Evaluation and optimisation of the colorectal cancer screening programme

To: the State Secretary for Health, Welfare and Sport
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Health Council of the Netherlands

contents

summary

At the request of the State Secretary for Health, Welfare and Sport, the Health Council of the Netherlands has conducted an evaluation of the colorectal cancer screening programme and reviewed what improvements could be made.

Colorectal cancer screening for all 55-75-year-olds since 2019

Colorectal cancer is a common form of cancer, with nearly 13,000 people being diagnosed in 2021. Since the early stage of colorectal cancer is clearly identifiable and develops slowly, the disease can be detected and treated at this early stage. Population screening for colorectal cancer was introduced in 2014. The programme was introduced gradually because the target group was too large to allow everyone to start at the same time. Implementation was completed in 2019, and since then, everyone between the ages of 55 and 75 has been given the opportunity to be screened once every two years. The screening relies on a stool test that is used to look for blood in faeces. If the test indicates higher haemoglobin levels than the cut-off value, this will be followed by referral for a colonoscopy. This colon examination detects and removes adenomas (an early stage of colorectal cancer) and colorectal cancer. In 2021, over 1.6 million people made use of the population screening, and colorectal cancer was detected in more than 2,700 participants.

Population screening appears to be effective

The ultimate goal of the population screening is to reduce mortality as a result of colorectal cancer. It has not yet been possible to demonstrate such a decrease, because the screening programme was only fully implemented a short time ago, and it takes years before an impact of population screening on mortality can be demonstrated. However, there are results from the trial screening programme, the current screening programme and modelling that indirectly show that the programme prevents mortality as a result of colorectal cancer. Based on those data, the Committee expects that the intended goal will be achieved in due course. The Committee considers the risk-benefit ratio of the screening programme to be favourable: the benefit (preventing death) outweighs the risks (such as unnecessary referrals for colonoscopies where no relevant abnormalities are detected and the associated burden and concern).

The current programme should not be modified at this stage

The Committee has assessed whether further improvement of the screening programme can be achieved through calibration of the cut-off value, the interval or the age limits of the target group or by applying risk stratification (distinguishing between subgroups).

This appeared not to be the case in the current situation. There are insufficient persuasive arguments in favour of modifying the screening programme at this time, given that the risk-benefit ratio is favourable under the current setup and the screening programme is still being developed. This does preclude possible improvements being made in the future. In view of this aspect, the Committee has made a number of recommendations.

Review of potential improvements in the future

The Committee recommends carrying out a review into offering a one-off stool test (FIT) for participants around the age of 50, prior to the regular screening. In the opinion of the Committee, this may have health benefits for participants with colorectal cancer or an early stage of colorectal cancer. A trial screening programme may show to what extent health gains are indeed achieved and how significant the disadvantages are. The Committee recommends that the trial screening programme be carried out at a regional level and it should not be offered nationwide until the results are in. After all, a one-off test for participants around the age of 50 may yield insufficient health benefits and entail too many disadvantages as well as an unfavourable risk-benefit ratio.

The Committee also recommends that a review be carried out into risk stratification, so the advantages and disadvantages, participation rates, cost effectiveness and feasibility can be determined. A partial study into these aspects is already underway: Erasmus MC is reviewing various screening intervals depending on the haemoglobin levels detected in faeces.
The Committee expects risk stratification to have added value in the future. It is, however, crucial that a broad discussion be conducted beforehand to determine what the targets should be and what is regarded as an improvement to the risk-benefit ratio.

Finally, the Committee recommends continued investment in increasing the participation rate among the youngest target groups and among people with a low socio-economic status.

01 introduction

1.1 Motivation

In 2009, the Health Council of the Netherlands advised biennial screening of men and women between the ages of 55 to 75 for colorectal cancer.[1] This screening programme was started in 2014. The government believes that it is important to regularly evaluate cancer screening programmes.

1.2 Request for advisory report

The State Secretary for Health, Welfare and Sport asked the Health Council of the Netherlands to evaluate the first six years of the colorectal cancer screening programme and to assess the benefit, risks, effectiveness and cost effectiveness of the programme. In addition, the State Secretary asked the Health Council of the Netherlands to look at how the outcomes of the colorectal cancer screening programme could be improved. The Health Council of the Netherlands was specifically asked to report on the following:

- potentially lowering the age of participation from 55 to 50 years of age;
- the benefit and desirability of risk stratification with the aim of improving the risk-benefit ratio for specific groups;
- an assessment of promising medium- and long-term developments in medical technology.

The request from the State Secretary for an advisory report can be found at www.gezondheidsraad.nl. The Committee on Population Screening considered the State Secretary's questions. The composition of the Committee can be found at the back of this advisory report.

1.3 Methodology

The Committee based its advice on data and reports from the national colorectal cancer screening programme, and on modelling research carried out by Erasmus MC. In addition, peer-reviewed publications from scientific journals were also used. A number of experts were consulted for specific information about colorectal cancer and the screening programme (a list of these experts can be found at the back of this advisory report). The Committee also arranged a hearing with representatives from 12 organisations. KWF Kankerbestrijding (KWF Dutch Cancer Society), Maag Lever Darm Stichting (Gastroenterological Foundation), Nederlandse Vereniging Maag Darm Leverartsen (Dutch Society for Gastro-enterologists), Stichting Darmkanker Nederland (Foundation Bowel Cancer Netherlands), Vereniging zonder winstoogmerk Stop Darmkanker (Non-profit association Stop Bowel Cancer Belgium), Bevolkings-onderzoek Nederland (Population Screening Netherlands), laboratories that process FIT tests, Nederlandse Vereniging voor Heelkunde (Dutch Society for Surgery), Nederlandse Vereniging voor Radiologie (Dutch Society for Radiology), Nederlandse Vereniging voor Pathologie (Dutch Society for Pathology), Verpleegkundigen en Verzorgenden Nederland (Nurses and Carers Netherlands) and Vereniging Klinische Genetica Nederland (Dutch Society for Clinical Genetics). During this hearing, the representatives shared their perspectives with the Committee and the Committee took these perspectives into account in their advisory

report. The report of the hearing can be found on the website of the Health Council of the Netherlands.

1.4 Reading guide

Chapter 2 describes the setup of the current colorectal cancer screening programme. In Chapter 3, the Committee evaluates the achievements of the screening programme and discusses the benefits, risks and cost effectiveness of the current programme. Chapter 4 discusses potential improvements, such as possible changes to the cut-off value and screening age range, and the use of risk stratification. In Chapter 5, the Committee formulates its advice.

02 colorectal cancer screening programme

Colorectal cancer is very common, with nearly 13,000 people being diagnosed in 2021. Since the early stage of colorectal cancer is clearly identifiable and develops slowly, the disease can be detected and treated early. The national colorectal cancer screening programme was introduced in 2014 and has been fully implemented since 2019. All men and women between the ages of 55 and 75 are invited to be screened once every two years. In 2021, over 1.6 million people were screened and colorectal cancer was detected in more than 2,700 participants.

2.1 Numbers on colorectal cancer

Cancer can develop in the small intestine, the large intestine and the rectum. Colorectal cancer is the collective term used for both cancers of the large intestine and rectum. This report focuses on population screening for colorectal cancer.

Colorectal cancer is a common form of cancer. In 2021, nearly 13,000 people were diagnosed with colorectal cancer and more than 4,500 people died of it.[2,3] The 10-year prevalence (all people diagnosed with colorectal cancer in the past 10 years and still alive) was over 82,000 people in early 2021.[3] On average, 67% of patients were still alive after 5 years (five-year survival).[3] Colorectal cancer most commonly occurs in older people: more than half of patients are aged 70 or over.[3] Compared to other types of cancer, the number of new patients with colorectal cancer (12,900) in 2021 was slightly lower than the number of new patients with breast cancer (15,700), skin cancer (14,900), lung cancer (14,700) and prostate cancer (13,700).[4]

2.2 Progression of colorectal cancer, early detection and treatment

Colorectal cancer develops over many years and usually starts with the development of a benign tumour. Such tumours are called adenomas and are common. On average, approximately 30% of people have one or more adenomas; this percentage increases with age.[5] In most cases, an adenoma will not progress at all. However, if it does progress, then an advanced adenoma will develop. This can then eventually develop into colorectal cancer.

