Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer

PhD dissertation

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Jakob Søgaard Juul
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Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer
PREFACE
MOTIVATION

My interest in primary care research and cancer diagnostics was initially sparked during a three-month employment at the Research Unit for General Practice in Aarhus in the summer of 2011. During this stay, I explored the symptom presentation of colorectal cancer in general practice and learned that the clinical truth does not always correspond to the truth stated in medical books.

After graduating from medical school in 2013, I spent six months working in a general practice and here this knowledge was further confirmed: During these six months, I saw many individuals with gastrointestinal symptoms, but only few with colorectal disease. Prioritising between individuals in need of additional diagnostic workup was a notoriously difficult task, in particular for the individuals who did not fulfil the criteria for urgent referral to colonoscopy.

During my many encounters in the clinic, I started to wonder how to optimise this process and aid the general practitioners (GPs) in the diagnostic workup of individuals who did not fulfil these criteria.

On a winter day in 2014, I met with Peter Vedsted to discuss these matters, and the initial steps were taken for the conduction of the present PhD dissertation.
OUTLINE OF THE DISSERTATION

This PhD dissertation consists of 10 chapters. Chapter 1 outlines the background of the research area and I present the idea why the faecal immunochemical test may be of value in general practice for patients with non-alarm symptoms. At the end of the chapter, the hypothesis and aims are presented. Chapter 2 contains a thorough description of the methods used in the three papers, and Chapter 3 summarises the results. Chapter 4 discusses the strengths and limitations of the three papers, and Chapter 5 discusses the results. In Chapter 6, I conclude on each paper and reflect on the perspectives of the found results. In Chapter 7, I address how the studies may call for future research. Chapter 8 contains the references used in the PhD dissertation, and Chapter 9 and Chapter 10 are English and Danish summaries.

The appendices include the invitation for arranging the training course (sent to the chairmen of the GP clusters in the Central Denmark Region) and the invitation for participating in the training course (sent to the GPs in the Central Denmark Region). Furthermore, the appendices contain the clinical guideline, the information letter and the online material sent to the GPs at inclusion. The scientific papers on which this dissertation is based are included at the end of the dissertation. I will refer to these papers throughout the dissertation by using their roman numerals:


**Paper II:** Juul JS, Bro F, Carlsen AH, Hornung N, Andersen B, Laurberg S, Olesen F, Vedsted P. “Clinical uptake and use of faecal immunochemical test after implementation in Danish general practice”. [Submitted]

**Paper III:** Juul JS, Hornung N, Andersen B, Laurberg S, Olesen F, Vedsted P. “Diagnostic value of using the faecal immunochemical test in general practice on patients presenting with non-alarm symptoms of colorectal cancer”. [Submitted]
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CHAPTER 1:
INTRODUCTION
1.1 GENERAL INTRODUCTION

General practice plays a key role in diagnosing colorectal cancer (CRC). However, due to the complex symptomatology, it can be difficult to identify individuals with CRC in general practice.

The introduction of the cancer patient pathway (CPP) for CRC in 2008 started a new era in the diagnosis of CRC in Denmark. CRC was now defined as an “acute” disease, and individuals presenting with specific alarm symptoms could be urgently referred to colonoscopy for further diagnostic investigation. However, many individuals with CRC do not present with alarm symptoms. These patients constitute a particular challenge for the GP. Nevertheless, no standardized diagnostic strategy has been established to help the GPs identify the individuals at risk of CRC in the low-risk population seen in general practice.

This PhD dissertation investigates the applicability of using the faecal immunochemical test (FIT) in general practice to identify individuals at risk of CRC although they do not present with alarm symptoms of CRC. Firstly, we explored the diagnostic activity in general practice and the incidence of CRC in individuals invited to screening for CRC. Secondly, we made the FIT available for GPs in the Central Denmark Region and assessed the dissemination and clinical use of the FIT, and the diagnostic value of the FIT for detecting CRC and other serious bowel disease in individuals with non-alarm symptoms of CRC.

The following chapter starts out by outlining the background for this research area and concludes by stating the hypothesis and aims of the dissertation.
CRC is the collective name for cancer in the colon and rectum. This type of cancer usually originates from precursor lesions in the colonic or rectal wall and develops from pre-malignant adenomas into adenocarcinomas. Only few adenomas develop into CRC, but the risk of an adenoma becoming malignant increases with the size and the grade of dysplasia (1). The colon can be divided into anatomical segments on the basis of the location in the abdomen. The *proximal part* consists of the caecum, the ascending and the transverse colon, and the *distal part* consists of the descending and sigmoid colon (Figure 1.1). The sigmoid colon transitions into the rectum, and together they constitute the most distal parts of the gastrointestinal tract. Approx. 60% of all CRCs are located in the sigmoid colon and rectum (2,3).

The risk of CRC increases with age, and more than 85% of all incidents occur in individuals aged ≥60 years (2). The cancer staging at diagnosis is essential for the choice of treatment and assessment of prognosis.
Staging of CRC is based on the TNM classification system, which describes the growth of the tumour (T stage), lymph node metastases (N stage) and distant metastases (M stage). The Union for International Cancer Control (UICC) maintains the TNM system as a tool for doctors to stage cancer types on the basis of certain standards. The values of T, N and M in combination determine the overall stage of the CRC. The overall stage is divided into stage I–IV, where IV is the most advanced cancer stage (Table 1.1) (4,5).

The choice of treatment is based on an individual assessment of the patient, and several factors must be considered, including the stage of the CRC, the patient’s general condition and comorbidity. It is beyond the scope of this dissertation to give a detailed description of the treatment of CRC, but it should be mentioned that a resection of the tumour and the appertaining colon segment is necessary in the vast majority of cases. For stage III and in some cases of stage II, this is supplemented by post-operative chemotherapy. Patients with distant metastases (stage IV) are most often treated with chemotherapy and palliative care, but curative treatment can also be attempted in some cases (3).

<table>
<thead>
<tr>
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<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>I</td>
<td>T1/T2</td>
<td>N0</td>
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<td>II A</td>
<td>T3</td>
<td>N0</td>
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<td>II B</td>
<td>T4</td>
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<td>III A</td>
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<td>III C</td>
<td>Any T</td>
<td>N2</td>
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<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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**Table 1.1: UICC and TNM staging of colorectal cancer.** T stage indicates tumour growth (Tis: carcinoma in situ. T1: tumour invades submucosa. T2: tumour invades muscularis propria. T3: tumour has grown through the intestinal wall. T4: tumour invades adjacent organs). N stage indicates lymph node metastasis (N0: no lymph node metastasis. N1: metastasis to 1-3 lymph nodes. N2: metastasis to ≥ 4 lymph nodes). M stage indicates distant metastasis (M0: no distant metastasis. M1: distant metastasis are present). The UICC stage is usually referred to as stage I-IV without subdivision into stages A, B, and C. Adapted from the American Joint Committee on Cancer (AJCC) staging manual 2002 (4).
1.2.1 Colorectal cancer epidemiology

CRC is one of the most common cancers worldwide and a leading reason for cancer-related death (6). This is also true in Denmark, where CRC is the second most common cancer in both genders with approx. 5600 incidents in 2015 (7). The high incidence is partly related to the implementation of a Danish national screening programme for CRC in 2014, which has implied a 20% increase in the number of annual CRC diagnoses from 2013 to 2015 (7). Despite this increase, the annual mortality rate has remained fairly stable over the same period of time at approx. 21 per 100,000 for colon cancer and 7 per 100,000 for rectal cancer (8). The overall 5-year survival rate of CRC in Denmark was 63% in 2014, but this rate has notably improved during the last decade. Nevertheless, the survival rate in Denmark still remains the lowest in the Nordic countries (2,9–11).

The prognosis of CRC is strongly correlated with the cancer stage at diagnosis. Therefore, one explanation for the poor survival rate in Denmark could be that Danish CRC patients are generally diagnosed in late stages (12). An annual report by the Danish Colorectal Cancer Group showed that 20% of CRCs were diagnosed in stage IV in 2015 and 15% in stage I (2). Approx. 80% of individuals diagnosed with a stage I cancer will be alive after 5 years, whereas this applies to <15% of individuals with stage IV cancers. These figures underline the clinical importance of diagnosing CRC in early stages to ensure the best prognosis for the patients, but the figures also suggest that improvements in the diagnosis of cancer can still be made.
1.3 EARLY DETECTION OF COLORECTAL CANCER

CRC is most frequently diagnosed through general practice (13,14). The period from the first experience of a symptom until treatment initiation consists of a series of time intervals, which can be subject to delay (Figure 1.2) (15). It is beyond the scope of this dissertation to give a comprehensive description of each time interval. However, it should be mentioned that the interest, in recent years, has centered on measuring and reducing potentially avoidable delays in the diagnostic interval (e.g. the time from the first presentation of a symptom to a health care professional (GP) until the diagnosis is made) as this time interval represents the majority of the time spent in primary and secondary care.

![Figure 1.2: The Aarhus Statement.](image-url)

There are several potential gains of reducing avoidable delays in the time intervals on the CRC pathway, including: higher patient satisfaction, reduced costs of treatment, earlier detection of CRC and better prognosis (16–18). However, it has been widely debated whether early detection would actually affect the outcome
of CRC (19–25). A recent review partly settled this by showing a possible association between the time to diagnosis and the outcome of CRC (26). Among the studies included in the review were studies on the waiting time paradox in the CRC diagnostics which showed that longer diagnostic intervals affect the mortality in CRC patients (27,28). These findings were recently supported in a multinational study by Tørring et al. (29). In addition, evidence from screening indicates that longer follow-up time between faecal immunochemical testing and colonoscopy is associated with poorer CRC outcome (30).

As it is not possible to conduct randomized controlled trials on this subject, most of the evidence on the topic is based on observational studies. Nevertheless, increasing evidence suggests an association between the time to diagnosis and CRC outcome. Therefore, developing new strategies to reduce avoidable delay will be essential to optimise the CRC diagnostics and ensure early detection of CRC.

1.3.1 Strategies for improving cancer diagnostics in Denmark

Strategies to improve the cancer diagnostics in Denmark have been a main focus of the Danish health authorities in recent years. The development and implementation of the Danish national cancer (action) plans have caused considerable changes in the structure and organization of the diagnostic procedures (31).

One of the main changes was the implementation of CPPs in 2008 (32). For CRC, this implied that the GPs could now urgently refer patients aged ≥40 years with so-called alarm symptoms (described in section 1.5.2) to a colonoscopy and bypass the normal referral pathway and waiting time. The CPP for CRC has been revised continuously, most recently in 2016 (33). As a supplement to the organ-specific pathways, two additional diagnostic strategies have been implemented/planned to provide a setup for referral of individuals according to the nature of the symptoms (known as the Danish three-legged strategy) (34). A
CPP for serious non-specific symptoms of cancer was implemented in 2012 to specifically target patients with serious symptoms that do not fit into the conventional CPPs (35). The third pathway is planned for individuals presenting with low-risk-but-not-no-risk symptoms (described in section 1.5.3), and developing diagnostic strategies for patients presenting with these symptoms is expected to play a key role in future cancer diagnostics.
1.4 SCREENING FOR COLORECTAL CANCER

In an attempt to circumvent the diagnostic route through general practice and avoid the possible delays that may arise in this pathway, a national screening programme for CRC was implemented in Denmark in March 2014. Studies show that screening may reduce the CRC mortality in the screened age group (36–38). The programme uses the faecal immunochemical test (FIT) as a first-line test, which is followed by colonoscopy if the test is positive (≥100 μg/L) (39). All citizens aged 50-74 years are invited to participate, regardless of socio-economic status (SES) and morbidity, and the order of invitation is randomly determined from the month of birth. Invitations are sent out by letter, and invited citizens participate by performing an enclosed FIT and sending it for analysis at one of the five regional departments that are in charge of analysing the FITs. Results from the first years of screening (prevalence phase) show a participation rate of 63%, a positivity rate of approx. 7% and a positive predictive value (PPV) for CRC after a positive FIT of approx. 6% (40).

Despite the introduction of the screening programme, the majority of annual CRCs are still expected to be diagnosed through symptomatic presentation in general practice (41,42). So far, no study has investigated the amount of CRCs occurring outside the Danish screening programme in the invited population. For GPs this is of special interest since non-participants diagnosed with CRC may have low socio-economic status (SES) and poor CRC prognosis (43–45).

Recent questionnaire studies have indicated that the majority of screening participants with a positive FIT have lower gastrointestinal (GI) symptoms (46–49). If this is true, the majority of individuals with a positive FIT and diagnosis of CRC through screening may have attended general practice before participation, and this could provide the GPs with the possibility to detect CRC if the FIT is available in general practice.
1.5 DIAGNOSING COLORECTAL CANCER IN GENERAL PRACTICE

1.5.1 Introduction to Danish general practice

The Danish health care system is tax-funded, and the majority of residents in Denmark have free and direct access to general practice. GPs own their clinics and either work alone (single-handed practice) or together with other GPs (partnership practice). Each GP serves approx. 1600 patients who are listed with their practice. This setup is known as the “patient list system”, which ensures continuity of care and allows the GP not only to have knowledge about the individual patients, but also about their family as family members are often listed with the same GP (50, 51). An important feature of Danish general practice is the gatekeeper function to secondary care. Based on clinical assessment, symptom presentation and/or test results, the GP decides when to refer a patient to further assessment, e.g. at a hospital or private specialist. It is estimated that approx. 10% of consultations in general practice end up with a referral (51). The gatekeeper system has been suspected to partly explain the poor cancer survival in Denmark (52). However, it is broadly recognised as the optimal system for a well-structured health care system (53, 54). Therefore, the focus has recently been directed towards optimizing the diagnostic procedure and expanding the diagnostic opportunities for the GPs.

1.5.2 Alarm symptoms of colorectal cancer and their validity in general practice

It is estimated that approx. 6% of the consultations in general practice are due to abdominal symptoms (55). On average, a Danish GP will encounter one new CRC case each year. This patient must be found among all the other patients with similar symptoms, but benign conditions (42). This constitutes a major diagnostic challenge for the GP. The CPP for CRC allows the GP to identify individuals with alarm symptoms of CRC and can be seen as a tool for GPs to prioritize between patients at risk of CRC. Alarm symptoms include: rectal bleeding,
change in bowel habits, iron deficiency anaemia, weight loss and abdominal pain.

A study investigating the prevalence of alarm symptoms in the Danish population has shown that <33% of individuals experiencing an alarm symptom consult a GP (56). This, together with the facts mentioned below, underlines that the CPPs and alarm symptoms only constitute part of the solution for improving the CRC diagnostics in general practice.

![CAPER studies: PPVs for symptoms of colorectal cancer](image)

**Figure 1.3**: The CAPER studies: PPVs for symptoms of colorectal cancer. The upper horizontal row indicates the PPV for CRC for individual symptoms. The remaining cells state the PPV for a combination of symptoms. The stated PVVs are adjusted for age and gender. Reprinted from “The CAPER studies: five case-control studies aimed at identifying and quantifying the risk of cancer in symptomatic primary care patients” by W. Hamilton et al. 2009. British Journal of Cancer, vol. 101, p. S82 (57).
Firstly, a wide range of studies have shown that the PPVs for alarm symptoms of CRC are low (Figure 1.3) (57–63). Thus, only few individuals with alarm symptoms of CRC actually have the disease.

Secondly, alarm symptoms are poorly defined, and some studies have shown great variations in the use of CPPs among GPs (64,65). The world in general practice is not black and white. The severity of a symptom can be seen as a continuum, going from harmless to definitely indicating a risk of serious disease (Figure 1.4) (34). Even symptoms listed as alarm symptoms can thus take different forms of severity, and the GP must interpret the presented symptoms by using his/her clinical knowledge.

Thirdly, approx. 50% of CRC cases present with other symptoms than alarm symptoms (66). Patients presenting with these non-alarm symptoms do not fulfil the criteria for urgent referral in the CPP. Therefore, they must be diagnosed by other pathways.

Fourthly, the implementation of CPPs primarily seems to have expedited the diagnostic pathway for patients presenting with alarm symptoms. A Danish study has shown a reduction in the diagnostic interval for individuals referred in a CPP of 23 (21;25) days, whereas a reduction of 9 (7;12) days was seen for individuals referred outside the CPP (67).

It is thus important for GPs to be aware that the CRC symptom presentation is complex and that individuals may present with a wide variety of symptoms and signs in general practice.

\[\text{Figure 1.4: The symptom continuum. A symptom can take different forms of severity, going from “certainly not serious” to “definitely serious”. In between these extremes are the “low-risk-but-not-no-risk” symptoms that may or may not be signs of serious disease. Reprinted from “A differentiated approach to referrals from general practice to support early cancer diagnosis – the Danish three-legged strategy” by P. Vedsted et al. 2015. British Journal of Cancer, vol. 112, p.S66 (34).}\]
1.5.3 Non-alarm symptoms of colorectal cancer

Non-alarm symptoms of CRC are a heterogeneous group of uncharacteristic and vague symptoms that the GP does not interpret as serious enough to fulfil the criteria for referral in the CPP (66). However, these symptoms may still be signs of serious disease and can therefore be categorized as low-risk-but-not-no-risk symptoms (14).

This group of patients constitutes a particular diagnostic challenge for the GP, who will often take a “watchful waiting” approach. This results in a longer diagnostic interval for these individuals compared to individuals with alarm symptoms (27,67). This may lead to stage progression and poor prognosis of the CRC, as also mentioned earlier (26–28).

A recent study has shown that individuals who are later diagnosed with CRC visit their GP more frequently and have more tests performed than the average patient in the year preceding a CRC diagnosis (68). One possible explanation for this could be that the patient’s symptoms in this time period do not fulfil the criteria for urgent referral (non-alarm symptoms), but the symptoms are serious enough for the GP to initiate further investigations, e.g. point-of-care (POC) testing. This could indicate a diagnostic window that may result in earlier diagnosis of CRC and identification of patients in earlier cancer stages. However, the identification of patients with non-alarm symptoms is tricky, and no clear diagnostic strategy is currently available in general practice for this group of patients. Therefore, new tools are needed to assist the GPs in the diagnostic workup of patients presenting with non-alarm symptoms.
1.6 THE Fecal IMMUNOCHEMICAL TEST

The FIT detects microscopic blood in stools by binding of antibodies to human globin, which is indicative of lower GI bleeding (69,70). Compared to the guaiac faecal occult blood test (gFOBT), the FIT has shown better diagnostic performance in detecting CRC and adenomas (71–74). Two types of FITs exist: a qualitative test based on a visually read dipstick technique, which is often used as a POC test, and a quantitative test, which is analysed on fully automated devices (69). An important difference between the two types of FITs is that the quantitative test allows adjustment of the cut-off value, which is an important feature when applying the test in different clinical environments.

