormously since then. The increased cost of treatment means that screening is more cost-effective than the figures quoted here suggest.

Even if it is assumed that *all* actual treatment costs are double those presented in Table 9, annual screening of people aged fifty to eighty has an ICER of less than EUR 20,000. If one assumes that only the cost of treating advanced cancer is higher than assumed in the basic analysis (i.e. that the initial cost of treating stage IV cancer is twice as high, that the initial cost of treating a stage III case is the same as that of treating a stage IV case, and that the cost of terminal treatment for those who ultimately die from colorectal cancer is twice as high), biennial iFOBT screening actually becomes cost-saving.[377]

If the discount rates are revised to 1.5 and 4 per cent,[378] the ICER for biennial $iFOBT_{50}$ screening of people aged 55-75 works out at EUR 2,600; if the age range is widened to fifty to eighty, the ICER is EUR 4,100.

Assuming that people at elevated familial risk do not participate in screening, but that the existing CBO guidelines are followed, both the cost and the effects of the screening programme diminish: biennial screening of people aged fifty-five to seventy-five results in an ICER of EUR 3,700 (compared with EUR 3,900). The same strategies remain the most cost-effective.

If unrelated medical costs incurred during saved years of life are taken into account, the CER (compared with no screening) works out around EUR 4,000 higher, at EUR 6,200.[381] However, even this figure is significantly lower than that for cervical cancer screening (EUR 11,300 before unrelated medical costs are taken into consideration).[382]

Colonoscopy capacity

Once a screening strategy has been defined (subsection 12.2), the introduction of screening and the associated demand for colonoscopy capacity needs to be matched with the existing capacity and the capacity that will come on line in the future. To ensure that the capacity need does not exceed the supply, consideration should be given to initially restricting screening to a fairly narrow age range, using a longer interval or applying a higher positivity threshold value to iFOBT test results.[383] These options are examined in more detail in subsections14.8 and 14.9.

Conclusions

Modelling supports the following conclusions:

- FOBT screening in the Netherlands would have a favourable CER
- iFOBT would be more effective and more cost-effective than gFOBT
- The optimum cut-off value for colonoscopy referral is 50 ng/ml (OC-Sensor)

- Biennial screening of people aged fifty-five to seventy-five would have a favourable cost-effect ratio (EUR 2,200 per life year saved); such screening would be more cost-effective than other cancer screening programmes in the Netherlands, such as the cervical cancer screening programme (EUR 11,300 per QALY).

Provisional cost-effect analysis of sigmoidoscopic screening

In 2010, the results are expected of randomised trials set up to determine the effect of sigmoidoscopy screening on colorectal cancer mortality and incidence.[29,30] In anticipation of the findings, the cost and effect of sigmoidoscopic screening in the Netherlands have been forecast using MISCAN-Colon. Because the only data from the trials currently available are the initial results of the NORCCAP trial,[178] the forecasts were necessarily based on provisional calculations. The MISCAN-Colon predictions are consistent with the NORCCAP results.

The model output indicates that, if people aged fifty-five to seventy-five received sigmoidoscopic screening every five years, the reduction in colorectal cancer mortality associated with 100 per cent participation would be 34 per cent; the reduction associated with 30 per cent participation would be 11 per cent. For $iFOBT_{50}$ screening, the reduction related with full participation works out lower (23.5 per cent), but the reduction likely to result from a realistic participation rate (60 per cent) is higher (17 per cent). The corresponding figures for $iFOBT_{75}$ (22 and 15 per cent) show a similar pattern.

The ICER for sigmoidoscopic screening – calculated by comparing screening every five years between the ages of fifty-five and seventy-five with screening every five years between the ages of fifty-five and seventy (the next most efficient regime) – is EUR 3,700 at 100 per cent participation, or EUR 5,200 at a realistic participation rate of 30 per cent. The ICER for biennial $iFOBT_{50}$ screening is EUR 3,900 at 100 per cent participation, or EUR 3,600 at 60 per cent participation. The ICER for sigmoidoscopy screening rises as the participation rate falls because the implications of people missing an occasional round of screening are much greater and the associated treatment costs much higher. With iFOBT screening, the ICER remains very similar at a lower participation rate, because the cost of screening is lower.

When interpreting the model output, it is important to bear three points in mind. First, the results of the screening trials are not yet available. Hence the size of the effect is not yet known. The model assumption that it takes twenty years for a

detectable adenoma to become malignant is based on expert opinion. Because the effect data are uncertain, any cost-effectiveness analysis based upon them must also be uncertain. The conclusions ultimately drawn will to a significant extent be shaped by the influence that the unpleasantness of the screening test and the follow-up examination (colonoscopy) is assumed to have on potential participants.

Second, participation in sigmoidoscopic screening was roughly 30 per cent in CORERO-I, whereas participation in iFOBT screening (CORERO-I, FOCUS) was about 60 per cent. The considerably higher level of participation, coupled with the fact that iFOBT screening is particularly cost-effective, means that iFOBT screening should be made available regardless of what is decided concerning sigmoidoscopy screening. So the latter could only be made available alongside iFOBT screening (as an option). From the cost-effectiveness perspective, this would not present a problem, although sigmoidoscopy screening is less cost-effective than iFOBT screening.

Furthermore, a multi-option programme does entail logistic challenges, for which possible solutions should be validated before any commitment is made. It is also worth noting that we currently have no evidence that implementing a multi-option programme would result in higher participation or increase the effectiveness of screening. In an Italian trial, participation amongst subjects given a choice between iFOBT and sigmoidoscopy was no higher than amongst those offered iFOBT only.[182] The findings of trials in Australia confirm this picture.[122,243] In a French trial, subjects were first invited to complete gFOBT screening and the acceptance rate was 57 per cent.[199] When sigmoidoscopy was subsequently offered to those who had not participated, only 2 per cent took up the offer. It is not known whether there is any value in making sigmoidoscopy available to people who have had a iFOBT test that proved negative.

Third, the additional endoscopy capacity that sigmoidoscopy screening would necessitate needs to be taken into account when considering the desirability of this form of screening. If 30 per cent of the target group were to opt for sigmoidoscopy, the annual number of sigmoidoscopies required in the years ahead would rise to more than 230,000.

12.2 Screening strategy

Viewed against the background of the published research data, what do the findings of the modelling exercise imply for the screening strategy?

Positivity threshold

Italian researchers have advised against using a higher positivity threshold than the 100 ng/ml recommended by the manufacturer of OC-Sensor.[132,133] With $iFOBT_{200}$ screening, the positivity rate proved to be half that associated with $iFOBT_{100}$, but one sixth of colorectal cancers and nearly half of advanced adenomas were liable to be missed.[133] The Dutch trial findings confirm that the increase in specificity is outweighed by the loss of sensitivity (Table 3).[202,384]

From the cost-effectiveness viewpoint, 50 ng/ml is the optimum positivity threshold (see subsection 12.1). The Committee nevertheless has reservations about the desirability of using such a low positivity threshold, particularly in the introductory phase. Some 8.4 per cent of people participating in $iFOBT_{50}$ screening would require referral. For the people concerned, referral implies undergoing an unpleasant procedure that entails a risk (albeit a small one) of serious complications; for the system, it implies considerable pressure on the available colonoscopy capacity. The data presented in Table 3 show that lowering the positivity threshold from 75 to 50 ng/ml would mean a sharp (more than 30 per cent) increase in positive test results, from 6.4 to 8.4 per cent. From the Table, it is also apparent that $iFOBT_{75}$ is capable of detecting nearly all (93 per cent) of the cases of colorectal cancer that would be picked up by means of $iFOBT_{50}$ screening. With such a low positivity threshold, it is reasonable to assume that most of the undetected cases of colorectal cancer would involve early-stage tumours, which would probably be picked up in a later round of screening, while still at a relatively early stage of development.[155] A lower positivity threshold has more effect on the detection of advanced adenomas than on the detection of colorectal cancer.[385,386]

Studies conducted in other countries amongst patients referred for colonoscopy confirm the belief that the optimum positivity threshold is 75 ng/ml.[145,148]

The Committee provisionally recommends adopting a positivity threshold of 75 ng/ml.

Number of faecal samples

Is it best to use a single faecal sample, or several? Japanese researchers assessed the performance of (Monohaem) iFOBT testing based on the analysis of one, two and three faecal samples, with all participants also undergoing colonoscopy.[159] The higher the number of samples analysed, the greater the sensitivity of the system for cancer, the respective figures being 56, 83 and 89 per cent. At the same

time, the specificity of the testing fell from 97 to 94 per cent. However, an Italian study involving the use of OC-Sensor failed to find any evidence that any one strategy was significantly superior to the others.[386] The participation rate amongst subjects asked to provide two faecal samples was 56 per cent, which is entirely normal in Italy. It is anticipated that, by the end of 2009, CORERO-II will yield additional information regarding variations between single-sample and two-sample screening, in terms of the rates of participation and detection.

For the time being, the Committee advises single sampling. This advice is motivated by the concern that any increase in sensitivity achieved through multiple sampling could be offset by lower levels of participation. In the context of biennial screening for gradually developing abnormalities, regular participation is likely to be more important than high test sensitivity.[386]

Screening interval

In the Minnesota trial, annual gFOBT screening was found to reduce colorectal cancer mortality by 33 per cent; with a screening interval of two years, the reduction was 20 per cent.[89] In an Italian study, the number of interval cancers (colorectal cancers developing in the interval between screening rounds, following a negative or false positive test) was observed to rise sharply in gFOBT screening. In the second year of the interval, the number was twice as high as in the first year.[112]

In iFOBT screening, however, the Italian researchers found no difference between the first and second years.[112] The greater the sensitivity of a test, the less advantage there is in having a shorter interval.[142] There is a paucity of data concerning interval cancer. Nakama calculated that the sensitivity of a single iFOBT declined as the test interval was increased from one to two and three years, from 90 per cent to 83, to 71.[387] The disadvantage of screening every year, as opposed to every second year, is that screening costs are almost doubled, while the desirable effects and savings increase by smaller amounts. In terms of cost-effectiveness, therefore, biennial screening is a more attractive option (see subsection 12.1).

Participants whose test results are positive and who subsequently receive high-quality colonoscopy, in the context of which no advanced neoplasms or only ‘small’ adenomas are detected, leading to their complete removal, do not require re-screening for ten years.[223,388]

The Committee recommends a screening interval of two years following a negative iFOBT test and ten years following a false positive iFOBT test and high-quality colonoscopy. In making this recommendation, the Committee has assumed that all participants will be advised to consult their GPs if they should experience problems.

Target group

Participants in the Nottingham and Funen trials were between forty-five and seventy-five at entry. Experts recommend that screening should start later in life, i.e. at the age of fifty or fifty-five.[128,389] In England and Finland, the target group for the national screening programme is people aged between sixty and seventy, at least for the time being.[10,11,390] In Scotland, however, the target age group is fifty to sixty-nine.[125]

The argument against screening people under the age of fifty-five is that the incidence of colorectal cancer in younger people is low. In the Netherlands, more than 90 per cent of all new cases involve people more than fifty-five years old. Researchers in Australia, Denmark and the UK found that it was more effective and more efficient to screen people aged seventy to seventy-five than those aged fifty to fifty-five.[12,128,391] This observation is supported by the MISCAN calculations (Tables 11 and 12).

Colorectal cancer incidence and mortality in men of a given age are comparable with the figures for women four to eight years older.[392] It has therefore been suggested that screening should start earlier in life for men. However, modelling suggests that the cost-effectiveness of a programme would not be improved by such a strategy.[393] The reason being that the greater risk of colorectal cancer in men is offset by their shorter life expectancy.

Deciding on an appropriate stop age for the target group is more difficult. Although colorectal cancer remains common in (unscreened) people aged 75+, this will change after the introduction of a screening programme; screening of a certain age group has a deferring effect in older age groups. Someone who, for example, was last screened at the age of seventy-five, is unlikely to develop colorectal cancer within ten years, particularly if he or she has had more negative tests results in the recent past.[174] The time that it takes for an adenoma to become malignant *and* cause health problems,[41] and simulation modelling indicate that there is little to be gained from continuing screening in persons aged 75. As people get older, comorbidity is increasingly influential. Men aged eighty have an

average life expectancy of seven years; the figure for women of the same age is nine years (http://statline.cbs.nl).

Along with cost-effectiveness, the Committee believes it is important to consider quality of life. However, there is a paucity of direct data. What is known is that endoscopy becomes more difficult as age increases.[394] The time from insertion into the rectum to identification of the base of the cecum takes longer, making the process more arduous for the subject. [395-399] Furthermore, the risk of complications is greater in older people.[249]

The Committee recommends that the target group for screening should be men and women between the ages of fifty-five and seventy-five. From the age of seventy-five, it is advisable for the desirability of screening to be decided on an individual basis, in consultation with a GP. If GPs refer older patients for screening as appropriate, there is no need for them to be systematically called up by the screening organisation.

12.3 Conclusion

iFOBT screening is preferable to gFOBT screening in terms of participation, effectiveness and cost-effectiveness. The optimum positivity threshold for colonoscopy is 50 ng/ml. In view of the limited colonoscopy capacity available, a positivity threshold of 75 ng/ml is desirable in the short term.

The Committee recommends a screening programme based on biennial single-sample $iFOBT_{75}$ testing of people aged 55-75. Assuming a participation rate of 60 per cent, such a programme could be expected to prevent an average of 1,428 colorectal cancer deaths a year. This is more than twice the number of deaths prevented by breast cancer screening and equates to EUR 2,200 per life year gained. Hence, colorectal cancer screening would be more cost-effective than other cancer screening programmes in the Netherlands, such as the cervical cancer screening programme (EUR 11,300 per QALY).[382]

Chapter 13

Acceptance and participation

The uptake is the primary determinant of effectiveness for a screening programme; the level of participation has a greater influence than the sensitivity of the screening test. Scientific research into participation in colorectal cancer screening has focused largely on the test options, with a view to identifying the test that supported the highest participation rate. However, the nature of the test itself is only one of the factors that influence acceptance and participation. A new screening programme requires an implementation strategy geared to the intended participants and the organisational arrangements. The implementation strategy adopted needs to take account of the various phases of a process of change: orientation, education, acceptance, change, and consolidation of change.[400] The potential participants have to be informed and involved (orientation); the target group can then be told about the advantages and disadvantages of participation (education) so that informed participation decisions may be made.

Increasing significance is attached to ensuring that participation decisions can be made freely.[35,401,402] One important factor influencing freedom of choice is adequate information. However, the conceptualisation and measurement of informed choice are at an early stage of development.[403-405]

In this section of the report, the Committee reviews the factors influencing participation in screening (particularly iFOBT screening) and in follow-up examination (colonoscopy). The section ends with a number of conclusions regarding participation and the education of prospective participants.

13.1 The screening test

Roughly half of the people invited to take part in gFOBT screening actually participate. The participation rate is therefore much lower than the rates achieved in the Netherlands for breast cancer screening (82 per cent in 2006) or cervical cancer screening (five-year coverage 77 per cent in 2003).[406,407] The screening trials demonstrated convincingly that participation in iFOBT screening was 12 to 13 percentage points higher than participation in gFOBT screening.[27,32]

The iFOBT test method is more user-friendly than gFOBT testing, but there is probably scope for further improvement.

13.2 Orientation, education and acceptance

One of the fundamental differences between curative medicine and screening is that the former is demand-oriented (geared to meeting demand that originates from patients), while the latter is supply-oriented (aimed at generally healthy people). This means that potential screening participants must first be persuaded that participation is worthwhile. Persuasion requires that the potential participant is made aware of at least the following: the likelihood of the condition, the seriousness of the condition and the benefits and drawbacks of participation. Without such knowledge, there can be no informed choice. However, there is a considerable gap between knowledge and action.

One of the main reasons that people do not participate in screening programmes is that they are not persuaded of their value: ‘I don’t have any problems of that kind’; ‘I have a healthy lifestyle’; ‘no one in my family has ever had that’ and ‘I keep a close eye on things myself’ are common responses.[408-410] Non-participants are more inclined than participants to underestimate the risk of colorectal cancer or the likelihood of treatment being successful if the condition is detected early.[409] However, it is not the case that participants are more knowledgeable than non-participants.[411] In FOCUS, acceptance of an eighteen-page information booklet was investigated.[412] Only 20 per cent of respondents answered all the factual questions correctly. This finding is consistent with the general observation that knowledge of the symptoms and risks of colorectal cancer is poor the Netherlands by European Union standards.[413]

There are significant differences in the information required by potential participants.[402] Some of these differences are associated with background, gender and socio-economic status, while others relate to inter-personal differences in the approach to decision-making. Some people are inclined to follow advice given

by the authorities or a doctor without question, while others always want to make informed decisions that reflect their personal circumstances.[403] Information about screening programmes needs to take account of both decision-making strategies. Invitation letters should at least be accompanied by basic information about the screening, including the benefits and harms. In addition, potential participants and their families should be told where to go for more information.[403] Interactive decision aids facilitate deliberation and lead to better-informed decisions.[414-416]

It is vital to ensure that participation in screening can be based on informed choice, but informed choice is not easy to achieve.[402] Decision-making involves complex risk assessment. Many people have difficulty with reading or arithmetic and consequently overestimate the benefit of screening. Screening providers are inclined to stress such benefits and trivialise the drawbacks. The extent to which the provision of balanced, comprehensive information actually leads to informed choice is not known.

While iFOBT testing is itself entirely safe, a positive test result implies referral for colonoscopy. Potential participants must therefore be made aware of the albeit small risk of serious complications associated with colonoscopy before they decide whether to have the initial test. The general rule is that any risk of serious consequences must be highlighted, however small that risk may be.

The way that information about breast and cervical cancer screening is currently disseminated can serve as inspiration for the colorectal cancer screening programme. On behalf of the Centre for Population Screening, a body of information based on the Irwig model has been developed to support the Dutch cancer screening programmes.[403,417] As part of this exercise, the following list of information domains that must be covered in connection with cancer screening has been drawn up:

- the aim of screening
- the target disease or condition, including its seriousness, the scope for treatment and its potential implications for everyday life
- the prevalence of the disease
- the screening test
- the significance of a positive test result, including the *a priori* risk of false positives
- the significance of a negative test result, including the *a priori* risk of false negatives
- the potential side-effects of screening
- the yield
- what can be done in the event of a positive test result

- the possible outcomes of follow-up testing/examination
- the voluntary nature of screening
- the nature of the programme.

On the basis of expert advice, each information domain and subject has been designated as belonging in the basic information package or a supplementary information package.

All the basic information is now included in the leaflets that accompany invitation letters for breast and cervical cancer screening, while the supplementary information is available from the RIVM website (www.rivm.nl/bevolkingsonderzoeknaarkanker). In addition, research has been carried out to ascertain what information people in the target group actually want. The findings have been used to make further changes to the information that is provided.

For quality control reasons, invitation letters and the accompanying leaflets have been standardised at the national level on the basis of input from the various stakeholders. The draft material has been rewritten to make it more accessible and tested on the target group to verify that it can readily be understood. A similar procedure has been followed with the test result letters. From 1 January 2010, result letters will sent to all participants in both screening programmes. The revised letters will reflect the information provided by the GP when the subject visits the surgery. The best way of communicating a positive test result is currently being investigated.

The Committee believes that the effectiveness of screening should be included in the list of information domains. The Committee also recommends that the letter communicating a negative test result should remind the recipient about the possibility of false negative results and the consequent importance of attending every time one is invited to take the screening test.

13.3 Organisational matters

Call-up arrangements

With FOBT screening, the normal procedure is for potential participants to be sent a test kit and a letter inviting them to take part in the programme. People who do not initially respond are sent a reminder letter; reminder letters have a significant influence on the ultimate participation rate.[199] The rate of participation secured by this approach varies considerably; figures from 30 to 71 per cent have been reported.[122,124] It has proved possible to boost participation in lower socio-economic groups by several percentage points by writing to potential par-

ticipants about the screening before sending the invitation letters.[418] The timing of reminders also appears to be important: reminding non-participants after only three months, as opposed to the normal six months, was found to improve participation in cervical cancer screening. It is likely that waiting six months gives the impression that the matter is not very urgent, but this not has been investigated scientifically.

Systems that incorporate intermediate steps between invitation and testing – e.g. collecting a test kit from a pharmacy or requesting a test kit by sending in a reply card – tend to have poor participation rates. Home visits, on the other hand, tend to increase participation,[419] but are impractical in the context of a national programme and introduce a sense of coercion.

GP

In the US, many doctors provide FOBT screening in the context of normal surgery contact. When carrying out a physical examination, a faecal sample is collected using a digital rectal examination. This rather inelegant method of single-sample in-office testing allows the patient little opportunity to consider his/her options and has a sensitivity of less than 5 per cent; it is consequently strongly discouraged.[420]

In France, a participation rate of more than 80 per cent was achieved, at least initially, in programmes where GPs invited their patients to take part in screening in the context of a personal consultation, and gave them a test kit to take away.[15,96,113,120] However, the GPs were only able to sustain the necessary level of commitment for a few months. Patients who had not been approached were then sent the test kit by post. The average participation rate worked out at roughly 50 per cent, i.e. no higher than that achieved by more conventional approaches. In an Italian RCT, a personal invitation to participate from a GP did not result in a higher response rate than sending out test kits by post.[28,182]

More generally, some form of GP involvement in cancer screening often appears to increase participation, but not always.[79,90,93,96,131,152,170,182] It is not clear whether the positive influence observed in the context of cervical cancer screening[421,422] is likely to be mirrored in the context of colorectal cancer screening.

When test kits are sent by post, the named sender of the invitation letter can be the screening organisation or the recipient's GP. Some researchers have suggested that GP-signed letters may produce a better response rate than letters from a central institution. However, there is no conclusive evidence for or against this hypothesis. One FOBT screening study found that participation was higher if

invitation letters were signed by the recipient's GP, as opposed to an unfamiliar person or organisation.[423] Potential participants in the Nottingham trial were therefore contacted by their GPs.[90,93,96] The UK nevertheless ultimately moved away from this approach because of the workload implications for the GPs; since switching to an institutional signatory, there has been no discernible decline in the response rate. Centralised call-up also has the advantage of facilitating control.[12,13] For this reason, a number of cervical cancer screening organisations in the Netherlands use the GP-signatory model only for reminder letters. This approach has not been found to have an adverse effect on participation. A good alternative may be for invitation letters to be sent out centrally, but with the GP's name and facsimile signature at the bottom (subject to his/her consent, of course).