Because colorectal cancer often develops slowly and has a clear early stage in the form of adenomas, colorectal cancer can be detected and treated early. When (advanced) adenomas are detected, they are removed so that they can no longer develop into colorectal cancer.

The treatment for colorectal cancer consists of surgical removal of the tumour, often including removal of a (large) part of the bowel, sometimes combined with chemotherapy, immunotherapy or radiotherapy (radiation).

2.3 National screening programme

The national colorectal cancer screening programme was introduced for people between the ages of 55 and 75 in 2014, on the advice of the Health Council of the Netherlands[1]. The screening programme was introduced in phases because it was not possible to start all age groups in one go, due to the large number of people eligible for the screening programme. Over a five-year period, new age groups were added to the screening programme each year until it covered the entire target population by the end of 2019. This means that since then, all people between the ages of 55 and 75 are invited every two years to take part in the screening programme. Participants are offered a stool test that is used to look for blood in their stool (faeces). If there is more blood in the stool than a predetermined limit (cut-off value), follow-up tests will be carried out to determine whether there is colorectal cancer or advanced adenomas.

2.3.1 Stool test

As adenomas or colorectal cancer can lead to loss of blood, the presence of blood in stool is an indicator of the presence of adenomas or colorectal cancer. A faecal immunochemical test (FIT) is used in the screening programme. Participants receive a test tube through the post for use at home. Participants can collect a small amount of stool (a sample) to send off for testing. The stool is then tested in a laboratory to determine whether there is any haemoglobin (Hb), a protein found in blood, in the stool. This is done using a test fluid. The test fluid contains antibodies that bind to Hb, making the fluid cloudy. The cloudier the fluid becomes, the more Hb is present. A test result is considered to be ‘positive’ (an unfavourable result) within the screening programme if the Hb concentration is higher than 47 micrograms per gram of faeces (µg Hb/g faeces). This value is referred to as the cut-off value.

2.3.2 Follow-up tests

If the stool test yields a positive result, the participant is referred for a colonoscopy. A colonoscopy is a visual examination of the entire large intestine. It is a onerous medical procedure because, prior to the examination, the bowel must be cleared by using a strong laxative and a certain fasting period is required. The procedure is also often perceived as painful and unpleasant. In addition, there is a small to very small risk of complications (such as bleeding or perforation of the colon), and, in rare cases, a colonoscopy can cause death. The aim of the procedure is to detect adenomas and colorectal cancer. If one or more adenomas are detected, they will usually be removed immediately. After a few years, another colonoscopy will be performed to see if new adenomas have developed. Some large adenomas and most tumours cannot be immediately removed. A biopsy is first taken and examined. Depending on the result, follow-up examinations (e.g. a CT scan) will be performed or a treatment plan will be drawn up. If the colonoscopy does not detect any adenomas or colorectal tumours, the participant does not need to

participate in the screening programme again for the next 10 years, as colorectal cancer takes many years to develop. The optimal length of time between colonoscopy and the following screening round is currently being researched.

2.3.3 Scope of the screening programme

More than a million people take part in the colorectal cancer screening programme every year, and a few thousand are then diagnosed with colorectal cancer. In 2021, more than 2.3 million people were invited to take part and over 1.6 million participated in the screening programme (see Figure 1).[6] Of those 1.6 million people, more than 74,000 (over 4%) got a positive (unfavourable) test result (the concentration of Hb in the stool was higher than the cut-off value). They were referred for a colonoscopy, which was performed in almost 85% of cases. Not everyone who qualifies for a colonoscopy based on the stool test undergoes this procedure. This is partly because people opt out themselves, but there are also medical reasons not to perform the procedure. Colorectal cancer was detected in 4.5% of people who underwent a colonoscopy (over 2,700 cases), while advanced adenomas were found in 27% (nearly 17,000 cases). This means that 1.2% of all participants have a finding that is considered relevant (colorectal cancer or an early stage thereof).

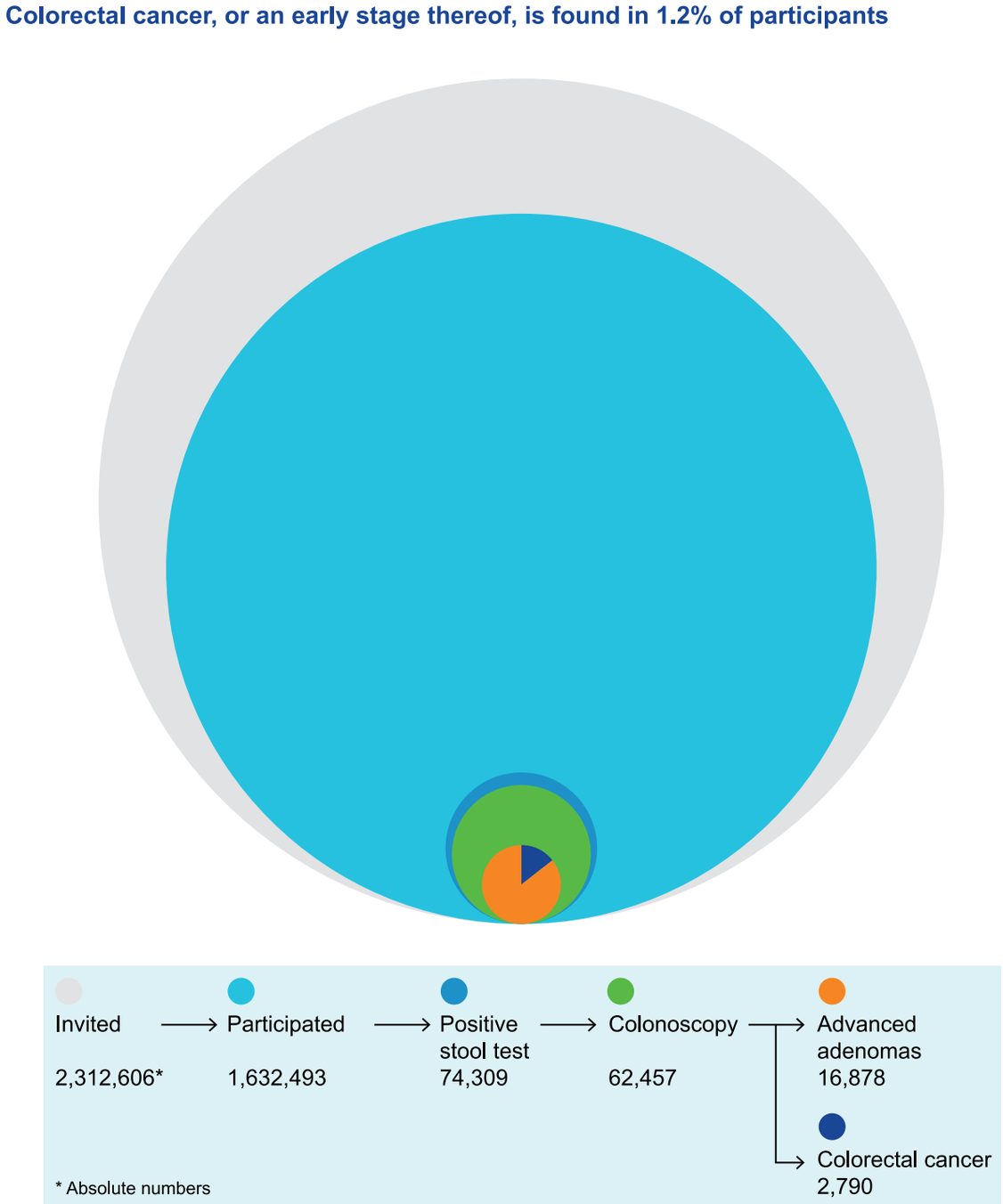

Figure 1 Scope of the colorectal cancer screening programme in 2021.[6] The number of participants in the various phases of the screening programme is shown.