The performance of the FIT has mainly been investigated in relation to screening using the quantitative FIT. In a large review article, the sensitivity was found to be approx. 80% and the specificity above 90% (75). However, it is important to recognize that the performance of the FIT depends on the chosen cut-off value (76–80). Thus, a low cut-off value will result in high sensitivity and low specificity, which may imply a relatively high number of false positive test results. In contrast, a high cut-off value will mean low sensitivity and high specificity, which may imply more false negative test results. Furthermore, the performance of the FIT in a screening population cannot directly be transferred to a symptomatic population because the performance of a test may change when applied on different subpopulations (spectrum bias) (81). Therefore, to gain insight into the value of using the FIT in a symptomatic population, it is necessary to perform studies in general practice on patients with symptoms of CRC.

1.6.1 Use of the FIT in general practice

Before initiation of this PhD project, Danish GPs only had limited access to the FIT through the CPP for patients with serious non-specific symptoms of cancer. No logistic setup for requesting a FIT existed, nor did GPs have direct access to
the test as part of their daily clinical tools. However, a recently updated version of the National Institute for Health and Excellence (NICE) guidelines for patients suspected of cancer stated that a test for blood in stools could be used for some symptoms of CRC (82). Studies investigating the performance of the FIT in general practice have only recently been published (83–92). They generally conclude that the FIT will be a valuable tool for detecting CRC in general practice. However, the studies vary regarding choice of FITs (qualitative vs. quantitative) and chosen cut-off value. Furthermore, all studies have investigated the use of FIT in symptomatic patients who had already been referred to endoscopy by their GP. These patients may have higher risk of CRC than individuals with non-alarm symptoms. No previous study has investigated whether the FIT can be used in the diagnostic workup of patients with non-alarm symptoms of CRC. Using the FIT in this group of patients seems intriguing as diagnostic pathways already exist for patients with alarm symptoms. Therefore, assessing whether the FIT can be used as a valuable diagnostic tool in patients presenting with non-alarm symptoms of CRC may help improve the future CRC diagnostics.

Figure 1.5: The faecal immunochemical test (FIT).
1.7 INTRODUCTION AT A GLANCE

- CRC is a potentially curable disease when diagnosed in early stages.
- Despite recent improvements, the 5-year survival of CRC in Denmark is still the lowest among the Nordic countries.
- Various strategies to improve CRC diagnostics have been implemented in recent years, including screening and a CPP.
- Despite the screening for CRC, the majority of CRC cases are expected to be found through symptomatic presentation in general practice.
- Alarm symptoms of CRC have low PPVs and approx. 50% of all annual CRC cases present with non-alarm symptoms that do not prompt urgent referral for investigation of CRC in the CPP.
- Increasing evidence suggests that the FIT may be used on symptomatic patients in general practice.
- No previous study has investigated whether the FIT could be a valuable tool in the diagnostic workup of patients presenting with non-alarm symptoms of CRC in general practice.
1.8 HYPOTHESES AND AIMS

On the basis of the challenges of diagnosing CRC in general practice, we hypothesised that the FIT would be a valuable tool for GPs in the diagnostic workup of patients with non-alarm symptoms of CRC in general practice.

We hypothesised that CRC would still have to be diagnosed outside the screening programme in the screened age group. We also hypothesised that screened individuals with a positive FIT and CRC have experienced newly emerged GI symptoms and that they have had higher rates of diagnostic activity in general practice in the time leading up to the screening compared to individuals with a negative FIT and no CRC.

Furthermore, we hypothesised that GPs would use the FIT as a diagnostic tool if provided with the opportunity and that the FIT could be used for detecting CRC and other serious bowel diseases in individuals presenting with non-alarm symptoms of CRC in general practice.

These hypotheses gave rise to the aims of this PhD dissertation, which were:

1. To investigate the diagnostic activity in general practice and the cumulative incidence of CRC in individuals invited to the Danish national screening programme for CRC (paper I).

2. After establishing access to the FIT for GPs in general practice for diagnostic use in individuals presenting with non-alarm symptoms of CRC:
   i. To explore the dissemination and clinical use of the FIT in general practice and assess whether participation in a training course on FIT use affected the clinical uptake (paper II).
   ii. To investigate the diagnostic value of using the FIT in general practice in individuals presenting with non-alarm symptoms of CRC (paper III).
Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer
CHAPTER 2:

MATERIALS AND METHODS
The following chapter contains a description of the methods used in the PhD dissertation. An overview of the aims, design, setting, study population, data sources and outcomes used for paper I-III is provided in Table 2.1. Due to the importance of the Danish registries, the chapter starts out by describing each data source used in the papers of the dissertation and the data collected.

<table>
<thead>
<tr>
<th>PAPER I</th>
<th>PAPER II</th>
<th>PAPER III</th>
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<tr>
<td>AIM</td>
<td>To investigate the diagnostic activity in general practice and the cumulative incidence of CRC in individuals invited to the Danish national screening programme for CRC</td>
<td>To explore the dissemination and clinical use of the FIT in general practice and assess whether participation in a training course on FIT use affected the clinical uptake</td>
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<td>STUDY DESIGN</td>
<td>Population-based cohort design</td>
<td>Non-randomised controlled trial with a phased introduction of a complex intervention</td>
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<td>SETTING</td>
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<td>Central Denmark Region</td>
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<td>STUDY POPULATION</td>
<td>Individuals aged 50-74 years invited to attend the Danish screening programme for CRC on 1 March 2014 – 31 December 2014</td>
<td>GPs in the Central Denmark Region and individuals aged ≥30 years listed with the practices</td>
</tr>
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<td>DATA SOURCES</td>
<td>- The Danish National Patient Register</td>
<td>- The Patient List Register</td>
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<td></td>
<td>- The Danish Cancer Registry</td>
<td>- Randers Regional Hospital</td>
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<td>- The Danish Colorectal Cancer Screening Database</td>
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<td>- The Danish National Prescription Registry</td>
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<td>- The Patient List Register</td>
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<td>- Statistics Denmark</td>
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<td>OUTCOMES</td>
<td>- Diagnostic activity in general practice preceding the invitation to FIT screening</td>
<td>- Rate of general practices starting to use the FIT</td>
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<td></td>
<td>- Cumulative incidence of CRC following the invitation to FIT screening</td>
<td>- Monthly rate of requested FITs</td>
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<td>- Monthly rate of positive FITs and indications of use</td>
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*Table 2.1: Overview of the methodological approach used for paper I-III.*
2.1 DATA SOURCES AND DATA COLLECTION

2.1.1 The CPR number and the Danish civil registration system

The CPR number is a personal identification number allocated to all individuals in Denmark at birth or migration. The 10-digit number is unique and composed by: date of birth (first six digits) and a unique identification number (last four digits). The last four digits reveal the gender of the holder: odd numbers for males and even numbers for females. The CPR number is registered in the Danish Civil Registration System (CRS), which contains information on vital status, death and migration (93). The CPR number is also important in register-based research as it allows linkage of all national databases at the individual level.

In this dissertation, all data used in the three papers were linked through the CPR number. For paper I, the CRS was used to collect information on vital status, death and migration in the study population.

2.1.2 The Danish National Patient Register

All information on hospitalizations in Denmark is registered in the Danish National Patient Register (NPR) (94). The NPR contains data from both private and public hospitals and serves as a basis for remuneration of hospitals in Denmark. The database is updated continuously and contains detailed information about provided services, e.g. date of admission, date of discharge, procedures performed during admission and diagnoses. Since 1994, all diagnoses have been coded according to the International Classification of Disease, 10th revision (ICD-10) (95). The database also holds supplementary information, e.g. cancer stage. The data registered from the private sector and the data on supplementary information are generally considered to be less complete.

For paper I, the NPR was used to collect information on previous diagnoses of Crohn’s disease (ICD-10: DK500-9), ulcerative colitis (ICD-10: DK510-9), familial adenomatous polyposis (FAP) (ICD-10: DD126F), hereditary nonpolyposis colo-
rectal cancer (HNPCC) (ICD-10: DC188A) and adenomas followed by regular colonoscopy (ICD-10: DZ018B).

For paper III, the NPR was used to obtain information on performed sigmoidoscopies, colonoscopies and computed tomography (CT) colonographies, and CRC stages.

For both paper I and III, information from the NPR was used to generate the Charlson Comorbidity Index (CCI) score. As the information used for calculating CCI score was entirely based on information from the NPR, the next section contains a short description of the CCI used in this dissertation.

2.1.2.1 The Charlson Comorbidity Index

The CCI score provides a tool for assessing an individual’s comorbidity based on the history of diagnoses. It was developed as a measure of the one-year mortality risk and gives a weighted index of the number and severity of diseases. The CCI used in this dissertation is based on the work by Charlson et al., which was later updated to ICD-10 codes by Quan et al. (96,97). In both paper I and III, we collected information on diagnoses for the 10 years preceding the index date and calculated the CCI score by assigning between one and six points for specific conditions. One point was given for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes without end-organ damage. Two points were given for diabetes with end-organ damage, hemiplegia, moderate to severe renal disease, non-metastatic solid tumour, leukaemia and lymphoma. Three points were given for moderate to severe liver disease. Six points were given for metastatic cancer and AIDS. The total number of points were added and categorized into low (CCI score of 0), moderate (CCI score of 1-2) and severe (CCI score of ≥3).
2.1.3 The Danish Pathology Register

Pathology departments in Denmark are obliged to report pathologic data to the Danish Pathology Register (DPR). The register is updated continuously. The most important content is the pathologic diagnosis, which is coded according to the Danish version of the Systematized Nomenclature of Medicine (SNOMED) (98). The SNOMED code consists of six digits: one letter and five numbers. The letter defines one of six areas used to describe the pathological sample: the topography (T) stating the anatomical location, the morphology (M) describing any structural changes in cells or tissue, the aetiology (Æ) stating the causal factors associated with the disease, the function (F) stating normal or abnormal functions, diseases (S) encompassing disorders or syndromes diagnosed from the pathologic investigation, and procedure (P) stating any procedure used during investigation. The numbers are used to specify and further differentiate the sample (in the description below, X represents a random number). Only the T-code and the M-code are mandatory and must be reported by the pathologist.

In paper III, we used data from the DPR to identify diagnoses of colorectal disease (T67XXX or T68XXX), including CRC (M8XXX3 or M8XXX6), inflammatory bowel disease (IBD: M4XXX5 or S62140. Crohn’s disease: S62160. Microscopic colitis: S62530. Lymphocytic colitis: S62533. Collagenous colitis: S62536. Ulcerative colitis: 62550) and high-risk adenomas (high-grade dysplasia: M8XXX2. Size >1cm: M8XXX0 and ÆADX1-9X. ≥3 adenomas: M8XXX0). The location of the CRC was identified by the SNOMED code for topography (T).

2.1.4 The Danish Cancer Registry

The Danish Cancer Registry (DCR) contains information on all incident cancers in Denmark (99). It is updated once a year with information on cancer incidents from the previous year. The database gathers information from various databases (e.g. the NPR, the DPR and the Danish Register of Causes of Death) to provide complete information on cancer diagnoses in Denmark, including date
of diagnosis, histological type of cancer, anatomical location and cancer stage. If an individual is diagnosed with two separate cancers, these are recorded in two separate files.

For paper I, the DCR was used to collect data on CRCs (ICD-10: DC180-9 and DC200-9) and UICC stages.

2.1.5 The Danish Colorectal Cancer Screening Database

In connection with the implementation of the Danish national screening programme for CRC, the Danish Colorectal Cancer Screening Database (DCCSD) was established to monitor the quality of the screening programme (100). The database comprises information obtained from the Invitation and Administration Module, the NPR and the DPR, and it contains data on participation, investigation and diagnoses for individuals invited to participate in the screening.

For paper I, the DCCSD was used to collect dates of invitation, FIT results, performed colonoscopies and CT colonographies, and CRC diagnoses resulting from the CRC screening.

2.1.6 The Danish National Prescription Registry

The Danish National Prescription Registry (DNPR) contains information on all prescription medications dispensed at Danish pharmacies, but this does not include over-the-counter sale (101). The data is updated continuously and comprises four main categories: data on the user, data on the prescriber, data on the prescribed medications and data on the dispensing pharmacy. Medications are identified by the Anatomical Therapeutic Chemical (ATC) classification code (102).

For paper I, we collected information on prescriptions for medications against haemorrhoids (ATC: C05A) and medications with anticoagulatory effect (non-
steroidal anti-inflammatory drugs (NSAID) (ATC: M01A), acetylsalicylic acids (ASA) (ATC: B01AC06, N02BA01, N02BA51) and anticoagulants (ATC: B01A)).

2.1.7 The Danish National Health Service Register

The Danish National Health Service Register (NHSR) provides continuously updated information on activities in primary health care, e.g. services provided by general practice and private clinics (103). The data from general practice are based on the GPs’ invoices sent to the regional health administration and include information on the citizen, the provider and the service performed. Information on services is divided into three categories: 1) basic services (including face-to-face consultations, telephone consultations, email consultations, home visits, preventive consultations and out-of-hour services), 2) additional services (including blood samples, contraceptive counselling and psychometric tests) and 3) laboratory tests performed in general practice, i.e. point-of-care testing (including C-reactive protein measurements, haemoglobin measurements and lung function tests). The database does not hold information on test results.

For paper I, the NHSR was used to collect information on consultations and haemoglobin measurements. For paper III, the NHSR was used to collect supplementary data on sigmoidoscopies and colonoscopies performed in private practices that were not registered in the NPR.

2.1.8 Provider number and patient lists

More than 99% of the Danish population are listed with a general practice (51). The provider number ensures that the GP receives reimbursement from public authorities, which makes the service free of charge for the listed patients. GPs can either share a provider number (partnership practices) or have one of their own (single-handed practices). For research purposes, the provider number allows linkage between a general practice and the patients listed with this particular practice. Information on patient lists is stored in the Patient List Register.
For paper I, the Patient List Register was used to identify individuals who were not listed with a practice. For paper II, the Patient List Register was used to collect information on the patient composition in each general practice.

### 2.1.9 Statistics Denmark

Statistics Denmark is a state-owned institution providing statistical information on the Danish population and society (104). Researchers can apply for information on Danish citizens (e.g. educational level) and get access to perform analyses on the servers of Statistics Denmark. This provides access to the encrypted anonymous data and offers linkage to data from other registries.

For paper I, we used data from Statistics Denmark to gain information on the country of origin of the included individuals (categorised into: Danish, western country and non-western country) and their educational level (categorised into: basic (<10 years), medium (10-15 years) or long education (>15 years), as defined by the International Standard Classification of Education (ISCED) (105)). We also collected information on their labour market affiliation (categorised into: working, unemployed or retired) and marital status (dichotomised into: living with a partner or living alone/single).

All analyses of the dissertation were performed on the servers of Statistics Denmark using Stata 14. Due to the regulations on anonymous data reporting, we could not report data containing less than three observations.

### 2.1.10 Additional data sources

For Papers II and III, information on FIT requests, FIT values and indications for using the FIT were stored on the servers at the Department of Clinical Biochemistry at Randers Regional Hospital, and this information was provided by this institution. For paper III, the information on CRC stages was supplemented by reviewing the electronic patient records.
2.2 PAPER I

2.2.1 Study design

The aim of this study was to investigate the diagnostic activity in general practice and the cumulative incidence of CRC in individuals invited to the Danish national screening programme for CRC. This was investigated using a historical population-based cohort study.

2.2.2 Study participants

Men and women aged 50-74 years who were invited to participate in the Danish screening programme for CRC from 1 March 2014 to 31 December 2014 (prevalence screening) were eligible for inclusion in the study.

Individuals were excluded if they were not listed with a GP, had died within one month after receiving the screening invitation, had lived outside Denmark at some point during the year preceding the screening invitation or had a previous diagnosis of colorectal disease, including colorectal cancer, Crohn’s disease, ulcerative colitis, FAP, HNPCC or adenomas followed by regular colonoscopy.

2.2.3 Outcome measures

2.2.3.1 Diagnostic activity in general practice preceding the invitation to FIT screening

This primary outcome on pre-screening diagnostic activity was assessed from the day when the individual was invited to the FIT screening until one year preceding the screening invitation. Daytime face-to-face consultations in general practice (incl. home visits) and point-of-care haemoglobin measurements in general practice (photometric analysis) were used as proxies for diagnostic activity, including health-care seeking and symptom presentation that could relate to colorectal pathology.

The diagnostic activity was compared for screening participants vs. non-participants, individuals with a positive FIT in the screening vs. individuals
with a negative FIT, and individuals with a CRC detected in the screening vs. individuals with a positive FIT and no CRC detected in the screening. Participants were defined as individuals who had performed a FIT, and a positive FIT was defined as a FIT value of ≥100 μg/L. For the analyses of CRC vs. no CRC, only individuals who had a colonoscopy performed were compared to ensure that the conclusion of no CRC was verified by a diagnostic investigation.

2.2.3.2 Cumulative incidence of CRC following the invitation to FIT screening

This outcome was investigated in the year following the screening invitation. Individuals were followed in registers from the day when they were invited to the FIT screening until CRC diagnosis, death, migration or end of follow-up.

To allow assessment of the number of CRCs diagnosed outside the screening programme, we stratified CRC incidents into three subgroups: participants diagnosed in the screening, participants diagnosed outside the screening and non-participants. In addition to investigating the incidence, we also assessed the risk of being diagnosed with a stage IV CRC in participants vs. non-participants.

2.2.4 Statistical analyses

The index date was defined as the date on which the individual was invited to participate in the screening for CRC.

The diagnostic activity in general practice was investigated by estimating the rate of consultations and haemoglobin measurements in the year leading up to the index date. To increase the statistical power, this was done in intervals of three months. The rates were compared by estimating incidence rate ratio (IRR) using negative binomial regression models with cluster robust variance estimation to account for heterogeneity between individuals. The IRR were adjusted for age, gender, marital status, country of origin, level of education, labour market affiliation, comorbidity, prescriptions of medications against haemorrhoids.
and medications with an anticoagulatory effect (NSAIDs, ASAs and anticoagu-
lants).