The attitude of GPs towards bowel screening is important in this regard. A 2004 survey of four hundred Amsterdam GPs (response rate: 32 per cent) found that only half were in favour of national screening (compared with 92 per cent of gastroenterological specialists).[424,425] It is not known whether the results of the screening trials have since brought about any shift in opinion. A survey of GPs who had participated in CORERO-I found that their attitudes were generally positive, but their views were purely retrospective.

13.4 Participant characteristics

Socio-demographic determinants

CORERO-I demonstrated that non-participation was particularly associated with men aged fifty to fifty-nine, lower socio-economic status and city dwellers.[32] Other studies have made similar findings.[18,119,124,412,426] In FOCUS, participation in iFOBT screening was higher amongst women than amongst men (63 vs. 56 per cent). The study did not find that age had a great deal of effect on participation,[27] but participation in Nijmegen was higher than in Amsterdam (62 vs. 57 per cent). Participation was lower amongst ethnic minority groups than amongst the ethnic majority.[427] A similar mismatch has been observed in other countries.[92,428]

Other factors

Research has also shown that non-participants tend to regard colorectal cancer screening as a low priority, to have experience of other chronic or serious conditions, to be in poor health, or to have recently experienced a family bereave-

ment.[412] In Italy, 86 per cent of people who had already participated in iFOBT screening also took part in the next round of screening. Some 19 per cent of non-participants in the first round of screening *did* participate in the second round.[18]

13.5 Participation in follow-up colonoscopy

Referral compliance following a positive screening result varies from 70 to 95 per cent,[12,15,17,135,140,160,161,164,167] with outlier values of up to 96 per cent (CORERO-I)[32] or even higher.[199,429] In FOCUS, the figure was 84 per cent.[27] After exclusion of medical reasons for advising against colonoscopy despite the positive result (recent colonoscopy, serious disease, etc), the figure for the Amsterdam component of FOCUS was 89 per cent and the figure for CORERO-I was 98 per cent.

The non-medical reasons for non-compliance with referral are not known. Possible reasons include fear of the procedure, failure to understand just what one has started on (despite the information provided) and the trouble involved in making a special visit to a medical centre to discuss the colonoscopy (when perhaps they feel the matter could be dealt with over the phone or at a more convenient time).[429] The latter possibility is being investigated in the context of the COCOS trial.

The Committee believes that it is important to minimise potential financial obstacles to referral compliance, such as health insurance policies requiring a personal contribution to the cost.

13.6 Conclusions

To sum up, the acceptance of and participation in colorectal cancer screening are influenced by the nature of the screening test, socio-demographic factors and perceived benefit. Other factors that may play a role are fear of (the drawbacks of) the test, the presence of (other/chronic) illnesses and related medication use and recent bereavement. The influence of GP involvement on participation is unclear.

The cited studies leave a degree of uncertainty regarding the significance of the above-mentioned determinants, their interrelationships and the mechanisms by which their influence is exerted. Nor is it apparent whether colorectal cancer (like cervical cancer) is more common in people who do not participate in screening.

Increasing significance is attached to ensuring that participation decisions can be made freely. Every individual is free to choose whether he or she wishes

to participate in screening. Ideally, the individual should be able to reach his/her decision by weighing up the likelihood of personally experiencing the benefits and drawbacks of screening. However, the Committee feels it would be a mistake to assume that people always make decisions rationally, or that the greater their knowledge the more they will be inclined towards healthy behaviour. Nevertheless, in its role as the provider of screening, the government has an obligation to ensure that potential participants have an equal opportunity to make an informed choice.

Chapter **14**

Quality assurance and organisation

14.1 Policy context

Screening for disease is not a logical extension of ordinary medical practice. The ethical position is quite different. Screening involves an unsolicited offer to apparently healthy persons. These exceptional characteristics mean that screening is justified only if it is demonstrably advantageous. Early detection is not in itself sufficient to justify screening; early detection must have a health benefit. Since the people who undergo screening are in principle healthy and only a minority of them stand to benefit directly from participation, it is by no means implausible that the desirable effects of a given form of screening will be outweighed by the undesirable effects (false positive results, false negative results, overdiagnosis, overtreatment, etc). Hence, it is very important that the design of a screening programme meets high quality standards, maximises desirable effects and minimises undesirable effects. Because a screening programme is made up of numerous diverse constituent activities, professional organisation and effective management are vital.[383,430]

The Committee believes that screening should be provided in the context of a national, population-based programme. Opportunistic screening is unlikely to result in a high level of quality and participation and would consequently be less effective and cost more in terms of health impairment and medical consumption.[431-436] Quality demands structured provision.

The Committee endorses the recommendation of the National Cancer Control Programme report on the introduction of colorectal cancer screening,[383] namely that the scheme should tie in with the existing cancer screening infrastructure, which from 1 January 2010 will comprise five regional executive bodies.

14.2 National organisational structure

The National Cancer Control Programme report provides a blueprint for the organisation of screening and the sequence of subordinate activities that it entails.[383] That sequence starts with the dissemination of information and continues via the identification of people who belong to the target group from the records kept by municipal authorities, to the invitation of potential participants, testing and ultimately the communication of test result and referral to the curative care sector.

Numerous different actors are involved in running the various national cancer screening programmes, each with distinct tasks and responsibilities. In brief: the Minister of Health, Welfare and Sport is responsible for establishing and terminating screening programmes, having taken advice from the Health Council. The Minister decides (again in the light of advice from the Health Council) whether to license proposed new programmes and significantly modified programmes under the Population Screening Act (WBO). The Ministry delegates national supervision to the RIVM's Centre for Population Screening (CvB), which also has the task of distributing funds to the (five) screening organisations. The CvB is responsible for ensuring that the delegated screening programmes are implemented by the relevant actors in a qualitatively appropriate manner and within the defined parameters. Instruments such as the Public Health Grant Scheme and the WBO licensing system can be used to exert control and impose quality requirements. Meanwhile, the system of national programme committees guarantees input from the various professional groups and stakeholders. The screening organisations hold the WBO licences, have access to the General Municipal Register (GBA) and have the task of running the programmes within their regions. They are also responsible for regional coordination. The Health Care Inspectorate (IGZ) monitors the quality of the screening services, partly through the *Visible Care* programme.

The Committee sees considerable merit in the National Cancer Control Programme blueprint. In addition, the Committee wishes to underline the need to develop a quality system, in the context of which particular attention should be given to:

- certification and auditing of the screening organisations
- a national reference facility
- monitoring and evaluation, including the necessary ICT infrastructure
- knowledge and innovation support.

Reference facility

When breast cancer screening was introduced, in 1989, the State Secretary for Health decided that the expertise built up in the Nijmegen trial (1975-1988) should be consolidated by establishing a national reference centre at Nijmegen. The responsibilities of this National Expert and Training Centre for Breast Cancer Screening (LRCB) include, first, the initial and refresher training of screening radiologists, radiographers and pathologists. Second, the LRCB provides medical quality assurance by conducting regular on-site audits of the twenty-six reading units. On request, the LRCB also undertakes consultations and coordinates the scientific research that underpins the screening. The LRCB monitors developments in the screening and diagnosis of breast cancer and advises on the introduction of new methods (such as digital screening mammography[437]).[438-441] Many of the Centre's tasks could in principle be performed on a distributed regional basis, but there would probably be efficiency and quality implications. Over the last twenty years, the LRCB has proved its value and won international recognition.[442]

In the field of cervical cancer screening, quality assurance focuses primarily on the pap smear (pathology), and a system of regional coordinating pathologists (RCPs) has been developed. This approach also facilitates the maintenance of high quality standards.

In iFOBT-based screening, however, testing is automated and its quality is easy to control (subsection 14.4). The focus of quality assurance is not therefore the screening test, but the follow-up testing and examination (colonoscopy, histopathology). Because the screening organisations have no direct control over these activities (in the Netherlands, the funding and management of screening is separated from the funding and management of follow-up care), the quality assurance arrangements for colorectal cancer screening require particular attention.

The Committee advises considering a mixed system based on (1) a national reference facility and (2) a regional coordinating gastroenterologist/endoscopist for each screening organisation. One of a reference body's main functions would be performing on-site audits, in the context of which the 'negative' colonoscopies preceding diagnosis would be reviewed in interval cancer cases.

This implies video-recording all colonoscopies performed in screening referral cases and archiving the recordings.

The Committee regards a coordinating gastroenterologist as an essential discussion partner for the auditors; he or she would have the task of monitoring quality in the region – particularly the quality of screening follow-up – by examining performance indicator data provided by the screening organisation. The coordinating endoscopist would maintain contacts with the other specialists involved in screening follow-up, with whom he or she would analyse and discuss results.

Registration, monitoring and evaluation

Data routinely collected in the context of screening, follow-up and treatment are required in order to monitor the quality of the screening and to evaluate the effectiveness and efficiency of the programme. Monitoring and evaluation are only useful if key data – participation rate, referral rate, referral compliance, yield, PPV, completion rate, tumour characteristics, polyps measuring ≥ 10 mm, etc – are covered by uniform national definitions and recording practices, and if such data are available in good time. These data are only of value if they can be compared with the standard, over time, or across operators or organisations. It is therefore necessary for the relevant actors to make appropriate arrangements before screening begins.

The breast and cervical cancer screening programmes demonstrate the importance of evaluation. In these programmes, particular attention is given to monitoring and (long-term) effects.[443] National evaluation serves to support direction of the programmes and their incremental improvement.[406,407,433,441,444-453] It also facilitates the evaluation of new developments, so that, for example, innovations can be trialled on a regional basis.[438,454]

To enable international comparative quality assessment of the screening programme, it must be compatible with international standards in this field. To this end, it can be useful to draw upon the experience of other countries by, for example, referring to resources such as the NHS National Bowel Cancer Screening Programme Pathology Reporting pro forma (www.virtualpathology.Leeds.ac.uk/NBCS/Documents) and joining the International Colorectal Cancer Screening Network (ICRCSN). The latter is a network of people involved in screening programmes, through which knowledge and experience are exchanged and which is developing a minimum set of common CRC screening indicators to measure, evaluate and compare screening programmes on an international level.[455]

In the USA, Norway and the UK, the recording, feedback and publication of surgical outcomes is leading to improvements in local recidivism, postoperative morbidity and mortality, survival and in-patient days.[4,5,6] In 2006, colorectal surgeons established the Dutch Surgical Colorectal Audit (DSCA) Foundation. Drawing on experience in the USA, Norway (where Rectal Cancer Registries were established in 1993) and the UK (National Bowel Cancer Audit introduced in 1998), the DSCA set up a medical audit system for colorectal cancer surgery in 2008. More than 90 per cent of the relevant hospitals support this system by providing data on intervention outcomes and patient characteristics, which are stored in a central databank in anonymised form. From April 2009, the participating centres receive quarterly summaries of key data plus a quality assessment. Once a year, an itemised performance report will also be made available, from which each participating centre will be able to see how its outcomes compare with those of peer centres in the Netherlands.

Knowledge and innovation support

It is important that support is provided for knowledge and innovation, including a system for the collection, storage and registration of human tissue and other material, and participant data. Such support is important to facilitate the flanking scientific research needed for ongoing improvement of the screening programme. The logistic systems and infrastructure of the bowel screening programme need to be designed with flanking research in mind. The Committee notes that this field of research is highly dynamic.

14.3 Target population, at-risk groups

The Minister asked the Health Council to pay particular attention in its report to the approach to be taken with at-risk groups. Certain aspects of this topic have been covered earlier in this report: in subsection 5.5, where the issue of risk profiling was explored, the Committee concluded that there are no workable, evidence-based selective screening methods; in subsection 12.2, the Committee stated its view that there was no justification for starting to screen men earlier in life than women. In this subsection, the Committee considers what should be done about people with a family history of colorectal cancer.

According to the existing CBO guidelines,[53] surveillance is indicated where a person’s elevated familial risk of colorectal cancer is 10 per cent or more (see subsection 5.4). However, this guidance was formulated at a time when there was

no well-organised screening programme based on a sensitive screening test. If such a programme is introduced, the CBO may revise its advice to bring it into line with the *European Guidelines for Quality Assurance on Colorectal Cancer Screening*, which are currently under development (http://europeancancernetwork.org). The observation that adenomas do not appear to demonstrate faster growth rates in people with a family history of colorectal cancer than in other people is likely to be relevant in this context.[457,458]

The issue under consideration here is what account the design of the screening programme should take of people with a family history of colorectal cancer. In its deliberations, the Committee has chosen to distinguish between people with a family history who have been advised to undergo surveillance colonoscopy and other people with a family history who did not yet get such an advice.

Invitation letters must indicate that screening is not intended for people who are already under a surveillance regime.

The Committee does not, however, believe that people with a family history of colorectal cancer should automatically be excluded from participating in the screening programme. In the Dutch Pilots, family anamnesis was not considered until the intake consultation prior to colonoscopy following a positive screening test. At that stage, it is possible to assess the anamnesis more closely and refer the patient to a genetics centre if appropriate.[53]

The CBO guidelines[53] also apply to people who have a family history of colorectal cancer, but whose screening test results are negative. It is therefore desirable that invitation letters, supporting information and test result letters should explain what a family history of colorectal cancer says about a person's risk of developing the disease and the implications for prevention. Potential screening participants should be told that someone with first-degree relatives (FDRs) who developed colorectal cancer before the age of seventy is advised to discuss the matter with his/her GP, regardless of the screening test result. However, the guidelines do not recommend referral for genetic advice or surveillance in cases where the subject has one FDR who developed colorectal cancer after the age of fifty (Table 2).[53]

The Committee recognises that a screening programme is not a particularly good mechanism for the identification of people with a seriously elevated familial risk of colorectal cancer. In the context of screening, without verification, it is not possible to obtain reliable reports of colorectal cancer in the immediate family and underreporting is common.[459] It is pertinent to ask whether people with a family history of colorectal cancer will consult their GPs, will comply with surveillance if selected or will be willing to undergo regular colonoscopy. A French

study of people with an elevated familial risk found that only 28 per cent followed medical advice to undergo colonoscopy.[460] Many people at elevated familial risk prefer other forms of screening.[461]

The nature of the information about familial risk provided to invitees requires careful consideration. A large proportion of the population have one FDR who has been diagnosed with colorectal cancer above the age of fifty. Given the size of this group and the fact that referral for genetic advice or surveillance is not indicated, a conservative approach is in order. Indeed, it is open to question whether it is desirable for the information to make the point that one's risk of colorectal cancer is greater if an immediate family member has had the disease. The reason being that people often choose not to participate in bowel or breast cancer screening if there is no history of the disease in the family.[408]

There are more appropriate mechanisms for detecting hereditary and familial colorectal cancer than a screening programme, one being the testing of tumour material from colorectal cancer patients where a hereditary dimension is suspected. Screening brings numerous cases of colorectal cancer to light and provides ample opportunity for investigating whether these cases involve hereditary or familial cancer.[62,63]

14.4 iFOBT screening

OC-Sensor (OC Hemodia) and MagStream (Hem-Sp, HaemSelect) are fully automated tests, and automated testing facilitates quality assurance.[112] Both tests require dedicated systems, implying the purchase of equipment for (automatic) sample analysis, at a cost of roughly EUR 70,000 per unit, excluding maintenance contracts. On the other hand, opting for an automated test system means rapid sample processing and modest manpower requirements.

Several quantitative iFOBT tests are currently under development (FOB Gold, Ridascreen, Sentinel), which will not require special equipment.[462] It will be possible to perform these tests in any laboratory using non-dedicated systems, without any loss of qualitative consistency.

Consistent performance is important since minor changes in sensitivity and specificity can greatly change the number of referrals for colonoscopy. To be involved in iFOBT screening, a laboratory must comply with ISO 15189 *Medical Laboratories - Particular requirements for quality and competence*. They will also need to follow appropriate internal quality control procedures and participate in an external quality assessment scheme (EQAS). The Committee recommends that one screening laboratory should act as a reference laboratory and that the Netherlands should participate in the development of a European EQAS, with

a view to promoting quality assurance at the European level and increasing the reliability and comparability of the screening results.

Stability

In the context of iFOBT testing, the quality of the faecal samples used is very important, because globin is more prone to denaturation than haem. In an Israeli study, no deterioration in test performance was observed when faecal samples were analysed after storage for at least three weeks at 4 or 20 degrees Celsius; performance was impaired however, by storage at 28 degrees.[138,463]

Research within FOCUS revealed that the performance of the OC-Sensor test declined as the interval between sampling and analysis increased.[464] Of the samples that reached the laboratory within four days, 8.7 per cent were positive (50 ng/ml). Among those arriving after five or more days, 5.8 per cent were positive and among those arriving after seven or more days the figure was 4.1 per cent, i.e. less than half that for the speedily processed samples. As the positivity rate fell, so did the yields, particularly the adenoma yield. These findings need to be drawn to the attention of potential participants (who need to be encouraged to send in their samples as quickly as possible and to refrigerate samples that cannot be dispatched immediately) and taken into account in the context of quality control. Consideration should be given to asking people whose samples are above a certain age at the time of receipt to repeat the test. One difficulty here is that, in research, 39 per cent of participants failed to give the date of sampling.[464] The possibility of sample quality being influenced by seasonal and other effects needs to be investigated. In hot weather, samples may well deteriorate rapidly in a post box, but almost no relevant research data are available. In Australia, testing is confined to the cooler months. Canada is considering a similar policy, which also has in its favour the fact that, in the summer, there is a risk of delays due to staff shortages over the holiday period.

The Committee recommends organising laboratory analysis so that faecal samples can be tested as soon as possible following arrival, or placed in cold storage. The need for such arrangements strengthens the argument for centralisation, which is also important in relation to reliability, quality assurance and evaluation. It is vital that every step of the process is carefully recorded and dated. Special effort should be made to encourage participants to date their samples. Where this date is not available, the call-up date should be used as a pessimistic indicator of the interval since sampling.

14.5 Follow-up

Alignment of screening and curative care

The quality of screening is determined partly by alignment between the screening programme and the curative care sector. It is important to take such alignment into account from the outset. If, as currently happens, the follow-up to a positive test result involves referral by the GP to any given hospital, there is a lot of scope for things to go wrong. The potential benefit of early detection can be partially negated by problems associated with the referral or by lack of experience or specific training on the part of the relevant medical specialists.[15,440] A positive FOBT is liable, for example, to be followed up by a less appropriate diagnostic procedure, such as a double-contrast barium enema or sigmoidoscopy, rather than colonoscopy.[465]

In breast cancer screening programmes in the UK, Finland and Sweden, follow-up is provided within the screening organisation (in assessment centres), with a view to eliminating potential problems such as those described. Another option is to follow the US 'mamma clinics' model by creating a network of clinics, each with a dedicated team of gastroenterologists and other specialists involved in the diagnosis and treatment of colorectal cancer. The clinics would make state-of-the-art diagnosis available to all, whether attending in the context of the screening programme or on another basis.[440,466] Specialist centres can enhance survival rates and access to specialised diagnostic techniques, while reducing waiting times and boosting client satisfaction levels.[467-470]

The dedicated team concept is gaining ground in the Netherlands, as witnessed by the report *Zorgketen kankerpatiënten moet verbeteren* (Care chain for cancer patients has to improve). The National Cancer Control Programme's Secondary Prevention Subcommittee confirmed the observation that, where cervical and breast cancer are concerned, diagnosis is not always prompt or properly aligned with screening.[440,471] Disciplinary proceedings show that in some cases, a positive screening test does not result in referral for diagnosis and treatment. Furthermore, the exchange of data and communication between screening organisations and curative care providers leaves room for improvement. To address these problems a Post-Screening Subcommittee has been formed. With regard to breast cancer screening, the subcommittee has made the following recommendation: 'The screening organisation should make clear arrangements with the mamma clinics regarding matters within its sphere of activity and should continuously monitor the clinics' quality and capacity. Client referral should take place

through the screening organisations themselves, with the GP playing a supporting role and always being kept up to date.'[471]

The Committee has adopted this National Cancer Control Programme recommendation and reiterates it in the context of colorectal cancer screening. The Committee favours the establishment of a network of bowel specialist centres within hospitals where there are at least two certified endoscopists and where the pathology, surgery, radiotherapy and oncology departments can demonstrably contribute to a high-quality care chain. This implies adaptation of the referral policy and the negotiation of arrangements with health insurers.

Colonoscopy

One of the principles of screening is that high-quality diagnostic follow-up should be available within a reasonable space of time (e.g. three weeks) to people whose test results are positive. Table 13 shows the yield associated with colonoscopy: with screening,[48-52] in response to symptoms[83] and after a positive $iFOBT_{75}$.test.[27,202] Amongst people referred following iFOBT screening, colorectal cancer and advanced adenomas are detected significantly more often. This underlines the importance of high quality standards.

Table 13 Diagnostic yield of colonoscopy screening, colonoscopy on medical indication (symptoms), and colonoscopy following a positive $iFOBT_{75}$. Percentages.

Diagnosis	Colonoscopy screening (n=52 346)[48-52]	Colonoscopy because of symptoms (n=4623)[83]	Colonoscopy after a positive $iFOBT_{75}$ (n=9136)[27,202]
Colorectal cancer	0.8	6.1	8.2
Advanced adenomas	6.7	7.4	43.4

Notably, colorectal cancer is detected more often one to three years after colonoscopy and polypectomy than one would expect in view of the normal course of the disease after clearing.[226,472-475] One of the most likely explanations for the unexpectedly high incidence of early interval cancer is failure to pick up or fully remove tumours or large adenomas during the index examination.[475] This hypothesis is supported by the observation that there is considerable performance variation from one endoscopist to the next.[204-206] Hence, screening is justified only if the follow-up colonoscopy is optimal. But what is optimal?

