Diagnosing colorectal cancer in primary care

The value of symptoms, faecal immunochemical tests, faecal calprotectin and anaemia

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To my family

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Abstract

Background Colorectal cancer (CRC) is the third most common cancer in men and the second most common in women worldwide. Adenomas can be precursors to CRC, and inflammatory bowel disease (IBD) can present with the same symptoms as CRC. The majority of patients with CRC initially consult primary care. Symptoms associated with CRC are also common among primary care patients, but seldom caused by any significant disease. Reliable diagnostic aids would be helpful in deciding which patients to refer. Faecal immunochemical tests (FITs) are commonly used for this purpose in primary care in Sweden, but there is little evidence to support this use. Faecal calprotectin (FC) has been suggested as an additional test.

Aim To explore how doctors in primary care investigate patients with suspected CRC, the value of FITs, symptoms and presence of anaemia in diagnosing CRC and adenomas in primary care, and whether FC tests could contribute to diagnosis.

Methods Three studies **(1-3)** were carried out in Region Jämtland Härjedalen, Sweden. There was no screening programme for CRC. We used a point of care qualitative dip-stick 3-sample FIT with a cut-off of 25-50μg haemoglobin/g faeces, and a calprotectin enzyme-linked immunosorbent assay (ELISA) test with a cut-off of 100 μg/g faeces. **1:** A retrospective, population-based study including all patients diagnosed with CRC or adenomas with high-grade dysplasia (HGD) during the period 2005-2009 that initially consulted primary care. Symptoms, FIT results, anaemia and time to diagnosis were retrieved from medical records. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated from FIT results at the region's health centres 2008-2009. (Paper I.) **2:** A prospective cohort study including consecutive patients where primary care doctors requested FITs and/or FC tests, at four health centres, from 30 Jan 2013 to 31 May 2014. FITs, FC tests, haemoglobin and iron deficiency tests were analysed; patients and doctors answered questionnaires about symptoms. Patients were examined with bowel imaging or followed for two years. Findings of CRC, adenomas with HGD, adenomas with low grade dysplasia (LGD) ≥1 cm and IBD were registered. (Papers II and III.) **3:** A qualitative study of interviews with eleven primary care doctors. We explored what made them suspect CRC, and their practices regarding investigation and referral with particular attention to their use of FITs. Qualitative content analysis with an inductive approach was used for the analysis. (Paper IV.)

Results 1: Paper I: Of 495 patients 323 (65.3%) started the investigation in primary care. FITs were analysed in 215. In 23 cases with CRC, FITs were negative; 15 (65.2%) had anaemia. In 33 cases with CRC, FITs were performed due to asymptomatic anaemia; 10 (30.3%) had negative FITs. The time from start of investigation, to the diagnosis of CRC or adenomas with HGD, was significantly longer for patients with negative FITs.
2: 377 patients (9 diagnosed with CRC, 10 with IBD) were included.
Paper II: Concordance of positive answers about symptoms from patients and doctors was generally low. Rectal bleeding (recorded by 43.5% of patients and 25.6% of doctors) was the only symptom related to CRC and IBD. The FIT showed a better PPV than rectal bleeding for CRC and IBD. When patients recorded rectal bleeding, the FIT had a PPV of 22.6% and a NPV of 98.9% for CRC and IBD.
Paper III: The best test for detecting CRC and IBD was the combination of a positive FIT and/or anaemia with a sensitivity, specificity, PPV and NPV of 100%, 61.7%, 11.7% and 100% respectively. The FC test had no additional value to the FIT alone.
The sensitivity, specificity, PPV and NPV of the FIT for CRC in study **1** was estimated at 88.4%, 73.3%, 6.2% and 99.7% respectively. In study **2**, corresponding figures were 88.9%, 67.4%, 6.3% and 99.6% respectively.
3: Paper IV: We identified four categories: "Careful listening – with awareness of the pit-falls", "tests can help – the FIT can also complicate the diagnosis", "to refer or not to refer – safety margins are necessary", and "growing more confident – but also more humble". All doctors had found their own way to handle FIT results in the absence of guidelines.

Conclusion The diagnostic process when suspecting CRC can be described as navigating uncertain waters with safety margins. FITs were often used by primary care doctors but with considerable variations in interpretation and handling of results. Rectal bleeding was the only symptom related to CRC and IBD, but the FIT showed a better PPV than rectal bleeding. The combination of a negative FIT and no anaemia may be useful as a rule-out test when CRC is suspected in primary care, and this potentially also applies when patients present with rectal bleeding. Further studies are needed to confirm this and to determine the optimal FIT cut-off value for this use.

