General discussion

The general aim of this thesis was to evaluate the performance of the national colorectal cancer (CRC) screening programme with biennial faecal immunochemical testing (FIT) in the Netherlands during the implementation phase. In this chapter, I first will discuss the most important findings of this thesis. Secondly, I will discuss the methodological considerations of the studies described in this thesis. Finally, I will elaborate on future perspectives and draw final conclusions.

9.1 MOST IMPORTANT FINDINGS OF THE DUTCH COLORECTAL CANCER SCREENING PROGRAMME DURING THE IMPLEMENTATION PHASE

From 2014 until 2017, 5.3 million individuals were invited to participate. A total of 3.9 million individuals returned their FIT. The FIT was positive for 223,043 individuals. A total of 180,398 individuals underwent a colonoscopy. During colonoscopy, 14,084 CRCs and 76,022 AA were diagnosed. Based on these promising results during the implementation phase, it is expected that on the long-term CRC-related mortality will decrease, which is observable by 2029. Below the most important performance indicators of the Dutch CRC screening programme will be discussed separately, combining results of different chapters of this thesis.

Participation rate FIT

In **Chapter 2** we observed a very high participation rate (71.3%) in the first year of the national CRC screening programme. In the study described in **Chapter 4** we evaluated participation in the second screening round and estimated a consistent participation of 93% among the individuals that previously participated. The high FIT participation rate is still one of the highest across the world, as was also confirmed in **Chapter 8**.[1] Such high participation rate to primary screening test offered by the Dutch government is also observed in the two other large cancer screening programmes; 78.8% for breast cancer and 64.6% for cervical cancer.[2,3] High participation rate is a relevant finding, as high participation will eventually result in high CRC detection rates per invitee.[4-6] In the pilot study a stable FIT participation between 60-62% was observed over four screening rounds.[7] If the results of the pilot study reflect what will take place in the national screening programme, the participation rate will remain high in coming years.

Despite the high participation in screening in the Netherlands, still almost 30% of the population does not participate in the CRC screening programme. The question is how much effort should be put in reaching out to nonparticipants. Striving for 100% uptake of the primary screening test should in my opinion not be the goal. It is of great importance that all individuals participating in screening do make an informed choice. The goal should be to increase the number of individuals making an informed choice to participate in screening. We know from previous studies among the Dutch population, that reasons for

nonparticipation are often related to lack of knowledge about CRC.[8,9] Therefore, reaching out to nonparticipants is beneficial and should be undertaken. Up to now, it is unknown how to approach this in the Netherlands.

FIT positivity

In chapter 2, we described that weekly monitoring revealed that FIT positivity rate in the Dutch CRC screening programme was higher than anticipated, with an age-adjusted positivity rate of 10.7% at the cut-off of 15 µg Hb/g faeces. Consequently, a higher number of individuals were referred for colonoscopy. This higher positivity rate together with the lower than anticipated PPV for CRC and AA, resulted in the urgency to adjust the CRC screening programme. The outcomes of the programme were evaluated with a decision analysis tool, aiming to identify the best option to optimise the screening programme. Three options were evaluated: increase cut-off, postpone screening in selected age groups and forego screening in older age groups. This analysis showed that increasing the cut-off level not only resulted in lowest decrease in CRC deaths prevented, but also resulted in a balance between harms and benefits of screening in accordance with that aimed for at start of the programme.[10] The age-adjusted positivity rate of 6.7% at the higher FIT cut-off was now in line with the expected positivity rate of 6.4%.

The higher than anticipated positivity rate and subsequent adjustment of the FIT cut-off was widely debated. How could it possible that after extensive preparations, the national CRC screening programme differed so considerably from expectations? The debate was mostly on similarity of different FIT brands. The FIT brand selected through public tender was FOB-Gold (Sentinel, Italy), which differed from the brand OC Sensor (Eiken, Japan) that was used in the pilot studies. Because equal performance of the two FIT brands was uncertain, accuracy of the two FIT brands were compared.[11] Main finding of this study was that faecal Hb concentrations and FIT positivity differed, but similar detection of CRC or AA at a pre-set positivity rate was observed. It is of note that, although FIT positivity rate differed, OC-Sensor had higher positivity rates at lower FIT cut-offs. Therefore, using FOB-Gold instead of OC-Sensor is not the explanation for the higher positivity rate at the start of the programme. Another more likely explanation is that the manufacturers of the stool tests have improved the test itself. Several programmes had shown that the FIT had a worse performance at higher ambient temperature.[12,13] In a response to this unfavourable outcome, we assumed that the buffer of the test has been improved resulting in better preservation of faecal Hb. Other recent studies also using new generation FITs showed no impact on clinical outcome at higher ambient temperatures and delayed sample return time, indicating improved FIT performance.[14,15] One of these studies proved in laboratory a better Hb stability using FITs with improved buffer.[15]

