# Colorectal cancer screening by means of repeated faecal immunochemical testing (FIT)

Atija Kapidzic

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# CRC screening by means of repeated FIT testing

**Darmkanker screening door middel van herhaald testen met een immunochemische feces occult bloed test**

PROEFSCHRIFT

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**Promotor (en)**: Prof.dr. E.J. Kuipers

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*Voor mijn ouders*

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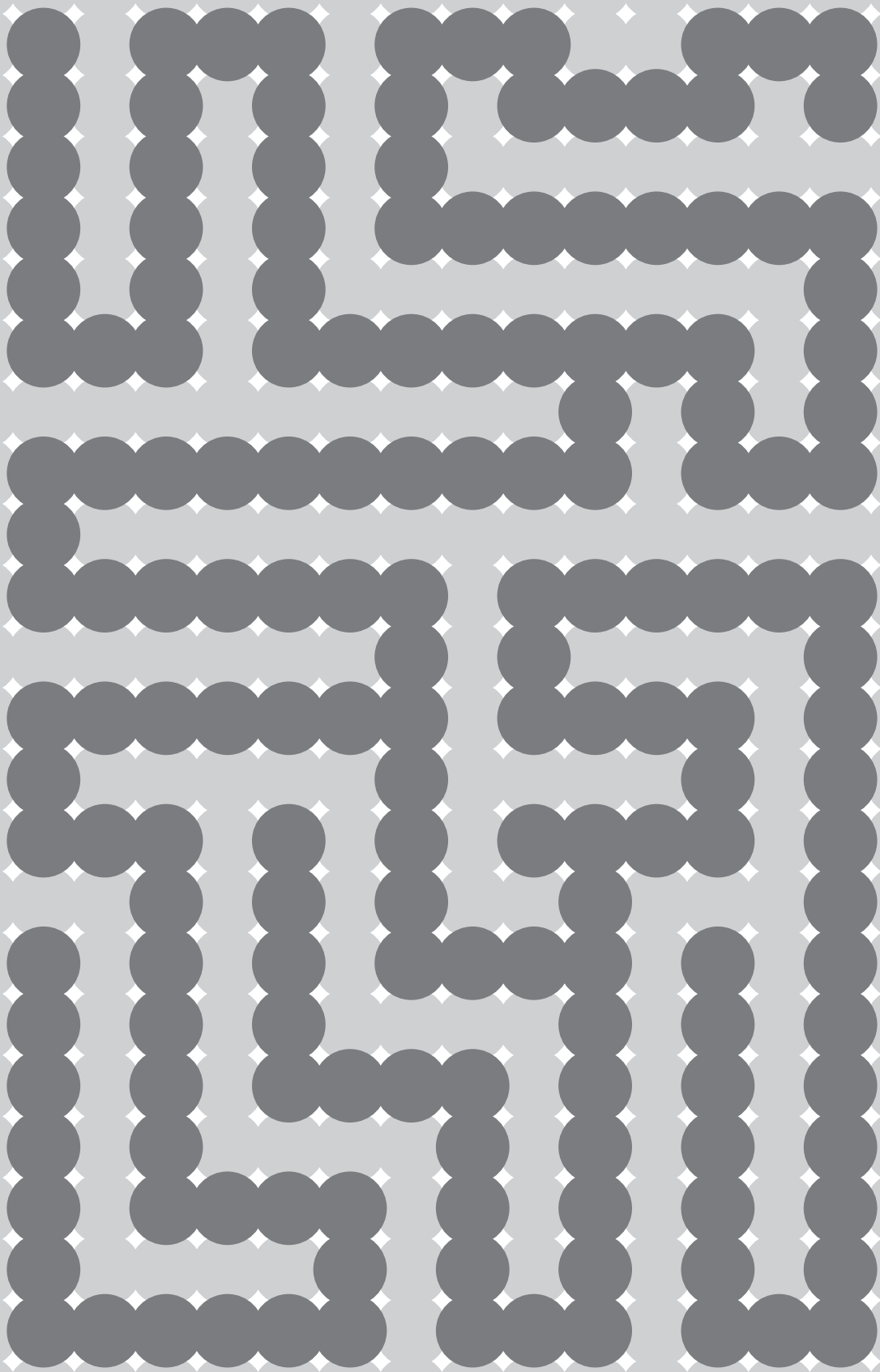

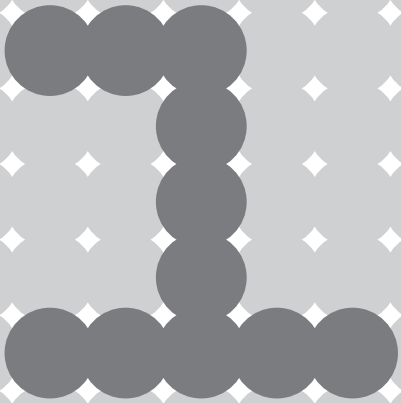

# General introduction and outline of the thesis

Atija Kapidzic, Lieke Hol, Monique E. van Leerdam, and Ernst J. Kuipers

*Adapted from the review 'Coloncarcinoom – preventie en screening' written for Farmacotherapie Online 2013*

## GENERAL INTRODUCTION ON CRC

Colorectal cancer (CRC) is a major health concern. Approximately 1.2 million people are diagnosed with CRC each year worldwide. The disease thus accounts for almost 10% of all cancers [1]. The highest incidence rates are seen in the Western world, including Europe, the USA, Australia, and New Zealand [2]. The lowest incidence rates are found in Africa and South-Central Asia. The geographic differences appear to be attributable to differences in dietary and environmental exposures. The lifetime incidence of CRC in patients at average risk is about five percent [1]. Rates are substantially higher in men than in women [2]. In the USA for example, the incidence of CRC is about 25% higher in men than in women [3]. Common risk factors and potentially modifiable behaviours include physical inactivity, obesity, and smoking, as well as having a first-degree relative with CRC [4-6]. Age is also a major risk factor for CRC. Before the age of 40 years CRC is uncommon, except in patients with a genetic predisposition [7, 8]. Beyond the age of 50 years incidence rates rapidly increase [2]. Sporadic CRC thus typically affects men and women between the ages of 55 and 85 years. This group consists of approximately 80% of CRC patients.

Adenocarcinoma of the large intestine can no longer be considered as one disease but rather a family of diseases with different precursor lesions, different molecular pathways, and different end-stage carcinomas with varying prognoses [9]. Most sporadic CRCs arise from colorectal adenomas, some of which progress from early to advanced adenoma to invasive cancer via the suppressor pathway leading to microsatellite stable carcinomas [10, 11]. A study by the National Polyp Study Workgroup showed that endoscopic removal of adenomatous polyps resulted in a lower-than-expected incidence of CRC compared with reference populations [12]. After a follow-up period of up to 23 years (with a median follow-up of 16 years), a CRC mortality reduction of 53% was seen among patients with adenomas removed compared with the expected mortality in the general population [13]. This research supports the view that colorectal adenomas progress to adenocarcinomas, and that removing adenomatous polyps will prevent colorectal cancer. Only a minority of adenomatous polyps however ultimately develop into CRC. Based on epidemiological studies, an estimated 2.6-5.6% of advanced adenomas annually progress to invasive CRC [14]. Size and histopathology determine the risk on malignant transformation. The National Polyp Study Workgroup introduced the concept of advanced adenomas defined as adenomas ≥ 10 mm, or an adenoma with more than 25% villous component, and/or high-grade dysplasia, as these factors appeared to be independently associated with the progression to CRC [15, 16]. Other independent factors that are associated with the probability that a patient will develop other adenomatous polyps or cancer elsewhere in the colon, are three or more adeno-

mas, age ≥ 60 years, proximal adenomas, and male gender [17, 18]. In addition to the adenoma-carcinoma sequence, there has been increasing attention for a different route of colorectal carcinogenesis in the recent years, ie, the 'serrated polyp pathway'. Approximately up to 35% of CRCs are believed to arise along this serrated pathway developing from the precursor lesion known as the sessile serrated adenoma (also referred to as the sessile serrated polyp) [9]. Sessile serrated adenomas lead to carcinomas with CpG island methylated phenotype (CIMP) positive carcinomas, which can be either microsatellite instable or microsatellite stable. The remaining 5% of carcinomas arise from conventional adenomas in patients with germ line mutations of mismatch repair genes (such as Lynch syndrome), leading to CIMP-negative microsatellite instable carcinomas [9]. It is increasingly believed that from a biologic point of view right- and left-sided polyps behave differently, where right-sided polyps are more often believed to follow the serrated neoplastic pathway instead of the adenoma-carcinoma-sequence [9]. It is known that a certain group of the serrated polyps have a higher chance of becoming malignant. In the past, all serrated polyps were classified simply as hyperplastic polyps and were considered to have no malignant potential. The recognition of the serrated neoplastic pathway has been important in the prevention of interval cancers through colonoscopy surveillance programmes [19].

CRC usually requires intense treatment. This is accompanied by a considerable burden to the patient, a high risk of complications and high costs. The chance of being cured of CRC is strongly dependent on the stage at which the disease is discovered. Mortality rates from CRC have progressively declined in the USA and in many other Western countries [20]. This improvement can partly be attributed to detection and removal of polyps, detection of CRCs at an earlier stage, and more effective treatment, particularly adjuvant therapy [21]. If tumor growth is limited to the submucosa (stage I), the five-year survival rate is 94%. When the disease is metastasized (stage IV), the five-year survival rate drops to less than 20% despite intense multi-modality treatment [21]. Despite advances in treatment, 40-50% of patients presenting with a symptomatic CRC eventually die of metastatic disease [1]. Importantly, CRC is characterized by a long preclinical stage (Figure 1), with the progression from early adenoma to invasive cancer taking years [14, 22]. CRC fulfills the screening criteria of Wilson and Jungner, as it is an important health problem with significant morbidity and mortality, as the disease has a detectable and treatable precursor (adenomas), and early detection of CRC improves the prognosis [23, 24]. A final important screening criteria is that the overall benefits of screening should outweigh the potential harm and costs [23, 24]. A study based on micro-simulation models found four screening strategies, namely ten-yearly colonoscopy, annual Hemoccult SENSA (a guaiac-based faecal occult blood test) or faecal immunochemical test, and five-yearly flexible sigmoidoscopy in conjunction with Hemoccult SENSA every two to

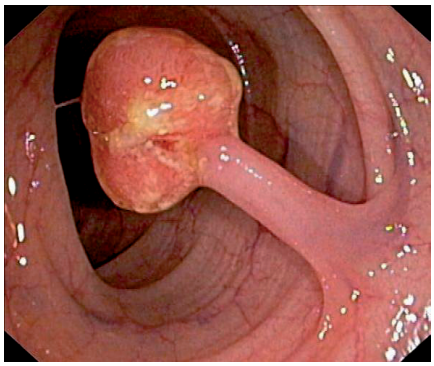

**Figure 1** Pedunculated adenoma with signs of minimal bleeding at the base of the stalk

three years comparably cost-effective assuming an equally high adherence [25]. Furthermore, the various CRC screening methods all have cost-effectiveness ratios which are considerably better than those of other generally accepted screening programmes, such as those for breast cancer and cervical cancer [26]. CRC screening is therefore desirable not only to reduce the CRC incidence and mortality, but also to reduce the costs associated with CRC treatment.

Aforementioned CRC characteristics make the disease more suitable for population screening than any other malignancy. In 2003, the European Commission recommended that CRC screening should be offered to all men and women aged between 50-75 years [27]. From January 2014 onwards, a nationwide screening programme using biennial FIT as a primary screening method is gradually being implemented in the Netherlands.

## SCREENING STRATEGIES

The primary aim of screening is to detect and treat the disease at the earliest stage possible, thereby influencing survival as well as detecting and removing pre-malignant lesions and thus reducing the incidence. Several methods are available for screening. These methods differ in the degree of supporting evidence, test-related burden, attendance, diagnostic yield and therefore effectiveness (Table 1, derived from Kuipers et al, Nat Rev Clin Oncol, 2013). CRC screening tests can broadly be divided into early detection tools and cancer-prevention tools. Early detection tools include stool-based screening tests, such as guaiac-based faecal occult blood tests (gFOBTs) and faecal immunochemical tests for haemoglobin (FITs). These are non-invasive screening methods which use inexpensive assays for detection of microscopic amounts of blood that the majority of cancers and a considerable proportion of advanced adenomas give rise to.

Patients with a positive test are typically referred for endoscopy, such as sigmoidoscopy and colonoscopy, which are examples of a cancer-prevention tool. These screening methods are invasive and expensive, but are capable of early detection and can also prevent CRC by removal of precursors. Abovementioned CRC screening methods are discussed in the text below [28].

**Table 1** Population screening in the Rotterdam region (50-74 years in age)*

| Screening method | Adherence (%) | Positive test (%) | Positive predictive value[α] (%) | True positives (per 1,000 invited) |
|---|---|---|---|---|
| gFOBT | 50 | 2.8 | 45 | 6 |
| FIT | 62 | 8.1 | 42 | 21 |
| Sigmoidoscopy | 32 | 10.2 | 100 | 33 |
| CTC | 34 | 8.6 | 71 | 21 |
| Colonoscopy | 22 | 8.7 | 100 | 19 |
| Two-round FIT | 62-63 | 14.1 | 33-42 | 34 |
| Sigmoidoscopy and FIT | 57 | 16.8 | 100, 42[β] | 43 |

* Those with a positive screening test were recommended colonoscopy (except when colonoscopy was used as the primary screening test), which enabled the determination of the positive predictive value of the primary screening test (the proportion of subjects that during colonoscopy were diagnosed with advanced neoplasia). The uptake of the test was multiplied by the positivity rate and positive predictive value to determine the number of true positives identified with advanced neoplasia per 1,000 invited

[α] Proportion of subjects with a positive primary screening test that were found to have advanced colorectal neoplasia on secondary screening by colonoscopy; [β] 100 and 42, respectively, for sigmoidoscopy and FIT; CTC: CT-colonography; FIT: faecal immunochemical test; gFOBT: guaiac-based faecal occult blood test

## Stool-based screening tests

*Guaiac-based faecal occult blood tests*

Guaiac-based FOBTs (gFOBTs) get their name from the paper used in the device, which is from *Guaiacum* trees. When the guaiac-impregnated paper comes into contact with hydroxyperoxidase, it oxidizes leading to a blue color change in a process that is catalyzed by haem, a constituent of haemoglobin molecules. The tests are used qualitatively to detect microscopic amounts of haem in the stool. The test card typically consists of two small panels for a faecal smear and testing is usually performed with three test cards (each with two panels) to be used with three consecutive bowel movements. gFOBTs are inexpensive, easy to use, and simple to distribute, which is important from a public health perspective [29].

For many years, gFOBts were the only CRC screening method for which prospective evidence with respect to long-term outcomes existed. Three randomized controlled trials showed that repeated annual or biennial gFOBT screening reduces the CRC-related

mortality by approximately 16% [30]. These trials offered annual or biennial gFOBT screening to 31,000-76,000 subjects in different age ranges varying between 45 and 80 years. Studies were performed in the USA, the UK, and Denmark for follow-up periods from 10-15 years, and compared results against similar numbers of controls. A more recent study showed that the effect of gFOBT screening on CRC-related mortality persists even after 30 years [31]. Observational studies that compared populations who did and who did not undergo screening are consistent with these randomized trials [32, 33].

Attendance is an important factor in the effectiveness of a nationwide screening programme. The participation rates in the first round of gFOBT screening vary between 47-67% [34-37]. Randomized trials demonstrated lower participation rates for gFOBT compared to FIT screening, which is partially caused by the more demanding sample collection procedure (three consecutive stool samples) of gFOBTs [34-36]. Furthermore, for the effectiveness of FOBT screening in general it is required that invitees are repeatedly screened. A Scottish gFOBT screening study showed that of people that participated in the first round of gFOBT screening, a high percentage attended subsequent rounds (approximately 85%) [37].

The limited sensitivity for detecting cancer and the poor performance in detecting adenomas is the main shortcoming of gFOBTs [29]. The limited sensitivity was among others demonstrated in a study from the USA in which 4,024 subjects aged 50-79 years underwent both a gFOBT and a colonoscopy [38]. Among patients with a negative gFOBT, 4.5% of women and 8.6% of men were diagnosed with advanced neoplasia by colonoscopy. There is a variation in reported sensitivities and specificities between studies, which is a consequence of a differences in test variants used, the number of samples and method of faecal collection, whether the gFOBTs are rehydrated or not (this increases sensitivity at the cost of specificity), and the number of positive samples that are used as threshold for referral. Single tests with a standard gFOBT (ie, Hemoccult II) have a sensitivity for CRC of 13-38% [39, 40]. If a more sensitive gFOBT is used (Hemoccult SENSA), this percentage rises to 64-80%, although this is at the cost of a lower specificity [41].

Another disadvantage of gFOBTs is that haem remains relatively chemically stable as it passes through the gastro-intestinal tract. Therefore, in upper gastro-intestinal bleeding the majority of haem passes into the colon possibly resulting in false-positive results. Also, the fact that their analysis cannot be automated makes gFOBT labour-intensive and reader-dependent [29]. In addition, gFOBTs are not human-specific and can react with haem from dietary meat [29]. This may lead to false-positive gFOBT results, although randomized trials comparing gFOBT and FIT screening have demonstrated similar false-positivity rates between the two strategies [34, 35]. Hence, dietary restrictions are no longer considered necessary for gFOBT screening [29, 42]. Likewise, patients taking

medication that might enhance bleeding (eg, aspirin, NSAIDs and anticoagulants) do not have to stop prior to testing [43, 44].

*Faecal immunochemical tests*

Faecal immunochemical tests (FITs) detect human globin by means of an antibody-based assay (Figure 2). Globin is the protein component of haemoglobin. The antibodies are attached to latex, dye or enzymes, which form complexes in the presence of globin. The degree of agglutination is read as an optical change and translated to a concentration of haemoglobin per amount of faeces per sample solution. As globin present in blood from the upper gastro-intestinal tract is gradually digested during its passage towards the colon, FITs are more specific to bleedings in the lower gastro-intestinal tract than gFOBTs [29, 45]. At the same time however, this characteristic of globin might lower FIT sensitivity for lesions in the proximal colon (so-called right-sided lesions). Furthermore, FITs do not cross-react with traces of dietary, non-human blood in stools, as globin is human-specific [29, 46]. Additionally, FIT sampling is considered easier for screenees to carry out, and FITs are able to detect smaller amounts of blood in the faeces (10 µgram haemoglobin/gram faeces which corresponds with 50 ng haemoglobin/ml sample solution, versus 200 µgram /gram faeces, respectively) [29].

The idea for applying an immunochemical method to detect microscopic blood loss was first proposed in the 1970s, and commercialization of the technology began in the 1980s [47, 48]. Both qualitative and quantitative FITs have been developed. Qualitative tests require visual interpretation of the test result and provide a positive or negative test result at a fixed cut-off level. Quantitative tests are analyzed automatically and provide the actual haemoglobin concentration in the stool sample. This method has important advantages for quality control, reproducibility and capacity [29, 49]. An additional advantage of quantitative FIT screening is the ability to determine the optimal cut-off level for a nationwide screening programme (ie, the amount of haemoglobin


**Figure 2** Faecal immunochemical test (OC-Sensor Micro, Eiken Chemical Co, Japan)

above which the test is considered positive and screenees are referred for colonoscopy), based on the colonoscopy resources available and/or personal risk profile [50].

FIT screening is associated with a higher participation rate than gFOBT screening. Two population-based studies from the Netherlands, in which screening-naïve subjects aged 50-75 years were randomly assigned to undergo either gFOBT or FIT screening, found a 13% higher attendance in the first round of FIT than with gFOBT screening [34, 35]. This can be attributed to the ease of handling of the FIT. The higher attendance has been confirmed in other studies, and studies on repeated FIT screening furthermore suggest that FIT uptake tends to remain stable through multiple screening rounds [51-53]. This is of key importance since the influence and effect of any screening method are firstly determined by whether patients actually take the test.

Furthermore, FITs have a lower blood-detection threshold and therefore a higher sensitivity for detecting advanced neoplasia [29]. The aforementioned two population-based Dutch studies showed that advanced neoplasia was detected more than three times as frequent with FIT when compared with gFOBT [34, 35]. Per 1,000 screenees, gFOBT (with colonoscopy referral as soon as one panel tested positive) identified six subjects with advanced neoplasia compared to 21 subjects with FIT at a cut-off of 50 ng/ml, which is equivalent to 10 µg haemoglobin per gram of faeces [54, 55]. Both trials demonstrated a higher diagnostic yield and a similar positive predictive value. This implies that for both tests the number needed to scope was the same, but the detection rate was higher due to a higher positivity rate of the FIT [54, 55]. Studies on repeated FIT screening have shown a drop in positivity rate, subsequent demand for colonoscopy and positive predictive value [51, 53, 56]. The detection rate of advanced neoplasia remained however higher with repeated FIT compared to repeated gFOBT screening [35, 51]. Furthermore, an Italian CRC screening study on four rounds of biennial FIT screening showed stable attendance rates and test characteristics between the second, third and fourth rounds [53]. These findings would imply that long-term FIT screening is superior to gFOBT screening in reducing CRC mortality, as it appears to be associated with fewer missed cancers compared with gFOBT screening. Using risk-based stratification based on questionnaire data in combination with FIT outcomes for selection of screenees for colonoscopy, was found to increase the accuracy of FIT-based screening and could be used in the preselection for colonoscopy in CRC screening programmes [57].

Although gFOBT screening uses multiple faecal samples per test round, FIT screening is routinely performed on a single stool sample. Advanced neoplasia can bleed intermittently and therefore may be missed with singe stool sampling. Screening by means of a 2-sample FIT increases test sensitivity (ie, reduces the risk of missing advanced lesions). A study comparing 1-sample versus 2-sample FIT screening reported no differences in attendance rate while significantly more advanced neoplasia were detected in the first screening round with 2-sample FIT (25 versus 19 advanced neoplasia detected per

1,000 participants) [58]. The trade-off however was reduced specificity, as the additional yield in detecting advanced neoplasia was achieved only by a greater demand for colonoscopy. Another study found that 3-day FIT sampling had a reduced attendance rate compared with gFOBT, but had no associated interval cancers during two years of follow-up [59]. Based on the evidence from first round screening, 2-sample FIT screening with referral for colonoscopy when both tests are positive, which would yield a colonoscopy programme with a high positive predictive value, can be considered in case of limited colonoscopy capacity. In case of unrestricted colonoscopy capacity, 2-sample FIT screening with referral for colonoscopy when at least one test is positive appears to have the highest diagnostic yield. In between these two extremes, using 1-sample FIT screening was shown the be the most efficacious method [58]. These results can be used for optimal screening strategy planning, tailored to a range of local needs and colonoscopy capacities. Further information on repeated FIT screening with multiple samples is needed.

A pivotal aspect concerning population-based screening are naturally the costs involved with a certain strategy. A study using the validated MISCAN-Colon microsimulation model estimated costs and effects of different screening strategies using 1-sample FIT for cut-off levels ranging from 50-200 ng/ml [50]. For each cut-off level, screening strategies were assessed with various age ranges and screening intervals. It was found that the optimal cut-off level was 50 ng/ml, which had the highest sensitivity and lowest specificity. The decreased specificity of screening was outweighed by the fact that fewer rounds were needed compared with screening with higher cut-off levels to be equally effective [50]. Cost-effectiveness analyses from this group furthermore showed that using higher cut-off values was most cost-effective when there is limited colonoscopy capacity [60]. In addition to this adaptation, the age ranges of the invited subjects could be narrowed. More than one FIT sample can provide additional health benefits at acceptable costs, as was shown in several studies comparing the costs of FIT screening with either one, two, or three FITs [61-63]. However, a cost-effectiveness analysis comparing the added effect of multiple FIT samples per screening round to the effect of screening with 1-sample FIT, found that increasing the screening intensity of 1-sample FIT (ie, greater age range and/or shorter screening interval) was more cost-effective than providing two FITs within one screening round [64]. In a situation where attendance to screening does not differ between strategies, it was therefore recommended to intensify screening with 1-sample FIT over providing two FIT samples within one screening round [64]. This analysis was based on data from one screening round. Data from repeated screening rounds are needed to get a good estimate of the correlation of test outcomes between successive screening rounds.

A matter that is not often being addressed, but that is very relevant on a population level, is whether participating in a CRC screening programme has an effect on quality

of life (QOL). Benefits such as life-years gained due to early detection and subsequent early treatment should be outweighed by the effect on QOL, such as the anxiety and distress with respect to the invitation and the test as well as test burden. Two studies that investigated QOL effects showed that screening did not appear to have adverse emotional effects in the longer term (44 weeks) [65, 66]. These studies focused on colonoscopy- and FS-based screening. Two other studies among participants in a FOBT screening programme and one FS screening study assessing anxiety associated with CRC screening, showed that most of the participants did not experience an increase in anxiety compared to an age- and gender-matched group not invited for screening and a group of non-participants of the screening programme [67-69]. Our study group demonstrated that FIT slightly outperforms gFOBT with a lower level of reported discomfort and overall burden [70]. However, additional information on QOL among participants in FIT screening is required.

Based on the technological advances of FIT screening, and the above mentioned evidence in which it was clearly shown that FIT outperforms gFOBT in terms of a higher attendance and diagnostic yield, in May 2011 the Dutch Health Council recommended the Minister of Health, Welfare and Sport that a nationwide FIT-based CRC screening programme should be implemented in the Netherlands [71]. On January 2014, a biennial FIT screening programme was started in which men and women in the ages between 55-75 years are gradually invited for biennial FIT screening using a cut-off of 75 ng/ml. Similar FIT screening regimens are currently applied to men and women despite eminent sex disparities in prevalence and anatomic distribution of advanced neoplasia. Several colonoscopy based screening studies have reported a higher incidence and prevalence of advanced neoplasia in men compared to women [14, 38, 72, 73]. Furthermore, a number of studies where subjects received a FOBT prior to colonoscopy found a higher sensitivity of FOBTs in men [74, 75]. Data on possible gender differences in a population-based setting with FIT as a primary screening tool are required to assess whether the current similar use of cut-off values in men and women is reasonable.

## Colon imaging and direct visualization

*Flexible sigmoidoscopy*

Flexible sigmoidoscopy (FS) is an endoscopic technique that examines the distal part of the colon (ie, rectum, sigmoid and descending colon). The usual bowel preparation for screening purposes consists of a single phosphate enema (120 ml), which can be administered by the screenee at home. During FS, which is usually performed without sedation, small polyps up to 9 mm in diameter can be removed. In case of larger polyps or more than three small polyps screenees are rescheduled for complete colonoscopy. Complications associated with FS such as bleeding and perforation occur because of

the screening procedure itself (0.01-0.03%) or due to the follow-up colonoscopy (0.26-0.55%) [76, 77].

Until 2009, gFOBTs were the only CRC screening method supported by prospective, randomized evidence on endpoints of cancer incidence and mortality. The publication of four large, prospective, randomized trials comparing FS screening with no screening provided information on these endpoints in FS screening [78-82]. These studies conducted in Italy, Norway, the UK, and the USA, have shown a 18-23% reduction in the overall incidence of CRC by a single FS screen after a follow-up period of 11 years [78, 79, 81, 82]. As expected, this reduced incidence was attributable to a reduction in the incidence of distal CRC (24-36%). Furthermore, these studies found that FS screening was associated with a reduction in distal CRC-related mortality ranging from 27-50%, whereas the effect on proximal CRC-related mortality was not statistically significant [78, 79, 81, 82]. These trials have shown that CRC screening by means of a single round of endoscopy of the distal colon and rectum leads to an almost twofold greater reduction of CRC-related mortality than biennial gFOBT screening, and also reduces CRC incidence [78, 79, 81, 82]. This effect persists for the full duration of the follow-up period in the studies, thereby providing evidence that a negative FS can be followed by a ten-year screening interval, and does not to be repeated after five years, as most guidelines currently recommend [83-85].

Just as with other screening strategies, the total effect of sigmoidoscopy screening on a population level is, among others, influenced by the degree of participation. A major shortcoming associated with FS screening is the relatively low participation rate. A Dutch randomized controlled trial, carried out in the Rotterdam area, found a 32% attendance rate for FS screening, which was significantly lower than the attendance for both gFOBT (50%) and FIT (62%) screening [35]. The aforementioned Norwegian study reported a high attendance rate (64%), but it should be pointed out that in most Scandinavian countries screening often seems to have a remarkably high uptake [80, 86]. In the trials performed in Italy and the UK, a maximum of one-third of patients took part on population level [78, 79]. Due to this relatively low participation rate, the screening effect on the entire population is limited. A possible way to increase the attendance is by offering subjects different screening modalities, either as a direct choice or as two-step approach in which subjects who decline a first offer for screening with a certain test (eg, FS or colonoscopy) are offered an alternative test, which is usually less invasive and therefore less sensitive (eg, FIT) [87, 88]. Another shortcoming of FS screening is the failure to detect proximal lesions. This could be improved by combining FS with FIT, but this may further impair the attendance [89].

CRC screening by means of FS is a good alternative to FOBT screening, given its long-term preventive effect and higher diagnostic yield compared with a single FOBT screening. The attendance rates however remain insufficient, and implementation is hampered

by complex logistical aspects. This makes sigmoidoscopy screening not the method of choice in the Netherlands.

*Total colonoscopy*

With colonoscopy the entire large bowel is visualized. This screening modality can be used as a primary screening instrument, but it is also indicated for secondary screening of subjects with a positive FOBT, sigmoidoscopy or CTC. During colonoscopy polyps can be immediately removed. The usual bowel preparation for screening purposes consists of oral complete bowel lavage which most screenees take at home. Colonoscopy is usually performed after intravenous administration of a benzodiazepine (in particular midazolam) with or without an analgesic.

The main advantage of colonoscopy screening is that it enables visualization of the whole colon and at the same time allows for direct removal of neoplastic lesions, where other screening tests require colonoscopy for confirmation and removal. It is therefore that total colonoscopy is considered by many as the gold standard for the detection of colorectal neoplasia [85]. Accordingly, colonoscopy is widely used for primary CRC screening in many countries such as Canada, Germany, Poland, and parts of the USA [90, 91]. The bowel preparation is often regarded as the most burdensome part of the entire colonoscopic procedure [92, 93]. Colonoscopy has a low risk of complications. Clinically significant complications necessitating hospitalization occur in 0.07-0.3% of screenees, including perforation and bleeding [72, 94, 95]. Just as with FS screening, studies on colonoscopy screening show a relatively low attendance, between 3-40% [96-98]. These numbers correspond with the findings of a Dutch CRC screening trial in which subjects were randomized for either colonoscopy or CTC [99]. A significantly lower attendance rate was seen in the colonoscopy group (22%) compared with subjects that were primary invited for CTC screening (34%, $p<0.001$). Results from questionnaires distributed to screening-naïve individuals however, have shown that most of them would prefer endoscopic screening over FOBT screening after reading information about this screening method (ie, more favourable risk reduction of CRC-related mortality by endoscopic screening) [100].

Even though colonoscopy is considered the gold standard, colorectal neoplasia can be missed. Back-to-back colonoscopy studies showed that colonoscopists miss a proportion of adenomas ranging from 2% for adenomas > 1cm in diameter to 26% for adenomas ≤ 5 mm in diameter in patients with sporadic or hereditary neoplasia [101, 102]. In a US cohort of patients, CRC was identified after adenoma removal in approximately 0.5% of subjects within a three-year follow-up period [103]. Most of these lesions must have been missed at baseline colonoscopy given the slow transition from adenoma to CRC [14]. Another colonoscopy study showed that about 10% of neoplastic polyps are incompletely removed, with a wide variation between endoscopists [104].

This data emphasize the need for quality assurance in colonoscopy, for primary and secondary screening, as well as surveillance. Various studies have shown that the risk of post-endoscopy cancer is inversely associated with the baseline adenoma detection rate, which depends on the experience of the endoscopist and the quality of the bowel preparation [90, 105-107]. A range of guidelines for quality assurance in screening colonoscopy thus have been developed, all with similar recommendations regarding the monitoring of key indicators, such as the adequacy of the bowel preparation, caecal intubation, adenoma detection, the adequacy of surveillance, and interval cancers [85, 108-110].

The failure in the preventive effect of colonoscopy is in particularly related to the proximal colon. A Canadian trial showed that a successful colonoscopy is strongly associated with a lower mortality rate, in particular for left-sided CRCs (OR 0.33; 95% CI 0.28-0.39) [111]. No preventive effect on right-sided CRCs was observed. A German case-control study however did find a protective effect for both left- and right-sided CRCs [112]. To date, there have been no randomized controlled trials assessing the effect of colonoscopy screening on CRC incidence and mortality. Such trials are of great importance, but are difficult to set up because of the large number of subjects and long follow-up periods required. Nevertheless, several of these studies are ongoing and are comparing colonoscopy with no screening or FIT screening [113, 114].

*CT-colonography*

CT-colonography (CTC) is a minimally invasive technique whereby images of the entire colon and rectum are made in order to trace advanced neoplasia. This technique allows a two- and three-dimensional visualization of the colon. Imaging of the bowel requires adequate bowel distension, which can be achieved with anal insufflation of carbon dioxide performed in combination with intra-venous administration tof an antimotility agent [99]. A typical CTC protocol involves bowel preparation with a low-fibre diet one day before the investigation combined with two 50 ml oral doses of iodine containing contrast. CTC is usually performed without sedation. If polyps are found, a colonoscopy is necessary to confirm the findings and remove lesions. There is consensus that all subjects with one or more polyps ≥ 10 mm or three or more polyps ≥ 6 mm should be referred for colonoscopy [83, 115]. A matter that remains controversial is the management of fewer polyps in which the largest polyp is 6-9 mm. If all patients with these polyps would be referred for colonoscopy, referral rates could increase to 30%. Since the overall screening prevalence of small advanced adenomas is approximately 0.3% and the frequency of CRC is estimated to be 0.01%, it seems reasonable to advise three-yearly CTC surveillance for patients with one or two 6-9 mm polyps [116-118].

CTC is a safe procedure with a low risk of complications. The risk of CTC-related perforation in a CRC screening setting was 0.005% [119]. A disadvantage that is considered to

be a major issue in certain countries such as Germany, is the potential harm caused by exposure to ionizing radiation, which may give rise to cancer later in life [120]. However, during the CTC the screened individual receives a radiation dose of 5 mSv. This amount is comparable to exposure for airline personnel of which it is known that they do not have an increased incidence of cancer compared with the general population [121]. Extra-colonic incidental abnormalities are detected frequently with CTC, because it visualizes the whole abdomen and the lower part of the thorax. This can be an advantage if these abnormalities are severe and treatable. However, abnormalities for which it is unclear whether early detection is useful may also be detected. The rate of these extra-colonic findings varied between 27-69% [122-124]. Findings of potential or unknown significance varied between 11-18% of patients. Additional diagnostic investigations or surgical interventions were recommended in 8-16% of these patients, which resulted in additional costs.

CTC has a very high sensitivity for cancer when read by a radiologist or technician [125]. The incidence of cancer five years after a negative CTC is low [126]. Therefore, a negative CTC only needs to be repeated after five years. In the earlier mentioned randomized trial in which subjects were randomized for either colonoscopy or CTC for primary screening, a significantly higher uptake was seen with CTC (34% versus 22%, $p<0.001$) [99]. The diagnostic yield for advanced neoplasia per 100 participants was higher with colonoscopy (8.7 versus 6.1 per 100 participants, $p=0.02$). When considering both uptake and yield however, the diagnostic yield for advanced neoplasia per 100 invitees was similar for both screening methods. The burden of screening was also assessed by this research group [92]. Colonoscopy invitees expected the screening procedure and bowel preparation to be more burdensome. However, in participants, CTC was scored as more burdensome than colonoscopy. This finding was mostly related to the burden of bowel distension during the procedure and prolonged complaints of disturbed bowel movements caused by the iodine contrast agent. Because of the substantial costs of the procedure and the high need for subsequent colonoscopy to confirm and remove lesions, CTC is in addition less cost-effective than other screening modalities, both for primary screening and for secondary screening after a positive FOBT [127]. CTC is thus only used in a nationwide CRC screening programme if a colonoscopy is incomplete.

## New screening strategies

*DNA markers*

Adenocarcinoma of the large intestine is no longer considered as one disease, but rather as a family of diseases with different molecular pathways and precursor lesions, with different end-stage carcinomas with varying prognoses. Colorectal neoplasms shed DNA in the stool where it can be isolated and tested for the presence of mutations acquired

during carcinogenesis [128-130]. DNA marker tests are thus based on methylation and mutation analyses, the detection of long DNA and of microsatellite instability.

Individual tests can make use of single or multiple DNA markers to optimize performance [131]. The currently available DNA marker tests require the collection of one entire bowel movement, and specimens must be shipped with an icepack. There is no need for dietary or medication restrictions [132]. A case-control study involving 252 patients with CRC, 133 patients with adenomas ≥ 1 cm, and 293 individuals with normal colonoscopy results (controls), identified 85% of patients with CRC and 54% of patients with adenomas ≥ 1 cm with 90% specificity using the best-performing tests [133]. A recent study involving 65 patients with CRC and 757 patients with advanced adenomas, found similar results using a multitarget stool DNA test (sensitivity of 92% respectively 42% for CRC and advanced adenomas with a specificity of 95%) [134]. Despite their better sensitivity for CRC, a cost-effectiveness analysis showed that both the gFOBT and FIT are preferable to DNA markers [135]. Lastly, RNA and protein biomarkers are widely being explored as screen-detection tools for CRC and precursors of cancer. As with DNA, these markers reflect the mechanisms of exfoliation of neoplastic cells and secretion of mucus-containing abnormal glycoproteins in CRC. These experimental techniques are routinely assessed in case-control studies. More large, population-based trials are still required to further assess performance characteristics in average-risk individuals.

*Video-capsule endoscopy*

Video capsule endoscopy (VCE) is a minimally invasive technique designed to provide diagnostic imaging of the gastrointestinal tract [136]. It is an ingestible capsule with a 172-degree video imager at each end, which provides images of excellent resolution with a 1:8 magnification, which is higher than of conventional endoscopes. The capsule moves passively trough the colon by peristalsis, does not inflate the bowel, and images the mucosa in the collapsed state. These images are transmitted to an external data recorder carried by the screenee. The capsule is discarded with a bowel movement after completion of the investigation, and the data are read with dedicated software.

As with optimal colonoscopy, a preparation is given prior to colon capsule endoscopy. This type of imaging requires passage of the capsule within eight to ten hours. Therefore, preparation consists of colon lavage combined with repeated intake of a prokinetic drug. One regimen that has been used consists of the patient taking a clear liquid diet following a light breakfast the morning prior to the procedure [137]. The evening prior to the examination, patients take three liters of polyethylene glycol (PEG). The morning of the procedure, the patient drinks another liter of PEG between six and seven a.m. and the capsule is ingested at eight a.m., and Bisacodyl for example can then be given during the procedure to increase transit of the capsule.

A study in the non-screening setting comparing VCE and colonoscopy in 109 patients found a sensitivity and specificity of 84% and 64% respectively, for the detection of polyps ≥ 6 mm. For polyps ≥ 10 mm, the sensitivity and specificity were 88% and 95%, respectively. Other studies, including a meta-analysis involving 837 patients found similar high values [138-140]. VCE does not allow for biopsy or polyp removal, so patients with lesions detected during the examination will be referred for subsequent colonoscopy for further evaluation and/or treatment. A factor that limits the widespread use of VCE as a primary screening method are the high costs, approximately €600-700. This is considerably higher than costs associated with screening by means of FOBTs or endoscopy. Other shortcomings are the amount of time required to read the capsule images and the need for colon lavage and prokinetic drugs after intake of the capsule [139, 141].

## CONCLUSIONS

CRC is a major health problem, with a high incidence and mortality worldwide. The disease is characterized by a recognizable and treatable precursor lesion, the adenomatous polyp, making it suitable for screening. Various community studies have provided a wealth of information on different screening methods regarding attendance, diagnostic yield and cost-effectiveness, but also information on optimal programme organization and quality assurance. Based on the technological advances of FIT screening, and the above mentioned evidence in which it was clearly shown that FIT outperforms gFOBT in terms of a higher attendance and diagnostic yield, FIT screening has become the first-choice FOBT for CRC screening. Repeated rounds of FIT screening increase programme sensitivity, thereby achieving a higher diagnostic yield than with more invasive screening strategies, such as sigmoidoscopy and colonoscopy. On January 2014, a FIT screening programme was therefore started in the Netherlands in which men and women in the ages between 55-75 years are gradually invited for biennial FIT screening using a cut-off of 75 ng/ml [142]. This age-range was chosen based on cost-effectiveness analyses that have shown than screening in this age group is most cost-effective [50, 64]. Biennial FIT screening at a cut-off level of 50 ng/ml was preferred based on these same analyses, but a cut-off level of 75 ng/ml with a gradual implementation of FIT screening was chosen due to limited colonoscopy capacity [60] (Figure 3). In 2014, men and women in the ages of 63, 65, 75, and 76 years are invited [142]. It is estimated that all subjects in the ages between 55-75 years will have been invited at least once for FIT screening in 2019 [142].

Many aspects of screening still remain to be investigated. Little is known on repeated rounds of 1-sample FIT screening and the additional value of a second round of 2-sample FIT screening. FIT screening is currently equally applied in men and women, despite eminent sex disparities in prevalence and anatomic distribution of advanced neoplasia.

More information is needed on this matter, as well as on the effect of FIT screening on quality of life. This information is of great value, since it can be used to anticipate on several aspects of the national screening programme.