The cumulative incidence of CRC was assessed using the Kaplan-Meier method. Participants diagnosed with CRC outside the screening programme were de-

fined as: 1) a participant with a CRC registered in the DCR who had a negative FIT and no CRC registered in the DCCSD or 2) a participant with a CRC regis-
tered in the DCR who had a positive FIT in the screening but no registered co-
lonoscopy, CT colonography or CRC registered in the DCCSD.

We estimated the risk of being diagnosed with a stage IV CRC using a Poisson regression model with time at risk as exposure while taking into account the competing risk of being diagnosed with a lower stage of cancer.
2.3 PAPER II

2.3.1 Study design

The overall aim of this study was to explore the dissemination and clinical use of the FIT, after establishing access to the FIT in general practice. Furthermore, we assessed whether participation in a training course on FIT use affected the clinical uptake. This was done by conducting a non-randomised controlled trial with a phased introduction of a complex intervention.

The study took place in the Central Denmark Region from 1 September 2015 to 31 August 2016 (12 months). General practices and their affiliated GPs were stepwise included in clusters which were constituted by the 18 municipality-based GP clusters in the Central Denmark Region. Using a stepwise cluster inclusion enabled us to roll out the complex intervention at large scale and to include all general practices in the Central Denmark Region. Clustering of the general practices was only used to facilitate the introduction of the intervention, and the dissemination and clinical use of the FIT was investigated at general practice level (described in section 2.4.6 Statistical analyses).

2.3.1.1 Inclusion of clusters

During the first seven months of the one-year study period, all GP clusters in the Central Denmark Region were included in the study. At the day of inclusion, the GPs in the cluster could start requesting the FIT.

The date of inclusion was determined by randomly allocating the GP clusters to a monthly start-up date in which the chairman of the GP cluster was invited to arrange a training course on the use of the FIT. This training course constituted one of three main elements in the complex intervention (described in section 2.3.3.2.1 Training course). The invitation was flexible; this implied that the chairman could arrange the course to take place in any of the seven months to best suit the GPs’ preferences and other events in the GP cluster. The chairman
could also decline the invitation if it did not fit into the schedule of the GP cluster. Thus, a GP cluster was included on the first working day in the month in which the training course was arranged. GP clusters that declined to arrange the training course were included on the first working day in the month after confirmation of not arranging the meeting.

2.3.2 Setting and study participants

The Central Denmark Region is one of five regions in Denmark and has approx. 1.2 million inhabitants and 825 GPs working in 385 general practices. GPs in Denmark had limited access to faecal immunochemical testing prior to this study, and no logistic setup existed for ordering and analysing the FIT from general practice.

The study participants consisted of all general practices in the Central Denmark Region, including their affiliated GPs and listed patients aged ≥30 years. Data was collected for each general practice from the date of inclusion until six months after inclusion. The characteristics of the general practices, the GPs and the listed patients were assumed to be constant after inclusion in the study. If a general practice closed down during the study period, this practice was censored from the analyses at the date of practice closure. If a general practice opened during the study period, it was included at the date of opening.

2.3.3 Complex intervention

To facilitate the introduction of the FIT in general practice, a complex intervention was developed prior to study start; this intervention was allocated to each GP cluster when included in the study (106).

2.3.3.1 Developing the intervention

The process of developing the intervention was divided into three parts and followed the recommendations from the UK Medical Research Council (107).
Firstly, the Behavioural Change Wheel was used as a framework to identify possible barriers for the GPs to start using the FIT (108). These included lack of knowledge about the FIT, lack of opportunity to use the FIT and lack of motivation to start using the FIT. Based on local experiences, theories on normalisation and literature on continuous medical education, three major intervention elements were selected to overcome these barriers (109–112): 1) a training course, 2) a clinical instruction and 3) a logistic setup to allow ordering and analysing of the FIT. These elements formed the basis of the intervention model.

Secondly, the intervention model was pilot tested in a three-month period among 10 GPs in the Central Denmark Region. During the pilot period, individual interviews were conducted with GPs to allow identification of issues within each element that needed adjustment before using the intervention model in a large-scale setting. The interviews revealed that the GPs preferred a flexible clinical instruction, which allowed them to use their own clinical judgement instead of having to comply with a rigid guideline. Furthermore, when requesting a FIT, GPs preferred a simple setup of the ordering system that was similar to existing ordering procedures for diagnostic tests in general practice.

Thirdly, after the pilot period, the intervention model was adjusted and revised in accordance with the feedback from the GPs in the pilot study and set up for use in a large-scale setting.

In addition to the intervention elements, arrangements were made with the Organisation of General Practitioners in the Central Denmark Region to provide remuneration of GPs when requesting a FIT (corresponding to 20€ per requested test). This covered the time spent on instructing the patient on how to perform the test and on requesting the FIT in the online ordering system.
2.3.3.2 Intervention elements

2.3.3.2.1 Training course

The conduction of the training course depended on whether the chairman of the GP cluster decided to arrange it. If the course was arranged, it was conducted within the first month after inclusion (Table 2.2). Participation was optional, and attending GPs were registered to allow identification of the general practices that had participated in the lecture. All GPs in the Central Denmark Region were allowed to use the FIT, regardless of participation in the training course, and they could start using the test from the date of inclusion.

The course was arranged as a lecture of 45-60 minutes, which consisted of two parts. The first part was performed by a senior researcher and contained a general introduction to the diagnostic procedures of CRC in general practice and an update on the newest research. The second part was performed by the PhD student (Jakob Søgaard Juul) and contained an introduction to the FIT, a description of the FIT use during the study period and an overview of the logistics of

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<tr>
<td>Date of inclusion</td>
<td>Invitation letter</td>
<td>Mandatory</td>
</tr>
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<td>10 FIT kits</td>
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<tr>
<td></td>
<td>Clinical instruction</td>
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<td>Online educational material</td>
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<td>Approx. one month after inclusion</td>
<td>Mail with status on FIT requests</td>
<td>Mandatory</td>
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<tr>
<td>During the first month of inclusion</td>
<td>Training course</td>
<td>Optional</td>
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</table>
ordering and analysing the FIT. The training course was interactive with opportunity for questions and discussion, and the course was based on international literature and guidelines focusing on the Danish general practice setting.

2.3.3.2.2 Clinical instruction

The clinical instruction was a mandatory intervention element, and all general practices in the Central Denmark Region received it. The instruction was sent to the GPs at the date of inclusion together with a box of FIT kits. In addition, the GPs received an e-mail explaining that it was now possible to use the FIT from general practice and a link to the website www.praksis.dk (in Danish) with detailed information on the study, an online version of the clinical instruction and PowerPoint slides from the training course. A second e-mail was sent approx. one month after inclusion; this e-mail contained a status on FIT requests in the GP cluster and in the Central Denmark Region (Table 2.2).

The instruction contained a list of suggested symptoms and signs for using the FIT and described the recommended clinical actions on positive and negative test results. Furthermore, it contained an overview of the logistics in the study.

Indications for using the FIT: On the basis of the pilot study, it was left to the GPs clinical knowledge and judgement to decide on which patients to use the FIT. However, it was a prerequisite for using the FIT that the patient was aged ≥30 years and that the GP did not interpret the patient’s symptoms as alarm symptoms of CRC (these patients should be urgently referred to the CPP as usual).

To support the GPs in deciding which patients were eligible for faecal immunochemical testing, a list of suggested symptoms and signs was provided. As earlier mentioned, symptoms constitute a continuum and can take different forms of severity (34). Therefore, change in bowel habits, abdominal pain and unexplained anaemia were included as suggested indications if the GP did not interpret the symptoms as eligible for urgent referral in the CPP. We also included
investigation for irritable bowel syndrome (IBS) as an indication for using the FIT. This was done to allow identification of patients with rectal bleeding, which is considered a red flag symptom in the diagnostic workup of IBS (113,114). Finally, we included uncharacteristic symptoms (e.g. weight loss and loss of appetite) for patients who were not found eligible for urgent referral in the CPP for serious non-specific symptoms of cancer.

**Recommended actions on FIT results:** In this study, the FIT was used as a rule-in test, and the cut-off value was set at 50 μg/L. For individuals with a positive FIT (≥50 μg/L), urgent referral to colonoscopy was recommended. A negative FIT (<49 μg/L) was recommended to guide the direction of the most appropriate diagnostic strategy alongside with safety-netting and “watchful waiting”.

2.3.3.2.3 Logistic setup

The logistic setup was also a mandatory intervention element, which allowed all GPs in the Central Denmark Region to start requesting the FIT from the date of inclusion.

FITs were packed in kits together with an instruction on how to correctly perform a FIT, a collection paper and a postage-paid envelope addressed to Randers Regional Hospital. This was managed by the company that was also in charge of packing the FITs for the Danish screening programme. The FIT kits were then packed in boxes of 10 kits and delivered to a regional distributor, who forwarded the kits to general practices in the Central Denmark Region. GPs could order new supplies of FIT kits during the whole study period.

The GPs requested FITs through WebReq, an online ordering system which is normally used by Danish GPs to request laboratory tests. When requesting a FIT, the GPs registered the patient’s symptoms by ticking a box in the ordering system. The box contained indications from the clinical instruction, including a free-text field for other symptoms. It was possible to tick more than one indica-
tion. All FITs requested through the study period were sent to the Department of Clinical Biochemistry at Randers Regional Hospital and analysed by the OC-Sensor DIANA (Eiken Chemical Company, Ltd., Japan). The OC-Sensor has a measuring range of 35-1000 μg/L (stated as <35 μg/L for FIT values below the detection limit), and FIT results were returned electronically to the GP with a quantified value. If the FIT was unsuitable for analysis, a notice stating this was returned to the GP. Laboratory staff analysing the collected FITs were blinded to the project. Doctors performing colonoscopy were not blinded to the FIT results, but they had no affiliation with the project.

2.3.4 Outcome measures

2.3.4.1 Rate of general practices starting to use the FIT

The primary outcome of the study assessed the dissemination of the FIT and was stratified for participation in the training course. The date when a general practice started using the FIT was defined as the first registered date on which a FIT was requested from the clinic, regardless of test result.

2.3.4.2 Monthly rate of requested FITs

This outcome assessed the clinical use of the FIT and was stratified for participation in the training course. The rate was estimated as an average for all general practices in the Central Denmark Region. To account for practice size, the rate was calculated per 1,000 patients aged ≥30 years listed with the practice. Invalid FITs that were followed up by a new test within 30 days were excluded to avoid overestimating the use of the FIT.

2.3.4.3 Monthly rate of positive FITs and indications of use

These outcomes assessed the clinical use of the FIT and were stratified for participation in the training course. It estimated whether practices that attended the
course used the FIT on the same type of population as non-attending practices. Invalid FITs that were followed up by a new test within 30 days were excluded.

2.3.5 Statistical analyses

All analyses were performed for the first six months after inclusion to ensure that all general practices had similar follow-up time. For all analyses, the date of inclusion was set to a joint index date (time=0) to account for the stepwise inclusion. The use of laboratory tests in Danish general practice is registered under provider number. Therefore, all analyses were performed at general practice level as we did not have information on the individual GP’s FIT use. General practices with at least one attending GP in the training course were defined as participants (course clinics), and general practices with no attending GPs were defined as non-participants (no-course clinics). General practices in a GP cluster which had decided not to arrange the training course were defined as no-course clinics.

The rate of general practices that started using the FIT was assessed by the cumulative incidence using the Kaplan-Meier method. The difference in proportion of general practices that started using the FIT was tested by the log rank test. The hazard ratio for starting to use the FIT for course clinics compared to no-course clinics was estimated using the Cox proportional hazards model. This was adjusted for practice characteristics (number of patients aged ≥ 30 years listed with the practice and type of practice, e.g. singlehanded or partnership) and date of inclusion of general practices.

The monthly rate of FIT use and the monthly rate of positive tests were estimated by Poisson regression analysis. Differences between course clinics and no-course clinics were estimated by calculating the incidence rate ratio and were adjusted for practice characteristics and the date of inclusion. The outcomes
were not adjusted for the age and gender of the patients as no differences were found for these factors between course clinics and no-course clinics.
2.4 PAPER III

2.4.1 Study design

This study was based on the establishment of diagnostic access to the FIT for GPs in the Central Denmark Region, which is described in paper II regarding the dissemination and clinical use.

The overall aim of this study was to investigate the diagnostic value of using the FIT in general practice in individuals presenting with non-alarm symptoms of CRC. This was done by conducting a prospective cohort study in which we assessed whether the FIT could be used to detect CRC and other serious bowel disease (SBD) in individuals aged ≥30 years with non-alarm symptoms of CRC.

The study took place in the Central Denmark Region from 1 September 2015 to 31 August 2016 (12 months).

2.4.2 Study participants

We included all individuals aged ≥30 years who had performed a valid FIT (defined as a FIT result within the measuring range of the OC Sensor DIANA) in general practice during the study period. Included individuals were followed up from the day of the FIT request until three months after. A follow-up time of three months was used as individuals with a positive FIT should be urgently referred to diagnostic investigation.

Individuals with an invalid FIT were excluded due to lack of information on test results. An invalid FIT was defined as a FIT that had been unsuitable for analysis and thus did not have a quantified value. In addition, only one FIT result per individual was included. This was either the latest performed FIT or the FIT that was requested immediately before the referral to the diagnostic investigation (colonoscopy or CT colonography) as this FIT was assumed to be decisive for further investigation.
2.4.3 Outcome measures

2.4.3.1 FIT requests and diagnoses

This primary outcome assessed the number of requested FITs, the FIT results, the number of performed diagnostic investigations (sigmoidoscopy, colonoscopy or CT colonography), and the number of CRCs (incl. locations and stages) and other serious bowel diseases (SBD) diagnosed after performance of the FIT.

SBD was defined as a diagnosis of either inflammatory bowel disease (IBD) or high-risk adenomas (HRA). IBD included: Crohn’s disease, ulcerative colitis and microscopic colitis (collagenous colitis and lymphocytic colitis) (115). In accordance with the literature, HRA was defined as high-grade dysplasia, size ≥1 cm, or ≥3 adenomas (1,116). Stages of CRC were defined from the UICC stages (4). The location of CRC was categorised into the proximal colon (including caecum, the ascending colon and the transverse colon), the distal colon (including the descending colon and the sigmoid colon) and the rectum.

2.4.3.2 Symptoms and signs reported for requesting FITs

This outcome assessed the distribution of indications for using the FITs, the rate of positive FITs, and the PPVs for CRC and SBD for individual symptoms or a combination of 2 or ≥3 symptoms.

2.4.3.3 Rate of positive FITs and PPVs for CRC and SBD at different age and for gender

This outcome assessed the rate of individuals with a positive FIT and the PPV for having a diagnosis of either CRC or SBD when the GP decided to request a FIT and when the FIT result was positive. Furthermore, we stratified for age and gender to assess whether these covariates influenced the PPV.
2.4.3.4 PPVs for CRC and SBD at different FIT values

This outcome assessed the PPV of having either CRC or SBD in relation to the FIT value. This was to assess whether there was a lower limit of blood in stools in which a diagnosis of either CRC or SBD was unlikely.

2.4.3.5 Likelihood of CRC and SBD in relation to FIT value, age and gender

This outcome assessed the association between a positive FIT and a diagnosis of either CRC or and SBD for each of the variables: FIT value, age and male gender.

2.4.4 Sample size

On the basis of a previously published report on the reasons for consulting a GP in Denmark, we expected each GP to request 1-2 FITs per week (55). Thus, when taking the stepwise inclusion of GP clusters into account, we expected approx. 33,600 FITs to be requested during the study period.

As we used a lower cut-off value than the Danish screening programme and the FIT was used exclusively on symptomatic patients, we expected a higher rate of positive FITs than the 7% found in the Danish screening programme (described in section 1.4 “Screening for colorectal cancer”, p. 24) (40). Therefore, this rate was estimated to be approx. 10%. After assessing the literature on performance of the FIT in both symptomatic patients and in screening, we expected an overall PPV for CRC of approx. 10% when the FIT was positive.

Thus, we expected a total of 336 CRCs (10% of 3,600 positive FITs) to be diagnosed during the study period.

2.4.5 Statistical analyses

The PPVs for CRC and SBD were assessed for individuals aged ≥30 years with a performed valid FIT during the study period. To avoid overestimation, the PPVs for CRC and SBD after a positive FIT were calculated using all individuals with a positive FIT as the denominator. Likewise, the false negative rate was calculat-
ed using all individuals with a negative test as the denominator. P-values were calculated by Fisher’s exact test.

For analyses on the PPV for CRC and SBD at different FIT values, we stratified FIT values on the basis of three thresholds: 50-99, 100-499, 500-999 and ≥1000 μg/L.

The association between a positive FIT and a diagnosis of either CRC or SBD for FIT value, age and male gender was assessed by calculating the odds ratio using a logistic regression model. To account for confounding, each variable was adjusted for the remaining two variables. Age was introduced as a categorical variable using 10 year intervals (30-39, 40-49, 50-59, 60-69, 70-79 and ≥80 years). The FIT value was also categorical, using the same thresholds as described above.

The OC Sensor DIANA states FIT values in μg/L. Thus, in order to indicate the exact FIT results, all FIT values in this dissertation are stated in μg/L. However, proposals for standardizing report units of the FIT have been made (117). Therefore, the FIT values can be recalculated into μg/g by the equation: μg haemoglobin per g faeces = \(((\text{ng haemoglobin}/mL\ buffer) \times mL\ buffer)/mg\ faeces\ collected\). According to the manufacturer, the OC Sensor on average collects an average of 10 mg faeces and contains 2 ml buffer.
2.5 ETHICS AND APPROVAL

2.5.1 Paper I

The study was approved by the Danish Data Protection Agency (j.no. 2014-41-3143). Approval from the Committee on Health Research Ethics in the Central Denmark Region was not required as the study was register-based and did not require establishment of a biobank.

2.5.2 Paper II & III

The study was approved by the Danish Data Protection Agency (j.no. 2015-41-3913) and obtained ethical clearance from the Committee on Health Research Ethics in the Central Denmark Region (j.no. 142/2014). The Danish Health and Medicines Authority gave legal permission to obtain information from patient records (3-3013-1026/1/SABN). The Danish College of General Practitioners and the Committee of Multipractice Studies in General Practice under the Organization of General Practitioners in Denmark recommended GPs to participate in the study (MPU 05-2015). The study was registered on ClinicalTrials.gov (Identifier: NCT02308384).
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CHAPTER 3:

RESULTS
This chapter contains an outline of the main results of the dissertation. For further details, please see the papers included in the appendix.