2.4 Hereditary and familial colorectal cancer

There are certain groups that have are at a higher than average risk of colorectal cancer. These include people with Lynch Syndrome (an inherited condition that greatly increases the risk of colorectal cancer) and with Familial Adenomatous Polyposis (an inherited condition in which hundreds of polyps occur in the large intestine from a young age, also greatly increasing the risk of colorectal cancer).[7,8] In addition, the risk of colorectal cancer may be increased in people with a first- or second-degree relative who has, or has had, colorectal cancer (at a younger age). Early detection of colorectal cancer in these groups falls within standard care and is therefore outside the scope of the screening programme and this advisory report.

03 evaluation

The ultimate goal of the population screening is to reduce colorectal cancer mortality. It is not yet possible to demonstrate such a decrease, because the screening programme was only fully implemented a short time ago, and it takes years before an impact of population screening on mortality can be demonstrated. However, results from the trial screening programme, the current screening programme and modelling indirectly show that the programme prevents colorectal cancer mortality. Based on these data, the Committee expects that the intended goal of the screening programme will be achieved in due course. Based on the current situation, the Committee considers the risk-benefit ratio of the screening programme to be favourable.

3.1 Reducing mortality as a result of colorectal cancer

The ultimate goal of the colorectal cancer screening programme is to reduce colorectal cancer mortality. This goal can be achieved firstly by detecting and treating colorectal cancers at an early stage and secondly, by preventing colorectal cancer from developing. The chance of survival is greater if colorectal cancer is detected at an early stage, and detection and removing adenomas prevents colorectal cancer from developing.
It takes at least 7 years before an effect of screening on mortality as a result of colorectal cancer can be demonstrated.[9] As the screening programme was introduced in 2014 and was not fully implemented until 2019, it is not yet possible at this point to establish whether the original goal will be met. However, there are three indicators that do indirectly show that the screening programme is preventing colorectal cancer and deaths from it.

The first indicator is the outcome of the trial colorectal cancer screening programme carried out between 2006 and 2014, which took the form of a scientific study. The results of this study have not yet been published. The study compared data from over 15,000 screened people with those of over 4 million unscreened people over a follow-up period of almost 13 years. The early years of the study saw an increase in the number of colorectal cancer cases. This is because the initial screening of all participants detected pre-existing adenomas and colorectal cancers (a so-called ‘prevalence round’). In the following years, the number of cases decreased and showed that screening can prevent the development of colorectal cancer (hazard ratio (HR) 0.78; confidence interval 0.68-0.90) and reduce colorectal cancer mortality by a factor of 2.5 (HR 0.39; confidence interval 0.29-0.53). While these results are promising, there is an important caveat: the trial is subject to bias because the screened population was healthier than the control group. The magnitude of the effects of screening may therefore have been slightly overestimated. In addition, the type of FIT and cut-off value used in the trial screening programme were different from the current screening programme, and the screening age was 50-75 years. Two other observational studies, conducted in Italy, on the effect of screening with the FIT and colorectal cancer mortality are also available.[10,11] These studies also saw a beneficial

effect (36% and 41% reduction in mortality), but these were smaller than the effect in the Dutch study (61%). This can possibly be explained by the differences between the studies. In the Italian studies, the number of participants was smaller, the participation rate was lower, there was a shorter follow-up period and higher cut-off values were used.

Hazard ratio and confidence interval

The hazard ratio represents the ratio of the risk of a given outcome (in this case, of developing or dying from colorectal cancer) between two groups (here, the screened versus the unscreened group). The confidence intervals are also included. A confidence interval is a statistical measure that indicates how likely a particular research outcome is. In this advisory report, the 95% confidence interval is used in each case, meaning that with 95% certainty, the outcome actually lies between the values of the confidence interval.

In addition to the trial screening programme, there is also evidence from the current screening programme suggesting that screening may, in the longer term, reduce deaths from colorectal cancer. The current screening programme shows that screening usually detects colorectal cancer at an early stage.[12] The chance of cure and survival is greater if colorectal cancer is detected earlier. In addition, it has been shown that the annual number of new cases of colorectal cancer (incidence) has decreased since the introduction of population screening. This decrease in incidence can also be seen in late-stage colorectal cancers, and moreover, the incidence was lower than the expected incidence if no screening were to be performed.[9,13] A third indicator is provided by modelling research (cost-effectiveness analysis), which estimated the effects of colorectal cancer screening. The results suggest that the screening programme prevents colorectal cancer (possibly up to about 4,500 cases by 2044) and reduces mortality from it (possibly up to about 3,000 cases by 2044).[14] However, this data should be interpreted with caution as assumptions have been made in the model and the results will have wide margins of uncertainty due to the long time period modelled.

Distribution of stages of colorectal cancer

The stage is a measure of the severity of the disease, which is determined by the size of the tumour and the presence of metastases. In stage I, the tumour is confined to the intestinal wall. In stage II, the tumour has grown through the intestinal wall but has not spread to the lymph nodes. Stage III involves a tumour with growth through the intestinal wall and local lymph node metastases and stage IV involves a tumour with growth through the intestinal wall and metastases to other organs and/or tissue. Stage III and IV colorectal cancers are generally more difficult to treat and result in a higher burden of disease and mortality rate than stage I and II colorectal cancers (early-stage colorectal cancer). Stage III and IV colorectal cancers are regarded as late-stage cancers.

3.2 Risk-benefit ratio

There are advantages (benefits) and disadvantages (risks) associated with the screening programme. It is important that the risk-benefit ratio is favourable: participants in the screening programme should not suffer more harm than benefit from participation. The main benefit is that the screening programme prevents colorectal cancer and deaths from it (see 3.1). To assess the risk-benefit ratio, the committee additionally looked at various outcomes (see outcome data box) and disadvantages of the screening programme.

Approximately 70% of people who are invited for screening for the first time decide to take part in the screening programme.[6] This is similar to the breast cancer screening programme.[15] Once people have decided to participate, they generally go on to participate in subsequent screening rounds. Participation in follow-up rounds (repeat participation) is therefore high, at around 90%. Other outcomes also show a clear difference between the first screening round and follow-up rounds (see Table 1). This is because the first round is a prevalence round, which detects pre-existing adenomas and colorectal cancers.

Table 1 Screening programme outcomes in participants who completed one or more screening rounds, disaggregated by sex[18]

Men	1st round	2nd round	3rd round	4th round	Women	1st round	2nd round	3rd round	4th round
Average age (in years)	64.2	64.6	68.5	71.1	Average age (in years)	64.1	64.6	68.5	71.2
Participation*	100%	90.9%	91.4%	91.5%	Participation*	100%	91.8%	91.2%	90.5%
Referral rate	7.6%	5.0%	5.0%	5.3%	Referral rate	4.8%	3.4%	3.5%	3.8%
Detection rate of colorectal cancer per 1,000 participants	5.2	2.2	2.4	2.6	Detection rate of colorectal cancer per 1,000 participants	3.0	1.5	1.7	1.9
Detection rate of advanced adenomas per 1,000 participants	29.8	14.7	13.5	12.7	Detection rate of advanced adenomas per 1,000 participants	14.8	8.0	7.9	8.7
Colorectal cancer PPV#	8.6%	5.2%	5.5%	5.8%	Colorectal cancer PPV#	7.9%	5.3%	5.8%	5.9%
Advanced adenoma PPV#	49.0%	34.5%	31.4%	30.8%	Advanced adenoma PPV#	39.5%	27.7%	26.4%	27.6%
Colorectal cancer *NN to scope*†	11.6	19.2	18.2	17.2	Colorectal cancer *NN to scope*†	12.7	18.9	17.2	17.0
Advanced adenoma *NN to scope*$	2.0	2.9	3.2	3.2	Advanced adenoma *NN to scope*$	2.5	3.6	3.8	3.6
Colorectal cancer sensitivity§	86.7%	74.3%	77.1%	-	Colorectal cancer sensitivity§	80.9%	71.4%	71.3%	-

* As this table only includes participants who actually participated in one or more screening rounds, in this case participation in the first round is by definition 100%.
\# PPV: positive predictive value of the FIT
† *Number needed to scope* to detect 1 case of colorectal cancer
$ *Number needed to scope* to detect 1 case of advanced adenoma
§ The sensitivity is calculated up to and including the 3rd round; no data are yet available for the 4th round.