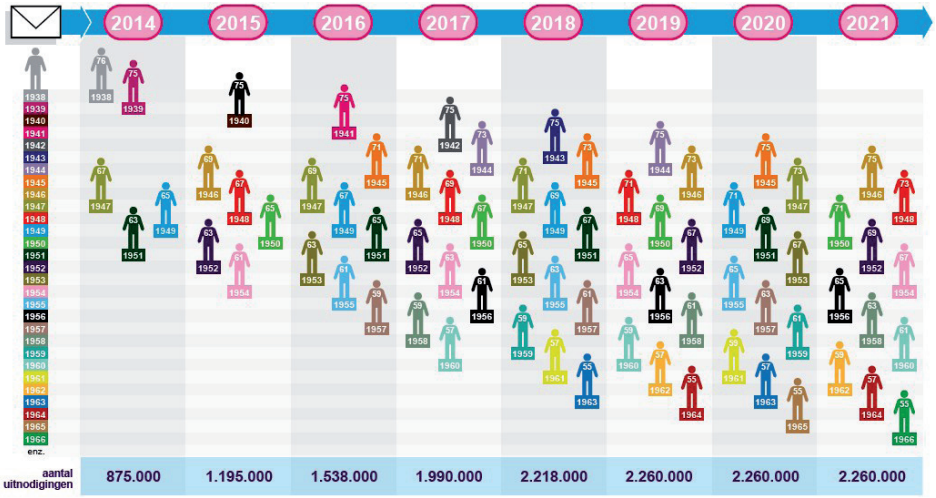


**Figure 3** Gradual implementation of the Dutch colorectal cancer screening programme [142]

## AIM OF THIS THESIS

The general aim of this thesis is to explore various aspects of faecal immunochemical test screening (ie, uptake and diagnostic yield of repeated screening, the best screening strategy in terms of number of FIT samples, gender-specific differences, quality of life, and second look colonoscopies). The papers are based on important data derived from the first two rounds of a large prospective population-based screening trial called the 'CORERO'-trial (ie, colorectal cancer screening in the Rotterdam region). This study was implemented in 2006. In the first round (CORERO-I), 18,419 individuals aged 50-74 years were randomly assigned to either gFOBT, FIT or sigmoidoscopy screening. Based on the results from the CORERO-I trial, 10,952 asymptomatic average-risk individuals were invited for FIT screening in the second round (CORERO-II). These two trials have provided a unique database that formed the basis for the successive CORERO-III trial, in which asymptomatic average-risk subjects were invited for a third round of FIT screening. Data derived from these three CORERO rounds will be presented and discussed in this thesis.

## OUTLINE OF THIS THESIS

This thesis starts with an overview of what is currently known about colorectal cancer screening (**chapter 1**). Various community studies have provided important information on different screening methods, in which attendance, diagnostic yield of advanced neoplasia and cost-effectiveness were analyzed. Based on this information, the Minister of Health, Welfare and Sport decided on May 25th 2011 that a screening programme should be implemented in the Netherlands. The gradual implementation of a national screening programme has started since January 2014. Men and women in the ages of 50-75 years are invited for biennial FIT screening using a cut-off level of 75 ng/ml, which corresponds to 15 µg haemoglobin/g faeces.

Many aspects of screening still remain to be investigated. This thesis assessed several of these matters regarding (repeated) FIT screening. It is known that successive screening rounds are required to optimize the impact of FIT screening on a population level. Participation and detection rates in successive rounds attribute to the effectiveness of FIT-based programmes. Information concerning sustained attendance and diagnostic performance over repeated rounds of FIT screening is very limited. We therefore evaluated attendance and detection rates of three rounds of FIT screening in a Dutch population-based CRC screening programme (**chapter 2**). Furthermore, we know that advanced neoplasia can bleed intermittently and therefore may be missed with single stool sampling. Screening by means of a 2-sample FIT increases test sensitivity (ie, reduces the risk of missing advanced lesions). A previous study comparing 1- versus 2-sample FIT screening reported no differences in attendance rate yet significant higher detection rate of advanced neoplasia with first round 2-sample FIT screening [58]. Two-sample FIT screening thus seems more effective than one-sample FIT screening, but it is unknown whether this advantage persists over repeated screening rounds, a prerequisite for optimal screening by means of FIT. We therefore conducted a study in which we aimed to determine attendance and diagnostic yield of repeated two sample FIT screening. In addition, we compared these data with repeated 1-sample FIT screening (**chapter 3**).

Until now, similar FIT screening regimens are applied to men and women despite eminent sex disparities in prevalence and anatomic distribution of advanced neoplasia. Several colonoscopy based screening studies have reported a higher incidence and prevalence of advanced neoplasia in men compared to women. Furthermore, a number of studies where subjects received an FOBT prior to colonoscopy found a higher sensitivity of FOBTs in men. These data were obtained from studies with colonoscopy as a primary screening tool and might have a different underlying risk than the (screening-naïve) population screened with FIT. Data on gender differences in a population-based setting with FIT

as a primary screening tool are lacking. We therefore determined potential gender differences in performance of FIT in an average risk, screening-naïve population (**chapter 4**). Subsequently, we used the micro-simulation model MISCAN-Colon to determine the optimal screening strategies for men and women and to study whether screening differently in men and women is beneficial in term of cost-effectiveness (**chapter 5**).

A matter that is not often being addressed, but that is very relevant on a population level, is whether participating in a CRC screening programme has an effect on quality of life. Little is known on this matter, neither for participants with a negative nor for those with a positive test result. We therefore assessed whether participating in a CRC screening programme affects quality of life by sending participants a questionnaire, which included validated measures on generic health-related quality of life, generic anxiety and screen-specific anxiety. Both FIT and FS participants were addressed (**chapter 6**). The final question addressed in this thesis concerns second look colonoscopies. Little is known about the need for these colonoscopies in a screening population. Multiple colonoscopies per patient can have a substantial impact on the required colonoscopy capacity and therefore health care system. In this study we evaluated the number and risk factors for second look colonoscopies in FIT-based CRC screening (**chapter 7**). Lastly, in **chapter 8**, the conclusions of this thesis and future perspectives are discussed.

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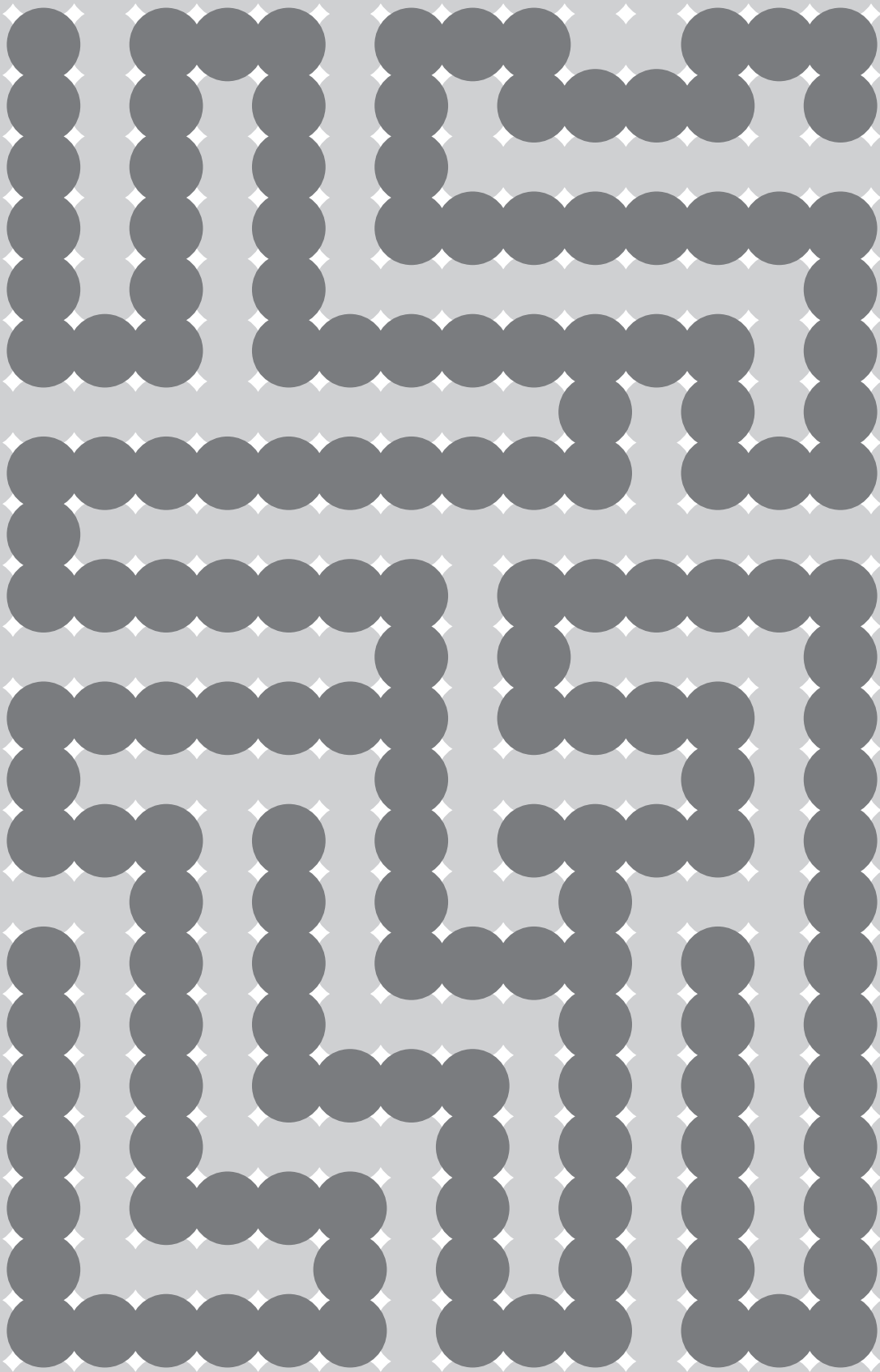

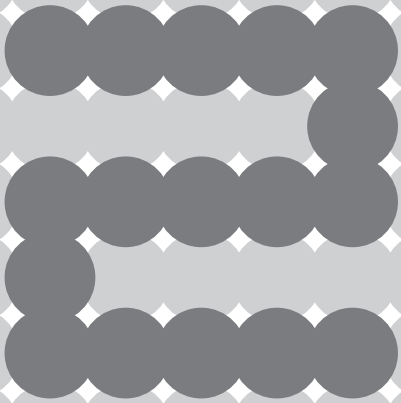

# Attendance and yield over three rounds of population-based faecal immunochemical test screening

Atija Kapidzic, Elisabeth J. Grobbee, Lieke Hol, Aafke H.C. van Roon, Anneke J. van Vuuren, Wolfert Spijker, Kirsten Izelaar, Marjolein van Ballegooijen, Ernst J. Kuipers, and Monique E. van Leerdam

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## ABSTRACT

### Introduction:

Faecal immunochemical test (FIT) screening for colorectal cancer (CRC) requires timely successive rounds for an optimal preventive effect. However, data on attendance and trend in yield over multiple rounds of FIT screening are limited. We therefore conducted a consecutive third round of FIT screening in a population-based CRC screening trial.

### Methods:

Average-risk subjects aged 50-74 years were approached for three rounds of 1-sample FIT (OC-sensor Micro, Eiken Chemical, Japan) screening. Subjects with a haemoglobin level ≥ 50 ng/ml (≥ 10 µg haemoglobin/g faeces) were referred for colonoscopy. Subjects with a positive FIT in previous rounds were not re-invited for FIT screening.

### Results:

In the first round 7,501 subjects were invited. Participation rate was 62.6% in the first, 63.2% in the second, and 68.3% in the third round ($p<0.001$). In total, 73% (5,241/7,229) of all eligible subjects participated in at least one of three rounds. The positivity rate was significantly higher in the first (8.4%) compared to the second (6.0%) and third (5.7%) screening round ($p<0.001$). The detection rate of advanced neoplasia declined from the first to subsequent rounds (round 1: 3.3%; round 2: 1.9%; round 3: 1.3%, $p<0.001$). The positive predictive value for advanced neoplasia was 40.7% in the first, 33.2% in the second and 24.0% in the third screening round ($p<0.001$).

### Conclusions:

Repeated biennial FIT screening is acceptable with increased participation in successive screening rounds, and more than 70% of all eligible subjects participating at least once over three rounds. The decline in screen-detected advanced neoplasia over three screening rounds is compatible with a decreased prevalence of advanced neoplasia as a result of repeated FIT screening. These findings provide strong evidence for the effectiveness of FIT screening and stress the importance of on-going research over multiple screening rounds.

## INTRODUCTION

Colorectal cancer (CRC) is a major health concern worldwide. Screening using faecal occult blood testing (FOBT) results in detection and treatment of CRC at an earlier stage, which is associated with improved survival. A meta-analysis based on four large randomized controlled trials demonstrated that guaiac FOBT (gFOBT) reduces CRC-related mortality [1]. A recently published study showed that the effect of gFOBT screening on CRC mortality persists for many years [2]. Economic analyses found gFOBT screening to be cost-effective [3]. More recently, faecal immunochemical testing (FIT) gained ground based on randomized trials showing higher attendance as well as a higher sensitivity for detection of advanced neoplasia with a similar specificity [4, 5]. Moreover, quantitative measurement of faecal human globin concentrations offers the opportunity to provide tailored screening for specific regions or countries based on available colonoscopy capacity and cost-effectiveness analyses [3, 6]. FIT screening has therefore become the first-choice faecal occult blood test for CRC screening [7]. Various CRC screening programmes worldwide currently rely on FIT or are about to start with or switch to FIT-based screening.

The sensitivity of a single round of FIT screening for the detection of advanced neoplasia is however limited. Recent studies showed that FIT at a low cut-off detects approximately 85% of CRCs and up to 35% of large adenomas [8, 9]. Successive screening rounds are required to optimize the impact of FIT screening on a population level. Participation and detection rates in successive rounds attribute to the effectiveness of FIT-based programmes. Longitudinal adherence of the same subjects represents a critical factor, but information concerning sustained attendance and diagnostic performance over repeated rounds of FIT screening is very limited.

We and others demonstrated a stable attendance rate over two rounds of FIT screening, with detection of substantial numbers of advanced lesions in both rounds [10, 11]. Data on further rounds in FIT screening with longer follow-up periods are scarce. One relatively small Italian study on four rounds of a biennial FIT screening programme reported stable attendance rates and test performances. However, the attendance rate of 56% during the first round was relatively low [12]. Further data on repeated FIT screening are warranted, as these provide more insight in the programme sensitivity of FIT screening. Such information is also required to address the important question whether FIT screening with higher sensitivity for advanced neoplasia can be applied with longer screening intervals than biennial gFOBT screening [7].

We therefore evaluated attendance and detection rates of three rounds of FIT screening in a Dutch population-based CRC screening programme.

## METHODS

### Study population/study design

Details about the design of this on-going population-based CRC screening programme have been described previously [4, 10]. In short, demographic data of all individuals between 50-74 years living in the southwest of the Netherlands were obtained from municipal population registers. Random samples were taken from the target population by a computer-generated algorithm (Tenalea, Amsterdam, the Netherlands). Since there was no CRC screening programme at the time of the trial in the Netherlands, the target population was screening-naïve when first approached. Individuals with a history of inflammatory bowel disease or CRC, as well as those who had undergone a colonoscopy, sigmoidoscopy or barium contrast enema in the last 3 years, those with an estimated life expectancy of less than 5 years, and subjects who were unable to give informed consent were excluded from the study. Subjects were not invited for the third screening round in case of a positive FIT in the first or second screening round, when they had become older than 74 years, when they had moved out of the region, or when they had died. Recruitment took place between November 2006 and December 2012.

### Intervention; FIT screening

With each screening round, one FIT (OC-sensor Micro, Eiken Chemical, Japan) was sent by mail to collect a single sample of one bowel movement. The test result was considered positive when the haemoglobin concentration in the FIT sample was ≥ 50 ng/ml, which corresponds to ≥ 10 µg haemoglobin/g faeces. Study subjects were initially divided over three groups to undergo repeated FIT testing at different screening intervals in the second round (ie, one, two and three years, respectively). No differences in attendance and detection rate were found between the different intervals [10]. The positive predictive value did also not differ between the three screening intervals (one-year interval: 36.2%; two-year interval: 32.9%; three-year interval: 30.6%; p=0.773) (derived from [10]). We therefore included subjects with a one-, two-, and three-year interval between the first and second round. Based on these results, a two-year interval was applied to all groups in the third screening round. In total, 5,482 subjects were invited for third round screening (1,838 subjects in the group with a previous one-year interval between the first and second round; 1,835 subjects with a two-year interval; and 1,809 subjects with a three-year interval).

### Follow-up evaluation; colonoscopy

Subjects with a positive FIT were scheduled for colonoscopy within 4 weeks. In case the colonoscopy was incomplete a CT-colonoscopy was performed. Experienced endoscopists, all board-certified gastroenterologists who had performed at least over 1,000 colo-

**Table 1** Overview of participation and FIT performance characteristics per screening round

| | **Round 1** % (95% CI) | **Round 2** % (95% CI) | **Round 3** % (95% CI) | p-value |
|---|---|---|---|---|
| Eligible invitees (n) | 7229 | 6111 | 5423 | |
| Participation rate | 62.6 (61.4-63.7) | 63.2 (62.0-64.4) | 68.3 (67.1-69.5) | <0.001 |
| Positivity rate | 8.4 (7.6-9.2) | 6.0 (5.2-6.7) | 5.7 (5.0-6.5) | <0.001 |
| Colonoscopies performed (n) | 364 (95.8%) | 223 (97.0%) | 200 (94.8%) | |
| **Detection rate** | | | | |
| Non-advanced neoplasia | 1.7 (1.3-2.1) | 1.2 (0.9-1.6) | 1.6 (1.2-2.1) | 0.259 |
| Advanced neoplasia | 3.3 (2.8-3.8) | 1.9 (1.5-2.4) | 1.3 (1.0-1.7) | <0.001 |
| Advanced adenoma | 2.8 (2.3-3.3) | 1.7 (1.4-2.2) | 1.2 (0.9-1.6) | <0.001 |
| Colorectal cancer | 0.5 (0.3-0.7) | 0.2 (0.1-0.4) | 0.1 (0.1-0.3) | 0.007 |
| **Positive predictive value** | | | | |
| Advanced neoplasia | 40.7 (35.7-45.8) | 33.2 (27.3-39.6) | 24.0 (18.6-30.4) | <0.001 |
| Advanced adenoma | 34.6 (29.9-39.7) | 30.0 (24.4-36.4) | 21.5 (16.4-27.7) | 0.005 |
| Colorectal cancer | 6.0 (4.0-9.0) | 3.1 (1.5-6.4) | 2.5 (1.0-5.9) | 0.094 |

FIT = faecal immunochemical test (OC-sensor Micro), cut-off value 50 ng haemoglobin/ml; advanced neoplasia was defined as an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high grade dysplasia, and/or colorectal cancer

noscopies, performed all colonoscopies for the current trial. The maximum reach of the endoscope, adequacy of bowel preparation as well as the characteristics and location of any polyps were recorded. Gastrointestinal pathologists evaluated all removed polyps. Patients with a positive colonoscopy entered a surveillance programme according to guidelines of the Dutch Society of Gastroenterology, while subjects with a negative colonoscopy were referred back to the screening programme, but were considered not to require FIT screening for ten years.

### Screen-detected and interval carcinomas

Except for individuals who had moved out of the Netherlands, all recruited participants were followed for the development of CRC. Screen-detected cancers were defined as cancers identified at colonoscopy performed after a positive test result. Interval cancers were defined as colorectal cancers diagnosed within the time period between attendances to screening. Interval cancers were identified through linkage with the Dutch Comprehensive Cancer Centre (www.iknl.nl).

### Statistical analysis

For each screening round, we calculated the attendance rate (AR), the positivity rate (PR), the detection rate (DR) of CRC and advanced adenomas, and the positive predictive value (PPV) for CRC and advanced adenomas.

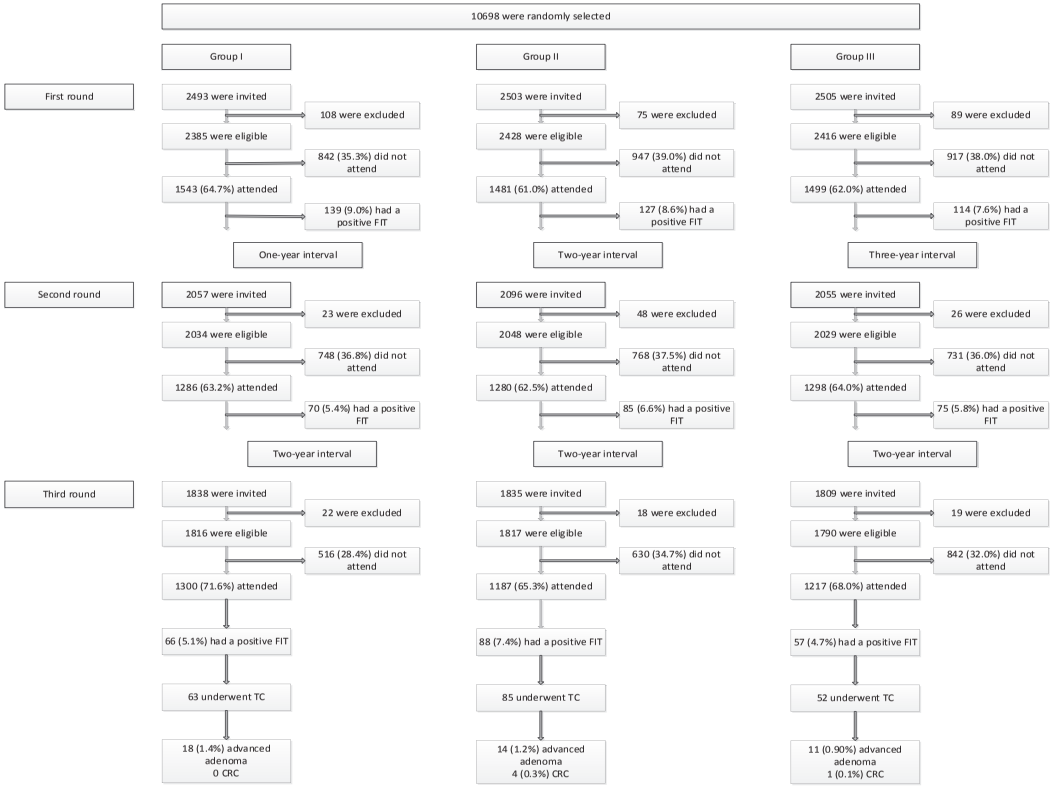


**Figure 1** Trial profie

**Group I:** Invitees were invited for a second 1-sample FIT screening round after 1 year; Group II: Invitees were invited for a second 1-sample FIT screening round after 2 years; Group III: Invitees were invited for a second 1-sample FIT screening round after 3 years; Groups I-III: Invitees were invited for a third 1-sample FIT screening round after two years; FIT = faecal immunochemical test (OC-sensor Micro), cut-off value 50 ng haemoglobin/ml; TC = total colonoscopy; Advanced adenoma was defined as an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high-grade dysplasia; CRC = colorectal cancer

**Table 2** Number of times invitees participated displayed for the number of times they were eligible

| Times eligible | Times participated | | | | Total |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | |
| 0 | 272 (100) | - | - | - | 272 |
| 1 | 374 (33.6) | 740 (66.4) | - | - | 1114 |
| 2 | 181 (26.2) | 85 (12.3) | 426 (61.6) | - | 692 |
| 3 | 1433 (26.4) | 473 (8.7) | 610 (11.2) | 2907 (53.6) | 5423 |
| Total | 2260 | 1298 | 1036 | 2907 | 7501 |



The AR was calculated by dividing the number of participants by all eligible subjects (defined as all invitees minus the excluded subjects). The PR was defined as the proportion of participants having a positive test result. The DR was defined as the proportion of participants being diagnosed with advanced neoplasia. This was calculated as the number of screened individuals diagnosed with advanced neoplasia divided by all screened individuals with an analyzable FIT test. Advanced neoplasia included CRC and advanced adenomas. An advanced adenoma (AA) was defined as an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high grade dysplasia. When more than one lesion was present, the screenee was classified according to the most advanced lesion. The PPV refers to the subjects diagnosed with advanced neoplasia (AN) proportionally to screenees with a positive FIT undergoing subsequent colonoscopy, or in case the colonoscopy was incomplete a CT-colonoscopy (n=3). For the overall adenoma detection rate (ADR), we used both advanced and non-advanced adenoma.

Differences in proportions between groups were analyzed by Chi-square testing. Differences in means between groups were tested using the Student t-test. AR, PR, DR, and PPV were calculated and described as proportions with 95% confidence intervals (95% CI). We fitted a logistic regression model to the data to determine differences in participation and FIT characteristics between the different groups that attended the third screening round (ie, subjects that had participated one, two or three times over the three rounds). To determine the number of true positives per 1,000 invitees (subjects with a positive FIT identified with AN during follow-up colonoscopy) per screening round, the AR was multiplied by the PR and the PPV. The percentage of stable attenders was defined as the number of subjects attending all rounds while they were eligible, divided by the total amount of subjects that were eligible over the three rounds. The cumulative attendance was defined as the number of eligible invitees attending at least once. To assess differences in AR between the three rounds, a generalized estimating equation was used to account for clustering at the level of the invitee. The test characteristics in the first two rounds of 1-sample FIT screening were compared to those in the third screening round by using a logistic regression model [10]. The diagnostic yield was

**Table 3** Participation and FIT performance characteristics for subjects who have been invited in all three screening rounds (n=5,482), by number of consecutive tests performed (ie, one, two, or three out of three rounds)

| | Times participated | | | |
|---|---|---|---|---|
| | 1 out of 3 rounds | 2 out of 3 rounds | 3 out of 3 rounds | p-value |
| Participants eligible for three rounds (n) | 281 | 516 | 2907 | |
| Positive tests in the third round (n) | 33 | 45 | 133 | |
| % (95% CI) | 11.7 (8.5-16.1) | 8.7 (6.6-11.5) | 4.6 (3.9-5.4) | <0.001 |
| Colonoscopies performed n (%) | 31 (94.0) | 43 (95.6) | 126 (94.7) | |
| **Detection rate** | | | | |
| Advanced neoplasia (n)<br>% (95% CI) | 13<br>4.6 (2.7-7.8) | 7<br>1.4 (0.6-2.8) | 28<br>1.0 (0.7-1.4) | <0.001 |
| Advanced adenoma (n) | 12 | 6 | 25 | |
| % (95% CI) | 4.3 (2.4-7.4) | 1.2 (0.5-2.6) | 0.9 (0.6-1.3) | <0.001 |
| Colorectal cancer (n) | 1 | 1 | 3 | |
| % (95% CI) | 0.4 (0.1-2.5) | 0.2 (0.0-1.4) | 0.1 (0.0-0.3) | 0.32 |
| **Positive predictive value** | | | | |
| Advanced neoplasia % (95% CI) | 41.9 (26.1-59.6) | 16.3 (8.0-30.4) | 22.2 (15.8-30.3) | 0.01 |
| Advanced adenoma % (95% CI) | 38.7 (23.5-56.5) | 14.0 (6.4-27.8) | 19.8 (13.8-27.7) | 0.01 |
| Colorectal cancer % (95% CI) | 3.2 (0.5-19.6) | 2.3 (0.3-14.7) | 2.4 (0.8-7.1) | |

Advanced neoplasia was defined as an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high grade dysplasia, and/or colorectal cancer (CRC); DR: detection rate; PPV: positive predictive value; 95% CI: 95% confidence interval

compared to that of different CRC screening methods. All p-values were two-sided and considered significant if < 0.05. All tests were conducted using SPSS version 20.0.

### Ethical approval

The Dutch National Health Council and the Institutional Review Board of the Erasmus MC University Medical Centre approved the study. All screenees gave written informed consent.

## RESULTS

### Attendance

Baseline characteristics and the results of the first and second 1-sample FIT screening rounds have previously been described [4, 10]. Briefly, during the first round, a total of 7,501 average-risk subjects were invited to participate in screening. Participation rates in the first, second and third round were 62.6% (4,523/7,229, 95% CI 61.4-63.7), 63.2%

(3,864/6,111, 95% CI 62.0-64.4), and 68.3% (3,704/5,423, 95% CI 67.1-69.5), respectively (p<0.001) (Table 1). Figure 1 shows the trial profile for each screening round for the three groups (group I: one-year interval between the first and second round; group II: two-year interval between the first and second round; group III: three-year interval between the first and second round; group I-III: two-year intervals between the second and third round). Seventy-three percent (5,482/7,501) of the initial cohort was eligible to be invited for the third screening round. In total, 1,247 subjects were not eligible for successive screening rounds because they had become 75 years or older (round 2: n=342; round 3: n=295), or had had a positive FIT in previous rounds (round 1: n=380; round 2: n= 230). In addition, subjects were excluded during the first or second round because they had moved away (n=233), had died (n=170), or met one of the exclusion criteria (n=369).

In total, 5,482 subjects were invited to attend the third screening round (Table 1). A total of 59 subjects (1.1%) were excluded (47 subjects met one of the exclusion criteria, eleven had moved away and one had died) (Figure 1). Out of 5,423 eligible invitees, 3,704/5,423 (68.3%; 95% CI 67.1-69.5) returned a FIT. The test was analyzable in 3,700 (99.9%) subjects. Of the participants in the third round, 78.5% (2,907/3,704) attended all three rounds, 13.9% (516/3,704) attended two rounds, and 7.6% (281/3,704) had attended no previous round (Table 3). With respect to the non-participants in first-round screening, 18.8% (437/2,330, 95% CI 17.2-20.4) attended the second round, while 23.2% (471/2,031, 95% CI 21.4-25.1) of second round non-participants attended the third round.

The number of times invitees participated during three screening rounds displayed for the number of times invitees were eligible is summarized in Table 2. In total, 7,229 of 7,501 invitees were at least once eligible for screening. The proportion of stable attenders (ie, invitees attending all rounds while they were eligible) was 56.3% (4,073/7,229) (Table 2). The cumulative attendance rate (ie, eligible invitees attending at least one screening round) was 72.5% (5,241/7,229).

**Proportion of positive tests**

In total, 380/4,523 (8.4%, 95% CI 7.6-9.2%) tested positive in the first round, 230/3,864 (6.0%, 55% CI 5.2-6.7) in the second round, and 211/3,704 (5.7%, 95% 5.0-6.5) in the third round (Table 1). The positivity rate (PR) was significantly higher in the first compared to the second and third round (both p<0.001), whereas the PR was similar in round two and three (p=0.67). Individuals that participated for the first time in the third round had a significantly higher PR compared to individuals who underwent repeated screening (p<0.001) (Table 3).

**Follow-up and test performance characteristics**

The detection rate (DR) and positive predictive value (PPV) for advanced neoplasia for the three rounds are described in Table 1. In the third round, 200 (94.8%) of 211 screenees that tested positive underwent a complete colonoscopy. The remaining 11 subjects either refused colonoscopy (n=10), or turned out to have too severe co-morbidity to benefit from an endoscopic procedure (n=1). The DR of advanced neoplasia (AN) was 3.3% (95% CI 2.8-3.8) in the first, 1.9% (95% CI 1.5-2.4) in the second, and 1.3% (95% CI 1.0-1.7) in the third round ($p<0.001$). The PPV for AN was 40.7% (95% CI 35.7-45.8) in the first, 33.2% (95% CI 27.3-39.6) in the second, and 24.0% (95% CI 18.6-30.4) in the third round ($p<0.001$) (Table 1). The DR declined significantly over the three screening rounds. In addition, the PPV only differed significantly between the second and third screening round ($p=0.02$), but not between first and second round screening ($p=0.07$). The overall adenoma detection rate (ie, of both advanced and non-advanced adenoma) in this study over three screening rounds was 57.4% (95% CI 53.9-60.8).

Both the DR and PPV were significantly higher in individuals that participated for the first time (Table 3, subgroup 1 out of 3 rounds) compared to individuals that underwent repeated screening (Table 3: subgroup 2 out of 3 rounds and subgroup 3 out of 3 rounds; DR: $p<0.001$; PPV: $p=0.01$).

The number of true positives (subjects with a positive FIT identified with AN during follow-up colonoscopy) per 1,000 subjects invited was 21 in the first round and 34 after two consecutive screening rounds [7]. After three consecutive rounds of FIT screening, this number was 43 per 1,000 invitees.

**Interval carcinomas**

After record linkage with the Dutch Comprehensive Cancer Centre, 43 CRCs were found in the total study population. Thirty-four CRCs (79.1%) were screen-detected tumours, of which 22 (65%) were detected in the first, seven (21%) were detected in the second and five (15%) were detected in the third screening round. The remaining nine (20.9%) were interval carcinomas of which three were detected between the first and second round and six between the second and third round. Two of the interval cancers between the first and second round were detected in participants with a negative FIT: one Stage III tumour (FIT result at baseline, 24 ng/ml) was detected nine months after baseline screening, and one stage II tumour (FIT result at baseline, 7 ng/ml) was diagnosed two years and five months after FIT screening. The third CRC was diagnosed at stage I in a subject with a positive FIT but negative colonoscopy [10]. One year and four months after the index colonoscopy, a subsequent colonoscopy was performed because of symptoms and revealed a tumoor located at 50 cm of the anal verge. Two of the interval cancers between the second and third round were detected in participants with a negative 2$^{nd}$ round FIT: one stage IV tumour was detected 12 months after 2$^{nd}$ round screening (FIT

result at 2nd round, 48 ng/ml), and one stage III tumour was detected 5 months after 2nd round FIT screening (FIT result at 2nd round, 0 ng/ml). Two of the interval cancers were diagnosed in subjects with a positive 2nd round FIT but negative subsequent colonoscopy. In one subject, a second colonoscopy because of symptoms revealed a stage III CRC in the sigmoid twenty-four months after the index colonoscopy. A stage I CRC was diagnosed in the splenic flexure thirty-six months after the index colonoscopy. The fifth and sixth CRC were diagnosed in subjects who had a negative FIT result in the first round (24 respectively 0 ng/ml), were ineligible for the second round due to age, and developed a CRC two years and ten months (stage II) respectively three years and two months (stage III) after first round screening.



## DISCUSSION

This is a population-based study on the performance of repeated FIT screening with three rounds. Given the scarcity of information on impact of repeated FIT screening, such data are of major importance for countries considering or planning the implementation of population-based FIT screening. We observed a high and increasing attendance and a decline in detection rate of advanced adenoma over three consecutive rounds.

A very important early indicator for an effective population-based screening programme is uptake. We observed a high attendance per screening round that increased over successive screening rounds. Uptake in previous FOBT studies varied, but data of our group and others showed through randomized studies that FIT screening results in a higher uptake compared to gFOBT screening [4, 5, 13-18]. Furthermore, we found a relatively high percentage of stable attenders of 56% (4,073/7,229) (ie, subjects attending all rounds while they were eligible). Obviously, participation depends on the willingness of participants to repeat screening. We previously observed that a positive attitude towards CRC screening, and sufficient knowledge on CRC screening are strong predictors for participation in successive rounds [19]. This suggests that increased awareness on CRC screening and sufficient information on CRC and FIT screening may have enhanced the uptake in successive rounds, as the target population was screening-naïve when first approached. In our study, previous non-attenders were re-invited. Scottish investigators reported that such practice improves uptake [16]. This is in line with our findings, where response in non-responders of previous rounds was 18.8% in round two (when inviting non-responders of the first round), and 23.2% in round three (when inviting non-responders of the second round), thus contributing to overall participation.

The considerable decrease in DR of advanced neoplasia from 3.3% to 1.3% over the three rounds supports the notion that consecutive FIT screening has a beneficial effect by decreasing the prevalence of AN. In contrast, an Italian study on repeated FIT screen-

ing revealed a stable DR of advanced neoplasia over successive rounds (1.5-1.3%) [12]. That study however applied a higher cut-off value (100 ng/ml). The initial decrease in DR in our study is likely to be explained by the enhanced sensitivity of a FIT at a low cut-off (50 ng/ml), compared to FIT screening with a higher cut-off value. In the Italian study, where average-risk subjects in the same age group as in our study were invited, the detection rate of AN was 1.5% in the first round. Even when adopting the higher cut-off of 100 ng/ml as used in this study, our detection rate of AN remained higher in the first round (2.5%) [20]. This difference may be explained by the lower attendance rate during the first round than seen in our cohort (56% versus 62%) [4, 12]. Based on the above we postulate that FIT screening at a low cut-off results in a high DR and thus high sensitivity, subsequently causing a decline in DR in following rounds. In line with the decrease in DR, also a decline in PPV for advanced neoplasia was observed over repeated screening rounds. The false-positive rate (FPR), defined as subjects that had a positive FIT, but no advanced neoplasia on follow-up colonoscopy (ie, only non-advanced neoplasia, hyperplastic polyps and/or no findings at all), did not rise over the three screening rounds (FPR round 1: 5.1%; round 2: 4.1%; round 3: 4.4%, p=0.050). This indicates that the decrease in PPV was mainly due to the decrease in DR. Such a decrease in PPV in following screening rounds is what one would expect and prefer, since it is a confirmation of the effectiveness of the screening programme. The question raised based on our data, is whether the PPV has decreased too much, whether eg, the screening interval of two years that was based on the less sensitive gFOBTs used in the past, is too short. Possible ways to increase the PPV are indeed lengthening the interval, but also by using higher cut-off levels in consecutive rounds. This would of course, as a price for the higher PPV, decrease programme sensitivity and consequently the effectiveness. Evidently, there is an optimum for the PPV, where it is neither too low, nor too high. Whether a PPV for advanced neoplasia of 23% is below that optimum depends on local resources. This also needs considering the long term incidence and mortality reduction, while comparing different intensities of screening. Naturally, the models used for these analyses must be validated for whether they reproduce the low PPV in successive screening rounds as presented in this study.

Strong indicators to assess the effectiveness of a CRC screening programme are the number of screen-detected and interval CRCs over consecutive rounds. A decline in the total number of CRCs was seen in this study, from 25 (88% screen-detected carcinomas) to 13 (54% screen-detected carcinomas). Subjects with a negative colonoscopy were referred back to the screening programme, and were considered not to require FIT screening for ten years. The reason we chose to do so and not to offer them another FIT in subsequent rounds, is because we know from previous studies that the chance of finding advanced lesions in these subjects is very low. Brenner et al. showed in a population-based case-control study that people with a previous negative colonoscopy

had a strongly reduced risk of CRC compared to people who had never undergone colonoscopy [21]. Lower risks, even beyond ten years after negative colonoscopy, were observed for both left- and right-sided CRC, and therefore it was concluded that screening intervals for CRC screening by colonoscopy could be longer than the commonly recommended ten years in most cases [22]. A retrospective analysis found similar results, ie, that the risk of developing CRC remains decreased for more than ten years after a negative colonoscopy [23]. Findings of a more recent study also support the ten-year examination interval recommended by existing guidelines for persons at average risk who had a negative colonoscopy. Even a single negative colonoscopy was associated with a very low long-term risk of CRC [24]. However, more data are necessary to determine the optimal interval between negative colonoscopy after positive FIT and referal back to the screening programme. Another strong indicator to determine the impact of a screening programme and especially to compare it to other screening tests, is by the overall diagnostic yield of advanced neoplasia over time. For three consecutive rounds of 1-sample FIT screening, the diagnostic yield per 1,000 invitees was 43 in this study. Three rounds of FIT-based screening using a cut-off of 50 ng/ml reached a higher yield than sigmoidoscopy or colonoscopy screening, when accounting for the low uptake of these more invasive screening methods (the diagnostic yields of advanced neoplasia per 1,000 invitees of primary sigmoidoscopy and colonoscopy screening are 33 respectively 19) [7].

This study has several limitations. Recruitment took place in a population that at baseline had limited knowledge on CRC and CRC screening. Such awareness likely increased over time, particularly because of the onset of a national CRC screening programme in 2014. This may have positively affected the participation rate in the second and third screening round. Different screening intervals were applied in the second round. However, these intervals are unlikely to influence the results, since detection rates of advanced neoplasia as well as the PPV (one-year interval: 36.2%; two-year interval: 32.9%; three-year interval: 30.6%; p=0.773) were similar after a one-, two- or three-year interval, respectively [10].

In this population-based CRC screening study on three rounds of 1-sample FIT screening, an increase in uptake over successive screening rounds was seen. This implies that repeated FIT screening is acceptable on a population level. Furthermore, a decline in DR and PPV was seen over three consecutive rounds, suggesting that consecutive FIT screening has a beneficial effect on decreasing the prevalence of advanced neoplasia. A decrease was seen in the number of screen-detected and interval CRCs over consecutive screening rounds, providing further and even stronger evidence for the effectiveness. These results stress the importance of on-going research over multiple screening rounds. To optimize the effectiveness of screening programmes, more emphasis should be put on improving the uptake, especially that of previous non-responders.