### 3.1 PAPER I

Of the 390,552 invited individuals, 376,198 (96.3%) were included in the study. Of these, 245,299 (65%) participated in the FIT screening, and 16,206 (6.6%) of the participants had a positive FIT result. Among individuals with a positive FIT, 14,862 (91.7%) had a colonoscopy or a CT colonography performed, and a total of 907 (6.1% of 14,862) CRCs were detected.

**3.1.1 Diagnostic activity in general practice preceding the invitation to FIT screening**

Participants in the screening for CRC had significantly higher rates of consultations than non-participants (average of 1.05 (95% confidence interval [CI] 1.04;1.06) vs. 0.93 (CI: 0.92;0.94) consultations per three months). This was also seen for haemoglobin measurements (average of 0.065 (CI: 0.064;0.066) vs. 0.055 (CI: 0.053;0.057) measurements per three months) (Figure 3.1 A). Participants were more likely to be female, have a high educational level and low CCI score.

Individuals with a positive FIT had higher rates of consultations than individuals with a negative FIT (average of 1.31 (CI: 1.28;1.34) vs. 1.03 (CI: 1.02;1.04) consultations per three months) (Figure 3.1 B). The same was seen for haemoglobin measurements (average of 0.09 (CI: 0.08;0.1) vs. 0.064 (CI: 0.063;0.065) measurements per three months). A small insignificant increase in consultations was seen for individuals with a positive FIT in the last three months preceding the invitation compared with the 3-month period earlier (IRR=1.06 (CI: 1.04;1.08) vs. IRR=1.04 (CI: 1.02;1.06), respectively). Individuals with a positive FIT were more likely to be male, have a low educational level and high CCI score. In addition, individuals with a positive FIT were more often prescribed medications with anticoagulatory effect.
The rates of consultations for individuals with a screen-detected CRC were lower in the year preceding the screening invitation than for individuals with no CRC (average of 1.14 (CI: 1.04;1.25) vs. 1.29 (CI: 1.26;1.32) consultations per three months) (Figure 3.1 C). Stratifying for CRC stages did not change this (results not shown). There were no significant differences in the rates of haemoglobin measurements (average of 0.093 (CI: 0.074;0.115) vs. 0.086 (CI: 0.080;0.092) measurements per three months). Individuals with CRC diagnosed in the screening were more often males and tended to have less comorbidity than individuals without CRC.

Figure 3.1 A-C: Diagnostic activity in general practice for subgroups in CRC screening. The estimates were made for 3-month intervals during the 12 months preceding the screening invitation. The upper graph illustrates the unadjusted rates of consultations and haemoglobin measurements for individuals in different subgroups. The lower graph illustrates the IRRs for comparison of subgroups adjusted for age, gender, country of origin, educational level, labour market affiliation, marital status, CCI score, and prescriptions for medications against haemorrhoids and for medications with anticoagulatory effect (NSAID, ASA and anticoagulants).
3.1.2 Cumulative incidence of colorectal cancer following the invitation to FIT screening

One year after the screening invitation, 1,215 incident cases of CRC had been detected in the included individuals. Of these, 976 were diagnosed among participants and 239 among non-participants (Table 3.1). Of CRCs diagnosed in participants, 69 cases were found outside the screening programme (60 participants after a false negative FIT and 9 participants after not receiving colonoscopy despite a positive test) (Figure 3.2). Thus, in total, 308 (25.3%) CRCs were diagnosed outside the screening programme. Nonparticipants diagnosed with CRC were more likely to be males, have low SES and moderate to severe CCI score. The overall risk of getting a stage IV CRC was 0.035% (CI: 0.026;0.047) for non-participants and 0.021% (CI: 0.015;0.027) for participants; this corresponds to a 65% increased risk for non-participants.

Figure 3.2: Cumulative incidence of CRC in the year following the screening invitation, stratified into CRCs detected through the screening and outside the screening programme. In total, 907 CRCs were diagnosed in the screening (red curve) and 308 CRCs were diagnosed outside the screening programme (blue and green curves).
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Table 3.1: Cumulative incidence of CRC for subgroups of individuals invited to the Danish screening programme for CRC. The cumulative incidence was assessed in the year following the screening invitation.

<table>
<thead>
<tr>
<th>Category</th>
<th>CRC</th>
<th>No CRC</th>
<th>Total</th>
<th>Cumulative incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>976</td>
<td>244,323</td>
<td>245,299</td>
<td>0.4</td>
</tr>
<tr>
<td>Non-participants</td>
<td>239</td>
<td>130,660</td>
<td>130,899</td>
<td>0.2</td>
</tr>
<tr>
<td>Positive FIT</td>
<td>916</td>
<td>15,290</td>
<td>16,206</td>
<td>6.0</td>
</tr>
<tr>
<td>Negative FIT</td>
<td>60</td>
<td>229,033</td>
<td>229,093</td>
<td>0.03</td>
</tr>
<tr>
<td>Colonoscopy after a positive FIT</td>
<td>907</td>
<td>13,955</td>
<td>14,862</td>
<td>6.5</td>
</tr>
<tr>
<td>No colonoscopy despite a positive FIT</td>
<td>9</td>
<td>1,335</td>
<td>1,344</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Table 3.1: Cumulative incidence of CRC for subgroups of individuals invited to the Danish screening programme for CRC. The cumulative incidence was assessed in the year following the screening invitation.
In total, seventeen of the eighteen GP clusters in the Central Denmark Region chose to arrange the training course, and 160 (42%) general practices had at least one GP represented at the course (Table 3.2). The proportion of single-handed practices was larger for no-course clinics (48%) than for course clinics (32%). Seven general practices closed after being included in the study. No general practices opened during the study period.

Table 3.2 The stepwise inclusion of GP clusters. All 385 general practices in the Central Denmark Region were included in the study over 7 months, which ensured a joint follow-up time of 6 months.
3.2.1 Rate of general practices starting to use the FIT

After six months, 93% of course clinics had started to use the FIT compared to 73% of no-course clinics (p<0.01). In total, 81% of the general practices in the Central Denmark Region started to use the FIT during the first six months after inclusion (Figure 3.3). The hazard ratio of starting to use the FIT was 2.10 (CI: 1.68;2.64) for course clinics compared to no-course clinics. When adjusting for practice characteristics and date of inclusion, the hazard ratio was 1.99 (CI: 1.55;2.54).

![Graph showing rate of general practices starting to use the FIT](image)

**Figure 3.3: Rate of general practices starting to use the FIT.** No difference was seen between course clinics and no-course clinics during the first 14 days. Hereafter, the rates started to deviate and significantly more course clinics started to use the FIT than no-course clinics (p<0.01) during the six months after inclusion.
3.2.2 Monthly rate of requested FITs

During the six months after inclusion, the average FIT use for the general practices in the Central Denmark Region was 0.35 (CI: 0.32;0.37) tests per month. The overall IRR for requesting a FIT was 1.75 (CI: 1.41;2.18) for course clinics compared to no-course clinics. When we adjusted for the date of inclusion and practice characteristics, the IRR was 1.64 (CI: 1.29;2.08). The difference was only significant in the first four months after inclusion. (Figure 3.4). Beyond these four months, the rate among course clinics declined and tended to converge with the rate among no-course clinics.

Figure 3.4: Monthly rate of FIT use. Rates were calculated per 1000 patients aged ≥30 years listed with the practice and stratified for participation in the training course.
3.2.3 Monthly rate of positive FITs and indications of use

During the six months, the overall rate of positive FITs was 15% (CI: 14;17). No-course clinics had a slightly higher rate of positive tests between two and three months after inclusion (Figure 3.5). However, no overall significant difference was found between the positivity rates of course clinics and no-course clinics (IRR=0.89 (CI: 0.73;1.08)). This did not change when adjusting for the date of inclusion and practice characteristics (IRR: 0.94 (CI: 0.77;1.15)). No significant clinical differences were present in the indications for using the FIT.

![Figure 3.5: Monthly rate of positive FITs. Rates were stratified for participation in the training course.](image-url)
3.3 PAPER III

3.3.1 FIT requests and diagnoses

In total, 3,745 FITs were requested during the study period. Of these, 91 (2.4%) FITs were invalid and 192 (5.1%) additional FITs were excluded to ensure only one test per individual. Thus, a total of 3,462 (92.5%) FITs were included in the analyses. Of these, 540 (15.6%) were positive and 2,921 (84.4%) were negative.

Three months after the FIT request, 416 (77.0%) individuals with a positive FIT had had a diagnostic investigation performed. Among these, 51 (PPV: 9.4% (CI: 7.0;11.9)) were diagnosed with CRC and 73 (PPV: 13.5% (CI: 10.6;16.4)) with SBD. Of the CRCs, 34 (66.7%) were detected in UICC stage I and II and 10 (19.6%) in stage IV. In total, 21 (41.2%) CRCs were located in the proximal colon, 16 (31.4%) in the distal colon and 14 (27.4%) in the rectum.

Among all individuals with a negative FIT, 418 (14.3%) had had a diagnostic investigation performed after three months. Less than three of these individuals (<0.1%) were diagnosed with CRC and 26 (0.9%) with SBD.

3.3.2 Symptoms and signs reported for requesting FITs

In total, the GPs reported symptoms for 3,114 (89.8%) individuals. Of these, 1,169 (33.7%) had one symptom, 1,165 (36.3%) had two symptoms and 780 (22.5%) had three or more symptoms. The positivity rates did not differ notably for number of presented symptoms. However, the PPV for CRC was slightly higher for individuals with one reported symptom (11.4% (CI: 6.6;17.0) vs. 7.9% (CI: 4.0;11.7) for two symptoms and 8.2% (CI: 3.0;13.4) for three or more).

The most frequently reported symptoms were change in bowel habits (53.9% of individuals) and abdominal pain (45.6% of individuals). These symptoms had a positivity rate of 15.5% (CI: 13.9;17.2) and 13.3% (CI: 11.6;15.0), respectively. The PPV for CRC when the FIT was positive was 9.3% (CI: 5.9;12.7) for change in bowel habits and 8.6% (CI: 4.8;12.4) for abdominal pain.
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The symptom with the fewest FIT requests was anaemia (12.3% of individuals), but this was also the symptom with the highest positivity rate (20.5% (CI: 16.7;24.4)) and the highest PPV for CRC when the FIT was positive (11.5% (CI: 4.7;18.3)). Interestingly, symptoms categorised as “other” had the highest PPV for SBD (21.3% (CI: 12.7;30.0)), but the lowest for CRC (5.6% (CI: 0.7;10.5)).
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Requested FITs</th>
<th>Positive FITs</th>
<th>SBD after a positive FIT</th>
<th>CRCs after a positive FIT</th>
<th>Rate of positive FITs</th>
<th>PPV for SBD when the GP requested the FIT</th>
<th>PPV for CRC when the GP requested the FIT</th>
<th>PPV for SBD if the FIT was positive</th>
<th>PPV for CRC if the FIT was positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>228</td>
<td>30</td>
<td>NA</td>
<td>0</td>
<td>13.2 (8.7;17.6)</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Males</td>
<td>101</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>8.9 (3.3;14.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Females</td>
<td>127</td>
<td>21</td>
<td>NA</td>
<td>0</td>
<td>16.5 (10.0;23.1)</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>40-49 years</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>620</td>
<td>57</td>
<td>NA</td>
<td>4</td>
<td>9.2 (6.9;11.5)</td>
<td>NA</td>
<td>0.6 (0.1;1.3)</td>
<td>NA</td>
<td>7.0 (1.8;13.9)</td>
</tr>
<tr>
<td>Males</td>
<td>269</td>
<td>19</td>
<td>NA</td>
<td>NA</td>
<td>7.1 (4.0;10.1)</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
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<tr>
<td>Females</td>
<td>351</td>
<td>38</td>
<td>NA</td>
<td>NA</td>
<td>10.8 (7.6;14.1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>50-59 years</td>
<td></td>
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</tr>
<tr>
<td>All</td>
<td>723</td>
<td>79</td>
<td>9</td>
<td>5</td>
<td>10.9 (8.6;13.2)</td>
<td>1.2 (0.4;2.1)</td>
<td>0.7 (0.1;1.3)</td>
<td>11.4 (4.2;18.6)</td>
<td>6.3 (0.8;11.8)</td>
</tr>
<tr>
<td>Males</td>
<td>323</td>
<td>43</td>
<td>4</td>
<td>NA</td>
<td>13.3 (9.6;17.0)</td>
<td>1.2 (0.1;2.5)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Females</td>
<td>400</td>
<td>36</td>
<td>5</td>
<td>NA</td>
<td>9.0 (6.2;11.8)</td>
<td>1.3 (0.2;2.3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>60-69 years</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All</td>
<td>877</td>
<td>129</td>
<td>17</td>
<td>14</td>
<td>14.7 (12.4;17.1)</td>
<td>1.9 (1.0;2.9)</td>
<td>1.6 (0.8;2.4)</td>
<td>13.2 (7.3;19.1)</td>
<td>10.9 (5.4;16.3)</td>
</tr>
<tr>
<td>Males</td>
<td>382</td>
<td>69</td>
<td>9</td>
<td>10</td>
<td>18.1 (14.2;21.9)</td>
<td>2.4 (0.8;3.9)</td>
<td>2.6 (1.0;4.2)</td>
<td>13.0 (4.9;21.2)</td>
<td>14.5 (6.0;23.0)</td>
</tr>
<tr>
<td>Females</td>
<td>495</td>
<td>60</td>
<td>8</td>
<td>4</td>
<td>12.1 (9.3;15.0)</td>
<td>1.6 (0.5;2.7)</td>
<td>0.8 (0.1;1.6)</td>
<td>13.3 (4.5;22.2)</td>
<td>6.7 (0.2;13.2)</td>
</tr>
<tr>
<td>70-79 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>791</td>
<td>155</td>
<td>28</td>
<td>15</td>
<td>22.1 (19.0;25.4)</td>
<td>4.0 (2.5;5.4)</td>
<td>2.1 (1.1;3.2)</td>
<td>18.1 (11.9;24.2)</td>
<td>9.7 (5.0;14.4)</td>
</tr>
<tr>
<td>Males</td>
<td>304</td>
<td>70</td>
<td>11</td>
<td>9</td>
<td>23.0 (18.3;27.8)</td>
<td>3.6 (1.5;5.7)</td>
<td>3.0 (1.0;4.9)</td>
<td>15.7 (7.0;24.5)</td>
<td>12.9 (4.8;20.9)</td>
</tr>
<tr>
<td>Females</td>
<td>597</td>
<td>85</td>
<td>17</td>
<td>6</td>
<td>21.4 (17.4;25.5)</td>
<td>4.3 (2.5;6.3)</td>
<td>1.5 (0.5;2.7)</td>
<td>20.0 (11.3;28.7)</td>
<td>7.1 (1.5;12.6)</td>
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<tr>
<td>80 years</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>All</td>
<td>313</td>
<td>90</td>
<td>13</td>
<td>13</td>
<td>28.8 (23.7;33.8)</td>
<td>4.2 (1.9;6.4)</td>
<td>4.2 (1.9;6.4)</td>
<td>14.4 (7.0;21.8)</td>
<td>14.4 (7.0;21.8)</td>
</tr>
<tr>
<td>Males</td>
<td>141</td>
<td>45</td>
<td>6</td>
<td>9</td>
<td>31.9 (24.3;39.7)</td>
<td>4.3 (0.9;7.6)</td>
<td>6.4 (2.3;10.5)</td>
<td>13.3 (3.0;23.7)</td>
<td>20.0 (7.8;32.2)</td>
</tr>
<tr>
<td>Females</td>
<td>172</td>
<td>45</td>
<td>7</td>
<td>4</td>
<td>26.2 (19.5;32.8)</td>
<td>4.1 (1.1;7.1)</td>
<td>2.3 (0.1;4.6)</td>
<td>15.6 (4.5;26.6)</td>
<td>8.9 (0.2;17.5)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3462</td>
<td>540</td>
<td>73</td>
<td>51</td>
<td>15.6 (14.4;16.8)</td>
<td>2.1 (1.6;2.6)</td>
<td>1.5 (1.1;1.9)</td>
<td>13.5 (10.6;16.4)</td>
<td>9.4 (7.0;11.9)</td>
</tr>
<tr>
<td>Males</td>
<td>1520</td>
<td>255</td>
<td>31</td>
<td>34</td>
<td>16.8 (14.9;18.7)</td>
<td>2.0 (1.3;2.8)</td>
<td>2.2 (1.5;3.0)</td>
<td>12.2 (8.1;16.2)</td>
<td>13.3 (9.1;17.5)</td>
</tr>
<tr>
<td>Females</td>
<td>1942</td>
<td>285</td>
<td>42</td>
<td>17</td>
<td>14.7 (13.1;16.2)</td>
<td>2.2 (1.5;2.8)</td>
<td>0.9 (0.5;1.3)</td>
<td>14.7 (10.6;18.9)</td>
<td>6.0 (3.2;8.7)</td>
</tr>
</tbody>
</table>

Table 3.4: Numbers of requested FITs, positive FITs (cut-off 50 µg/L), and diagnosed CRCs and other serious bowel disease (SBD) after a positive FIT, stratified for gender and age groups. Positive predictive values (PPV) are given for CRC and SBD when the GP decided to request FIT and when FIT was positive.
3.3.3 Rate of positive FITs and PPVs for CRC and SBD at different age and for gender
The overall rate of positive FITs was 15.6% (CI: 14.4;16.8) (Table 3.4). The rate was slightly higher for males (16.8% (CI: 14.9;18.7)) than females (14.7% (CI: 13.1;16.2)) and increased with age to a maximum of 31.9% (CI: 24.1;39.7) for males aged ≥80 years. However, a high number of positive tests was seen among females aged 30-39 years (16.5% (CI: 10.0;23.1)).

The overall PPV for CRC when the GP decided to request a FIT was 1.5% (CI: 1.1;1.9), and 9.4% (CI: 7.0;11.9) if the FIT was positive. In comparison, the PPV for SBD was 2.1% (CI: 1.6;2.6) when requesting a FIT, and 13.5% (CI: 10.6;16.4) when the FIT was positive. In general, the PPV for detecting either CRC or SBD increased with age. Females had a significantly higher PPV for SBD than CRC (SBD: 14.7% (CI: 10.6;18.9) vs. CRC: 6.0% (CI: 3.2;8.7) (p<0.01)), whereas males were more often diagnosed with CRC (CRC: 13.3% (CI: 9.1;17.5) vs. SBD: 12.2% (CI: 8.1;16.2)) and had significantly higher PPV for CRC compared to females (p<0.01)).