The first requirement is that a sound protocol should be followed. In the COCOS trial, endoscopists work to a fixed protocol based on US guidelines.[476] Second, cecal intubation is a generally accepted target in at least 90 per cent of

all colonoscopies and more than 95 per cent of screening colonoscopies.[476,477] Completion of the examination can be verified by saving still images of at least two of the three accepted 'proofs' (visualisation of the appendiceal orifice, and Bauhin's valve and intubation of the ileum) in an endoscopic database. Endoscopists who do not achieve a completion rate of at least 90 per cent are much more likely to miss abnormalities than endoscopists who do realise the completion target.[231,478] FOCUS and CORERO both satisfied this quality requirement, with completion rates of 94 and 99 per cent, respectively.[27,202] It has been shown, however, that there is considerable variation in endoscopists' completion rates.[479,480] One evaluation study found that in some regions of the UK, only half of colonoscopies were complete.[481] Later studies revealed little or no improvement.[479,482] Research in a Dutch hospital indicated a completion rate of 79 per cent.[483] In a more recent study, which looked at eighteen hospitals in the province of North Holland, the (corrected) completion rate worked out at 91 per cent.[83]

A third, less easily verified quality requirement relates to withdrawal time (between cecal intubation and completion of the colonoscopy), i.e. the time devoted to examining the colorectal mucosa. Adenomas overlooked during colonoscopy nearly always prove to have been hidden in a fold of the bowel (those on the proximal side being difficult to observe when withdrawing the endoscope) or in the rectum.[226] At least eight minutes should be devoted to withdrawal of the endoscope. A US research team found that experienced gastroenterologists (≥ 3,000 colonoscopies at the study outset) who took sufficient time detect advanced neoplasia more often (in 6.4 per cent of cases) than equallyia experienced but less painstaking colleagues (2.6 per cent).[480] However, in an interventional study in which endoscopists were encouraged to spend at least seven minutes withdrawing the endoscope and given personalised performance feedback, no increase was observed in the number of polyps detected, despite a rise in the percentage of endoscopists complying with the quality requirement, from 65 to nearly 100 per cent.[484] The researchers therefore assumed that there was no causal relationship between withdrawal time and adenoma detection rates.

This brings us to the fourth quality indicator: the adenoma detection rate (ADR) or, preferably, the advanced adenoma yield.[477] The disadvantage of the ADR is that it partly reflects the frequency with which diminutive adenomas (less than 6 millimetres), when what really matters is the detection of advanced adenomas.

The ability to satisfy the requirements set out above depends on training, experience and quality enhancement.[480] In a UK study in which only 71 per cent of endoscopists achieved a completion rate of ≥ 90 per cent, fewer than half of them performed more than a hundred colonoscopies a year.[482] In Germany, only endoscopists who have performed at least two hundred colonoscopies and fifty supervised polypectomies in the preceding two calendar years are allowed to participate in colonoscopy screening. To remain certified, an endoscopist has to perform at least two hundred colonoscopies and ten polypectomies a year.[232]

Major quality improvements have been reported following the introduction of a quality control system, when adequate time is reserved for each examination and when entitlement to carry out colonoscopies is made dependent on test performance.[479] In the Netherlands, the relevant professional groups have agreed appropriate certification requirements, which in practice only gastroenterologists satisfy.[485]

The Committee concludes that, if the potential benefit of iFOBT screening is to be realised, steps must be taken to ensure that the quality of colonoscopy examinations is of an appropriate standard. The Committee recommends that – as in the UK – a special assessment procedure should be introduced, including theory and skills tests, which all endoscopists must pass in order to be involved in the screening programme. The Committee also wishes to see the creation of a network of centres that have at least two gastroenterologists. The quality of colonoscopy can be assured by measuring certain key parameters, such as completion rate, ADR and complication rate.

Histopathology

The abnormalities biopsied or removed during colonoscopy are examined in a pathology laboratory, following standard procedures. In most cases, the pathologist can make a diagnosis on the basis of a standard colouration. The main categories relevant in this context are: neoplasia (adenoma or adenocarcinoma), non-neoplastic abnormality (polyp other than adenoma, inflammation, other), and no abnormality. An individual may have several types of abnormality – and therefore several diagnoses – at the same time.

The pathology report is important in the context of screening for two reasons: 1) it is the basis for formulating a policy for the individual patient; 2) it serves as input for the monitoring and evaluation of screening programmes.

For the individual patient, the distinction that matters most is between neoplasia (adenomas and adenocarcinomas) and non-neoplastic diagnosis. If the

patient has an adenocarcinoma, treatment in accordance with the guideline *Colon Carcinoma* (www.cbo.nl) is indicated. If an adenoma is detected, the most important question is whether the abnormality has been fully removed, since the biggest risk factor for adenoma patients in relation to the development of colorectal cancer is incomplete adenoma removal.[472,486,487] It is worth pointing out that this matter is not explicitly addressed by the surveillance guidelines.[54] Furthermore, each adenoma is classified by tissue type (tubular, tubulovillous and villous) and by the degree of dysplasia – traditional classes: slight, moderate and serious; nowadays usually: high-grade (corresponding to serious dysplasia) and low-grade (slight or moderate dysplasia) and size.

Such classification is very important for the surveillance programme (see subsection 14.6) and especially for monitoring of the screening programme. Protocolised and standardised nationally uniform reporting of detected abnormalities – as in cervical and breast cancer screening – is an absolute condition. In the Netherlands, such reporting is facilitated by the availability of the PALGA system, which all pathology laboratories use.[488] An introduction protocol for resection preparations made in connection with colorectal cancer and in accordance with the CBO guidelines on colon carcinoma is already available and currently being introduced. A similar protocol for adenomas is under development.

14.6 Surveillance

Surveillance following polypectomy is an essential part of the screening strategy, because screening identifies adenomas. The effectiveness and efficiency of screening are directly related to the effectiveness and efficiency of surveillance. However, the existing surveillance regime following a polypectomy reads as follows: first re-examination after three years if three or more adenomas have been found, and after six years if one or two have been found.[54] This regime should be followed regardless of the size or tissue type of the adenomas. The Committee believes it would be unduly onerous to implement the existing surveillance guidelines[54] in the context of any new screening programme.

Understandably, there have been no controlled studies which sought to measure the effectiveness of surveillance using incidence of mortality as an outcome measure. Consequently, the guidelines are based almost exclusively on short-term research that looked at the risk for subsequent adenomas following polypectomy, even though by no means all adenomas are malignant. A Danish study, in which the standard Danish population served as the control group and the observation period was up to twenty-four years, concluded that surveillance reduced the incidence of colorectal cancer by 35 per cent.[489] Where colorectal cancer did

develop, it was usually detected early, with the result that colorectal cancer mortality was 88 per cent lower compared to a standard population.[489] However, various other studies have shown that the effect of surveillance depends largely on the adequacy of the initial colonoscopy and polypectomy (see also 14.5).

The guidelines referred to above were written with normal clinical practice in mind, rather than screen-detected adenomas. Furthermore, the guidelines are stricter than justified by the evidence,[490] and in practice are interpreted more strictly still.[491-495] Often, for example, a patient is placed under surveillance following the removal of hyperplastic polyps, or the interval between examinations is shorter than that recommended.[496]

A sizeable proportion – 25 to 40 per cent of all colonoscopies – are performed for surveillance purposes.[83,497,498] This is increasingly seen as inappropriate. The existing guidelines question whether this excessive practice is efficient, since a) the yield is much lower than with an initial examination,[495] b) any benefit has to outweigh the complication risk, and c) the capacity available for performing colonoscopies is limited. New US guidelines recommend a follow-up colonoscopy at longer intervals in cases where one or two small tubular adenomas have been detected.[499] They acknowledge that discontinuing colonoscopy surveillance but continuing average-risk screening may be appropriate for patients with low-risk adenomas.

Furthermore, the situation will change dramatically when colorectal cancer screening is introduced. Modelling indicates that, if the existing guidelines were followed, almost half of all the colonoscopies required would have to be reserved for surveillance,[383] even though the yield of such examinations is low.[495,500,501] The Committee anticipates that updated guidelines will result in better use being made of the available colonoscopy capacity by shifting the focus from excessive surveillance to screening and diagnosis. This may be expected to greatly improve the quality of care for patients with colorectal cancer.[502]

The Committee believes that there is good reason to update the Netherlands' surveillance guidelines[54], as indeed has previously been proposed.[491] It is questionable, for example, whether colonoscopy surveillance is necessary following the removal of one or two adenomas of less than < 10 millimetres.[490,503,504] A British study of rigid sigmoidoscopy (average observation period: fourteen years) made the reassuring observation that, in participants from whom one or more rectal adenomas < 10 millimetres had been removed, the risk of cancer of the rectum was four in 11,909 person-years, i.e. 40 per cent lower than in the general population; where tubular adenomas were concerned, the risk was 60 per cent less.[486] Similarly, an Italian study (observation period: 10.5 years) found that, following

the removal of ‘small’ adenomas, the colorectal cancer risk was considerably lower than in the general populace (SIR: 0.13).[222] Recent research backs up these observations. In a US colonoscopy screening trial, almost five hundred war veterans had one or two ‘small’ tubular adenomas removed. Amongst these veterans, their risk of developing an advanced adenoma or colorectal cancer within 5.5 years proved to be no greater than in a control group of three hundred participants in whom no adenomas had been detected during screening.[474] A large case-control study revealed that the risk of colorectal cancer in the ten years following removal of one or two small tubular adenomas was 64 per cent lower – odds ratio: 0.36 (0.18 to 0.76) – than in the control group, whose members had not undergone colonoscopy.[505] In people with advanced adenomas or three or more adenomas, the ten-year risk was not significantly lower, but the five-year risk was (odds ratio: 0.27 (0.10 to 0.77)).[505]

The Committee recommends urgent revision of the surveillance guidelines[54] to bring them into line with the *European Guidelines for Quality Assurance in Colorectal Cancer Screening*. The Committee believes that, following the removal of one or two ‘small’ adenomas, the normal screening regime should apply; hence, re-testing would not be necessary for ten years after a satisfactory colonoscopy and polypectomy. There are strong arguments in favour of such an approach, which would reduce the number of surveillance colonoscopies needed substantially.[497]

14.7 Care consumption

A general practice will acquire at least one new colorectal cancer patient a year as well as having a total of nine living (former) patients. The average hospital will gain more than a hundred new patients a year and will have a total of six hundred on its roll.[81] For more than 90 per cent of people who develop colorectal cancer, surgery is possible.[81] In 4 to 12 per cent of cases, endoscopic removal of the tumour is sufficient.[51,168,179]

In 2005, there were a hundred endoscopy units in the Netherlands. A questionnaire-based survey with a 98 per cent response rate found that there were at that time 598 endoscopists: 221 gastroenterologists, 213 internists, 123 surgeons and 41 paediatricians.[506] In 2004, almost 410,000 endoscopies were performed, of which 117,000 were colonoscopies (719 per 100,000 of the population) and 70,000 sigmoidoscopies (431 per 100,000). It is not known what proportion of these procedures were performed for screening purposes and would not therefore have been necessary if a national screening programme were in place. However,

a study in North Holland concluded that 10 per cent of the colonoscopies in that province involved 'asymptomatic' subjects.[83] It is likely that the gradual increase in the number of colonoscopies – estimated at 6 per cent per year[497] – is largely attributable to screening, since there has been no increase in the list of circumstances under which colonoscopy is indicated, although population aging must be a factor. The number of colonoscopies varies from roughly five hundred per 100,000 in Flevoland and North Brabant to almost a thousand in Overijssel and Groningen. The average waiting time for colonoscopy was more than five weeks (range: one to fifteen weeks).[506]

The number of registered gastroenterologists has quadrupled since 1990 and stood at 260 (240 FTEs) on 1 January 2007; at that time, there were also 124 gastroenterology residents. Each year, twenty-two residents begin the six-year programme of training necessary to become a gastroenterologist. From 2010, the intake will be increased to thirty-five a year; this figure anticipates the introduction of screening to some extent.

In the context of the Ministry's *Sneller beter* (Better Faster) programme, a number of hospitals are seeking to reduce the interval between the manifestation of symptoms and primary therapy.[508] From referral by a GP to hospital admission normally takes about sixteen weeks. At more or less every step between those two events, time could be saved by clear agreements on the division of responsibilities and better planning. One hospital has, for example, been able to cut the waiting time for endoscopy from five weeks to one; another reduced the interval between the first clinic visit and admission from fifty-nine days to fourteen.

In surgery, significant capacity has been freed up by the ERAS (Enhanced Recovery After Surgery) programme. This quality programme could be used by endoscopists as the basis for the development and testing of best-practice models.

Between 1994 and 2007, the annual number of colorectal cancer-related hospital admissions rose from 10,200 to 17,400, but the average duration of stay was cut from twenty days to twelve. In the same period, the number of day admissions went up from 3,400 to 9,400 (www.prismant.nl). Breakthroughs in chemotherapy can lengthen median survival of patients with metastasised colorectal cancer, but the treatment and supervision of the patients involved is very labour-intensive.

The cost of caring for colorectal cancer patients was EUR 232 million in 2003; 0.4 per cent of the overall health care expenditure in the Netherlands.[509] The bulk of the cost (72 per cent) is associated with the intramural care of men aged 70-79 and women aged 75-84 (www.rivm.nl/vtv). The cost per patient depends largely on the stage that the disease has reached. It is become more com-

mon – even in cases of early-stage disease, where the potential health gains are more modest – to use expensive new drugs to achieve small life extensions. As the cost of treatment rises, the cost-effectiveness of screening increases (see subsection 12.1).[377]

14.8 Phased introduction

If the decision is taken to set up a national screening programme, the screening activities introduced in the context of the trials should gradually be extended to the rest of the country. It is not realistic to expect the necessary care capacity to be immediately available. Step-wise introduction is essential so that the necessary colonoscopy capacity can be built up, the supply of and demand for colonoscopy can be kept in step and major inequalities between regions can be avoided; it is also necessary in order to address any teething problems that may arise and to make sure that people who are already experiencing symptoms don't face extended waiting times.

The Committee considers it unnecessary to spread out the introduction of a screening programme over a period as long as ten years; five years is a realistic goal. The Committee does not believe that the additional capacity requirement is as great as suggested by a National Cancer Control Programme working group.[383] Complete rollout of the programme would necessitate a maximum – based on the existing surveillance guidelines – of 78,000 additional colonoscopies in year 6, rather than the 129,000 suggested by the working group (see Table 14).

This Committee's forecast is much lower for several reasons. First, it is based on data for the period 2010-2015, whereas the working group's figure is based on average data for the next thirty years. Second, the Committee is assuming an entry age of fifty-five, rather than fifty; this implies about 20,000 fewer colonoscopies a year. Third, the Committee favours using a positivity threshold of 75 ng/ml, rather than 50 (see subsection 12.2); this would mean 6.4 per cent of tests resulting in referral, as opposed to 8.4 per cent – which translates to 23,000 fewer colonoscopies a year. Furthermore, if the surveillance guidelines[54] are updated in good time (see subsection 14.6), the annual number of additional colonoscopies needed in year 6 would be significantly smaller than 78,000, and this would subsequently compensate to a large extent for the increase in demand that population aging may be expected to bring.

Five years is also regarded as realistic because there is now considerably more colonoscopy capacity available than there was in 2005.[506] Assuming annual growth of 6 per cent,[497] the number of colonoscopies being performed

may be expected to rise from 119,000 in 2005 to 157,000 in 2010. The main driver of this volume growth is opportunistic screening. Assuming that 10 per cent of the available capacity is being used to support opportunistic screening,[83,497] this equates to roughly 16,000 colonoscopies. The introduction of programmatic screening will tend to suppress the demand for opportunistic screening. It is also reasonable to suppose that the programme will gradually reduce the number of colonoscopies performed in response to the manifestation of symptoms, thus releasing capacity.

The Committee supports the National Cancer Control Programme proposal regarding the use of a gradually expanding invitation scheme to cover more age groups over the implementation years,[383] subject to the understanding that, over the five-year rollout period, the screening regions increase their capacity on a linear basis to the level ultimately required. This implies all regions following a similar rollout timetable. The Committee favours a combination of two forms described by the working group: a) the most cost-effective form; and c) a form based on call-up of the oldest cohort first. This would ensure that all members of the target age group have the opportunity to participate in screening at least once. If such an approach were adopted, people aged sixty-five or seventy-five would be called up in year 1; in year 2, people aged sixty-three, sixty-five, sixty-seven or seventy-five would receive a call-up; in year 3 it would be the turn of people aged sixty-one, sixty-three, sixty-five, sixty-seven, sixty-nine and seventy-five; and so on until year 6, by which time the call-up of the entire target group (people aged fifty-five to seventy-five) would be on schedule.

The Committee recommends that, under the supervision of the Centre for Population Screening (CvB), each screening organisation draws up a rollout plan for its region and submits it to the Minister for licensing under the Population Screening Act.

It is important to prevent unnecessary inter-regional differences arising in the approach taken. Experience indicates that a uniform approach is preferable where various key component activities (call-up, data collection, referral, complaint processing, etc) are concerned. Standardisation of these activities can be addressed by an inter-regional working group and implemented following CvB approval.

14.9 Capacity

The capacity needs associated with staged introduction of an $iFOBT_{75}$ screening programme are set out below, assuming a participation rate of 60 per cent.

Screening

By the time full coverage is reached in year 6 (2015 in Table 14), each year 1.9 million people will be invited to participate and 1.1 million screening tests will be performed. The OC-Sensor Diana can process 280 samples per hour. Allowing for breaks, refilling with supplies and a number of dilution series, an analyst can deal with 1,500 tests per day, or 300,000 per year. This implies 4 FTEs for full coverage. For quality reasons, centralisation is important (see subsection 14.4), with a maximum of one laboratory per screening region. There are five screening regions, so that implies five machines, each operated by one LBO (lower vocational education level) analyst with limited supervision. Such a set up would be sufficient to cope even if, for example, the participation rate were 80 per cent.

Colonoscopy for follow-up diagnostic and surveillance purposes

Assuming 1,500 examination hours per year and two colonoscopies per hour, one endoscopist FTE can perform 3,000 colonoscopies a year.[383] At 60 per cent participation, 78,000 colonoscopies will be required in year 6 (Table 14). This equates to twenty-six FTEs (but a larger number of endoscopists, since only a few endoscopists full spend all their time performing colonoscopies).

Little is yet known about the scope for using nurse endoscopists, but the point is worth making that the colonoscopies to be performed will be at the high end of the difficulty range (Table 13). The Netherlands Association of Gastroenterologists (NVMDL) is currently setting up a special nurse endoscopy programme.

Table 14 Impact of implementing an $iFOBT_{75}$ screening programme (attendance 60 per cent) on colonoscopy capacity need, CRC indicence and mortality. Source: MISCAN-Colon.

Year	Invitations	Colonoscopies	CRC incidence vs no screening	CRC mortality vs no screening
2010	258,000	12,500	1,091 (11%)	
2011	570,000	26,000	1,793 (17%)	
2012	969,000	42,000	2,325 (22%)	-39 (-0,7%)
2013	1,286,000	56,000	2,649 (25%)	-164 (-3%)
2014	1,685,000	72,000	2,824 (25%)	-276 (-5%)
2015	1,873,000	78,000	1,996 (18%)	-434 (-8%)
2030	2,151,000	126,000	- 1,345 (-9%)	-2,099 (-28%)
2039	2,000,000	127,000	- 1,836 (-12%)	-2,480 (-29%)
Annual average (2010-2039)	1,871,000	101,000	-268 (0%)	-1,428 (-19%)

A quality system based on five regional coordinating gastroenterologists (0.3 FTEs each) implies 1.5 FTEs. This brings the total number of endoscopists needed to 4.5 FTEs in year 1 and 27.5 FTEs in year 6 of the implementation period. The increased intake of gastroenterology residents (see subsection 14.7) is intended partly to provide the necessary personnel and should be sufficient to do so.

Pathology

The required pathology capacity will be determined by the number of abnormalities biopsied or removed and the number of people needed for quality monitoring. About half of referrals following positive iFOBT tests result in the detection of advanced neoplasia. In addition, adenomas are detected, which pathology testing shows not to be advanced, but which are biopsied for other reasons. The assumption that 60 per cent of colonoscopies will lead to biopsies is therefore likely to be conservative. On the basis of this assumption, the 78,000 colonoscopies required in year 6 will lead to 46,800 histological examinations. It is estimated that that number of examinations will occupy 9.2 pathologist FTEs; this assumes 1,500 working hours a year and 4.7 examinations per hour.[383] The performance of the examinations will also necessitate the availability of support personnel.

Some of the patients in question will require surgery. This will lead to histological examinations of resection specimens. The pathologist has an essential role in the quality assurance of surgery by assessing the completeness of tumour excision. However, because cancer can become symptomatic at any time, performing such examinations is part of the existing pathology workload; the introduction of screening will not increase the capacity needed in this context. Nevertheless, some of these examinations will be needed sooner than otherwise would have been the case. As a result, there will be a peak of +25 per cent in years 4 and 5 (when there will be 2,700 to 2,800 additional colorectal cancer diagnoses), but beyond year 10 there will be fewer new cases of colorectal cancer detected than there would have been without screening.

A quality system like that used for the cervical cancer screening programme, with five regional coordinating pathologists (0.3 FTEs each) implies 1.5 FTEs. The duties of these RCPs will include refresher training, consultation, evaluation of yields, site visits and lab audits, contributing to the annual report and attending screening organisation meetings. After all, pathology diagnoses will be the primary outcome on which the programme is evaluated. Taken together, the

assumptions set out above imply a total pathologist capacity requirement of 10.7 FTEs in year 6. It will be necessary to investigate the possibility of not only creating additional capacity, but also freeing up capacity by means such as delegating certain duties to analysts.

Surgery, oncology, radiotherapy

In the first seven years, 1,100 to 2,800 more colorectal cancer diagnoses must be expected than would otherwise have been the case (Table 14). However, screening will lead to colorectal cancer being detected at an early stage more often. Of the people diagnosed with colorectal cancer as a result of screening, an estimated 25 per cent will not require surgery, but can be treated endoscopically.[168,179] This will mean fewer additional operations. Ultimately, the Committee anticipates an annual average of 1,150 surgical procedures being needed in the first ten year than would have been performed if screening had not been introduced. After year 10, a downturn in the incidence of colorectal cancer may be expected. The 1,150 operations will require 3,450 hours of surgery time (assuming two hours for colon surgery, five hours for rectal surgery) and 13,800 in-patient days (1,150x12). The number of operations needed in cases where adenomas cannot be effectively removed endoscopically is expected to be small. Moreover, in the first ten years, screening will generate demand for additional medical-oncological treatment and for preoperative radiotherapy for two hundred people with rectal carcinoma (0.33x1,150x0.5).