The follow-up rounds principally detect adenomas and colorectal cancers that developed after the first screening round. Therefore, the referral rate, detection rate, positive predictive value and sensitivity are higher in the first round than in follow-up rounds. These rates increase again in later follow-up rounds, as the incidence of colorectal cancer increases with older age. The number needed to scope (NNscope) is higher in follow-up rounds than in the first round, as successful screening requires more and more people to undergo a colonoscopy to detect further adenomas or colorectal cancer. Results in table 1 also show that some outcomes differ for men and women. This can be explained in part by the fact that colorectal cancer is more common in men than in women.

When the outcomes of the current screening programme are compared with the expectations when the screening programme was introduced,[1] they seem to be well aligned. The positive predictive value for colorectal cancer, the detection rate for colorectal cancer and the NNscope for colorectal cancer are similar to the anticipated values. The participation rate is higher and the risk of complications is lower than expected, which is favourable. By contrast, the referral rate and sensitivity are less favourable (lower) than expected. However, there are a number of caveats to these comparisons. Expectations were based on findings from trial screening programmes, but there are relevant differences between those trial screening programmes and the current screening programme.

Outcomes of the colorectal cancer screening programme

Participation: the number of people who decide to respond to the invitation to the screening programme and submit a stool test.
Referral rate: percentage of participants who have a positive test result and are referred for follow-up testing.
Detection rate: the number of participants per 1,000 participants with colorectal cancer. The detection rate is also calculated for advanced adenomas.
Positive predictive value: percentage of participants with colorectal cancer found compared to the total number of participants with a positive test result who underwent a colonoscopy. The positive predictive value is also calculated for advanced adenomas.
Number needed to scope (NNscope): the number of participants who need to undergo a colonoscopy to detect one case of colorectal cancer. This outcome is also calculated for advanced adenomas.
Sensitivity: the probability of a positive test result in a participant with colorectal cancer.
Risk of complications: the risk of a complication as a result of a colonoscopy. Four categories of complications are registered: mild complications (hospitalisation <4 days), moderate complications (hospitalisation for 4-10 days), severe complications (hospitalisation >10 days) and fatal complications. Complications occurring within 30 days of the colonoscopy are included.

The population participating in the trial screening programmes was younger (participation was possible from the age of 50) and more women than men took part. A lower cut-off value was also applied and a different method was used to analyse the stool test. In addition, expectations were based on data from an initial screening round only. From this, the

Committee concludes that the differences between prior expectations and the current outcomes of the screening programme have been explained well, and that the outcomes fit with a favourable risk-benefit ratio.

The main drawback of the screening programme is the high percentage of unnecessary referrals. It appears that more than 60% of colonoscopies revealed no relevant findings (advanced adenomas or colorectal cancer).[6] This means that a false positive test result is returned in many cases. A false positive result can cause anxiety and stress that later turns out to have been unnecessary. In addition, the burden of a colonoscopy is high and participants are medicalised unnecessarily. A colonoscopy can also result in complications, such as intestinal perforation or bleeding, but the risk of this is very low (<1%).[6] Another major drawback is that the screening programme leads to a certain degree of overdiagnosis and overtreatment. Overdiagnosis refers to the detection of advanced adenomas or colorectal cancers that would not have been found without screening and would not have presented with symptoms. The extent of overdiagnosis cannot be determined because it is not clear which adenomas and colorectal cancers will present with symptoms and which adenomas will develop into colorectal cancer. It is known that most adenomas do not develop into colorectal cancer. Overdiagnosis has also been shown to increase with age and with declining health.[16] In addition to overdiagnosis, there is also overtreatment. Most adenomas do not develop into colorectal cancer, but all adenomas are removed during the colonoscopy, as it is impossible to determine in advance which adenomas are harmless and which are not. This leads to overtreatment, as the vast majority of adenomas are removed unnecessarily. A final drawback of the screening programme is the false negative test results. A false negative result occurs if the test result was negative, but colorectal cancer is still diagnosed before the next screening round. This is then referred to as an interval cancer. False negative results and interval cancers may result in unwarranted reassurance or reduced confidence in the screening programme. Interval cancers are not common; the interval cancer rate is about 10 in every 10,000 participants.[17]

Although, according to the Committee, these disadvantages are significant and should not be underestimated, the benefits of screening (prevention of colorectal cancer and deaths from it) outweigh the disadvantages. The Committee concludes that the risk-benefit ratio of the screening programme is favourable in its current setup.

3.3 Cost effectiveness

To determine the cost-effectiveness of the screening programme, a model-based cost-effectiveness analysis was performed using the MISCAN-Colon model (microsimulation screening analysis) in which the costs and effects of the screening programme can be forecast over a long period of time.[19] This analysis shows that the screening programme in its current setup is cost-effective in the long term, compared to a situation

without a screening programme.[14] This does not mean that the screening progress does not cost money, but that in the long run, the cost of the screening programme will be recouped through savings on treatment costs due to fewer colorectal cancers.

3.4 International comparison

There are several other European countries where colorectal cancer screening programmes are offered. Comparing results between these countries and the Netherlands is not easy, as the epidemiology of colorectal cancer differs and there are many differences in the setup of screening programmes and the organisation of health care. In most countries, screening is offered nationwide (such as in France, the United Kingdom (UK), Denmark, Spain, Italy), while in others (such as in Sweden, Finland, Belgium, Portugal, Germany) it is only offered regionally at the time of publishing this advisory report.[20-24] In addition, different screening tests and analytical methods are used, different cut-off values are applied when using the FIT (ranging between 15 µg Hb/g and 80 µg Hb/g faeces), starting ages differ (ranging between 50 and 60 years), finishing ages vary (ranging between 69 and 75 years), and different intervals are applied. As a result, referral rates and detection rates differ, among other things, and it cannot be concluded that one country is performing better than another. To achieve the ultimate objective of the screening programme, it is important to achieve a sufficiently high participation rate. It appears that the current way of inviting participants to the screening programme and organising screening programmes in the Netherlands results in a very high participation rate (of around 70%) compared to other countries such as, for example, France where participation is at around 30%.[24]

04
potential improvements

The Committee has assessed whether further improvement of the screening programme can be achieved through calibration of the cut-off value, the interval or the age limits of the target group. This appeared not to be the case in the current situation. There are insufficient grounds for modifying the screening programme at this time, given that the risk-benefit ratio is favourable under the current setup and the screening programme is still in its infancy. There are also insufficient grounds for applying risk stratification in the current situation. Research is also needed to examine what changes could potentially lead to improvements in the screening programme in future. In addition, there should be a discussion on what is considered to be an improvement in the risk-benefit ratio.

4.1 Cut-off value

Since the middle of 2014, a cut-off value of 47 µg/g faeces has been used for the FIT in the screening programme. A cut-off value of 15 µg/g faeces was used in the first six months of the programme, but this resulted in too many referrals and an unfavourable ratio of true positive to false positive test results. This made the risk-benefit ratio unfavourable. Increasing the cut-off value to 47 µg/g faeces balanced the ratio of true positive to false positive test results, resulting in a favourable risk-benefit ratio.[25]

The Committee reviewed the cut-off value again in 2019 and advised against changing it.[26] The Committee judged that the risk-benefit ratio of the screening programme with the current cut-off value was favourable and that the results of the screening programme were sufficiently in line with expectations at the time the programme was introduced. Lowering the cut-off value would result in an increase in the number of false positive test results and unnecessary referrals. Increasing the cut-off value would result in an increase in the number of missed adenomas and colorectal cancers.