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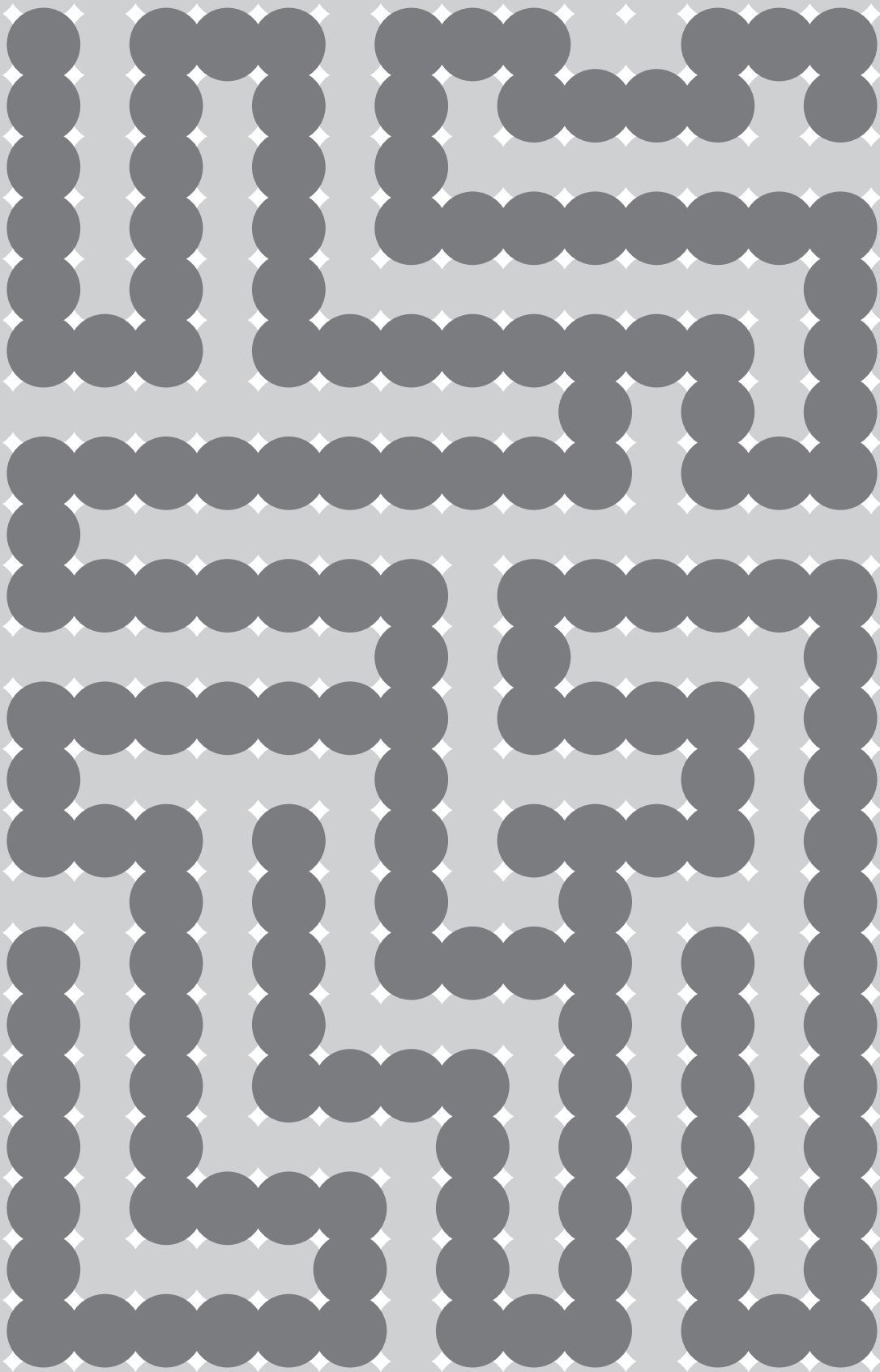

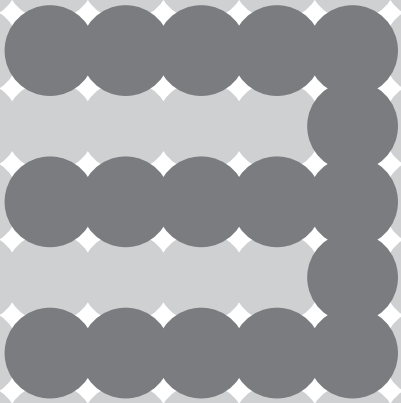

# Attendance and diagnostic yield of repeated two-sample faecal immunochemical test screening for colorectal cancer

Atija Kapidzic, Aafke H.C. van Roon, Lieke Hol, Anneke J. van Vuuren, Marjolein van Ballegooijen, Iris Lansdorp-Vogelaar, Wolfert Spijker, Kirsten Izelaar, Monique E. van Leerdam, and Ernst J. Kuipers

*Submitted*

## ABSTRACT

### Background & Aims:

Colorectal cancer (CRC) screening by means of faecal immunochemical testing (FIT) requires successive rounds for an optimal preventive effect. The diagnostic yield of advanced neoplasia may increase with the use of 2-sample FIT. We therefore conducted a population-based CRC screening trial focusing on attendance and diagnostic yield of repeated 2-sample FIT screening.

### Methods:

A representative sample of the Dutch population (n=3,197) aged 50-74 years was randomly selected and invited by mail for two rounds of FIT screening with a two-year interval. Per round, invitees received two FITs (OC-Sensor Micro, Eiken Chemical, Japan) to sample from two consecutive bowel movements. At each round, the test result was considered positive if at least one of both tests was positive at a cut-off of 50 ng haemoglobin/ml buffer (10 µg haemoglobin/g faeces). Test characteristics were determined for three scenarios: (A) two rounds with 1-sample FIT, (B) two rounds with 2-sample FIT, and (C) first round 2-sample FIT and second round 1-sample FIT (ie, the first FIT of the 2-sample FIT was positive). These scenarios were compared to data on repeated 1-sample FIT screening derived from a previous study in the same setting and population.

### Results:

Attendance was similar in both rounds (round 1: 61.3%, 1,875/3,057; round 2: 61.3%, 1,582/2,579; p= 0.992). The positivity rate (PR), detection rate (DR), and positive predictive value (PPV) for advanced neoplasia of 2-sample FIT were significantly higher in the first (PR 12.8%; DR 4.1%; PPV 34.1%) than in the second round (PR 8.4%; p<0.001; DR 1.7% p<0.001; PPV 21.1% p=0.011). The PR in the second round was lower for 1-sample (scenario A: 5.6%, 95% CI 4.6-6.9) than for 2-sample FIT (scenario B: 8.4%, 95% CI 7.1-9.8), whereas the DR (scenario A: 1.3, 95% CI 0.8-2.0; scenario B: 1.7, 95% CI 1.2-2.5) and the PPV (scenario A: 24, 95% CI 16-34; scenario B: 21, 95% CI 15-29) did not differ. After two rounds of screening, the diagnostic yield for scenario A at a cut-off of 50 ng/ml was 27.8 subjects with advanced neoplasia per 1,000 invitees, compared to 34.0 for scenario B, 31.7 for scenario C, and 29.3 per 1,000 invitees for two rounds of repeated 1-sample FIT screening (29.3 versus 27.8, p=0.696; 29.3 versus 34.0, p=0.241; 29.3 versus 31.7, p=0.542).

### Conclusions:

Two-sample FIT screening is associated with a stable and high attendance during repeated screening rounds. The DR of advanced neoplasia of 2-sample FIT screening

decreases significantly in the second round. Using 2- instead of 1-sample FIT does not result in a higher DR of advanced neoplasia in the second round. The present data, unique in that over 3,000 average-risk individuals were invited for 2-sample FIT screening over two consecutive rounds, did not show a significantly higher diagnostic yield for 2-sample versus 1-sample FIT screening at a cut-off of 50 ng/ml. This supports a preference for 1-sample FIT screening.

## INTRODUCTION



Repetitive screening with guaiac-based faecal occult blood tests (gFOBTs) reduces CRC-related mortality [1]. This effect of gFOBT screening on CRC mortality persists for many years [2]. Today, the faecal immunochemical test (FIT) is replacing the classical gFOBT as a screening method, based on acceptability and effectiveness leading to a superior detection rate of subjects with advanced neoplasia [3]. The possibility to adjust the positivity rate of FIT to meet available resources provides a significant additional benefit to FIT screening [4, 5]. Population-based FIT screening is therefore currently being implemented in several countries, including the Netherlands [6].

Advanced neoplasia can bleed intermittently and therefore may be missed with single stool sampling. Screening by means of a 2-sample FIT increases test sensitivity (ie, reduces the risk of missing advanced lesions). A previous study comparing 1- versus 2-sample FIT screening reported no differences in attendance rate yet a significant higher detection rate of advanced neoplasia with first round 2-sample FIT screening [7]. Two-sample FIT screening thus seems more effective than one-sample FIT screening, but it is unknown whether this advantage persists over repeated screening rounds, a prerequisite for optimal screening by means of FIT. Until now, data on successive 2-sample FIT screening are lacking. The aim of this study was to determine attendance and diagnostic yield of repeated 2-sample FIT screening. Furthermore, we aimed to compare these data with repeated 1-sample FIT screening.

## METHODS

### Study population/design

Details about the design of this on-going population-based CRC screening programme have been described previously [3, 8]. In brief, demographic data of all individuals between the ages of 50-74 years in the southwest of the Netherlands were obtained from municipal population registers. A random sample was taken from the target population by a computer-generated algorithm (Tenalea, Amsterdam, the Netherlands). Allocation

to 1- or 2- sample FIT screening occurred prior to invitation. Since there was no CRC screening programme at the time of the trial in the Netherlands, the target population was screening-naïve when first approached. Individuals with a history of inflammatory bowel disease or CRC, as well as those who had undergone a colonoscopy, sigmoidoscopy, or barium contrast enema in the last three years, and those with an estimated life expectancy of less than five years were excluded from the study. Recruitment took place between November 2008 and May 2011.

**Two-sample FIT screening**

With each screening round, two FITs (OC-sensor Micro, Eiken Chemical, Japan) were sent by mail with the instruction to take one sample per FIT of two bowel movements on consecutive days, and to write down the sampling dates on both test tubes. When both tests were performed on the same day, one additional FIT was sent to the screenee to make sure that of each individual two different stool samples were available. The test result was considered positive when the haemoglobin concentration in at least one FIT sample was ≥ 50 ng/ml buffer, which corresponds to 10 µg haemoglobin/g faeces.

**Follow-up evaluation; colonoscopy**

Subjects with a positive FIT were scheduled for colonoscopy within four weeks. In case of incomplete colonoscopy, a CT-colonoscopy was performed. All colonoscopies were performed by experienced endoscopists (> 1,000 colonoscopies performed). The maximum reach of the endoscope, the quality of bowel preparation, as well as the characteristics and location of any polyps were recorded. All removed polyps were evaluated by experienced gastrointestinal pathologists. Patients with a positive colonoscopy entered a surveillance programme according to the guideline of the Dutch Society of Gastroenterology, while patients with a negative colonoscopy were referred back to the screening programme, but were considered not to require FIT screening for ten years.

**Screen-detected and interval carcinomas**

Except for individuals who had moved out of the Netherlands, all recruited participants were followed for the development of CRC. Screen-detected cancers were defined as cancers identified at colonoscopy performed after a positive test result. Interval cancers were defined as colorectal cancers diagnosed within the time period between two consecutive screening rounds. Interval cancers were identified through linkage with the Dutch Comprehensive Cancer Centre (www.iknl.nl) which has data on all cancers diagnosed in the Netherlands.

**Statistical analysis**

Analyses were performed for three scenarios: (A) two rounds with 1-sample FIT (ie, only taking the first FIT of the 2-sample testing into account and using a cut-off of 50 ng/ml), (B) two rounds with 2-sample FIT, considering a positive screening result once at least one of both tests was positive at a cut-off of 50 ng/ml, and (C) first round screening with 2-sample FIT and the second round with 1-sample FIT, again at the same cut-off of 50 ng/ml. We provided confidence intervals for all FIT characteristics. Finally, the three scenarios were compared to our previous published results performed in the same population with two rounds of 1-sample FIT screening [8].

For each screening round, we calculated the attendance rate (AR), the positivity rate (PR), the detection rate (DR) of CRC and advanced adenomas (together defined as advanced neoplasia), and the positive predictive value (PPV) for CRC and advanced adenomas. The AR was calculated by dividing the number of participants by all eligible subjects (defined as all invitees minus the excluded subjects). The PR was defined as the proportion of participants having a positive test result. The DR was defined as the proportion of participants having advanced neoplasia. This was calculated as the number of screened individuals with advanced neoplasia divided by all screened individuals with an analyzable FIT. Advanced neoplasia included CRC and advanced adenomas. An advanced adenoma (AA) was defined as an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high-grade dysplasia. When more than one lesion was present, the screenee was classified according to the most advanced lesion. The number needed to screen (NNscreen) was calculated as the number of analyzable FITs needed to find one advanced neoplasia or CRC. The PPV describes the number of advanced neoplasia among screenees with a positive FIT, who underwent a colonoscopy or in case the colonoscopy was incomplete a CT-colonography (n=2). The number needed to scope (NNscope) describes the number of colonoscopies to find one screenee with an advanced neoplasia or CRC.

For the cumulative test characteristics, we combined counts of the two screening rounds to acquire new numerators and denominators. For the calculation of the diagnostic yield over two rounds we considered the total number of advanced lesions and all individuals who had been eligible at least once over two screening rounds (eg, invitees of 75 years and older during the second round were considered eligible invitees). This strategy most closely mimics population-based screening programmes. Differences in proportions between groups were analyzed by Chi-square testing. Differences in means between groups were tested using the Student t-test. Proportions were displayed with 95% confidence intervals (95% CI). The cumulative attendance was defined as the number of eligible invitees attending at least once. To assess differences in attendance rate between the two rounds of 2-sample FIT screening, a generalized estimating equation was used to account

for clustering at the level of the invitee. All p-values were two-sided and considered significant if < 0.05. All tests were conducted using SPSS version 20.0.

### Ethical approval

The Dutch National Health Council and the Institutional Review Board of the Erasmus MC University Medical Centre approved the study. All screenees gave written informed consent.

## RESULTS

### Attendance

Baseline characteristics and the results of the first 2-sample FIT screening rounds have previously been described [8]. In short, of the 3,197 subjects invited for 2-sample FIT screening in the first round, 140 individuals (4.4%) were excluded from analyses (136 subjects met one of the exclusion criteria, one had moved away, and three had died). A total of 1,875 out of 3,057 eligible invitees (61.3%; 95% CI 59.6-63.0) attended 2-sample FIT screening in the first round. Both FIT samples were analyzable in 1,874 screenees (99.5%) (Figure 1). A total of 421 (13.2%) individuals were not re-invited for the second screening round (239 subjects had tested positive during the first screening, 115 individuals had become 75 years of age or older, 43 had died, and the remaining 24 subjects had moved out of the region). In total 2,636 average-risk subjects were invited for the second screening round of which 57 (2.2%) invitees were excluded (51 individuals met one of the exclusion criteria, five had moved away, and one had died). Baseline characteristics including age, gender, and socio-economic status were similar for invitees for first and second round screening. Out of 2,579 eligible invitees, 1,582 (61.3%; 95% CI 59.4-63.2%) responded to the second round 2-sample FIT invitation. The two FIT samples were analyzable in 1,580 subjects (99.9%) (Figure 1).

Of first round participants that were eligible for the second round 92.1% (1,406/1,525; 95% CI 90.7-93.4) also attended the second screening round. A total of 16.7% of eligible non-participants in the first round attended the second screening round (176/1,054; 95% CI 14.6-19.1). The cumulative attendance rate over two rounds was 67.1% (2,051/3,057).

### Test characteristics per screening round

The test characteristics of two rounds of 1-sample (scenario A) and two rounds of 2-sample FIT screening (scenario B) at a cut-off of 50 ng/ml are displayed in Table 1. The PR of 2-sample FIT screening was significantly higher in the first round compared with the second round (12.8% versus 8.4%, p<0.001). Similar results were seen with 1-sample FIT screening (9.0% versus 5.6%, p<0.001). In the second round, the PR with scenario

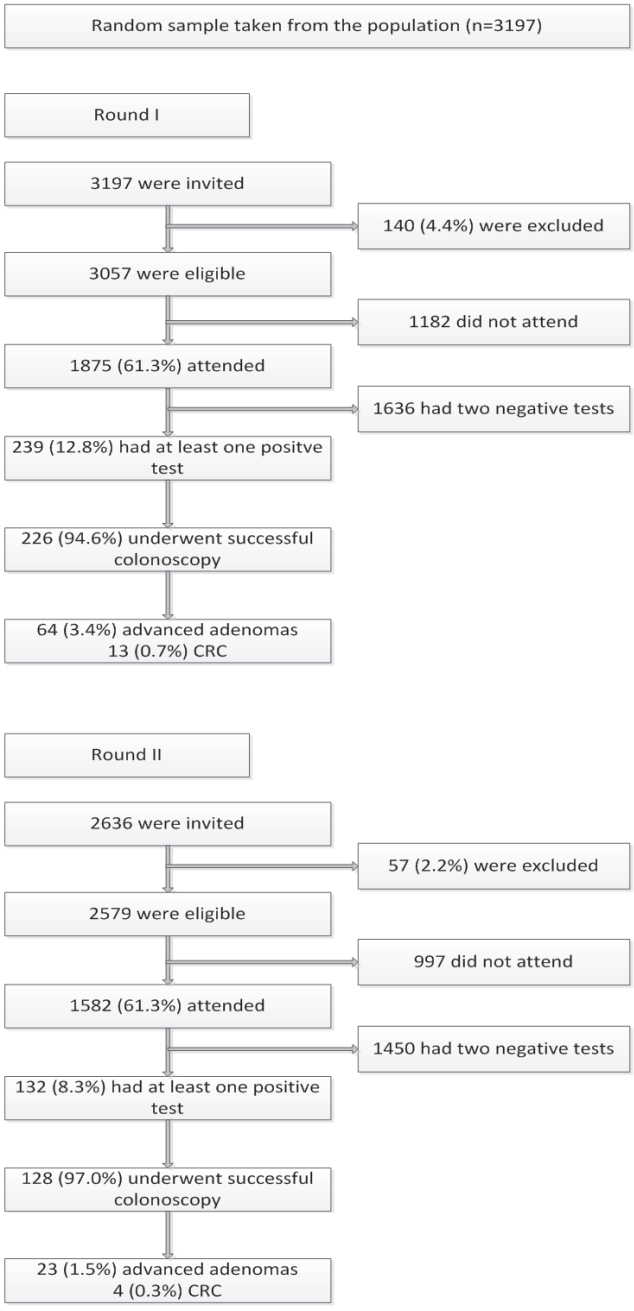


**Figure 1** Trial profile
A positive test was defined as a at least one FIT (faecal immunochemical test, OC-sensor Micro) with a result of 50 ng haemoglobin/ml or more; An advanced adenoma was defined as an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high-grade dysplasia; CRC = colorectal cancer

**Table 1** Test characteristics of different FIT screening strategies (cut-off value 50 ng/ml)

| | Round 1 | | Round 2 | |
|---|---|---|---|---|
| | **1-sample FIT** | **2-sample FIT** | **1-sample FIT** | **2-sample FIT** |
| | % (95% CI), n | % (95% CI), n | % (95% CI), n | % (95% CI), n |
| Positivity rate | 9.0 (7.8-10.4), 169 | 12.8 (11.3-14.3), 239 | 5.6* (4.6-6.9), 89 | 8.4* (7.1-9.8), 132 |
| Colonoscopy | 94.7 (160) | 94.6 (226) | 95.5 (85) | 97.0 (128) |
| Detection rate | | | | |
| AN | 3.5 (2.7-4.4), 65 | 4.1 (3.3-5.1), 77 | 1.3* (0.8-2.0), 20 | 1.7* (1.2-2.5), 27 |
| CRC | 0.6 (0.4-1.1), 12 | 0.7 (0.4-1.2), 13 | 0.3 (0.1-0.7), 4 | 0.3 (0.1-0.7), 4 |
| Number needed to screen | | | | |
| AN | 29 (23-37) | 24 (20-30) | 77* (50-125) | 59* (40-83) |
| CRC | 156 (91-250) | 143 (83-250) | 395 (143-1000) | 333 (143-1000) |
| Positive predictive value | | | | |
| AN | 41 (33-48), 65 | 34 (28-41), 77 | 24* (16-34), 20 | 21* (15-29), 27 |
| CRC | 8 (5-14), 13 | 6 (3-10), 13 | 5 (2-12), 4 | 3 (1-8), 4 |
| Number needed to scope | | | | |
| AN | 2.5 (2.0-3.0) | 2.9 (2.5-3.6) | 4.3* (3.0-6.4) | 4.7* (3.5-6.7) |
| CRC | 15 (7.4-21) | 17 (10-29) | 21.3 (8.4-56) | 32 (13-83) |

* $p < 0.05$ compared with the test characteristic in the first screening round
AN: advanced neoplasia = CRC and advanced adenoma; CRC: colorectal cancer; advanced adenoma: an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high-grade dysplasia

A (5.6%, 95% CI 4.6-6.9) was lower than with scenario B (8.4%, 95% CI 7.1-9.8). Of the participants with at least one positive test in the second round, 128 of 132 screenees (97.0%) underwent a colonoscopy. In two subjects the colonoscopy was incomplete and therefore an additional CT-colonography was performed. No abnormalities were seen on the two CT-colonographies. The remaining four subjects refused colonoscopy (Figure 1). The DR of advanced neoplasia of 2-sample FIT screening was significantly higher in the first round compared with the second round (4.1% versus 1.7%, p<0.001). Therefore, the NNscreen was higher in the second round compared with the first round (59 versus 24, p<0.001). Similar results were seen with 1-sample FIT screening (DR: 1.3% versus 3.5%, p<0.001; NNscreen: 77 versus 29, p<0.001). The DR of advanced neoplasia with scenario A and B, 1.3% (95% CI 0.8-2.0) respectively 1.7% (95% CI 1.2-2.5), was similar in the second round. The PPV was significantly higher in the first round compared with the second round of 2-sample FIT screening (34% versus 21%, p=0.011). Subsequently, the NNscope in the second round was higher compared with the first round (4.7 versus 2.9, p=0.011). Similar results were seen with 1-sample FIT screening (PPV: 24% versus 41%, p=0.008; NNscope 4.3 versus 2.5, p=0.008). The PPV for advanced neoplasia with

scenario A and B, 24% (95% CI 16-34) respectively 21% (95% CI 15-29), was similar in the second round.

### Test characteristics after two screening rounds

The cumulative test characteristics after two screening rounds are shown in Table 2, in which scenario A (two rounds of 1-sample FIT screening), B (two rounds of 2-sample FIT screening), and C (first round 2-sample, second round 1 sample FIT screening) are displayed. In this study we invited all patients for 2-sample FIT screening. The diagnostic yield of scenario A therefore did not include screenees in whom only the second FIT sample was positive and an advanced neoplasia was found. We therefore compared scenario A with a cohort of 1-sample FIT screening on which we reported previously [8]. The test characteristics of two rounds of 1-sample FIT screening (scenario A) were similar to the test characteristics of the cohort with 1-sample FIT screening by van Roon et al. Scenarios B and C showed a higher PR when compared to two rounds of 1-sample FIT by van Roon et al. (scenario B: 10.7% versus 7.2%, p<0.001; scenario C: 9.5% versus 7.2%, p<0.001). Scenario B furthermore showed a lower PPV than the 1-sample FIT cohort by van Roon et al. (29% versus 37%, p=0.024).

Figure 2 displays the diagnostic yields of scenarios A, B, C, and of the two rounds of 1-sample FIT screening (van Roon et al). The diagnostic yield for scenarios A and B (and consequently C) after one round was 21.3 (95% CI 16.7-27.0) and 25.2 (95% CI 20.2-31.4),

**Table 2** Cumulative test characteristics over two screening rounds of different FIT screening strategies (cut-off value 50 ng/ml)

| | **2 Rounds 1–sample FIT** | **2 Rounds 2-sample FIT** | **1st Round 2-sample, 2nd round 1-sample FIT** | **2 Rounds 1-sample FIT** (van Roon et al.) |
|---|---|---|---|---|
| | Scenario A | Scenario B | Scenario C | |
| | % (95% CI), n | % (95% CI), n | % (95% CI), n | % (95% CI), n |
| Positivity rate | 7.5 (6.6-8.4), 258 | 10.7* (9.7-11.8), 371 | 9.5* (8.6-10.5), 328 | 7.2 (6.6-7.9), 401 |
| Colonoscopy | 95.0 (245) | 94.3 (354) | 94.8 (311) | 95.0 (381) |
| Detection rate | | | | |
| Advanced neoplasia | 2.5 (2.0-3.0), (85) | 3.0 (2.5-3.6), (104) | 2.8 (2.3-3.4), (97) | 2.6 (2.2-3.0), (142) |
| CRC | 0.5 (0.3-0.8), (16) | 0.5 (0.3-0.8), (17) | 0.5 (0.3-0.8), (17) | 0.4 (0.3-0.6), (22) |
| Positive predictive value | | | | |
| Advanced neoplasia | 35 (29-41), (85) | 29* (25-34), (104) | 31 (26-37), (97) | 37 (33-42), (142) |
| CRC | 7 (4-10), (16) | 5 (3-8), (17) | 6 (3-8), (17) | 6 (4-9), (22) |
| Diagnostic yield | 27.8 (22.5-34.3) | 34.0 (28.1-41.1) | 31.7 (26.1-38.6) | 29.3 (24.9-34.5) |

* $p < 0.05$ compared with the same test characteristics with 2 rounds of 1-sample FT screening by van Roon et al.

Diagnostic yield: subjects with advanced neoplasia per 1,000 invitees; AN: advanced neoplasia = CRC and advanced adenoma; CRC: colorectal cancer; advanced adenoma: an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high-grade dysplasia

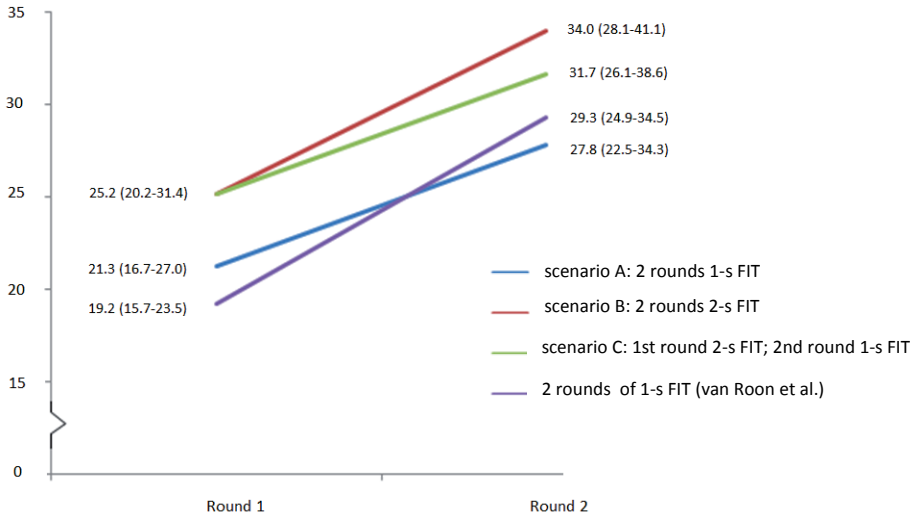


**Figure 2:** Cumulative diagnostic yield (screenees identified with advanced neoplasia per 1,000 invited) with the different screening strategies at a cut-off of 50 ng/ml
1-s FIT: 1-sample FIT; 2-s: 2-sample FIT; The diagnostic yield was calculated after one screening round and after two screening rounds. Therefore, a yield is given after two rounds with 1-sample FIT (scenario A, blue line), two rounds with 2-sample FIT (scenario B, red line), and a first round with 2-sample followed by a second round with 1-sample FIT (scenario C, green line). Furthermore, the yield is shown for 2 rounds with 1-sample FIT derived from van Roon et al. (purple line)

respectively. After two rounds, the diagnostic yield for scenarios A, B, and C increased to 27.8 (95% CI 22.5-34.3), 34.0 (95% CI 28.1-41.1), and 31.7 (95% CI 26.1-38.6), respectively. At a cut-off level of 50 ng/ml, the diagnostic yield of scenarios A, B, and C after one and after two screening rounds did not significantly differ with the diagnostic yield of the 1-sample FIT cohort by van Roon et al. (Table 2). Switching from scenario C to B yielded 7 (95% CI 3-15) additional advanced lesions, for which 43 additional colonoscopies had to be performed (NNscope = 6.1) (Figure 2). The NNscope to detect one advanced lesion was 4.3 for second round 1-sample FIT. After one screening round, a higher diagnostic yield was seen with 2-sample FIT screening than with 1-sample FIT screening (van Roon et al) at cut-off levels of ≥ 75 ng/ml, ≥ 100 ng/ml and ≥ 125 ng/ml. After two rounds a higher diagnostic yield was seen with 2-sample FIT screening at a cut-off level of ≥ 100 ng/ml and ≥ 125 ng/ml (Table 3).

## Interval carcinomas

After record linkage with the Dutch Comprehensive Cancer Centre, 19 CRCs were found in the total study population with 2-sample FIT screening. Seventeen CRCs (89.5%) were screen-detected (Figure 1), of which thirteen (77%) were detected during first and four (24%) during second round screening. The other two (10.5%) were interval cancers.

One interval carcinoma was diagnosed in a subject who had a positive first round FIT but negative subsequent colonoscopy. The second colonoscopy because of symptoms revealed a stage II tumor in the caecum three years and four months after the index colonoscopy. The second carcinoma was diagnosed in a subject who had a positive first round FIT but refused follow-up colonoscopy. One year and six months after the positive FIT a colonoscopy because of symptoms revealed a stage IV tumor in the rectosigmoid.

**Table 3** Diagnostic yield after one and two rounds for the three FIT screening scenarios at different cut-off levels

| | **Diagnostic yield** | | | |
|---|---|---|---|---|
| | **2 Rounds 1-sample FIT** | **2 Rounds 2-sample FIT** | **1st Round 2-sample, 2nd round 1-sample FIT** | **2 Rounds 1-sample FIT** |
| | Scenario A | Scenario B | Scenario C | Van Roon et al. |
| Cut-off (ng/ml) | | Round 1 | | |
| 50 | 21.3 (16.7-27.0) | 25.2 (20.2-31.4) | 25.2 (20.2-31.4) | 19.2 (15.7-23.5) |
| 75 | 19.0 (14.7-24.5) | 23.6* (18.8-29.6) | 23.6* (18.8-29.6) | 16.1 (12.9-20.1) |
| 100 | 18.0 (13.8-23.4) | 21.3* (16.7-27.0) | 21.3* (16.7-27.0) | 14.9 (11.8-18.7) |
| 125 | 17.7 (13.6-23.0) | 20.3* (15.8-25.9) | 20.3* (15.8-25.9) | 14.2 (11.3-18.0) |
| 150 | 16.0 (12.1-21.1) | 19.0 (14.7-24.5) | 19.0 (14.7-24.5) | 14.0 (11.1-17.8) |
| 175 | 14.7 (11.0-19.7) | 18.0 (13.8-23.4) | 18.0 (13.8-23.4) | 13.0 (10.2-16.6) |
| 200 | 13.4 (9.9-18.2) | 16.4 (12.4-21.5) | 16.4 (12.4-21.5) | 12.4 (9.6-15.9) |
| | | Round 1 + Round 2 | | |
| 50 | 27.8 (22.5-34.3) | 34.0 (28.1-41.1) | 31.7 (26.1-38.6) | 29.3 (24.9-34.5) |
| 75 | 25.2 (20.2-31.4) | 31.4 (25.8-38.2) | 29.8 (24.3-36.4) | 24.4 (20.4-29.1) |
| 100 | 22.9 (18.2-28.9) | 29.1* (23.7-35.7) | 26.2 (21.1-32.5) | 21.7 (17.9-26.2) |
| 125 | 21.6 (17.0-27.4) | 26.8* (21.7-33.2) | 24.2 (19.3-30.3) | 20.0 (16.4-24.4) |
| 150 | 19.6 (15.3-25.2) | 25.2 (20.2-31.4) | 22.6 (17.9-28.5) | 19.4 (15.9-23.7) |
| 175 | 17.7 (13.6-23.0) | 23.2 (18.4-29.2) | 20.9 (16.4-26.7) | 18.0 (14.6-22.1) |
| 200 | 16.4 (12.4-21.5) | 21.3 (16.7-27.0) | 19.3 (15.0-24.8) | 16.3 (13.1-20.3) |

* $p < 0.05$ compared with the diagnostic yield at that cut-off level with 2 rounds of 1-sample FIT screening by van Roon et al.

Diagnostic yield: subjects with advanced neoplasia per 1,000 invitees. The diagnostic yield was calculated after one and after two screening rounds

## DISCUSSION

To our knowledge, this is the first population-based study to evaluate the participation and diagnostic yield of repeated 2-sample FIT-based CRC screening. Two-sample FIT screening is associated with a stable and high attendance similar to screening with 1-sample FIT. Our study demonstrated that second round 2-sample FIT screening yields

fewer advanced neoplasia compared to the first screening round. Furthermore, the diagnostic yield of two rounds of 2-sample FIT screening at a cut-off of 50 ng/ml (scenario B), or first round 2-sample and a second round 1-sample FIT screening (scenario C) was not significantly higher than that of two rounds of 1-sample FIT screening [8]. Given the lack of information on this matter, these data are of utmost importance for countries considering or planning the implementation of population-based FIT screening.

One of the most important factors to be taken into account when choosing a screening strategy is the acceptability of that strategy. The stable and high attendance over two rounds similar to 1-sample FIT screening underlines the acceptability of a 2-sample regimen. This underlines that the burden of FIT sampling of consecutive bowel movements does not impair participation to screening. Furthermore, the number of advanced neoplasia detected determines the effectiveness of CRC screening. The optimal number of FITs is in this respect very relevant. In this study we were able to compare second round 1- and 2-sample FIT screening (scenarios A and B). Scenario A took only the first test result of repeated 2-sample FIT testing into account. This theoretical analysis was discrepant with the real-life situation, in which we also referred subjects to colonoscopy if they had the second test of 2-sample FIT positive. That implies that those subjects were in reality not invited in the second round, since they had had a colonoscopy within the previous two years. Had we not done so, one might expect that the actual yield of second round FIT screening might have been slightly higher than observed, since subjects who were possibly at high risk for advanced lesions had already been identified with the second FIT sample in the first round. In the second round, 2-sample FIT (scenario B) resulted in a higher PR, but a similar DR and PPV compared to 1-sample FIT (scenario A). In addition, the number needed to scope to detect one additional advanced lesion when switching from the 1- to the 2-sample strategy in the second round (NNScope: 6.1) was higher than the NNScope for 1-sample FIT screening (4.3). Therefore, the additional value of a second test in the second round seems to be limited, since more colonoscopies are required to detect an additional advanced lesion.

No differences were seen when comparing the cumulative test characteristics of scenario A with previously published data of a group we invited for two rounds of 1-sample FIT screening (van Roon et al). Scenario B (two rounds of 2-sample FIT screening) showed a higher PR, but lower PPV when compared to the 1-sample FIT cohort by van Roon et al. The higher PPV together with a lower PR after two screening rounds would make 1-sample FIT more favourable over screening with 2-sample FIT. The PPV is a measure for efficient use of colonoscopy resources. As screening colonoscopies are performed on healthy individuals, the number of unnecessary colonoscopies must be brought to an absolute minimum. In particular since all colonoscopies carry a small risk of serious complications, such as bleedings and perforations [9, 10]. The diagnostic yield over two rounds (ie, the cumulative sensitivity of several screening rounds) did not significantly

differ between 1-sample and 2-sample FIT screening at a cut-off of 50 ng/ml [8]. A higher diagnostic yield was seen at higher cut-off levels with 2-sample FIT screening after one and after two screening rounds. This again demonstrates that screening at a cut-off of 50 ng/ml is highly effective. Adding a second test can be considered at higher cut-off levels. Relevant in this matter are further the number of interval cancers found with 1-sample and 2-sample FIT screening. In the first round, 18 and 13 CRCs were detected and 3 (14.3%) and 2 (13.3%) interval carcinomas between the first and second round with respectively 1- and 2 sample FIT screening. The similar percentage of interval CRCs, although a very small number, may also be more in favour of a scenario with 1-sample FIT screening. This finding is supported by a cost-effectiveness analysis reporting that intensifying screening with 1-sample FIT over multiple screening rounds was more cost-effective than providing 2-sample FIT within one screening round [11]. It was therefore recommended to increase the number of screening rounds with 1-sample FIT, before considering to increase the number of FIT samples provided per screening round.



Some limitations must be acknowledged. First, small differences in performance of 1- versus 2-sample FIT screening may become significant when applied to very large populations. Second, more awareness about CRC and advanced adenomas may have occurred over time, in particular since we started at baseline with recruitment of subjects in a screening-naïve population. No differences were however seen in attendance between the two screening rounds.

In conclusion, 2-sample FIT screening is associated with a stable and high attendance. The detection rate of advanced neoplasia considerably decreases in the second round of two-sample FIT screening. Using 2- instead of 1-sample FIT during the second screening round does not result in a higher DR in a second screening round. The diagnostic yield of two rounds of 2- is similar to two rounds of 1-sample FIT screening at a cut-off of 50 ng/ml. This implies that at low cut-off levels 1-sample FIT screening should be preferred over 2-sample FIT screening.

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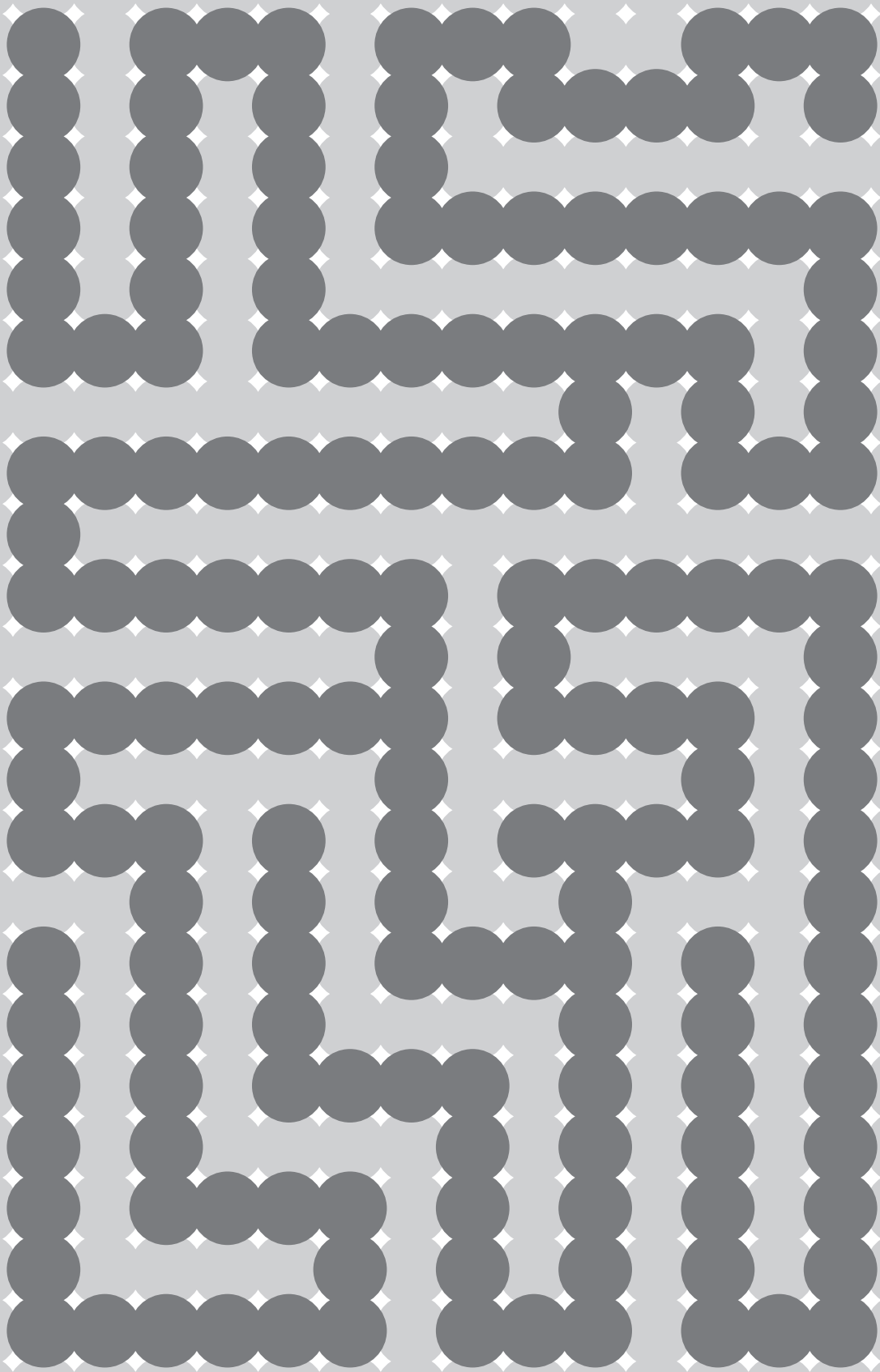

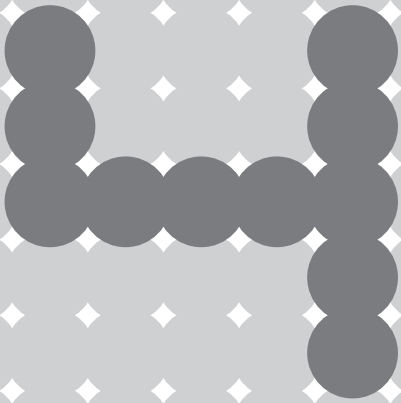

# Gender differences in faecal immunochemical test performance for early detection of colorectal neoplasia

Atija Kapidzic, Miriam P. van der Meulen, Lieke Hol, Aafke H.C. van Roon, Caspar W.N. Looman, Iris Lansdorp-Vogelaar, Marjolein van Ballegooijen, Anneke J. van Vuuren, Jacqueline C.I.Y. Reijerink, Monique E. van Leerdam, and Ernst J. Kuipers

*Submitted*

## ABSTRACT

### Background & Aims:

Faecal immunochemical tests (FITs) are widely used in colorectal cancer screening. Programmes use the same faecal haemoglobin threshold for colonoscopy referral for men and women, but it is unclear whether FIT performs equally in both sexes. We therefore assessed FIT performance in men and women.

### Methods:

A prospective cohort study was performed, in which in total 10,008 average-risk subjects (aged 50-74 years) were invited for first and 8,316 average-risk subjects (aged 51-74 years) for second round screening with a single FIT (OC-sensor Micro, Eiken Chemical, Japan). Subjects with a haemoglobin level of ≥ 50 ng/ml (≥ 10 μg haemoglobin/g faeces) were referred for colonoscopy. The test characteristics were assessed by sex for a range of FIT cut-offs.