Participation to follow-up colonoscopy

The high FIT participation rate in the current Dutch programme did not apply to participation to follow-up colonoscopy. The observed participation to the colonoscopy follow-up after a positive FIT of 77.8% in the Netherlands is below the recommended acceptable level of 85%, which is a major concern.[16] In **Chapter 8** we observed a higher participation rate to follow-up colonoscopy in surrounding countries. One explanation for the low participation may be that not all colonoscopy results were integrated in ScreenIT (6-8% of all FIT positives), because some individuals may have had a colonoscopy in centres outside the screening programme. Still, effort should be undertaken to increase this low participation rate, because individuals without appropriate follow-up after a positive FIT were seven times more likely to die from CRC than individuals with appropriate follow-up.[17] Higher participation rates could possibly be reached by active involvement of the general practitioner (GP), as described in chapter 8. Especially the involvement of GPs is subject of continuous debate in the Netherlands. At the start, GPs received the result of individuals with a positive FIT if participants entered GP details in the reply form. Since 2017, a reply form is no longer included and consequently GP contact information is often not provided anymore. This situation makes involvement of GPs to increase colonoscopy follow-up difficult. Currently, options to automatically obtain individuals GPs details from existing databases are explored. If legally and technically possible, the FIT result can automatically be sent to the GP which may have a positive impact on the number of individuals with a complete follow-up after positive FIT.

Involvement of the GP would only lead to an increase in colonoscopy participation, if individual's motives for nonparticipation are unjustified. In 2017 a qualitative study using interviews among Dutch invitees was carried out. This qualitative study showed a wide variety of motives for nonparticipation: low risk perception for CRC, alternative explanation for blood loss, not realising consequence of positive FIT, resentment against colonoscopy, aversions to organisational structure, or unwilling to visit a hospital (Bertels et al. *submitted*). The authors concluded that based on these outcomes increasing individual's risk-perception for CRC might be the most effective to increase colonoscopy participation rate, but needs to be further studied. Potentially, GPs can play an important role in explaining risks of CRC to their own patients. Besides individuals' motive, co-morbidities may often be the reason for nonparticipation. However, individuals are not excluded prior to invitation based on their medical history.

Colorectal cancer and advanced adenoma detection

As discussed above, in Chapter 2 we described that the screening programme was optimised by increasing the FIT cut-off. This was predominantly decided because of a lower than anticipated PPV. As described in **Chapter 1**, the Health Council preferred a FIT cut-off of 15 µg Hb/g faeces over 10 µg Hb/g faeces, aiming for a more optimal balance between true and false positives. The PPV as observed in the first half year of 2014 of 42.1% was below