3.3.4 PPVs for CRC and SBD at different FIT values
The PPV for detecting CRC increased with higher FIT values (Figure 3.6), whereas the PPV for SBD remained fairly stable when the FIT value exceeded 100 µg/L. The PPV for CRC when the FIT was 50-99 µg/L was 2.5% (CI: 0.1;5.0), whereas this increased to 27.1% (CI: 19.0;35.3) for individuals with a FIT value of >1000 µg/L. For SBD, the PPV was 6.4% (CI: 2.5;10.2) for FIT values between 50-99 µg/L vs. 18.6% (CI: 11.5;25.8) for FIT values of ≥1000 µg/L.

3.3.5 Likelihood of CRC and SBD in relation to FIT value, age and gender
The association between a positive FIT and a diagnosis of either CRC or SBD is shown for FIT value, age and gender in Table 3.5. For each increase in FIT value, the odds of having CRC increased by a factor of 3 and the odds of having SBD by a factor of 1.4. The odds of having CRC or SBD increased equally for every
10-year increase in age. Finally, males had twofold higher odds of being diagnosed with CRC than women if the FIT was positive.

Figure 3.6: Positive predictive value for CRC and SBD stratified for FIT values. The overall PPV after a positive FIT was 9.4\% (CI: 7.0;11.9) for CRC and 13.5\% (CI: 10.6;16.4) for SBD.

Table 3.5: Association between a positive FIT and a diagnosis of either CRC or SBD. The association was assessed for FIT value, age and gender, respectively. The FIT value was categorized into 50-99, 100-499, 500-999 and ≥1000 μg/L. Age was categorized into 10-year intervals.
Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer
CHAPTER 4:
DISCUSSION OF METHODS
This chapter discusses the methodological strengths and limitations of the three studies presented in this dissertation to allow a critical evaluation of the results and the conclusions drawn from the studies (presented in Chapter 5).

4.1 DESIGN

4.1.1 The cohort study (paper I)

For paper I, we conducted a nationwide historical population-based cohort study to make an observational study of the use of general practice and assess the number of CRC diagnoses among individuals invited to screening for CRC from 1 March 2014 to 31 December 2014. Screening invitation defined the population, and the outcomes were diagnostic activity in general practice and the incidence of CRC in the year following the invitation. Although the diagnostic activity in general practice was assessed in the year preceding the screening invitation, it can still be regarded as a cohort study because the outcome was investigated over time and thus was not a simple cross-sectional study design. Consequently, the design is an observational study with a well-defined cohort and time-dependent observations.

By using prevalence screening, we were able to investigate the use of the FIT in a population possibly prevalent of lower GI symptoms and CRC. For the aim of this study, it was important that we used a population that had not been screened before as individuals who are diagnosed with CRC through screening and who unsubscribe to the screening programme will not be invited to the second round of screening, which could introduce a potential selection problem.

4.1.2 The non-randomised controlled trial (paper II)

For paper II, we conducted a non-randomised controlled trial with a phased introduction of complex intervention. All GP clusters in the Central Denmark
Region were included stepwise during the initial seven months of the study period.

Although the date of inclusion was determined by random allocation of GP clusters to a monthly start in the study, the date of inclusion could be changed to another of the initial seven months in the study period; this depended on the chairman of the GP cluster and his/her possibility and desire to setup the training course. This, together with the fact that participation in the training course was voluntary, implies that this study is non-randomised.

The limitation of using a non-randomised trial is that it could have introduced a risk of confounding of estimates (118). This is discussed in section “4.4.3 Confounding”. We could have conducted a randomised trial in which GPs were randomised to either an intervention group or control (usual care). One of the major strengths of using this design would have been that both known and unknown confounders would have been evenly distributed between groups before the start of the study (118). However, as GPs in the Central Denmark Region did not have systematic access to the FIT prior to the study, we did not have the possibility to conduct analyses comparing the FIT use between groups. Another approach could have been to randomly allocate GPs to an intervention group (receiving the training course) and a control group (receiving no training course). However, we wanted to offer all GPs in the Central Denmark Region the same opportunity and to create as much attention as possible on the FIT. Therefore, we chose to make the training course voluntary.

A strength of using the stepwise inclusion was that it enabled us to conduct the study as a large-scale study and allocate the intervention to all included clusters. This was important to ensure a high number of FIT requests during the study period, which would imply a high statistical precision of the reported results (described in section 4.3 “statistical methods and precision”).
In addition, the stepwise inclusion enabled us to conduct the training course in each GP cluster, regardless of geographical location. If we had used a common date of inclusion for all clusters, we would have been able to offer only a limited number of training courses; these would most likely have been located in the major cities of the region. This could potentially have resulted in low participation among GPs in the rural areas.

A limitation of using stepwise inclusion was that not all GPs were included at the same time. This might have implied that the last included GPs had other motivations or reasons for starting to use the FIT than the GPs who were included first. However, we accounted for this by adjusting for inclusion time in the analyses of the dissemination and clinical use of the FIT.

We chose to use GP clusters in the Central Denmark Region as clusters in the study. The primary reason for this was that these GPs already had regular meetings and established collaboration across clinics within each cluster. Thus, by including them all at once, we avoided potential confusions of allowing only part of the GP cluster to use the FIT. In addition, it was logistically more straightforward to handle the intervention at GP cluster level as it is municipality-based and has a clearly defined geographical location.

4.1.3 The prospective cohort study (paper III)

The overall purpose of using this study design was to investigate the implications on the CRC diagnostics of low-risk individuals in general practice when giving the GPs access to the FIT. A strength of using this design was that the FIT was used in daily clinical practice and thus reflected the clinical reality for both the GPs and the patients. This implies that the results reported in paper III gives a realistic picture of the use of the FIT in this setting. The study was not designed as a study of diagnostic performance of the FIT. As a consequence, we could not estimate the sensitivity, specificity and negative predictive value...
(NPV) since only individuals with a positive FIT were intended to have colonoscopy. We believe that it would have been unethical to perform colonoscopy on all individuals with a negative FIT and not in line with the real-life clinical setting. The performance of the FIT is well investigated in both screening (background population) and in general practice in individuals referred to colonoscopy by the GP (high-risk individuals). In both settings, the FIT has been found to have a relatively high sensitivity (>80-90%) and specificity (>90%). Thus, we believe it is reasonable to assume that the performance of the FIT in individuals with non-alarm symptoms of CRC will be somewhere in between these two populations. Furthermore, it has been shown that most symptomatic CRCs are seen in the final three months before the diagnosis. Therefore, it could be assumed that most CRCs will have emerged during the 3-month follow-up (119).

4.1.3.1 Other diagnostic alternatives than the FIT

If we look beyond the use of faecal immunochemical testing in general practice, other approaches have been investigated to improve the identification of individuals with CRC and reduce delays in the diagnostic process.

Symptom scoring systems, such as the Bristol-Birmingham (BB) equation and the CAPER score, have shown better performance in identifying individuals with CRC than the current NICE guidelines (120). The main advantage of these models is that they can combine multiple symptoms, signs and risk factors of CRC to estimate the risk of CRC on an individual level. The primary use of these models is to prioritise between patients at high and low risk of CRC.

A Dutch study reorganised the diagnostic pathway for CRC by providing GPs with direct access to colonoscopy and reducing the number of visits to outpatient clinics (121). This was shown to decrease the diagnostic delay and reduce the number of diagnostic tests in general practice. The number of endoscopic investigations increased, but mainly due to more follow-up investigations.
However, the pathway was intended for individuals highly suspected of CRC, and individuals with low-risk symptoms were not recommended for referral.

Finally, research on biomarkers and tumour markers are developing rapidly (122). However, whereas their role in targeted therapy of CRC is recognised, their potential role in the diagnosis of CRC remains unsolved. Thus, so far, studies have primarily assessed the use of biomarkers and tumour markers in the screening for CRC without drawing any final conclusions on its applicability.

For this study, we wanted to apply a low-cost, safe and easy-to-use method in general practice for identifying individuals with colorectal disease in a low-risk population. Furthermore, we did not want this method to imply major structural changes in the GPs’ clinical life. Thus, for the aim of this study, the FIT was preferred compared to other possible methods.
4.2 THE INTERVENTION

In order to facilitate the introduction of the FIT in general practice, a complex intervention was developed. The intervention aimed to overcome barriers for GPs to use the FIT. Three major intervention elements were included in the intervention model: a training course (voluntary for GPs), a clinical instruction on FIT use (mandatory for all GPs) and a logistic setup to allow the request and analyses of FITs from general practice (mandatory for all GPs).

The strength of this developing process was that it followed the international guidance from the UK Medical Research Council and used an internationally accepted framework for developing interventions (the Behavioural Change Wheel) (107,108). Furthermore, the intervention model was tested in a small group of pilot practices before large-scale implementation. This allowed us to identify and adjust for issues in the intervention that might have led to project failure in the worst-case scenario. A limitation was the short time period for pilot-testing the intervention model, which did not allow interpretation of the long-term sustainability of the intervention.

The intervention ensured that all GPs in the Central Denmark Region were provided with the opportunity to use the FIT.

4.2.1 Training course

Previous studies have shown that educational meetings can be used to change the clinical behaviour towards a more desired practice (110,123). However, the effect is likely to be smaller and less effective for changing complex behaviour.

In this study, the training course was used to provide GPs with knowledge of the FIT and how to use it and to motivate GPs to get started. Furthermore, it gave opportunity to engage with the GPs and to clarify questions and concerns about faecal immunochemical testing and CRC diagnostics. As previously mentioned the training course was optional for GPs, but all GPs in the Central Den-
mark Region were provided with the opportunity of requesting the FIT, regardless of participation in the training course.

The flexible setup of arranging the training course ensured that only one GP cluster decided not arrange the course. According to the study design, general practices in this GP cluster were regarded as no-course clinics. The total number of general practices in this particular GP cluster was small (9 of 385 practices in the region) and did not affect the overall attendance rate in the training course.

In total, 42% of all general practices in the Central Denmark Region participated in the course. This is comparable with the rate reported in a recent study from the Central Denmark Region on continuous medical education for GPs (124). GPs participate in continuous medical education for many reasons, including keeping up-to-date with new knowledge and special interest in specific subjects (125). In this study, we cannot rule out that primarily GPs with a special interest in the FIT and CRC diagnostics chose to participate in the course. This might have implied that GPs in course clinics were more likely to start using the FIT and integrate it in their daily practice, which may partly explain the difference between course clinics and no-course clinics. However, as we arranged the training course in collaboration with the chairman of the GP cluster, it was often scheduled as an after-work meeting together with other subjects of relevance for the GPs in the cluster. This approach may have ensured participation from GPs who would otherwise not have attended the course.

A limitation of arranging the training course as a joint meeting for all GPs in the GP cluster was that GPs from practices in other cities than the place of the venue had to take time off to be able to attend. Consequently, primarily partnership practices were able to send a colleague to the meeting, whereas many single-handed GPs were unable to attend due to work obligations. As an alternative to the joint meetings, we could have conducted the meeting in each general prac-
Discussion of methods

tice, but this would have been time consuming and not feasible due to the large number of included practices.

Another limitation was that we defined participants in the training course at general practice level. By doing so, we assumed that attending GPs educated the other staff in their practice, but we cannot be sure that this was actually the case. Furthermore, for partnership practices, we were not able to assess if all GPs at a provider number had started using the FIT or whether the rate of requested FITs differed within each practice. However, as we could not collect information on the FIT use among the individual GPs, we decided to use this approach.

4.2.2 Clinical instruction

The clinical instruction used in the intervention aimed to provide GPs with knowledge on how to use the FIT by listing suggested indications and recommended actions on FIT results and by providing an overview of the logistic chain. The instruction was a mandatory and important element of the intervention; this part constituted the primary information on the study and how to use the FIT for the practices with no GP participating in the training course.

As earlier mentioned, the use of CPPs vary among GPs (64,65), and the GPs’ interpretation of alarm symptoms may thus also differ. By letting the GPs use their own clinical judgement to decide on which patients to use the FIT, we believe that the results in this study realistically reflect the use of the FIT on individuals with non-alarm symptoms of CRC. If we had chosen to use a rigid guideline with fixed indications, it may have caused reluctance among the GPs to use the FIT or have forced the GPs to use the FIT in situations in which they actually believed that it was inappropriate or unnecessary.

A limitation was that we do not know if some GPs may have used the FIT on other groups of patients than intended. However, it was clearly stated in the clinical instruction that the FIT was not an alternative to the CPPs and that indi-
individuals with alarm symptoms of CRC should still be urgently referred in the CPP. Furthermore, the training course prepared the GPs by providing knowledge on the target population for using the FIT, and the indications were reported when they requested a FIT. For these reasons, we believe that the GPs knew the intended population for faecal immunochemical testing and that we established a uniform use of the test.

Based on literature from screening and knowledge of FIT performance according to different cut-off values, we decided to use a cut-off value of 50 μg/L (76–80). We prioritised a high sensitivity because the investigated individuals were symptomatic, and we wished to miss as few diagnoses as possible. In hindsight, it may have been better to use a cut-off value at the lower limit of the measuring range of the OC Sensor (35 μg/L) to allow assessment of the diagnoses in the lowest detectable intervals. However, setting a cut-off value is a trade-off between a high number of (potentially unnecessary) diagnostic investigations and the risk of missing diagnoses. In our case, it should also be considered that small amounts of blood in stools are normal (126). It is questionable how many extra CRCs and SBDs would have been diagnosed with a lower range cut-off value compared to the number of colonoscopies that would then also have been markedly higher.

Finally, we decided that the FIT should be used as a rule-in test due to the low prevalence of CRC in general practice and because the test was used in a “low risk” population. If the FIT had been used as a rule-out test, it may have introduced a risk of missing CRC diagnoses. We cannot be sure whether some GPs used the FIT as a rule-out test. However, the GPs were specifically instructed to use it as a rule-in test, both at the training course and in the clinical instruction. Therefore, we believe that the majority of GPs used the FIT as intended.
4.2.3 Logistics

The logistical setup in the study was also mandatory and provided all GPs in the Central Denmark Region with the opportunity of requesting the FIT from their practice and having it analysed on the Department of Clinical Biochemistry at Randers Regional Hospital.

A major strength of this setup was that we used already established logistic pathways for packing and distributing the FIT to the GPs and that the Department of Clinical Biochemistry had the necessary equipment and staff with expertise in analysing FITs. In addition, all elements in the FIT kits were tested and approved through the Danish national screening programme for CRC, and an agreement with the national postal service ensured that FIT samples were collected every day. This is especially relevant since antibody bindings are degraded over time and are susceptible to ambient temperature. Thus, screening studies have shown a slight decrease in the positivity rates during summer (127,128). We cannot rule out that some false negative test results may have occurred in paper III due to transport time variability. However, for the above reasons, we believe this risk to be minimal.

Another strength was the setup of a system in WebReq that allowed collection of the GPs’ clinical indications for using the FIT. This was especially of importance in paper III since it allowed assessment of the GPs’ reasons for using the FIT. However, a limitation of using this system was that in order for the system to be integrated into the WebReq, it had to be manually launched by a regional employee when a GP cluster was included in the study. This implied that the launch in some cases was delayed for some days. Furthermore, the GPs could order the FIT without ticking the indications. In total, the above reasons implied that approx. 10% of individuals did not have any registered indications.

A limitation of the logistic setup was that we do not know whether the FIT kits were distributed to all the general practices at inclusion. The GPs were informed
in the invitational letter (Table 2.2) that they would receive a box with FIT kits and provided with contact information to the research group, which enabled them to notify the research group if they had not received the kits. In such case, a new box of FIT kits was sent to the practice. During the study period, the research group was contacted by 10 general practices which had not received the kits, but the actual number might have been higher. This implies that some general practices may not have started using the FIT.
4.3 STATISTICAL METHODS AND PRECISION

4.3.1 Paper I

The large study population combined with the thorough analyses of the diagnostic activity in three-month intervals ensured a generally high statistical precision in the estimates of consultations and haemoglobin measurements. However, the use of three-month intervals could have blurred more sudden changes in the diagnostic activity in the last months preceding the screening invitation. Therefore, to investigate this, we also conducted the analyses using monthly intervals, but this did not change the overall results of the study.

Using negative binomial regression for assessing differences in the diagnostic activity allowed us to calculate the IRR of having a consultation or a haemoglobin measurement within the three-month interval between the subgroups. We could also have used Poisson regression for the analyses, but negative binominal regression is generally preferred when overdispersion may be present in the dataset. Overdispersion is seen when the observed variance is greater than the expected variance, which is the case in the majority of observational studies (129).

We used daytime face-to-face consultations and haemoglobin measurements as proxies for symptom presentation in general practice. This approach has been used in previous studies and is a well-investigated and accepted method (68,130). However, it has both advantages and disadvantages. Consultations with preventive focus were left out of the analyses as these have specific codes in the Danish National Health Service Register (103). Therefore, consultations reported in this study primarily represent “new events” of symptoms and disease. A limitation was that the database does not state the reason for the consultation. However, by using haemoglobin measurements, we got an indication if the GP had found it sufficiently relevant to initiate further investigation. Still, we cannot be sure that all consultations were due to newly emerged GI symptoms.
Instead of using haemoglobin measurements, we could also have chosen to use a GI-specific test. However, we did not do this since the patient’s symptom presentation could be diverse, and the GP may not suspect GI-related disease in the first few consultations. Therefore, using haemoglobin level as a proxy provide a universal measure to indicate if the GP suspects that “something is wrong”; this suspicion may be related to GI symptoms if the patient is later diagnosed with CRC. In Denmark, GI-specific tests are performed at the hospital and most often requested if the GP has a specific suspicion of a particular disease rather than a general diagnostic workup. Therefore, we believe that using these GI-specific tests may imply an underestimation of the diagnostic tests.

4.3.2 Paper II

Due to the large number of general practices and GPs in the Central Denmark Region, the statistical precision in paper II was high.

All estimates comparing course clinics with no-course clinics were adjusted for practice characteristics (practices size and number of patients aged ≥30 years) since practices with many GPs and patients were more likely to start using the FIT. Furthermore, we adjusted for the date of inclusion to account for a possible difference in using FIT depending on when the practice was included.