### Results:

In total 59.8% of men and 64.6% of women attended the first round ($p<0.001$). At a cut-off level of 50 ng/ml, the positivity rate was significantly higher among men (10.7%) compared to women (6.3%, $p<0.001$) in the first round. The detection rate was 4.4% for men and 2.2% for women ($p<0.001$) in the first round. The positive predictive value in the first round was 42% for men and 37% for women ($p=0.265$). A significantly higher false-positive rate (FPR) in men (6.3%) than in women (4.1%, $p<0.001$) was found. Similar differences in these test characteristics were seen in the second round.

### Conclusions:

At a cut-off level of 50 ng/ml the FIT positivity rate was higher in men, reflected by both a higher detection rate and a higher FPR. The higher FPR in men implies that specificity is lower in men than in women. The positive predictive value did not differ between men and women at this cut-off level. The use of the same cut-off value in men and women in FIT screening is recommended based on equal test performance in terms of positive predictive value.

## INTRODUCTION

Screening by means of a guaiac-based faecal occult blood test (FOBT) reduces colorectal cancer (CRC)-related mortality [1]. More recently, faecal immunochemical tests (FIT) proved more effective than guaiac-based FOBT due to both a higher uptake and higher detection rate of advanced neoplasia [2-4]. This explains the strong worldwide interest in faecal immunochemical tests as a primary screening tool [5-9]. Until now, similar FIT screening regimens are applied in men and women despite eminent sex disparities in prevalence and anatomic distribution of advanced neoplasia.

Several colonoscopy based screening studies have reported a higher incidence and prevalence of advanced neoplasia in men compared to women [10-13]. The positive predictive value and detection rate of both FOBTs depend on the prevalence of advanced neoplasia in the tested population. As a consequence, guaiac-based FOBT screening results in a lower positivity and detection rate and may result in a higher proportion of false positive test results in women [14-16].

A Scottish gFOBT screening study reported more screen-detected CRCs in men (64.5%) compared to women (35.5%), whereas the number of interval CRCs was similar in both groups (men: 49.8% versus women: 50.2%) [17]. These data suggest that gFOBT is less sensitive when used in women. This finding was confirmed by a German study, where subjects received a FOBT (gFOBT or FIT) prior to a screening colonoscopy. The authors found a substantial higher sensitivity and positive predictive value in men than in women for both FOBTs [18]. Another study which compared FIT with primary screening colonoscopy also found a higher sensitivity of FIT in men [19]. Aforementioned data were obtained from studies with colonoscopy as a primary screening tool and might have a different underlying risk than the (screening-naïve) population screened with FIT.

Data on gender differences in a population-based setting with FIT as a primary screening tool are lacking. In this study we therefore determined potential gender differences in performance of FIT in an average risk, screening-naïve Dutch population.

## MATERIALS AND METHODS

This study was based on the CORERO-I and –II studies, the primary results of which have been described elsewhere [4, 20]. In brief, 10,008 (aged 50-74 years) were approached for first and 8,316 screenees (aged 51-74 years) for second round screening. The demographic data of all invitees were obtained from municipal population registers in the wider Rotterdam region. Random samples were taken from the target population by a computer-generated algorithm (Tenalea, Amsterdam, the Netherlands). Since there was no CRC screening programme at the time of the trial in the Netherlands, the target

population was screening-naïve when first approached. Individuals with a history of inflammatory bowel disease or CRC, as well as those who had undergone a colonoscopy, sigmoidoscopy or barium contrast enema in the last 3 years and those with an estimated life expectancy of less than 5 years were excluded from the study. Subjects were not invited for the second screening round in case of a positive FIT in the first screening round, when they had become older than 74 years of age, when they had moved out of the region, or when they had died. Recruitment took place between November 2006 and December 2010.

**Interventions**

With each screening round, one FIT (OC-sensor Micro, Eiken Chemical, Japan) was sent by mail to collect a single sample of one bowel movement. The test was considered positive when the haemoglobin concentration in the FIT sample was ≥ 50 ng/ml, which corresponds to 10 µg haemoglobin/g faeces. In the second round, study subjects were divided over three groups to undergo repeated FIT testing at different screening intervals (ie, one, two and three years, respectively) [20]. Based on these results, a two-year interval was applied to all groups in the third screening round.

**Follow-up evaluation**

Subjects with a positive FIT were scheduled for colonoscopy within 4 weeks. All colonoscopies were performed by experienced endoscopists, who had performed over 1,000 colonoscopies. The maximum reach of the endoscope, adequacy of bowel preparation as well as the characteristics and location of any polyps were recorded. Experienced gastrointestinal pathologists evaluated all removed polyps. Patients with a positive colonoscopy entered a surveillance programme according to guidelines of the Dutch Society of Gastroenterology, while subjects with a negative colonoscopy were referred back to the screening programme, but were considered not to require FIT screening for ten years.

**Statistical analysis**

Differences in proportions between men and women for the test characteristics were analyzed by Chi-square testing. In case of more than two categorical variables, we changed to contingency table analyses [21]. Faecal haemoglobin concentrations were assessed in men and women. Differences between gender were analyzed using the Mann-Whitney U test, as the data were not normally distributed. The normality of the distribution of continuous variables was assessed using a normal Q-Q plot. The positivity rate (PR), positive predictive value (PPV) and detection rate (DR) were calculated and described as percentages with 95% confidence intervals (95% CI). The PR was defined as the proportion of participants having a positive FIT. The PPV depends on sensitivity and specificity,

but also on the baseline prevalence of a disease in the population. Here, the PPV for detection of advanced neoplasia was defined as the number of subjects with advanced neoplasia divided by all FIT-positive screenees who underwent colonoscopy. Advanced neoplasia included CRC and advanced adenomas. An advanced adenoma was defined as an adenoma with a diameter ≥ 10 mm, and/or with a ≥ 25% villous component, and/or high grade dysplasia. The DR was defined as the proportion of participants being diagnosed with advanced neoplasia divided by all screened individuals with an analyzable screening test. The number needed to scope (NNscope) describes the number of colonoscopies to find one screenee with an advanced neoplasia or CRC. The number needed to screen (NNscreen) was calculated as the number of complete screening tests needed to find one advanced neoplasia or CRC. All test characteristics were separately calculated for cut-off levels of 50, 75, 100, 125, 150, 175 and 200 ng/ml, respectively. FIT test characteristics and FIT concentrations were adjusted for age via logistic regression. True-positives were participants with a positive FIT result and advanced neoplasia detected during colonoscopy. False-positives were participants with a positive FIT result and non-advanced adenoma or no findings detected during colonoscopy. Likewise, the false-positive rate (FPR) was defined as subjects who had a positive FIT, but no advanced neoplasia on follow-up colonoscopy (ie, only non-advanced adenoma, hyperplastic polyps or no findings at all), divided by the total number of screenees. All tests were conducted using SPSS version 20.0 and a p-value below 0.05 was considered statistically significant using 2-sided tests.



### Ethical approval

The study was approved by the Dutch National Health Council and the Institutional Review Board of the Erasmus MC University Medical Centre (MEC-2005-264 and MEC-2008-029). All screenees gave written informed consent.

## RESULTS

The trial profile as described previously is summarized in Figure 1 [4, 20]. In total, 59.8% (95% CI 58.4-61.2) of men and 64.6% (95% CI 63.2-65.9) of women attended the first round ($p<0.001$), and 61.3% (95% CI 59.8-62.8) of men and 65.6% (95% CI 64.2-67.1) of women attended the second round ($p<0.001$), respectively.

### Proportion of positive tests

In the first round, 306 male screenees (10.7%; 95% CI 9.6-11.9%) and 197 female screenees (6.3%; 95% CI 5.5-7.2%) tested positive at a cut-off level of 50 ng/ml ($p<0.001$). Men showed significantly higher positivity rates than women at the full range of FIT cut-

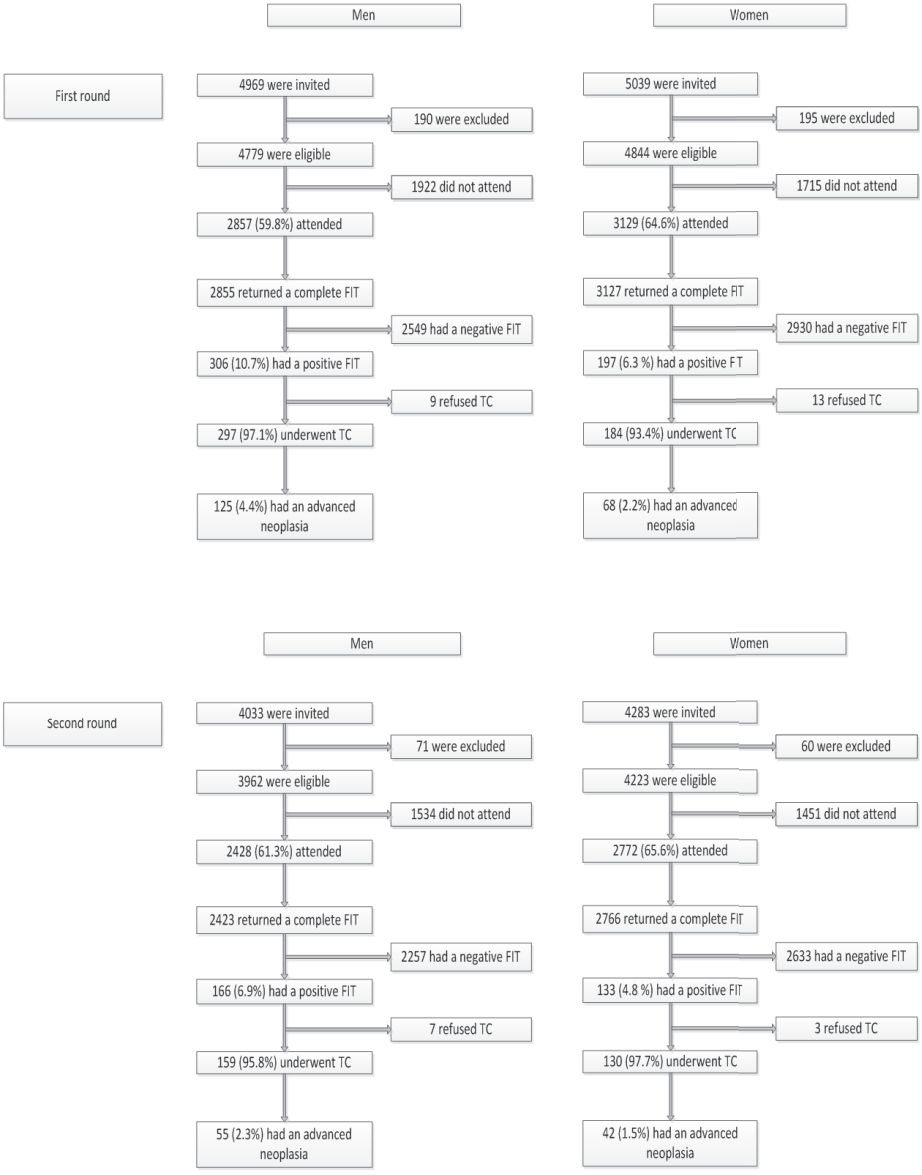


**Figure 1** Trial profile
FIT: faecal immunochemical test; TC: total colonoscopy

off levels in the first round (Table 1). In the second round, 6.8% (95% CI 5.9-7.9%) of men (n=166) and 4.8% (95% CI 4.1-5.7%) of women (n=133) tested positive at a cut-off level of 50 ng/ml (p=0.002). The proportion of positive tests remained significantly higher in males up to the cut-off level of 125 ng/ml. Above this cut-off level no significant differ-

**Table 1** Test characteristics of FIT at different cut-off levels

| | FIRST SCREENING ROUND | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Positivity rate | | | | Positive predictive value | | | | Detection rate | | | | | | | |
| | Men | | Women | | Men | | Women | | Men | | | | Women | | | |
| Cut-off | | | | | AN | CRC | AN | CRC | AN | | CRC | | AN | | CRC | |
| ng/ml | n | % (95% CI) | n | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | n | % (95% CI) | n | % (95% CI) | n | % (95% CI) | n | % (95% CI) |
| 50 | 306 | 10.7 (9.6-11.9)* | 197 | 6.3 (5.5-7.2) | 42 (37-48) | 6.1 (4-9) | 37 (30-44) | 6.0 (3-11) | 125 | 4.4 (3.7-5.2)* | 18 | 0.6 (0.4-1.0) | 68 | 2.2 (1.7-2.7) | 11 | 0.4 (0.2-0.6) |
| 75 | 228 | 8.0 (7.0-9.0)* | 147 | 4.7 (4.0-5.5) | 51 (45-58)* | 7.7 (5-12) | 40 (32-48) | 7.2 (4-13) | 113 | 4.0 (3.3-4.7)* | 17 | 0.6 (0.4-1.0) | 55 | 1.8 (1.4-2.3) | 10 | 0.3 (0.2-0.6) |
| 100 | 195 | 6.8 (6.0-7.8)* | 122 | 3.9 (3.3-4.6) | 55 (48-62) | 9.0 (6-14) | 44 (35-53) | 8.7 (5-15) | 104 | 3.6 (3.0-4.4)* | 17 | 0.6 (0.4-1.0) | 50 | 1.6 (1.2-2.1) | 10 | 0.3 (0.2-0.6) |
| 125 | 173 | 6.1 (5.2-7.0)* | 112 | 3.6 (3.0-4.3) | 57 (49-64) | 8.9 (6-14) | 46 (37-56) | 9.4 (5-17) | 95 | 3.3 (2.7-4.1)* | 15 | 0.5 (0.3-0.9) | 49 | 1.6 (1.2-2.1) | 10 | 0.3 (0.2-0.6) |
| 150 | 158 | 5.5 (4.8-6.4)* | 103 | 3.3 (2.7-4.0) | 60 (52-67) | 9.8 (6-16) | 48 (38-58) | 9.2 (5-17) | 91 | 3.2 (2.6-3.9)* | 15 | 0.5 (0.3-0.9) | 47 | 1.5 (1.1-2.0) | 9 | 0.3 (0.1-0.6) |
| 175 | 147 | 5.2 (4.4-6.0)* | 92 | 2.9 (2.4-3.6) | 60 (52-68) | 9.9 (6-16) | 49 (39-60) | 9.2 (5-17) | 85 | 3.0 (2.4-3.7)* | 14 | 0.5 (0.3-0.8) | 43 | 1.4 (1.0-1.8) | 8 | 0.3 (0.1-0.5) |
| 200 | 141 | 4.9 (4.2-5.8)* | 88 | 2.8 (2.3-3.5) | 60 (52-68) | 9.6 (6-16) | 51 (40-61) | 9.6 (5-18) | 82 | 2.9 (2.3-3.6)* | 13 | 0.5 (0.3-0.8) | 42 | 1.3 (1.0-1.8) | 8 | 0.3 (0.1-0.5) |
| | **SECOND SCREENING ROUND** | | | | | | | | | | | | | | | |
| Cut-off | Positivity rate | | | | Positive predictive value | | | | Detection rate | | | | | | | |
| | Men | | Women | | Men | | Women | | Men | | | | Women | | | |
| | | | | | AN | CRC | AN | CRC | AN | | CRC | | AN | | CRC | |
| ng/ml | *n* | % (95% CI) | *n* | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) | n | % (95% CI) | n | % (95% CI) | n | % (95% CI) | n | % (95% CI) |
| 50 | 166 | 6.8 (5.9-7.9)* | 133 | 4.8 (4.1-5.7) | 35 (28-42) | 3.8 (2-8) | 32 (25-41) | 3.8 (2-9) | 55 | 2.3 (1.7-2.9)* | 6 | 0.2 (0.1-0.6) | 42 | 1.5 (1.1-2.0) | 5 | 0.2 (0.1-0.4) |
| 75 | 131 | 5.4 (4.6-6.4)* | 96 | 3.5 (2.8-4.2) | 36 (28-45) | 3.2 (1-8) | 36 (27-46) | 4.2 (2-11) | 45 | 1.9 (1.4-2.5) | 4 | 0.2 (0.1-0.4) | 34 | 1.2 (0.9-1.7) | 4 | 0.1 (0.1-0.4) |
| 100 | 100 | 4.1 (3.4-5.0)* | 79 | 2.9 (2.3-3.5) | 44 (34-54) | 4.3 (2-11) | 37 (27-48) | 5.1 (2-13) | 41 | 1.7 (1.2-2.3)* | 4 | 0.2 (0.1-0.4) | 29 | 1.0 (0.7-1.5) | 4 | 0.1 (0.1-0.4) |
| 125 | 83 | 3.4 (2.8-4.2)* | 68 | 2.5 (1.9-3.1) | 47 (37-59) | 5.1 (2-13) | 36 (25-48) | 4.5 (2-13) | 37 | 1.5 (1.1-2.1)* | 4 | 0.2 (0.1-0.4) | 24 | 0.9 (0.6-1.3) | 3 | 0.1 (0.0-0.3) |
| 150 | 70 | 2.9 (2.3-3.6) | 61 | 2.2 (1.7-2.8) | 49 (37-60) | 6.1 (2-15) | 37 (26-50) | 5.0 (2-14) | 32 | 1.3 (0.9-1.9) | 4 | 0.2 (0.1-0.4) | 22 | 0.8 (0.5-1.2) | 3 | 0.1 (0.0-0.3) |
| 175 | 63 | 2.6 (2.0-3.3) | 55 | 2.0 (1.5-2.6) | 51 (38-63) | 6.8 (2-17) | 39 (27-52) | 5.6 (2-16) | 30 | 1.2 (0.9-1.8) | 4 | 0.2 (0.1-0.4) | 21 | 0.8 (0.5-1.2) | 3 | 0.1 (0.0-0.3) |
| 200 | 58 | 2.4 (1.9-3.1) | 49 | 1.8 (1.3-2.3) | 50 (37-63) | 5.6 (2-16) | 40 (27-54) | 6.2 (2-18) | 27 | 1.1 (0.8-1.6) | 3 | 0.1 (0.0-0.4) | 19 | 0.7 (0.4-1.1) | 3 | 0.1 (0.0-0.3) |

* $p < 0.05$ scores for men compared to scores for women in that particular FIT cut-off level

FIT: faecal immunochemical test; CRC: colorectal cancer; AN: advanced neoplasia: adenoma ≥ 10 mm, villous component (≥ 25% villous) or high-grade dysplasia

ences were seen in positivity rates between both sexes in the second round (Table 1). In both rounds gender was significantly associated with the positivity rate after adjusting for age.

Figure 2 shows the difference between men and women per FIT cut-off category in the first and second round. In the first round, 1,422 men (49.8%) and 1,656 women (53.0%) had a FIT result of 0 ng/ml. This was 1,779 (72.8%) and 2,096 (75.1%) in the second round, respectively. Men more often had haemoglobin levels of 50-99 ng/ml (3.9% versus 2.4%, p=0.001), 100-149 ng/ml (1.3% versus 0.6%, p=0.006), and ≥ 200 ng/ml (4.9% versus 2.8%, p<0.001) in the first round compared to women. In the second round, men more often had haemoglobin levels of 100-149 ng/ml (1.2% versus 0.6%, p=0.027).

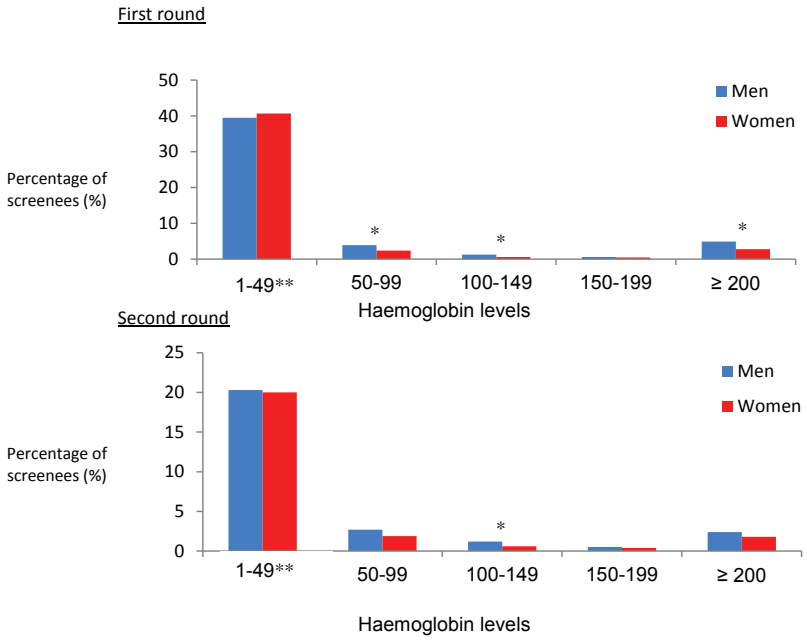


**Figure 2** Distribution of haemoglobin concentrations (ng/ml) among FIT screenees per gender
* Significant difference in the percentage of screenees for that FIT cut-off category; ** The FIT result was 0 ng/ml in 51.4% of cases (n=3078) in the first round and in 74.0% of cases (n=3875) in the second round; FIT: faecal immunochemical test

## Test characteristics

For both screening rounds, the uptake of colonoscopy among subjects with a positive FIT was high (round I: 97% of men and 93% of women, p=0.050; round II: 96% for both men and women, p=0.955, Figure 1).

In the first round, differences in PPV for advanced neoplasia between men and women were only significant at a cut-off level of 75 ng/ml (men: 51% (95% CI 45-58); women: 40% (95% CI 32-48), p=0.032) (Table 1). At higher cut-off levels, the PPV for advanced neoplasia tended to be higher in men, but these differences did not reach statistical significance. In the second round, no differences in PPV between men and women were observed. Likewise, the NNScope for advanced neoplasia and CRC were similar in both sexes. In the first round, the NNScope to find an advanced neoplastic lesion in men decreased from 2.4 (95% CI 2.1-2.7) using a cut-off level of 50 ng/ml to 1.7 (95% CI 1.5-1.9) at a cut-off level of 200 ng/ml. In women, the NNScope to find an advanced neoplastic lesion decreased from 2.7 (95% CI 2.3-3.3) to 2.0 (95% CI 1.6-2.5). In the second round, a similar pattern of decreasing NNscope was seen with increasing cut-offs. In both rounds gender was not significantly associated with the PPV for advanced neoplasia after adjusting for age. A significantly higher FPR in men was found in both rounds at a cut-off level of 50 ng/ml: FPR round I: 6.3% in men versus 4.1% in women, p<0.001; FPR round II: 4.6% in men versus 3.3% in women, p=0.017). This difference remained significant until a cut-off level of 100 ng/ml in the first round, and a cut-off level of 75 ng/ml in the second round. Men showed higher detection rates of advanced neoplasia than women for the full range of FIT cut-off levels in the first round, and therefore the NNscreen to find an advanced neoplasia was significantly lower in men (Table 1). At a cut-off level of 50 ng/ml, the NNscreen to detect one subject with advanced neoplasia was 23 (95% CI 19-27) in men and 46 (95% CI 37-59) in women (p<0.001). In the second round, men also tended to have higher detection rates of advanced neoplasia compared to women, but these differences were only significant at cut-off levels of 50 ng/ml, 100 ng/ml, and 125 ng/ml, respectively (Table 1). Likewise, a lower NNscreen to detect one advanced neoplasia was seen in men at these cut-off levels (cut-off 50 ng/ml: men 44 (95% CI 34-59), women 66 (95% CI 50-91), p=0.046; cut-off 100 ng/ml: men 59 (95% CI 44-83), women 95 (95% CI 67-143), p=0.045; cut-off 125 ng/ml: men 65 (95% CI 48-91), women 115 (95% CI 77-167), p=0.028, respectively). Gender was significantly associated with the DR of advanced neoplasia after adjusting for age in the first round, but not in the second round.

**Faecal haemoglobin concentrations and true- and false-positivity**

No differences were seen when comparing the faecal haemoglobin concentrations between true-positive men and women (326 ng/ml (IQR 118; 982) versus 359 ng/ml (IQR 146; 1054), p=0.840) and false-positive men and women (115 ng/ml (IQR 69; 327) versus 120 ng/ml (IQR 71-289), p=0.647) for the first and second round combined.

## DISCUSSION

Information on gender differences in population-based FIT screening was limited until now. This study, in which conclusions were based on a large number of screening-naïve men and women in a two-round FIT screening setting, provides insight in this matter. We observed higher positivity rates in men at the full range of cut-off levels. This was reflected by higher true-positive rates (detection rates) and higher false-positive rates (FPR). Likewise, the number needed to screen was lower in men for all cut-off levels. Although we observed a higher PPV for advanced neoplasia in men, these gender differences only reached significance at a single cut-off level of 75 ng/ml in the first round. With increasing cut-off levels we do see that the PPV tends to be higher in men. Data on the performance of FIT in men and women are of key importance given the current widespread use of FIT as primary screening tool.

Similar differences in detection rates of advanced neoplasia between both sexes were found in two colonoscopy screening studies [11, 12]. The higher detection rate is related to a higher prevalence of advanced lesions in men. Since negative screenees did not undergo a colonoscopy in our study, we were unable to calculate the FIT sensitivity and specificity. However, the relative difference in detection rates of advanced neoplasia between men and women in our study is higher than what one would expect based on the relative risk for developing CRC in the screening age group (Comprehensive Cancer Centre the Netherlands). This may indicate a higher FIT sensitivity in men. This is in line with two colonoscopy screening studies where subjects received a FOBT prior to colonoscopy (gFOBT or FIT). Both reported a higher test sensitivity in men [18, 19]. Furthermore, the higher FPR in men may be the result of a lower test specificity. Specificity is defined by the proportion of people without the disease that also test negative. We do not know the exact number of people without disease (advanced neoplasia) since people with a negative FIT did not undergo colonoscopy. However, given the higher underlying prevalence of advanced neoplasia in men, the number of men without advanced neoplasia will consequently be lower than the number of women. Therefore, the higher number of male screenees with a false-positive test indicates that the FIT specificity is lower in men. This is in line with the results of the two aforementioned colonoscopy screening studies [18, 19]. In addition, we calculated the FPR for the scenario in which subjects with a positive FIT, who had no adenoma or CRC at follow-up colonoscopy (ie, only hyperplastic polyps or no findings at all). After including also the non-advanced adenomas, we did not see any differences between men and women for the different cut-off levels. This would imply that the higher FPR in men is mainly caused by positive FITs due to detection of non-advanced adenomas. Our finding of similar positive predictive values of FIT in men and women contrasts with a German study on the performance of one guaiac and several immunochemical faecal occult blood tests.

In this study men had substantially higher positive predictive values than women at any FIT cut-off point [21].

The key question in the interpretation of these findings is whether and to what extent the observed gender differences are of clinical and/or public health relevance. Some studies suggest the cut-off should differ between men and women to reach the same FIT sensitivity in men and women. However, we think it is better to determine the optimal cut-off by other measures, in particular PPV, since the PPV is a measure for efficient use of colonoscopy resources, and also for the individual reflects the chance that unnecessary harm is done. As screening colonoscopies are performed on healthy individuals, the number of unnecessary colonoscopies must be brought to an absolute minimum. In particular since all colonoscopies carry a small risk of serious complications, such as bleeding and perforation [22, 23]. In addition, colonoscopy capacity is limited and costly. The higher FPR in men in both screening rounds indicates that a significantly larger number of men underwent follow-up colonoscopy and did not have advanced neoplasia. However, the chance that a colonoscopy is unnecessary after a positive FIT is equal in men and women, which is demonstrated by the similar PPV at a cut-off level of 50 ng/ml. Therefore, one could argue not to change cut-off values in men and women. If a higher cut-off than 50 ng/ml is used, the PPV in women could be improved by a higher cut-off, but this would be at the expense of the NNscreen in women. Optimal cut-off values for men and women can further be determined by taking other major determinants into account, including the incidence of neoplasia, the life expectancy, the intended screening interval, and cost-effectiveness. This can be realized using the current data combined with a microsimulation model [24-26]. The resulting information will be of great value, since FIT screening is expected to become current practice in more and more countries in the upcoming years.

Some limitations must be acknowledged. As already mentioned above, it was not possible to explicitly estimate sensitivity and specificity, because negative screenees did not undergo colonoscopy. Second, different screening intervals were applied in the second round. However, these intervals did not influence the results, since detection rates and positive predictive values of advanced neoplasia were comparable for the different intervals [20]. Furthermore, perhaps if our study population had been larger, differences in PPV would have become significant for all cut-off levels, indicating a better test performance in men. Finally, we tried to determine gender differences between proximal and distal advanced lesions, but our numbers were too small to consider for this manuscript.

In conclusion, this population-based trial provides important data on performance of one-sample FIT screening in men and women at different cut-off levels. Men have higher positivity rates than women, reflected by both higher detection rates and a higher FPR. A higher FPR in men implies that specificity is lower in men than in women.

Positive predictive values did not differ significantly for most cut-off levels. The resulting harm-to-benefit ratio, reflected in the positive predictive value, did not differ. Therefore, the use of similar cut-off values in men and women in a FIT screening setting seems reasonable.

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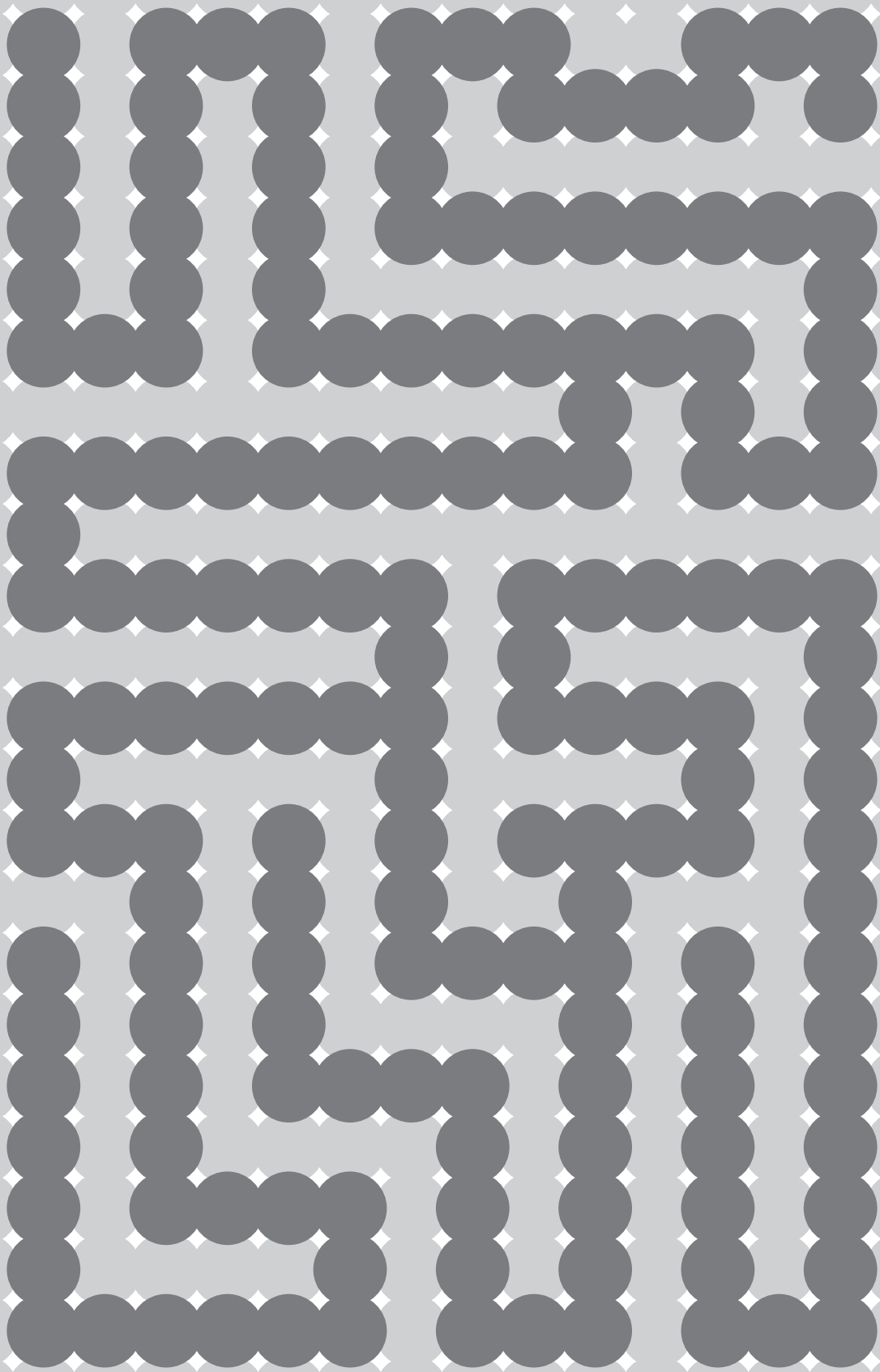

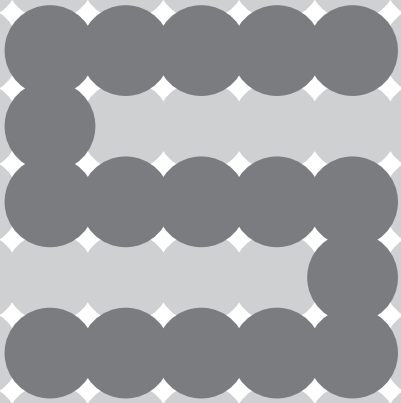

# Do men and women need to be screened differently with faecal immunochemical testing? A cost-effectiveness analysis

Miriam P. van der Meulen, Atija Kapidzic, Monique E. van Leerdam, Alex van der Steen, Ernst J. Kuipers, Manon C. Spaander, Harry de Koning, Lieke Hol, and Iris Lansdorp-Vogelaar

*Submitted*

## ABSTRACT

### Introduction:

Several studies have shown that positivity and detection rates of (advanced) colorectal neoplasia with faecal immunochemical test for haemoglobin (FIT) differ between men and women. Studies systematically evaluating the effect of these differences on FIT screening strategies are lacking.

### Methods:

We estimated gender-specific FIT sensitivity and specificity based on first round positivity and detection rates in men and women observed in a FIT screening pilot (CORERO-1). Subsequently, we used the MISCAN-Colon model to estimate the harms, benefits and costs of 480 different gender-specific FIT screening strategies. We determined whether screening stratified by gender was more cost-effective than offering men and women the same screening strategy.

### Results:

FIT sensitivity for non-advanced adenomas (1.0% versus 19.1% per lesion) and advanced adenomas (26.5% versus 46.7% per lesion) was significantly lower in women than in men. Consequently, annual FIT screening from age 50-80 was less effective in participating women compared to participating men (65% versus 71% mortality reduction). FIT screening resulted in fewer quality adjusted life years (QALYs) gained (91 versus 116) and higher costs (€152,175 versus €40,899) in women compared to men. However, the *incremental* costs and benefits of this strategy compared to less intensive screening strategies were very similar (approximately €6,000 per QALY). Consequently, screening strategies stratified by gender resulted in similar costs and QALYs gained as uniform screening.

### Conclusion:

FIT is less sensitive in women, especially for adenomas, and therefore screening with FIT is also less effective in women. However, FIT screening remains highly cost-effective in women. Despite the differences in sensitivity and effectiveness of FIT, FIT screening stratified by gender does not have benefits in terms of cost-effectiveness over uniform FIT screening.

## INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality in the Western world [1]. Screening can prevent part of these deaths by early detection and treatment of CRC and its precursor lesions. Repeated screening by means of guaiac faecal occult blood testing (gFOBT) reduces CRC mortality by approximately 16% as shown in several trials [2-5]. Recently, faecal immunochemical testing for haemoglobin (FIT) was shown to be associated with higher adherence and diagnostic yield than gFOBT screening [6-11]. As a consequence, several countries, such as Italy, Australia, Japan and the Netherlands, have adopted FIT for population-based screening. Other countries are considering to do so based on ongoing pilots with FIT [12].

Until now, FIT screening strategies have been adopted with the same approach for both sexes despite age and sex disparities in prevalence of advanced neoplasia and a higher life expectancy in women. We previously showed that for primary colonoscopy screening this is a sensible strategy because the lower prevalence of advanced neoplasia in women is compensated by a higher life expectancy [13]. However, this was based on the assumption that test characteristics for colonoscopy did not differ between men and women. For FOBT screening, there are strong indications that the test characteristics do differ between men and women. A Scottish gFOBT screening study reported more screen-detected CRCs in men compared to women, whereas the number of interval CRCs was similar in both groups. This suggested that gFOBT is less sensitive in women than men [14]. Two other studies evaluating characteristics of a FIT prior to a colonoscopy screening found a higher sensitivity of FIT for advanced neoplasia in men compared to women [15, 16]. One of these studies also reported a significant lower specificity in men compared to women [15]. This latter finding was confirmed in the Rotterdam population-based FIT screening CORERO-trial, suggesting a lower specificity based on a higher false positive rate in men compared to women [17].

Differences in test characteristics will probably affect the (cost-)effectiveness of FIT screening in men and women. They might possibly also affect the optimal cut-off, screening age range and interval. Microsimulation modelling can take all these aspects into account and estimate costs and quality adjusted life years (QALYs) gained with various screening strategies. In this study, we therefore used the micro-simulation model MISCAN-Colon to estimate test characteristics of FIT screening for men and women based on the CORERO-trial. Subsequently, we used the model to determine the optimal screening strategies for men and women and to study if screening men and women with a different screening strategy is beneficial in terms of cost-effectiveness.

## MATERIALS AND METHODS

We developed two separate versions of the microsimulation model MISCAN-Colon for men and women to estimate the benefits, harms and costs of FIT-based screening by gender. We estimated sensitivity and specificity of FIT based on the positivity and detection rates in men and women observed in the CORERO-trial. We then simulated populations of men and women screened with various FIT screening strategies to determine the gain in quality adjusted life years (QALYs) and the costs of each screening strategy compared to no screening. We performed an incremental cost-effectiveness analysis to determine efficient screening strategies for men and women. Then, we made a comparison of costs and effects between screening stratified by gender and uniform screening strategies.

### The CORERO-trial

The CORERO-1 trial was a randomized controlled trial comparing attendance and detection rates of gFOBT, FIT and sigmoidoscopy at first round screening. For the current study we only used the data of FIT screening. Details from this trial have been described elsewhere [8, 9]. In short, screening-naïve subjects aged 50-74 years, living in the southwest of the Netherlands were selected through municipal population registers. Screenees assigned in the FIT study arm received a kit with a single FIT (OC-sensor Micro, Eiken Chemical, Japan). A cut-off of 50 ng haemoglobin/ml (equivalent to 10 µg haemoglobin/g faeces) was used to indicate a positive test result. This was followed by the recommendation for a diagnostic colonoscopy. In total, 4,969 men and 5,039 women were invited to participate in FIT screening. A total of 59.8% of men and 64.6% of women returned the test. At a cut-off of 50 ng/ml, the positivity rate was higher among men (10.7%) compared to women (6.3%), see Table 1. Also, the detection rates of men were higher: a CRC was found in 0.63% of men versus 0.35% of women, advanced adenomas were found in 3.8% of men versus 1.8% of women, and non-advanced adenomas in

**Table 1** Observed and simulated positivity rates and detection rates of the FIT with a cut-off of 50 ng/ml

| | | Positivity rate | Detection rate of nonadvanced adenomas | Detection rate of advanced neoplasia |
|---|---|---|---|---|
| **Men** | Observed N= 2857 | 10.7% | 2.56% | 4.38% |
| | Simulated with equal FIT characteristics | 8.60% | 1.80% | 3.48% |
| | Simulated with genderspecific FIT characteristics | 10.75% | 2.55% | 4.38% |
| **Women** | Observed N= 3129 | 6.30% | 0.86% | 2.17% |
| | Simulated with equal FIT characteristics | 7.89% | 1.50% | 2.72% |
| | Simulated with genderspecific FIT characteristics | 6.29% | 0.86% | 2.17% |

2.6% of men versus 0.9% of women. The positive predictive value (PPV) for advanced neoplasia was the same in men (42.1%) and women (37.0%) (p=0.265). Positivity rates, detection rates and the PPV at higher cut-offs can be found elsewhere [17].

**MISCAN-Colon**

The MISCAN-Colon model has been extensively described elsewhere in previous publications [18-20], its standardised model profile is available online [21] and in the appendix. In brief, the MISCAN-Colon model simulates the relevant life histories of a large population of individuals from birth to death. CRC arises in this population according to the adenoma-carcinoma sequence [19, 22]. More than one adenoma can occur in an individual and each adenoma can independently develop into a CRC. Adenomas may progress in size from small (≤ 5 mm) to medium (6-9 mm) to large (≥ 10 mm). Although most adenomas will never turn into cancer, some will eventually become malignant. Cancer starts as a symptomless process and can progress from localized cancer stage I to metastasized cancer stage IV. In every stage, there is a probability of the CRC being diagnosed due to the development of symptoms versus symptomless progressing into the next stage. Once CRC has been clinically diagnosed, survival depends on the stage in which the cancer was detected. The 5-year survival rate is on average 90% if the disease is diagnosed while still localised, 68% for regional disease, and less than 10% for disseminated disease. At any time during the development of the disease, the process may be interrupted because a person dies of other causes.

FIT screening can lead to detection of colorectal neoplasia before clinical diagnosis; a screened individual with a positive FIT will be referred for a colonoscopy for the detection and removal of adenomas and early-stage cancers. CRC incidence and/or CRC-related mortality can thus be reduced. The life years gained by screening are calculated as the difference in model-predicted life years lived in the population with and without CRC screening.

**Study population**

MISCAN-Colon was calibrated to gender-specific pre-screening data on the age-specific incidence [23] and prevalence of CRC, and multiplicity distribution of adenomas from autopsy studies [24-31]. The size distribution of adenomas was calibrated to the size distribution of adenomas detected in a colonoscopy trial [32]. Finally, MISCAN-Colon was calibrated to reductions in CRC incidence and mortality observed in randomized controlled trials evaluating the effectiveness of screening with either guaiac faecal occult blood tests or a flexible sigmoidoscopy and showed good concordance with the trials results [33]. In this study we modelled the age distribution of the Dutch population aged 25 to 85 years in 2015 and all individuals were followed until death.