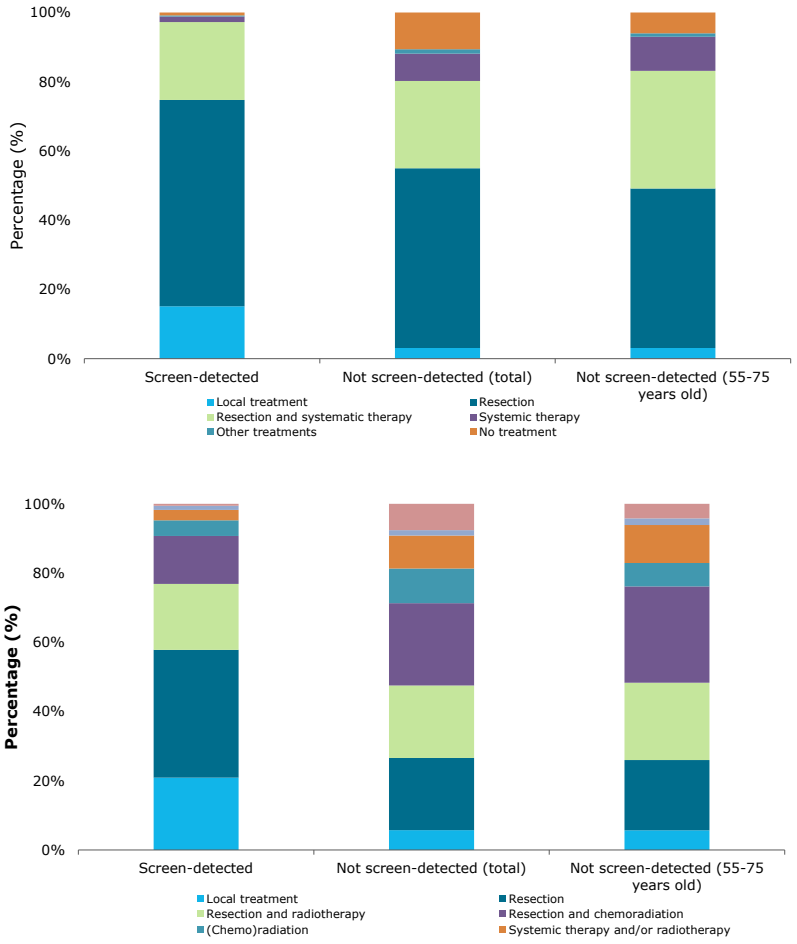
this desired PPV of 51.6%. As a result of the increased FIT cut-off, the PPV for CRC and AA increased to a more desirable level of 49.1%. However, the detection rate decreased for CRC (5.8‰ to 4.4‰) and AA (30.8‰ to 20.6‰), indicating that CRCs will be missed in the first screening round. We hypothesised in Chapter 2 that missed CRCs or AAs in the first screening round, may be detected in the second screening round. In **Chapter 4** we therefore evaluated the impact of the increased FIT cut-off on outcomes of the second screening round. We concluded that using a higher FIT cut-off has limited impact on the CRC and AA detection because a substantial part of the missed lesions will be detected in subsequent screening round. However, after two screening rounds the cumulative yield of CRC and AA is still lower for those tested with the higher cut-off in the first year compared to those tested with the lower cut-off in the first year. It is expected that this difference will become insignificant after more screening rounds. The limited impact of the increased cut-off is also confirmed in **Chapter 5** indicating a small difference in sensitivity between the two FIT cut-offs. Based on both the outcomes of the second screening round and number of interval CRCs, we can cautiously conclude that indeed programme performance has been optimised by increasing the FIT cut-off. Currently, there is no urgent need to change the FIT cut-off. However, it is important to obtain additional information on stage distribution in subsequent rounds, to ensure that CRCs detected in the second round still have a favourable stage distribution at both FIT cut-offs.

In Chapter 4 we also showed that individuals with a faecal Hb concentration between 15-47 µg Hb/g faeces (below FIT cut-off) were 23.2 more likely to have a CRC or AA detected in the consecutive screening round than individuals with no detectable faecal Hb. This makes the previous faecal Hb concentration an important risk factor, which could potentially be used for personalised screening as will be discussed in more detail in the next section.

Stage distribution

In **Chapter 3,** stage distribution of CRCs were compared, showing a more favourable stage distribution (stage I and II) in screen-detected CRCs (66.7%) than in symptom-detected CRCs (39.8%). These findings are in line with expectations, aiming for early detection of cancers thereby improving survival. The results are a promising sign that CRC screening may decrease CRC-related morbidity and eventually mortality rates. Nevertheless, stage distribution of screen-detected CRCs in subsequent screening rounds should be monitored closely to make sure that majority of screen-detected CRCs will still be detected in an early stage. The more favourable stage distribution had also a direct impact on the treatment. Since the introduction of screening in the Netherlands a shift in treatment options was observed for individuals with CRCs detected through screening (Figure 1).[18] Screen-detected CRC patients on average received less invasive and curative treatment compared to symptom-detected CRC patients. This result is satisfying and is an indication that CRC-related morbidity will decrease in coming years.

Figure 1: Treatment options of screen-detected versus non screen-detected (a) colon cancers or (b) rectal cancers in 2015 in the Netherlands.