The Committee does not have at its disposal all the data needed to make more precise calculations. It is nevertheless the Committee's belief that, given the necessary commitment, the extra care can be provided, provided that budgetary adjustments are made where necessary.

14.10 Conclusions and recommendations

The Committee makes the following recommendations:

- a colorectal cancer screening programme, as described in subsection 14.8, should be introduced in phases
- an organisational structure as described in the National Cancer Control Programme report[383] (see subsection 14.2) should be adopted, with a view to assuring quality and – if the iFOBT test method is used – sustainability
- if it is decided that a screening programme is to be set up, clear arrangements should be made with the relevant professions and care providers regarding

    - the development of integrated (multidisciplinary) guidelines covering the entire chain from screening to diagnosis, treatment, after care and surveillance, together with the updating of the surveillance guidelines
    - ways of assuring the quality of follow-up colonoscopy, including direct referral by the screening organisation (see subsection 14.5) and the creation of a reference facility (see subsection 14.2)
    - the provision of data for quality control and evaluation of the screening programme, together with regular reporting
    - public accountability for follow-up diagnosis, treatment and surveillance within the *Visible Care* programme
- budgetary provision should be made for monitoring and evaluation, for a reference system and for the promotion of knowledge and innovation-oriented scientific research (necessary to keep service screening up to date)
- the introduction of screening for colorectal cancer should be accompanied by a national public information campaign. The primary objective of this campaign should be to increase awareness of colorectal cancer and the potential benefits and harms of screening and subsequent investigation. It is important that the campaign takes account of the differences that exist in people's information needs. Furthermore, the campaign needs to be coordinated with, and to involve all relevant stakeholder groups, at the national, regional and local levels
- to enable people to make informed choices, a system of basic information and supplementary information should be developed, similar to those established in connection with screening for breast cancer and cervical cancer. In this context, particular attention should be given to the national uniformity of information provision in the various phases of the screening process
- sound arrangements should be made for monitoring and evaluation of the participation rate and the quality of the public information activities, in the context of which insight should be sought into the reasons for (non-) participation. The Committee attaches particular importance to the monitoring of informed choice.

Chapter 15

Answers to specific questions raised by the Minister

15.1 Is introduction of a colorectal cancer screening programme desirable?

Colorectal cancer is a serious disease and a major health problem. Primary prevention has limited scope. However, improved (albeit expensive) treatment is increasing the five-year survival rate in patients with metastasised colorectal cancer. Although significant scientific advances have been made in relation to hereditary predisposition to colorectal cancer, the progress has yet to translate into enhanced preventive or therapeutic intervention.

Colorectal cancer is preceded by a prolonged adenomal condition, which is relatively easy to detect and treat. Furthermore, colorectal cancer remains in an early preclinical stage for several years. These two facts provide an excellent window of opportunity for screening. It has been demonstrated that screening by means of guaiac testing for occult blood in faeces (gFOBT) can substantially reduce colorectal cancer mortality. The results of Dutch Pilots have shown that participation and yields can be improved significantly by using an immunochemical variant of the faecal test (iFOBT). The test characteristics of the iFOBT are attractive: in the first screening round, it is at least as sensitive as sigmoidoscopy for colorectal cancer, and programme sensitivity is boosted by screening every two years. Where a positive test result is followed up by colonoscopy, colorectal cancer is detected in 8 per cent of cases and precursors to the disease (advanced adenomas) in a further 44 per cent of colonoscopies. The main drawback of

screening is the risk of serious complications arising from the follow-up examination (colonoscopy). This risk is small, however, and outweighed by the health benefit attainable through screening. A national iFOBT screening programme would have a favourable cost-effectiveness ratio. Effective screening would reduce the cost of treating metastasised colorectal cancer, which has risen enormously. On the basis of a conservative estimate of the treatment costs, an $iFOBT_{75}$ screening programme would cost EUR 2,200 per life year gained. This figure is less than the corresponding figures for other cancer screening programmes in the Netherlands, such as the cervical cancer screening programme (EUR 11,300). For every colorectal cancer death prevented, 785 people would need to take an iFOBT and seventy-one would need to undergo follow-up colonoscopy.

An iFOBT programme therefore meets the criteria for responsible screening, provided that sufficient care capacity of an adequate quality is available.

15.2 Is the introduction of a colorectal cancer screening programme feasible? How should a possible screening programme be phased in, taking the available care capacity into account?

The Netherlands has a good screening infrastructure. No major problems were encountered in the Pilots. The main challenges are assuring appropriate quality standards and making sufficient colonoscopy capacity available. The Committee considers a national screening programme quite feasible, provided that the recommendations set out in subsection 14.8 are implemented. The number of additional colonoscopies to be performed each year would be a maximum of 78,000, given a complete rollout of the screening programme (Table 14).

15.3 Which new methods of screening for colorectal cancer are likely to become available within five to seven years? (I wish to ascertain whether any foreseeable developments have infrastructural or operational implications.)

In the medium term, the Committee does not expect development of any new test methods to reach the stage where they may be considered realistic alternatives to iFOBT testing. There are several serious candidate methods, but it is likely to be about ten years before any advantage that they may have over iFOBT testing can be demonstrated in large-scale trials and by modelling.

In 2010, the results are expected from sigmoidoscopy screening trials in the UK and Italy. If it appears from these results that sigmoidoscopy is an attractive

option, simulation modelling for the Netherlands will have to be adapted. Because participation is substantially lower in sigmoidoscopic screening than in iFOBT screening, a programme based exclusively on sigmoidoscopic screening is not desirable in the Netherlands. Consideration might be given to setting up a feasibility study in which people were able to choose between iFOBT testing and sigmoidoscopy.

The Committee recommends designing a national screening programme so that trials of potentially preferable test methods could be performed as flanking studies within the context of the operational programme. The Committee concludes that an iFOBT screening programme would not be unduly susceptible to foreseeable developments.

15.4 Should the screening programme pay particular attention to groups with a non-hereditary elevated risk of colorectal cancer, e.g. by means of individual risk profiling?

More than 90 per cent of the new colorectal cancer cases involve people older than fifty-five. The Committee recommends that the target group for screening should be men and women aged fifty-five to seventy-five. Approaches such as individual risk profiling are still under development and their (added) value has not yet been demonstrated. The Committee sees no reason to start screening men earlier in life than women.

The Committee does not believe that people with a family history of colorectal cancer should automatically be excluded from participating in the screening programme. Rather, it recommends that the information leaflet and result letters should explain the implications of a strong family history of colorectal cancer and advise anyone with concerns to contact his or her GP, regardless of the screening test result. Furthermore, invitation letters should make it clear that screening is not intended for people who are already under surveillance. The Committee also recommends that, at the colonoscopy intake consultation following a positive screening test, patients should be asked about the family history of colorectal cancer and referred to a genetics centre if referral is indicated by the guidelines on hereditary colorectal cancer.

References

1 Nadere standpuntbepaling bevolkingsonderzoek darmkanker. Brief dd 15 mei 2006 van de minister van VWS aan de voorzitter van de Tweede Kamer.

2 Towler BP, Irwig L, Glasziou P, Weller D, Kewenter J. Screening for colorectal cancer using the faecal occult blood test, hemoccult. Cochrane Database Syst Rev 2004;(4)

3 Gezondheidsraad. Bevolkingsonderzoek naar dikkedarmkanker. Den Haag: Gezondheidsraad; 2001: publicatie nr 2001/01.

4 Ballegooijen M van, Habbema JDF, Loeve F, Geul KW, Kleibeuker JH, Nagengast FM *et al*. Screening op colorectaal kanker in Nederland: tijd om te starten. Rotterdam: Erasmus MC; 2003.

5 Signaleringscommissie Kanker. Vroege opsporing van dikkedarmkanker. Minder sterfte door bevolkingsonderzoek. Amsterdam: KWF Kankerbestrijding; 2004.

6 Visser M dew, van Ballegooijen M, Bloemers SM, van Deventer SJ, Jansen JB, Jespersen J *et al*. Report on the Dutch consensus development meeting for implementation and further development of population screening for colorectal cancer based on FOBT. Cell Oncol 2005; 27(1): 17-29.

7 Council of the European Union (16 December 2003). Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC). OJ L 2004; 327: 34-38.

8 Von Karsa L, Anttila A, Ronco G, Ponti A, Malila N, Arbyn M *et al*. Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening - First Report. Lyon: International Agency for Research on Cancer; 2008.

9 Benson VS, Patnick J, Davies AK, Nadel MR, Smith RA, Atkin WS. Colorectal cancer screening: a comparison of 35 initiatives in 17 countries. Int J Cancer 2008; 122(6): 1357-1367.

10 Malila N, Anttila A, Hakama M. Colorectal cancer screening in Finland: details of the national screening programme implemented in Autumn 2004. J Med Screen 2005; 12(1): 28-32.

11 Anonymous. Screening for bowel cancer starts in UK. BMJ 2006; 332: 990.
12 UK Colorectal Cancer Screening Pilot Group. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. BMJ 2004; 329(7458): 133-135.
13 Bowel Cancer Screening Pilot Monitoring and Evaluation Steering Committee. Final evaluation report. Canberra: Department of Health and Ageing; 2005.
14 Steele RJ, McClements PL, Libby G, Black R, Morton C, Birrell J *et al*. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. Gut 2009; 58(4): 530-535.
15 Steinmetz J, Spyckerelle Y, Gueguen R, Dupre C. Colorectal cancer screening in Health Examination Centers. Gastroenterol Clin Biol 2006; 30(6-7): 832-837.
16 Goulard H, Boussac-Zarebska M, Ancelle-Park R, Bloch J. French colorectal cancer screening pilot programme: results of the first round. J Med Screen 2008; 15(3): 143-148.
17 Manfredi S, Piette C, Durand G, Plihon G, Mallard G, Bretagne JF. Colonoscopy results of a French regional FOBT-based colorectal cancer screening program with high compliance. Endoscopy 2008; 40(5): 422-427.
18 Zorzi M, Fedato C, Naldoni C, Sassatelli R, Sassoli de Bianchi P, Senore C *et al*. Screening for colorectal cancer in Italy: 2007 survey. Epidemiol Prev 2009; 33(3 (supplemento 2)): 57-74.
19 Ee HC, Semmens JB, Hoffman NE. Complete colonoscopy rarely misses cancer. Gastrointest Endosc 2002; 55(2): 167-171.
20 Saito H. Colorectal cancer screening using immunochemical faecal occult blood testing in Japan. J Med Screen 2006; 13 Suppl 1: S6-S7.
21 Seeff LC, Richards TB, Shapiro JA, Nadel MR, Manninen DL, Given LS *et al*. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. Gastroenterology 2004; 127(6): 1670-1677.
22 Levin TR. Editorial: It's time to make organized colorectal cancer screening convenient and easy for patients. Am J Gastroenterol 2009; 104(4): 939-941.
23 Saito H. Screening for colorectal cancer: current status in Japan. Dis Colon Rectum 2000; 43(10 Suppl): S78-S84.
24 Gezondheidsraad. Wet bevolkingsonderzoek: vormen van screening op darmkanker. Den Haag: Gezondheidsraad; 2005: 2005/01WBO.
25 Masclee A. Coloncancer screening: Implementation and evaluation of colorectal screening for precancerous lesions, short report on first population. Maastricht: Maastricht University Medical Center; 2008.
26 Gezondheidsraad. Wet bevolkingsonderzoek: proefbevolkingsonderzoek naar darmkanker. Den Haag: Gezondheidsraad; 2005: 2005/03WBO.
27 Rossum LG van, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH *et al*. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008; 135(1): 82-90.

28 Weissfeld JL, Schoen RE, Pinsky PF, Bresalier RS, Church T, Yurgalevitch S *et al*. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. J Natl Cancer Inst 2005; 97(13): 989-997.

29 UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet 2002; 359(9314): 1291-1300.

30 Segnan N, Senore C, Andreoni B, Aste H, Bonelli L, Crosta C *et al*. Baseline findings of the Italian multicenter randomized controlled trial of “once-only sigmoidoscopy”--SCORE. J Natl Cancer Inst 2002; 94(23): 1763-1772.

31 Gezondheidsraad. Wet bevolkingsonderzoek: screening op darmkanker met sigmoïdoscopie of FOBT. Den Haag: Gezondheidsraad; 2006: 2006/02WBO.

32 Hol L, van Leerdam ME, van Ballegooijen M, van Vuuren AJ, van Dekken H, Reijerink JCIY *et al*. Screening for colorectal cancer; randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and sigmoidoscopy. Gut Online First, published on August 10, 2009 (doi:10.1136/gut.2009.177089).

33 Bretthauer M, Ekbom A, Malila N, Stefansson T, Fischer A, Hoff G *et al*. [Politics and science in colorectal cancer screening]. Tidsskr Nor Laegeforen 2006; 126(13): 1766-1767.

34 Gezondheidsraad. Wet bevolkingsonderzoek: screening op darmkanker via individuele risicoprofielen. Den Haag: Gezondheidsraad; 2006: 2006/06WBO.

35 Health Council. Screening: between hope and hype. Den Haag:Health Council; 2008: 2008/05E (www.gr.nl).

36 Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO; 1968: Public Health Papers No. 34.

37 Young GP, Mandel J, Sung JJY, Allison JE, Atkin W, Benamouzig R *et al*. Guidelines for evaluation of new screening tests: application to colorectal and gastric cancers. (submitted). submitted 2009.

38 Bossuyt PM, Lijmer JG, Mol BW. Randomised comparisons of medical tests: sometimes invalid, not always efficient. Lancet 2000; 356(9244): 1844-1847.

39 Bossuyt PM, Irwig L, Craig J, Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ 2006; 332(7549): 1089-1092.

40 Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. Cancer 1975; 36(6): 2251-2270.

41 Lansdorp-Vogelaar I, van Ballegooijen M., Boer R, Zauber A, Habbema JD. 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(11): 2410-2419.

42 Shinya H, Wolff WI. Morphology, anatomic distribution and cancer potential of colonic polyps. Ann Surg 1979; 190(6): 679-683.

43 Health Council.The benefit of population screening for breast cancer with mammography. Den Haag: Health Council; 2002: publicatie nr 2002/03E (www.gr.nl).

44 Cuzick J, Cafferty FH, Edwards R, Moller H, Duffy SW. Surrogate endpoints for cancer screening trials: general principles and an illustration using the UK Flexible Sigmoidoscopy Screening Trial. J Med Screen 2007; 14(4): 178-185.

45 Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007; 18(3): 581-592.

46 Steenbergen LN van, Lemmens VE, Louwman MJ, Straathof JW, Coebergh JW. Increasing incidence and decreasing mortality of colorectal cancer due to marked cohort effects in southern Netherlands. Eur J Cancer Prev 2009; 18(2): 145-152.

47 Signaleringscommissie Kanker. Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag. Amsterdam: KWF Kankerbestrijding; 2004.

48 Betés M, Munoz-Navas MA, Duque JM, Angos R, Macias E, Subtil JC *et al*. Use of colonoscopy as a primary screening test for colorectal cancer in average risk people. Am J Gastroenterol 2003; 98(12): 2648-2654.

49 Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J *et al*. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006; 355(18): 1863-1872.

50 Segnan N, Senore C, Andreoni B, Azzoni A, Bisanti L, Cardelli A *et al*. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. Gastroenterology 2007; 132(7): 2304-2312.

51 Hüppe D, Hartmann H, Felten G, Kemen M, Tannapfel a, Gillessen A *et al*. Die Vorsorgekoloskopie rettet Leben - Ergebnisse der Herner Vorsorgedatei. Effectiveness of screening colonoscopy in a community-based study. Z Gastroenterol 2008; 45: 1-8.

52 Khalid-de Bakker C, Jonkers D, Hameeteman W, Masclee A, Stockbrügger R. Primary colonscopy screening for colorectal cancer in a workplace-based community: first results of participation and acceptance. (http://www.nvge.nl/uploads/tA/XP/tAXPm-b1dHIPJtoPx3Hu9g/Abstractboekje-najaar-2007.pdf)

53 Vereniging Klinische Genetica Nederland. Erfelijke darmkanker. Landelijke richtlijn. Versie 1.0. Utrecht: 2008 (www.cbo.nl): 2008.

54 Kwaliteitsinstituut voor de Gezondheidszorg CBO. Follow-up na poliepectomie. Utrecht: CBO; 2002.

55 Olsson L, Lindblom A. Family history of colorectal cancer in a Sweden county. Fam Cancer 2003; 2(2): 87-93.

56 Hemminki K, Sundquist J, Bermejo JL. How common is familial cancer? Ann Oncol 2008; 19(1): 163-167.

57 Jong AE de, Vasen HF. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006; 64(10): 367-370.

58 Sandhu MS, Luben R, Khaw KT. Prevalence and family history of colorectal cancer: implications for screening. J Med Screen 2001; 8(2): 69-72.

59 Baglietto L, Jenkins MA, Severi G, Giles GG, Bishop DT, Boyle P *et al*. Measures of familial aggregation depend on definition of family history: meta-analysis for colorectal cancer. J Clin Epidemiol 2006; 59(2): 114-124.
60 Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer 2006; 42(2): 216-227.
61 Maul JS, Burt RW, Cannon-Albright LA. A familial component to human rectal cancer, independent of colon cancer risk. Clin Gastroenterol Hepatol 2007; 5(9): 1080-1084.
62 Staal-Rosier PM, Rabeling-Keus IM, Kruyt M. [Inadequate referral for genetic evaluations of patients with colorectal carcinoma]. Ned Tijdschr Geneeskd 2009; 153(4): 124-128. [In Dutch]
63 Overbeek LI, Hoogerbrugge N, van Krieken JH, Nagengast FM, Ruers TJ, Ligtenberg MJ *et al*. Most patients with colorectal tumors at young age do not visit a cancer genetics clinic. Dis Colon Rectum 2008; 51(8): 1249-1254.
64 Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003; 348(10): 919-932.
65 Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P *et al*. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005; 352(18): 1851-1860.
66 Hampel H, Stephens JA, Pukkala E, Sankila R, Aaltonen LA, Mecklin JP *et al*. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. Gastroenterology 2005; 129(2): 415-421.
67 Iwama T, Mishima Y, Utsunomiya J. The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg 1993; 217(2): 101-108.
68 Chen TH, Chiu YH, Luh DL, Yen MF, Wu HM, Chen LS *et al*. Community-based multiple screening model: design, implementation, and analysis of 42,387 participants. Cancer 2004; 100(8): 1734-1743.
69 Gezondheidsraad. Screenen op chlamydia. Den Haag: Gezondheidsraad; 2004: 2004/07.
70 Hakama M, Miller AB, Day NE, (editors). Screening for cancer of the uterine cervix. Lyon: International Agency for Research on Cancer; 1986.
71 Gezondheidsraad. Neonatale screening. Den Haag: Gezondheidsraad; 2005: 2005/11.
72 Hakama M, Pukkala E, Saastamoinen P. Selective screening: theory and practice based on high-risk groups of cervical cancer. J Epidemiol Community Health 1979; 33(4): 257-261.
73 Gezondheidsraad. Interim-advies inzake de vroegtijdige opsporing van borstkanker. Den Haag: Gezondheidsraad; 1981: 1981/15.
74 A controlled trial of multiphasic screening in middle-age: results of the South-East London Screening Study. 1977. Int J Epidemiol 2001; 30(5): 935-940.
75 Naish J. Our health, our care, our say. Journal of Medical Screening 2006; 13: 56-57.
76 Kim DJ, Rockhill B, Colditz GA. Validation of the Harvard Cancer Risk Index: a prediction tool for individual cancer risk. J Clin Epidemiol 2004; 57(4): 332-340.
77 Inspectie voor de Gezondheidszorg. Toezicht op preventief medisch onderzoek. Den Haag: IGZ; 2008.

78 Worthley DL, Smith A, Bampton PA, Cole SR, Young GP. Many participants in fecal occult blood test population screening have a higher-than-average risk for colorectal cancer. Eur J Gastroenterol Hepatol 2006; 18(10): 1079-1083.
79 Corbett M, Chambers SL, Shadbolt B, Hillman LC, Taupin D. Med J Aust 2004; 181(8): 423-427.
80 Gondos A, Bray F, Brewster DH, Coebergh JW, Hakulinen T, Janssen-Heijnen ML *et al*. Recent trends in cancer survival across Europe between 2000 and 2004: a model-based period analysis from 12 cancer registries. Eur J Cancer 2008; 44(10): 1463-1475.
81 Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV, Coebergh JWW. Van meten naar weten. 50 jaar kankerregistratie. Eindhoven: Integraal Kankercentrum Zuid, 2005: 2005.
82 Meulenbeld HJ, van Steenbergen LN, Janssen-Heijnen ML, Lemmens VE, Creemers GJ. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. Ann Oncol 2008; 19(9): 1600-1604.
83 Terhaar sive Droste JS, Craanen ME, van der Hulst RW, Bartelsman JF, Bezemer DP, Cappendijk KR *et al*. Colonoscopic yield of colorectal neoplasia in daily clinical practice. World J Gastroenterol 2009; 15(9): 1085-1092.
84 Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA 2008; 300(23): 2765-2778.
85 Duijnhoven FJB van, Bueno de Mesquita HB, Ferrari P, Jenab M, Boshuizen HC, Ros MM *et al*. Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 2009; 89(5): 1441-1452.
86 Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis 2005; 7(3): 204-213.
87 Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E *et al*. Sensitivity, but not specificity, of a quantitative immunochemical fecal occult blood test for neoplasia is slightly increased by the use of low-dose aspirin, NSAIDs, and anticoagulants. Am J Gastroenterol 2009; 104(4): 933-938.
88 Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM *et al*. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993; 328(19): 1365-1371.
89 Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999; 91(5): 434-437.
90 Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW *et al*. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996; 348(9040): 1472-1477.
91 Jørgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002; 50(1): 29-32.
92 Kewenter J, Brevinge H, Engaråas B, Haglind E, Åhrén C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Scand J Gastroenterol 1994; 29: 468-473.

93 Kronborg O, Fenger C, Olsen J, Jørgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996; 348(9040): 1467-1471.

94 Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev 2007; (1): CD001216.

95 Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol 2008; 103(6): 1541-1549.

96 Faivre J, Dancourt V, Lejeune C, Tazi MA, Lamour J, Gerard D *et al*. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. Gastroenterology 2004; 126(7): 1674-1680.