### Screening strategies

FIT screening was simulated in the population starting in year 2015. Individuals were offered screening according to different FIT screening schedules varying by:

- Age to start screening: 40, 45, 50, 55, 60 and 65 years
- Age to stop screening: 70, 75, 80 and 85 years
- Screening interval: 1, 1.5, 2 and 3 years

The cut-off level for a positive FIT result varied between 50, 75, 100, 150 and 200 ng/ml. These different screening schedules with varying start and stop ages, intervals, and cut-off levels resulted in a total of 480 different screening strategies per gender.

If adenomas were detected individuals entered a surveillance programme according to the Dutch guidelines for follow-up after polypectomy [34], ie, a colonoscopy after five years or three years. We assumed that surveillance colonoscopies would be performed until at least 75 years of age or until the stop age for screening, whichever was latest. If no adenomas were found at diagnostic colonoscopy, the individuals were assumed to be at low-risk for CRC and did not return to the screening programme until after ten years.

### Attendance

To identify the optimal screening strategies for people that are adherent with screening, we analysed the strategies with full attendance (100%). In the sensitivity analysis, we looked at alternative attendance levels based on the CORERO-1 trial, see Appendix 1.

### Test characteristics

The sensitivity and specificity of FIT were fitted to the positivity and detection rates of men and women observed in the first round of the CORERO-trial, which we discuss in the analysis section. The sensitivity of colonoscopies was assumed to be 75% for adenomas with a diameter of 1-5 mm, 85% for adenomas 6-9 mm, and 95% for adenomas ≥ 10 mm and CRC [35]. The specificity of colonoscopy was assumed to be 90%, thereby assuming that 10% of the population without adenomas or cancer did have hyperplastic polyps, lipomas or other lesions that lead to polypectomy and pathology after colonoscopy.

### Costs

In the base-case analyses, we included screening and treatment costs as presented in Table 2. FIT costs were assumed to be €21.90 based on an internal study. The assumed costs of a colonoscopy were based on estimates in the COCOS-trial: €192 for a negative colonoscopy and €329 for a colonoscopy with polypectomy [36]. Because of the recent discussion on colonoscopy costs in the US [37], we considered costs that were twice and four times as high in a sensitivity analysis. Costs for colonoscopy complications were based on DTC-rates (Diagnosis Treatment Combination), derived from the Dutch Health Care Authority [38]. Costs for treatment of CRC were divided into three clinically relevant

phases of care: initial treatment, continuous care and terminal care. Initial treatment costs were based on DTC rates, except for Oxaliplatin. The costs for Oxaliplatin were derived from the Dutch Health Care Insurance Board [39]. We assumed that during the continuous care phase, individuals would follow the Dutch CRC treatment guidelines [40], and costs for periodic control were based on DTC rates. Terminal care costs were based on a Dutch last-year-of-life-cost-analysis [41]. We assumed that these costs increased with stage at diagnosis, at a rate observed for US patients [42, 43]. Dutch terminal care costs for individuals who died from CRC were approximately 40% of the US costs. We further assumed that terminal care costs of CRC patients who die from other causes were also 40% of the US costs.

**Table 2** Calibrated specificity and per lesion sensitivity of the FIT with a cut-off of 50 ng/ml to CORERO-1 data for men and women

| | Men | Women | Total population |
|---|---|---|---|
| Specificity | 95.0% | 95.9% | 95.5% |
| Sensitivity per nonadvanced adenoma | 19.1% | 1.0%* | 10.0% |
| Sensitivity per advanced adenoma | 46.7% | 26.5% | 34.3% |
| Sensitivity per crc long before clinical diagnosis | 46.7%** | 42.9% | 45.0% |
| Sensitivity per crc short before clinical diagnosis | 78.4% | 77.8% | 79.2% |

* Sensitivity per nonadvanced adenoma in women varied slightly over the cut-offs but did not decrease with a higher cut-off, therefore we decided to use the average sensitivity for each cut-off
** Sensitivity per colorectal carcinoma long before clinical diagnosis was lower then of advanced adenomas at the same cut-off, therefore we assumed the same sensitivity as for advanced adenomas



## Analysis

*Estimating FIT sensitivity and specificity*

FIT sensitivity and specificity were estimated by minimizing the difference between observed and expected (ie, model simulated) trial outcomes. Trial outcomes used for estimation were gender-specific 1) positivity rates, and detection rates of 2) CRC, 3) advanced adenomas and 4) non-advanced adenomas for a total of 8 trial outcomes (4 outcomes for both gender). An advanced adenoma was defined as an adenoma of 10 mm or greater in size, and/or with 25% or greater villous component and/or high-grade dysplasia. The observed detection rate of advanced adenomas was fitted to the detection rate of large (ie, ≥ 10 mm) adenomas in the model, since the model does not incorporate histology.

We modelled sensitivity by giving each lesion a probability to cause a positive FIT. We assumed that the probability that a CRC bleeds and can be detected by FIT (ie, test sensitivity) depends on the time until clinical diagnosis, in concordance with findings for gFOBT. To assess whether FIT sensitivity and specificity significantly differed between

men and women, we estimated FIT characteristics twice: once assuming that sensitivity and specificity were the same for men and women and once assuming gender-specific sensitivity and specificity. FIT characteristics differed significantly between men and women if the goodness-of-fit (GOF) of the model with gender-specific FIT characteristics was significantly better than the GOF of the model assuming equal FIT characteristics for men and women. The GOF of each model was calculated as the sum of deviances between observed and simulated outcomes using the following formula:

$$2 * \left[ obs * \left( ln\left(\frac{obs}{n}\right) - ln\left(\frac{sim}{m}\right)\right)\right] \; + \; 2 * \left[ (n - obs) * \left( ln\left(\frac{n - obs}{n}\right) - ln\left(\frac{m - sim}{m}\right)\right)\right]$$

The difference between the GOFs of the two models is chi-squared distributed with three (difference in number of parameters between the models) degrees of freedom. If the difference in GOF exceeded 7.2, the improvement in GOF was significant and FIT sensitivity and specificity differed significantly between men and women. In that case, we used the model with gender-specific FIT characteristics to determine the optimal FIT screening strategy for men and women.

*Cost-effectiveness analysis*

To estimate the optimal screening strategies for men and women and in the total population, we used the MISCAN-Colon model to estimate costs and number of QALYs gained due to screening compared to the situation without screening for all screening strategies. Costs and QALYs gained were discounted by 3% per year [44]. Strategies that were more costly and less effective than other strategies were ruled out by simple dominance. Strategies that were more costly and less effective than a combination of other strategies were ruled out by extended dominance. The remaining strategies were not dominated and considered 'efficient'. On a plot of costs versus QALYs gained (Figures 1 and 2), the line that connects the efficient strategies is called the efficient frontier, which implies that all dominated strategies lie below this line. The incremental cost-effectiveness ratio (ICER) of an efficient strategy was determined by comparing its additional costs and effects to those of the next less costly and less effective efficient strategy. An ICER of less than €20,000 was assumed to be cost-effective.

*Screening strategies stratified by gender*

Finally, to determine the benefit of screening stratified by gender on a population level, we combined strategies on the cost-efficiency frontier of men and with strategies on the cost-efficiency frontier of women, based on the ICER. For this purpose, we first combined the strategy with the lowest ICER for either men or women with a strategy of no screening in the other gender. We subsequently combined screening strategies with a similar ICER in both genders. The costs and QALYs gained for men and women were summed

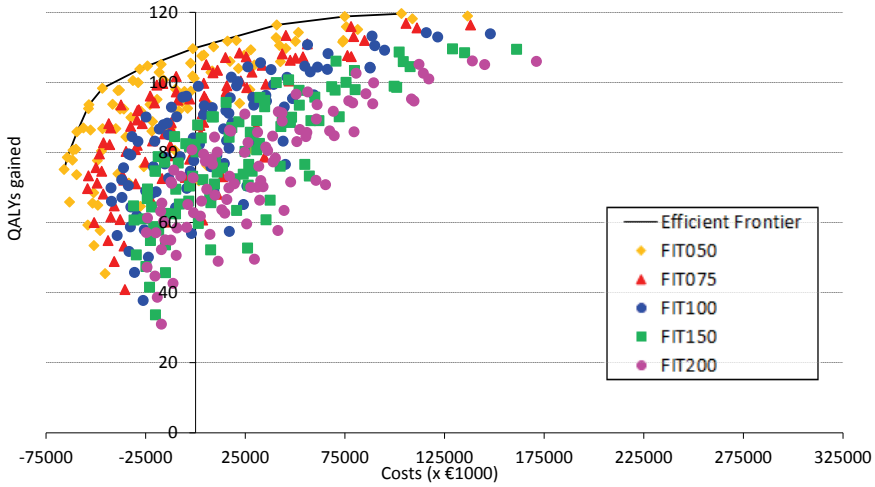


**Figure 1** Costs and QALYs gained per 1,000 particiating men of FIT with 5 different cut-offs and with different starting and stopping age and screening interval, 3% discounted

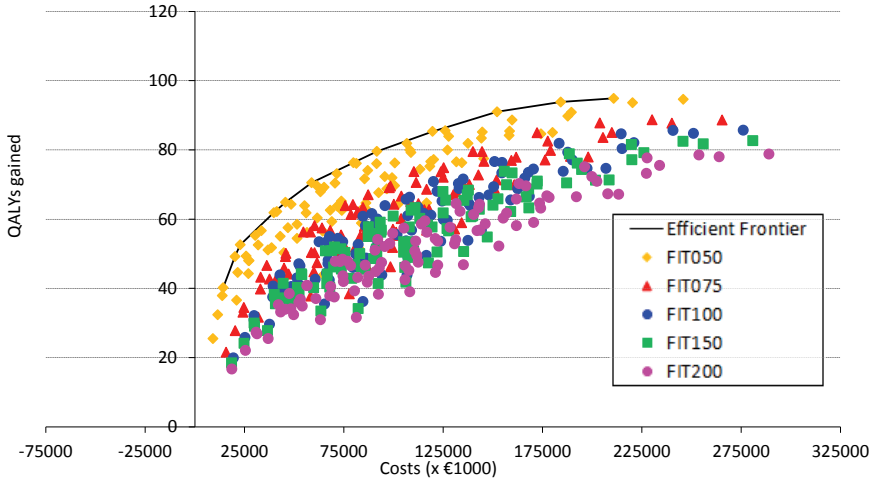


**Figure 2** Costs and QALYs gained per 1,000 particiating women of FIT with 5 different cut-offs and with different starting and stopping age and screening interval, 3% discounted

and compared to the cost-efficient screening strategies of uniform screening in the total population for each of these strategy combinations.

### Sensitivity analysis

We performed five sensitivity analyses on different test characteristics of FIT: (i) we assumed only a difference in specificity between men and women; (ii) we assumed only

sensitivity differed, and (iii) we assumed no difference in sensitivity and specificity of FIT between men and women; (iv) we assumed a difference in sensitivity of CRC between men and women similar to the difference in sensitivity of advanced adenomas; (v) we assumed that a percentage of adenomas do not bleed and can therefore never be detected by FIT, unless they grow. Besides FIT characteristics, we performed sensitivity analyses on attendance, colonoscopy costs, treatment costs and discounting factor, see Appendix 1.

## RESULTS

### FIT characteristics

When we replicated the CORERO-1 trial with equal FIT characteristics for men and women, the simulated positivity rate and detection rates were higher in men than in women due to the difference in prevalence of colorectal neoplasia (Table 1). The simulated positivity and detection rates were however lower than the observed rates in men and vice versa in women. To replicate the observed FIT positivity and detection rates by gender (Table 1 and Appendix 2), we had to assume that FIT specificity was lower for men than women at a cut-off of 50 ng/ml (FIT 50) (95.0% versus 95.9%), while specificity was similar in higher cut-offs (Table 2). Sensitivity per advanced and non-advanced adenoma was higher for men than for women at each cut-off (FIT 50: 46.7% versus 26.5% per advanced adenoma and 19.1% versus 1.0% per non-advanced adenoma). The sensitivity for CRC was similar in men and women (FIT 50: 46.7% versus 42.9% per CRC long before clinical diagnosis and 78.4% versus 77.8% per CRC short before clinical diagnosis) (Table 2). When the CORERO-1 trial was replicated with these FIT characteristics, the simulated positivity and detection rates were indeed close to the observed rates in men and women (Table 1). The goodness-of-fit (GOF) of reproducing the CORERO-1 trial significantly improved with gender-specific test characteristics compared to equal test characteristics for men and women (0.008 compared to 56.3, difference of 56.3).

### Screening outcomes

Annual FIT 50 screening between 50 and 75 years led to more profound reduction in CRC incidence and mortality in men than in women (Table 3). The relative difference in incidence reduction between men and women (52.5% versus 44.1%; relative difference 19.0%) was greater than the difference in mortality reduction (71.3% versus 65.1%; relative difference 9.6%). Women had less life years gained, less life years gained spent in therapy and less QALYs than men. The screening programme, including also diagnostic and surveillance colonoscopies and complications, cost €423,536 in men and €389,937 in women. The cost-savings due to avoided treatment costs were higher in men than

**Table 3** Outcomes of an annual screening programme with FIT with a cut-off of 50 ng/ml, screening from age 50-80 years per 1,000 participants (100% attendance)

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | **Screen** | **No screen** | **Difference** | **Screen** | **No screen** | **Difference** |
| CRC incidence | 34.99 | 73.60 | 52.47 | 33.52 | 59.93 | 44.07 |
| CRC deaths | 11.51 | 40.17 | 71.34 | 12.07 | 34.61 | 65.13 |
| QALYs gained* | | | 116 | | | 91 |
| Life years lost* | 116.19 | 228.01 | -111.82 | 120.04 | 212.79 | -92.76 |
| Life years in therapy* | 271.64 | 279.91 | -8.27 | 267.47 | 243.95 | 23.52 |
| Lifetime complications in screening programme | 3.58 | | 3.58 | 2.86 | | 2.86 |
| Lifetime diagnostic colonoscopies after positive FIT | 848.50 | 73.60 | 774.90 | 740.96 | 59.93 | 681.03 |
| Number Needed to Scope to prevent one death | 54.08 | | | 54.84 | | |
| Screening costs (€)* | 181,841 | 0 | 181,841 | 207,728 | 0 | 207,728 |
| Diagnostic costs (€)* | 98,663 | 0 | 98,663 | 64,882 | 0 | 64,882 |
| Surveillance costs (€)* | 139,963 | 0 | 139,963 | 114,931 | 0 | 114,931 |
| Complications costs (€)* | 3,069 | 0 | 3,069 | 2,397 | 0 | 2,397 |
| Total screening costs | 423,536 | 0 | 423,536 | 389,937 | 0 | 389,937 |
| Treatment costs (€)* | 588,168 | 970,816 | -382,647 | 551,333 | 789,096 | -237,762 |
| Total costs (€)* | 1,011,705 | 970,816 | 40,889 | 941,270 | 789,096 | 152,175 |

* 3% discounted

**Table 4** Screening strategies on the cost-efficiency frontier in men, 3% discounted

| **Cut-off** | **Start age** | **Stop age** | **Interval** | **# Screens** | **Costs*** | **QALY gained*** | **Costs (€)/ QALY gained** | **ICER** |
|---|---|---|---|---|---|---|---|---|
| FIT 050 | 60 | 70 | 2 | 6 | -65,871 | 75 | -877 | -877 |
| FIT 050 | 60 | 69 | 1.5 | 7 | -64,340 | 79 | -819 | 443 |
| FIT 050 | 55 | 69 | 2 | 8 | -59,464 | 86 | -692 | 668 |
| FIT 050 | 55 | 70 | 1.5 | 11 | -53,394 | 94 | -570 | 784 |
| FIT 050 | 55 | 74.5 | 1.5 | 14 | -46,640 | 98 | -474 | 1,439 |
| FIT 050 | 55 | 79 | 1.5 | 17 | -27,889 | 104 | -269 | 3,439 |
| FIT 050 | 50 | 74 | 1.5 | 17 | -24,064 | 105 | -230 | 4,210 |
| FIT 050 | 50 | 80 | 1.5 | 21 | -1,214 | 110 | -11 | 4,609 |
| FIT 050 | 50 | 80 | 1 | 31 | 40,889 | 116 | 351 | 6,219 |
| FIT 050 | 45 | 80 | 1 | 36 | 74,940 | 119 | 631 | 14,152 |
| FIT 050 | 40 | 80 | 1 | 41 | 103,434 | 120 | 865 | 35,820 |

* Per 1,000 participants

women (€382,647 savings versus €237,762 savings). Overall, screening resulted in lower costs in men compared to women (€40,889 versus €152,175).

When all strategies were considered (also varying screening age range and interval), costs were higher and life years gained lower in women compared to men for all strategies (Figures 1 and 2). FIT 50 strategies resulted in more QALs gained and lower total costs than the strategies with higher cut-offs for both genders (Figures 1 and 2). Therefore, higher cut-offs were ruled out by simple dominance. From the least intensive strategy on the cost-efficiency frontier to the most intensive strategy on the cost-efficiency frontier (Tables 4 and 5), the interval varied from 2-1 year(s) in men and from 3-1 year(s) in women. The starting age varied from 60-40 years in both men and women, the screening strategy starting at 40 years had an ICER above the Dutch threshold of €20,000 per QALY gained in both men and women and was therefore no longer considered cost-effective. The age to stop screening varied from 69-80 years in both genders.

In women, one strategy with a three-year interval was cost-efficient, while in men only strategies with an interval of two years or less were cost-efficient. Furthermore, the starting age of efficient strategies was slightly higher in women. For instance, screening yearly between 55-80 years was cost-efficient in women, while in men cost-efficient strategies with a one-year interval started at age 50 or younger. However, there was also overlap in efficient strategies, as seven screening strategies were on the cost-efficiency frontier of both men and women (Table 4 and 5). Screening with less intensive strategies had a smaller ICER in men than in women, eg, screening between 55-70 years with a 1.5-year interval had an ICER of €784 in men versus €1,977 in women, while the ICER of women was similar to that of men in the more intensive screening strategies (eg, annual screening between 50-80 years had an ICER of €6,219 in men and €5,729 in women).

**Table 5** Screening strategies on the cost-efficiency frontier in women, 3% discounted

| Cut-off | Start age | Stop age | Interval | # Screens | Costs* | QALY gained* | Costs (€)/ QALY gained | ICER |
|---|---|---|---|---|---|---|---|---|
| FIT 050 | 60 | 69 | 3 | 4 | 14,267 | 40 | 355 | 355 |
| FIT 050 | 60 | 70 | 2 | 6 | 20,213 | 49 | 411 | 660 |
| FIT 050 | 60 | 69 | 1.5 | 7 | 22,870 | 53 | 435 | 781 |
| FIT 050 | 60 | 70 | 1 | 11 | 39,761 | 62 | 643 | 1,819 |
| FIT 050 | 55 | 70 | 1.5 | 11 | 45,623 | 65 | 704 | 1,977 |
| FIT 050 | 55 | 74.5 | 1.5 | 14 | 58,807 | 71 | 834 | 2,311 |
| FIT 050 | 55 | 75 | 1 | 21 | 91,601 | 80 | 1151 | 3,637 |
| FIT 050 | 55 | 80 | 1 | 26 | 119,719 | 85 | 1403 | 4,854 |
| FIT 050 | 50 | 80 | 1 | 31 | 152,175 | 91 | 1672 | 5,729 |
| FIT 050 | 45 | 80 | 1 | 36 | 184,237 | 94 | 1963 | 11,388 |
| FIT 050 | 40 | 80 | 1 | 41 | 210,798 | 95 | 2222 | 25,250 |

* Per 1,000 participants

Even with the less intensive strategies, the ICERs of men and women did not differ that much that it was more cost-effective to screen men every 1.5 years before screening women every 2 years for example. The ICER of the second screening strategy on the cost-efficiency frontier of men was €443, while the ICER of the first strategy on the cost-efficiency frontier for women was €355. This indicates that introducing FIT screening in women instead of intensifying FIT screening in men will result in more QALYs gained per extra euro spend. The most effective strategy with an ICER below the Dutch threshold of €20,000 per QALY gained was annual screening at a cut-off of 50 ng Hb/ml between 45-80 years old for both genders.

**Screening in the total population**

We combined the strategies on the cost-efficiency frontier for men and women based on ICER to a total of 22 screening strategies (Figure 3, Appendix Table 3). Four of these strategies included the same screening strategy for men and women. These screening strategies were all also on the cost-efficiency frontier of the total population (screening from 55 to 75 with 1.5-year interval and screening from 40, 45 or 50 to 80 with a one-year interval). The least intensive strategy for screening stratified by gender consisted of screening men only. In the less intensive screening strategies screening stratified by gender was dominating screening uniformly, albeit the difference was small. For example, screening both men and women every 3 years from 60 to 69 years gained less QALYs (53) with fewer savings (€24,095) than screening men every 2 years from 60 to 70 years and screening women every 3 years from 60 to 69 years (57 QALYs with €25,396



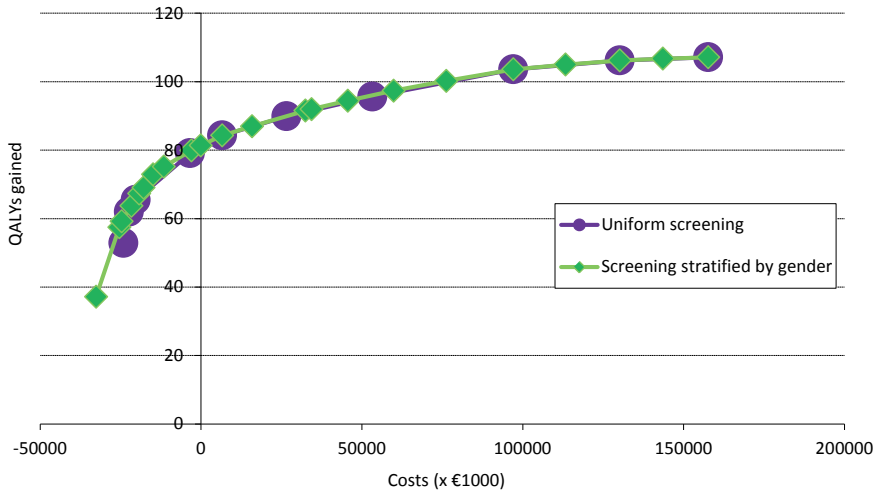


**Figure 3** Costs and QALYs gained of strategies on the cost-efficiency frontier per 1,000 participants with uniform screening and screening stratified by gender, 3% discounted

savings). The widest gap in QALYs gained between the efficient frontiers of uniform and screening stratified by gender occurred at savings of around €15,000: 70 QALYs gained with uniform screening, compared to approximately 73 QALYs gained with screening stratified by gender, a difference of less than 5%. In the more intensive screening programmes, there was no difference between gender stratified and uniform screening.

### Sensitivity analysis

The performed sensitivity analyses resulted in different strategies to be on the efficient frontier. However, in all sensitivity analyses the added value of screening stratified by gender compared to uniform screening was marginal (Appendix 4). At a willingness-to-pay threshold of €20,000 per QALY gained, the difference in QALYs gained between uniform screening and screening stratified by gender did not exceed 2,5 QALY per 1,000 participants (approximately 2.5%).

## DISCUSSION

Our study demonstrates that FIT screening was more (cost-)effective in men than women due to a higher prevalence of colorectal neoplasia among men and a better test sensitivity for adenomas. Nevertheless, screening women remained highly cost-effective. Despite the difference in cost-effectiveness compared to no screening, the ICER of different screening strategies did not differ substantially between men and women and the optimal screening strategies for men and women were often the same or very similar. As a result, FIT screening stratified by gender was not substantially more cost-effective than uniform FIT screening. This finding therefore supports that men and women can be offered the same screening strategy.

Potential explanations for the higher sensitivity of FIT in men are a higher tendency for bleeding in adenomas in men, a greater proportion of adenomas in the left hemicolon in men, gender differences in haemoglobin concentration of blood and a lower colonic transit in women than men [14]. As expected, due to the differences in prevalence and in FIT sensitivity for adenomas, QALYs gained were higher and costs were lower for FIT screening in men compared to women. Given this difference in QALYS gained and costs compared to no screening between men and women, it may come as a surprise that the incremental cost-effectiveness ratios are quite similar between sexes. The cost-effectiveness of intensifying screening is however determined by the yield of the additional screening rounds. At the first screening round, men have a much higher prevalence of (advanced) neoplasia than women, but during each subsequent screening round, the prevalence of (advanced) neoplasia in screened men will decrease and will become lower than the prevalence of advanced neoplasia in unscreened women.

As a consequence, the yield of initiating screening in women is higher than the yield of intensifying screening in men. This effect can be seen from the ICER of the first strategy on the cost-efficiency frontier of women, which is lower than the ICER of the second strategy on the cost-efficiency frontier of men. Thus, it is better to initiate screening in women before intensifying screening in men. A similar thing holds for further intensification of FIT screening: the yield of intensifying screening depends on the residual amount of non-detected neoplasia. The lower sensitivity of FIT in women necessitates more frequent screening, while the lower initial prevalence of neoplasia might compensate this. Therefore, several screening strategies were on the cost-efficiency frontiers of both men and women and had a similar ICER, especially in the more intensive screening programmes. The screening strategy with the most QALYs gained that was still cost-effective was also the same in men and women.

Our study findings are in line with one previous study estimating FIT sensitivity and specificity by testing with FIT prior to colonoscopy [15]. This German study, like ours, found a lower per person sensitivity for advanced neoplasia of 30.7% for women compared to 47.7% for men. Our sensitivity estimates may seem lower than these estimates, but our values concern a per lesion sensitivity. A screenee can have multiple lesions each with a probability to cause a positive FIT and a FIT can be positive for other reasons than colorectal neoplasia (eg, haemorrhoids). Therefore, the sensitivity on a person-level is higher than the per-lesion sensitivity. The per person sensitivity of advanced neoplasia corresponding with the estimated per-lesion sensitivity and specificity, calculated from the model output, is quite similar to the German study (32.5% for women, versus 55.4% for men).

To our knowledge, no other cost-effectiveness analyses have been performed that determined the optimal FIT screening strategy by gender nor assessing the benefit of FIT screening stratified by gender compared to uniform screening. In an earlier study we showed no benefit for screening stratified by gender with colonoscopy screening [13], but in contrast to the current analysis we assumed the primary screening test (colonoscopy in that study, FIT in this study) to have equal test characteristics in men and women. In an earlier cost-effectiveness analysis we already showed a cut-off of 50 ng/ml is most cost-effective in the total population [45]. Even though the sensitivity and specificity of FIT differs between men and women, our study showed a cut-off of 50 ng/ml is most cost-effectiveness in both genders. In an earlier cost-effectiveness analysis we already showed a cut-off of 50 ng/ml is most cost-effective in the total population [45]. Even though the sensitivity and specificity of FIT differs between men and women, our study showed a cut-off of 50 ng/ml is most cost-effectiveness in both genders.

**Limitations**

Two limitations are noteworthy. First, we assumed that all differences in the prevalence of adenomas and CRC incidence between men and women were caused by a difference in adenoma onset and probability to progress to CRC. Furthermore, we assumed no differences in dwelling time of adenomas. However, if the relative risk of adenomas is the same as the relative risk of CRC in men compared to women, it is highly likely that the dwelling time of adenomas does not differ much. In a German study we saw a relative risk of non-advanced adenomas similar to the relative risks of CRC in the Netherlands in the corresponding age group (RR 1.5) [15]. Second, we did not assume a different degree of correlated FIT results over rounds between the genders, even though we introduced that a proportion of adenomas are non-bleeding adenomas in a sensitivity analysis, this proportion did not differ between men and women. If this proportion does differ, it might also have influence on the preferred screening ages and interval, in theory making differential screening in men and women more beneficial. There are not enough data yet to study this phenomenon for men and women separately and there are no aetiological reasons to assume a difference between the genders.

**Implications**

Various investigators have argued that CRC screening should be stratified based on gender because of the difference in prevalence of (advanced) neoplasia [46, 47] and the gender related differences in FIT accuracy [14]. Our study shows that the added value of gender-based screening is at most marginal. In less intensive screening programmes, screening stratified by gender is only slightly more cost-effective than screening men and women with the same screening strategy, while for more intensive screening programmes the optimal strategy is often the same in men and women. Screening by gender also has disadvantages: it might complicate the organization of the screening programme and may even result in lower attendance. Men and women may be confused by the differential recommendations to the point that they no longer adhere to the recommendations. Even a slight impact of stratified screening recommendations on adherence will easily offset its marginal benefit. On the other hand, gender-based screening may increase adherence with screening recommendations because participants feel that the recommendations are better tailored to their risk.

**Future research**

Future research is needed in this area to determine what the impact of risk-stratified screening is on adherence. Another area for future research is to evaluate the comparative effectiveness of FIT screening and other screening modalities in men and women separately. Since sensitivity of FIT is lower in women than men, the comparative effectiveness of FIT with other screening modalities might be different. The additional

sensitivity of colonoscopy compared to FIT for example is higher in women compared to men, while earlier studies showed not much difference in cost-effectiveness between a FIT screening programme and a colonoscopy screening programme [48]. If the lower sensitivity of FIT in women does not apply to other stool-based tests, the comparative effectiveness of newer tests such as stool-DNA-tests, could also be different than in men.

**Conclusion**

In conclusion, this study shows that the effectiveness of FIT screening is higher in men than in women due to a higher FIT sensitivity and a higher prevalence of neoplasia in men. However, optimal screening strategies do not differ much in men and women with respect to interval, age range and FIT cut-off. The most effective FIT screening strategy at a threshold of €20,000 per QALY gained is the same for both men and women. It is therefore not necessary to stratify FIT screening by gender, as stratified screening does not have benefits in terms of cost-effectiveness over uniform FIT screening.

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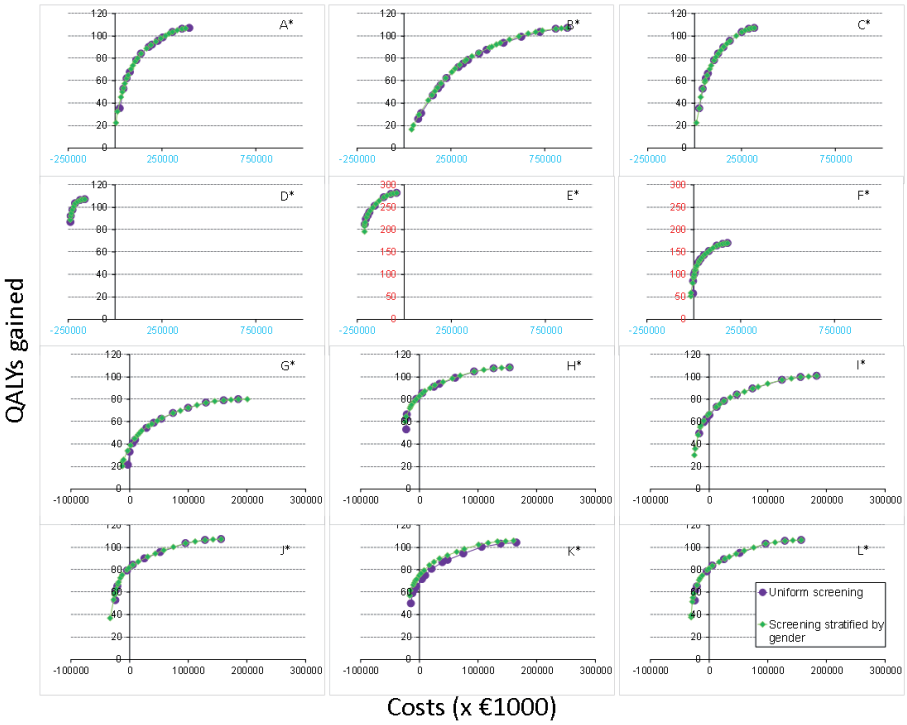



**Appendix 1** Costs and QALYs gained of strategies on the cost-efficiency frontier per 1,000 participants with uniform screening and screening stratified by gender with different assumptions in the sensitivity analysis, 3% discounted if not other specified

*Sensitivity analysis with: A, double colonoscopy costs; B, quadruple colonoscopy costs; C, double treatment costs; D, half treatment costs; E, 0% discounting; F, QALYs gained 1.5% discounted and costs 4% discounted; G, attendance as observed in the CORERO-trial, H, equal FIT characteristics for men and women; I, systematic FIT failure; J, differing sensitivity in men and women but equal specificity; K, differing specificity in men and women but equal sensitivity; L, differing CRC sensitivity additional to other sensitivity and specificity differences

**Appendix 2** Summary of model assumptions of the base-case and sensitivity analyses

| Variable | Base Analysis | Sensitivity analysis |
|---|---|---|
| **Test characteristics** | | |
| ***FIT*** | Calibrated to CORERO-1 data separately for men and women, see Appendix 2 | Equal test characteristics, see Appendix 2<br>Only difference in sensitivity/Only difference in specificity<br>Difference in CRC sensitivity with same rate as difference in advanced adenomas |
| | No systematic FIT failure | Proportion of adenomas with systematic FIT failure (non-bleeding adenomas) |
| ***Sensitivity colonoscopy*** | | |
| 1-5 mm adenomas | 75% | |
| 6-9 mm adenomas | 85% | |
| ≥10 mm adenomas | 95% | |
| carcinomas | 95% | |
| ***Specificity*** | 90% | |
| **Adherence** | | |
| Screening test | 100% | 59.8% for men and 62.2% for women |
| Diagnostic test | 100% | 97.1% for men and 95.6% for women |
| Surveillance test | 100% | 80% |
| **Quality of life loss** | | |
| Colonoscopy | 2 days lost per colonoscopy | |
| CRC from diagnosis onward | Initial treatment stage 1 till IV: 0.12; 0.18; 0.24; 0.70<br>Continuous care stage 1 till IV: 0.12; 0.18; 0.24; 0.70<br>Terminal care death by CRC: 0.70<br>Terminal care death by other cause: 0.12; 0.18; 0.24; 0.70 | |
| Fatal complications after colonoscopy | $3.29^{\wedge}10^{5}$ in positive colonoscopies | |

**Appendix 1** Summary of model assumptions of the base-case and sensitivity analyses (continued)

| Variable | Base Analysis | | | | Sensitivity analysis |
|---|---|---|---|---|---|
| **Screening costs** | | | | | |
| FIT | €21.90 | | | | |
| Diagnostic costs inside screening programme (positive/negative) | €329/€192 | | | | Double colonoscopy costs/quadruple colonoscopy costs |
| Costs complications after colonoscopy | €1372 | | | | |
| **Treatment costs** | Initial treatment | Continuous care | Terminal care death CTC | Terminal care death other cause | Half/Double |
| | €13,773 | €375 | €19,282 | €4,848 | |
| | €18,180 | €375 | €19,282 | €4,407 | |
| | €20,935 | €375 | €20,384 | €5,729 | |
| | €27,546 | €375 | €27,546 | €15,426 | |
| **Discounting** | 3% | | | | No discounting/1.5% discounting on QALY's and 4% on costs |

**Appendix 3** Calibrated specificity and sensitivity per adenoma of the FIT to CORERO-1 data for men and women

| | Men | Women | Total population |
|---|---|---|---|
| **FIT 75 ng Hb/mL** | | | |
| Specificity | 97.1% | 97.1% | 97.1% |
| Sensitivity per nonadvanced adenoma | 14.2% | 1.0%* | 7.1% |
| Sensitivity per advanced adenoma | 42.1% | 20.3% | 29.7% |
| Sensitivity per CRC long before clinical diagnosis | 43.2%** | 37.8%** | 41.1% |
| Sensitivity per CRC short before clinical diagnosis | 78.0%** | 73.8%** | 76.4% |
| **FIT 100 ng Hb/mL** | | | |
| Specificity | 97.7% | 97.8% | 97.8% |
| Sensitivity per nonadvanced adenoma | 11.3% | 1.0%* | 6.1% |
| Sensitivity per advanced adenoma | 38.1% | 18.1% | 26.8% |
| Sensitivity per CRC long before clinical diagnosis | 43.2% | 37.8% | 42.4% |
| Sensitivity per CRC short before clinical diagnosis | 78.0% | 73.8% | 77.4% |
| **FIT 150 ng Hb/mL** | | | |
| Specificity | 98.5% | 98.3% | 98.4% |
| Sensitivity per nonadvanced adenoma | 9.0% | 1.0%* | 4.9% |
| Sensitivity per advanced adenoma | 33.1% | 17.3% | 24.2% |
| Sensitivity per CRC long before clinical diagnosis | 35.4% | 32.4% | 35.0% |
| Sensitivity per CRC short before clinical diagnosis | 71.8% | 69.0% | 71.4% |
| **FIT 200 ng Hb/mL** | | | |
| Specificity | 98.7% | 98.7% | 98.7% |
| Sensitivity per nonadvanced adenoma | 7.8% | 1.0%* | 4.5% |
| Sensitivity per advanced adenoma | 30.0% | 15.6% | 21.9% |
| Sensitivity per CRC long before clinical diagnosis | 30.0%*** | 27.0% | 28.5% |
| Sensitivity per CRC short before clinical diagnosis | 63.8% | 63.2% | 65.0% |

* Sensitivity per nonadvanced adenoma in women varied slightly over the cut-offs but did not decrease with a higher cut-off, we decided to use the average sensitivity for each cut-off

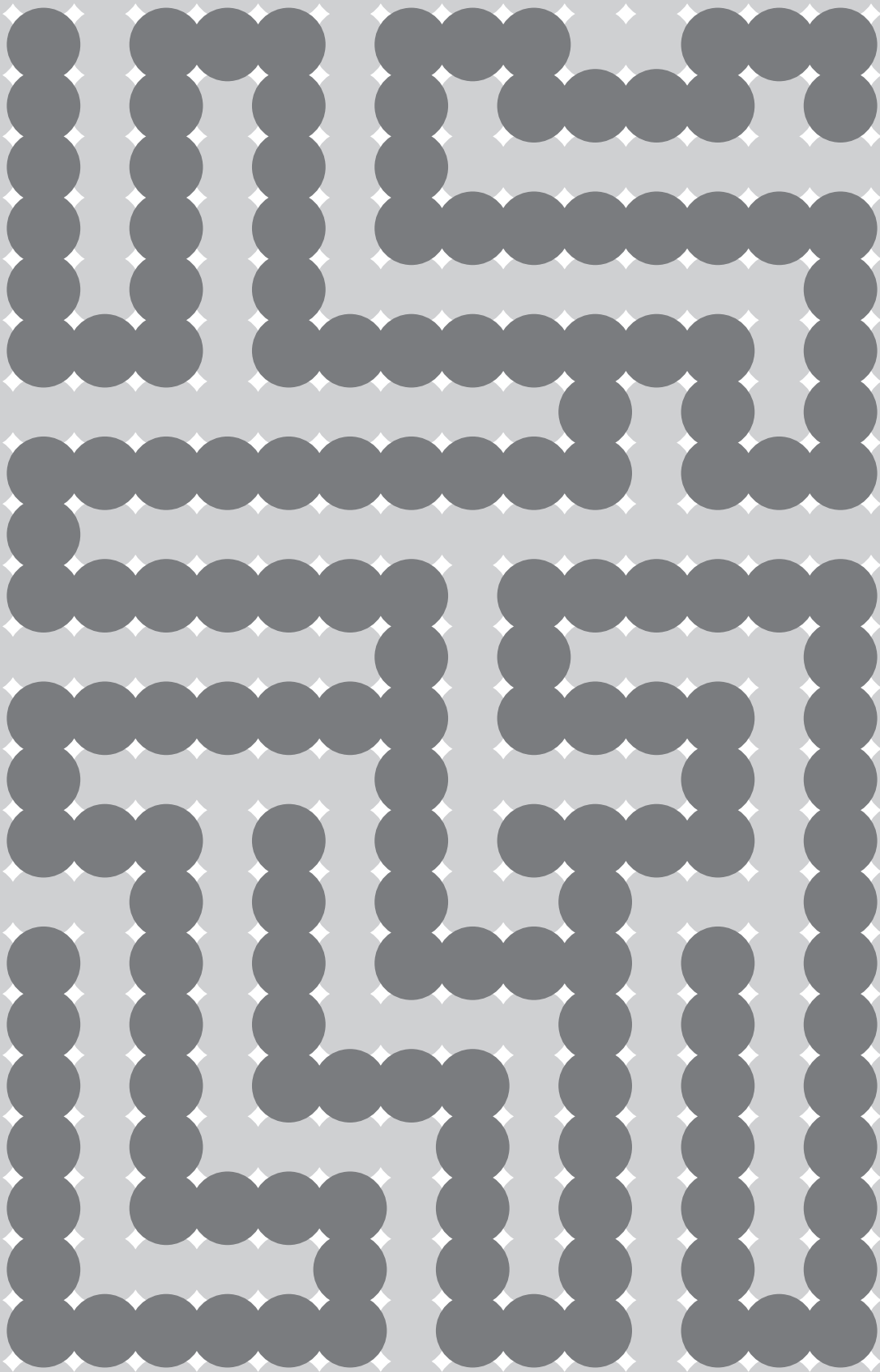
** Sensitivity per colorectal carcinoma was lower than of colorectal carcinoma at a higher cut-off, therefore we assumed the same sensitivity as the higher cut-off

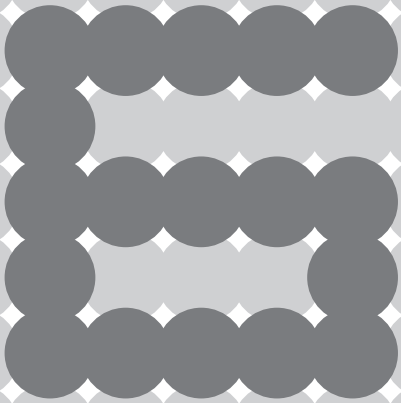
*** Sensitivity per colorectal carcinoma long before clinical diagnosis was lower than of advanced adenomas at the same cut-off, therefore we assumed the same sensitivity as for advanced adenomas

**Appendix 4** Screening strategies on the cost-efficiency frontier with uniform screening and all combined strategies for screening stratified by gender, 3% discounted

| Cut-off | Start age | | Stop age | | Interval | | # Screens | | Costs* | QALY gained* | Costs/ QALY gained | ICER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **M** | **W** | **M** | **W** | **M** | **W** | **M** | **W** | | | | |
| **Differential screening** | | | | | | | | | | | | |
| FIT 050 | 60 | x | 70 | x | 2 | x | 6 | x | -32,602 | 37 | -877 | -877 |
| FIT 050 | 60 | | 70 | | 2 | 3 | 6 | 4 | -25,396 | 57 | -442 | 355 |
| FIT 050 | 60 | | 70 | | 1.5 | 3 | 7 | 4 | -24,638 | 59 | -416 | 443 |
| FIT 050 | 60 | | 70 | | 1.5 | 2 | 7 | 6 | -21,634 | 64 | -339 | 660 |
| FIT 050 | 55 | 60 | 70 | | 2 | | 8 | 6 | -19,222 | 67 | -285 | 668 |
| FIT 050 | 55 | 60 | 70 | | 2 | 1.5 | 8 | 7 | -17,880 | 69 | -259 | 705 |
| FIT 050 | 55 | 60 | 70 | | 1.5 | | 11 | 7 | -14,875 | 73 | -204 | 783 |
| FIT 050 | 55 | 60 | 75 | 70 | 1.5 | | 14 | 7 | -11,533 | 75 | -153 | 1,031 |
| FIT 050 | 55 | 60 | 75 | 70 | 1.5 | 1 | 14 | 11 | -3,002 | 80 | -38 | 1,819 |
| FIT 050 | 55 | | 75 | 70 | 1.5 | | 14 | 11 | -41 | 81 | -1 | 1,977 |
| FIT 050 | 55 | | 75 | | 1.5 | | 14 | | 6,618 | 84 | 79 | 2,311 |
| FIT 050 | 55 | | 80 | 75 | 1.5 | | 17 | 14 | 15,898 | 87 | 183 | 3,439 |
| FIT 050 | 55 | | 80 | 75 | 1.5 | 1 | 17 | 21 | 32,461 | 92 | 355 | 3,637 |
| FIT 050 | 50 | 55 | 75 | | 1.5 | 1 | 17 | 21 | 34,355 | 92 | 373 | 4,210 |
| FIT 050 | 50 | 55 | 80 | 75 | 1.5 | 1 | 21 | | 45,664 | 94 | 484 | 4,609 |
| FIT 050 | 50 | 55 | 80 | | 1.5 | 1 | 21 | 26 | 59,866 | 97 | 615 | 4,854 |
| FIT 050 | 50 | | 80 | | 1.5 | 1 | 21 | 31 | 76,258 | 100 | 761 | 5,286 |
| FIT 050 | 50 | | 80 | | 1 | | 31 | | 97,096 | 104 | 937 | 6,219 |
| FIT 050 | 50 | 45 | 80 | | 1 | | 31 | 36 | 113,290 | 105 | 1079 | 11,388 |
| FIT 050 | 45 | | 80 | | 1 | | 36 | | 130,143 | 106 | 1226 | 14,152 |
| FIT 050 | 40 | 45 | 80 | | 1 | | 41 | 36 | 143,558 | 107 | 1345 | 25,250 |
| FIT 050 | 40 | | 80 | | 1 | | 41 | | 157,660 | 107 | 1472 | 35,820 |
| **Uniform screening** | | | | | | | | | | | | |
| FIT 050 | 60 | | 69 | | 3 | | 4 | | -24,059 | 53 | -455 | -455 |
| FIT 050 | 60 | | 70 | | 2 | | 6 | | -22,393 | 62 | -361 | 182 |
| FIT 050 | 60 | | 69 | | 1.5 | | 7 | | -20,293 | 65 | -310 | 612 |
| FIT 050 | 55 | | 70 | | 1.5 | | 11 | | -3,384 | 79 | -43 | 1,240 |
| FIT 050 | 55 | | 74.5 | | 1.5 | | 14 | | 6,618 | 84 | 79 | 1,922 |
| FIT 050 | 55 | | 79 | | 1.5 | | 17 | | 26,551 | 90 | 295 | 3,563 |
| FIT 050 | 50 | | 80 | | 1.5 | | 21 | | 53,283 | 96 | 557 | 4,655 |
| FIT 050 | 50 | | 80 | | 1 | | 31 | | 97,096 | 104 | 937 | 5,506 |
| FIT 050 | 45 | | 80 | | 1 | | 36 | | 130,143 | 106 | 1226 | 12,648 |
| FIT 050 | 40 | | 80 | | 1 | | 41 | | 157,660 | 107 | 1472 | 29,749 |

* Per 1,000 participants





# Quality of life in participants of a colorectal cancer screening programme

Atija Kapidzic, Ida J. Korfage, Leonie van Dam, Aafke H.C. van Roon, Jacqueline C.I.Y. Reijerink, Ann G. Zauber, Marjolein van Ballegooijen, Ernst J. Kuipers, and Monique E. van Leerdam

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## ABSTRACT

### Background:

Little is known about the effect of participating in a CRC screening programme on quality of life (QOL), neither for participants with a negative nor for those with a positive test result. These findings, however, are important to evaluate the impact of CRC screening.