Enkel sammanfattning på svenska

Bakgrund

Tjock- och ändtarmscancer är den tredje vanligaste cancerformen hos kvinnor och den fjärde vanligaste hos män i Sverige. Majoriteten av de som drabbas kontaktar först primärvården men trots det träffar en primärvårdsläkare bara på i genomsnitt högst ett fall per år. Symptomen är framför allt diarré, ändrade avföringsvanor, ont i magen, ändtarmsblödning, trötthet och viktnedgång och kan vara diffusa och svårtolkade. Dessa symptom är också vanliga bland primärvårdspatienter som inte har någon allvarlig sjukdom. Det kan därför vara en utmaning för primärvårdsläkare att avgöra vilka patienter som behöver remitteras för ytterligare utredning. Tarmcancer blöder ofta och sedan länge används prover för blod i avföringen, faeces-hemoglobin (F-Hb), som diagnostiskt hjälpmedel i Sverige, men det finns inga studier som utvärderat nyttan av denna användning. Prov för kalprotektin (en markör för tarminflammation) i avföringen har föreslagits som alternativt prov.

Tarmpolyper, särskilt de med höggradiga cellförändringar, kan vara förstadier till cancer. Inflammatoriska tarmsjukdomar kan ge samma symptom som cancer och behöver också remitteras för ytterligare utredning.

Syfte

Att undersöka hur primärvårdsläkare utreder patienter med misstänkt tjock- och ändtarmscancer, värdet av F-Hb-prover, symptom och lågt blodvärde i diagnostiken i primärvården, och om prov för kalprotektin i avföringen kan bidra till diagnostiken.

Metoder

Tre studier **(1-3)** genomfördes i Region Jämtland Härjedalen.

1: En tillbakablickande studie med alla fall av tjock- och ändtarmscancer samt polyper med höggradiga cellförändringar som rapporterades under åren 2005 – 2009, och där utredningen inleddes i primärvården. Uppgifter om symptom, F-Hb-resultat, blodvärde och tiden det tog innan diagnosen ställdes hämtades från journaler.

2: En framåtblickande studie med alla patienter där primärvårdsläkare vid fyra hälsocentraler ordinerade prover för F-Hb och/eller kalprotektin 2013-01-30 – 2014-05-31. Prover togs för F-Hb, kalprotektin, blodvärden och järnvärden. Patienter och läkare fyllde i enkäter om symptom. Alla patienter genomgick tarmundersökning eller följdes upp i två år. Fynd av tjock- och ändtarmscancer, polyper och inflammatorisk tarmsjukdom registrerades.

3: En studie där elva primärvårdsläkare intervjuades om vad som fick dem att misstänka tjock- och ändtarmscancer och om deras utredningspraxis särskilt med tanke på F-Hb-prover. Intervjuerna analyserades med kvalitativ metodik.

Resultat

1. Av 495 patienter startade 323 utredningen i primärvården, F-Hb-prover analyserades hos 215. I 23 cancerfall var F-Hb-provet normalt, 15 av dessa hade lågt blodvärde. 33 fall hade inga symptom men lågt blodvärde, 10 av dessa hade normalt F-Hb-prov. Tiden till diagnos var längre för de som hade normala F-Hb-prover.

2: 377 patienter ingick i studien, varav 9 fick diagnosen tjock-och ändtarmscancer och 10 inflammatorisk tarmsjukdom. Blödning från ändtarmen var det enda symptomet som var relaterat till tjock- och ändtarmscancer, men F-Hb-provet var bättre på att förutsäga cancer och inflammatorisk tarmsjukdom än blödningen. De som rapporterade blödning från ändtarmen men hade normalt F-Hb-prov hade mycket liten risk att ha cancer.

Det bästa provkombinationen för att upptäcka tjock- och ändtarmscancer och inflammatorisk tarmsjukdom var avvikande F-Hb-prov och/eller lågt blodvärde som upptäckte 100% av fallen. Kalprotektinprov tillförde inget utöver F-Hb-prov.

3: I intervjuerna beskrev läkarna vikten av att lyssna på patienterna men samtidigt undvika fallgropar, till exempel att fastna för patientens tidigare diagnoser. Prover kunde vara till hjälp men svaren på F-Hb-proverna kunde också vara svåra att ta ställning till. Remittering för ytterligare undersökningar behövde ske med säkerhetsmarginal. Med ökad erfarenhet upplevde man att man blev säkrare i sina beslut men också mer ödmjuk. Alla läkare hade hittat sina egna sätt att bedöma F-Hb-provsvaren.