97 Bertario L, Russo A, Crosignani P, Sala P, Spinelli P, Pizzetti P *et al*. Reducing colorectal cancer mortality by repeated faecal occult blood test: a nested case-control study. Eur J Cancer 1999; 35(6): 973-977.

98 Faivre J, Tazi MA, El MT, Lejeune C, Benhamiche AM, Dassonville F. Faecal occult blood screening and reduction of colorectal cancer mortality: a case-control study. Br J Cancer 1999; 79(3-4): 680-683.

99 Lamah M, Norris J, Caffarey SM, Broughton M, Marks CG. Effect of faecal occult blood testing on colorectal cancer mortality in the surveillance of subjects at moderate risk of colorectal neoplasia: a case-control study. Int J Colorectal Dis 2001; 16(5): 313-317.

100 Lazovich D-A, Weiss NS, Stevens NG, White E, McKnight B, Wagner EH. A case-control study to evaluate efficacy of screening for faecal occult blood. J Med Screening 1995; 2: 84-89.

101 Saito H, Soma Y, Koeda J, Wada T, Kawaguchi H, Sobue T *et al*. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. Int J Cancer 1995; 61(4): 465-469.

102 Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS. Effect of fecal occult blood testing on mortality from colorectal cancer. A case-control study. Ann Intern Med 1993; 118(1): 1-6.

103 Wahrendorf J, Robra BP, Wiebelt H, Oberhausen R, Weiland M, Dhom G. Effectiveness of colorectal cancer screening: results from a population-based case-control evaluation in Saarland, Germany. Eur J Cancer Prev 1993; 2(3): 221-227.

104 Zappa M, Castiglione G, Grazzini G, Falini P, Giorgi D, Paci E *et al*. Effect of faecal occult blood testing on colorectal mortality: results of a population-based case-control study in the district of Florence, Italy. Int J Cancer 1997; 73(2): 208-210.

105 Costantini AS, Martini A, Puliti D, Ciatto S, Castiglione G, Grazzini G *et al*. Colorectal cancer mortality in two areas of Tuscany with different screening exposures. J Natl Cancer Inst 2008; 100(24): 1818-1821.

106 Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ *et al*. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000; 343(22): 1603-1607.

107 Atkin W. Options for screening for colorectal cancer. Scand J Gastroenterol Suppl 2003;(237): 13-16.

108 Bonneux L. Arguments against implementing a population-based screening programme for colorectal cancer. Ned Tijdschr Geneeskd 2008; 152(32): 1777. Dutch

109 Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004; 351(26): 2704-2714.

110 Cheng TI, Wong JM, Hong CF, Cheng SH, Cheng TJ, Shieh MJ *et al*. Colorectal cancer screening in asymptomatic adults: comparison of colonoscopy, sigmoidoscopy and fecal occult blood tests. J Formos Med Assoc 2002; 101(10): 685-690.

111 Gyrd-Hansen D, Sogaard J, Kronborg O. Analysis of screening data: colorectal cancer. Int J Epidemiol 1997; 26(6): 1172-1181.

112 Zappa M, Castiglione G, Paci E, Grazzini G, Rubeca T, Turco P *et al*. Measuring interval cancers in population-based screening using different assays of fecal occult blood testing: the District of Florence experience. Int J Cancer 2001; 92(1): 151-154.

113 Souques M, Zummer K. Le test hémoccult IIr: résultats de 16 ans de pratique dans le service de prévention et dépistage des tumeurs de la ville de Paris. Presse Med 2000; 29(18): 983-986.

114 Allison JE, Feldman R, Tekawa IS. Hemoccult screening in detecting colorectal neoplasm: sensitivity, specificity, and predictive value. Long-term follow-up in a large group practice setting. Ann Intern Med 1990; 112(5): 328-333.

115 Robinson MH, Moss SM, Hardcastle JD, Whynes DK, Chamberlain JO, Mangham CM. Effect of retesting with dietary restriction in Haemoccult screening for colorectal cancer. J Med Screen 1995; 2(1): 41-44.

116 Moss SM, Hardcastle JD, Coleman DA, Robinson MH, Rodrigues VC. Interval cancers in a randomized controlled trial of screening for colorectal cancer using a faecal occult blood test. Int J Epidemiol 1999; 28(3): 386-390.

117 Bouvier V, Launoy G, Herbert C, Lefevre H, Maurel J, Gignoux M. Colorectal cancer after a negative Haemoccult II test and programme sensitivity after a first round of screening: the experience of the Department of Calvados (France). Br J Cancer 1999; 81(2): 305-309.

118 Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996; 334(3): 155-159.

119 Weller D, Coleman D, Robertson R, Butler P, Melia J, Campbell C *et al*. The UK colorectal cancer screening pilot: results of the second round of screening in England. Br J Cancer 2007; 97(12): 1601-1605.

120 Tazi MA, Faivre J, Dassonville F, Lamour J, Milan C, Durand G. Participation in faecal occult blood screening for colorectal cancer in a well defined French population: results of five screening rounds from 1988 to 1996. J Med Screen 1997; 4(3): 147-151.

121 Rae LC, Gibberd RW. Survival of patients with colorectal cancer detected by a community screening program. Med J Aust 2000; 172(1): 13-15.

122 The Multicentre Australian Colorectal-neoplasia Screening (MACS) Group. A comparison of colorectal neoplasia screening tests: a multicentre community-based study of the impact of consumer choice. Med J Aust 2006; 184(11): 546-550.

123 Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol 2004; 39(9): 846-851.

124 Malila N, Oivanen T, Malminiemi O, Hakama M. Test, episode, and programme sensitivities of screening for colorectal cancer as a public health policy in Finland: experimental design. BMJ 2008; 337: a2261.

125 Steele RJ, McClements PL, Libby G, Black R, Morton C, Birrell J *et al*. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. Gut 2009; 58(4): 530-535.

126 Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2002; 137(2): 96-104.

127 Whynes DK. Cost-effectiveness of screening for colorectal cancer: evidence from the Nottingham faecal occult blood trial. J Med Screen 2004; 11(1): 11-15.

128 Gyrd-Hansen D, Sogaard J, Kronborg O. Colorectal cancer screening: efficiency and effectiveness. Health Econ 1998; 7(1): 9-20.

129 Lejeune C, Arveux P, Dancourt V, Bejean S, Bonithon-Kopp C, Faivre J. Cost-effectiveness analysis of fecal occult blood screening for colorectal cancer. Int J Technol Assess Health Care 2004; 20(4): 434-439.

130 Zheng S, Chen K, Liu X, Ma X, Yu H, Chen K *et al*. Cluster randomization trial of sequence mass screening for colorectal cancer. Dis Colon Rectum 2003; 46(1): 51-58.

131 Federici A, Giorgi RP, Borgia P, Bartolozzi F, Farchi S, Gausticchi G. The immunochemical faecal occult blood test leads to higher compliance than the guaiac for colorectal cancer screening programmes: a cluster randomized controlled trial. J Med Screen 2005; 12(2): 83-88.

132 Castiglione G, Zappa M, Grazzini G, Rubeca T, Turco P, Sani C *et al*. Screening for colorectal cancer by faecal occult blood test: comparison of immunochemical tests. J Med Screen 2000; 7(1): 35-37.

133 Castiglione G, Grazzini G, Miccinesi G, Rubeca T, Sani C, Turco P *et al*. Basic variables at different positivity thresholds of a quantitative immunochemical test for faecal occult blood. J Med Screen 2002; 9(3): 99-103.

134 Crotta S, Castiglione G, Grazzini G, Valle F, Mosconi S, Rosset R. Feasibility study of colorectal cancer screening by immunochemical faecal occult blood testing: results in a northern Italian community. Eur J Gastroenterol Hepatol 2004; 16(1): 33-37.

135 Fernandez JL, Gallegos M, Brochero A, Arevalo C, Piccioni H, Gutierrez GH. [Screening for colorectal cancer with an immunological fecal occult blood test]. Acta Gastroenterol Latinoam 1999; 29(2): 73-78.

136 Itoh M, Takahashi K, Nishida H, Sakagami K, Okubo T. Estimation of the optimal cut off point in a new immunological faecal occult blood test in a corporate colorectal cancer screening programme. J Med Screen 1996; 3(2): 66-71.

137 Nakama H, Zhang B, Zhang X, Fukazawa K. Age-related cancer detection rate and costs for one cancer detected in one screening by immunochemical fecal occult blood test. Dis Colon Rectum 2001; 44(11): 1696-1699.

138 Vilkin A, Rozen P, Levi Z, Waked A, Maoz E, Birkenfeld S *et al*. Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. Am J Gastroenterol 2005; 100(11): 2519-2525.

139 Yoshinaga M, Motomura S, Takeda H, Yanagisawa Z, Ikeda K. Evaluation of the sensitivity of an immunochemical fecal occult blood test for colorectal neoplasia. Am J Gastroenterol 1995; 90(7): 1076-1079.

140 Guittet L, Bouvier V, Mariotte N, Vallee JP, Arsene D, Boutreux S *et al*. Comparison of a guaiac-based and an immunochemical fecal occult blood test in screening for colorectal cancer in a general average-risk population. Gut 2006;

141 Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. Br J Cancer 2003; 89(1): 23-28.

142 Saito H, Soma Y, Nakajima M, Koeda J, Kawaguchi H, Kakizaki R *et al*. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncol Rep 2000; 7(4): 815-819.

143 Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150(3): 162-169.

144 Levi Z, Hazazi R, Rozen P, Vilkin A, Waked A, Niv Y. A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test. Aliment Pharmacol Ther 2006; 23(9): 1359-1364.

145 Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E *et al*. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med 2007; 146(4): 244-255.

146 Li S, Wang H, Hu J, Li N, Liu Y, Wu Z *et al*. New immunochemical fecal occult blood test with two-consecutive stool sample testing is a cost-effective approach for colon cancer screening: results of a prospective multicenter study in Chinese patients. Int J Cancer 2006; 118(12): 3078-3083.

147 Wong BC, Wong WM, Cheung KL, Tong TS, Rozen P, Young GP *et al*. A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. Aliment Pharmacol Ther 2003; 18(9): 941-946.

148 Wong WM, Lam SK, Cheung KL, Tong TS, Rozen P, Young GP *et al*. Evaluation of an automated immunochemical fecal occult blood test for colorectal neoplasia detection in a Chinese population. Cancer 2003; 97(10): 2420-2424.

149 Nakama H, Kamijo N, Miyata K, Abdul Fattah AS, Zhang B, Uehara Y. Sensitivity and specificity of several immunochemical tests for colorectal cancer. Hepatogastroenterology 1998; 45(23): 1579-1582.

150 Allison JE, Sakoda LC, Levin TR, Tucker JP, Tekawa IS, Cuff T *et al*. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007; 99(19): 1462-1470.

151 Castiglione G, Zappa M, Grazzini G, Sani C, Mazzotta A, Mantellini P *et al*. Cost analysis in a population based screening programme for colorectal cancer: comparison of immunochemical and guaiac faecal occult blood testing. J Med Screen 1997; 4(3): 142-146.

152 Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. J Med Screen 2003; 10(3): 117-122.

153 Smith A, Young GP, Cole SR, Bampton P. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. Cancer 2006; 107(9): 2152-2159.

154 Burch JA, Soares-Weiser K, St John DJ, Duffy S, Smith S, Kleijnen J *et al*. Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review. J Med Screen 2007; 14(3): 132-137.

155 Oort FA, Terhaar sive Droste JS, van der Hulst RWM, van Heukelem HA, Loffeld RJLF, Wesdorp ICE *et al*. Higher cut off values for FIT in CRC-screening: less colonoscopies, same detection rates for curable cancers. Submitted.

156 Allison JE, Levin T, Sakoda L, Tucker J, Tekawa I, Pauly MP. The new fecal occult blood tests have poor application sensitivity for significant polyps in average risk subjects. Gastroenterology 2002; 122: A592-A593.

157 Graser A, Stieber P, Nagel D, Schaefer C, Horst D, Becker CR *et al*. Comparison of CT Colonography, Colonoscopy, Sigmoidoscopy, and Fecal Occult Blood Tests for the Detection of Advanced Adenoma in an Average Risk Population. Gut 2009; 58: 241-248.

158 Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005; 129(2): 422-428.

159 Nakama H, Yamamoto M, Kamijo N, Li T, Wei N, Fattah AS *et al*. Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia. Hepatogastroenterology 1999; 46(25): 228-231.

160 Launoy GD, Bertrand HJ, Berchi C, Talbourdet VY, Guizard AV, Bouvier VM *et al*. Evaluation of an immunochemical fecal occult blood test with automated reading in screening for colorectal cancer in a general average-risk population. Int J Cancer 2005; 115(3): 493-496.

161 Chen LS, Liao CS, Chang SH, Lai HC, Chen TH. Cost-effectiveness analysis for determining optimal cut-off of immunochemical faecal occult blood test for population-based colorectal cancer screening (KCIS 16). J Med Screen 2007; 14(4): 191-199.

162 Castiglione G, Visioli CB, Ciatto S, Grazzini G, Bonanomi AG, Rubeca T *et al*. Sensitivity of latex agglutination faecal occult blood test in the Florence District population-based colorectal cancer screening programme. Br J Cancer 2007; 96(11): 1750-1754.

163 Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E *et al*. Identification of colorectal adenomas by a quantitative immunochemical faecal occult blood screening test depends on adenoma characteristics, development threshold used and number of tests performed. Aliment Pharmacol Ther 2009; 29(8): 906-917.

164 Zorzi M, Falcini F, Fedato C, Grazzini G, Sassoli de Bianchi P, Senore C. Screening for colorectal cancer in Italy: 2006 survey. Epidemiol Prev 2008; 32(2): 55-68.

165 Ciatto S, Martinelli F, Castiglione G, Mantellini P, Rubeca T, Grazzini G *et al*. Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. Br J Cancer 2007; 96(2): 218-221.

166 Dancourt V, Lejeune C, Lepage C, Gailliard MC, Meny B, Faivre J. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. Eur J Cancer 2008; 44(15): 2254-2258.

167 Hughes K, Leggett B, Del MC, Croese J, Fairley S, Masson J *et al*. Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community. Aust N Z J Public Health 2005; 29(4): 358-364.

168 Rossum LGM van, van Rijn AF, Van Munster IP, Fockens P, Jansen JBMJ, Laheij RJF *et al*. Earlier stages of colorectal cancer detected with immunochemical faecal occult blood tests. Neth J Med 2009; 67(5): 182-186.

169 Yang KC, Liao CS, Chiu YH, Yen AM, Chen TH. Colorectal cancer screening with faecal occult blood test within a multiple disease screening programme: an experience from Keelung, Taiwan. J Med Screen 2006; 13 Suppl 1: S8-13.

170 Young GP, St John DJ, Cole SR, Bielecki BE, Pizzey C, Sinatra MA *et al*. Prescreening evaluation of a brush-based faecal immunochemical test for haemoglobin. J Med Screen 2003; 10(3): 123-128.

171 Berchi C, Bouvier V, Reaud JM, Launoy G. Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France. Health Econ 2004; 13(3): 227-238.

172 Rossum LG van, van Rijn AF, Verbeek ALM, van Oijen MGH, Laheij RJF, Fockens P *et al*. Colorectal cancer screening comparing no screening, immunochemical and guaiac faecal occult blood tests: a cost-effectiveness analysis (submitted). soon to be published 2008;

173 Parekh M, Fendrick AM, Ladabaum U. As tests evolve and costs of cancer care rise: reappraising stool-based screening for colorectal neoplasia. Aliment Pharmacol Ther 2008; 27(8): 697-712.

174 Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M., Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2008; 149(9): 659-669.

175 Mulder SA, Ouwendijk RJ, Giard RW, van Leerdam ME, Kuipers EJ. Risk analyses for screening sigmoidoscopy based on a colorectal cancer (CRC) population. Scand J Gastroenterol 2009; 44(2): 205-210.

176 Shapero TF, Hoover J, Paszat LF, Burgis E, Hsieh E, Rothwell DM *et al*. Colorectal cancer screening with nurse-performed flexible sigmoidoscopy: results from a Canadian community-based program. Gastrointest Endosc 2007; 65(4): 640-645.

177 Putten PG van, van Leerdam ME, Kuipers EJ. The views of gastroenterologists about the role of nurse endoscopists, especially in colorectal cancer screening. Aliment Pharmacol Ther 2009; 29(8): 892-897.

178 Hoff G, Grotmol T, Skovlund E, Bretthauer M. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ 2009; 338: b1846.

179 Bretthauer M, Gondal G, Larsen K, Carlsen E, Eide TJ, Grotmol T *et al*. Design, organization and management of a controlled population screening study for detection of colorectal neoplasia: attendance rates in the NORCCAP study (Norwegian Colorectal Cancer Prevention). Scand J Gastroenterol 2002; 37(5): 568-573.

180 Peto R. Limitations of trial. BMJ 2009; 338: 1518.

181 Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G. 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(6): 635-642.

182 Segnan N, Senore C, Andreoni B, Arrigoni A, Bisanti L, Cardelli A *et al*. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. J Natl Cancer Inst 2005; 97(5): 347-357.

183 Bleiberg H, Autier P, Huet F, Schrauwen AM, Staquet E, Delaunoit T *et al*. Colorectal cancer (CRC) screening using sigmoidoscopy followed by colonoscopy: a feasibility and efficacy study on a cancer institute based population. Ann Oncol 2006; 17(8): 1328-1332.

184 Hoff G, Sauar J, Vatn MH, Larsen S, Langmark F, Moen IE *et al*. Polypectomy of adenomas in the prevention of colorectal cancer: 10 years' follow-up of the Telemark Polyp Study I. A prospective, controlled population study. Scand J Gastroenterol 1996; 31(10): 1006-1010.

185 Lieberman DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 2001; 345(8): 555-560.

186 Loeve F, Brown ML, Boer R, van Ballegooijen M, van Oortmarssen GJ, Habbema JD. Endoscopic colorectal cancer screening: a cost-saving analysis. J Natl Cancer Inst 2000; 92(7): 557-563.

187 Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 1995; 123(12): 904-910.

188 Newcomb PA, Storer BE, Morimoto LM, Templeton A, Potter JD. Long-term efficacy of sigmoidoscopy in the reduction of colorectal cancer incidence. J Natl Cancer Inst 2003; 95(8): 622-625.

189 Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992; 326(10): 653-657.

190 Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol 1999; 34(4): 414-420.

191 Cotterchio M, Manno M, Klar N, McLaughlin J, Gallinger S. Colorectal screening is associated with reduced colorectal cancer risk: a case-control study within the population-based Ontario Familial Colorectal Cancer Registry. Cancer Causes Control 2005; 16(7): 865-875.

192 Brenner H, Arndt V, Stegmaier C, Ziegler H, Sturmer T. Reduction of clinically manifest colorectal cancer by endoscopic screening: empirical evaluation and comparison of screening at various ages. Eur J Cancer Prev 2005; 14(3): 231-237.

193 Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000; 343(3): 162-168.

194 Schoenfeld P, Cash B, Flood A, Dobhan R, Eastone J, Coyle W *et al*. Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 2005; 352(20): 2061-2068.

195 Ikeda Y, Mori M, Miyazaki M, Yoshizumi T, Maehara Y, Sugimachi K. Significance of small distal adenoma for detection of proximal neoplasms in the colorectum. Gastrointest Endosc 2000; 52(3): 358-361.

196 Anderson JC, Alpern Z, Messina CR, Lane B, Hubbard P, Grimson R *et al*. Predictors of proximal neoplasia in patients without distal adenomatous pathology. Am J Gastroenterol 2004; 99(3): 472-477.

197 Betes IM, Munoz-Navas MA, Duque JM, Angos R, Macias E, Subtil JC *et al*. Diagnostic value of distal colonic polyps for prediction of advanced proximal neoplasia in an average-risk population undergoing screening colonoscopy. Gastrointest Endosc 2004; 59(6): 634-641.

198 Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Using risk for advanced proximal colonic neoplasia to tailor endoscopic screening for colorectal cancer. Ann Intern Med 2003; 139(12): 959-965.

199 Denis B, Gendre I, Aman F, Ribstein F, Maurin P, Perrin P. Colorectal cancer screening with the addition of flexible sigmoidoscopy to guaiac-based faecal occult blood testing: A French population-based controlled study (Wintzenheim trial). Eur J Cancer 2009; In Press.

200 Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH *et al*. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA 1999; 282(11): 1061-1066.

201 Brenner H, Chang-Claude J, Seiler CM, Sturmer T, Hoffmeister M. Potential for colorectal cancer prevention of sigmoidoscopy versus colonoscopy: population-based case control study. Cancer Epidemiol Biomarkers Prev 2007; 16(3): 494-499.

202 Hol L, Wilschut JA, van Ballegooijen M, van Vuuren AJ, van der Valk H, Reijerink JCIY *et al*. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. Br J Cancer 100, 1103-1110. 2009.

203 Bretthauer M, Skovlund E, Grotmol T, Thiis-Evensen E, Gondal G, Huppertz-Hauss G *et al*. Inter-endoscopist variation in polyp and neoplasia pick-up rates in flexible sigmoidoscopy screening for colorectal cancer. Scand J Gastroenterol 2003; 38(12): 1268-1274.

204 Atkin W, Rogers P, Cardwell C, Cook C, Cuzick J, Wardle J *et al*. Wide variation in adenoma detection rates at screening flexible sigmoidoscopy. Gastroenterology 2004; 126(5): 1247-1256.

205 Levin TR, Farraye FA, Schoen RE, Hoff G, Atkin W, Bond JH *et al*. Quality in the technical performance of screening flexible sigmoidoscopy: recommendations of an international multi-society task group. Gut 2005; 54(6): 807-813.

206 Pinsky PF, Schoen RE, Weissfeld JL, Kramer B, Hayes RB, Yokochi L. Variability in flexible sigmoidoscopy performance among examiners in a screening trial. Clin Gastroenterol Hepatol 2005; 3(8): 792-797.

207 Collett JA, Olynyk JK, Platell CF. Flexible sigmoidoscopy screening for colorectal cancer in average-risk people: update of a community-based project. Med J Aust 2000; 173(9): 463-466.

208 Brevinge H, Lindholm E, Buntzen S, Kewenter J. Screening for colorectal neoplasia with faecal occult blood testing compared with flexible sigmoidoscopy directly in a 55-56 years' old population. Int J Colorectal Dis 1997; 12(5): 291-295.