A limitation of the analyses was that we were not able to gather information on the FIT use among individual GPs. Thus, for partnership practices, we cannot rule out that only part of the GPs registered in a general practice were responsible for the FIT use in the entire practice.

Another limitation was the short follow-up period. Due to the stepwise inclusion, the last included general practices only had six months in the study. Therefore, we were only able to compare the initial six months after inclusion. A longer follow-up period would have allowed a more accurate evaluation of the sustainability of the implementation.
Finally, we used the rate of positive tests and indications for FIT use as proxies to assess whether course clinics and no-course clinics used the FIT on the same population. As the patient composition was similar between the groups, we believe that these proxies can be used to compare the FIT use between the groups.

4.3.3 Paper III

Although we conducted the study in a large scale, the statistical precision in paper III was low. This was primarily due to an overestimation of how many FITs would be requested during the study period (3,745 vs. 33,600 FITs). The assumptions on which the calculation was made were thought to be reasonable and based on national and international literature (see Chapter 2.3.6). In the calculation, we did not account for the possibility that some GPs may not start using the FIT and that a lower FIT use could be expected during holidays and vacations, but this is unlikely to account for the whole overestimation. Other reasons could be that the prevalence of non-alarm symptoms was lower than expected, the GPs’ interpretation of non-alarm symptoms was stricter than intended, or that the GPs may have restricted the test for the complicated cases and refrained from using it on more “healthy” individuals. However, the idea behind the whole setup of the study was that the GPs could use the FIT on individuals they found relevant as long as they were aged ≥30 years and did not have symptoms and signs that fulfilled the criteria for urgent referral in the CPP. Thus, although the number of requested FITs was lower than originally expected, we still believe that it realistically reflects the GPs’ clinical use of the FIT on individuals with non-alarm symptoms of CRC and that the overestimation of FIT use primarily reflects the discrepancy between register-based estimations and clinical reality. We could have increased the statistical precision by conducting the study at a national scale. However, this would have been costly and would also have been more complicated in terms of e.g. capacity for FIT anal-
yses. Furthermore, it would have been difficult to conduct the training course in all 98 municipalities of Denmark.

The PPVs in paper III were calculated by using all individuals with a positive FIT as the denominator. Instead, we could have based our calculations on individuals with a positive FIT and a diagnostic investigation. By doing this, we would have made sure that the conclusion of no CRC or SBD was verified by a diagnostic investigation. However, since 23% of individuals with a positive FIT were not investigated, using this approach could both have overestimated and underestimated the effect of using the FIT on non-alarm symptoms, depending on the number of CRCs and SBDs in the non-investigated group. By using all individuals with a positive FIT in the analyses, we have most likely underestimated the effect. However, in contrast to the other method, we know the direction in which the estimate would most likely change.

The assumption that the PPVs in paper III may have been underestimated is further supported by the fact that the individuals were only followed for three months after the FIT request. Thus, some individuals may have been diagnosed after the follow-up period ended. However, we expect this number to be small since individuals with a positive FIT were recommended to be urgently referred to diagnostic investigation through the CPP for CRC.
4.4 INTERNAL VALIDITY

4.4.1 Selection bias

Selection bias refers to a systematic error in the selection of a study population, which results in a systematic difference between the investigated population and the population of interest (118).

4.4.1.1 Paper I

In paper I, we sampled the study population based on the invitation to participate in the Danish national screening programme for CRC. Due to the random order in which individuals are invited to screening and the fact that all citizens between 50-74 years are invited regardless of comorbidity and SES, we believe that selection bias in paper I was minimal. However, we cannot rule out that some selection problems were present due to a selection in who decided to participate in the screening. Thus, primarily individuals with high SES and low CCI score were registered as participants. If more individuals with low SES and high CCI score had decided to participate in the screening, it most likely would have led to a higher number of individuals with a positive FIT. However, the IRR estimates were based on the average number of consultations and haemoglobin measurements, and we do not believe that a slightly higher number of individuals with a positive FIT would have changed the overall estimates or the conclusions of the study.

4.4.1.2 Paper II

In paper II, we included all general practices in the Central Denmark Region. Overall, the general practices, their GPs and the listed patients were assumed to be comparable across the region. However, differences in the composition of GPs and patients may have been present between GP clusters located in rural areas and GP clusters located in urban areas. However, since the outcomes in
paper II were not compared between GP clusters, we believe that selection bias in this regard is not relevant.

4.4.1.3 Paper III

In paper III, we included all individuals aged ≥30 years with a valid FIT during the study period. To estimate the diagnostic value of using the FIT, we only included one test per individual; this was either the last requested test or the one requested immediately before the diagnostic investigation. We assumed that this FIT was decisive for further investigation and thus was related to the outcomes.

It was important for the aim of the study to link the relevant FIT result to the findings from the diagnostic investigation. As an alternative, we could have chosen not to exclude additional FITs and assume that all requested FITs were independent investigations. However, some GPs may have requested a new FIT as part of a safety-netting approach or because the first test was performed wrongly. We could also have chosen to include only the first requested FIT per individual as this was unaffected of previous testing, but the GPs may have had good reasons for requesting a new test. Therefore, we believe that the approach used in this paper is the most correct for identifying the relevant FIT result.

4.4.2 Information bias

Information bias refers to a bias arising from a systematic measurement error (118). Information bias is often referred to as misclassification and can be categorised into: 1) non-differential misclassification (where the measurement error is equal between groups) and 2) differential misclassification (where the measurement error is larger in one group). Non-differential misclassification will usually underestimate the measure of association, whereas differential misclassification could lead to both overestimation and underestimation (118).

The data in the Danish registries are generally believed to be of high quality and largely unbiased. The strength of the Danish registries is that the data are col-
lected prospectively and independently of any research project, which reduces the risk of differential misclassification and recall bias. However, information bias may still occur due to systematic measurement errors or misclassification of subjects and will mostly be considered as non-differential misclassification.

The risk of information bias is generally considered to be low in this dissertation. However, some important sources of potential information bias will be addressed below.

4.4.2.1 Paper I

In the analyses of CRC incidence, some non-participants with CRC may have started their diagnostic pathway before receiving the screening invitation and may thus have been misclassified as diagnosed with CRC outside screening. This could have overestimated the number of non-participants diagnosed with CRC in the year after the invitation. From the available data, we cannot determine how many this concerns, but it most likely only concerns individuals diagnosed in the first few weeks after receiving the invitation as most individuals must be expected to have received diagnostic investigation shortly after referral from primary care.

As mentioned in chapter 4.3.1, we cannot be sure that all registered consultations were due to GI symptoms; this may have led to an overestimation of the rates of consultations. In addition, only haemoglobin measurements performed in general practice were included in the study. As some GPs may use hospital laboratories for requesting analyses of haemoglobin, the rates of haemoglobin measurements may have been underestimated. How this possible information bias would have influenced the IRR estimates depends on the difference in the misclassification between subgroups. However, as consultations and haemoglobin measurements were conducted independently of this study and prior to the
screening invitation, we assume this potential bias to be non-differential, which implies that the IRRs may have been underestimated.

4.4.2.2 Paper II & III

In paper II and III, approx. 10% of the patients’ symptoms and signs were not reported. We cannot predict how these missing data may have affected the outcomes in the two papers. However, we assessed the missing data regarding the distribution between patient groups and general practices, and it did not show any signs of differentiated misclassification (not shown). Nevertheless, the results of symptoms and signs in the two papers should be interpreted with care.

The fact that no diagnostic investigation was registered in 23% of individuals with a positive FIT may have been due to missing data. However, we minimised this risk by collecting data from both the NPR and the NHSR to ensure that diagnostic investigations performed in private practices were also included. Other possible explanations for the large number of non-investigated individuals may be that the GP, for relevant reasons, decided not to refer the patient to diagnostic investigation despite the positive FIT or that the GP missed or did not react to the test result after the analyses. Depending on the amount of patients who by mistake were not referred to a diagnostic investigation, the PPV for CRC and SBD after a positive FIT may have been underestimated.

4.4.3 Confounding

A confounder is an independent risk factor for the investigated outcome, but it is also associated with the exposure (118). The problem of confounding is that it can mask the effect of an exposure on the outcome or create an association, where there is actually none.

Several ways exist to control for potential confounding in observational studies (e.g. matching, stratifying or adjusting). Nevertheless, it is only possible to con-
trol for known confounders. Thus, unknown/unidentified confounders may still be present in the analyses.

4.4.3.1 Paper I

In the analyses of the diagnostic activity in general practice, we adjusted for a wide range of potential confounders. However, we cannot rule out the possibility of residual confounding or confounding from unknown factors. Firstly, comorbidity may have been a reason for residual confounding. The CCI score accounts for only 17 comorbid conditions and thus may leave out additional comorbidity that could be a reason for increased health-care seeking. We chose to use the CCI score since it is regarded among the best methods to measure comorbidity (131–133). Furthermore, it was not possible to collect diagnoses registered in primary care since the Danish authorities made the existing database inaccessible for researchers in 2015. Secondly, medicine with anticoagulatory effect could also be a source of residual confounding since it did not hold information on over-the-counter sale of drugs with anticoagulatory effect (primarily NSAIDs). This information was not available in the DNPR. Thus, residual confounding from these two covariates may therefore account for some of the difference between subgroups.

The fact that we did not exclude individuals with a previous diagnosis of cancer may also have been a source of confounding. We chose to keep this population in the study since excluding them would have led to a considerable underestimation of the CCI scores. However, when knowing their history, the GPs may have acted differently to this group of patients if they presented newly emerged symptoms. Nevertheless, we believe to have reduced this source of potential confounding by adjusting for CCI score in the analyses.
4.4.3.2 Paper II & III

As mentioned in section 4.1.2 “The non-randomised controlled trial”, the design used in paper II introduced a risk of confounding of estimates. Thus, to account for differences between course clinics and no-course clinics we adjusted for practice characteristics, including the size and type of the practice, in the estimates on dissemination and clinical use of the FIT. We also tested for differences between patients listed with the practices and GPs working in the practices, but since no difference was found, these variables were not included in the multivariate analyses. Furthermore, we adjusted for inclusion time of the general practices to account for differences in FIT use depending on when the practice was included.

The fact that we in paper III did not account for the time period in which the FIT was requested may have confounded the positivity rates and PPVs. However, the results from paper II showed that the positivity rates did not change considerably over time. Therefore, we believe that the population in which the GPs used the FIT did not change and that FITs requested at the beginning of the study period were requested for the same population as the FITs requested at the end of the study period. Thus, this source of confounding is expected to be negligible in this study.
4.5 EXTERNAL VALIDITY

4.5.1 Generalisability

4.5.1.1 Paper I

We included individuals aged 50-74 years who were invited to participate in a FIT-based screening programme. The study was nationwide and based on a large study population. Therefore, we consider the study population to be generalizable to the average population invited to the Danish screening programme.

The incidence of CRC outside the screening programme is dependent on participation rates and the age of the individuals invited to screening. Thus, if the participation rate is lower than in the Danish programme, the number of CRCs diagnosed outside the screening programme can be expected to be higher. As a consequence, these results may only be generalizable to countries that use a FIT-based screening programme on similar individuals aged 50-74 years. Results on the diagnostic activity in general practice may be generalizable to other countries with a similar structure of the health care with GPs acting as gatekeepers to secondary care.

4.5.1.2 Paper II & III

The general practices in the Central Denmark Region, the GPs working in them and the listed patients are assumed to be representative of general practices in Denmark. Thus, results from paper II & III are expected to be generalizable on a national scale.

Generalization of the results to other countries requires careful consideration. However, we believe that the results of paper II and III can be extrapolated to countries with a similar structure of health-care settings with GPs acting as gatekeepers to secondary care and urgent referral pathways from general practice for individuals presenting alarm symptoms of CRC.
Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer
CHAPTER 5:

DISCUSSION OF RESULTS
5.1 PAPER I

5.1.1 Diagnostic activity

In paper I, we found that screening participants generally had higher diagnostic activity in general practice in the year preceding the screening compared to non-participants. Participants were more likely to be female, have high SES and low comorbidity. Considering that low SES is usually related to high use of general practice, this finding was surprising (134). However, low SES has also been found to be related to non-participation in screening programmes (44). As the difference in diagnostic activity remained constant throughout the year preceding the screening, it was more likely due to a difference in the health-care seeking behaviour and the threshold for acting on symptoms between the two groups than a true difference in symptom prevalence (134). This is supported by findings from a recent study, which shows that low use of health care services is related to non-participation in screening (44).

Individuals with a positive FIT had higher diagnostic activity in the year preceding the screening invitation than individuals with a negative FIT, including a small increase in the diagnostic activity in the last three months preceding the invitation. FIT positives were more often males, had low SES, more comorbidity and had more prescriptions of medications with anticoagulatory effect. Despite the small increase in diagnostic activity, these findings do not support that the majority of individuals with a positive FIT in the screening had newly emerged GI symptoms. If this was the case, we would have expected a steeper increase in the diagnostic activity preceding the invitation. Nevertheless, other studies have indicated that the majority of individuals with a positive FIT have lower GI symptoms (46–49). As these studies are based on questionnaire data, recall bias among individuals with a positive FIT may have contributed to the findings. However, our results are an average measure. Consequently, some individuals
may have prevalent symptoms. On the basis of the present results it seems unlikely to be as many as reported in previous studies.

The finding of a correlation between a positive FIT and prescriptions of medications with anticoagulatory effect is supported by the fact that a known side effect of these medications is increased risk of bleeding (135). However, it is generally believed that medications with anticoagulatory effect do not affect the performance of the FIT and that treatment with these agents does not need to be stopped before faecal immunochemical testing (136–138).

Finally, we found no indication that individuals with CRC diagnosed in the screening attended general practice more in the year preceding the invitation. This was also the case when we stratified for CRC stages. Surprisingly, we found that individuals with CRC detected in screening had lower diagnostic activity preceding the invitation than individuals with no CRC. As mentioned in chapter 4.4.3.1, this may partly be explained by residual confounding from comorbidity, but it may also be attributed to a more active health-care seeking behaviour among individuals with no CRC.

5.1.2 Cumulative incidence of CRC

Approx. 25% of CRCs diagnosed in the invited population in the year after screening was found outside the screening programme. As screening rounds are biennial, the proportion may increase even more. A recent study from the Scottish Bowel Screening Programme showed that approx. 75% of CRCs diagnosed in individuals invited to screening was detected outside the screening programme (139). In contrast to our study, the Scottish study had a follow-up period of two years, a lower participation rate and used the gFOBT as a first-line test. To further assess the incidence of CRC outside the screening programme in the invited population, large-scale and long-term studies are needed.
It is generally believed that 75-80% of annual CRCs must be found by other routes than screening (41,42). This can be demonstrated by observing the overall CRC incidence in Denmark from 2015 (5600 incidents) and the number of screen-detected CRCs in the same period (1125 incidents) (7,40). However, the overall CRC incidence may be expected to decrease after full implementation of the screening programme as CRC precursors (adenomas) are removed (140). Nevertheless, the present results indicate that CRC will still have to be diagnosed on symptomatic presentation in general practice, also in the screened age group.

A recent study has shown a possible diagnostic window for detecting CRC in general practice (68). For individuals in the screened age group, this knowledge may be important as our results show that non-participants in screening seem to have higher risk of being diagnosed with late-stage CRC. As non-participants often had low SES and high comorbidity, and as these factors were associated with having a positive FIT in screening, providing diagnostic access to the FIT outside the screening programme in general practice may be important to ensure earlier CRC diagnosis among these patients.
5.2 PAPER II

5.2.1 Dissemination and clinical use of the FIT

In paper II, we found that 81% of general practices in the Central Denmark Region started to use the FIT during the initial six months after inclusion and that the average FIT use was 0.35 (CI: 0.32;0.37) tests per month per 1,000 patients aged ≥30 years listed with the practice. These results suggest that the majority of general practices adapted and integrated the FIT as part of their daily clinical life. Nevertheless, 19% of the general practices did not start to use the FIT. From the present analyses, we cannot address the reasons for non-initiation of FIT use, and this issue is also beyond the scope of this study. However, one way to explore this could be by using the Normalisation Process Theory (NPT). The NPT is an action theory that explores what people do to embed and integrate new innovations in practice and provides a tool for researchers to understand and explain these processes (109). In summary, the NPT states four main components that are decisive for normalization: coherence (sense-making of the innovation); cognitive participation (commitment to the innovation); collective action (what participants do to make the intervention function) and reflexive monitoring (the participants’ perception of advantages and disadvantages of the intervention). Thus, the processes that determined whether or not a general practices chose to start using the FIT are complex and most likely a combination of the above mentioned factors.

The rate of general practices that started using the FIT was significantly higher among course clinics. These clinics initially also had significantly higher monthly rates of FIT use than no-course clinics. These findings are in line with the literature, which indicates that an educational meeting can be used to change clinical behaviour (110,123). However, the findings may also be explained by the fact that more partnership practices were among the course clinics. Adjusting for practice characteristics and inclusion time only changed the estimates slightly,
which suggests that the training course mainly contributed to the difference (see chapter 4.4.1.2). The difference may also be explained if the GPs attending the training course had special interest in the FIT and CRC and thus were more motivated to start using the FIT. However, for reasons discussed in chapter 4.2.1, we believe that the training course was attended by a wide range of the GPs in the Central Denmark Region.

In the initial months after inclusion, the monthly FIT use was significantly higher in course clinics than in no-course clinics, but the difference began to level out after four months. Due to the stepwise inclusion, we had a minimum follow-up time of six months and decided to analyse only the initial six months after inclusion. However, extrapolating the study period to 12 months indicated that the monthly rate of the course clinics approached the rate of the no-course clinics and that both rates settled at approx. 0.2 FITs per month (results not shown). This suggests that the training course did not have a sustainable influence on the FIT use, despite an initial boost. Instead, the average FIT use declined to a steady level, which was found to be independent of any external factors. This also indicates a basic need for the test in general practice.

We did not find any major differences in the positivity rates and indications between course clinics and no-course clinics. This suggests that the GPs used the FIT on the same population. The slightly higher positivity rate among no-course clinics in the second and third month after inclusion may be due to chance or an initial adaption period, but there is no indication of a systematic difference in the FIT use between the groups.
To our knowledge, this is the first study to investigate whether the FIT can be used to detect CRC and SBD in individuals presenting non-alarm symptoms of CRC in general practice. With a cut-off value of 50 μg/L, we found an overall PPV of 9.4% (CI: 7.0;11.9) for CRC and of 13.5% (CI: 10.6;16.4) for SBD.