### Methods:

Participants from CRC screening trials were sent a questionnaire, which included validated measures on generic health-related QOL, generic anxiety and screen-specific anxiety. Both faecal immunochemical test (FIT) and flexible sigmoidoscopy (FS) participants, either with negative or positive test results, were addressed.

### Results:

The response rate was 73% (1,289/1,772) for FIT and 78% (536/689) for FS participants, with mean ages varying from 63-66 years. Positive FIT participants had worse physical (PCS-12, 47.1 versus 48.3, p=0.02), but equal mental QOL scores (MCS-12, 51.1 versus 51.6, p=0.26). Positive and negative FS participants had similar QOL scores. Both FIT and FS participants with a positive test result reported more screen-specific anxiety than negative FIT and FS participants. Positive and negative FS participants had similar generic anxiety scores.

### Conclusion:

Our findings indicate that the burden of participating in CRC screening may be limited. Conducting a prospective study to confirm these results is recommended.

## INTRODUCTION

Worldwide, colorectal cancer (CRC) is the third most common malignancy in males and the second most common in females [1]. CRC is the second cause of cancer related death in developed countries [1, 2]. Five-year survival is over 90% when the disease is detected in an early stage (stage I), compared to less than 10% for CRC with distant metastases (stage IV). Population-based screening programmes can reduce CRC-related mortality by early detection and treatment of CRC, but also by removal of pre-malignant lesions (adenoma) [3-5].

Different CRC screening tests are available. These mainly include faecal occult blood tests (FOBTs) and endoscopy, in particular flexible sigmoidoscopy (FS) and colonoscopy. The latter techniques enable visualization of a part or of the entire colon. However, these techniques are more invasive and more expensive than FOBTs. Randomized controlled trials (RCTs) showed that screening by means of FOBTs followed by colonoscopy if indicated, reduces CRC-related mortality by 15–33% [6, 7]. More recently, a RCT with a median follow-up of 11.2 years from the UK showed that once-only FS screening between 55 and 64 years of age can substantially reduce colorectal cancer incidence and mortality [3], although another similar FS screening RCT did not observe a mortality reduction after seven years [8].

Several Western countries have started or are considering introduction of FOBT or FS screening. In both FOBT and FS based screening programmes, participants with a positive test are referred for colonoscopy. In the decision on the introduction of a population-based CRC screening programme, benefits like life-years gained due to early detection and subsequent early treatment need to be outweighed against the burden of screening, such as the anxiety and distress due to participation, both with respect to the invitation and the test itself, as well as related to positive test results, whether truly or false positive. Anxiety in a screened population has previously been assessed for PAP smear results in cervical screening, where scores for generic and screen-specific anxiety were significantly higher in women with an abnormal smear [9]. The only two studies that investigated quality of life (QOL) effects in CRC screening showed that screening did not appear to have adverse emotional effects in the longer term (> 4 weeks) [10, 11]. These studies were focussed on colonoscopy- and FS-based screening. More information on QOL among participants in CRC screening is needed.

In this study, we aimed to assess QOL of participants in a FOBT- and FS-based CRC screening programme. The main research question of the study was whether QOL differed in participants with a positive test result compared to participants with a negative test result and whether QOL differed between participants with true- and false-positive results. Furthermore, we evaluated whether differences in QOL were related to age, gender and social economic status. These findings can help to determine the impact of CRC screening, so quality of life and anxiety of a CRC screening programme can be clarified.

## MATERIALS AND METHODS

### Study population

Between November 2006 and December 2010, two Dutch population-based randomized CRC screening trials (CORERO-I and –II trial) were conducted in the southwest of the Netherlands with a target population of approximately 350,000 inhabitants. Average risk individuals, aged between 50-74 years, were invited and if eligible included for FS or successive rounds of faecal immunochemical test (FIT) screening [12, 13]. Within this cohort we conducted a retrospective observational study between December 2010 and April 2011. We addressed all participants of the CORERO-I or -II trial who had a positive screening test and a random sample of participants with a negative screening test (reference group).

A FIT value of 50 ng/ml or more was considered positive. A positive FS was defined as a sigmoidoscopy that revealed a polyp with a diameter ≥ 10 mm, an adenoma with ≥ 25% villous component or high grade dysplasia, serrated adenoma, ≥ 3 adenomas, ≥ 20 hyperplastic polyps, or CRC [12]. Positive participants were referred for colonoscopy. All positive FIT participants were addressed and an equal number of controls was randomly selected (negative FIT participants). All positive FS participants were addressed as well. Because of power considerations we randomly selected twice as many controls, ie, negative FS participants.

All selected screen participants were addressed with a questionnaire (see below for further details), an informed consent form and an accompanying letter, asking them to complete and return the questionnaire. A reminder was sent four weeks afterwards to all non-respondents. It was clarified in the letter that the choice to not participate in this questionnaire study would not have any consequences for health care or follow-up. Data on the amount of time that had elapsed between participation in the CRC screening programme and completion of the questionnaire were obtained through the regional screening organization. Information on gender, age, marital status, income, education, country of birth and comorbidity was obtained through the questionnaire. Educational level was classified as low (primary school or lower technical education), intermediate or high (college/university degree).

### Content of the questionnaire

The questionnaire included the following validated measures:

Generic HRQoL was assessed through the 12-item Short-Form Health Survey (SF-12) and the EuroQol classification (EQ-5D). The SF-12 consists of 12 items in the physical and mental domains. These 12 items are used to construct physical and mental summary measures (PCS-12 and MCS-12; scoring range from 0-100) [14]. Age- and sex-adjusted SF-12 norm scores are available from Statistics Netherlands [15]).

The EQ-5D classification consists of 5 items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Classification scores can be linked to a utility score with 0 indicating 'death' and 1 indicating 'full health' [16]. The EQ-5D is complemented by a visual analogue scale on current health, the Valuation of Own Health, which is anchored at the lower end (0) by 'worst imaginable health state' and at the upper end (100) by 'best imaginable health state'.

Generic anxiety was assessed by the STAI-6, a validated short version of the State Trait Anxiety Inventory, containing 6 items on, eg, feeling at ease or upset. Scores range from 20 (almost never anxious) to 80 (almost always anxious), with higher scores correlating with greater anxiety. A STAI-score of over 44 defines an individual as highly anxious [17]. To measure the screen-specific anxiety (ie, the psychological impact of a positive CRC screening test) we used the Psychological Consequences Questionnaire (PCQ). The PCQ measures the consequences of screening on three dimensions, ie, emotional, physical and social functioning. Ratings for symptoms within each dimension vary from 0 (not at all) to 3 (quite a lot of time). The added ratings indicate the level of dysfunction with higher scores indicating more dysfunction. Since the subscales are highly correlated, we also report an overall PCQ score (score range 0-36). We used the Dutch version as adapted by Rijnsburger and colleagues [18].

Perceived risk of developing CRC was assessed through a Cancer Worry Scale [19]. The CWS consists of items like 'During the past week, how often have you thought about your own chances of developing cancer?' and; 'During the past week, how often have thoughts about getting cancer affected your mood?'. For each question, participants were given the following four response items: 'Not at all or Rarely', 'Sometimes', 'Often', and 'Almost all the time'.

Furthermore, the questionnaire included items on how people make decisions regarding their health in general and how people look back at the screening procedure as a whole. This last topic contained questions on whether people would participate in the CRC screening programme again and whether participants would recommend participating to a friend or relative.



**Statistical analyses**

In accordance with guidelines missing items in the STAI and PCQ scales were imputed by participants' own average score if at least 50% of these items had been completed [20]. To assess non-response bias we compared gender and age of the respondents with those of the non-respondents. Differences between the groups in background variables, in health-related QOL, generic and screen-specific anxiety scores, worries regarding cancer and in general attitude towards screening were assessed using Mann Whitney U tests for continuous variables and Chi-square tests for categorical ones. We tested the relationship between generic anxiety and screen-specific anxiety scores on the one

hand and the time period that had elapsed since the screening on the other hand by comparing scores of participants who had a screening test 4-12 months before completion of the questionnaire versus 12-24 months versus > 24 months. Furthermore, we examined whether QOL scores differed between FIT participants with a true and false positive test result.

Statistical analyses were performed using SPSS for Windows, version 15. A p-value less than 0.05 (referring to two-sided statistical tests) was considered significant. The ethics review committee of the Erasmus MC, University Medical Centre Rotterdam, approved the research protocol (MEC-2010-411).

## RESULTS

### Response and respondent characteristics

All participants of the CORERO-I and -II trial who had either a positive FIT result (cut-off 50 ng/ml, n=857) or a positive FS (n=227) were sent a questionnaire (n=1,084). A questionnaire was also sent to a randomly selected group of 1,377 participants with a negative screening test (ie, a negative FIT (915 out a total of 7,825 participants) or a negative FS (462 out of a total of 1,971 participants)). All FS participants participated in the CRC screening programme 3 to 5 years prior to filling out the questionnaire, with a mean interval time of 44 months. FIT participants participated in the CRC screening programme varying from five years to four months prior to filling out the questionnaire, with a mean interval time of 15 months and 26 months for negative respectively positive FIT participants (data not shown).

Response rates for FIT and FS participants varied between 73% and 82% (Figure 1). The respondents' characteristics are shown in Table 1. Participants with a positive FIT result were more often male (60.8% versus 46.5%, p<0.001) and were older than participants with a negative FIT result (mean age 65.5 versus 63.0 years, p<0.001). A similar pattern was seen in FS participants: more were male (64.2% versus 57.3% males, p=0.125) and were older of age (mean age 66.1 versus 63.9 years, p<0.001) in the group with a positive test result. No differences were observed with respect to education, income, marital status and country of birth between those with a positive and negative test result. Compared to non-responders, responders in the FIT group were more often male (53% versus 42%, p<0.001). No differences in age existed between these two groups. There were no differences regarding gender distribution and age between FS responders and non-responders (data not shown).

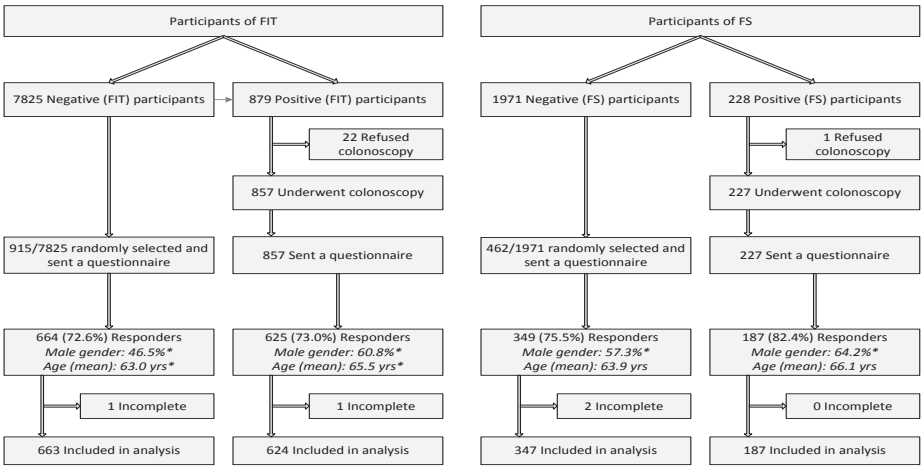


**Figure 1** Flowchart of study responders

* Statistically significant difference ($p < 0.05$) between responders and non-responders within the same screening strategy

**Table 1** Background characteristics of responders by type of CRC screening

| | Faecal immunochemical test | | | Flexible sigmoidoscopy | | |
|---|---|---|---|---|---|---|
| | Negative test result (n=663) | Positive test result (n=624) | p-value | Negative test result (n=347) | Positive test result (n=187) | p-value |
| Age (years) | | | | | | |
| Mean (SD) | 63.0 (± 6.1) | 65.5 (± 6.4) | <0.001 | 63.9 (± 6.3) | 66.1 (± 6.7) | <0.001 |
| Male gender (%) | 308 (46.5) | 380 (60.8) | <0.001 | 199 (57.3) | 120 (64.2) | 0.13 |
| Education (%) | | | 0.15 | | | 0.65 |
| Low | 211 (32.3) | 209 (34.4) | | 106 (31.1) | 61 (33.2) | |
| Medium | 273 (41.8) | 267 (43.9) | | 142 (41.7) | 69 (37.5) | |
| High | 169 (25.8) | 129 (21.2) | | 92 (26.9) | 52 (28.2) | |
| Income (%) | | | 0.08 | | | 0.82 |
| < 22.125 euros | 178 (31.1) | 174 (32.6) | | 86 (28.7) | 52 (31.4) | |
| 22.125 – 44.250 euros | 248 (43.3) | 237 (44.4) | | 130 (43.3) | 71 (42.8) | |
| > 44.250 euros | 147 (25.7) | 123 (23.1) | | 84 (28.0) | 43 (26.0) | |
| Marital status (%) | | | 0.13 | | | 0.18 |
| Married/cohabiting | 571 (87.2) | 523 (84.4) | | 305 (89.2) | 154 (83.7) | |
| Living alone | 84 (12.8) | 97 (15.7) | | 37(10.8) | 30 (16.3) | |
| Country of birth (%) | | | 0.85 | | | 0.41 |
| the Netherlands | 616 (93.5) | 579 (94.3) | | 316 (92.4) | 177 (95.2) | |

CRC: colorectal cancer; SD: standard deviation

## Quality of life scores

*Generic QOL*

SF-12 scores regarding physical health were significantly lower in FIT participants with a positive test result than in those with a negative result, indicating worse functioning in this group (Table 2). Furthermore, positive FIT participants had significantly worse EQ-5D scores and rated their own health worse than participants with a negative test result. QOL scores did not differ between positive and negative FS participants. When comparing the SF-12 scores to the age-adjusted norm scores for the Dutch population, we found that for both FIT and FS participants of 65 years and older, the PCS-12 scores were higher, indicating better physical functioning in participants than in the general

**Table 2** Mean scale scores of responders with a negative and responders with a positive test result

| | **Faecal immunochemical test** | | | **Flexible sigmoidoscopy** | | |
|---|---|---|---|---|---|---|
| | Negative test result (n=663) | Positive test result (n=624) | p-value | Negative test result (n=347) | Positive test result (n=187) | p-value |
| *Generic HRQoL* | | | | | | |
| SF-12 (0-100)* | | | | | | |
| Physical health (PCS-12) | 48.3 (8.9) | 47.1 (9.4) | 0.02 | 48.1 (8.8) | 47.0 (9.3) | 0.20 |
| Mental health (MCS-12) | 51.6 (8.9) | 51.1 (9.2) | 0.26 | 52.0 (8.5) | 50.3 (9.6) | 0.11 |
| EuroQoL* | | | | | | |
| EQ-5D (0-1) | 0.85 (0.19) | 0.82 (0.20) | 0.02 | 0.85 (0.17) | 0.80 (0.24) | 0.13 |
| Rating of own health (0-100) | 77.3 (16.7) | 74.5 (16.9) | <0.001 | 76.5 (16.6) | 72.8 (18.6) | 0.01 |
| *Generic anxiety** | | | | | | |
| STAI-6 (20-80) | 43.8 (5.2) | 43.3 (5.2) | 0.03 | 42.6 (4.8) | 43.3 (4.5) | 0.25 |
| *Screen-specific anxiety** | | | | | | |
| PCQ | | | | | | |
| Emotional scale (0-15) | 1.03 (2.1) | 1.79 (2.7) | <0.001 | 1.29 (2.2) | 1.81 (2.7) | 0.02 |
| Physical scale (0-12) | 0.73 (1.6) | 1.11 (1.9) | <0.001 | 0.87 (1.6) | 1.22 (2.2) | 0.12 |
| Social scale (0-9) | 0.46 (1.2) | 0.78 (1.5) | <0.001 | 0.61 (1.2) | 0.78 (1.6) | 0.56 |
| Total score (0-36) | 2.22 (4.3) | 3.67 (5.4) | <0.001 | 2.77 (4.4) | 3.81 (5.8) | 0.03 |

* For SF-12 and EuroQoL a higher score indicates better health
For Generic anxiety and Screen-specific anxiety a higher score indicates more anxiety

HRQoL: Heath-Related Quality of Life; SF-12: Medical Outcomes Study 12-Item Short Form Health Survey; PCS-12: Physical Component Health Related Quality of Life Scores; MCS-12: Mental Component Health Related Quality of Life Score; EuroQoL: European Quality of Life; EQ-5D: European Quality of Life-5 Dimensions; STAI-6: Six-item State Trait Anxiety Inventory; PCQ: Psychological Consequences Questionnaire

population (CBS StatLine). FIT participants under the age of 65 showed worse physical functioning compared to the general population. No difference was seen for FS participants under the age of 65. The mental health-related QOL-scores were lower than those in the general population, indicating worse mental functioning in our participants (CBS StatLine).

*Generic anxiety and screen-specific anxiety*

The STAI-6 score was significantly lower in FIT participants with a positive test result, indicating less generic anxiety in these participants compared to negative FIT participants (Table 2). STAI-6 scores did not differ between positive and negative FS participants.

**Table 3a** Mean scale scores of responders with a negative test result, for the whole group and per time period passed between participation in the screening programme and filling out the questionnaire

| | **Negative faecal immunochemical test** | | | | |
|---|---|---|---|---|---|
| | Negative test result (n= 663) | 4-12 months | 13-24 months | 25 months or more | p-value** |
| *Generic HRQoL* | | | | | |
| SF-12 (0-100)* | | | | | |
| Physical health (PCS-12) | 48.3 (8.9) | 48.9 (9.0) | 47.6 (9.0) | 50.5 (6.3) | 0.05 |
| Mental health (MCS-12) | 51.6 (8.9) | 51.7 (8.5) | 51.6 (9.2) | 50.4 (9.3) | 0.68 |
| EuroQoL* | | | | | |
| EQ-5D (0-1) | 0.85 (0.19) | 0.85 (0.17) | 0.84 (0.20) | 0.89 (0.17) | 0.28 |
| Rating of own health (0-100) | 77.3 (16.7) | 78.9 (14.9) | 75.5 (18.3) | 82.0 (11.3) | 0.05 |
| *Generic anxiety** | | | | | |
| STAI-6 (20-80) | 43.8 (5.2) | 43.7 (5.4) | 43.9 (5.0) | 44.0 (6.0) | 0.85 |
| *Screen-specific anxiety** | | | | | |
| PCQ | | | | | |
| Emotional scale (0-15) | 1.03 (2.1) | 1.00 (2.1) | 1.06 (2.1) | 0.84 (2.0) | 0.30 |
| Physical scale (0-12) | 0.73 (1.6) | 0.64 (1.4) | 0.84 (1.7) | 0.38 (1.0) | 0.16 |
| Social scale (0-9) | 0.46 (1.2) | 0.43 (1.2) | 0.50 (1.2) | 0.41 (1.6) | 0.44 |
| Total score (0-36) | 2.22 (4.3) | 2.07 (4.1) | 2.40 (4.5) | 1.63 (4.3) | 0.36 |

* For SF-12 and EuroQoL a higher score indicates better health
For Generic anxiety and Screen-specific anxiety a higher score indicates more anxiety

** Indicates the significance level of differences in observed scores between groups that participated in the CRC screening programme 4-12 months, 13-24 months or ≥ 25 months previously

HRQoL: Heath-Related Quality of Life; SF-12: Medical Outcomes Study 12-Item Short Form Health Survey; PCS-12: Physical Component Health Related Quality of Life Scores; MCS-12: Mental Component Health Related Quality of Life Score; EuroQoL: European Quality of Life; EQ-5D: European Quality of Life-5 Dimensions; STAI-6: Six-item State Trait Anxiety Inventory; PCQ: Psychological Consequences Questionnaire

**Table 3b** Mean scale scores of responders with a positive test result, for the whole group and per time period passed between participation in the screening programme and filling out the questionnaire

| | Positive faecal immunochemical test | | | | |
|---|---|---|---|---|---|
| | Positive test result (n= 624) | 4-12 months | 13-24 months | 25 months or more | p-value** |
| *Generic HRQoL* | | | | | |
| SF-12 (0-100)* | | | | | |
| Physical health (PCS-12) | 47.1 (9.4) | 47.4 (10.1) | 46.7 (10.4) | 47.1 (8.7) | 0.61 |
| Mental health (MCS-12) | 51.1 (9.2) | 52.5 (8.5) | 50.8 (10.0) | 50.8 (9.1) | 0.26 |
| EuroQoL* | | | | | |
| EQ-5D (0-1) | 0.82 (0.20) | 0.84 (0.20) | 0.81 (0.23) | 0.82 (0.19) | 0.28 |
| Rating of own health (0-100) | 74.5 (16.9) | 77.4 (13.1) | 72.9 (18.9) | 74.5 (16.6) | 0.32 |
| *Generic anxiety** | | | | | |
| STAI-6 (20-80) | 43.3 (5.2) | 42.8 (5.4) | 43.4 (4.8) | 43.5 (5.3) | 0.53 |
| *Screen-specific anxiety** | | | | | |
| PCQ | | | | | |
| Emotional scale (0-15) | 1.79 (2.7) | 1.69 (2.6) | 1.79 (2.6) | 1.81 (2.8) | 0.81 |
| Physical scale (0-12) | 1.11 (1.9) | 1.05 (1.9) | 1.09 (1.7) | 1.12 (2.0) | 0.86 |
| Social scale (0-9) | 0.78 (1.5) | 0.79 (1.6) | 0.83 (1.5) | 0.75 (1.5) | 0.72 |
| Total score (0-36) | 3.67 (5.4) | 3.54 (5.5) | 3.72 (5.1) | 3.67 (5.5) | 0.85 |

* For SF-12 and EuroQoL a higher score indicates better health
For Generic anxiety and Screen-specific anxiety a higher score indicates more anxiety
** Indicates the significance level of differences in observed scores between groups that participated in the CRC screening programme 4-12 months, 13-24 months or ≥ 25 months previously
HRQoL: Heath-Related Quality of Life; SF-12: Medical Outcomes Study 12-Item Short Form Health Survey; PCS-12: Physical Component Health Related Quality of Life Scores; MCS-12: Mental Component Health Related Quality of Life Score; EuroQoL: European Quality of Life; EQ-5D: European Quality of Life-5 Dimensions; STAI-6: Six-item State Trait Anxiety Inventory; PCQ: Psychological Consequences Questionnaire

Total PCQ scores were significantly higher in FIT and FS participants with a positive test result, indicating more screen-specific anxiety in these participants compared to participants with a negative test result (Table 2).

No statistically significant differences were found in generic anxiety, screen-specific anxiety and QOL scores between negative FIT participants and positive FIT participants who underwent a colonoscopy 4-12 months versus 12-24 months versus > 24 months before completion of the questionnaire (Table 3). QOL scores, generic anxiety and screen-specific anxiety did not differ between positive FIT participants who subsequently had a negative (false positive FIT) versus a positive (true positive FIT) colonoscopy (Table 4).

**Table 4** Mean scale scores of responders with a positive test result (FIT) by result of the colonoscopy

| | **Negative colonoscopy after positive FIT (n= 288)** | **Positive colonoscopy after positive FIT (n= 184)** | p-value |
|---|---|---|---|
| *Generic HRQoL* | | | |
| SF-12 (0-100)* | | | |
| Physical health (PCS-12) | 46.7 (9.7) | 47.6 (9.1) | 0.34 |
| Mental health (MCS-12) | 50.8 (9.1) | 51.4 (9.5) | 0.29 |
| EuroQoL* | | | |
| EQ-5D (0-1) | 0.81 (0.21) | 0.82 (0.22) | 0.14 |
| Rating of own health (0-100) | 74.2 (16.7) | 75.7 (15.9) | 0.29 |
| *Generic anxiety** | | | |
| STAI-6 (20-80) | 43.5 (4.9) | 43.5 (5.4) | 1.00 |
| *Screen-specific anxiety** | | | |
| PCQ | | | |
| Emotional scale (0-15) | 1.74 (2.7) | 1.76 (2.7) | 0.83 |
| Physical scale (0-12) | 1.06 (1.8) | 1.09 (2.0) | 0.72 |
| Social scale (0-9) | 0.81 (1.4) | 0.80 (1.7) | 0.18 |
| Total score (0-36) | 3.60 (5.3) | 3.65 (5.7) | 0.97 |

* For SF-12 and EuroQoL a higher score indicates better health
For Generic anxiety and Screen-specific anxiety a higher score indicates more anxiety

FIT: faecal Immunochemical test; HRQoL: Heath-Related Quality of Life; SF-12: Medical Outcomes Study 12-Item Short Form Health Survey; PCS-12: Physical Component Health Related Quality of Life Scores; MCS-12: Mental Component Health Related Quality of Life Score; EuroQoL: European Quality of Life; EQ-5D: European Quality of Life-5 Dimensions; STAI-6: Six-item State Trait Anxiety Inventory; PCQ: Psychological Consequences Questionnaire



## Overall acceptance

The vast majority of FIT participants would encourage friends and/or relatives to undergo screening (negative FIT participants: 95%, positive FIT participants: 92%; p=0.060) and was willing to attend a successive screening round (negative FIT participants: 99%, positive FIT participants 92%; p<0.001) (Figure 2). The same positive attitude towards screening was found in FS participants, who reported similarly high scores for encouraging friends and/or relatives to undergo screening (negative FS participants: 97.4%, positive FS participants: 99.4%; p=0.024) and willingness to attend a successive screening round (negative FS participants: 92.7, positive FS participants: 95.6%; p=0.253).

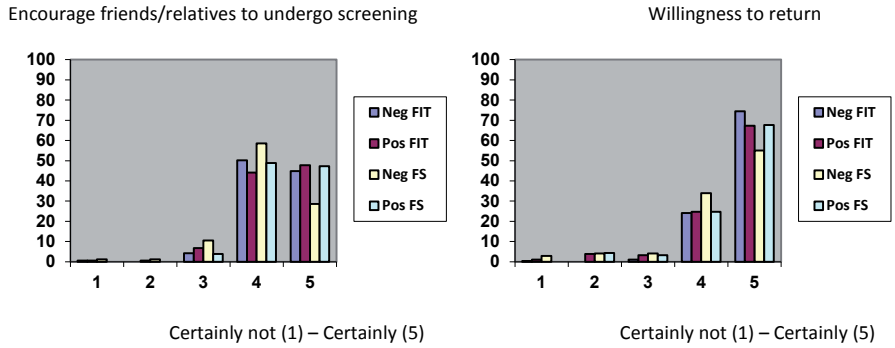


**Figure 2** Scores on the advice subjects would give and willingness to return
Using a 5-point Likert scale (0-100 scale): scores on the advice subjects would give to others to participate in screening and willingness of screenees to return for successive screening rounds
FIT: faecal immunochemical test; FS: flexible sigmoidoscopy

## DISCUSSION

This study examined the QOL of participants in a CRC screening programme. The response rate was high. Participants with a positive FIT had slightly worse QOL scores than participants with a negative FIT test. Furthermore, no significant differences were seen in QOL-scores between positive FIT participants with either a negative or a positive colonoscopy. No differences were found in QOL scores between positive and negative FS participants. Both FIT and FS participants with a positive test result had higher PCQ scores than negative participants, indicating more screen-specific anxiety in these groups. Overall, these findings may indicate that the burden of participating in a CRC screening programme is limited.

Few studies investigated QOL in relation to CRC screening. Taupin et al. performed a study among primary colonoscopy screening participants [10]. Participants completed the Short-Form (SF-36) QOL assessment at baseline and at a mean of 39 days after colonoscopy. Baseline QOL measures were similar to those of a matched general population sample. Thirty percent of all participants reported positive changes in mental health and vitality after colonoscopy, irrespective of the outcome. Unfortunately long term effects on QOL were not assessed. The PLCO Trial (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) investigated QOL among screening FS participants [11]. FS participants were interviewed by telephone at different time intervals (at baseline, shortly after notification and nine months after notification of screening results). Control-arm participants (no screening) completed a baseline and 1-year follow-up assessment. After nine months FS participants with abnormal screening results did not show higher levels of intrusive thoughts about cancer than those with normal results (p= 0.096; odds ratio

= 1.9, 95% confidence interval = 0.89 to 4.2). These results are in line with our study, where we found similar QOL scores among negative and positive FS participants.

In our study, we found that both FIT and FS participants with a positive test result showed significantly more screen-specific anxiety than participants with a negative test result. To indicate clinical relevance we used the minimal important difference (MID), defined as the smallest change in a patient-reported outcome that is perceived by patients as beneficial or that would result in a change of treatment. MID was operationalised as a difference of at least half a standard deviation [21]. Although some differences in QOL scores were statistically significant, all differences in QOL scores between negative and positive FIT and FS participants were rather small and none of them exceeded the MID. These are therefore not clinically relevant. Two other studies among participants in a FOBT-screening programme and one FS screening study, assessing worries associated with CRC screening, showed that most of the participants did not experience an increase in anxiety [22-24]. Control groups consisted of an age- and gender-matched group not invited for screening [22, 24] respectively persons who had received the invitation letter but had not attended the screening programme) [23]. Furthermore, participants did not develop adverse psychological effects 17 months after screening [23, 24].

Literature on CRC screening shows that even in subjects with a false positive test result, screening for CRC has no adverse effect on anxiety on the long term [24, 25]. Population-based screening studies regarding prostate and breast cancer found similar results [26, 27]. Apparently, a false positive test result does not negatively affect participants' QOL. These findings are in accordance with our study, since QOL scores were similar in positive FIT participants with either a negative or a positive colonoscopy. Possible explanations for these mainly positive effects of CRC screening in participants with a true positive result could be that, although participants are worried because of the possibility of having colorectal cancer, they are either simultaneously relieved that they found out on time and will be screened regularly to prevent colorectal cancer, or they are reassured because they soon underwent treatment. In case of a false positive result, we hypothesized that participants are relieved that no abnormalities were found during further investigations.

In our study we addressed large numbers of participants in a CRC screening programme. Both participants with a positive and negative test result who underwent either FOBT or FS were included. Another strength is that the response rate to the questionnaire was high. Furthermore, validated measures were used to assess QOL and we were able to compose a questionnaire that enables to understand the impact of screening on participants' QOL. A review of instruments to measure the QOL of participants in a CRC screening programme reinforced the importance of such a questionnaire [6]. We unfortunately have no information on QOL of non-participants, and we have no information on QOL, nor psychological or physical, prior to FIT or FS testing. These

baseline values are essential to make a correct comparison, and to correct for the effect of factors like age (screen-positive participants were older than screen-negative participants). Participants in a screening study might not reflect the general population and might react differently. We did however look at mean SF-12 scores in the general Dutch population. Furthermore, we don't have data on QOL and anxiety of the entire screening process (eg, after performing the screening test, while waiting for the test result, after colonoscopy, etc.). Because the majority of responders were of Caucasian ethnicity, our results cannot be extrapolated to a non-Caucasian population. Further studies in a non-Caucasian population are therefore needed.

In summary, this retrospective questionnaire survey on QOL among participants of a FIT or FS CRC screening programme, showed slightly worse QOL scores among positive FIT participants compared to FIT negative participants. Compared to the general Dutch population, mental health-related QOL scores were lower among all participants. Screen specific anxiety was significantly higher among both positive FIT and FS participants, indicating that a positive test result has a negative impact on participants' emotional well-being, although differences were small and not clinically relevant. With respect to cost-effectiveness analyses that aim to assess quality adjusted life years lost or gained by screening, our results suggest that the impact of FIT and FS screening on experienced QOL after the screening process will be modest. A prospective study needs to be conducted, where participants receive questionnaires at different time points during the entire screening process. Only this way, we will fully be able to evaluate the impact of screening on QOL and anxiety and anticipate on possible negative side-effects.

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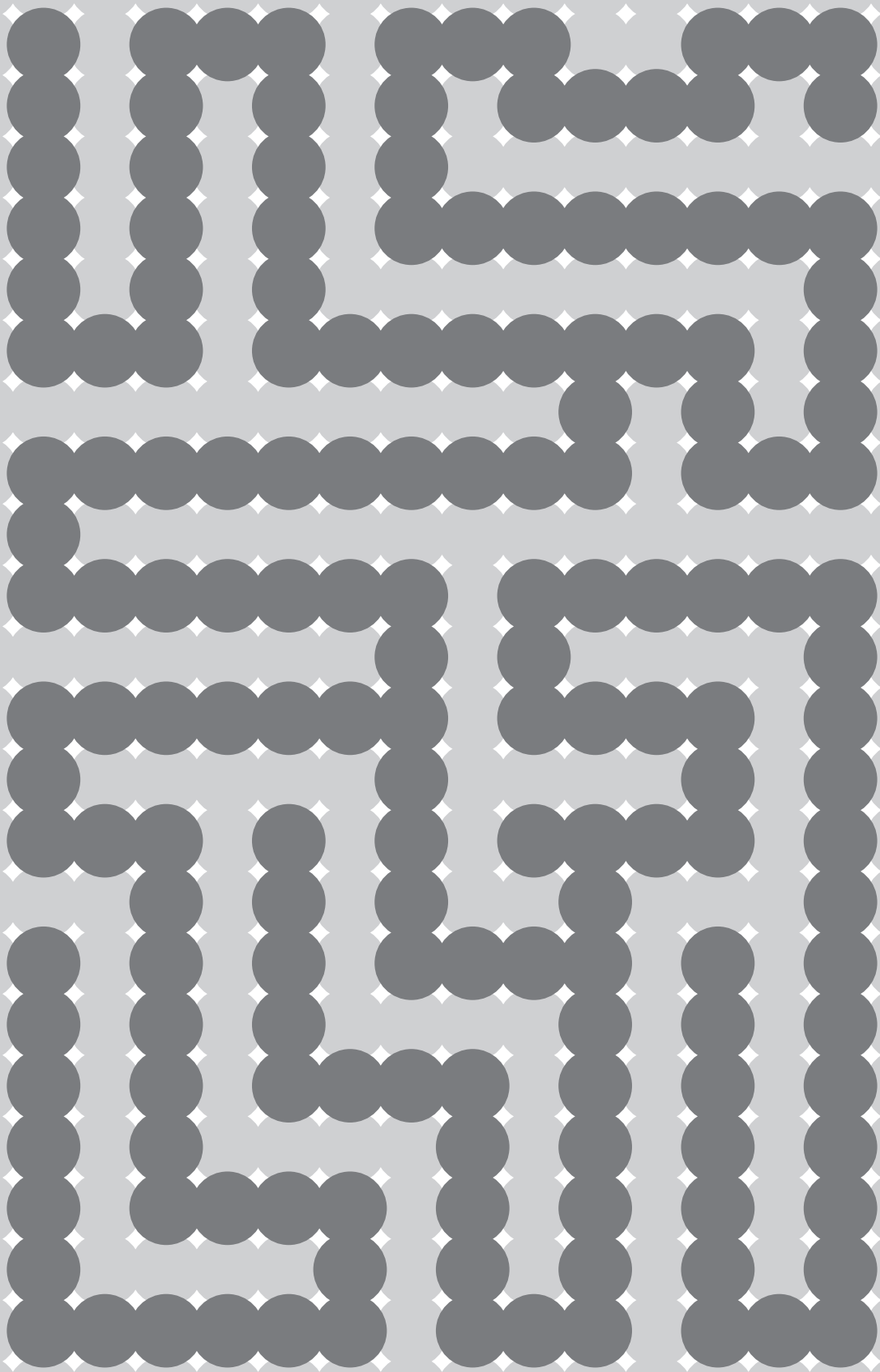

# Second look colonoscopies and the impact on capacity in FIT-based colorectal cancer screening

Esmée J. Grobbee, Atija Kapidzic, Anneke J. van Vuuren, Monique E. van Leerdam, Iris Lansdorp-Vogelaar, Caspar W.N. Looman, Marco J. Bruno, and Manon C.W. Spaander

*Submitted*

## ABSTRACT

### Objectives:

Colonoscopies after positive faecal immunochemical testing (FIT) have a high prevalence of advanced neoplasia. En bloc or piecemeal resection of advanced neoplasia is associated with a high rate of local residual or recurrent neoplasia at the resection site. Second look colonoscopies are indicated to assess completeness of removal of advanced neoplasia. These colonoscopies can have a substantial impact on the colonoscopy capacity and health care system. This study is the first to evaluate the number and risk factors for second look colonoscopies in FIT-based CRC screening.