209 Wu X, Chen VW, Martin J, Roffers S, Groves FD, Correa CN *et al*. Subsite-specific colorectal cancer incidence rates and stage distributions among Asians and Pacific Islanders in the United States, 1995 to 1999. Cancer Epidemiol Biomarkers Prev 2004; 13(7): 1215-1222.

210 Kremers SP, Mesters I, Pladdet IE, van den BB, Stockbrugger RW. Participation in a sigmoidoscopic colorectal cancer screening program: a pilot study. Cancer Epidemiol Biomarkers Prev 2000; 9(10): 1127-1130.

211 Bleiberg H, Autier P, Huet F, Schrauwen AM, Staquet E, Delaunoit T *et al*. Colorectal cancer (CRC) screening using sigmoidoscopy followed by colonoscopy: a feasibility and efficacy study on a cancer institute based population. Ann Oncol 2006; 17(8): 1328-1332.

212 Nicholson FB, Korman MG. Acceptance of flexible sigmoidoscopy and colonoscopy for screening and surveillance in colorectal cancer prevention. J Med Screen 2005; 12(2): 89-95.

213 Taylor T, Williamson S, Wardle J, Borrill J, Sutton S, Atkin W. Acceptability of flexible sigmoidoscopy screening in older adults in the United Kingdom. J Med Screen 2000; 7(1): 38-45.

214 Levin TR, Conell C, Shapiro JA, Chazan SG, Nadel MR, Selby JV. Complications of screening flexible sigmoidoscopy. Gastroenterology 2002; 123(6): 1786-1792.

215 Maule WF. Screening for colorectal cancer by nurse endoscopists. N Engl J Med 1994; 330(3): 183-187.

216 Wallace MB, Kemp JA, Meyer F, Horton K, Reffel A, Christiansen CL *et al*. Screening for colorectal cancer with flexible sigmoidoscopy by nonphysician endoscopists. Am J Med 1999; 107(3): 214-218.

217 Anderson ML, Pasha TM, Leighton JA. Endoscopic perforation of the colon: lessons from a 10-year study. Am J Gastroenterol 2000; 95(12): 3418-3422.

218 Robinson MH, Hardcastle JD, Moss SM, Amar SS, Chamberlain JO, Armitage NC *et al*. The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer. Gut 1999; 45(4): 588-592.

219 Gezondheidsraad. Wet bevolkingsonderzoek: CT-colografie en coloscopie vergeleken. Den Haag: 2009: 2009/03WBO.

220 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS *et al*. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329(27): 1977-1981.

221 Brenner H, Chang-Claude J, Seiler CM, Sturmer T, Hoffmeister M. Does a negative screening colonoscopy ever need to be repeated? Gut 2006; 55(8): 1145-1150.

222 Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001; 48(6): 812-815.

223 Singh H, Turner D, Xue L, Targownik LE, Bernstein CN. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. JAMA 2006; 295(20): 2366-2373.

224 Heresbach D, Barrioz T, Lapalus MG, Coumaros D, Bauret P, Potier P *et al*. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. Endoscopy 2008; 40(4): 284-290.

225 Rijn JC van, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006; 101(2): 343-350.

226 Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. Ann Intern Med 2004; 141(5): 352-359.

227 Rockey DC, Paulson E, Niedzwiecki D, Davis W, Bosworth HB, Sanders L *et al*. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. Lancet 2005; 365(9456): 305-311.

228 Arnesen RB, von BE, Adamsen S, Svendsen LB, Raaschou HO, Hansen OH. Diagnostic performance of computed tomography colonography and colonoscopy: a prospective and validated analysis of 231 paired examinations. Acta Radiol 2007; 48(8): 831-837.

229 Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA *et al*. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003; 349(23): 2191-2200.

230 Bressler B, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology 2007; 132(1): 96-102.

231 Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009; 150(1): 1-8.

232 Brenner H, Hoffmeister M, Brenner G, Altenhofen L, Haug U. Expected reduction of colorectal cancer incidence within 8 years after introduction of the German screening colonoscopy programme: estimates based on 1,875,708 screening colonoscopies. EJC 2009; 1-7.

233 Rex DK, Rahmani EY, Haseman JH, Lemmel GT, Kaster S, Buckley JS. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. Gastroenterology 1997; 112(1): 17-23.

234 Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000; 343(3): 169-174.

235 Sieg A, Theilmeier A. [Results of coloscopy screening in 2005--an Internet-based documentation]. Dtsch Med Wochenschr 2006; 131(8): 379-383.

236 Niv Y, Hazazi R, Levi Z, Fraser G. Screening colonoscopy for colorectal cancer in asymptomatic people: A meta-analysis. Dig Dis Sci 2008; 53: 3049-3054.

237 DeBourcy AC, Lichtenberger S, Felton S, Butterfield KT, Ahnen DJ, Denberg TD. Community-based preferences for stool cards versus colonoscopy in colorectal cancer screening. J Gen Intern Med 2008; 23(2): 169-174.

238 Thiis-Evensen E, Seip B, Vatn MH, Hoff GS. Impact of a colonoscopic screening examination for colorectal cancer on later utilization of distal GI endoscopies. Gastrointest Endosc 2006; 64(6): 948-954.

239 Denberg TD, Coombes JM, Byers TE, Marcus AC, Feinberg LE, Steiner JF *et al*. Effect of a mailed brochure on appointment-keeping for screening colonoscopy: a randomized trial. Ann Intern Med 2006; 145(12): 895-900.

240 Joseph DA, Rim SH, Seeff LC. Use of colorectal cancer test - United States, 2002, 2004 and 2006. JAMA 2008; 299: 2501.

241 Pox C, Schmiegel W, Classen M. Current status of screening colonoscopy in Europe and in the United States. Endoscopy 2007; 39(2): 168-173.

242 Denberg TD, Melhado TV, Coombes JM, Beaty BL, Berman K, Byers TE *et al*. Predictors of nonadherence to screening colonoscopy. J Gen Intern Med 2005; 20(11): 989-995.

243 Scott RG, Edwards JT, Fritschi L, Foster NM, Mendelson RM, Forbes GM. Community-based screening by colonoscopy or computed tomographic colonography in asymptomatic average-risk subjects. Am J Gastroenterol 2004; 99(6): 1145-1151.

244 Bokemeyer B, Sieg A, Düffelmeyer M, Bock H. Internet-basierte Online-Dokumentation der Vorsorge-Koloskopie. Gastro Nachrichten 2004; 42, 8/04: 6-8.

245 Soon MS, Kozarek RA, Ayub K, Soon A, Lin TY, Lin OS. Screening colonoscopy in Chinese and Western patients: a comparative study. Am J Gastroenterol 2005; 100(12): 2749-2755.

246 Strul H, Kariv R, Leshno M, Halak A, Jakubowicz M, Santo M *et al*. The prevalence rate and anatomic location of colorectal adenoma and cancer detected by colonoscopy in average-risk individuals aged 40-80 years. Am J Gastroenterol 2006; 101(2): 255-262.

247 Kim DH, Pickhardt PJ, Taylor AJ, Leung WK, Winter TC, Hinshaw JL *et al*. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med 2007; 357(14): 1403-1412.

248 Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD *et al*. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008; 359(12): 1207-1217.

249 Rabeneck L, Paszat LF, Hilsden RJ, Saskin R, Leddin D, Grunfeld E *et al*. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. Gastroenterology 2008; 135(6): 1899-1906, 1906.

250 Korman LY, Overholt BF, Box T, Winker CK. Perforation during colonoscopy in endoscopic ambulatory surgical centers. Gastrointest Endosc 2003; 58(4): 554-557.

251 Sieg A, Hachmoeller-Eisenbach U, Eisenbach T. Prospective evaluation of complications in outpatient GI endoscopy: a survey among German gastroenterologists. Gastrointest Endosc 2001; 53(6): 620-627.

252 Viiala CH, Zimmerman M, Cullen DJ, Hoffman NE. Complication rates of colonoscopy in an Australian teaching hospital environment. Intern Med J 2003; 33(8): 355-359.

253 Iqbal CW, Cullinane DC, Schiller HJ, Sawyer MD, Zietlow SP, Farley DR. Surgical management and outcomes of 165 colonoscopic perforations from a single institution. Arch Surg 2008; 143(7): 701-706.

254 O'Leary BA, Olynyk JK, Neville AM, Platell CF. Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy. J Gastroenterol Hepatol 2004; 19(1): 38-47.

255 Sieg A, Brenner H. Cost-saving analysis of screening colonoscopy in Germany. Z Gastroenterol 2007; 45(9): 945-951.

256 Sonnenberg A, Delco F. Cost-effectiveness of a single colonoscopy in screening for colorectal cancer. Arch Intern Med 2002; 162(2): 163-168.

257 Bretagne JF, Ponchon T. Do we need to embrace adenoma detection rate as the main quality control parameter during colonoscopy? Endoscopy 2008; 40(6): 523-528.

258 Berg M van den, van Gils PF, van Kranen HJ. Literatuuronderzoek naar methoden voor dikkedarmkankerscreening. Bilthoven: RIVM; 2007: V/2702/14001.

259 Gossum A van, Navas MM, Fernandez-Urien I, Carretero C, Gay G, Delvaux M *et al*. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. N Engl J Med 2009; 361(3): 264-270.

260 Taylor SA, Laghi A, Lefere P, Halligan S, Stoker J. European Society of Gastrointestinal and Abdominal Radiology (ESGAR): consensus statement on CT colonography. Eur Radiol 2007; 17(2): 575-579.

261 Jensch S, van Gelder RE, Florie J, Thomassen-de Graaf MA, Lobe JV, Bossuyt PM *et al*. Performance of radiographers in the evaluation of CT colonographic images. AJR Am J Roentgenol 2007; 188(3): W249-W255.

262 Pickhardt PJ, Hanson ME, Vanness DJ, Lo JY, Kim DH, Taylor AJ *et al*. Unsuspected extracolonic findings at screening CT colonography: clinical and economic impact. Radiology 2008; 249(1): 151-159.

263 Graaf Y van der. [Echografic screening of the abdominal aorta in older men is not useful]. Ned Tijdschr Geneeskd 2008; 152: 751. Dutch.

264 Pickhardt PJ, Taylor AJ, Kim DH, Reichelderfer M, Gopal DV, Pfau PR. Screening for colorectal neoplasia with CT colonography: initial experience from the 1st year of coverage by third-party payers. Radiology 2006; 241(2): 417-425.

265 Fletcher RH. Colorectal cancer screening on stronger footing. N Engl J Med 2008; 359(12): 1285-1287.

266 Kuehle CA, Langhorst J, Ladd SC, Zoepf T, Nuefer M, Grabellus F *et al*. Magnetic resonance colonography without bowel cleansing: a prospective cross sectional study in a screening population. Gut 2007; 56(8): 1079-1085.

267 Halligan S, Altman DG, Taylor SA, Mallett S, Deeks JJ, Bartram CI *et al*. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 2005; 237(3): 893-904.

268 Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. Ann Intern Med 2005; 142(8): 635-650.

269 Sosna J, Morrin MM, Kruskal JB, Lavin PT, Rosen MP, Raptopoulos V. CT colonography of colorectal polyps: a metaanalysis. AJR Am J Roentgenol 2003; 181(6): 1593-1598.

270 Edwards JT, Mendelson RM, Fritschi L, Foster NM, Wood C, Murray D *et al*. Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community-based study. Radiology 2004; 230(2): 459-464.

271 Johnson CD, Fletcher JG, Maccarty RL, Mandrekar JN, Harmsen WS, Limburg PJ *et al*. Effect of slice thickness and primary 2D versus 3D virtual dissection on colorectal lesion detection at CT colonography in 452 asymptomatic adults. AJR Am J Roentgenol 2007; 189(3): 672-680.

272 Florie J, van Gelder RE, Schutter MP, van RA, Venema HW, de JS *et al*. Feasibility study of computed tomography colonography using limited bowel preparation at normal and low-dose levels study. Eur Radiol 2007; 17(12): 3112-3122.

273 Jensch S, de Vries AH, Peringa J, Bipat S, Dekker E, Baak LC *et al*. CT colonography with limited bowel preparation: performance characteristics in an increased-risk population. Radiology 2008; 247(1): 122-132.

274 Juchems MS, Ehmann J, Brambs HJ, Aschoff AJ. A retrospective evaluation of patient acceptance of computed tomography colonography (“virtual colonoscopy”) in comparison with conventional colonoscopy in an average risk screening population. Acta Radiol 2005; 46(7): 664-670.

275 Taylor SA, Slater A, Burling DN, Tam E, Greenhalgh R, Gartner L *et al*. CT colonography: optimisation, diagnostic performance and patient acceptability of reduced-laxative regimens using barium-based faecal tagging. Eur Radiol 2008; 18(1): 32-42.

276 Zalis ME, Perumpillichira JJ, Magee C, Kohlberg G, Hahn PF. Tagging-based, electronically cleansed CT colonography: evaluation of patient comfort and image readability. Radiology 2006; 239(1): 149-159.

277 Ridley LJ. Allergic reactions to oral iodinated contrast agents: reactions to oral contrast. Australas Radiol 1998; 42(2): 114-117.

278 Gelder RE van, Venema HW, Serlie IW, Nio CY, Determann RM, Tipker CA *et al*. CT colonography at different radiation dose levels: feasibility of dose reduction. Radiology 2002; 224(1): 25-33.

279 Gelder RE van, Venema HW, Florie J, Nio CY, Serlie IW, Schutter MP *et al*. CT colonography: feasibility of substantial dose reduction--comparison of medium to very low doses in identical patients. Radiology 2004; 232(2): 611-620.

280 Gelder RE van, Birnie E, Florie J, Schutter MP, Bartelsman JF, Snel P *et al*. CT colonography and colonoscopy: assessment of patient preference in a 5-week follow-up study. Radiology 2004; 233(2): 328-337.

281 Pickhardt PJ. Incidence of colonic perforation at CT colonography: review of existing data and implications for screening of asymptomatic adults. Radiology 2006; 239(2): 313-316.

282 Burling D, Halligan S, Slater A, Noakes MJ, Taylor SA. Potentially serious adverse events at CT colonography in symptomatic patients: national survey of the United Kingdom. Radiology 2006; 239(2): 464-471.

283 Sosna J, Blachar A, Amitai M, Barmeir E, Peled N, Goldberg SN *et al*. Colonic perforation at CT colonography: assessment of risk in a multicenter large cohort. Radiology 2006; 239(2): 457-463.

284 Lieberman D, Moravec M, Holub J, Michaels L, Eisen G. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. Gastroenterology 2008; 135(4): 1100-1105.

285 Pickhardt PJ, Hassan C, Laghi A, Zullo A, Kim DH, Iafrate F *et al*. Small and diminutive polyps detected at screening CT colonography: a decision analysis for referral to colonoscopy. AJR Am J Roentgenol 2008; 190(1): 136-144.

286 Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS *et al*. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008; 58(3): 130-160.

287 Zalis ME, Barish MA, Choi JR, Dachman AH, Fenlon HM, Ferrucci JT *et al*. CT colonography reporting and data system: a consensus proposal. Radiology 2005; 236(1): 3-9.

288 Butterly LF, Pohl H. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med 2008; 358(1): 89.

289 Pickhardt PJ. The natural history of colorectal polyps and masses: rediscovered truths from the barium enema era. AJR Am J Roentgenol 2007; 188(3): 619-621.

290 Hofstad B, Vatn MH, Andersen SN, Huitfeldt HS, Rognum T, Larsen S *et al*. Growth of colorectal polyps: redetection and evaluation of unresected polyps for a period of three years. Gut 1996; 39(3): 449-456.

291 Church JM. Clinical significance of small colorectal polyps. Dis Colon Rectum 2004; 47(4): 481-485.

292 Odom SR, Duffy SD, Barone JE, Ghevariya V, McClane SJ. The rate of adenocarcinoma in endoscopically removed colorectal polyps. Am Surg 2005; 71(12): 1024-1026.

293 Schoen RE, Weissfeld JL, Pinsky PF, Riley T. Yield of advanced adenoma and cancer based on polyp size detected at screening flexible sigmoidoscopy. Gastroenterology 2006; 131(6): 1683-1689.
294 Yoo TW, Park DI, Kim YH, Kim HS, Kim WH, Kim TI *et al*. Clinical significance of small colorectal adenoma less than 10 mm: the KASID study. Hepatogastroenterology 2007; 54(74): 418-421.
295 Butterly LF, Chase MP, Pohl H, Fiarman GS. Prevalence of clinically important histology in small adenomas. Clin Gastroenterol Hepatol 2006; 4(3): 343-348.
296 Sprung DJ. Prevalence of adenocarcinoma in small adenomas. Am J Gastroenterol 2006; 101: S199.
297 Kim DH, Pickhardt PJ, Taylor AJ. Characteristics of advanced adenomas detected at CT colonographic screening: implications for appropriate polyp size thresholds for polypectomy versus surveillance. AJR Am J Roentgenol 2007; 188(4): 940-944.
298 Moravec M, Lieberman DA, Holub J, Michaels L, Eisen GM. Rate of advanced pathologic features in 6-9 mm polyps in patients referred for colonoscopy screening. Gastrointest Endosc 2007; 65: AB127.
299 van Dam J, Cotton P, Johnson CD, McFarland BG, Pineau BC, Provenzale D *et al*. AGA future trends report: CT colonography. Gastroenterology 2004; 127(3): 970-984.
300 Lansdorp-Vogelaar I, van Ballegooijen M., Zauber AG, Boer R, Wilschut J, Habbema JD. At what costs will screening with CT colonography be competitive? A cost-effectiveness approach. Int J Cancer 2009; 124(5): 1161-1168.
301 Signaleringscommissie Kanker. Beeldvormende technieken binnen de kankerbestrijding: Vizier op de toekomst. Amsterdam: KWF Kankerbestrijding; 2005.
302 Liedenbaum MH, Venema HW, Stoker J. Radiation dose in CT colonography-trends in time and differences between daily practice and screening protocols. Eur Radiol 2008; 18(10): 2222-2230.
303 The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP 2007; 37(2-4): 1-332.
304 Iannaccone R, Laghi A, Catalano C, Mangiapane F, Lamazza A, Schillaci A *et al*. Computed tomographic colonography without cathartic preparation for the detection of colorectal polyps. Gastroenterology 2004; 127(5): 1300-1311.
305 Lefere P, Gryspeerdt S, Baekelandt M, van Holsbeeck B. Laxative-free CT colonography. AJR Am J Roentgenol 2004; 183(4): 945-948.
306 Lefere P, Gryspeerdt S, Marrannes J, Baekelandt M, van Holsbeeck B. CT colonography after fecal tagging with a reduced cathartic cleansing and a reduced volume of barium. AJR Am J Roentgenol 2005; 184(6): 1836-1842.
307 Johnson CD, Manduca A, Fletcher JG, Maccarty RL, Carston MJ, Harmsen WS *et al*. Noncathartic CT colonography with stool tagging: performance with and without electronic stool subtraction. AJR Am J Roentgenol 2008; 190(2): 361-366.
308 Liedenbaum MH, van Rijn AF, de Vries AH, Dekker HM, Thomeer M, van Marrewijk CJ *et al*. Using CT colonography as a triage technique after a positive fecal occult blood test in colorectal cancer screening. Gut 58, 1242-1249.

309 Regge D, Laudi C, Galatola G, Della Monica P, Bonelli L, Angelelli G *et al*. Diagnostic accuracy of computed tomographic colonography for the detection of advanced neoplasia in individuals at increased risk of colorectal cancer. JAMA 2009; 301(23): 2453-2461.

310 Gelder RE van, Nio CY, Florie J, Bartelsman JF, Snel P, De Jager SW *et al*. Computed tomographic colonography compared with colonoscopy in patients at increased risk for colorectal cancer. Gastroenterology 2004; 127(1): 41-48.

311 Vries AH de, Jensch S, Liedenbaum MH, Florie J, Nio CY, Truyen R *et al*. Does a computer-aided detection algorithm in a second read paradigm enhance the performance of experienced computed tomography colonography readers in a population of increased risk? Eur Radiol 2009; 19(4): 941-950.

312 Maccarty RL, Johnson CD, Fletcher JG, Wilson LA. Occult colorectal polyps on CT colonography: implications for surveillance. AJR 2006; 186: 1380-1383.

313 Sidransky D, Tokino T, Hamilton SR, Kinzler KW, Levin B, Frost P *et al*. Identification of ras oncogene mutations in the stool of patients with curable colorectal tumors. Science 1992; 256(5053): 102-105.

314 Deuter R, Muller O. Detection of APC mutations in stool DNA of patients with colorectal cancer by HD-PCR. Hum Mutat 1998; 11(1): 84-89.

315 Eguchi S, Kohara N, Komuta K, Kanematsu T. Mutations of the p53 gene in the stool of patients with resectable colorectal cancer. Cancer 1996; 77(8 Suppl): 1707-1710.

316 Traverso G, Shuber A, Levin B, Johnson C, Olsson L, Schoetz DJ, Jr. *et al*. Detection of APC mutations in fecal DNA from patients with colorectal tumors. N Engl J Med 2002; 346(5): 311-320.

317 Dong SM, Traverso G, Johnson C, Geng L, Favis R, Boynton K *et al*. Detecting colorectal cancer in stool with the use of multiple genetic targets. J Natl Cancer Inst 2001; 93(11): 858-865.

318 Osborn NK, Ahlquist DA. Stool screening for colorectal cancer: molecular approaches. Gastroenterology 2005; 128(1): 192-206.

319 Tagore KS, Lawson MJ, Yucaitis JA, Gage R, Orr T, Shuber AP *et al*. Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. Clin Colorectal Cancer 2003; 3(1): 47-53.

320 Calistri D, Rengucci C, Bocchini R, Saragoni L, Zoli W, Amadori D. Fecal multiple molecular tests to detect colorectal cancer in stool. Clin Gastroenterol Hepatol 2003; 1(5): 377-383.

321 Brand RE, Ross ME, Shuber AP. Reproducibility of a multitarget stool-based DNA assay for colorectal cancer detection. Am J Gastroenterol 2004; 99(7): 1338-1341.

322 Diehl F, Schmidt K, Durkee KH, Moore KJ, Goodman SN, Shuber AP *et al*. Analysis of mutations in DNA isolated from plasma and stool of colorectal cancer patients. Gastroenterology 2008; 135(2): 489-498.