Slutsatser

Vägen till diagnos av tjock och ändtarmscancer kan beskrivas som en seglats genom osäkra farvatten där man ska undvika att gå på grund. F-Hb-prover användes ofta av primärvårdsläkare men med påtaglig variation i hur provsvaren hanterades. Blödning från ändtarmen var det enda symptomet som var relaterat till tjock- och ändtarmscancer, men F-Hb-provet var bättre på att förutsäga cancer och inflammatorisk tarmsjukdom än blödningen var. Kombinationen av normalt F-Hb-prov och normalt blodvärde kan vara användbar för att utesluta tjock- och ändtarmscancer i primärvården, och detta kan också gälla när patienten rapporterar blod i avföringen. För att bekräfta detta behövs ytterligare studier.

Original papers

This thesis is based on the following papers:

I. Högberg C, Karling P, Rutegård J, Lilja M, Ljung T. Immunochemical faecal occult blood tests in primary care and the risk of delay in the diagnosis of colorectal cancer. Scand J Prim Health Care. 2013;31:209-14.

II. Högberg C, Karling P, Rutegård J, Lilja M. Diagnosis of colorectal cancer: Patients' symptoms and faecal immunochemical test results in primary care. A prospective study. (Submitted)

III. Högberg C, Karling P, Rutegård J, Lilja M. Diagnosing colorectal cancer and inflammatory bowel disease in primary care: the usefulness of tests for faecal haemoglobin, faecal calprotectin, anaemia and iron deficiency. A prospective study. Scand J Gastroenterol. 2017;52:69-75.

IV. Högberg C, Samuelsson E, Lilja M, Fhärm E. Could it be colorectal cancer? General practitioners' use of the faecal occult blood test and decision making – a qualitative study. BMC Fam Pract. 2015;16:153.

Abbreviations

CIN	chromosomal instability
CRC	colorectal cancer
ELISA	enzyme-linked immunosorbent assay
FC	faecal calprotectin
FIT	faecal immunochemical test
FOBT	faecal occult blood test
gFOBT	guaiac faecal occult blood test
GP	general practitioner
GSRS	gastrointestinal symptom rating scale
GSRS-IBS	gastrointestinal symptom rating scale – irritable bowel syndrome
Hb	haemoglobin
HGD	high-grade dysplasia
HRA	high risk adenoma
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IDA	iron deficiency anaemia
LGD	low-grade dysplasia
LRA	low risk adenoma
LR+	positive likelihood ratio
LR-	negative likelihood ratio
NPV	negative predictive value
OR	odds ratio
POC	point of care
PPV	positive predictive value

Background

Colorectal cancer (CRC) is the third most common cancer in men and the second most common in women worldwide.[1] Screening programmes for CRC are now ongoing in many countries.[2] However, even in countries with screening programmes, studies have shown that most patients with CRC are diagnosed after development of symptoms.[3, 4] Symptoms can be vague which can cause a delay in diagnosis, and this may result in a poorer outcome.[5, 6]

The majority of patients with CRC initially consult primary care.[7-10] In spite of this, primary care doctors seldom encounter patients that are diagnosed with CRC; it has been estimated that a doctor in primary care in Sweden sees less than one new case a year.[11] As symptoms suggestive of CRC are common among the general public and in patients consulting primary care,[12-14] it can be a challenge for primary care doctors to decide which patients to refer for further investigations. Reliable diagnostic aids that are easy to use in primary care would be of help.

Colorectal adenomas can be precursors of CRC.[15] Inflammatory bowel disease (IBD) can present with the same symptoms as CRC.[16]

Polyps, colorectal cancer and inflammatory bowel disease

Diagnosis is based on microscopic analysis of tissue samples by pathologists.

Polyps

Polyps are mostly asymptomatic, especially if they are small and located further up in the bowel than the rectum. There are considered to be two main molecular pathways of CRC development, the chromosomal instability (CIN) pathway and the serrated pathway. In the CIN pathway, CRC develops from adenomas and in the serrated pathway from serrated polyps. [17]

Adenomas

Adenomas can be tubular or villous, or a mixture of both. They can be classified by pathologists as showing low-grade dysplasia (LGD) or high-grade dysplasia (HGD). Adenomas with villous components and a larger diameter have a higher occurrence of HGD. Most adenomas are tubular and smaller than one centimetre.[18]

The European society of Gastrointestinal Endoscopy defines low risk adenomas (LRA) as one to two tubular adenomas of <10 mm with LGD.