### Methods:

All colonoscopies performed in average risk subjects, aged 50-74 years, who were approached for a maximum of three rounds of FIT screening were prospectively registered. A positive FIT was defined by a haemoglobin concentration of ≥ 50 ng/ml, which corresponds to ≥ 10 µg haemoglobin/g faeces. A second look colonoscopy was defined as any colonoscopy performed following a screening colonoscopy within one year.

### Results:

A total of 1,215 patients with a positive FIT underwent colonoscopy (57.4% male, median age 63 years (IQR 57-68 years), median faecal haemoglobin level 146 ng/ml (IQR 77-430 ng/ml)). A total of 105 (8.6%) patients underwent a second look colonoscopy with a median time of 63 days (IQR 35-101 days) between the index and second look colonoscopy. Thirty patients (2.5%) underwent more than one second look colonoscopy (range 2-9) leading to a total of 149 (12%) additional colonoscopies after the index colonoscopies. Main indications for a second look colonoscopy were assessment of completeness of removal of a neoplastic lesion (41.9%) and the need for further polypectomy (34.3%). Risk factors were advanced adenomas and poor bowel preparation ($p<0.001$). High faecal haemoglobin concentration was the only predictor of a second look colonoscopy before the index colonoscopy ($p<0.001$).

### Conclusions:

Second look colonoscopies have a substantial influence on colonoscopy capacity, increasing the demand with 12%. Identifying patients at risk for advanced neoplasia may reduce the number of second look colonoscopies and could have beneficial effects on costs and colonoscopy resources in CRC screening programmes.

## INTRODUCTION

Colorectal cancer (CRC) is a major cause of mortality and morbidity worldwide and ranks third among the leading causes of cancer [1]. Detecting and removing polyps during colonoscopy reduces CRC-related mortality [2, 3]. Colonoscopy is therefore widely appreciated as optimal test for detection and removal of adenomas [4, 5]. At present more and more CRC screening programmes are being implemented worldwide and recent EU guidelines recommend faecal immunochemical occult blood testing (FIT) for primary screening followed by colonoscopy in case of positive FIT [6, 7]. Colonoscopic examination is however not perfect in preventing CRC, as its miss rate for cancers and adenomatous polyps is low but not negligible [8, 9]. Missed and incompletely resected lesions are recognized as important contributors to interval colorectal cancers [10, 11]. A so-called second look colonoscopy is advised when there remains doubt about missed neoplastic lesions, completeness of removal of lesions, or after an incomplete examination the colon [12, 13]. Screening colonoscopies after positive FIT have a high prevalence of advanced neoplasia of around 35-45% [14-16]. En bloc, and especially piecemeal resection of advanced adenomas is associated with a relatively high rate of local residual or recurrent neoplasia at the resection site [12, 13, 17, 18]. One may therefore hypothesize that in a FIT-based screening setting an increased number of second look colonoscopies could be found [14-16]. Although multiple colonoscopies per patient could have a substantial impact on the required colonoscopy capacity and therefore health care system, little is known about the number of second look colonoscopies in a screening population. This is the first study to assess the number and indications of second look colonoscopies in in a FIT-based CRC screening programme and to identify patients at risk for a second look colonoscopy.

## METHODS

### Patients

Details about the design of this on-going population-based CRC screening programme have been described previously [14, 15]. In short, demographic data of all individuals between 50-74 years living in the southwest of the Netherlands were obtained from municipal population registers. In this screening programme the OC-sensor FIT (OC-sensor, Eiken Chemical, Japan) was used over multiple rounds with a maximum of three rounds. Intervals between rounds varied from one to three years. Individuals with a history of inflammatory bowel disease (IBD) or CRC, symptomatic patients, as well as those who had undergone a colonoscopy, sigmoidoscopy or barium contrast enema in the last 3 years, those with an estimated life expectancy of less than 5 years, and subjects who were unable to give informed consent, were excluded from the study. All patients with a positive FIT, defined by a haemoglobin concentration of

≥ 50 ng/ml which corresponds to ≥ 10 µg haemoglobin/g faeces, were referred for colonoscopy. Colonoscopies were performed in 18 peripheral centres and in 1 academic centre.

**Data collection**

Our primary endpoint was to assess the number and indications of secondary colonoscopies after the first screening colonoscopy following a positive FIT. A second look colonoscopy was defined as any secondary endoscopic procedure of the colon indicated within one year after the first screening colonoscopy, regardless of the endpoint reached, as often a second look colonoscopy was limited to the area where previous neoplastic lesions were removed [19]. Furthermore we looked for predictive factors to identify patients at risk. Predictive factors included age, sex, socio-economic status (low, average, high), bowel preparation, use of sedation, use of Buscopan, type of endoscopist, type of hospital, faecal haemoglobin concentration and presence of advanced neoplasia.

Data on colonoscopies were prospectively registered using a standardized endoscopy report completed after the colonoscopy by the performing endoscopist. The following variables were systematically assessed: sedation (Midazolam, Fentanyl, Propofol, none), level of bowel preparation (poor: < 90% of mucosa visible, medium: 90-99% of mucosa visible, good: 100% of mucosa visible), caecal intubation, detection of polyps or other lesions, and removal of polyps. Endoscopists were categorized as gastroenterologists, gastroenterology fellows, internists or nurse-endoscopists. Advanced neoplasia was defined as an adenoma of 10 mm or larger, an adenoma with 25% or more villous histology or with high-grade dysplasia and CRC. The overall quality of the colonoscopy was evaluated based on indicators as defined by Rex et al [20]. The caecal intubation rate (CIR) was defined as the proportion of colonoscopies in which the caecum was visualized. The adenoma detection rate (ADR) was defined as the number of colonoscopies that revealed at least one adenoma divided by the total number of colonoscopies. The faecal haemoglobin concentration (ng/ml) of all included patients was noted.

**Statistical analysis**

Descriptive data were reported as proportions or means with the standard deviation. For non-normally distributed data the median and interquartile range (IQR) were given. Chi-Square tests were used to analyze categorical data; continuous data were analyzed using Student's t-tests and Mann-Whitney U in case of a non-parametric distribution. Univariate logistic regression models were used to calculated odds ratios (OR) and 95% confidence intervals (CI). In case of a p-value < 0.20 variables were included in multivariate stepwise backward regression analysis. A two-sided p-value of < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS version 21.0.

## RESULTS

### Patient characteristics

A total of 1,215 patients, 698 men and 517 women, with a median age of 63 years (IQR 57-68 years), underwent a colonoscopy following a positive FIT. Patients' characteristics are summarized in Table 1. The median faecal haemoglobin concentration was 146 ng/ml (IQR 77 - 430).

### Colonoscopy characteristics

Of the 1,215 colonoscopies, more than half (52.0%) were performed under conscious sedation using both Midazolam and Fentanyl. Buscopan was used in 484 (39.8%) of the cases. Colonoscopies were performed by gastroenterologists (75.0%), followed

**Table 1** Baseline characteristics

| Variables | | (%) |
|---|---|---|
| Total number of patients | 1215 | |
| Age, mean (IQR) (years) | 63 (57-68) | |
| Male gender | 698 | (57.4) |
| Sedation | | |
| Midazolam | 348 | (28.6) |
| Fentanyl | 22 | (1.8) |
| Midazolam and Fentanyl | 632 | (52.0) |
| Propofol | 2 | (0.2) |
| No sedation | 172 | (14.2) |
| Not reported | 39 | (3.2) |
| Use of Buscopan | 484 | (39.8) |
| Endoscopist | | |
| Gastroenterologist | 911 | (75.0) |
| Internist | 66 | (5.4) |
| Gastroenterology fellow | 27 | (2.2) |
| Nurse-endoscopist | 156 | (12.8) |
| Not reported | 55 | (4.5) |
| Bowel preparation | | |
| Good | 885 | (72.8) |
| Medium | 241 | (19.8) |
| Poor | 29 | (2.4) |
| Not reported | 60 | (4.9) |
| Hospital | | |
| Academical | 255 | (21.0%) |
| Peripheral | 960 | (79.0%) |
| Faecal Hb concentration (IQR) (ng/ml) | 146 (77-430) | |

Hb: haemoglobin; IQR: interquartile range

by nurse-endoscopists (12.8%), internists, (5.4%) and fellows (2.2%). The bowel was adequately cleansed in 1,126 of 1,155 patients (97%). The caecum was reached in 97.3% of the performed index colonoscopies. The overall adenoma detection rate was 55%. Adverse events within 30 days occurred in 36 colonoscopies (3%), consisting mainly of mild bleedings (1.8%) managed during the index colonoscopy. Other adverse events were a decrease in saturation (0.4%) and blood pressure (0.2%) during colonoscopy. One perforation (0.09%) occurred after colonoscopy.

### Second look colonoscopies

A total of 105 (8.6%) patients underwent a second look colonoscopy within one year, with a median time between the index colonoscopy of 63 days (IQR 35-101 days). The most frequently reported indications for a second look colonoscopy were assessment of completeness of removal of a neoplastic lesion (41.9%) and need for further polypectomy (34.3%). Remaining indications were poor bowel preparation (13.3%), pre-surgical submucosal marking of an adenoma or malignancy (3.8%), and anticoagulant use (1.9%) (Table 2). In 20% of patients, in whom a second look colonoscopy was performed for completeness of removal of a neoplastic lesion, residual tissue was found at the resection site. In 55.6% of patients, in whom a second look colonoscopy was performed because of the need forfurther polypectomy, this was due to a large polyp (median size 20 mm, IQR 15-30 mm). Other indications for a second colonoscopy with polypectomy included lack of time (17%), high grade dysplasia or carcinoma (14%), complex location of the lesion (5.6%), and microscopically incompletely removed polyps (2.8%). Thirty patients (28.6%) underwent more than one follow-up colonoscopy (range 2-9 colonoscopies) leading to a total of 149 (12%) additional colonoscopies after the screening colonoscopy. The main indications for these subsequent colonoscopies were incomplete removal of the polyp and control for completeness of removal. In the group of patients receiving a second look colonoscopy, significantly more advanced neoplasia were found, respectively

**Table 2** Reasons for second look colonoscopy

| Reason | Total number n = 105 | (%) |
|---|---|---|
| Control of completeness of removal | 44 | (41.9) |
| Polypectomy | 36 | (34.3) |
| Poor bowel preparation | 14 | (13.3) |
| Marking adenoma / CRC | 4 | (3.8) |
| Anticoagulant drugs | 2 | (1.9) |
| Incomplete colonoscopy* | 4 | (3.8) |
| Obstructing CRC | 1 | (1.0) |

* Includes: looping, diverticulosis, diverticulitis

79.0% compared to 27.5% (p <0.001). In over half of colonoscopies with failed caecal intubation (1.4%), the decision was made not to repeat the colonoscopy and to refer the patient for CT-colonography.

### Factors associated with second look colonoscopy

Predictors for a second look colonoscopy in the univariate analysis are shown in Table 3. Bowel preparation and advanced neoplasia were the only significant predictors for a second look colonoscopy after multivariate analysis. The only predictive factor before the initial colonoscpy was FIT haemoglobin concentration (Figure 1).

**Table 3** Univariate analysis of variables associated with a second look colonoscopy

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Variable** | **OR (CI 95% )** | **p-value** | **OR (CI 95%)** | **p-value** |
| Gender (male) | 1,07 ( 0,71 – 1,61) | 0.73 | | |
| Age (years) | 1,02 (0,99 – 1,05) | 0.23 | | |
| SES | | | | |
| - Low | 1 (ref.) | | | |
| - Average | 0.71 (0.40-1.26) | 0.24 | | |
| - High | 0.71 (0.45-1.11) | 0.13 | | |
| Hospital (academic) | 1,19 (0,74 – 1,91) | 0.46 | | |
| Endoscopist | | | | |
| - Gastroenterologist | 1 (ref.) | | | |
| - Internist | 2.2 (1.1 – 4.4) | 0.02 | | |
| - Fellow | 1,35 (0,39 – 4,6) | 0.62 | | |
| - Nurse-endoscopist | 0,74 (0,37 – 1,46) | 0.393 | | |
| Use of sedation | 0.53 (0.32-0.88) | 0.014 | | |
| Use of Buscopan | 0.85 (0.55 – 1.33) | 0.482 | | |
| Poor bowel preparation | 14.4 (6.71-30.9) | <0.001* | 28.6 (10.8-75.3) | <0.001* |
| Advanced neoplasia | 9.91 (6.08-16.2) | <0.001* | 14.8 (8.06 – 27.3) | <0.001* |
| OC-sensor haemoglobin level (per 100 ng/ml) | 1,04 (1,02 – 1,06) | < 0.001* | | |

* Statistically significant
SES: socio-economic status

## DISCUSSION

In this population FIT-based screening programme we assessed the number and indications of second look colonoscopies. The results of our study indicate that 8.6% of our study population required a second look colonoscopy within one year after the initial screening colonoscopy. In 3.0% of patients more than 1 colonoscopy was performed

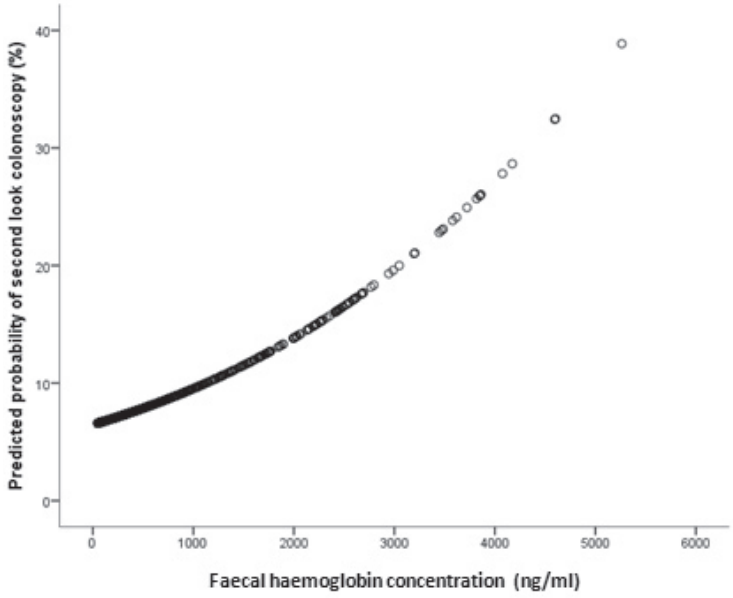


**Figure 1** Predicted probability of second look colonoscopy for faecal haemoglobin level

after the initial procedure, resulting in a 12% increase in required colonoscopy capacity. In 76% of patients a second look colonoscopy was performed for assessment of completeness of removal of neoplastic lesions or for further polypectomy of large or multiple lesions. Significant predictors for a second look colonoscopy were presence of advanced neoplasia and bowel preparation. The only significant predictor prior to the index colonoscopy was a high faecal haemoglobin concentration.

While second look colonoscopies could have a substantial impact on colonoscopy capacity, current knowledge on second look colonoscopies is limited. As more screening programmes are implemented worldwide, estimating the number of colonoscopies needed for CRC screening, ie, the required capacity becomes of increasing importance. To our knowledge this is the first study to evaluate the prevalence of second look colonoscopies as previous studies have mainly focused on colonoscopies after an incomplete colonoscopy due to failed caecal intubation [19, 21, 22]. In our cohort caecal intubation failed in only 3% of colonoscopies. Furthermore, many studies have suggested that a poor bowel preparation is a frequent reason for failure of colonoscopy [23, 24]. However, we found that, although a poor bowel preparation almost always leads to repetition of the procedure, it is an infrequent cause of the total number of second look colonoscopies.

Previous FIT-based screening cohort studies have shown that FIT-positive screenees have a high incidence of advanced adenomas of around 35-45% (15-17). The removal of such, often large, adenomas is complex, time consuming, and often followed by a second look colonoscopy to assess residual neoplastic tissue [25, 26]. We found that in over two-thirds of our patients a second look colonoscopy was performed because of an incomplete polypectomy or to examine the polypectomy scar for residual neoplastic tissue. According to literature data, a second look colonoscopy for the control after polypectomy occurs in around 1% or 2% of the procedures with endoscopic treatment and is usually limited to the previously treated area [19]. Our results indicate a much higher rate of second look colonoscopies. These findings are supported by the fact that significantly more advanced neoplasia were found in patients undergoing a second look colonoscopy. A second look colonoscopy is recommended to be performed within 2 to 6 months or at least within one year after piecemeal resection [17, 18]. Our findings are in line with these guidelines since over half of the second look colonoscopies were performed within 3 months following the index colonoscopy. It should be noted that in only 20% of patients residual tissue was found at a second look colonoscopy.

Advanced colorectal neoplasia is associated with a higher FIT haemoglobin concentration [27, 28]. This explains the relation between a high faecal haemoglobin concentration and the need for a second look colonoscopy. Our findings could be of clinical importance and guidance for endoscopists and patients. As a high faecal haemoglobin concentration is indicative of a more complex colonoscopy, it may help the attending physician to be prepared for a more difficult procedure and inform the patient accordingly.

Our study has some limitations. Although the data was prospectively collected, the number of second look colonoscopies were retrospectively analyzed which could lead to possible underreporting of the actual number of colonoscopies. A second shortcoming is that we lacked precise information regarding the colonoscopy experience per endoscopists. However, both CIR as well as ADR were well above standards as required for CRC screening [29, 30]. Thirdly, in the faecal samples with very high concentrations of haemoglobin, a prozone effect could have occurred. This could lead to measured values that are lower than the actual concentration in the sample in case of very high concentrations [31]. Such a prozone effect could lead to an underestimation of the true height of the faecal haemoglobin level for values above 1000 ng/ml.

In conclusion, we found that in 8.6% of screening colonoscopies a second look colonoscopy is performed, ranging from 2 to 9 colonoscopies per patient. This affects the screening colonoscopy capacity with an edditional 12%. In over two-thirds of patients a second look colonoscopy was performed for control of completeness of removal of neoplastic lesions or for additional polypectomy. FIT haemoglobin concentration was the only significant predictor prior to the screening colonoscopy. Our results suggest

that second look colonoscopies have a substantial influence on colonoscopy burden in a FIT-based screening setting and should be taken into account when estimating colonoscopy capacity.

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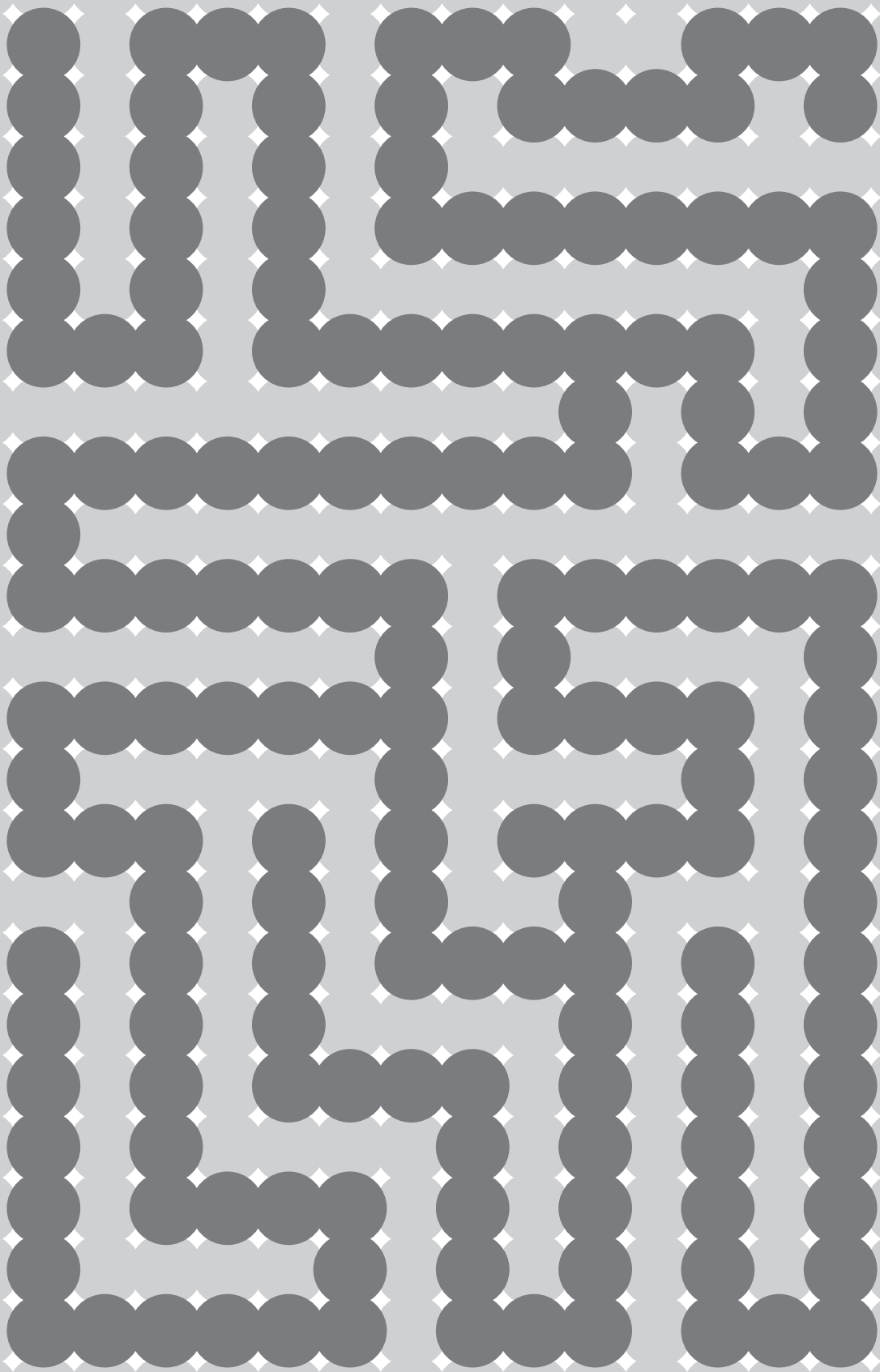

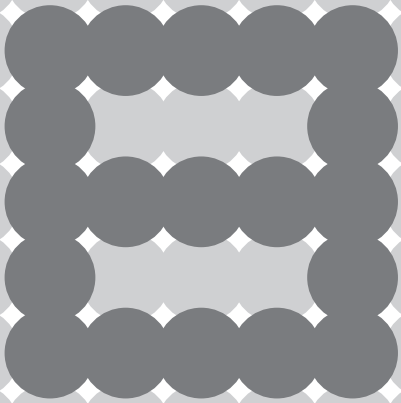

# Summary and general discussion

## INTRODUCTION

Colorectal cancer (CRC) is a major health concern worldwide. Approximately 1.2 million people are diagnosed with CRC each year worldwide and it accounts for almost 10% of all cancers [1]. The lifetime incidence of CRC in average risk-patients is about five percent [1]. Importantly, CRC is characterized by a long preclinical stage. The development from small adenoma to invasive cancer takes years [2, 3]. CRC can be prevented by removal of these adenomas, resulting in a lower CRC incidence and mortality [4-6]. CRC therefore fulfills the screening criteria of Wilson and Jungner, as it is an important health problem with significant morbidity and mortality, as the disease has a detectable and treatable precursor (adenomas), and early detection of CRC improves the prognosis [7, 8].

Several methods are available for screening. These methods differ in the degree of supporting evidence, test-related burden, attendance, diagnostic yield and therefore effectiveness. The FOBTs (faecal occult blood test) have the potential to decrease CRC related mortality. The traditional guaiac-based FOBT (gFOBT) is being increasingly replaced by the faecal immunochemical test (FIT), not only due to a higher test sensitivity, but also because its more patient-friendly usage [9]. Furthermore, since FIT findings can be quantitated, the cut-off value for a positive test can be adjusted to accommodate budget and manpower limitations for a target population [9]. FIT screening has therefore become the first-choice FOBT for CRC screening [10]. More invasive screening methods such as sigmoidoscopy and colonoscopy have the advantage that besides early detection of CRC they can also prevent CRC by directly removing precursors. However, repeated rounds of FIT screening increase programme sensitivity, thereby achieving a higher diagnostic yield than with more invasive screening strategies [10]. On January 2014, a FIT screening programme was therefore started in the Netherlands in which men and women in the ages between 55-75 years are gradually invited for biennial FIT screening using a cut-off of 75 ng/ml.

The results of the first and second round of FIT screening-trial helped to form the basis for the implementation of a nationwide FIT-based CRC screening programme in the Netherlands [11, 12]. The age-range from 55-75 years was chosen based on cost-effectiveness analyses that have shown that screening in this age group is most cost-effective [13, 14]. Biennial FIT screening at a cut-off level of 50 ng/ml was preferred based on these same analyses. However, a cut-off level of 75 ng/ml with a gradual implementation of FIT screening was chosen due to limited colonoscopy capacity [15]. In 2014, men and women in the ages of 63, 65, 75, and 76 years are invited. It is estimated that all subjects in the ages between 55-75 years are invited at least once for FIT screening in 2019 [16]. Furthermore, it is estimated that with an attendance rate of 60% approximately 2400 deaths will be prevented annually with full implementation of the CRC screening programme in the Netherlands (expected in 2032) [16]. Data on attendance and diagnostic

performance of FIT screening over repeated rounds are limited and of great value, since this can be used to anticipate on several aspects of the national screening programme. Various aspects of repeated FIT screening have been investigated using the CORERO-database involving three successive rounds of FIT screening.

## REPEATED FIT SCREENING

### Three rounds of population-based 1-sample FIT screening - attendance and diagnostic yield

For the effectiveness of FOBT-screening in general it is required that invitees are repeatedly screened, since the sensitivity of a single round of FIT screening for the detection of advanced neoplasia is limited. Studies have shown that FIT at a low cut-off detects up to 88% of CRCs and approximately 35% of advanced adenomas [17, 18]. Successive screening rounds are needed to optimize the impact of FIT screening on a population level. In particular, longitudinal adherence of the same subjects represents a critical factor. Information concerning sustained attendance and diagnostic performance over repeated rounds of FIT screening is limited. We and others demonstrated a stable attendance rate over two rounds of FIT screening, with detection of substantial numbers of advanced lesions in both rounds [12, 19]. Data on further rounds of FIT screening with longer follow-up periods are scarce. One relatively small Italian study on four rounds of a biennial FIT screening programme reported stable attendance rates and test performances [20]. The attendance rate of 56% during the first round was however relatively low compared to our data. Further data on repeated FIT screening will provide more insight in the programme sensitivity of FIT screening. In **chapter 2**, we therefore evaluated attendance and detection rates of three rounds of FIT screening in a Dutch population-based CRC screening programme. Average-risk subjects in the ages of 50-74 years were approached for three rounds of 1-sample FIT screening (OC-sensor Micro, Eiken Chemical, Japan). Subjects with a haemoglobin level ≥ 50 ng/ml (≥ 10 µg haemoglobin/g faeces) were referred for colonoscopy. Attendance rates in the first, second, and third round were 62.6%, 63.2%, and 68.3%, respectively ($p<0.001$). The proportion of stable attenders (ie, invitees attending all rounds while they were eligible) was 56.3%, and the cumulative attendance rate (ie, eligible invitees attending at least one screening round) was 72.5%. With respect to the non-participants in first-round screening, 18.8% attended the second round, while 23.2% of second round non-participants attended the third round. The detection rate of advanced neoplasia was 3.3% in the first, 1.9% in the second, and 1.3% in the third round ($p<0.001$). The positive predictive value for advanced neoplasia was 40.7% in the first, 33.2% in the second, and 24.0% in the third round ($p<0.001$).

*Conclusions and further research*

A very important early indicator for an effective population-based screening programme is uptake. A high and increasing attendance over three consecutive rounds was seen, as well as a relatively high percentage of stable attenders. This implies that repeated FIT screening is acceptable on a population level. The considerable decrease in detection rate of advanced neoplasia from 3.3% to 1.3% over the three rounds supports the notion that consecutive FIT screening has a beneficial effect by decreasing the prevalence of advanced neoplasia. In contrast, an Italian study on repeated FIT screening revealed a stable detection rate of advanced neoplasia over successive rounds (1.5-1.3%) [20]. That study however applied a higher cut-off value (100 ng ng/ml). The initial decrease in detection rate in our study is likely to be explained by the enhanced sensitivity of a FIT at a low cut-off (50 ng ng/ml), compared to FIT screening with a higher cut-off value.

In line with the decrease in detection rate, also a decline in positive predictive value for advanced neoplasia was observed over repeated screening rounds. The false-positive rate (FPR), defined as subjects that had a positive FIT, but no advanced neoplasia on follow-up colonoscopy (ie, only non-advanced neoplasia, hyperplastic polyps and/or no findings at all), did not rise over the three screening rounds (FPR round 1: 5.1%; round 2: 4.1%; round 3: 4.4%, p=0.050). This indicates that the decrease in positive predictive value was mainly due to the decrease in detection rate. Such a decrease in positive predictive value in following screening rounds is what one would expect and prefer, since it is a confirmation of the effectiveness of the screening programme. Further information is required to address the important question whether FIT screening with higher sensitivity for advanced neoplasia can be applied with longer screening intervals than biennial gFOBT screening. Possible ways to increase the positive predictive value are indeed lengthening the interval, but also by using higher cut-off levels in consecutive rounds. This would of course decrease programme sensitivity and consequently the effectiveness. Evidently, there is no optimum for the positive predictive value. Whether a positive predictive value for advanced neoplasia of 23% is too low depends on local resources. This also needs considering the long term incidence and mortality reduction, while comparing different intensities of screening.

## Two rounds of population-based 2-sample FIT screening - attendance and diagnostic yield

FIT screening is routinely performed on a single stool sample. However, advanced neoplasia may bleed intermittently and therefore may be missed with single stool sampling. FIT screening by means of multiple samples increases test sensitivity (ie, reduces the risk of missing advanced lesions). Until now, limited data are available regarding the most optimal numbers of FITs to be used. Trials pertain to a single screening round with FIT screening using multiple samples, and trials comparing 1- and 2-sample FIT screening

with regard to attendance and diagnostic yield are lacking [21-26]. Data from our research group in which 8,204 screening-naïve subjects were offered either 1- or 2-sample FIT screening, showed no differences in attendance while significantly more advanced neoplasia were detected in the first screening round with 2-sample FIT [27]. The higher diagnostic yield was a trade-off with reduced specificity, as the additional yield in detecting advanced neoplasia was achieved only by a higher demand for colonoscopy. Further information on consecutive rounds of FIT screening by means of multiple samples is needed. In **chapter 3**, we therefore aimed to determine attendance and diagnostic yield of repeated 2-sample FIT screening. Furthermore, we aimed to compare these data with repeated 1-sample FIT screening. Average-risk subjects in the ages of 50-74 years were approached for two rounds of 2-sample FIT screening (OC-sensor Micro, Eiken Chemical, Japan) with a two-year interval. Per round, invitees received two FITs to sample from two consecutive bowel movements. At each round, the test result was considered positive if at least one of both tests was positive at a cut-off of 50 ng haemoglobin/ml buffer. Test characteristics were determined for three scenarios: (A) two rounds with 1-sample FIT, (B) two rounds with 2-sample FIT, and (C) first round 2-sample FIT and second round 1-sample FIT (ie, the first FIT of the 2-sample FIT was positive). These scenarios were compared to data on repeated 1-sample FIT screening derived from a previous study in the same setting and population [27]. Attendance was similar in both rounds (round 1: 61.3%; round 2: 61.3%, p= 0.992). The positivity rate (PR), detection rate (DR), and positive predictive value (PPV) for advanced neoplasia of 2-sample FIT were significantly higher in the first (PR 12.8%; DR 4.1%; PPV 34.1%) than in the second round (PR 8.4%; p<0.001; DR 1.7% p<0.001; PPV 21.1% p=0.011). The positivity rate in the second round was lower for 1-sample (scenario A: 5.6%, 95% CI 4.6-6.9) than for 2-sample FIT (scenario B: 8.4%, 95% CI 7.1-9.8), whereas the detection rate (scenario A: 1.3, 95% CI 0.8-2.0; scenario B: 1.7, 95% CI 1.2-2.5) and the positive predictive value for advanced neoplasia (scenario A: 24, 95% CI 16-34; scenario B: 21, 95% CI 15-29) did not differ. After two rounds of screening, the diagnostic yield for scenario A at a cut-off of 50 ng/ml was 27.8 advanced neoplasia per 1,000 invitees, for scenario B 34.0 advanced neoplasia per 1,000 invitees, 31.7 for scenario C, and 29.3 per 1,000 invitees for two rounds of 1-sample FIT screening (29.3 versus 27.8, p=0.696; 29.3 versus 34.0, p=0.241; 29.3 versus 31.7, p=0.542).

*Conclusions and further research*

Two-sample FIT screening is associated with a stable and high attendance during repeated screening rounds. This underlines the acceptability of a 2-sample regimen, and thus demonstrates that the burden of FIT sampling of consecutive bowel movements does not impair participation to screening. Besides attendance, the number of advanced neoplasia detected is very important for the effectiveness of a CRC screening programme. The optimal number of FITs is very relevant in this aspect. Two-sample FIT

(scenario B) resulted in a higher positivity rate, but a similar detection rate and positive predictive value compared to 1-sample FIT (scenario A). When we compare our results with previous published data of a group derived from the same population that we invited for two rounds of 1-sample FIT screening, we see that two rounds of 2-sample FIT screening (scenario B) showed a higher positivity rate, but lower positive predictive value when compared to the 1-sample FIT cohort by van Roon et al. The similar PPV together with a lower PR would make 1-sample FIT more favourable over screening with 2-sample FIT. Furthermore, the diagnostic yield over two rounds (ie, the cumulative sensitivity of several screening rounds) did not significantly differ between 1-sample and 2-sample FIT screening at a cut-off of 50 ng/ml [12]. With increasing cut-off levels a higher diagnostic yield was seen with 2-sample FIT screening over both screening rounds. The same pattern was seen for the diagnostic yield after one round with 1-sample and 2-sample FIT screening. This demonstrates again that screening at a cut-off of 50 ng/ml is highly effective. The present data, unique in that over 3,000 average-risk individuals were invited for screening over two consecutive rounds, support a preference for 1-sample FIT screening at low cut-off levels. Further data on repeated rounds of screening with multiple samples is needed to confirm the observed pattern.

## GENDER DIFFERENCES IN FIT SCREENING

### Gender differences in FIT performance - attendance and FIT characteristics

There is evidence that participation to FOBT screening is lower among men than among women [28], even though the incidence of CRC and mortality rates are higher in men [29]. In European and Australian programmes, participation is higher in women than in men with FOBT screening, but is lower in women with sigmoidoscopy screening [28, 30, 31]. Until now, similar FIT screening regimens are applied to men and women despite eminent sex disparities in prevalence and anatomic distribution of advanced neoplasia. The prevalence of CRC and advanced colorectal adenomas has consistently been found to be higher among men than among women in colonoscopy-based studies [2, 32-34]. In a Scottish gFOBT screening study, more screen-detected CRCs in men compared to women were found, whereas the number of interval CRC was similar in both groups, suggesting that gFOBT is less sensitive when used in women [35]. A German study, in which subjects received a FOBT (gFOBT or FIT) prior to a screening colonoscopy, confirmed this finding; a substantial higher sensitivity and positive predictive value was found in men than in women for both FOBTs [36]. Another study which compared FIT with primary screening colonoscopy also found a higher sensitivity of FIT in men [37]. Aforementioned data were obtained from studies with colonoscopy as a primary screening tool and might have a different underlying risk than the (screening-naïve)

population screened with FIT. Data on gender differences in a population-based setting with FIT as a primary screening tool are sparse. In **chapter 4**, we therefore determined potential gender differences in performance of FIT in an average risk, screening-naïve Dutch population. A prospective cohort-study was performed, in which in total 10,008 average-risk subjects (aged 50-74 years) were invited for first and 8,316 subjects (aged 51-74 years) for second round screening with a single FIT (OC-sensor Micro, Eiken Chemical, Japan). Subjects with a haemoglobin level of ≥ 50 ng/ml were referred for colonoscopy. Test characteristics were assessed by sex for a range of cut-off levels. In both screening rounds, a higher attendance in women was found (first round: 64.4% versus 59.8%, p<0.001); second round: 65.6% versus 61.3%, p<0.001). A higher positivity rate (10.7%) and detection rate among men (4.4%) compared to women (PR: 6.3%, p<0.001; DR: 2.2%, p<0.001) was seen in the first round at a cut-off of 50 ng/ml. No difference in positive predictive value between men and women was found (42% (men) versus 37% (women), p=0.265). Furthermore, a significantly higher false-positive rate (ie, subjects that had a positive FIT, but no advanced neoplasia on follow-up colonoscopy) in men than in women was seen at a cut-off level of 50 ng/ml (6.3% versus 4.1%, p<0.001). Similar differences in these test characteristics were seen in the second round.

*Conclusions and further research*

The higher positivity rate in men at a cut-off of 50 ng/ml was reflected by both a higher true-positive rate (detection rate) and a higher false-positive rate (FPR). The higher detection rate is related to a higher prevalence of advanced lesions in men, and similar differences in detection rates of advanced neoplasia between both sexes were found in two colonoscopy screening studies [33, 34]. The higher FPR in men may be the result of a lower test specificity. Specificity is defined by the proportion of people without the disease that also test negative. We do not know the exact number of people without advanced neoplasia in our study since people with a negative FIT did not undergo colonoscopy. However, given the underlying prevalence of advanced neoplasia in men, the number of men without advanced neoplasia will consequently be lower than the number of women. Therefore, the higher number of male screenees with a false-positive test indicates that FIT specificity is lower in men. This is in line with the results of two aforementioned colonoscopy screening studies [33, 36, 37].

The key question in the interpretation of these findings is whether and to what extent the observed gender differences are of clinical and/or public health relevance. Some studies suggest the cut-off should differ between men and women to reach the same FIT sensitivity in men and women. However, we think it is better to determine the optimal cut-off by other measures, in particular positive predictive value, since the positive predictive value is a measure for efficient use of colonoscopy resources, and also for the individual reflects the chance on an unnecessary invasive test, eg, colonoscopy, with

risk on complications. In addition, colonoscopy capacity is limited and costly. The higher FPR in men in both screening rounds indicates that a significantly larger number of men underwent follow-up colonoscopy and did not have advanced neoplasia. However, the chance that a colonoscopy is unnecessary after a positive FIT is equal in men and women, which is demonstrated by the similar PPV at a cut-off level of 50 ng/ml. Therefore, one could argue not to change cut-off values in men and women. Optimal cut-off values for men and women can further be determined by taking other major determinants into account, including the incidence of neoplasia, the life expectancy, the intended screening interval, and cost-effectiveness. This can be realized using the current data combined with a microsimulation model [14, 15]. The resulting information will be of great value, since FIT screening is expected to become current practice in more and more countries in the upcoming years.

**Gender differences in FIT performance - cost-effectiveness analysis**

Therefore, in **chapter 5**, we aimed to determine optimal screening strategies for men and women using a microsimulation model to estimate test characteristics of FIT for men and women separately based on the CORERO trial. Subsequently, we used the model to determine the optimal screening strategies for men and women and to study if screening men and women with a different screening strategy is beneficial in terms of cost-effectiveness. Gender-specific FIT sensitivity and specificity were estimated based on first round positivity and detection rates in men and women observed in a FIT screening pilot (CORERO-1). Subsequently, the MISCAN-Colon model was used to estimate the harms, benefits and costs of 480 different gender-specific FIT screening strategies. These screening strategies varied with respect to the cut-off value (ie, 50, 75, 100, 150, and 200 ng/ml), the age to start and stop screening, and the interval between successive screening rounds. FIT sensitivity for non-advanced (1.0% versus 19.1% per lesion) and advanced adenomas (26.5% versus 46.7%) was significantly lower in women than in men. Consequently, annual FIT screening from age 50-80 was less effective in participating women (65% mortality reduction) compared to participating men (71% mortality reduction). FIT screening resulted in fewer QALYs gained (91 versus 116) and higher costs (€152,175 versus €40,889) in women compared to men. However, the *incremental* costs and benefits of this screening strategy compared to less intensive screening strategies were very similar (approximately €6000,- per QALY). Consequently, screening strategies stratified by gender resulted in similar costs and QALYs gained when compared to uniform screening.

*Conclusions and further research*

Various investigators have argued that CRC screening should be stratified based on gender because of the difference in prevalence of (advanced) neoplasia and the gender

related differences in FIT accuracy [32, 38]. Our study shows that the added value of gender-based screening is marginal. In less intensive screening programmes, screening stratified by gender is only slightly more cost-effective than screening men and women with the same screening strategy, while for more intensive screening programmes the optimal strategy is the same in men and women. Screening stratified by gender also has disadvantages as it might complicate the organization of the screening programme and may even result in lower attendance. Men and women may be confused by the differential recommendations to the point that they no longer attend. Even a slight impact of stratified screening recommendations on attendance will easily offset its marginal benefit. On the other hand, gender-based screening may increase adherence with screening recommendations because participants feel that the recommendations are better tailored to their risk. Future research is needed to determine what the impact of risk-stratified screening is on adherence. Another area for future research is to evaluate the comparative effectiveness of FIT screening with other screening modalities in men and women. Since sensitivity of FIT is lower in women than men, the comparative effectiveness of other screening modalities might be different. The additional sensitivity of colonoscopy compared to FIT for example is lower in men compared to women. Earlier studies showed not much difference in cost-effectiveness between a FIT screening programme and a colonoscopy screening programme [39]. If the lower sensitivity of FIT in women does not apply to other stool-based tests, the comparative effectiveness of newer tests such as stool-DNA-tests, could also be different in men than in women.