Modelling research shows that a lower cut-off value leads to an improvement of the screening programme in terms of cost-effectiveness (see cost-effectiveness analysis box).[27] A lower cut-off value results in more adenomas and colorectal cancers being detected, adding to life years gained. However, according to the committee, this improvement does not outweigh the disadvantages of a lower cut-off value: a further increase in the number of unnecessary referrals and unnecessary colonoscopies, associated with an increased burden, more anxiety and greater risk of complications. Overdiagnosis and overtreatment would also increase. Conversely, a higher cut-off value would lead to too many cancers being missed and a less (cost-)effective programme. At the current cut-off value, the risk-to-benefit ratio is favourable. The Committee therefore believes that there is no reason to change the cut-off value in the current situation. The capacity of colonoscopy centres is not a factor in this assessment, as it is expected that sufficient colonoscopy capacity could be available in the event of any reduction in the cut-off value.

Cost effectiveness analysis

A cost-effectiveness analysis (CEA) is a way of modelling (or simulating) and comparing the costs and effects of certain screening strategies. It also allows estimates of the possible long-term effects of screening on outcomes such as life years gained, quality adjusted life years gained (QALYs), cancers prevented, and screening tests and diagnostic procedures needed.

Erasmus MC performed a CEA using MISCAN-Colon: a microsimulation model specifically calibrated to the Dutch setting.[19] To perform the calculations, the model uses assumptions for indicators such as participation rates, the percentage of positive test results, the incidence of advanced adenomas and colorectal cancer and life expectancy. In the analysis comparing different alternative screening strategies, a participation rate of 100% for both screening and a colonoscopy was used. This is not feasible in practice, but it allows the screening strategies to be compared under similar conditions. Moreover, the optimum strategy will then be optimal for those who participate.

As with all statistical estimates, there is uncertainty around the results from MISCAN-Colon. Model predictions for the incidence of and mortality as a result of colorectal cancer in the Netherlands show a high degree of agreement with observed data. However, uncertainty is likely to be high around screening outcomes that are further into the future. Data for these are not available. While a CEA is one form of evidence in determining the optimum screening strategy, it is important to interpret its results with the aforementioned limitations in mind.

4.2 Interval

Since the introduction of the screening programme, the screening interval has been 2 years. A shorter interval (1 year) leads to more intensive screening, which will result in a decrease in the number of cancers arising between two rounds of screening (interval cancers) and an increase in the number of life years and QALYs gained. However, this is offset by several disadvantages. Annual screening will increase the burden on participants of the screening programme. False test results, overdiagnosis and overtreatment will occur more often than is currently the case. According to the committee, annual screening will not improve the risk-benefit ratio. The cost of the screening programme would also increase.

Extending the interval means fewer screening rounds per participant, reducing the burden and also the number of referrals and associated disadvantages. As colorectal cancer is generally a disease that develops slowly, the interval could probably be extended without increasing the risks too much, such as the occurrence of interval cancers. An initial indication of this was seen during the COVID-19 pandemic. During the first lockdown, the screening interval was, out of necessity, extended due to the suspension of screening programmes. As a result, for a limited number of participants, the interval was 2.5 years instead of 2 years. Overall, the impact of this extension seems to be limited. There was no difference in the interval cancer rate before, during or after the first COVID-19 wave and the positive predictive value and detection rates

were similar to those of participants with a regular interval.[28] However, this analysis should be interpreted with caution because the distribution of the stages of colorectal cancers detected has not yet been analysed and it was a limited group. As a result, it is not yet known whether the extended interval resulted in delayed diagnosis. This would be unfavourable because colorectal cancer detected at a later stage cannot be treated as easily as cancer detected at an early stage.

It is expected that for some participants, the risk-benefit ratio can be improved by extending the interval. A longer interval for those participants with very low Hb levels in the first screening round is currently being investigated by Erasmus MC.[29,30] From this, the effects, advantages and disadvantages of a longer interval will become clear. The Committee awaits the outcome of this study with interest.

4.3 Finishing age

The current target population of the screening programme is people between the ages of 55 and 75. Raising the finishing age to, for example, 80 could potentially improve the screening programme, due to increasing life expectancy and the higher incidence of colorectal cancer among people aged 75 and older.[3,31]

Modelling research shows that a finishing age above 75 years yields added life years and QALYs gained and can be efficient in terms of cost-effectiveness (see Figure 2).[27] However, there are also drawbacks to raising the finishing age. With screening at an advanced age, the individual risk-benefit ratio is highly dependent on the individual's life expectancy. Only if life expectancy is high enough can it be assumed that the benefits of screening at older ages outweigh the drawbacks.
A systematic review of trials of colorectal cancer screening shows that people with a life expectancy of 5 years or less do not benefit from colorectal cancer screening, and that a favourable risk-benefit ratio is likely to be realised only for people with a life expectancy of 10 years or more.[32] In 2021, the life expectancy of a 75-year-old was 12.3 years.[33] However, determining individual life expectancy is very difficult.
In addition, even at older ages, there are drawbacks to population screening, such as false test results, overdiagnosis and overtreatment, and the burden and risks of a colonoscopy. Moreover, the risks associated with a colonoscopy increase with age,[34] which will more commonly result in an unfavourable risk-benefit ratio for older individuals than for younger individuals. Finally, it is unclear to what extent screening at older ages still adds value for the group of people who have been participating in the screening programme for a number of years. Ultimately, people aged 75 will have been screened for 20 years. In participants with (an early stage of) colorectal cancer, any adenomas and tumours present will have been detected and removed during that time. Often, people remain under regular care (monitoring) for some time even after the age of 75.
In participants who did not develop adenomas during that entire time,

the Committee expects the likelihood that they will go on to develop colorectal cancer and die from it to be low.

As the risk-benefit ratio of screening above the age of 75 may be beneficial only for a specific, hard-to-identify target group, and the added value of screening beyond 20 years is expected to be limited, the Committee sees insufficient grounds for increasing the finishing age of the national screening programme.