323 Schuebel KE, Chen W, Cope L, Glockner SC, Suzuki H, Yi JM *et al*. Comparing the DNA hypermethylome with gene mutations in human colorectal cancer. PLoS Genet 2007; 3(9): 1709-1723.

324 Lenhard K, Bommer GT, Asutay S, Schauer R, Brabletz T, Goke B *et al*. Analysis of promoter methylation in stool: a novel method for the detection of colorectal cancer. Clin Gastroenterol Hepatol 2005; 3(2): 142-149.

325 Chen WD, Han ZJ, Skoletsky J, Olson J, Sah J, Myeroff L *et al*. Detection in fecal DNA of colon cancer-specific methylation of the nonexpressed vimentin gene. J Natl Cancer Inst 2005; 97(15): 1124-1132.

326 Huang Z, Li L, Wang J. Hypermethylation of SFRP2 as a potential marker for stool-based detection of colorectal cancer and precancerous lesions. Dig Dis Sci 2007; 52(9): 2287-2291.

327 Zhang W, Bauer M, Croner RS, Pelz JO, Lodygin D, Hermeking H *et al*. DNA stool test for colorectal cancer: hypermethylation of the secreted frizzled-related protein-1 gene. Dis Colon Rectum 2007; 50(10): 1618-1626.

328 Oberwalder M, Zitt M, Wontner C, Fiegl H, Goebel G, Zitt M *et al*. SFRP2 methylation in fecal DNA--a marker for colorectal polyps. Int J Colorectal Dis 2008; 23(1): 15-19.

329 Wang DR, Tang D. Hypermethylated SFRP2 gene in fecal DNA is a high potential biomarker for colorectal cancer noninvasive screening. World J Gastroenterol 2008; 14(4): 524-531.

330 Huang ZH, Li LH, Yang F, Wang JF. Detection of aberrant methylation in fecal DNA as a molecular screening tool for colorectal cancer and precancerous lesions. World J Gastroenterol 2007; 13(6): 950-954.

331 Petko Z, Ghiassi M, Shuber A, Gorham J, Smalley W, Washington MK *et al*. Aberrantly methylated CDKN2A, MGMT, and MLH1 in colon polyps and in fecal DNA from patients with colorectal polyps. Clin Cancer Res 2005; 11(3): 1203-1209.

332 Leung WK, To KF, Man EP, Chan MW, Hui AJ, Ng SS *et al*. Detection of hypermethylated DNA or cyclooxygenase-2 messenger RNA in fecal samples of patients with colorectal cancer or polyps. Am J Gastroenterol 2007; 102(5): 1070-1076.

333 Hellebrekers D, Lentjes M, Van den Bosch S, Daenen K, Akiyama Y, Yuasa Y *et al*. GATA4 and GATA5 are potential tumor suppressors and biomarkers in colorectal cancer. Clin Cancer Res 2009; 15(12): 3990-3997.

334 Melotte V, Lentjes M, Van den Bosch S, Hellebrekers D, Den Hoon J, Wouters K *et al*. N-Myc downstream regulated gene 4 (NDRG4) promoter methylation is a sensitive and specific biomarker for colorectal cancer. AACR Special Conference Advances in ColonCancer Research Boston, 2007;

335 Kim MS, Louwagie J, Carvalho B, Terhaar sive Droste JS, Park HL, Chae YK *et al*. Promoter DNA methylation of oncostatin m receptor-beta as a novel diagnostic and therapeutic marker in colon cancer. PLoS One 2009; 4(8): e6555.

336 Hellebrekers DM, Lentjes MH, van den Bosch SM, Melotte V, Wouters KA, Daenen KL *et al*. GATA4 and GATA5 are potential tumor suppressors and biomarkers in colorectal cancer. Clin Cancer Res 2009; 15(12): 3990-3997.

337 Glöckner SC, Dhir M, Yi JM, McGarvey KE, van Neste L., Louwagie J *et al*. Methylation of TFPI2 in stool DNA: a potential novel biomarker for the detection of colorectal cancer. Cancer Res 2009; 69(11): 4691-4699.

338 Melotte V, Lentjes MH, van den Bosch SM, Hellebrekers DM, de Hoon JP, Wouters KA *et al*. N-Myc downstream-regulated gene 4 (NDRG4): a candidate tumor suppressor gene and potential biomarker for colorectal cancer. J Natl Cancer Inst 2009; 101(13): 916-927.

339 Louwagie J, Bosch L, Van den Bosch S, Opdam M, Straub J, Otto G *et al*. Feasibility of a DNA methylation-based assay for non-invasive CRC screening using stool. AACR Special Conference Advances in ColonCancer Research Boston, 2007;

340 Kanaoka S, Yoshida K, Miura N, Sugimura H, Kajimura M. Potential usefulness of detecting cyclooxygenase 2 messenger RNA in feces for colorectal cancer screening. Gastroenterology 2004; 127(2): 422-427.

341 Lagerholm S, Lagerholm S, Dutta S, Nair P. Non-invasive detection of c-myc p64, c-myc p67 and c-erbb-2 in colorectal cancer. Scand J Gastroenterol 2005; 40(11): 1343-1350.

342 Myung SJ, Yang SK, Chang HS, Byeon JS, Kim KJ, Hong SS *et al*. Clinical usefulness of telomerase for the detection of colon cancer in ulcerative colitis patients. J Gastroenterol Hepatol 2005; 20(10): 1578-1583.

343 Yamao T, Matsumura Y, Shimada Y, Moriya Y, Sugihara K, Akasu T *et al*. Abnormal expression of CD44 variants in the exfoliated cells in the feces of patients with colorectal cancer. Gastroenterology 1998; 114(6): 1196-1205.

344 Ahmed FE, Vos P, Ijames S, Lysle DT, Allison RR, Flake G *et al*. Transcriptomic molecular markers for screening human colon cancer in stool and tissue. Cancer Genomics Proteomics 2007; 4(1): 1-20.

345 Chien CC, Chang CC, Yang SH, Chen SH, Huang CJ. A homologue of the Drosophila headcase protein is a novel tumor marker for early-stage colorectal cancer. Oncol Rep 2006; 15(4): 919-926.

346 Yajima S, Ishii M, Matsushita H, Aoyagi K, Yoshimatsu K, Kaneko H *et al*. Expression profiling of fecal colonocytes for RNA-based screening of colorectal cancer. Int J Oncol 2007; 31(5): 1029-1037.

347 Roon AC von, Karamountzos L, Purkayastha S, Reese GE, Darzi AW, Teare JP *et al*. Diagnostic precision of fecal calprotectin for inflammatory bowel disease and colorectal malignancy. Am J Gastroenterol 2007; 102(4): 803-813.

348 Davies RJ, Freeman A, Morris LS, Bingham S, Dilworth S, Scott I *et al*. Analysis of minichromosome maintenance proteins as a novel method for detection of colorectal cancer in stool. Lancet 2002; 359(9321): 1917-1919.

349 Karl J, Wild N, Tacke M, Andres H, Garczarek U, Rollinger W *et al*. Improved diagnosis of colorectal cancer using a combination of fecal occult blood and novel fecal protein markers. Clin Gastroenterol Hepatol 2008; 6(10): 1122-1128.

350 Grutzmann R, Molnar B, Pilarsky C, Habermann JK, Schlag PM, Saeger HD *et al*. Sensitive detection of colorectal cancer in peripheral blood by septin 9 DNA methylation assay. PLoS ONE 2008; 3(11): e3759.

351 Lofton-Day C, Model F, Devos T, Tetzner R, Distler J, Schuster M *et al*. DNA methylation biomarkers for blood-based colorectal cancer screening. Clin Chem 2008; 54(2): 414-423.

352 Leung WK, To KF, Man EP, Chan MW, Bai AH, Hui AJ *et al*. Quantitative detection of promoter hypermethylation in multiple genes in the serum of patients with colorectal cancer. Am J Gastroenterol 2005; 100(10): 2274-2279.

353 Engeland M van, Brichard G, Louwagie J, Stockbrügger R, Di Stefano I, Khalid C *et al*. Promising DNA methylation markers for specific and sensitive detection of colon cancer in blood. AACR Special Conference Advances in ColonCancer Research Boston, 2007;

354 Khair G, Monson JR, Greenman J. Epithelial molecular markers in the peripheral blood of patients with colorectal cancer. Dis Colon Rectum 2007; 50(8): 1188-1203.

355 Guo J, Xiao B, Zhang X, Jin Z, Chen J, Qin L *et al*. Combined use of positive and negative immunomagnetic isolation followed by real-time RT-PCR for detection of the circulating tumor cells in patients with colorectal cancers. J Mol Med 2004; 82(11): 768-774.

356 Hardingham JE, Kotasek D, Farmer B, Butler RN, Mi JX, Sage RE *et al*. Immunobead-PCR: a technique for the detection of circulating tumor cells using immunomagnetic beads and the polymerase chain reaction. Cancer Res 1993; 53(15): 3455-3458.

357 Shen C, Hu L, Xia L, Li Y. Quantitative real-time RT-PCR detection for survivin, CK20 and CEA in peripheral blood of colorectal cancer patients. Jpn J Clin Oncol 2008; 38(11): 770-776.

358 Yeh CS, Wang JY, Wu CH, Chong IW, Chung FY, Wang YH *et al*. Molecular detection of circulating cancer cells in the peripheral blood of patients with colorectal cancer by using membrane array with a multiple mRNA marker panel. Int J Oncol 2006; 28(2): 411-420.

359 Collado M, Garcia V, Garcia JM, Alonso I, Lombardia L, az-Uriarte R *et al*. Genomic profiling of circulating plasma RNA for the analysis of cancer. Clin Chem 2007; 53(10): 1860-1863.

360 Findeisen P, Rockel M, Nees M, Roder C, Kienle P, Von Knebel DM *et al*. Systematic identification and validation of candidate genes for detection of circulating tumor cells in peripheral blood specimens of colorectal cancer patients. Int J Oncol 2008; 33(5): 1001-1010.

361 Han M, Liew CT, Zhang HW, Chao S, Zheng R, Yip KT *et al*. Novel blood-based, five-gene biomarker set for the detection of colorectal cancer. Clin Cancer Res 2008; 14(2): 455-460.

362 Smirnov DA, Zweitzig DR, Foulk BW, Miller MC, Doyle GV, Pienta KJ *et al*. Global gene expression profiling of circulating tumor cells. Cancer Res 2005; 65(12): 4993-4997.

363 Hundt S, Haug U, Brenner H. Blood markers for early detection of colorectal cancer: a systematic review. Cancer Epidemiol Biomarkers Prev 2007; 16(10): 1935-1953.

364 Cordero OJ, Ayude D, Nogueira M, Rodriguez-Berrocal FJ, de la Cadena MP. Preoperative serum CD26 levels: diagnostic efficiency and predictive value for colorectal cancer. Br J Cancer 2000; 83(9): 1139-1146.

365 Melle C, Ernst G, Schimmel B, Bleul A, Thieme H, Kaufmann R *et al*. Discovery and identification of alpha-defensins as low abundant, tumor-derived serum markers in colorectal cancer. Gastroenterology 2005; 129(1): 66-73.

366 Saito N, Kameoka S. Serum laminin is an independent prognostic factor in colorectal cancer. Int J Colorectal Dis 2005; 20(3): 238-244.

367 Waas ET, Hendriks T, Lomme RM, Wobbes T. Plasma levels of matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-1 correlate with disease stage and survival in colorectal cancer patients. Dis Colon Rectum 2005; 48(4): 700-710.

368 Nielsen HJ, Brunner N, Frederiksen C, Lomholt AF, King D, Jorgensen LN *et al*. Plasma tissue inhibitor of metalloproteinases-1 (TIMP-1): a novel biological marker in the detection of primary colorectal cancer. Protocol outlines of the Danish-Australian endoscopy study group on colorectal cancer detection. Scand J Gastroenterol 2008; 43(2): 242-248.

369 Alexandrov T, Decker J, Mertens B, Deelder AM, Tollenaar RA, Maass P *et al*. Biomarker discovery in MALDI-TOF serum protein profiles using discrete wavelet transformation. Bioinformatics 2009; 25(5): 643-649.

370 Chen YD, Zheng S, Yu JK, Hu X. [Application of serum protein pattern model in diagnosis of colorectal cancer]. Zhonghua Zhong Liu Za Zhi 2004; 26(7): 417-420.Chinese

371 Noo ME de, Mertens BJ, Ozalp A, Bladergroen MR, van der Werff MP, van deVelde CJ *et al*. Detection of colorectal cancer using MALDI-TOF serum protein profiling. Eur J Cancer 2006; 42(8): 1068-1076.

372 Ward DG, Suggett N, Cheng Y, Wei W, Johnson H, Billingham LJ *et al*. Identification of serum biomarkers for colon cancer by proteomic analysis. Br J Cancer 2006; 94(12): 1898-1905.

373 Ransohoff DF, Martin C, Wiggins WS, Hitt BA, Keku TO, Galanko JA *et al*. Assessment of serum proteomics to detect large colon adenomas. Cancer Epidemiol Biomarkers Prev 2008; 17(8): 2188-2193.

374 Draisma G, Boer R, Otto SJ, van der Cruijsen I, Damhuis RA, Schröder FH *et al*. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003; 95(12): 868-878.

375 Bais AG, van Kemenade FJ, Berkhof J, Verheijen RHM, Snijders PJF, Voorhorst FJ *et al*. Human papillomavirus testing on self-sampled cervicovaginal brushes: an effective alternative to protect nonresponders in cervical screening programs. Int J Cancer 2007; 120(7): 1505-1510.

376 Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M., Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res 1999; 32(1): 13-33.

377 Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JDF, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. J Natl Cancer Inst 2009; 101(20): 1412-1422.

378 Brouwer WB, Niessen LW, Postma MJ, Rutten FF. Need for differential discounting of costs and health effects in cost effectiveness analyses. BMJ 2005; 331(7514): 446-448.

379 Bouvier AM, Jooste V, Bonnetain F, Cottet V, Bizollon MH, Bernard MP *et al*. Adjuvant treatments do not alter the quality of life in elderly patients with colorectal cancer: a population-based study. Cancer 2008; 113(4): 879-886.

380 Clerc L, Jooste V, Lejeune C, Schmitt B, Arveux P, Quantin C *et al*. Cost of care of colorectal cancers according to health care patterns and stage at diagnosis in France. Eur J Health Econ 2008; 9: 361-367.

381 Kok I de, Polder JJ, Habbema JDF, Berkers L-M, Meerding WJ, Rebolj M *et al*. The impact of healthcare costs in the last year of life and in all life years gained on the cost-effectiveness of cancer screening. Br J Cancer 2009; 100(8): 1240-1244.

382 Kok IMCM de, van Rosmalen J, Habbema JDF, van Ballegooijen M. Cost-effectiveness of cervical cancer screening in the Netherlands: comparison of different policies. Rotterdam: Eramus MC; 2009.

383 NPK Werkgroep 2. Bevolkingsonderzoek dikkedarmkanker: scenario's voor een goede invoering. Den Haag: Nationaal Programma Kankerbestrijding; 2009.

384 Rossum LG van, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, Verbeek AL *et al*. Cutoff value determines colorectal cancer screening performance with a semi-quantitative immunochemical faecal occult blood test (submitted). soon to be published 2008;

385 Guittet L, Bouvier V, Mariotte N, Vallee JP, Arsene D, Boutreux S *et al*. Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. Gut 2007; 56(2): 210-214.

386 Grazzini G, Visioli CB, Zorzi M, Ciatto S, Banovich F, Bonanomi AG *et al*. Immunochemical faecal occult blood test: number of samples and positivity cutoff. What is the best strategy for colorectal cancer screening? Br J Cancer 2009; 100(2): 259-265.

387 Nakama H, Kamijo N, bdul Fattah AS, Zhang B. Validity of immunological faecal occult blood screening for colorectal cancer: a follow up study. J Med Screen 1996; 3(2): 63-65.

388 Imperiale TF, Glowinski EA, Lin-Cooper C, Larkin GN, Rogge JD, Ransohoff DF. Five-year risk of colorectal neoplasia after negative screening colonoscopy. N Engl J Med 2008; 359(12): 1218-1224.

389 The guide to clinical preventive services 2005. Recommendations of the US Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2005.

390 Salkeld GP, Young JM, Solomon MJ. Consumer choice and the National Bowel Cancer Screening Program. The opportunity for informed choice in screening is limited. Med J Aust 2006; 184(11): 541-542.

391 Stone CA, Carter RC, Vos T, John JS. Colorectal cancer screening in Australia: an economic evaluation of a potential biennial screening program using faecal occult blood tests. Aust N Z J Public Health 2004; 28(3): 273-282.

392 Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer 2007; 96(5): 828-831.

393 Lansdorp-Vogelaar I, van Ballegooijen M., Zauber AG, Boer R, Wilschut J, Winawer SJ *et al*. Individualizing colonoscopy screening by sex and race. Gastrointest Endosc 2009; 70(1): 96-108.

394 Pabby A, Suneja A, Heeren T, Farraye FA. Flexible sigmoidoscopy for colorectal cancer screening in the elderly. Dig Dis Sci 2005; 50(11): 2147-2152.

395 Kim WH, Cho YJ, Park JY, Min PK, Kang JK, Park IS. Factors affecting insertion time and patient discomfort during colonoscopy. Gastrointest Endosc 2000; 52(5): 600-605.

396 Ristikankare M, Hartikainen J, Heikkinen M, Janatuinen E, Julkunen R. The effects of gender and age on the colonoscopic examination. J Clin Gastroenterol 2001; 32(1): 69-75.
397 Anderson JC, Messina CR, Cohn W, Gottfried E, Ingber S, Bernstein G *et al*. Factors predictive of difficult colonoscopy. Gastrointest Endosc 2001; 54(5): 558-562.
398 Bernstein C, Thorn M, Monsees K, Spell R, O'Connor JB. A prospective study of factors that determine cecal intubation time at colonoscopy. Gastrointest Endosc 2005; 61(1): 72-75.
399 Kondo S, Yamaji Y, Watabe H, Yamada A, Sugimoto T, Ohta M *et al*. A randomized controlled trial evaluating the usefulness of a transparent hood attached to the tip of the colonoscope. Am J Gastroenterol 2007; 102(1): 75-81.
400 Grol R. Implementatie: Effectieve verbetering van de patiëntenzorg. Maarssen: 2006.
401 Raffle AE. Information about screening - is it to achieve high uptake or to ensure informed choice? Health Expect 2001; 4(2): 92-98.
402 Entwistle V. Communicating about screening. Informed choice is important for screening, but not everyone wants or is able to analyse research data. Vikki Entwistle and colleagues propose a new approach to communication. BMJ 2008; 337: 789-791.
403 Irwig L, McCaffery K, Salkeld G, Bossuyt P. Informed choice for screening: implications for evaluation. BMJ 2006; 332(7550): 1148-1150.
404 Jepson RG, Hewison J, Thompson AG, Weller D. How should we measure informed choice? The case of cancer screening. J Med Ethics 2005; 31(4): 192-196.
405 Marteau TM, Dormandy E, Michie S. A measure of informed choice. Health Expect 2001; 4(2): 99-108.
406 Rebolj M, van Ballegooijen M, Berkers LM, Habbema JDF. Monitoring a national cancer prevention programme: Successful changes in cervical cancer screening in The Netherlands. Int J Cancer 2007; 120(4): 806-812.
407 Berkers LM, Ballegooijen van M, Kemenade van F, Rebolj M, Essink-Bot ML, Helmerhorst TJ *et al*. [The 1996 revision of the Dutch cervical cancer screening programme: increased coverage, fewer repeat smears and less opportunistic screening.] Ned Tijdschr Geneeskd 2007; 151: 1288-1294.Dutch.
408 McCaffery K, Borril J, Williamson S, Taylor T, Sutton S, Atkin W *et al*. Declining the offer of flexible sigmoidoscopy screening for bowel cancer: a qualitative investigation of the decision-making process. Soc Sci Med 2001; 53(5): 679-691.
409 Harewood GC, Wiersema MJ, Melton LJ, III. A prospective, controlled assessment of factors influencing acceptance of screening colonoscopy. Am J Gastroenterol 2002; 97(12): 3186-3194.
410 Voorde M ten. Onderzoek naar de non-respons bij het bevolkingsonderzoek borstkanker. Gamma 2008; 58(7): 7-9.
411 Rossum LGM van, van Oijen MGH, Bours A, Laheij RJF, Jansen JBMJ, Verbeek ALM. Previous unresponsiveness or reported unwillingness-to-be-screened and the paradox of subsequent participation in population-based colorectal cancer screening (submitted). submitted 2009;

412 Rijn AF van, van Rossum LGM, Deutekom M, Laheij RJF, Fockens P, Bossuyt PMM *et al*. Low priority main reason not to participate in a colorectal cancer screening program with a faecal occult blood test. Journal of Public Health 2008; 30: 461-465.

413 Keighley MR, O'Morain C, Giacosa A, Ashorn M, Burroughs A, Crespi M *et al*. Public awareness of risk factors and screening for colorectal cancer in Europe. Eur J Cancer Prev 2004; 13(4): 257-262.

414 Molenaar S, Sprangers MA, Postma-Schuit FC, Rutgers EJ, Noorlander J, Hendriks J *et al*. Feasibility and effects of decision aids. Med Decis Making 2000; 20(1): 112-127.

415 Kim J, Whitney A, Hayter S, Lewis C, Campbell M, Sutherland L *et al*. Development and initial testing of a computer-based patient decision aid to promote colorectal cancer screening for primary care practice. BMC Med Inform Decis Mak 2005; 5: 36.

416 Trevena LJ, Irwig L, Barratt A. Randomized trial of a self-administered decision aid for colorectal cancer screening. J Med Screen 2008; 15(2): 76-82.

417 Agt HME van, Fracheboud J, Rebolj M, Korfage IJ, de Koning HJ. Volledige, evenwichtige en eerlijke voorlichting over nut en risico's van bevolkingsonderzoek naar kanker. Rotterdam: Erasmus MC, afdeling Maatschappelijke Gezondheidszorg; 2008.

418 Roon AHC van, Hol L, van Ballegooijen M, van Vuuren AJ, Reijerink-Verheij JC, Habbema JDF *et al*. An advance notification letter increases attendance rate in colorectal cancer screening; a population-based randomized trial. Submitted.