Location

In Chapter 3 we showed that screen-detected CRCs were more often located in the left hemi colon compared to those CRCs detected without screening. Results of previous studies showed conflicting results.[19,20] Results from Chapter 5 however confirm our hypothesis of a lower FIT sensitivity for right-sided cancers, as many more interval cancers were located right-sided. First explanation might be that FIT is less sensitive for right-sided cancers due to degradation of Hb during colon transit.[21] Another explanation might be that FIT is less sensitive for sessile serrated lesions and this type of polyps are more often detected in the right colon. If these precancerous stages are missed with FIT screening, an increase in proportion of right-sided cancers will appear in the long-term.[22,23] However, this latter

hypothesis can only explain a part of the finding, as approximately 20-30% of the CRCs are thought to derive of the serrated neoplasia pathway. Probably it is a combination of hypotheses, longer transit and lower sensitivity for serrated lesions which makes FIT less suitable for right-sided lesions.

Interval cancers

In Chapter 5 we evaluated the interval CRC incidence rate and FIT sensitivity after the first screening round and the impact of the adjustment of FIT cut-off. We observed a low cumulative incidence of interval CRCs because of the high sensitivity of FIT for CRC. We also concluded that there is an optimum in FIT cut-off at which it is not beneficial (i.e. lowering referrals for colonoscopy with restricted resources) to further increase the FIT cut-off. The main reason for this is that above 80 µg Hb/g faeces there is a large decrease in FIT sensitivity for CRC, while decrease in positivity rate (i.e. number of referrals) is mild. This mild decrease in positivity rate at higher cut-offs was also observed in the FIT pilot study in England.[24] The current FIT cut-off in the Dutch CRC screening programme is far below 80 µg Hb/g faeces. This again confirms that the increase to 47 µg Hb/g faeces was a prudent decision to optimise the screening programme. The outcomes of the study in Chapter 5 however may be informative to design a more tailored screening strategy. Using the information of previous FIT result, individuals at highest risk for interval CRC can be identified. Recent analysis of our research group has shown that individuals with an Hb concentration just below the cut-off of 47 µg Hb/g faeces were 16 times more likely to have an interval CRC. Consequently, tailored screening intervals could be designed to increase the benefits of screening while reducing the harms.

Socioeconomic differences

In **Chapter 6** we evaluated differences in FIT screening by social economic status (SES). We used area SES and compared the performance indicators participation rate, positivity rate, PPV and detection rate for CRC and AA between different SES quantiles. We concluded that CRC and AA yield per invitee does not differ by SES in the Dutch CRC screening programme. FIT screening even has the potential to reduce health inequalities in CRC mortality, because of a higher yield in participants with the lowest SES. However, this is currently offset by the lower participation in this group. A recent review confirms this variation in participation across SES in organised programmes worldwide.[25] Targeting individuals with the lowest SES could be beneficial, as highest health gains can be achieved in this group. However, similar to participation in general, individuals' motive for nonparticipation is unknown. Therefore, it is not clear what the best method is to inform and motivate individuals with the lowest SES to participate in screening. In England extensive research has been conducted to assess the impact of different evidence-based interventions on participation among individuals with the lowest SES. All different types of written materials enclosed with the invitation had no impact on the participation rate; GIST (Goals, Ideas, Step-projects, and Tasks)-based leaflet, narrative leaflet or GP endorsed

invitation.[26] The only method that showed a small increase in participation rate for individuals with the lowest SES was an enhanced reminder letter.[26] Not only an association with SES was observed, but the overall participation increased with an enhanced reminder letter.

Consistency of FIT performance

In the study in **Chapter 7** we estimated consistency of FIT performance over time on positivity and detection rates of CRC and AA within a national FIT-based CRC screening programme. Variation was observed for FIT positivity rate and detection rates of CRC and AA between FIT specimen collection devices (batches) and reagent lots, but no difference in PPV was identified. Based on these outcomes we concluded that clinically the programme is performing well, but there is room for improvement of the current quality assessment of the FIT within the Netherlands. Currently, no acceptable ranges of variation in positivity rate or Hb concentration exist. As a consequence of the observed variation, a discussion was started among parties involved in the Dutch CRC screening programme. Surprisingly, the discussion was not on the result itself, but more on the current set-up of the Dutch quality assurance system for FIT screening. It was realised that there were no acceptable range for observed variation and how to deal with observed variation. A discussion was initiated on important quality aspect of the performance of the FIT test including acceptable range of variation and value assignment. Daily controls in the participating laboratories are currently supervised by the Dutch Foundation for Quality Assessment in Medical Laboratories (SKML). They are carrying out three groups of controls, as described in detail in Chapter 7. However, international standardisation of quality assessment is lacking. Consequently, a national working group 'Quality assurance FIT' was set-up. The aim of this working group is to improve quality assessment of FIT screening in the Netherlands, combining the expertise of different stakeholders.