Efficient screening strategies for the current Hb cut-off value

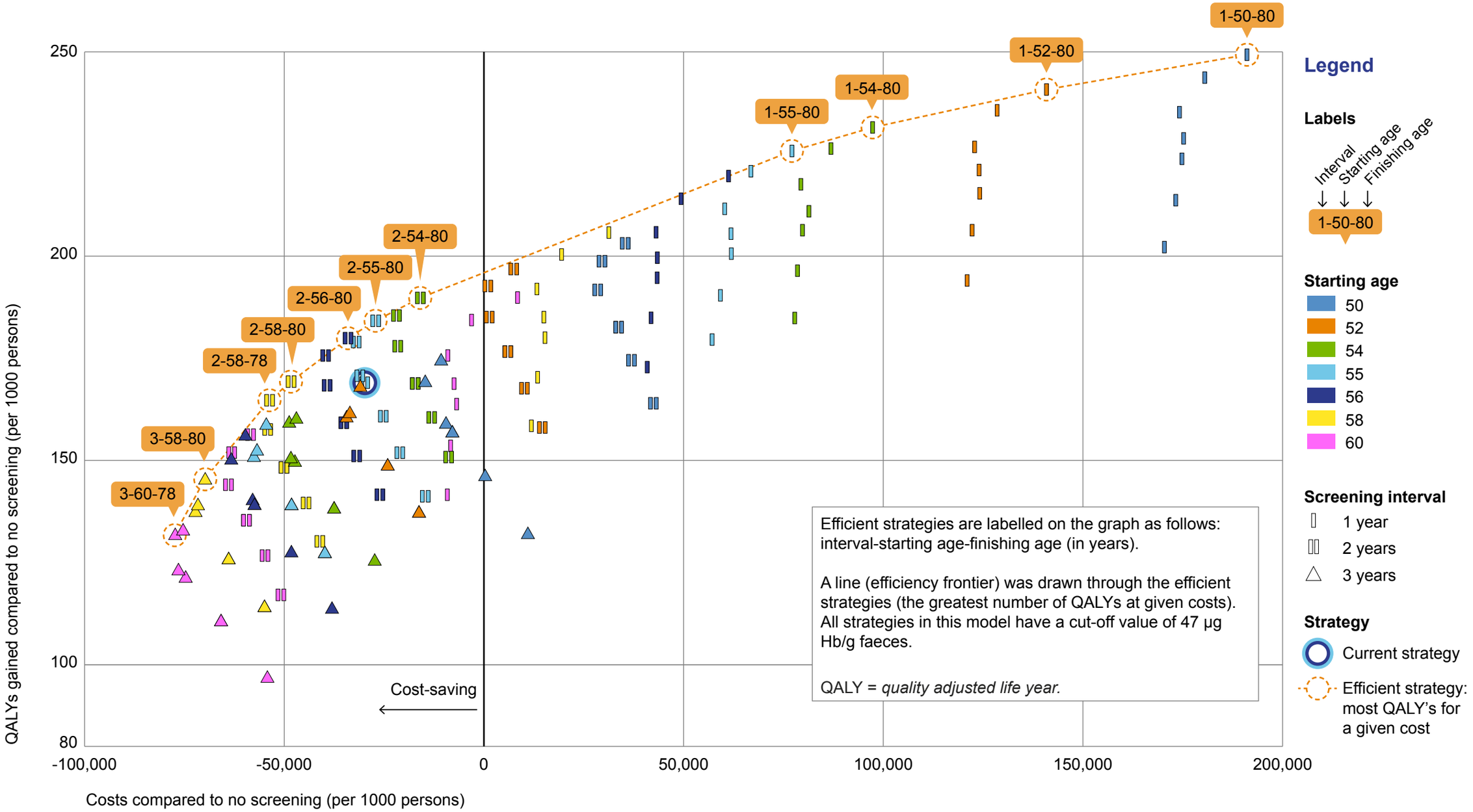

Figure 2 Cost-effectiveness of different screening strategies

4.4 Starting age

The Committee also looked at whether lowering the starting age could improve the screening programme. There are various patient groups and organisations that have long argued for a reduction of the screening age to 50. European Union guidelines also point to the possibility of starting screening at the age of 50, if the epidemiological situation warrants it.[35] There are various European countries that, like the Netherlands, offer a national screening programme with two-yearly FIT, but where the starting age is 50. Examples include Denmark, France, Spain, Italy, Slovenia and the UK (not yet implemented).[20,24,36-38] There are also countries where, as in the Netherlands, the starting age is higher (55-60 years; Norway, Ireland), and countries where screening is only offered regionally at the age of 50 (Flanders) or where there is no organised screening programme, but people can be screened on request at the age of 50 (Portugal, Germany (is currently implementing an organised programme)).[21,39-42] In the United States, screening is recommended from 45 years of age,[43] although there is no nationwide organised screening programme. The recommended screening method in the United States ranges from annually with an FIT to a colonoscopy every 10 years.
The rationale for the starting age is based primarily on modelling, which shows that the advantages would outweigh the disadvantages. However, only colonoscopy complications and the number of colonoscopies were cited as disadvantages. In addition, an increasing incidence of colorectal cancer among younger people is assumed. This trend has been observed in various high-income countries, including the Netherlands, for a few years now.[44]

Screening from the age of 50 will result in health benefits, as more advanced adenomas and colorectal cancers will be found than is currently the case. However, there are also drawbacks to a lower starting age. As advanced adenomas and colorectal cancer are rare in the 50-55 age group, many participants will be referred incorrectly and undergo unnecessary colonoscopies with the associated burden, anxiety and complication risks. These disadvantages will increase, but it cannot be estimated in advance to what extent and degree, nor whether over-diagnosis and overtreatment will also be more common. It is also uncertain how great the effects of a lower starting age on other important outcomes of the screening programme as a whole, such as the referral rate, detection rate, positive predictive value, NNscope and sensitivity, will be. Data on this from abroad are scarce and also difficult to translate to the Dutch situation due to differences in the epidemiology of colorectal cancer and different cut-off values and analytical methods for the FIT.
Another major uncertainty is the willingness to participate. In general, participation in screening is lower among younger people, as is the case in the current screening programme.[6] Lower participation rates will reduce the effectiveness and cost-effectiveness of the screening programme. In addition, modelling research shows that screening from 50 years of age with the current cut-off value and current interval is not an efficient

strategy in terms of cost-effectiveness (see Figure 2).[27] This is because with a low starting age, screening would be more frequent than is currently the case, while far fewer relevant findings will be made because the incidence in younger people is lower. Because screening will be more frequent and yield limited results, the incremental cost-effectiveness ratio will become less favourable than it currently is. Even with a lower cut-off value or a different interval, screening from the age of 50 was not found to be an efficient strategy.

So while there is no convincing evidence to show that the benefits of earlier screening outweigh the disadvantages, it is also clear to the Committee that some degree of health benefit remains. This applies to those people in whom colorectal cancer or an early stage thereof is already present at around 50 years of age. Offering one-off screening with the FIT to the entire target group at a younger age could help detect and treat some of these people in good time. People with a negative test result at around the age of 50 could then enter the regular screening programme at the age of 55. The advantage of such a pre-measurement would be that some degree of health benefit would be achieved, while the burden and disadvantages would be limited. The cost will also be lower than in the case of a blanket reduction in the starting age. Because it is not clear what the willingness to participate is, what exactly the yield, results and disadvantages will be, and what the implications of implementation are, a regional trial screening programme is needed before deciding on lowering the starting age of the current screening programme. This will allow these uncertainties to be investigated and also provide insight into their effects on the results of the screening programme as a whole (such as the positive predictive value and sensitivity). The Committee therefore also recommends conducting such a regional trial screening programme.

4.5 Risk stratification

The screening programme could potentially be improved by applying risk stratification (see box on the following page). Risk stratification based on sex, age and/or Hb level would potentially be relatively easy to incorporate into the screening programme, as no additional information or testing would be required before participants are assigned a specific screening strategy.

The Committee therefore focused on these forms of risk stratification. In addition, in the scientific literature, no other biomarkers or risk factors have been identified that are sufficiently predictive for use in risk stratification in a screening programme in the short term.

Risk stratification in screening

Risk stratification in screening means that the screening programme is structured differently for different subgroups of the target population, depending on the subgroup's characteristics and risk of colorectal cancer. An example of this is using a different cut-off value or screening interval for women than for men, because colorectal cancer is less common in women than in men. The aim of risk stratification is to improve the risk-benefit ratio for the subgroup, and therefore the risk-benefit ratio of the screening programme as a whole.

4.5.1 Sex

In general, men have a higher risk of colorectal cancer than women. Figures from the Netherlands Cancer Registry (Nederlandse Kanker-registratie, NKR) show that the incidence of colorectal cancer is higher for men than for women.[45] Because the incidence is not the same, the optimal cut-off value, screening age and/or interval may differ for men and women.

Using data from a Dutch pilot study conducted prior to the introduction of the screening programme, test characteristics for different cut-off values were calculated for men and women. Due to the higher incidence among men, the percentage of positive test results and detection rates in the first round were higher for men than for women.[46] After adjusting for age, there was no statistically significant difference in positive predictive value for advanced adenomas and colorectal cancer between men and women. Based on these data, a cost-effectiveness analysis was conducted to determine whether stratified screening by sex would be cost-effective.

The model analysis shows that two-yearly screening between 50 and 75 years is less effective for women than for men: fewer life years and QALYs are gained and the costs are higher.[47] In relation to cost-effectiveness, however, there is little difference between men and women in terms of what the most efficient screening strategy would be. Sex-specific screening would not improve the cost-effectiveness of the programme as a whole, as when the same strategy is used, the yields (early detection of adenomas and colorectal cancer) resulting from initiating screening of women are higher than the yields from more intensive screening of men.

More recent data from the screening programme shows that among participants who participated in all screening rounds, there is little difference in positive predictive value between men and women after the first screening round (see Table 1, Chapter 3). The NNscope to detect advanced adenomas and to detect colorectal cancer were also similar after the first round of screening. Regardless of the screening round, the sensitivity is higher for men than for women, but for both sexes the sensitivity decreases and stabilises after the first screening round. Despite a lower sensitivity and lower cumulative interval cancer rate for women, there was no difference in risk of interval cancer between men and women after adjusting for age and Hb level.[17] It is not clear why sensitivity is lower in women. Possible reasons for this include the number, size or location of tumours of the large intestine in women. However, a study into this shows

that the location of intestinal tumours did not explain the difference in sensitivity.[48]

The anticipated effects of risk stratification were also modelled using data from the current screening programme. The results show that from a cost-effectiveness perspective, women could generally be screened less frequently than men.[49] Screening could often start at a later age for women and stop at a younger age than for men. However, modelling also revealed cost-effective screening strategies where the setup was found to be the same for men and women. In addition, it appears that the greatest health benefits can be achieved with a strategy where the setup is completely identical or very similar for men and women.[49] This means that for the health benefits to be achieved, the added value of applying risk stratification by sex is limited.