5.3.1 Diagnostic value of using the FIT on non-alarm symptoms in general practice

Various studies have investigated the diagnostic performance of the FIT on symptomatic patients in general practice. These studies generally support using the FIT on symptomatic patients in general practice (83–92). However, due to a range of factors, it is a complex task to compare the literature on the use of the FIT. Firstly, as mentioned in chapter 1.6, two different types of FITs exist. The quantitative FIT is generally considered superior to the qualitative FIT due to an adjustable cut-off value and removal of inter-reader variability (141). Secondly, the amount of buffer solution and faeces collected differ between the FIT brands. Therefore, tests are not directly comparable (142,143). Thirdly, the performance of the FIT is dependent on the chosen cut-off value (78). As for the results of paper III, these facts imply that comparison with the existing literature should be done with care.

Another important reason why this study is not directly comparable with earlier studies on the FIT use in general practice is the difference in study population. In this study, we used the FIT on individuals with non-alarm symptoms of CRC, whereas the remaining literature primarily has included individuals who were already referred to colonoscopy from primary care. These individuals must be assumed to have more serious symptoms and a higher risk of CRC and SBD than our population. This assumption is supported by the fact that Mowat et al. found a PPV of 14.2% for CRC and of 25.6% for SBD, when using the same cut-off value and apparatus for analysing the FIT (OC Sensor) as in our study. Thus,
their higher PPVs indicate a higher prevalence of CRC and SBD in the population (89,118).

For these reasons, we consider the findings in paper III difficult to compare with the existing literature, and they underline the importance of distinguishing between these two populations and of choosing type of FIT and cut-off value.

The overall positivity rate was 15.6%. This is twice as high as the positivity rate in screening and lower than for alarm symptoms (e.g. Mowat et al. found a positivity rate of 23.5%) (40,89). Therefore, we believe that the positivity rate found in this study realistically reflect the positivity rate when using the FIT in individuals with non-alarm symptom since a higher positivity rate may have indicated that the FIT was used on individuals with more severe symptoms.

We found an overall PPV of 1.5% (CI: 1.1;1.9) for CRC when the GP decided to request a FIT. In comparison, the PPV is 2-8% for most alarm symptoms of CRC (57–63). These figures suggest that the GP’s decision to request a FIT for non-alarm symptoms raises the individual’s risk of having CRC from the average populations to just below the risk of an individual with an alarm symptom of CRC. This risk was further increased to exceed the risk of alarm symptoms if the FIT was positive.

In total, approx. 67% of CRCs diagnosed after a positive FIT was found in UICC stage I and II, whereas 20% was found in stage IV. In comparison, the non-missing stage distribution of screen-detected CRCs (2014-2015) was 64% in stage I & II and 10% in stage IV, whereas the overall distribution of CRCs diagnosed in 2015 (incl. screening) was 48% in stage I & II and 25% in stage IV (2,40). Thus, the number of stage I and II CRCs found in our study is similar to the number found for screening and significantly higher than the overall distribution (p<0.01). In addition, fewer stage IV CRCs were found compared to the overall distribution from 2015 (p<0.95). Therefore, the present results suggest that using the FIT on individuals with non-alarm symptoms of CRC may give a more fa-
vourable stage distribution of the CRCs compared to the current diagnostic pathway for symptomatic patients in general practice. Still, it is important to underline that these estimates are based on non-missing data (approx. 20% of CRC stages are unknown in both the data from screening and the overall distribution from 2015). Furthermore, as mentioned in chapter 4.3.3, the present results were limited by a low number of observations, and further studies are needed for unveiling the true effect on stage distribution.

In line with the literature on screening, we found that the positivity rates increased with age and were higher for males (144,145). However, we also saw that females aged 30-39 years had a relatively high positivity rate. This may have been caused by e.g. urogenital bleeding, which could have affected the FIT result. The exact reasons for the higher rate should be investigated in future studies to avoid possible false positive tests in this population. The PPV for CRC also increased with age and were higher for males. Furthermore, it increased with FIT value (89,146,147). In contrast, the PPV for SBD was higher in females and remained fairly stable at FIT values of ≥100 μg/L. Overall, these findings suggest that FIT value, age and gender should all be taken into account when assessing a FIT result. This was underlined by our finding that each of these variables independently influenced the risk of having CRC when the FIT was positive.

A recent study developed a prediction model to detect CRC in symptomatic patients by combining information on FIT value, age and gender (FAST score) (148). The research group concluded that the prediction model was highly accurate for CRC detection and could safely rule out CRC in individuals with a low FAST score. Thus, nuancing the interpretation of a FIT result by including information on FIT value, age and gender is clinically important and should be considered when using the FIT in general practice.
Three months after performance of the FIT, 26 individuals were diagnosed with SBD, and less than three individuals were diagnosed with CRC despite a negative FIT. In addition, we found no lower limit for positive FITs when CRC or SBD did not occur. When the FIT is used in a high-risk population, it seems to be a good rule-out test for CRC and SBD (84,88,89). However, the findings from this study indicate that false negative test results will occur despite using a low cut-off value. Thus, on the basis of these results we believe that the FIT should optimally be seen as a rule-in test when used in a low-risk population. As mentioned in chapter 1.6, choosing the cut-off value for the FIT is a trade-off between high number of false positive FITs (low cut-off) and high number of false negatives (high cut-off) (76–80). Therefore, the choice of cut-off value is ultimately a prioritisation between investigation capacity and the risk of missing diagnoses. The fact that some individuals in this study were diagnosed with CRC and SBD despite a negative FIT indicates that the majority of the GPs used the FIT as instructed and used “watchful waiting” and “safety netting” rather than ruling out CRC because of a negative test.

Unexplained anaemia was the indication that was less reported for using the FIT, but it was also the symptom/sign with the highest positivity rate (20.5% (CI: 16.7;24.4)) and the highest PPV for CRC (11.5% (CI: 4.7;18.3)). In Denmark, a guideline for the diagnostic workup of individuals with unexplained iron deficiency anaemia has been developed (149). Although iron deficiency anaemia is considered an important sign of CRC, it is reported to cause delay in the diagnosis of CRC (150–152). For these reasons and for the reasons described in chapter 2.3.3.2.2, we decided to recommend using the FIT on individuals with unexplained anaemia when the GP did not interpret this symptom/sign as eligible for urgent investigation in the CPP. In the present study, the PPV for CRC for anaemia in combination with a positive FIT was 11.5%. This is approx. five times as high as the PPV of CRC for anaemia as an alarm symptom (57). Thus, the findings from this study underline the importance of anaemia in detecting CRC.
Furthermore, since this study was performed in a low-risk population with a low pre-test risk of CRC, the results suggest that individuals with unexplained anaemia which is not considered an alarm symptom by the GP should have at least a FIT performed to test for microscopic blood in the stool. As the present study was not a study of diagnostic performance, we cannot make final conclusions on whether a negative FIT would rule out CRC in individuals with anaemia. However, since a low-risk population per definition have a low pre-test possibility of CRC, the clinical value of a negative test can be debated.

Interestingly, symptoms categorised as other than the ones stated in the clinical instruction had the highest PPV for SBD (CI: 21.3% (12.7;30.0)). When requesting a FIT because of “other” symptoms, the GPs could state the indication in a “free text” box. However, the GPs mostly used this text box to elaborate on symptoms and signs from the clinical instruction, which they already had ticked in the ordering system. Thus, in the majority of cases, we assume that the actual indication for requesting the FIT when “other symptoms” had been ticked was one or more of the indications defined in the instruction. This implies that the PPV of “other” symptoms may have been overestimated.
CHAPTER 6:

MAIN CONCLUSIONS AND PERSPECTIVES
6.1 PAPER I

6.1.1 Conclusions
Participants in the CRC screening had higher SES and higher diagnostic activity than non-participants. Individuals with a positive FIT had lower SES, higher comorbidity and higher diagnostic activity than individuals with a negative FIT. Individuals diagnosed with CRC in the screening had lower diagnostic activity than individuals with no CRC. Approx. 25% of CRCs diagnosed in individuals invited to screening were diagnosed outside the screening programme. Non-participants with CRC had low SES, high degree of comorbidity and a 65% higher risk of being diagnosed with CRC at stage IV than participants in the screening programme.

6.1.2 Perspectives
The results from this study do not support the hypothesis that the majority of individuals with a positive FIT and screen-detected CRC have newly emerged GI symptoms. Therefore, it is unlikely that these individuals could be detected earlier through symptomatic presentation in general practice if the FIT was available. However, as our results constitute only an average for all individuals, some individuals may have higher diagnostic activity than others.

Most cases of CRC must still be diagnosed in general practice, despite the screening programme. The majority of these cases will occur in individuals aged ≥75 years or non-participants in screening, but some cases also occur in individuals who have participated in the screening, e.g. due to false negative test results. Thus, also in the future, general practice will constitute a corner stone in the detection of CRC. Special notice should be paid to non-participants in screening since these individuals have higher risk of being diagnosed with late-stage CRC. The FIT may be a valuable diagnostic tool in general practice to detect CRCs outside the screening programme, as also stated in chapter 5.1.2.
6.2.1 Conclusions

More than 80% of general practices in the Central Denmark Region started to use the FIT within the first six months after inclusion. The training course had a significant impact on getting the general practices to start using the test and a temporary impact on the rate of the FIT use. The GPs seemed to use the test on the same population regardless of participation in the training course.

6.2.2 Perspectives

The introduction of the FIT in general practice for individuals with non-alarm symptoms of CRC provided the GPs with a supplementary diagnostic tool for a group of individuals that previously had relied solely on the clinical assessment by the GP. The fact that the majority of GPs started to use the FIT and seemed to incorporate the test as part of their everyday clinical life suggests that there is a clinical need for the FIT in the diagnostic workup of this group of patients.

If the FIT is to be introduced on a national scale, this study shows that a short training course is a good way of getting the GPs to start using the FIT. After a brief introductory phase, the average FIT use in the target population does not seem to depend on participation in the training course. Thus, deciding whether to offer a training course together with the introduction of the test in general practice will mainly depend on the desired rate of initiation. Good information material and efficient distribution of FIT kits to GPs are key elements that should be considered to ensure that the GPs have the necessary knowledge of how to use the test and for whom and that the FIT is made easily accessible to the practices.
6.3 PAPER III

6.3.1 Conclusions

This study is the first to investigate the use of the FIT in individuals presenting with non-alarm symptoms of CRC in general practice. In total, 15.6% of FITs were positive (≥50 μg/L), and the PPVs for detecting CRC and SBD were 9.4% and 13.5%, respectively. Among individuals with a positive FIT and CRC, 67% of diagnosed CRCs were found in early stages (UICC stage I and II). Despite the low cut-off value, some cases of false negative test results were found.

6.3.2 Perspectives

These results suggest that the FIT could be used in individuals with non-alarm symptoms of CRC to detect both CRC and other serious bowel diseases in general practice and that CRC stages may be more favourable than in individuals diagnosed through the current diagnostic pathway in general practice. Awareness of false negative test results is important when using the FIT in this population, but this is not different from usual care today. As stated earlier, individuals with non-alarm symptoms of CRC constitute a particular diagnostic challenge to GPs. Therefore, we consider these findings of great importance for the future planning of the diagnostic workup of individuals with non-alarm symptoms of CRC in general practice. The shift in stage distribution towards earlier stages indicates that using FITs in individuals with non-alarm symptoms of CRC may provide an important step towards earlier detection of CRC and ultimately improved prognosis and increased survival in patients with CRC. However, the full-scale implications are too early to predict. Nevertheless, in this study, we believe that we have revealed a possible diagnostic supplement for a group of patients that are difficult to handle. We also believe that the FIT deserves attention and consideration in the diagnostic workup of individuals with symptoms of CRC.
CHAPTER 7:
FUTURE RESEARCH
The results from this PhD dissertation invite for further research in several areas, which are outlined in the following section.

More research is generally needed on the use of the FIT in general practice before any final conclusions can be drawn on its possible value. So far, studies have supported the use in a “high-risk” population. It has been recommended to use the FIT as a rule-out test for CRC, whereas we are the first to suggest using the FIT as a rule-in test in detecting CRC and SBD in a “low-risk” population. Future studies will have to distinguish between these two populations when assessing if the FIT should be used in general practice and how to use it. Furthermore, studies of the diagnostic performance of the FIT in individuals with non-alarm symptoms would be important in the future to estimate the sensitivity, specificity and NPV in this population.

The reasons why some practices in our study did or did not start using the FIT could be investigated in a qualitative study, e.g. by using the NPT as a theoretical framework. This could potentially further increase the rate of general practices that start using the FIT and optimise the implementation process if it was decided to later introduce the FIT on a national scale.

In paper III, a long-term follow-up investigation of the 2,921 individuals with a negative FIT should be performed to investigate how many of these individuals that were later diagnosed with CRC or SBD. This could easily be accomplished in a historical cohort study by following the individuals from the day of the FIT request until diagnosis of CRC or SBD, death, migration, or end of study period. The same approach could be used for investigating the incidence of CRC or SBD in individuals with a positive FIT who did not receive further diagnostic investigation.

Using the FIT as a rule-in test in general practice may have placed increased workload on the departments performing colonoscopy. Therefore, we need to assess the implications in secondary care regarding the number and rate of per-
formed colonoscopies before and after introducing the FIT in general practice. Furthermore, it would be interesting to investigate whether the introduction of the FIT has implied an increased number of referrals in the CPP for CRC.

To illuminate the patients’ attitudes to and beliefs about faecal immunochemical testing and to assess potential benefits and harms related to using the FIT in general practice, qualitative studies assessing these issues among individuals who had a FIT performed during the study period could be of value.

Finally, because of this study, the Central Denmark Region has decided to prolong the period in which the general practices can use the FIT to at least the end of September 2018. As the statistical power of the estimates presented in paper III was low, updating the estimates with a higher number of FIT requests and diagnoses would imply a higher validity of the results. This could be done alongside with continuous evaluation of the average FIT use among the general practices in the Central Denmark Region.
CHAPTER 8:

REFERENCES
Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer


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Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer


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CHAPTER 9:

ENGLISH SUMMARY
**Introduction and aims:** It is expected that the majority of annual CRC cases must be diagnosed in general practice, despite screening. Around 50% will present with non-alarm symptoms. Little is known about whether the faecal immunochemical test (FIT) may aid the GP in the diagnostic workup of these individuals. The aim of this PhD dissertation was to investigate the applicability of using the FIT in general practice by assessing the diagnostic activity and the CRC incidence in individuals invited to a FIT-based screening for CRC and exploring both the FIT use and the diagnostic value for non-alarm symptoms after establishing diagnostic access to the FIT for GPs.

**Materials and methods:** A historical cohort study was conducted using Danish national registries to investigate the diagnostic activity in general practice in the year before an invitation to the Danish screening programme for CRC and the CRC incidence in the year after the screening invitation.

GPs in the Central Denmark Region were provided with access to the FIT by using a non-randomised trial with a phased introduction of a complex intervention. This was used to investigate the dissemination and clinical use of the FIT. The diagnostic value of using the FIT on individuals aged ≥30 years with non-alarm symptoms of CRC was assessed by a prospective cohort study.

**Results:** Screening participants had higher diagnostic activity than non-participants. FIT-positives had higher diagnostic activity than FIT-negatives. Individuals with CRC in the screening had lower diagnostic activity than individuals without CRC. Approx. 25% of CRCs diagnosed in the invited population in the year after invitation was found outside the screening programme. Non-participants with CRC had low socioeconomic status, high comorbidity and more severe CRC staging.

After establishing diagnostic access to the FIT in general practice, most general practices started using it and integrated it in daily clinical practice. In total, 51 CRCs (PPV=9.4%) and 73 (PPV=13.5%) serious bowel diseases (inflammatory
bowel disease and high-risk adenomas) were diagnosed after a positive FIT. Of CRCs, 67% were found in stage I/II and 20% in stage IV. Less than three (<0.1%) CRCs were found after a negative FIT.

**Conclusions:** The majority of individuals with a positive FIT and screen-detected CRC did not seem to have prevalence of gastrointestinal symptoms. CRC still occurred outside the screening programme in the invited population, primarily among non-participants.

There seems to be a clinical need for the FIT in Danish general practice. In addition, the FIT seems to be a useful diagnostic tool in general practice to detect CRC and other serious bowel diseases and may provide early detection of CRC in individuals with non-alarm symptoms of CRC. These findings are of importance in the future planning of the CRC diagnostics in general practice.
Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer
CHAPTER 10:
DANSK RESUMÉ
**Introduktion og formål:** Det forventes, at størstedelen af årlige tarmkræft-tilfælde skal diagnosticeres via almen praksis på trods af screening. Cirka 50% af tilfældene præsenterer sig uden klare alarm-symptomer. Afføringsprøven faecal immunochemical test (FIT) kan måske bruges af den praktiserende læge i udredningen af disse patienter. Formålet med denne ph.d.-afhandling var at undersøge den diagnostiske aktivitet og forekomsten af tarmkræft hos borgere, som var inviteret til det danske screeningsprogram for tarmkræft, og at undersøge brugen af FIT i almen praksis, herunder den diagnostiske værdi for ikke-alarm symptomer efter FIT blev introduceret som et nyt diagnostisk værktøj for praktiserende læger.

**Metode:** I et historisk kohortestudie anvendtes data fra danske nationale registre til at undersøge den diagnostiske aktivitet i almen praksis i året før invitation til screening for tarmkræft og forekomsten af tarmkræft i året efter invitationen.


**Resultater:** Højere diagnostisk aktivitet blev fundet hos screening-deltagere end ikke-deltagere. Individer med en positiv FIT havde højere diagnostisk aktivitet end individer med en negativ FIT. Lavere diagnostisk aktivitet blev fundet hos individer med tarmkræft, som blev opdaget ved screening, end hos individer uden tarmkræft. Cirka 25% af de tarmkræft-tilfælde, som blev diagnosticeret i den inviterede population i året efter invitationen, blev fundet uden for screening. Ikke-deltagere med tarmkræft havde lav socioøkonomisk status, høj komorbidity og senere kræftstadiier.