9.2 LIMITATIONS / METHODOLOGICAL CONSIDERATIONS

The most important event during the implementation phase of the Dutch CRC screening programme was the adjustment of FIT cut-off in the first year. As a consequence, we were able to compare important performance indicators by two cut-offs. A limitation of using data from the implementation phase of the Dutch CRC screening programme is that the screening programme was implemented by birth cohort. The conclusions in this thesis could therefore only be based on selected age groups and not on all age groups (55-75 years old) within the target population. Moreover, for the comparison of different rates of performance indicators by two FIT cut-offs, age-adjusted rates had to be calculated using direct standardisation. Because of large differences in the sample size per age group, wide confidence intervals (CI) were observed. Based on these wide CI, we concluded, for example for FIT sensitivity, that there was no significant difference between the different FIT cut-offs. However, the wide CI

indicates the uncertainty of the age-adjusted rates. Therefore we subsequently carried a logistic regression analysis, which showed a significant difference between the two cut-offs. Another limitation is that we started with older age groups; therefore the conclusions of this thesis are predominantly based on older age groups. In 2019, all age groups will have been invited at least once. More certainty about the performance indicators of the Dutch CRC screening programme should be obtained in the coming years, when all age groups have been invited, to ensure the programme is still performing in line with the expectations.

Another limitation is the completeness of the national information system (ScreenIT). ScreenIT is an excellent system which automates a large part of the screening process, from selection of eligible individuals of screening to obtaining result of endoscopy. However, in the first place it has been developed to structure the logistics of the screening process. As a result, obtaining data for scientific purpose has been a challenge. For example, for each individual polyp detected, pathology results cannot be linked directly to endoscopy results yet. This means that we know for a specific individual from the endoscopy report that there were four polyps detected and removed and one of them was large (> 10 mm). From the pathology report, we know that three of the polyps were adenomas and one was hyperplastic. We cannot distinguish whether the large polyp from the endoscopy was the adenoma or hyperplastic. In such situations we assumed the large polyp to be adenomatous, which is reasonable in most cases, but may have led to a small overestimation of AA. Another problem is that, especially as a result of long waiting periods in the first year, individuals may have had a colonoscopy scheduled outside of the screening programme. The results of these colonoscopies were not entered in ScreenIT. We estimated with data of national pathology database PALGA that 6-8% of the individuals with a positive FIT in 2014 had a colonoscopy outside the programme. It is expected that this percentage will be lower now the programme is fully implemented and waiting periods have been reduced and more colonoscopy centres joined the screening programme.

The last limitation is the difference in data collection and definition of performance indicators between the four CRC screening programmes described in Chapter 8. In France there is no national centralised information system collecting data on quality indicators and diagnostic yield. In Flanders a different definition of AA was used, because no data on size of the polyps was available. These limitations made it difficult to compare the CRC and AA yield of the four CRC screening programmes. This emphasises the importance of standardisation of important performance indicators for international comparison purposes.

9.3 FUTURE PERSPECTIVES

At the end of the implementation phase we may conclude that the Dutch CRC screening programme has reached a steady state and is performing in line with expectations. The main

goal should be to maintain this stable CRC programme with optimal programme performance. Nevertheless, there is always potential to further optimise a screening programme. The current programme could be expanded by inviting more age groups, a new test could be chosen or risk-factors could be used to invite those individuals' with highest CRC risk.

Expansion of the current screening programme

The Dutch CRC screening programme could be expanded in three ways: by lowering the starting age, lowering the FIT cut-off or adjusting the screening interval. Recently, the American Cancer Society changed their recommendations for CRC screening to start at a lower age (45 years old). The reason for this change is the observed increase in CRC incidence in young adults.[26] A similar increase has been observed in Europe.[28] Lowering the starting age will also be more in line with the European recommendation, that advices CRC screening in men and women aged 50-74.[29] However, it is unclear yet what the impact is of the increased incidence in young adults on the effectiveness of the Dutch CRC screening programme.