High risk adenomas (HRA) are defined as adenomas with villous histology or HGD, adenomas of ≥10 mm in size, or three adenomas or more.[19]

People with LRAs are at no greater risk of CRC than the average member of the population, while a study found that people with HRAs have a 3.6 - 6.6 times higher risk of CRC. Patients with adenomas also have an increased risk of CRC after polypectomy.[15]

Serrated polyps

Serrated polyps can be subdivided into hyperplastic polyps, sessile serrated polyps and traditional serrated adenomas.[20] Of these, the two latter have a higher risk of developing CRC, and sessile serrated polyps are the most common. Sessile serrated polyps are flat, mainly located in the right colon and can be difficult to see during colonoscopy. They also bleed less than villous adenomas.[21]

The European Society of Gastrointestinal Endoscopy recommends that patients with serrated polyps of <10 mm in size with no dysplasia should be classified as low risk, and that patients with serrated polyps of ≥10 mm or those with dysplasia should be classified as high risk.[19]

Colorectal cancer

The colon can be divided into the right (proximal) and the left (distal) colon. The right colon includes the caecum, ascending colon, right flexure and transverse colon. The left colon includes the left flexure, the descending colon and the sigmoid colon. The rectum is the most distal part of the large intestine with a length of approximately 15 centimetres. Approximately 30% of colorectal cancers are situated in the rectum. Approximately 55% of colon cancers are situated in the right colon and 45% in the left colon.[22]

Hereditary forms are estimated to contribute to 3 - 5% of CRC cases. Most CRCs are sporadic and develop via dysplastic adenomas.[23] Approximately 30% of CRCs develop from serrated polyps.[24]

Inflammatory bowel disease

IBD comprises ulcerative colitis, Crohn's disease and microscopic colitis (with the subgroups lymphocytic colitis and collagenous colitis). People with ulcerative colitis and Crohn's colitis have an increased risk of CRC, and surveillance of the colon is recommended after long term disease. [25, 26]

Epidemiology

There is a large variation in the incidence of **CRC** across the world. The estimated incidence in 2012 was highest in Australia/New Zealand (world age-standardised rates of 44.8/100 000 in men and 32.2/100 000 in women) and lowest in western Africa (world age-standardised rates 4.5/100 000 in men and 3.8/100 000 in women).[1]

In Sweden, CRC is the fourth most common cancer in men and the third most common in women.[27] During the period 2010 – 2014 there was on average 6100 new cases of CRC every year (world age-standardised rate 31.4/100 000 men and 24.9/100 000 women), and CRC is the third most common cause of cancer-related death.[28] CRC is uncommon before the age of 40, and only around 5% of all cases are diagnosed in patients younger than 50 years.[27] In Sweden, the risk of getting CRC before the age of 75 was 3.6% for men and 2.9% for women during 2010 – 2014.[28]

The relative 5-year survival rate has increased during the last few decades, and during the period 2010 – 2014 it was 64% for men and 67% for women. As the incidence has remained unchanged and the survival rate has increased during the last ten years, the prevalence has increased and in 2014 the number of people in Sweden living with CRC was 483/100 000 men and 515/100 000 women.[28]

The incidence of **IBD** in Scandinavia is among the highest in the world.[29] A study in the Uppsala Region of Sweden showed an incidence of 41.7/100 000 inhabitants and year (age-adjusted for the Swedish population) for IBD, including ulcerative colitis, Crohn's disease and microscopic colitis.[29-31] The mean age at the onset of IBD is lower than the mean age of persons being diagnosed with CRC, but 10 - 15% of those diagnosed with ulcerative colitis or Crohn's disease are 60 years and older.[32, 33] Microscopic colitis predominantly affects persons over the age of 60.[31]

Symptoms

Colorectal cancer

Rectal bleeding, change in bowel habits and weight loss are generally considered as alarm symptoms of CRC.