419 Courtier R, Casamitjana M, Macia F, Panades A, Castells X, Gil MJ *et al*. Participation in a colorectal cancer screening programme: influence of the method of contacting the target population. Eur J Cancer Prev 2002; 11(3): 209-213.

420 Collins JF, Lieberman DA, Durbin TE, Weiss DG. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. Ann Intern Med 2005; 142(2): 81-85.

421 Palm I, Kant A. General practice-based call system for cervical cancer screening: Attendance rate, participation of women with higher risk and quality assurance [Thesis]. Nijmegen: Katholieke Universiteit Nijmegen; 1997.

422 Tacken MA, Braspenning JC, Hermens RP, Spreeuwenberg PM, van den Hoogen HJ, de Bakker DH *et al*. Uptake of cervical cancer screening in The Netherlands is mainly influenced by women's beliefs about the screening and by the inviting organization (Epub ahead of print). Eur J Public Health 2007; 17(2): 175-185.

423 Pye G, Christie M, Chamberlain JO, Moss SM, Hardcastle JD. A comparison of methods for increasing compliance within a general practitioner based screening project for colorectal cancer and the effect on practitioner workload. J Epidemiol Community Health 1988; 42(1): 66-71.

424 Terhaar sive Droste JS, Craanen ME, Mulder CJJ, Heine GDN, Boot H. Een duidelijk signaal. Helft van de huisartsen vindt screening op colorectaalkanker nodig. Medisch Contact 2005; 60(36): 1420-1423.

425 Terhaar sive Droste JS, Heine GD, Craanen ME, Boot H, Mulder CJ. On attitudes about colorectal cancer screening among gastrointestinal specialists and general practitioners in the Netherlands. World J Gastroenterol 2006; 12(32): 5201-5204.
426 Wardle J, Miles A, Atkin W. Gender differences in utilization of colorectal cancer screening. J Med Screen 2005; 12(1): 20-27.
427 Deutekom M, van Rijn AF, Dekker E, Blaauwgeers H, Stronks K, Fockens P *et al*. Uptake of faecal occult blood test colorectal cancer screening by different ethnic groups in the Netherlands. Eur J Public Health 2009;
428 The UK CRC Screening Pilot Evaluation Team. Evaluation of the UK Colorectal Cancer Screening Pilot. Edinburgh: Department of Community Health Sciences, University of Edinburgh; 2003.
429 Rodger J, Steele RJ. Telephone assessment increases uptake of colonoscopy in a FOBT colorectal cancer-screening programme. J Med Screen 2008; 15(2): 105-107.
430 Tweede Kamer1988-1989, 21 264 3. Regels betreffende bevolkingsonderzoek. Memorie van Toelichting. Den Haag: SDU, 1989.
431 Beemsterboer PM, de Koning HJ, Warmerdam PG, Boer R, Swart E, Dierks ML *et al*. Prediction of the effects and costs of breast-cancer screening in Germany. Int J Cancer 1994; 58(5): 623-628.
432 Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004; 101(5 Suppl): 1201-1213.
433 Bos AB, van Ballegooijen M, van Gessel-Dabekaussen AA, Habbema JD. Organised cervical cancer screening still leads to higher coverage than spontaneous screening in The Netherlands. Eur J Cancer 1998; 34(10): 1598-1601.
434 Lynge E, Clausen LB, Guignard R, Poll P. What happens when organization of cervical cancer screening is delayed or stopped? J Med Screen 2006; 13(1): 41-46.
435 World Health Organization.International agency for research on cancer. IARC Handbooks of cancer prevention. Volume 10.Cervix cancer screening. Lyon: IARC Press; 2005.
436 Gelder R de, Bulliard JL, de Wolf C, Fracheboud J, Draisma G, Schopper D *et al*. Cost-effectiveness of opportunistic versus organised mammography screening in Switzerland. Eur J Cancer 2009; 45(1): 127-138.
437 Karssemeijer N, Roelofs AAJ, den Heeten GJ, Bijkerk KR, van Engen RE, Visser R *et al*. Digitale mammografie in het bevolkingsonderzoek naar borstkanker. Nijmegen: Landelijk Referentiecentrum voor bevolkingsonderzoek op Borstkanker (LRCB),UMC St Radboud; 2005.
438 Landelijk bevolkingsonderzoek naar borstkanker in Nederland. Optimalisatiestudie 1999-2001. Rotterdam/ Nijmegen: Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker en Landelijk Referentiecentrum voor bevolkingsonderzoek op Borstkanker; 2002.
439 Fracheboud J, Groenewoud JH, Boer R, Draisma G, de Bruijn AE, Verbeek AL *et al*. Seventy-five years is an appropriate upper age limit for population-based mammography screening. Int J Cancer 2005;
440 Holland R. Met vroege ontdekking zijn wij er nog niet. Oratie. Nijmegen: KU Nijmegen; 2000.

441 Otten JD, Karssemeijer N, Hendriks JH, Groenewoud JH, Fracheboud J, Verbeek AL *et al*. Effect of recall rate on earlier screen detection of breast cancers based on the Dutch performance indicators. J Natl Cancer Inst 2005; 97(10): 748-754.

442 Wolf CJM de, Perry NM, (editors). European guidelines for quality assurance in mammography screening. Brussels: 1996. Internet: (http://europa.eu.int).

443 Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker (LETB). Belangrijkste resultaten 2001 en 2002 bevolkingsonderzoek borstkanker. Rotterdam: Erasmus MC; 2004.

444 Groenewoud JH, Otten JD, Fracheboud J, Draisma G, van Ineveld BM, Holland R *et al*. Cost-effectiveness of different reading and referral strategies in mammography screening in the Netherlands. Breast Cancer Res Treat 2007; 102(2): 211-218.

445 Duijm LE, Groenewoud JH, de Koning HJ, Coebergh JW, van BM, Hooijen MJ *et al*. Delayed diagnosis of breast cancer in women recalled for suspicious screening mammography. Eur J Cancer 2009; 45(5): 774-781.

446 Beemsterboer PM, Warmerdam PG, Boer R, de Koning HJ. Radiation risk of mammography related to benefit in screening programmes: a favourable balance? J Med Screen 1998; 5(2): 81-87.

447 Berkers M, Rebolj M, van Ballegooijen M. Bevolkingsonderzoek naar baarmoederhalskanker in Nederland: een vergelijking van de jaren 1994, 2002 en 2003. Rotterdam: Instituut Maatschappelijke Gezondheidszorg, Erasmus MC; 2005.

448 Berkers L, van Ballegooijen M, van den Akker-van Marle ME, Meerding W. De effecten en kosten van verschillende wijzen van uitnodigen bij het bevokingsonderzoek baarmoederhalskanker. Rotterdam: Afdeling Maatschappelijke Gezondheidszorg, Erasmus MC; 2004.

449 Bos A, Rebolj M, Habbema JD, van Ballegooijen M. Non-attendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands. Int J Cancer 2006; 119 (10): 2372-2375.

450 Koning HJ de, van Ineveld BM, van Oortmarssen GJ, de Haes JC, Collette HJ, Hendriks JH *et al*. Breast cancer screening and cost-effectiveness; policy alternatives, quality of life considerations and the possible impact of uncertain factors. Int J Cancer 1991; 49(4): 531-537.

451 Koning HJ de, Draisma G, Fracheboud J, de BA. Overdiagnosis and overtreatment of breast cancer: microsimulation modelling estimates based on observed screen and clinical data. Breast Cancer Res 2006; 8(1): 202.

452 Ballegooijen M van, Rebolj M, Meerding WJ, van den Akker-van Marle ME, Berkers LM, Habbema JDF. De praktijk van het bevolkingsonderzoek naar baarmoederhalskanker in 2001. Rapport in het kader van de landelijke evaluatie van het bevolkingsonderzoek naar baarmoederhalskanker (LEBA): Deel 3. Rotterdam: Afdeling Maatschappelijke Gezondheidszorg, Erasmus MC; 2003.

453 Otto SJ, Fracheboud J, Looman CW, Broeders MJ, Boer R, Hendriks JH *et al*. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003; 361(9367): 1411-1417.

454 Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland. Rotterdam: Erasmus MC (LETB); 2005.

455 Benson VS, Patnick J, Davies AK, Nadel MR, Smith RA, Atkin WS. Colorectal cancer screening: a comparison of 35 initiatives in 17 countries. Int J Cancer 2008; 122(6): 1357-1367.

456 Khuri SF, Daley J, Henderson WG. The comparative assessment and improvement of quality of surgical care in the Department of Veterans Affairs. Arch Surg 2002; 137(1): 20-27.

457 Dove-Edwin I, Sasieni P, Adams J, Thomas HJ. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005; 331: 1047-1052.

458 Martínez ME, Baron JA, Lieberman DA, Schatzkin A, Lanza E, Winawer SJ *et al*. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology 2009; 136(3): 832-841.

459 Mitchell RJ, Brewster D, Campbell H, Porteous ME, Wyllie AH, Bird CC *et al*. Accuracy of reporting of family history of colorectal cancer. Gut 2004; 53(2): 291-295.

460 Cottet V, Pariente A, Nalet B, Lafon J, Milan C, Olschwang S *et al*. Low compliance with colonoscopic screening in first-degree relatives of patients with large adenomas. Aliment Pharmacol Ther 2006; 24(1): 101-109.

461 Schroy Iii PC, Glick JT, Robinson PA, Heeren T. Screening preferences of patients at familial risk of colorectal cancer. Dig Dis Sci 2007; 52(10): 2788-2795.

462 Rubeca T, Rapi S, Confortini M, Brogioni M, Grazzini G, Zappa M *et al*. Evaluation of diagnostic accuracy of screening by fecal occult blood testing (FOBT). Comparison of FOB Gold and OC Sensor assays in a consecutive prospective screening series. Int J Biol Markers 2006; 21(3): 157-161.

463 Rozen P, Waked A, Vilkin A, Levi Z, Niv Y. Evaluation of a desk top instrument for the automated development and immunochemical quantification of fecal occult blood. Med Sci Monit 2006; 12(6): MT27-MT32.

464 Rossum LG van, van Rijn AF, van Oijen MG, Fockens P, Laheij RJ, Verbeek AL *et al*. False negative faecal occult blood tests due to delayed sample return in colorectal cancer screening. Int J Cancer 2009;(I) [Epub ahead of print].

465 Singh H, Kadiyala H, Bhagwath G, Shethia A, El-Serag H, Walder A *et al*. Using a multifaceted approach to improve the follow-up of positive fecal occult blood test results. Am J Gastroenterol 2009; 104(4): 942-952.

466 Selby P, Gillis C, Haward R. Benefits from specialised cancer care. Lancet 1996; 348(9023): 313-318.

467 Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003; 349(22): 2117-2127.

468 Gillis CR, Hole DJ. Survival outcome of care by specialist surgeons in breast cancer: a study of 3786 patients in the west of Scotland. BMJ 1996; 312(7024): 145-148.

469 Kingsmore D, Ssemwogerere A, Hole D, Gillis C. Specialisation and breast cancer survival in the screening era. Br J Cancer 2003; 88(11): 1708-1712.

470 Kingsmore D, Hole D, Gillis C. Why does specialist treatment of breast cancer improve survival? The role of surgical management. Br J Cancer 2004; 90(10): 1920-1925.

471 Nationaal Programma Kankerbestrijding. Aansluiting van screening naar curatieve zorg. Praktische problemen en mogelijke oplossingen. Werkgroep 3. Den Haag; 2009.
472 Pabby A, Schoen RE, Weissfeld JL, Burt R, Kikendall JW, Lance P *et al*. Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. Gastrointest Endosc 2005; 61(3): 385-391.
473 Farrar WD, Sawhney MS, Nelson DB, Lederle FA, Bond JH. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 2006; 4(10): 1259-1264.
474 Lieberman DA, Weiss DG, Harford WV, Ahnen DJ, Provenzale D, Sontag SJ *et al*. Five-year colon surveillance after screening colonoscopy. Gastroenterology 2007; 133(4): 1077-1085.
475 Kwaliteitsinstituut voor de Gezondheidszorg CBO. Syllabus herziening richtlijn follow-up na poliepectomie. Utrecht: 2000.
476 Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE *et al*. Quality indicators for colonoscopy. Gastrointest Endosc 2006; 63(4 Suppl): S16-S28.
477 Rex DK, Bond JH, Winawer S, Levin TR, Burt RW, Johnson DA *et al*. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2002; 97(6): 1296-1308.
478 Imperiali G, Minoli G. Colonic neoplasm in asymptomatic patients with family history of colon cancer: results of a colonoscopic prospective and controlled study. Results of a pilot study of endoscopic screening of first degree relatives of colorectal cancer patients in Italy. Gastrointest Endosc 1999; 49(1): 132-133.
479 Ball JE, Osbourne J, Jowett S, Pellen M, Welfare MR. Quality improvement programme to achieve acceptable colonoscopy completion rates: prospective before and after study. BMJ 2004; 329(7467): 665-667.
480 Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med 2006; 355(24): 2533-2541.
481 Garvican L. Planning for a possible national colorectal cancer screening programme. J Med Screen 1998; 5(4): 187-194.
482 Taylor KM, Arajs K, Rouse T, Harris AW. Prospective audit of colonoscopy quality in Kent and Medway, UK. Endoscopy 2008; 40(4): 291-295.
483 Hackmann RJ, van der Putten AB, Loffeld RJ. [The yield of endoscopic follow-up after removal of adenomatous polyps from the colon]. Ned Tijdschr Geneeskd 1998; 142(30): 1720-1723. Dutch.
484 Sawhney MS, Cury MS, Neeman N, Ngo LH, Lewis JM, Chuttani R *et al*. Effect of institution-wide policy of colonoscopy withdrawal time > or = 7 minutes on polyp detection. Gastroenterology 2008; 135(6): 1892-1898.
485 Inadomi JM. In search of quality colonoscopy. Gastroenterology 2008; 135(6): 1845-1847.
486 Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992; 326(10): 658-662.

487 Robertson DJ, Greenberg ER, Beach M, Sandler RS, Ahnen D, Haile RW *et al*. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 2005; 129(1): 34-41.

488 Casparie M, Tiebosch AT, Burger G, Blauwgeers H, van de PA, van Krieken JH *et al*. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007; 29(1): 19-24.

489 Jørgensen OD, Kronborg O, Fenger C, Rasmussen M. Influence of long-term colonoscopic surveillance on incidence of colorectal cancer and death from the disease in patients with precursors (adenomas). Acta Oncol 2007; 46(3): 355-360.

490 Imperiale TF. Toward risk stratification for screening and surveillance of colorectal neoplasia: one small step for the colonoscopist. Gastroenterology 2007; 133(4): 1364-1367.

491 Mulder SA, Ouwendijk RJ, van Leerdam ME, Nagengast FM, Kuipers EJ. A nationwide survey evaluating adherence to guidelines for follow-up after polypectomy or treatment for colorectal cancer. J Clin Gastroenterol 2008; 42(5): 487-492.

492 Bampton PA, Sandford JJ, Young GP. Applying evidence-based guidelines improves use of colonoscopy resources in patients with a moderate risk of colorectal neoplasia. Med J Aust 2002; 176(4): 155-157.

493 Mysliwiec PA, Brown ML, Klabunde CN, Ransohoff DF. Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. Ann Intern Med 2004; 141(4): 264-271.

494 Boolchand V, Olds G, Singh J, Singh P, Chak A, Cooper GS. Colorectal screening after polypectomy: a national survey study of primary care physicians. Ann Intern Med 2006; 145(9): 654-659.

495 Seow CH, Ee HC, Willson AB, Yusoff IF. Repeat colonoscopy has a low yield even in symptomatic patients. Gastrointest Endosc 2006; 64(6): 941-947.

496 Bond JH. Should the quality of preparation impact postcolonoscopy follow-up recommendations? Am J Gastroenterol 2007; 102(12): 2686-2687.

497 Jansen JBMJ, van Rossum LGM, Laheij RJF. [Colorectal cancer screening: immunological test for faecal occult preferred.] Ned Tijdschr Geneeskd 2009; 153(28): 1361-1365. Dutch

498 Lieberman DA, Holub J, Eisen G, Kraemer D, Morris CD. Utilization of colonoscopy in the United States: results from a national consortium. Gastrointest Endosc 2005; 62(6): 875-883.

499 Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B *et al*. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin 2006; 56(3): 143-159.

500 Cafferty FH, Sasieni PD, Duffy SW. A deterministic model for estimating the reduction in colorectal cancer incidence due to endoscopic surveillance. Stat Methods Med Res 2009; 18(2): 163-182.

501 Nusko G, Hahn EG, Mansmann U. Risk of advanced metachronous colorectal adenoma during long-term follow-up. Int J Colorectal Dis 2008; 23(11): 1065-1071.

502 Brooks DD, Winawer SJ, Rex DK, Zauber AG, Kahi CJ, Smith RA *et al*. Colonoscopy surveillance after polypectomy and colorectal cancer resection. Am Fam Physician 2008; 77(7): 995-1002.

503 Bond JH. Polyp guideline: diagnosis, treatment, and surveillance for patients with nonfamilial colorectal polyps. The Practice Parameters Committee of the American College of Gastroenterology. Ann Intern Med 1993; 119(8): 836-843.

504 Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD *et al*. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112(2): 594-642.

505 Brenner H, Chang-Claude J, Seiler CM, Sturmer T, Hoffmeister M. Case-control study supports extension of surveillance interval after colonoscopic polypectomy to at least 5 yr. Am J Gastroenterol 2007; 102(8): 1739-1744.

506 Terhaar sive Droste JS, Craanen ME, Kolkman JJ, Mulder CJJ. Dutch endoscopic capacity in the era of colorectal cancer screening. Neth J Med 2006; 64(10): 371-373.

507 Crommentuyn R. Artsentekort soms nijpend. Medisch Contact 2009; 64(29-30): 1285-1287.

508 Pronk E. Darmkanker gestroomlijnd. Patiënten met coloncarcinoom kunnen veel sneller geholpen. Med Contact 2006; 61(4): 150-152.

509 Slobbe LCJ, Kommer GJ, Smit JM, Groen J, Meerding WJ, Polder JJ. Kosten van Ziekten in Nederland 2003. Zorg voor euro's - 1. Bilthoven: RIVM; 2006: 270751010.

A Request for advice

B The Committee

Annexes

Annex **A**

Request for advice

Letter dated 27 November 2008 (reference PG/ZP 2.895.635) from the Minister for Health, Welfare and Sport to the president of the Health Council.

[...] I shall be grateful if you will advise me regarding the feasibility and desirability of introducing colorectal cancer screening. Of course, the Wilson and Jungner criteria, which you advised me were still valid in your report *Screening: between hope and hype* (1 April 2008), should form the basis of your assessment. I also wish you to take account of international developments, insofar as they are relevant to the situation in the Netherlands.

Various screening methods have been investigated and compared in the trials. Please assess the various methods in the light of current scientific knowledge and advise me on their relative merits. Particular attention should be given to:

- outcomes (health benefit), cost and cost per life year gained;
- the target age group for screening;
- dcceptance and participation;
- the optimum screening interval;
- health care capacity requirements (people and resources).

Although I am aware that the various methods are at different stages of scientific validation, I wish you to address the following issues in your report:

1 Which new methods of screening for colorectal cancer and what innovations to existing methods are likely to become available within five to seven years? (I wish to ascertain whether any foreseeable developments have infrastructural or operational implications.)

2 The screening of groups deemed to be at elevated risk on the basis of factors other than age. In our country, the Foundation for the Detection of Hereditary Tumours (STOET) works at the national level to promote and coordinate the surveillance of people with an elevated familial risk of hereditary forms of cancer, including colorectal cancer. Should a screening programme pay particular attention to people who do not fall within the STOET target group, but are at elevated risk of colorectal cancer on the basis of factors other than age? When answering this question, please consider the merit of colorectal cancer screening on the basis of individual risk profiles.

3 The mechanism for introducing a screening programme. In view of the capacity problems previously highlighted, would stepwise implementation ease the impact on the health care system? What are the benefits and drawbacks of phased introduction? Is it feasible or desirable for various test methods to be used alongside one another in different regions?

The Minister for Health, Welfare and Sport,
[signed]
A.Klink, PhD

Annex **B**

The Committee

- Professor W.P.Th.M. Mali, MD, PhD, *chairman*
  professor of radiology, University Medical Centre Utrecht
- M. van Ballegooijen, MD, PhD, *advisor*
  epidemiologist, Erasmus Medical Centre Rotterdam
- G.H. de Bock, MD, PhD
  epidemiologist, Groningen University Medical Centre
- J. Braspenning, PhD
  psychologist, Scientific Institute for Quality of Healthcare, Nijmegen
- Professor G.J. Dinant, MD, PhD
  professor of general practice, Maastricht University Medical Centre
- Professor R. Holland, MD, PhD
  professor emeritus of oncological pathology, University Medical Centre St Radboud, Nijmegen
- Professor N. Hoogerbrugge, MD, PhD
  professor of hereditary cancer, University Medical Centre St Radboud, Nijmegen
- Professor J.B.M.J. Jansen, MD, PhD, *advisor*
  professor of gastroenterology, University Medical Centre St Radboud, Nijmegen
- J. Kleijnen, MD, PhD
  epidemiologist, Kleijnen Systematic Reviews, York, United Kingdom

- Professor E.J. Kuipers, MD, PhD, *advisor*
  professor of gastroenterology, Erasmus MC, University Medical Centre, Rotterdam
- A.J.J.Lock, MD, *advisor*
  Centre for population screening (RIVM), Bilthoven
- Professor G.A. Meijer, MD, PhD, *advisor*
  professor of pathology, VU University Medical Centre, Amsterdam
- A. Rendering, L.L.M, *observer*
  Ministry of Health, Welfare and Sport, The Hague
- Professor J. Stoker, MD, PhD, *advisor*
  professor of radiology, Academic Medical Centre, Amsterdam
- Professor R.A.E.M. Tollenaar, MD, PhD
  professor of oncological surgery, Leiden University Medical Centre, Leiden
- W.A. van Veen, MD, *secretary*
  Health Council, The Hague

The Health Council and interests

Members of Health Council Committees – which also include the members of the Advisory Council on Health Research (RGO) since 1 February 2008 – are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.