Rationale for lowering the FIT cut-off comes from a previous decision analysis. This analysis showed that increasing the FIT cut-off was the most effective option with limited colonoscopy resources compared to postpone screening in certain age groups.[10] The same could apply the other way around; lowering the FIT cut-off is the most effective option if the current programme can be expanded. The decision about whether lowering the FIT cut-off, widening the age range or shortening of the interval should be considered for expansion of the programme can be informed by model decision analyses. The outcomes of the studies included in this thesis can be used to inform several important decision model parameters.

New test modality

FIT has a high sensitivity for CRC, as also described in this thesis, but FIT has a lower sensitivity for AA (31%).[30] New test modalities are developed aiming for a higher sensitivity for CRC and AA. Stool DNA testing and video endoscopy seem to be promising new test modalities. They are not considered cost-effective yet, because their high costs do not outweigh the small additional benefit.[31] A new development is the use of protein biomarkers for the detection of CRC or AA, instead of or supplement to Hb protein. An early clinical phase of biomarker development study showed that new stool-based protein biomarkers have a higher discriminatory power than Hb protein alone.[30] A combination of 4 proteins resulted in a sensitivity for CRC of 80% similar to FIT and for AA of 45%, substantially higher than FIT. Potentially, these proteins could easily be implemented in a national FIT-based screening programme. Other promising new test modalities are FIT combined with blood markers for CRC or AA detection. A recent review concluded that most studies have not been able to prove improved FIT characteristics.[32] However, DNA hyper methylation markers seem most suitable, specifically methylated Septin 9 DNA plasma assay (^{m}SEPT9). This could be potentially a good alternative for CRC screening. However, it can only be cost-effective compared to

FIT-based screening if participation with FIT will drop below 70%.[33] The current participation rate in the Netherlands is still above 70%, therefore with the current test characteristics of ^{m}SEPT9 it is not a better option than FIT. When considering a new screening test it is important to realise that the new test should be relatively cheap to be a good candidate to introduce on population level. Decision analysis showed that costs of a new biomarker test should not exceed 7-fold the costs of FIT.[34] Another important aspect considering a new and more sensitive test for CRC is the associated specificity. If the new test has a lower specificity, this also should be taken into account when this test will be introduced on a population level. Lower specificity will lead to an increase in number of individuals with a false-positive result, resulting in more individuals undergoing an unnecessary colonoscopy.

Personalised screening strategy

Contemplating on the outcomes of the performance indicators described in this thesis, it seems that differential FIT cut-off by gender or previous screening result might lead to a more (cost-) effective screening programme. Decision analyses can be performed comparing such strategies to identify the optimal screening strategy for the current situation with uniform screening.[10] Other possible new strategies might be applying different FIT cut-offs for the first and subsequent screening rounds or allocating different intervals based on previous Hb concentration.

The first option for a more personalised screening strategy is to screen men and women differently. Men have higher CRC and AA detection rates and higher FIT sensitivity for CRC than women.[35] A tailored screening strategy could focus on similar sensitivity for both men and women by lowering the cut-off for women. The other way around is also an option, aiming for similar PPV for both men and women by lowering the cut-off for men.[36] However, long-term effectiveness of screening in terms of life years gained, estimated with decision modelling, it shows similar effectiveness for men and women. This is mainly the result of the fact that women will have a longer life expectancy than men. This is in line with previous results of our research group, showing that a different screening strategy for men and women is not cost-effective.[37] Note, this decision analysis assumed unlimited colonoscopy capacity. If programmes have limited colonoscopy resources, applying different screening strategies for men and women may be cost-effective, but this need to be further studied.

Faecal Hb concentration in previous screening round is another risk factor for the development of CRC and AA that also can be used for personalised screening. Individuals with a faecal Hb concentration below the cut-off (between 15 and 47 µg Hb/g faeces) are at higher risk for the detection of CRC or AA during consecutive screening rounds than individuals without any faecal Hb detected.[38-41] The biological hypothesis behind this finding is that adenomas will progressively bleed when developing to carcinoma, and therefore even low concentrations of Hb may be an indication of the presence of adenoma.[42] Therefore, individuals with high Hb concentration in the previous screening round may benefit from

shorter screening intervals. Contrary, individuals without detectable Hb in the previous screening round may benefit from extended screening intervals. Personalised screening based on faecal Hb concentration has two advantages over other known risk factors like smoking, obesity, food intake or family history. The estimated hazard ratios for individuals with small amount of faecal Hb concentration compared to those with no detectable faecal Hb concentration are considerably higher than those reported for e.g. lifestyle or family history.[41] Another advantage of using faecal Hb concentration of the previous screening round is its availability. This information is already being registered in the national information system (ScreenIT). Therefore, additional questionnaires on obtaining information on lifestyle and family history, which could jeopardise screening participation, are not needed.