## QUALITY OF LIFE IN PARTICIPANTS OF A CRC SCREENING PROGRAMME

A matter that is very relevant on a population level but not often addressed, is whether participating in a CRC screening programme has an effect on quality of life (QOL). Benefits such as life-years gained due to early detection and subsequent early treatment need to be outweighed against the burden of screening, such as the anxiety and distress due to participation, both with respect to the invitation and the test itself. Two studies that investigated QOL effects in CRC screening showed that screening did not appear to have adverse psychological effects in the longer term (ie, 44 weeks) [40, 41]. These studies focused on colonoscopy- and flexible sigmoidoscopy (FS)-based screening. Two other studies among participants in a FOBT screening programme and one FS screening study assessing worries associated with CRC screening, showed that most of the participants did not experience an increase in anxiety [42-44]. Control groups consisted of an age- and gender-matched group not invited for screening [42, 44] and persons who had received the invitation letter but had not attended the screening programme [43]. Our study group demonstrated that FIT slightly outperforms gFOBT with a lower

level of reported discomfort and overall burden [45]. More information on QOL among participants in CRC screening by means is needed. In **chapter 6**, we therefore assessed QOL of participants in a FOBT- and FS-based CRC screening programme. Participants were sent a questionnaire, which included validated measures on generic health-related QOL, generic anxiety and screen-specific anxiety. Both FIT and FS participants, either with positive or negative test results, were addressed. The response rate was 73% (1289 out of 1772) for FIT and 78% (536 out of 689) for FS participants, with mean ages varying from 63–66 years. Positive FIT participants had worse physical (PCS-12, 47.1 versus 48.3, p=0.02), but equal mental QOL scores (MCS-12, 51.1 versus 51.6, p=0.26). Positive and negative FS participants had similar QOL scores. Furthermore, QOL scores were similar in positive FIT participants with either a negative or a positive colonoscopy. Both FIT and FS participants with a positive test result reported more screen-specific anxiety than negative FIT and FS participants. Positive FIT participants had worse generic anxiety scores than negative FIT participants. Positive and negative FS participants had similar generic anxiety scores.

*Conclusions and further research*

In this questionnaire study with a high response rate both FIT and FS participants with a positive test result showed more screen-specific anxiety than participants with a negative test result, and FIT participants with a positive test showed worse mental QOL scores than participants with a negative test. To indicate clinical relevance the minimal important difference (MID) was used. The MID is defined as the smallest change in a patient-reported outcome that is perceived by patients as beneficial or that would result in a change of treatment. The MID was operationalised as a difference of at least half a standard deviation [46]. Although some differences in QOL scores were statistically significant, all differences in QOL scores between negative and positive FIT and FS participants were rather small and none of them exceeded the MID. These are therefore not clinically relevant. Literature on CRC screening shows that even in subjects with a false-positive test result, screening for CRC has no adverse effect on anxiety on the long-term [44, 47]. Population-based screening studies regarding prostate and breast cancer found similar results [48, 49]. Apparently, a false-positive test result does not negatively affect participants' QOL. These findings are in accordance with our study. Possible explanations for these mainly positive effects of CRC screening in participants with a true-positive result could be that, although participants are worried because of the possibility of having colorectal cancer, they are either simultaneously relieved that only pre-malignant lesions had been found and removed and that they will be screened regularly to prevent colorectal cancer, or they are reassured because an (asymptomatic) cancer was found and further treatment was initiated. In case of a false-positive result, we hypothesized that participants are relieved that no abnormalities were found dur-

ing further investigations. Overall, abovementioned results indicate that a positive FIT seems to have limited effect on the QOL of participants. A recent prospective study from Australia where 301 FIT participants received questionnaires after the result of the FIT was notified and one year after the result notification, found worse QOL scores and higher anxiety scores in positive FIT participants compared to negative FIT participants after the result of the FIT was notified and one year after the notification [50]. Increased anxiety did decline over time [50]. In contrast to our study, the results between positive and negative participants were clinically relevant. More prospective studies with a higher number of FIT participants needs to be conducted, to further investigate this matter. Only this way, we will fully be able to evaluate the impact of screening on QOL and anxiety and anticipate on possible negative side-effects.

## SECOND LOOK COLONOSCOPIES IN A FIT-BASED CRC SCREENING POPULATION

More and more CRC screening programmes are being implemented worldwide and recent EU guidelines recommend FIT for primary screening followed by colonoscopy in case of a positive FIT [51]. Colonoscopies are however not perfect in preventing CRC, with miss rates for CRC and adenomas that are low, but not negligible [52, 53]. Missed and incompletely resected lesions are recognized as important contributors to interval cancers [54, 55]. A so-called second look colonoscopy is advised in case of inadequate bowel cleansing, incomplete removal of lesions, or after an incomplete examination of the colon (eg, no caecal intubation) [56, 57]. Screening colonoscopies after positive FIT have a high prevalence of advanced adenomas of approximately 35-45% [12, 19, 58]. En bloc or piecemeal resection is associated with a relatively high rate of local residual or recurrent neoplasia at the resection site [56, 57, 59, 60]. Therefore, one may hypothesize that in a FIT-based screening setting an increased number of second look colonoscopies could be found [11, 12, 19]. Although multiple colonoscopies per patient could have a substantial impact on the required colonoscopy capacity and health care system, little is known about the number of second look colonoscopies in a screening population. In **chapter 7**, we therefore aimed to evaluate the number and indications of second look colonoscopies in FIT-based CRC screening. All colonoscopies performed in average-risk subjects, aged 50-74 years, who were approached for a maximum of three rounds of FIT screening were prospectively registered. A positive FIT was defined by a haemoglobin concentration ≥ 50 ng/ml. A second look colonoscopy was defined as any colonoscopy performed following a screening colonoscopy within one year. A total of 105 (8.6%) of patients underwent a second look colonoscopy, of whom 30 (28.6%) underwent more than one colonoscopy (range 2-9), leading to a total of 149 (12%) additional colonos-

copies. The most frequently reported indications for a second look colonoscopy were assessment of completeness of removal of a neoplastic lesions (41.9%) and need for further polypectomy (34.3%). Risk factors were advanced adenomas and poor bowel preparation ($p<0.001$). High faecal haemoglobin concentration was the only predictor of a second look colonoscopy before the index colonoscopy.

*Conclusions and further research*

The results of the present study indicate that in 8.6% of screening colonoscopies a second look colonoscopy was performed within one year after the initial screening colonoscopy. In 3% of patients more than one colonoscopy was performed after the initial procedure. A second look colonoscopy was performed in over two-thirds of our patients because the need for further popypectomy, and for assessment of complete removal of advanced neoplasia. According to literature, a second look colonoscopy for the control after polypectomy occurs in around 1% or 2% of the procedures with endoscopic treatment, and is usually limited to the previously treated area [61]. Our results indicate a higher rate of second look colonoscopies. These findings are supported by the fact that significantly more advanced neoplasia were found in patients undergoing a second look colonoscopy. Advanced colorectal neoplasia is associated with a higher FIT haemoglobin concentration [62, 63]. This explains the relation between a high faecal haemoglobin concentration and the need for a second look colonoscopy. Our findings could be of clinical importance and guidance for endoscopists and patients. As a high faecal haemoglobin concentration is indicative of a more complex colonoscopy, it may help the attending physician to be prepared for a more difficult procedure and inform the patient accordingly. Overall, the abovementioned results suggest that second look colonoscopies have a substantial influence on colonoscopy burden in a FIT-based screening setting and should be taken into account when estimating colonoscopy capacity.

## CONCLUSION

Based on the technological advances of FIT screening the Dutch Health Council recommended the Minister of Health, Welfare and Sport on May 2011 that a nationwide FIT-based CRC screening programme should be implemented in the Netherlands [64]. The results of the first and second CORERO-trials helped to form the basis for the implementation of this CRC screening programme. On January 2014, a biennial FIT screening programme was started in which men and women in the ages between 55-75 years are gradually invited for biennial FIT screening using a cut-off of 75 ng/ml [16]. In this thesis we investigated several aspects which could contribute to improving the current national screening programme. We found that 1-sample FIT screening at low cut-off

levels remains preferred over 2-sample FIT screening based on a similar diagnostic yield over two consecutive rounds. Furthermore, we performed a cost-effectiveness analysis in which it was shown that FIT screening stratified by gender does not have benefits in terms of cost-effectiveness over uniform FIT screening. Our study on quality of life in CRC screening participants indicated that a positive FT seems to have a limited effect on the QOL of participants. These findings support the current similar 1-sample FIT screening strategy in men and women. The increasing waiting lists for colonoscopies have shown to be challenge in the implementation of the national screening programme [65]. We found that in 9% of screening colonoscopies a second look colonoscopy was performed, ranging from 2 to 9 colonoscopies per patient, and resulting in a 12% increase in required colonoscopy capacity. In over two-thirds a second look colonoscopy was performed because of an incomplete polypectomy or to examine the polypectomy scar for residual neoplastic tissue. These results suggest that second look colonoscopies have a substantial influence on colonoscopy burden in a FIT-based screening setting and should be taken into account when estimating colonoscopy capacity.

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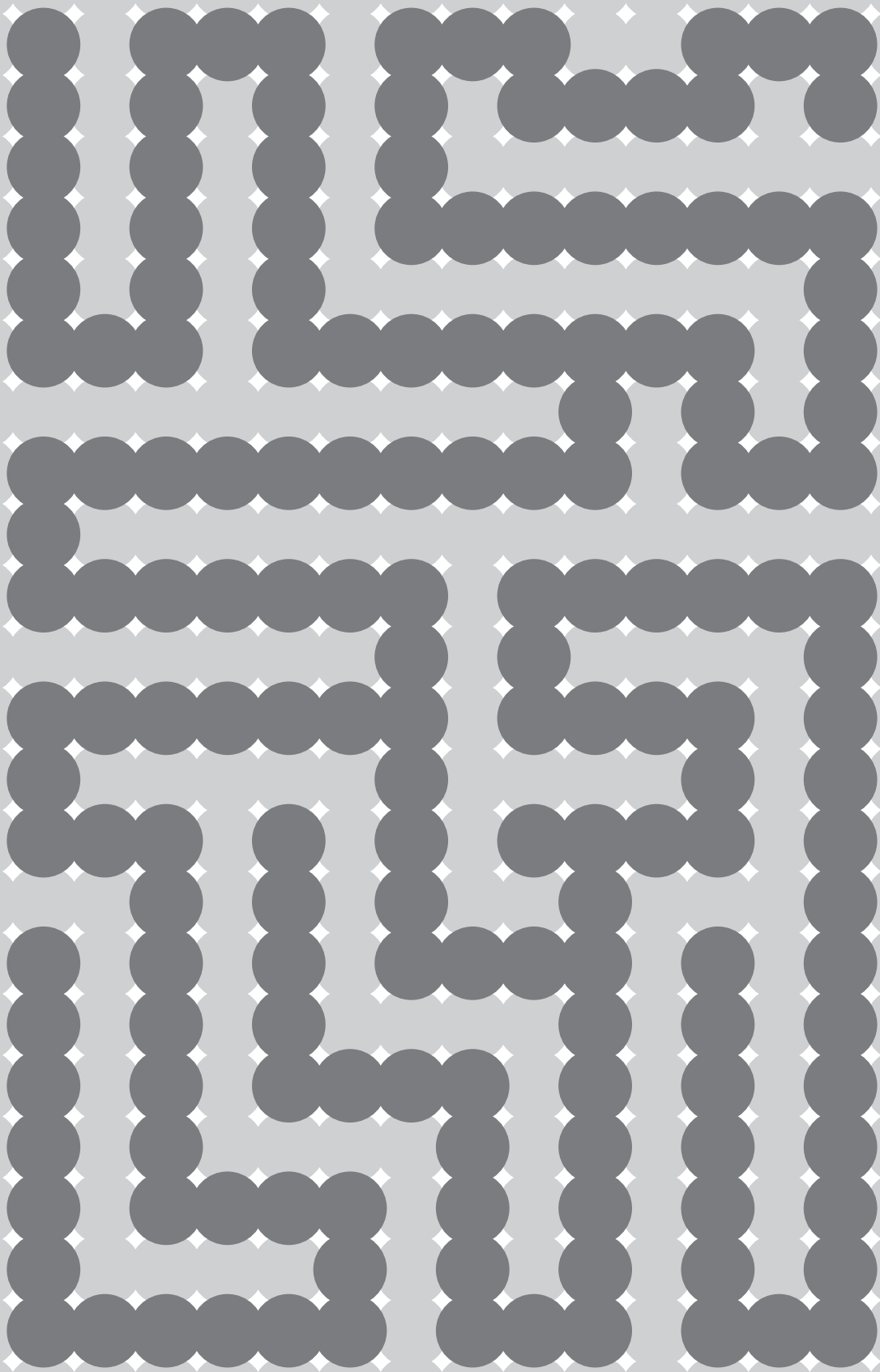


# Nederlandse samenvatting

Dikke darmkanker is een ziekte die veel voorkomt in de westerse wereld. Wereldwijd wordt de diagnose darmkanker gesteld bij circa 1.2 miljoen mensen per jaar en men heeft gedurende het leven een kans van 5% om ooit darmkanker te krijgen. Belangrijk is dat darmkanker wordt gekenmerkt door een lang voorstadium, waarbij de progressie van adenoom tot invasieve kanker jaren duurt. Darmkanker voldoet daarmee aan de criteria van Wilson en Jungner, aangezien het een belangrijk gezondheidsprobleem vormt dat een significante morbiditeit en mortaliteit kent, het een ziekte is met een behandelbaar voorstadium en vroege opsporing van darmkanker de prognose verbetert.

**Hoofdstuk 1** geeft een introductie over darmkanker, de verschillende screeningsmethoden die beschikbaar zijn voor screening naar darmkanker, en informatie over het landelijk bevolkingsonderzoek naar darmkanker dat in januari 2014 in Nederland van start is gegaan. Hierbij worden mannen en vrouwen in de leeftijd van 55-75 jaar geleidelijk uitgenodigd voor tweejaarlijkse screening met een immunochemische feces occult bloed test, de zogenaamde FIT. In dit hoofdstuk wordt verder een overzicht gegeven van de doelen en inhoud van dit proefschrift. Er zijn namelijk vele aspecten van FIT screening die nader dienen te worden onderzocht. Dit proefschrift richt zich op verscheidene onderdelen hiervan.

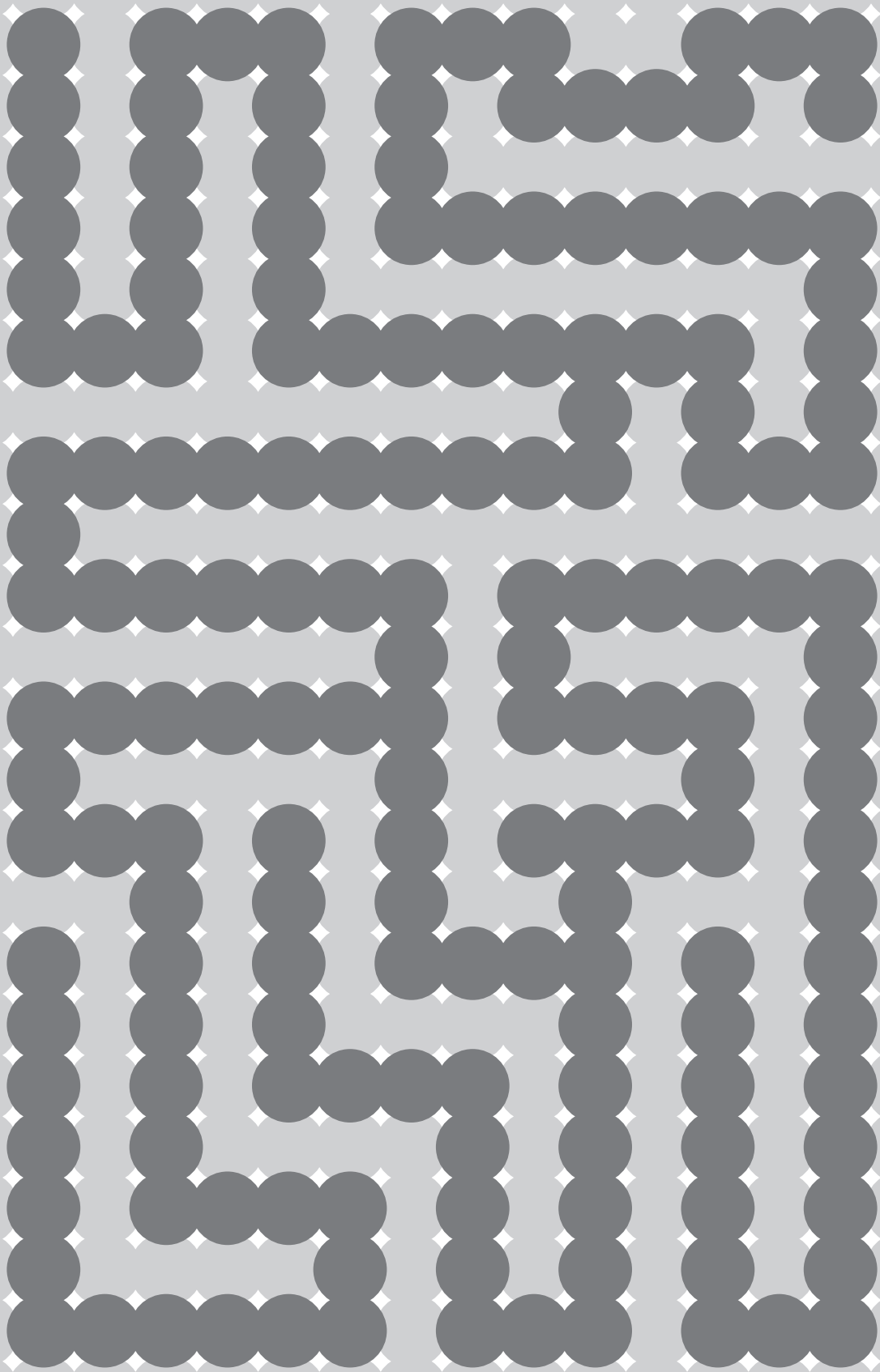
Het is bekend dat opeenvolgende screeningsronden nodig zijn om de impact van FIT screening op populatieniveau te optimaliseren. De deelname en detectiegraad van darmkanker en hoog-risico neoplasieën over opeenvolgende ronden dragen bij aan de effectiviteit van screeningsprogramma's middels FIT, maar de informatie hierover is beperkt. In **hoofdstuk 2** hebben we daarom de opkomst en detectiegraad van drie ronden screening met de FIT onderzocht. We vonden hierbij een hoge en toenemende opkomst over drie ronden, wat impliceert dat FIT screening acceptabel is op populatieniveau. Verder zagen we een daling in de detectie van darmkanker en hoogrisico neoplasieën, wat ondersteunt dat opeenvolgende FIT screening een positief effect heeft door het verminderen van het voorkomen van deze afwijkingen. We weten verder dat CRC en hoogrisico neoplasieën gemist kunnen worden met screening met één ontlastingstest. Door middel van screenen met twee ontlastingstesten verhoog je de test sensitiviteit; het risico op het missen van een afwijking wordt hierdoor verminderd. Een eerdere studie heeft laten zien dat er in de eerste ronde geen verschil was in opkomst tussen screening middels één en twee testen, maar dat er significant meer hoogrisico neoplasieën en darmkanker werden gevonden indien er gescreend wordt middels twee testen. Meer informatie is nodig over screenen met twee testen in vervolgronden. In **hoofdstuk 3** hebben we daarom gekeken naar de opkomst en opbrengst van herhaald screenen met twee testen, en deze uitkomsten vergeleken met herhaald screenen met één test. Hierbij vonden we dat herhaald screenen met twee testen gepaard gaat met

een stabiele en hoge opkomst gedurende twee screeningsronden. Dit ondersteunt het feit dat screening door middel van twee testen acceptabel is. Verder hebben we gekeken naar de zogenaamde 'diagnostische opbrengst', deze geeft weer hoeveel gevallen van darmkanker en hoogrisico neoplasieën er worden gevonden per 1,000 mensen die worden uitgenodigd voor twee ronden screening. De diagnostische opbrengt na twee ronden screening met twee testen was niet significant verschillend ten opzichte van de yield na twee ronden screening met één test. Derhalve heeft herhaald screenen met één ontlastingstest de voorkeur boven screenen met twee testen.

Momenteel worden er voor mannen en vrouwen dezelfde screeningsstrategieën gehanteerd. Verschillende screeningsstudies waarbij colonoscopie als primair screeningsinstrument werd gebruikt, hebben een hogere incidentie en prevalentie van darmkanker en hoogrisico neoplasieën in mannen ten opzichte van vrouwen laten zien. Verder heeft een aantal studies waarbij mensen een ontlastingstest voorafgaand aan de colonoscopie kregen een hogere sensitiviteit in mannen laten zien. Data over verschillen tussen mannen en vrouwen in een screeningssetting waarbij FIT het primaire screeningsinstrument is, ontbreken. Daarom hebben we in **hoofdstuk 4** mogelijke verschillen tussen mannen en vrouwen in effectiviteit van FIT screening onderzocht in een screening-naïeve populatie. In beide screeningsronden was de opkomst in vrouwen hoger. Verder hadden mannen een hoger positiviteitspercentage en detectiegraad voor darmkanker en hoogrisico neoplasieën dan mannen, maar werd geen verschil gezien in de positief voorspellende waarde tussen mannen en vrouwen. Tevens werd naast het hogere positiviteitspercentage ook een hoger 'fout-positiviteitspercentage' gezien bij mannen; dit zijn mensen die een positieve FIT hadden, maar waar bij colonoscopie geen darmkanker of hoogrisico neoplasieën werden gevonden. Het hogere positiviteitspercentage bij mannen werd daarmee weerspiegeld door zowel een hoger 'terecht-positiviteitspercentage' (de detectiegraad) als een hoger fout-positiviteitspercentage. De hogere detectiegraad hangt samen met de hogere prevalentie van darmkanker en hoogrisico neoplasieën in mannen. Het hogere fout-positiviteitspercentage impliceert dat de specificiteit in mannen lager is. Op basis van een gelijke effectiviteit van de FIT, die blijkt uit de gelijke positief voorspellende waarde bij mannen en vrouwen, wordt het gebruik van dezelfde afkapwaarde bij mannen en vrouwen aanbevolen. In **hoofdstuk 5** hebben we vervolgens door middel van het gevalideerde MISCAN-Colon microsimulatiemodel onderzocht of verschillend screenen in mannen en vrouwen kosteneffectief is. We vonden hierbij dat de effectiviteit van FIT screening hoger is in mannen dan in vrouwen door een hogere FIT sensitiviteit en een hogere prevalentie van darmkanker en hoogrisico neoplasieën in mannen. Optimale screeningsstrategieën verschillen echter niet tussen mannen en vrouwen wat betreft screeningsinterval, leeftijd en FIT afkapwaarden. De meest effectieve FIT screeningsstrategie bleek hetzelfde voor mannen en vrouwen. Het is daarom

niet noodzakelijk een andere strategie voor mannen dan voor vrouwen te gebruiken, aangezien deze strategie geen voordelen oplevert in kosteneffectiviteit ten opzichte van uniforme screening.

Op populatieniveau is het zeer belangrijk of deelname aan een screeningsprogramma naar darmkanker invloed heeft op de kwaliteit van leven (QOL). In **hoofdstuk 6** hebben we dit onderzocht door deelnemers vragenlijsten te sturen, waarbij gebruik werd gemaakt van gevalideerde maten voor het bepalen van de kwaliteit van leven en bezorgdheid. Zowel deelnemers aan de FIT als deelnemers aan screening met de sigmoidoscopie (FS) werden uitgenodigd om een vragenlijst in te vullen. Een hoog responspercentage onder beide groepen werd gezien. Positieve FIT deelnemers lieten slechtere fysieke, maar gelijke mentale QOL-scores zien ten opzichte van negatieve FIT deelnemers. Bij FS-deelnemers werden er geen verschillen gezien in QOL-scores tussen positieve en negatieve deelnemers. Verder lieten zowel positieve FIT- als FS-deelnemers meer bezorgdheid gerelateerd aan screening zien dan negatieve deelnemers. Hoewel bovengenoemde verschillen statistisch significant zijn, waren alle verschillen in scores tamelijk beperkt en niet klinisch relevant. Deze resultaten impliceren daarmee dat de belasting van deelname aan screening gering is. Een prospectieve studie dient te worden verricht om deze resultaten te bevestigen. Tot slot hebben we gekeken naar zogenaamde 'second look' colonoscopieën, scopieën die worden verricht binnen een jaar na de eerste screeningscolonoscopie. Er is weinig bekend over het voorkomen van deze scopieën in een screeningspopulatie, terwijl meerdere scopieën per patiënt een substantiële impact kunnen hebben op de colonoscopiecapaciteit. In **hoofdstuk 7** hebben we het aantal second look colonoscopieën in een FIT screeningsprogramma onderzocht. In bijna 9% van alle screenings colonoscopieën werd een second look colonoscopie verricht, variërend van 2 tot 9 scopieën per patiënt. Dit leidde tot een totaal van 149 (12%) additionele colonoscopieën. In twee-derde van de gevallen werden deze verricht ter nacontrole van een volledig verwijderde poliep of vanwege verdere poliepectomie die nodig was. De hoogte van de FIT uitslag was de enige significante voorspeller voorafgaand aan de screeningscolonoscopie. Deze resultaten suggereren dat second look colonoscopieën een substantiële bijdrage kunnen leveren aan de colonoscopiebelasting in een FIT screeningssetting en moeten worden meegenomen bij schattingen omtrent de colonoscopiecapaciteit. In **hoofdstuk 8** worden de belangrijkste bevindingen uit dit proefschrift en aanbevelingen voor toekomstig onderzoek beschreven.



# 10

## Dankwoord

Vele mensen hebben bijgedragen aan de totstandkoming van dit proefschrift. Een aantal van hen wil ik graag in het bijzonder bedanken voor hun betrokkenheid.

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D

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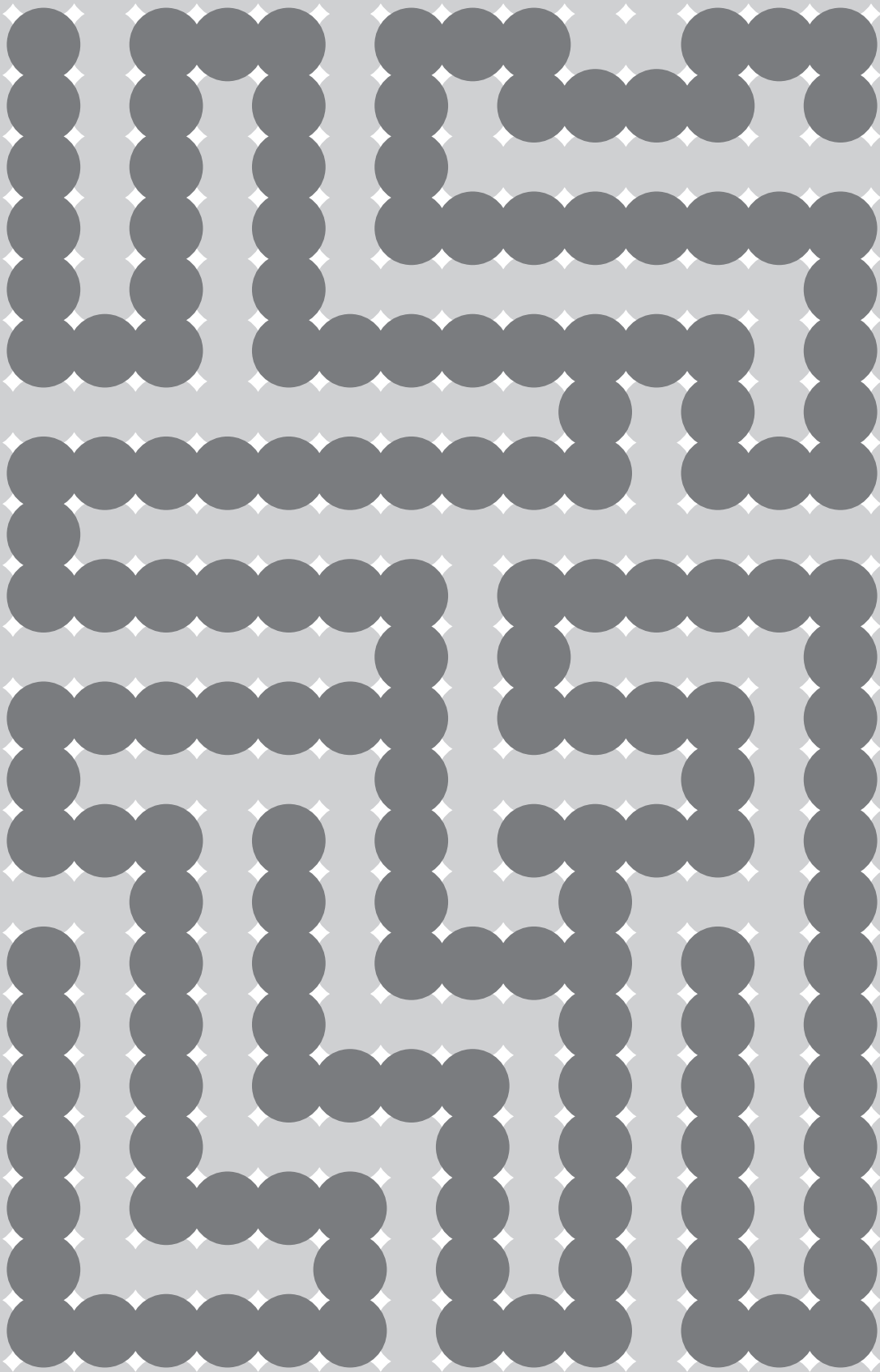
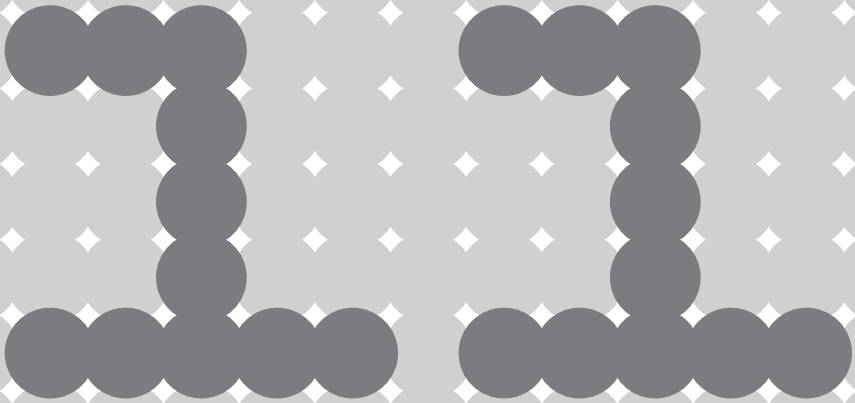
Atija





# PhD Portfolio

**Oral presentations**

2013 Attendance and diagnostic yield of repeated two-sample faecal immunochemical test screening in a randomized population-based colorectal cancer trial
*Digestive Disease Week, Orlando, USA*

2012 Quality of life in participants of a CRC screening programme
*United European Gastroenterology Week, Amsterdam, the Nederlands*

2012 Bevolkingsonderzoek darmkanker
*Congres bevolkingsonderzoek darmkanker (NVMDL & RIVM), Utrecht, the Netherlands*

**Poster presentations**

2014 Increase in participation rate with successive rounds of FIT screening
*Digestive Disease Week, Chicago, USA*

2012 Sex differences in performance of FIT in colorectal cancer screening
*United European Gastroenterology Week, Amsterdam, the Nederlands*

2012 Sex differences in localization of advanced colorectal neoplasia detected by FIT
*Digestive Disease Week, San Diego, USA*

**Attended workshops**

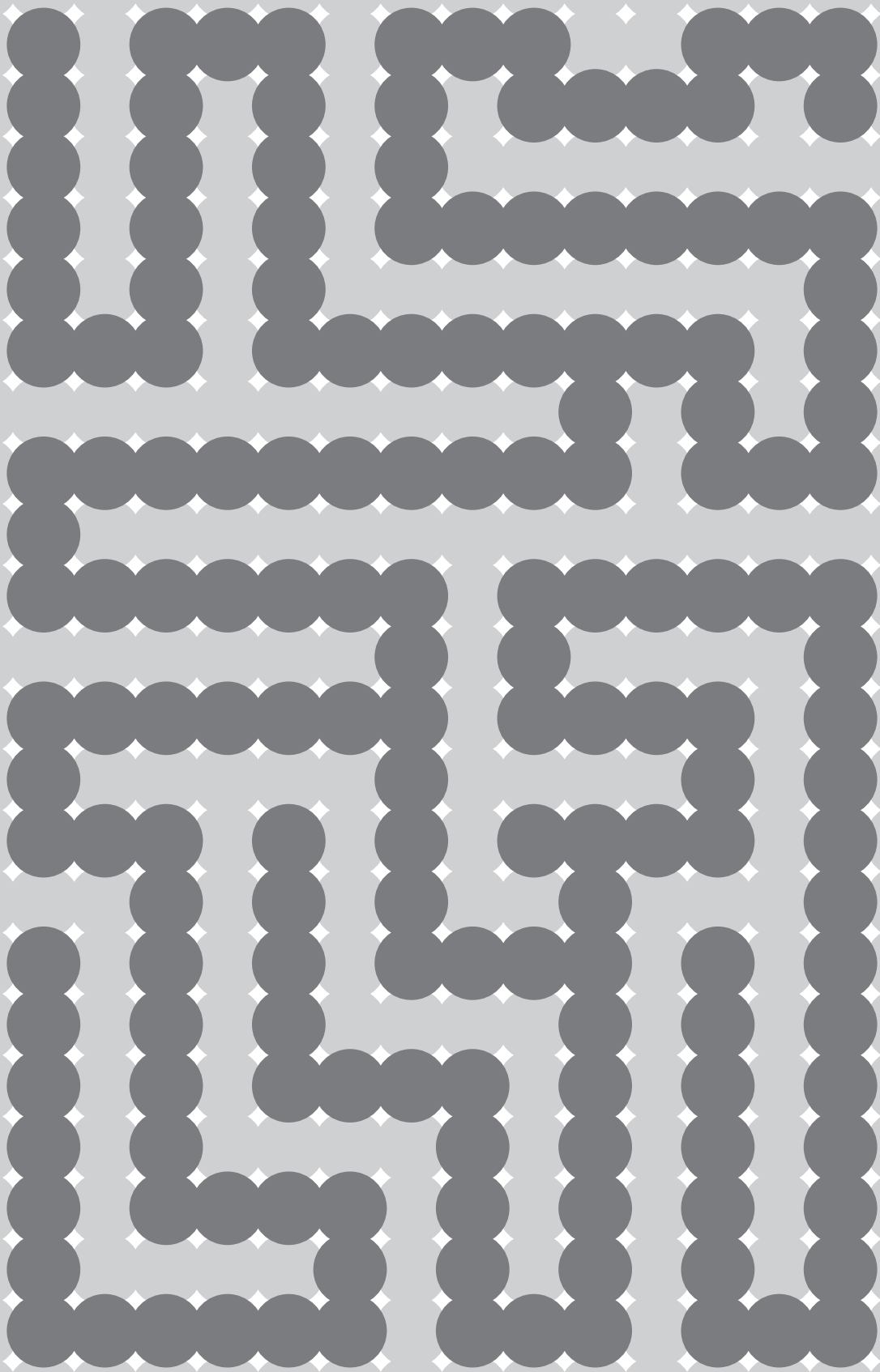
2012 Biomedical English writing and communication
*Erasmus University Medical Centre, Rotterdam, the Netherlands*

2012 Biostatistics for clinicians
*Netherlands Institute for Health Sciences, Rotterdam, the Netherlands*

2012 Regression analysis for clinicians
*Netherlands Institute for Health Sciences, Rotterdam, the Netherlands*

**Membership**

2011 Dutch Society of Gastroenterology



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## List of publications

1. Kapidzic A, Korfage IJ, van Dam L, van Roon AH, Reijerink JC, Zauber AG, van Ballegooijen M, Kuipers EJ, van Leerdam ME. Quality of life in participants of a colorectal cancer screening programme. *British Journal of Cancer 2012;107(8):1295-301*

2. Kapidzic A, Kuipers EJ. Coloncarcinoom – Preventie en Screening. *Farmacotherapie Online 2013, www.farmacotherapie.org*

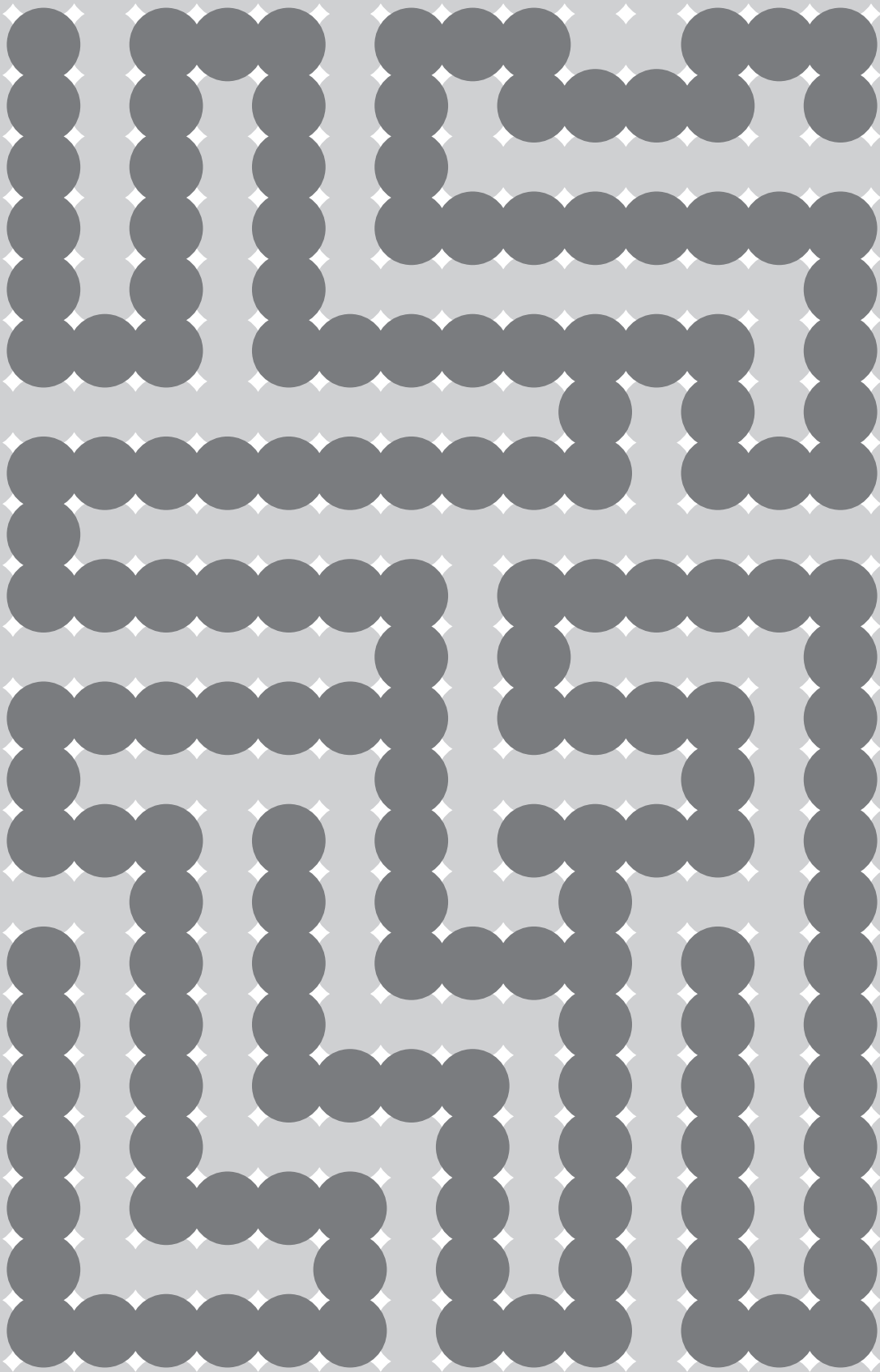
3. Kapidzic A, Grobbee EJ, Hol L, van Roon AH, van Vuuren AJ, Spijker W, Izelaar K, van Ballegooijen M, Kuipers EJ, van Leerdam ME. Attendance and yield over three rounds of population-based faecal immunochemical test screening. *American Journal of Gastroenterology 2014;109(8):1257-64*

4. Kapidzic A, van Roon AH, Hol L, van Vuuren AJ, van Ballegooijen M, Lansdorp-Vogelaar I, Spijker W, Izelaar K, van Leerdam ME, Kuipers EJ. Attendance and diagnostic yield of repeated two-sample faecal immunochemical test screening for colorectal cancer. *Submitted*

5. Kapidzic A, van der Meulen MP, Hol L, van Roon AH, Looman CW, Lansdorp-Vogelaar I, van Ballegooijen M, van Vuuren AJ, Reijerink JC, van Leerdam ME, Kuipers EJ. Gender differences in faecal immunochemical test performance for early detection of colorectal neoplasia. *Submitted*

6. van der Meulen MP, Kapidzic A, van Leerdam ME, van der Steen A, Kuipers EJ, Spaander MC, de Koning H, Hol L, Lansdorp-Vogelaar I. Do men and women need to be screened differently with faecal immunochemical testing? A cost-effectiveness analysis. *Submitted*

7. Grobbee EJ, Kapidzic A, van Vuuren AJ, van Leerdam ME, lansdorp-Vogelaar I, Looman CW, Bruno MJ, Spaander MC. Second look colonoscopies and the impact on capacity in FIT-based colorectal cancer screening. *Submitted*



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## Curriculum Vitae

Atija Kapidzic was born in Zvornik, Bosnia and Herzegovina on the 12th of June in 1987. In December of 1992 she moved to the Netherlands with her parents and brother. She graduated from secondary school at the Sint-Montfort College in Rotterdam in 2005, after which she attended the medical school at the Erasmus University in Rotterdam. During her medical studies she did a research internship regarding quality of life in participants of a colorectal cancer screening programme. This internship formed the basis for her PdH project at the department of Gastroenterology & Hepatology at the Erasmus University Medical Centre. Atija starts her residency of Gastroenterology at the Medisch Centrum Alkmaar in January of 2015.