Efter etablering af adgangen til FIT i almen praksis begyndte de fleste praktiserende læger at bruge testen og integrerede den som en del af de faste diagnosti-
ske værktøjer. I alt blev 51 tarmkæft-tilfælde (PPV=9.4%) og 73 andre alvorlige tarmsygdomme (PPV=13.5%) (inflammatorisk tarmsygdom og kolorektale adenomer) diagnosticeret efter en positiv FIT. Samlet set blev 67% af tarmkæft-tilfældene fundet i stadie I/II og 20% i stadie IV. Under tre (<0.1%) tarmkæft-tilfælde blev fundet efter en negativ FIT.

**Konklusion:** De fleste borgere med en positiv FIT og tarmkæft, som blev opdaget ved screening syntes ikke at have symptomer. KRC forekom stadig uden for screeningsprogrammet i den inviterede population, primært blandt ikke-deltagere.

Der synes at være behov for at have FIT tilgængelig i almen praksis. Afførings-prøven ser ud til at være et nyttigt diagnostisk værkøj til at diagnosticere tarmkæft og andre alvorlige tarmsygdomme, og synes samtidig at bidrage til tidligere identifikation af tarmkæft hos de borgere, der kommer til lægen med symptomer, som ikke kan betegnes som alarm-symptomer. Disse fund er vigtige i den fremtidige planlægning af tarmkæft diagnostikken i almen praksis.
Using the faecal immunochemical test in general practice: diagnostic workup of patients with non-alarm symptoms of colorectal cancer
Kære formand for ... Lægelaug.

Forskningsenheden for Almen Praksis i Aarhus, vil i løbet af efteråret 2015 og foråret 2016, igangsætte et studie i Region Midtjylland om brug af afføringsprøve for blod (iFOBT) i almen praksis til forbedret diagnostik af kolorektalkræft. Dette sker i samarbejde med Klinisk biokemisk Afdeling, Randers og Cancer i Praksis.

Formålet er at undersøge, om det er muligt at indføre iFOBT som en del af den praktiserende læges værktøj i udredningen af patienter med symptomer på kolorektalkræft. Det er den samme test, som bruges til screening for kolorektalkræft. Baggrunden er, at højest halvdelen af alle patienter med kolorektalkræft, debuterer med symptomer som kan henvises primært i kræftpakken. Ved at bruge iFOBT hos dem med vage og ukarakteristiske symptomer, er ideen at man for disse patienter tidligere kan henvisse til udredning for kolorektalkræft.

Studieperioden, vil praktiserende læger i Region Midtjylland få mulighed for at rekvirere en afføringsprøve for blod, iFOBT, på patienter med symptomer hvor kolorektalkræft ikke kan udelukkes, men hvor kriterierne for henvisning i kræftpakken ikke er opfyldt. Der er til projektet udarbejdet en vejledning i brug af iFOBT.

Vi vil derfor gerne tilbyde at det kan ske på et planlagt lægelaugsmøde. Tilrettelæggelse af dette vil ske i samråd med Cancer i Praksis. Der vil i forbindelse med arrangementer blive uddelt iFOBT-kits og vejledning til brug af iFOBT.

Praktiserende læger i ... Lægelaug er blevet tilfældigt udvalgt til at blive inkluderet i studiet d. ...

Undervisningen læggdes i månederne omkring inclusion.

Projektet er anbefalet af DSAMs og PLOs multipraksisudvalget og der er indhentet tilladelse til udførelse og analyse af data fra Videnskabsetisk komité, Datatilsynet og Sundhedsstyrelsen.

Du vil snarest blive kontaktet af Gry Stie fra Cancer i Praksis, til opsætning af dato for undervisningen.

Med venlig hilsen

Jakob Søgaard Juul
Læge, ph.d. studerende.
Forskningsenheden for Almen Praksis, Aarhus.

Nete Hornung
Ledende overlæge
Klinisk Biokemisk Afdeling, Randers

Peter Vedsted
Læge, Professor.
Forskningsenheden for Almen Praksis, Aarhus

Gry Stie
Faglig koordinator
Cancer i Praksis
Kære alment praktiserende læge i ... lægelaug

Du og dine kolleger i ... lægelaug inviteres hermed til efteruddannelse i primær diagnostik af kolorektalkræft i almen praksis. Undervisningen sker som et led i at det fra efteråret bliver muligt at benytte afførringsprøve for blod (iFOBT) i almen praksis.

**Efteruddannelsen er planlagt at foregå på lægelaugsmøde: d. X/X kl XX:XX.**

**Sted:**

Efteruddannelsen vil tage ca. 45 minutter og være en del af jeres samlede møde i lægelauget.

Baggrunden er, at højest halvdelen af patienterne med kolorektalkræft har symptomer, så de kan henvises i kæftpakken. Ved at bruge iFOBT hos patienter med vage og ukarakteristiske symptomer, kan disse patienter tidligere henvises til udredning for kolorektalkræft. Undervisningen vil derfor fokusere på brugen af iFOBT på patienter med symptomer på kolorektalkræft, som ikke opfylder kravene til henvisning i kæftpakken.

Testen er ikke en erstatning af kæftpakken for kolorektalkræft. Patienter som opfylder kravene til denne skal henvises som vanligt. iFOBT skal derimod ses som en diagnostisk procedure for den praktiserende læge til at differentiere en kompliceret patientpopulation.

På mødet informerer vi om hvordan man bruger iFOBT, rekvirerer testen og hvordan vi i perioden frem til ultimo 2016 evaluerer effekten af iFOBT i almen praksis.

Vi håber meget på at I har lyst til at deltage og at dette projekt vil være et skridt på vejen til bedre og tidligere diagnostik af kolorektalkræft.

Med venlig hilsen.

Forskningsenheden for Almen praksis.
Center for Forskning i Cancerdiagnostik i Praksis

Peter Vedsted Læge, Professor.
Forskningsenheden for Almen Praksis
Center for Forskning i Cancerdiagnostik i Praksis

Nete Hornung Ledende overlæge
Klinisk Biokemisk afdeling, Regionshospitalet Randers.

Gry Stie Cancer i Praksis
Region Midtjylland

KONTAKTOPLYSNINGER:
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Tlf.: +45 8716 8537/+45 6177 7404
VIGTIGT!
Patienter som opfylder kriterier for henvisning i kræftpakken for kolorektalcancer, skal henvises i kræftpakken og iFOBT er ikke indikeret på denne patientgruppe.

INDIKATIONER:
Testen anbefales benyttet på mænd og kvinder ≥ 30 år, der præsenterer symptomer og tegn som kunne være udtryk for kolorektalcancer, men hvor kravene til henvisning i kræftpakken ikke er opfyldt.

Det vil typisk være ved følgende indikationer:
- Affæringsændringer, som ikke skønnes at opfylde kravene til henvisning i kræftpakken for kolorektalcancer.
- Mavesmerter uden velforklaret årsag.
- Udredning for colon irritabile.
- Ukarakteristiske almene symptomer (herunder utilisigt vægttab, træthed, kvalme eller nedsat appetit uden velforklaret årsag).
- Anæmi eller fald i hæmaglobin≥10 % uden velforklaret årsag, som ikke skønnes at opfylde kravene til henvisning i kræftpakken for kolorektalcancer.

AKTIONER PÅ TESTRESULTAT AF iFOBT

Værdi ≥50 μg/l = Positiv:
Patienter 30-39 år: Henvisning til koloskopi med indikation “blod i afføringen påvist ved iFOBT”.
Patienter ≥40 år: Henvisning i kræftpakken for kolorektalcancer.

Værdi ≤ 49 μg/l = Negativ:
Alle patienter: Individuel klinisk vurdering og plan for videre forløb. iFOBT kan ikke bruges til at udelukke kræft og kan evt. gentages.
REKVISITION AF iFOBT via Webreq

Testen rekvireres via webreq i "Klinisk Kemi" og der udleveres test-sæt til patienten.

NAVN: Hæmoglobin F.

SKÆRMULDE: Normalvisning → "urin og fæces" ELLER Listevisning → "urin og fæces". Alternativt søg på: "Hæmoglobin F".

INDIKATIONSBØK: Udfyldes på bedst mulige vis før rekvision afsendes (Der kan afkrydse i flere bokse).

LABEL: Udskrives og påsættes prøvetagningsrøret, så det dækker mærket der i forvejen sidder på røret. Labeltekst skal læses fra top mod bund (billede).

YDELSENUMMER: 4419

Patienten udfører testen i hjemmet og sender den til analyse i medfølgende kuvert.

MODTAGELSE AF TESTRESULTAT

Testresultatet vil efter analyse foreligge i LABKA under navnet "F-Hæmoglobin". Testen er positiv hvis værdien er ≥ 50 µg/L.

GENBESTILLING AF NYE iFOBT-kits:

Bestilles over webshoppen på DKI (www.dki-logistics-healthcare.dk).

Varenummer: iFOBT kit (skriv iFOBT i søgefeltet eller klik på Prøve- og forsendelses-materiale). Bestilles i pakker af 10 stk. DKI leverer en gang om måneden.

KRITERIER FOR HENVISNING I KRÆFTPAKKEN FOR KOLOREKTALCANCER

<table>
<thead>
<tr>
<th>Gælder for personer ≥ 40 år med ét af følgende symptomer:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rektal blødning</td>
</tr>
<tr>
<td>Ændret afføringsmønster (&gt; 4 uger)</td>
</tr>
<tr>
<td>Blødningssænæmisk</td>
</tr>
<tr>
<td>Betydelige almensymptomer (fx vægttab, mavesmerter)</td>
</tr>
</tbody>
</table>

Kontaktoplysninger vedr. projektet

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Kontakt vedr. iFOBT og analysesvar

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8930 Randers NØ
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TLF: +45 7842 2301
Kære alment praktiserende læge i Region Midtjylland

Fra dags dato, til og med 30. august 2016, vil du og dine kolleger i dit lægelaug have mulighed for at rekvirere afføringsprøve for blod. Det er samme test, der bruges i screeningsprogrammet for kolorektalkræft.

Ca. 50 % af nye tilfælde af kolorektalkræft debuterer med uspecifikke symptomer og tegn, som ikke kvalificerer patienten til udredning via kræftpakken. Ved at benytte afføringsprøve for blod (iFOBT) på patienter med sådanne ukarakteristiske symptomer, vil man kunne identificere patienter med mikroskopisk blod i afføringen og dermed henvise til koloskopi.


Til en start modtager du en pakning med 10 stk. iFOBT-kits. Ét kit indeholder følgende:

1 stk. iFOBT-rør
1 stk. lynlåspose til iFOBT-rør
1 stk. vejledning i udførelse af afføringsprøve
1 stk. opsamlingspapir
1 stk. returkuvert

Ud over dette er der vedlagt en vejledning i brug af iFOBT, inkl. de typiske indikationer. Vi anbefaler, at du læser denne vejledning.

Alle lægelaug vil i forbindelse med indførelsen af testen blive tilbudt en kort efteruddannelse. Det vil foregå via dit lægelaug, hvis I er tilmeldt. Undervisningsmateriale vil efterfølgende være tilgængeligt på praksis.dk.

Resultaterne af denne undersøgelse af iFOBT i almen praksis vil danne basis for om ordningen skal permanentgøres som en del af primærudredningen af kolorektalkræft.

Med venlige hilsener

Jakob Søgaard Juul                  Peter Vedsted
Læge og Ph.d. studerende            Professor, Leder af CaP Aarhus
**Indhold mail**

**Afføringsprøve og tidligere diagnostik af kolorektalkræft**

Afføringsprøve for blod (iFOBT) indføres forsøgsvis i almen praksis i Region Midt. Det sker som led i en omfattende undersøgelse af, om testen kan benyttes i primærdiagnostikken af kolorektalkræft.

Sammen med muligheden for at rekvirere iFOBT, tilbydes praktiserende læger i Region Midtjylland efteruddannelse i primærdiagnostik af kolorektalkræft og brug af iFOBT i almen praksis. Det sker via de enkelte Lægelaug.

iFOBT er ikke en erstatning for kræftpakken for kolorektalkræft. Patienter som præsenterer sig med alarmsymptomer skal stadig henvises i kræftpakken. Testen anvendes i udredningen af patienter som præsenterer symptomer og tegn der kunne være på baggrund af kolorektalkræft, men ikke opfylder kravene til henvisning i kræftpakken.

Alle praktiserende læger i Region Midt vil løbende modtage pakker á 10 iFOBT-kits samt informationsmateriale, når de kan begynde at bruge testen.

**Indhold praksis.dk**

**Forsøgsvis indførelse af afføringsprøve for blod i almen praksis**

*Indhold:*

**Hvorfor iFOBT i almen praksis?**

**Anbefaling for brug af iFOBT i almen praksis?**

**Hvordan rekvireres iFOBT?**

**Analyse af iFOBT og analysesvar**

**Anbefalede aktioner på analysesvar**

**Bestilling af nye iFOBT-kits fra DKI**

**Detaljer vedrørende projekterioden**

**Anbefalinger og tilladelser**

**Kontaktoplysninger**
Hvorfor iFOBT i almen praksis?

Frem til 30. august 2016, kan praktiserende læger i Region Midt benytte immunologisk afføringsprøve for blod (immunochemical Faecal Occult Blood Test, iFOBT). Testen er den samme, der bruges i screeningsprogrammet for kolorektalkræft.

Årsagen er, at ca. 50 % af nye kolorektalkræft tilfælde debuterer med uspecifikke symptomer og tegn, som ikke kwalificerer patienten til primær henvisning til kræftpakken. Ved at benytte afføringsprøve for blod (iFOBT) på patienter med sådanne ukarakteristiske symptomer, vil man kunne identificere patienter med mikroskopisk blod i afføringen og dermed henvise tidligt og hurtigt til koloskopi.

I en projektperiode vil det blive afprøvet om testen har en plads i primær diagnostik af kolorektalkræft. Forskningsenheden for Almen Praksis (CaP) står for den videnskabelige del (http://cap.au.dk).

Anbefaling for brug af iFOBT i almen praksis?

Brugen af iFOBT beskrives som:

- Testen anbefales benyttet på mænd og kvinder ≥ 30 år, der præsenterer symptomer og tegn som kunne være udtryk for kolorektalcancer, men hvor kravene til henvisning i kræftpakken ikke er opfyldt.

Forslag til typiske indikationer kan være:

- Afføringsændring, som ikke skønnes at opfylde kravene til henvisning i kræftpakken for kolorektalcancer.
- Mavesmerter uden velforklaret årsag.
- Udredning for colon irritabile.
- Ukarakteristiske almene symptomer (herunder utilisigt vægttab, træthed, kvalme eller nedsat appetit uden velforklaret årsag).
- Anæmi eller fald i hæmoglobin≥10 % uden velforklaret årsag, som ikke skønnes at opfylde kravene til henvisning i kræftpakken for kolorektalcancer.

Disse indikationer er kun vejledende. Lægen kan finde testen indiceret af anden årsag.

Personer med symptomer og tegn, som opfylder kriterier for henvisning i kræftpakken for kolorektalkræft skal stadig henvises primært i krætpakken for kolorektalkræft. iFOBT er ikke en erstatning for krætpakken for kolorektalkræft.
Hvordan rekvireres iFOBT?

iFOBT rekvireres på Webreq i ”Klinisk Kemi” under navnet Hæmoglobin F. Testen findes under sektionen ”urin og fæces” i vinduet Normalvisning, eller under ”urin og fæces” i vinduet Listevisning. Alternativt, søg efter ”Hæmoglobin F”.


Patienten får testen udelaveret og udfører testen i hjemmet og afsender prøven i returkuverten.

Der er til projektpérioden oprettet en honoreringsaftale i samarbejde med PLO-m og Region Midtjylland for praksis arbejde med dette*.

*http://www.laeger.dk/portal/page/portal/LAEGERDK/Laegerdk/Om%20L%C3%A6geforeningen/L%C3%A6geforeningen%20Midtjylland/PLO%20%20Regionen/iFOBT-test%20%20almen%20praksis

Analyse af iFOBT og analysesvar

Alle tests analyseres på Biokemisk afdeling i Randers.

Analysesvaret kommer via LABKA (Navn: F-Hæmoglobin) og modtages i form af en værdi (µ/L). Prøven regnes for positiv ved iFOBT-værdi ≥50 µ/L og negativ for ≤49 µ/L.

Anbefalede aktioner på analysesvar

Følgende aktioner anbefales svarende til iFOBT-værdi.

- **Værdi ≥50 µg/l = Positiv:**
  Patienter 30-39 år: *Henvisning til koloskopi med indikation: ”Blod i afføring påvist ved iFOBT”.*
  Patienter ≥40 år: *Henvisning i kræftpakken for kolorektalcancer.*

  **Værdi ≤ 49 µg/l = Negativ:**
  Alle patienter: *Individuel klinisk vurdering og plan for videre forløb.* iFOBT kan ikke bruges til at udelukke kræft og kan evt. gentages.

iFOBT er en ”rule-in” test. Hvis iFOBT er positiv bør patienten derfor udredes for kolorektalkræft. Er iFOBT negativ, kan kolorektalkræft ikke udelukkes. I stedet kan man sammenholde det med sine øvrige kliniske oplysninger og tage en klinisk beslutning om fx at gentage iFOBT efter en uge, afprøve andre differentialdiagnostiske muligheder mv.
Bestilling af nye iFOBT-kits fra DKI

Der kan bestilles nye iFOBT-kits via webshoppen på DKI (www.dki-logistics-healthcare.dk).
Varenummer: iFOBT kit (skriv iFOBT i søgefeltet eller klik på Prøve- og forsendelsesmateriale). Kits bestilles i pakker af 10 stk. DKI leverer en gang om måneden.

Indholdet af 1 iFOBT-kit består af:
- 1 stk. iFOBT-rør
- 1 stk. lynlåspose til iFOBT-rør
- 1 stk. opsamlingspapir
- 1 stk. vejledning i udførelse af afføringsprøve
- 1 stk. returkuvert

Det anbefales at man ikke bestiller iFOBT-kits over webshoppen før man har modtaget den første pakning, inklusive vejledning for brug af iFOBT. Dette vil indikere at man er inkluderet i projektet og kan begynde at bruge testen.

Detaljer vedrørende projektperioden


Anbefalinger og tilladelser

Undersøgelsen er støttet af PLO-M og Region Midtjylland og der er anbefalet af DSAMs Multipraksisudvalg. Der er indhentet nødvendige tilladelser vedrørende gennemførelse og efterfølgende datahåndtering (herunder Datatilsynet og Videnskabsetiks Komite).

Kontaktoplysninger

Spørgsmål vedrørende procedurer og vejledning kan rettes til:

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