Ideally, all potential risk factors like gender, age and Hb concentration of the previous screening round will be combined in one prediction model. All these separate risk factors contribute to individual's risk of having a CRC or AA. All risk factors should be combined to determine a person's individual risk. A Flemish study showed that men aged 74 with Hb concentration of >200 µg Hb/g faeces were 58 times more likely to be diagnosed with a CRC than women aged 56 with Hb concentration of 15 µg Hb/g faeces.[43] It is unknown to what extent the complexity of personalised strategies will impact the adherence to screening. For genetic testing it is known that knowing your gene-based risk profile will increase the willingness to participate in screening with 43%.[44] It is unknown whether this increase in adherence would also hold for an approach using relatively simple risk factors like gender, age and faecal Hb concentration. It will be totally different from genetic testing and might not lead to the same increase. The overall participation in the Netherlands is already high, so we will be more concerned if personalised screening will negatively impact the high participation.

9.4 FINAL CONCLUSIONS AND RECOMMENDATIONS

From the results of the studies that are presented in this thesis, the following conclusions can be drawn:

- Piloting, planning and implementing of the Dutch CRC screening programme may serve as a best practice for many screening initiatives currently being organised worldwide.
- The FIT participation rate in the first screening round in the Netherlands (71.8%) was one of the highest across the world and remained stable in the second screening round.
- Participation in follow-up colonoscopy (77.8%) was short of the minimally acceptable level of 85% and lower than surrounding countries in Western-Europe.
- Adjustments of the cut-off from 15 to 47 µg Hb/ g faeces halfway through the first year of the programme was necessary to ensure that the programme met the intended balance of harms and benefits of CRC screening.

- Using a higher FIT cut-off (47 µg Hb/ g) had limited impact on the cumulative CRC and AA detection because a substantial part of the missed lesions was detected in the second screening round.
- There is a strong correlation between faecal Hb concentration and detection of CRC and AA in subsequent screening. Individuals with a faecal Hb concentration just below the current cut-off (15-47 µg Hb/g faeces) were 23 times more likely to have CRC or AA detected at subsequent screening than those without detectable faecal Hb.
- Screen-detected CRCs have more often a favourable stage distribution (stage I and II) (67%) than symptom-detected CRCs (40%). Screen-detected CRCs were more often located in the left colon and rectum (73%) than symptom-detected CRCs (65%).
- FIT showed a high sensitivity for CRC (85.5%) with an associated low cumulative incidence of interval CRCs.
- FIT screening could potentially have a higher yield in participants with the lowest SES, but this higher yield is currently offset by the lower participation in this group.
- The overall population-impact of the variations in FIT positivity and detection rates between specimen collection devices and reagent lots is expected to be modest, but there is room for improvement of quality assessment. Currently, acceptable ranges of variation are lacking.

Based on these conclusions, we formulated the following recommendations:

- Coming years CRC-related mortality rates need to be closely monitored to ensure that CRC-related mortality is indeed decreasing as a consequence of the introduction of CRC screening in the Netherlands.
- Given the low participation to follow-up colonoscopy (77.8%), future research should be undertaken to identify reasons for nonparticipation and options to increase colonoscopy participation rate to the recommend level of 85%.
- The observed variation in FIT performance between batches and lot reagents described in this thesis can be used as input for the international initiative for standardising FIT quality assessment and for improving a regular monitoring system to reduce the impact of test variation on detection of CRC and AA.
- Outcomes during the implementation phase are mainly based on older age groups. Close monitoring of participation rate, positivity rate and detection of CRC and AA is needed to obtain estimates for all age groups of the target population.
- Personalised screening based on previous faecal Hb concentration is an important next step to explore for further optimisation of the Dutch CRC screening programme. Future studies are needed that evaluate the effectiveness of applying different screening intervals based on previous faecal Hb concentration.

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