Based on all the above data, the Committee sees no grounds for introducing risk stratification by sex in the current situation.

4.5.2 Age

As with sex, the risk of colorectal cancer also varies between different age groups. The incidence of colorectal cancer increases with age.[45] As the incidence is higher in older age groups, the optimal cut-off value and/or interval could potentially differ between age groups.

However, data from the screening programme show that in the second, third and fourth screening rounds (actual participation), outcomes are quite stable despite the average age being consistently higher (see Table 1, Chapter 3). There is also no evidence to show that stratification by age improves the screening programme. Most studies that examined risk stratification by age also looked at sex. Using data from a Dutch study, specific cut-off values by sex and age were identified. Only if the goal is to equalise the specificity of the FIT and the probability of a relevant finding from a colonoscopy for everyone are higher cut-off values needed for women than for men and for younger people than for older people.[50]
No studies have been done on a different interval for different age groups. No modelling research into this form of risk stratification is available.

Based on these data, the Committee sees no grounds for applying risk stratification by age in the current situation.

4.5.3 Hb value

A third option for stratification is to apply a different interval to different Hb values. The Hb value is used in the FIT to determine the test result. If the Hb value is higher than the cut-off value, there is a greater risk of colorectal cancer or an early stage thereof. In this case, the test result is positive and a participant will be referred. If the Hb value is lower than the cut-off value, the risk of colorectal cancer is lower and a participant will not be referred. However, it was found that even when the Hb value is below

the cut-off value, the risk of colorectal cancer varies between different (categories of) Hb values. A higher value, just below or close to the cut-off value, indicates a higher risk of developing an (interval) cancer than a very low Hb value.[17,51]

As described earlier, Erasmus MC has started a study within the current screening programme in which participants with a negative test result are given a different screening interval depending on the Hb value from the FIT.[29,30] For participants with a very low Hb value, the screening interval is extended (3 years), for participants with a high Hb value (below the cut-off value) the interval is shortened (1 year) and for participants with an Hb value in between these, the interval remains at 2 years. This form of risk stratification is expected to improve the risk-benefit ratio by reducing the burden without increasing the risk of developing colorectal cancer too much. The Committee awaits the outcome of this study with interest.

4.5.4 Risk stratification in future

In future, risk stratification could be used in screening programmes in order to improve the risk-benefit ratio for participants. However, before risk stratification is used, it must first be determined what can be seen as improving the risk-benefit ratio. The Committee believes that it is very important to start this discussion. Various starting points are possible, both in terms of benefits and risks: maximise sensitivity or the positive predictive value, reduce unnecessary referrals or, for example, equalise sensitivity for different sub-populations, such as men and women. It is not possible to improve the screening programme for every participant and every outcome. This is because all outcomes are closely connected, and improving one outcome will result in a worsening of another outcome. For example, to make the sensitivity more equal for men and women, the specificity of the FIT for women needs to be lowered by lowering the cut-off value for them, but this is associated with more unnecessary referrals and all the disadvantages associated with that. Equal sensitivity can also be achieved by lowering the sensitivity for men by using a higher cut-off value for them, but this will lead to more missed adenomas and colorectal cancers. A study was conducted in Sweden using different cut-off values for men and women to determine the effects in practice. In the Stockholm-Gotland region, a cut-off value of 80 µg Hb/g faeces was used for men and a cut-off value of 40 µg Hb/g faeces was used for women. Initial results showed that this form of risk stratification led to an equal percentage of positive test results for men and women.[52] However, it also showed that risk stratification did not improve the programme as a whole. Sensitivity was significantly higher for women than men and the total cost of the screening programme was 16% higher than the cost would have been with equal cut-off values (80 Hb/g faeces for everyone). With the same cut-off values, the positive predictive value for colorectal cancer would be the same for men and women, but 23% of colorectal cancers in women would then be missed.[53] By contrast, there would not be any difference between men and women in terms of the sensitivity and

number of interval cancers.[54] A trial screening programme was conducted in Finland in which different cut-off values for men (70 µg Hb/g faeces) and women (25 µg Hb/g faeces) were also used.[22] One cut-off value for all participants was eventually chosen for the national screening programme,[55] primarily for practical reasons such as limited colonoscopy capacity, which means that the percentage of positive test results should not exceed 5%. As the epidemiology of colorectal cancer, the composition of the study populations, the setup of the (trial) screening programmes and the FIT used are different in Sweden and Finland from those in the Netherlands, the results of those two programmes are not directly transferable to the Dutch situation. Before some form of risk stratification can be implemented, its effect in the Dutch programme needs to be investigated. In addition, it is important to define in advance what is considered to be an improvement, so that it is clear which outcomes would drive changes to the programme.

4.6 Other potential improvements

4.6.1 Participation

Average participation in the colorectal cancer screening programme has been stable since its introduction, at between 71% and 73%. However, participation is lower than average in various sub-populations. Socio-economic status (SES, a variable combining education level, financial wealth and employment history) appears to play a role in participation in the screening programme. People with a lower SES are less likely to participate in the screening programme, whereas the yield of screening (i.e. detected adenomas and colorectal cancers) is significantly higher in this group.[56] It is therefore important to encourage participation among people with a lower SES. In addition to SES, age and gender play a role in participation. In general, younger people participate less often than older people, and men less often than women.[15]

A lack of knowledge and tailored communication seem to play a role in participation.[57] It is possible that information specifically tailored to the target group could help to ensure that potential participants are informed properly in good time about the screening programme and its advantages and disadvantages. Various initiatives have been launched to improve participation rates in specific groups. For example, research funds have been made available to determine how specific target groups can be better reached and informed.[58] The Committee believes that it is important to continue to invest in reaching groups with lower participation rates, especially those with a low SES.

4.6.2 Developments in medical technology

Much research has been done in recent years on early detection of colorectal cancer. Various biomarkers (proteins, DNA, microbes, volatile organic compounds) can be detected in blood, faeces, urine and/or via breath testing, opening up opportunities for new screening tests.

Biomarkers that, like the FIT, are measured in a stool sample obtained by the participant him/herself at home could be implemented relatively easily, as the test does not change for participants (a stool test is still required) and the implementation remains fairly similar (sending the stool test to participants). In the Netherlands, a study is currently underway within the screening programme to add other protein biomarkers to the FIT, looking not only at Hb levels but also at other proteins present.[59] The results of this study are expected over the next few years. It is uncertain whether the results will prompt changes to the screening programme. Although there is also a lot of research on other biomarkers in blood, stool, urine and breath in addition to this study,[60-64] these tests are still far ready to be implemented in the screening programme. This is because many biomarkers have not yet been studied as part of a screening programme (a 'healthy' population without symptoms). Translating research findings from a clinical setting to a screening population is essential, but hardly ever done. Mostly, this is because the biomarkers studied in the clinical setting show poor predictive value from colorectal cancer. In a screening population, the predictive value will be even lower, making these biomarkers unsuitable for population screening.

4.6.3 Sustainability

The screening is structured so that everyone eligible for the screening is sent a stool test at home. More than a million tests are sent out each year. As approximately 70% of recipients decide to participate, 30% of the tests remain unused and become waste. The National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM) and Bevolkingsonderzoek Nederland have taken steps to make the screening programme more sustainable by sending out, and using, fewer tests. As of 2021, only an invitation letter (i.e. no stool test) has been sent to people who did not respond to two previous rounds of invitation. This saves sending out tests that are very unlikely to be used anyway. There are various practical reasons for not immediately making savings on sending stool tests by, for example, letting people request a test themselves. The main reason is that participation is expected to be lower, especially among sub-populations that already participate less frequently (see §4.6.1). This is undesirable, because the yield of screening (i.e. detected adenomas and colorectal cancers) is particularly high in people with a low SES. In addition, a pre-notification letter is sent three weeks before the first invitation to the screening programme. This allows people to opt out on time if they do not want to participate, which also saves tests. Finally, the packaging material has been reduced.