Of these symptoms, **rectal bleeding** is the most studied. This can be subdivided into blood noticed on the toilet paper or mixed with the stools, and dark blood or bright blood, assuming that a patient's history of dark blood and/or blood mixed with stools is more likely to be caused by CRC. Different definitions of rectal bleeding and combinations with other

symptoms have been applied in different studies which complicates comparisons.[34] A summary of studies of rectal bleeding is presented in table 1. In four studies of patients in primary care, rectal bleeding as a single symptom was reported to have a positive predictive value (PPV) of 2.4% to 7.0% for CRC.[35 - 38] Another study in primary care reported a PPV of 2.4% in men and 2.0% in women.[39] In a study with questionnaires answered by referred patients, the PPV of dark rectal bleeding was 20.6%.[40] In one review, the pooled PPVs from five studies was estimated at 8.1% for those over 50 years of age.[41] Another review noted that PPVs of rectal bleeding for CRC broadly classified were ≥5% in more than half of the studies.[34]

There are fewer studies on **change in bowel habits**. This symptom can include diarrhoea, constipation and more or less frequent bowel movements. The PPV for CRC of diarrhoea as a single symptom was reported to be 0.94 – 1.1% in two primary care case-control studies.[37, 42] while a prospective population-based study noted that loose stools was connected to a 3-fold increased risk of CRC.[43] No evidence has been found for an increased risk of CRC in patients with constipation.[44]

Weight loss as a single symptom was reported to have a PPV of 1.2% and 1.0% in the two primary care studies mentioned above.[37, 42]

Combinations of the above described symptoms are not surprisingly connected to an increased risk of CRC. As an example, in a large cohort study the absolute risk of CRC for patients presenting with rectal bleeding plus changes in bowel habits was 1.9 versus rectal bleeding alone, and 1.7 versus change in bowel habits alone.[45] Combinations of symptoms are used in risk assessment tools.[42, 46]

However, the majority of patients with CRC have **other symptoms than these alarm symptoms** when they first consult primary care. A large case-control study that used information from electronic medical records showed that only 37% of cases had reported rectal bleeding, change in bowel habits or weight loss, but 30% had reported abdominal pain.[47]

Inflammatory bowel disease

The symptoms typical for IBD resemble those for CRC: diarrhoea, rectal bleeding, abdominal pain and weight loss.[16] Ulcerative colitis presents with bloody diarrhoea and urgency.[25] Crohn's disease has a more heterogeneous clinical feature and can present with weight loss, abdominal pain, abdominal mass, anorectal problems and also with diarrhoea, which is sometimes bloody.[26]

Table 1: Positive predictive values of rectal bleeding for colorectalcancer, as found in studies in primary care.

Author, publication year	Study characteristics, study population	Rectal bleeding, CRC	PPV of rectal bleeding for CRC (%)
Fijten, et al. (1995)[35]	Prospective. 83 GPs. Patients aged 18-75 years with rectal bleeding within previous 3 months.	269 bleeding, of which 9 CRC.	3.3%
Wauters, et al. (2000)[36]	Retrospective – prospective. Network of primary care practices. Patients with rectal bleeding and cases of CRC.	386 bleeding, of which 27 CRC.	7.0%
Ellis, et al 2005[122]	Prospective. 3 primary care practices. Patients aged ≥35 years with rectal bleeding identified by GPs during 1 year.	319 bleeding, of which 11 CRC.	3.4% total 2.4% blood on paper 4.9% blood in pan and on paper 9.7% dark blood 4.0% bright blood
Hamilton, et al 2005[37]	Retrospective, population-based, case-control. 21 general practices. Cases of CRC aged ≥40 years.	349 CRC, of which 148 with bleeding. 1744 controls, of which 73 with bleeding.	2.4% total 1.4% 40-69 years 4.8% >70 years
du Toit, et al 2006[38]	Prospective. 1 primary care practice. Patients aged ≥45 years with new onset rectal bleeding.	265 bleeding, of which 15 CRC.	5.7%
Lawrenson, et al 2006[45]	Retrospective. Data from the UK General Practice Research Data Base. Patients aged 40-89 years, new symptoms of rectal bleeding.	44 741 bleeding, 9143 CRC in total.	60-69 years: 5.99% men, 3.5% women 70-79 years: 7.69% men, 4.61% women.
Jones, et al 2007[39]	Retrospective. Data from to the UK General Practice Research Data Base. Patients aged ≥15 years, first ever occurrence of rectal bleeding.	15 289 bleeding, of which 338 CRC.	2.4% men 2.0% women
Hamilton, et al 2009[47]	Retrospective, population-based, case-control. Data from The Health Improvement Network database medical records. Cases of CRC aged ≥30 years.	5477 CRC, of which 853 with bleeding 38 314 controls, of which 460 with bleeding.	4.5% men ≥80 years. Lower PPVs in females and younger patients.
Ewing, et al 2016[42]	Retrospective, population-based, case-control. Data from the Swedish Cancer Registry and medical records. Cases of non-metastatic CRC ≥18 years.	542 CRC, 2139 controls.	3.9%

GP: General Practitioner CRC: colorectal cancer

Laboratory tests as diagnostic aids

Faecal occult blood

Traces of blood can often be found in the faeces of people with CRC. This can be examined with tests for occult blood.