05 advice

The ultimate goal of the population screening is to reduce colorectal cancer mortality. As the screening programme only started a few years ago, it is not yet possible to demonstrate a decrease in colorectal cancer mortality. Results from trial screening programmes, different outcomes from the current screening programme and modelling show indirectly that the programme can prevent deaths from colorectal cancer. Based on these data, it is expected that the intended goal will be achieved in due course.

As the screening programme only started a few years ago, its results are still a work in progress. The risk-benefit ratio of the screening programme is favourable in the current situation. The Committee therefore recommends not changing the cut-off value, interval or age limits of the target group, and not applying risk stratification for the time being.
The Committee also recommends carrying out regional trial screening programmes after the one-off screening using a FIT at around the age of 50 years serving as a precursor to regular screening. This will help determine the extent to which one-off screening provides health benefits and how great its disadvantages and risks are.

5.1. Evaluation

In 2014, the colorectal cancer screening programme was implemented in stages because the entire target group (all 55-75-year-olds) was too large to start everyone in one go. Introduction of the programme was completed in 2019, and since then the entire target group is invited for screening every two years. Due to this staggered implementation, the current results of the screening progress are still a work in progress. As the screening programme runs for longer, the results will stabilise and become more robust. This fact was a major factor for the Committee when evaluating the screening programme and considering changes to the programme.

As the screening programme is still relatively new, it is not yet possible to observe a decrease in colorectal cancer mortality, which is the ultimate goal of the screening programme. However, there are various indications that this goal is within reach. For example, results from trial screening programmes suggest that screening leads to less colorectal cancer and fewer deaths from colorectal cancer. The results from the current screening programme also point in the same direction: the incidence of colorectal cancer has declined and the colorectal cancers detected are often detected at an early stage, increasing the chances of cure and survival. In addition, modelling shows that the screening programme prevents colorectal cancer and reduces mortality from it. Taken together, these outcomes lead to the conclusion that the screening programme is effective and is expected to achieve the intended goal (reduction of colorectal cancer mortality) with time.

The Committee also assessed the risk-benefit ratio of the screening programme and concluded that it is favourable. The benefits of screening

(preventing colorectal cancer and deaths from it) outweigh the drawbacks, such as false test results and the associated unnecessary colonoscopies, anxiety and missed colorectal cancers. In addition, the main outcomes of the screening programme are generally in line with expectations at the time of its introduction. The results achieved were even better than expected in terms of participation (higher than expected) and the number of complications from colonoscopies (lower than expected). The referral rate and sensitivity are less favourable (lower), but this can be explained by the fact that expectations were based on trial screening programmes, which used a lower cut-off value and a different analytical method to the FIT, among other factors, and the composition of the population was different from that of the current screening programme. These outcomes therefore do not adversely affect the risk-benefit ratio.

5.2 Potential improvements

The Committee assessed whether the screening programme could be further improved by changing the cut-off value, screening interval or age limits of the target population. In addition, applying risk stratification could potentially improve the benefit-risk ratio for certain groups (and hence the programme as a whole). However, as the screening programme is still in its infancy and the risk-benefit ratio of the current setup is favourable, the Committee believes sufficient and very persuasive arguments are needed before changing the screening programme at this time. There are currently no such arguments according to the Committee:

- As far as lowering the cut-off value goes, while it may lead to more life years gained, it does not outweigh the increase in the number of unnecessary colonoscopies and the associated disadvantages and risks.
- Lengthening the interval could lead to a lower burden and fewer disadvantages, without increasing the risk of interval cancers too much. This is currently being investigated. The Committee will await the results before recommending any changes to the screening interval.
- Screening of over-75s is not suitable for a screening programme, as its risk-benefit ratio could be beneficial only for a specific and very hard-to-identify group. In addition, the committee expects the added value of such screening to be limited, as ultimately people aged 75 have been screened for 20 years and, where necessary, treated.
- Two-yearly screening of 50- to 55-year-olds has an unfavourable risk-benefit ratio, according to the Committee, because few cases of colorectal cancer or advanced adenoma will be detected in this age group due of its low incidence, while there will be many unnecessary referrals and colonoscopies. The incremental cost-effectiveness ratio will also be less favourable than it currently is. One-off screening with an FIT at around the age of 50 (followed by entry into the regular screening programme at the age of 55 in the event of a negative test result) could provide health benefits without too many disadvantages and risks. This would require a trial screening programme first.
- There is currently no evidence that risk stratification by age or sex

provides health benefits and improves the risk-benefit ratio. Research on risk stratification by Hb level is underway. The Committee recommends waiting for the outcome of this research.

5.3 Recommendations

5.3.1 Trial screening programme based on one-off screening at around the age of 50

The Committee recommends carrying out a trial screening programme based on a one-off FIT for participants around the age of 50, before entering the regular screening programme. People with a negative test result would then enter the regular screening programme at the age of 55. According to the Committee, such a pre-measurement could provide health benefits for participants with advanced adenoma or colorectal cancer, without burdening the entire target group with the screening programme and its drawbacks at an earlier age and for longer. The trial population screening programme may show to what extent health gains are indeed achieved and how significant the disadvantages are. The trial screening programme should also provide insights on willingness to participate and feasibility. The Committee recommends that the trial population screening programme be carried out at a regional level and it should not be offered nationwide until the results of the trial programme are in. After all, a pre-measurement for participants at around the age of 50 may very well yield insufficient health benefits and entail too many disadvantages as well as an unfavourable risk-benefit ratio.

5.3.2 Preparing for possible risk stratification in future

The Committee expects that risk stratification could add value in the future. When the screening programme has been running for a longer period, it will become clear whether there are outcomes, such as the positive predictive value or sensitivity, that differ largely between men and women, or between different age groups. It is possible that such differences could be eliminated with risk stratification, aiming at a similar risk-benefit ratio for each group and improving the programme as a whole. For this, however, it is important to determine in advance what outcomes need to drive the changes and what is considered to be an improvement. As all outcomes are connected to each other in the screening programme, improving one outcome will result in a worsening of another outcome. For example, improving sensitivity can be achieved by using a lower cut-off value, but that will also create further disadvantages, as there will be more unnecessary referrals. The Committee believes that it is very important to start the discussion on improving the risk-benefit ratio and defining how this can be done. In the Committee's view, this discussion should be held broadly, because the same issues are present in breast and cervical cancer screening programmes and may be approached differently. In addition, it is important to conduct scientific research on different forms of risk stratification in the screening programme to determine the advantages and disadvantages, participation rate, cost-effectiveness and feasibility.

5.3.3 Encouraging participation among certain groups

Participation in the colorectal screening programme is high. However, there are groups in which participation is below average. This is seen not only in the colorectal cancer screening programme, but also in the screening programmes for breast and cervical cancer. Lower participation rates are particularly seen in the youngest target groups and among people with a low socio-economic status. Because this leaves health gains untapped, the Committee believes that it is important to not lose sight of these groups. Continued investment should be made to reach these groups, for example through initiatives in neighbourhoods or districts to inform the target group about the screening programme, and through conducting scientific research into factors that influence participation.

5.3.4 Focus on primary prevention

Although the Committee has not been asked to advise on primary prevention, the Committee wishes to take the opportunity in this advisory report to stress its importance. A continued focus on primary prevention from the government can lead to health gains over time. The committee welcomes initiatives such as the National Prevention Agreement[65], and would like to see even greater efforts to prevent colorectal cancer by, for example, facilitating research into it and education on it.

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[a] Consulted experts are consulted by the committee because of their expertise. Consulted experts and observers are entitled to speak during the meeting. They do not have any voting rights and do not bear any responsibility for the content of the committee's advisory report.

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