Guaiac faecal occult blood tests

The guaiac faecal occult blood test (gFOBT) was first developed in the beginning of the 20th century, by Ismar Boas and others.[48] It was initially used for diagnosing peptic ulcer and gastric cancer. Guaiac reacts with hydrogen peroxidase in the presence of haem from red blood cells, which results in a colour change. However, the test is not specific to human haemoglobin, and animal blood from red meat and plant peroxides can give false positive results. Also, incomplete haemolysis of erythrocytes and substances such as ascorbic acid can give false negative results. Guaiac based methods detect the haem complex, which is not degraded during the passage of the bowels, and upper gastrointestinal bleedings can also give positive results.

GFOBTs are used in screening programmes in many countries.[2] Many studies have investigated the performance of gFOBTs in screening situations.[49 - 53] There are few studies on the use of gFOBTs as diagnostic aids.[54 – 56]

Faecal immunochemical tests

An immunochemical method for the detection of faecal occult blood was developed at the end of the 1970s.[57] Faecal immunochemical tests (FITs) have advantages over gFOBTs: they are more sensitive and react only to human haemoglobin, and so require no dietary instructions. Also, as haemoglobin gets degraded in the upper gastrointestinal tract, FITs do not detect upper gastrointestinal bleedings.

FITs can be qualitative or quantitative. Qualitative tests use immunochromatographical methods, are read visually and have fixed cut-off values. These are easy to use as point of care (POC) tests.

Quantitative tests use latex-agglutination or the enzyme linked immunosorbent assay (ELISA) technique and give a numeric result. This makes it possible to set the cut-off at different levels based on the requirements of the user. Quantitative tests can be automated and are suitable for analysing large amounts of tests such as in screening programmes.

There are difficulties in comparing different FITs. Tests from different producers do not have the same cut-off values, and the sensitivity varies between tests even with the same cut-off values.[58, 59]

The use of FITs in screening programmes is increasing,[2] and it is the recommended method for this purpose in the European Union and the United States.[60, 61] Many studies have reported on the results of FITs used for screening for CRC.[62] However, fewer studies have evaluated FITs as diagnostic aids in symptomatic patients.[63 - 69] These studies have enrolled patients referred to secondary care or where a decision on referral has already been made.

To my knowledge, there are no previous studies regarding FITs requested as diagnostic aids for symptomatic patients by primary care doctors before their decision on referral.

In spite of the lack of supporting evidence, there is a long tradition in Sweden of using faecal occult blood tests as diagnostic aids in symptomatic patients in primary care as well as in secondary care. During the first decade of the 21st century gFOBTs were gradually abandoned in favour of POC qualitative FITs. When using gFOBTs it was customary to analyse samples from three consecutive stools for each test, this routine has continued with FITs.[8]

Faecal calprotectin

Calprotectin is a protein with antimicrobial properties mainly found in neutrophilic granulocytes, monocytes and macrophages. It remains stable in stools at room temperature for seven days.[70, 71]

Calprotectin levels in faeces correlate with bowel inflammation, and faecal calprotectin (FC) tests are used as support in the differential diagnosis of IBD and irritable bowel syndrome (IBS).[16, 72] The cut-off values of the FC tests when used for this purpose are commonly 50 to 100 µg/g.[73, 74] Raised FC levels have also been noted in other bowel diseases including CRC.[75, 76] Studies on patients referred to secondary care have shown that FC tests with a cut-off value of 50 µg/g had sensitivities of 68-95% for CRC.[63, 64, 68, 77, 78]

To my knowledge, there are no previous studies on the usefulness of FC tests as diagnostic aids, either alone or in combination with FITs, when CRC is suspected in primary care.

Anaemia and iron deficiency

Anaemia has a well-known connection to CRC. Loss of blood with the faeces can lead to iron deficiency and iron deficiency anaemia (IDA). One population-based study has shown that 38% of patients with CRC had IDA at the time of CRC diagnosis,[79] and a large case-control study in primary care showed that IDA had a PPV for CRC of 13.3% in men of >60 years old.[80] Anaemia is also common in patients with IBD.[81]

Definitions of anaemia and iron deficiency vary between laboratories. Anaemia is diagnosed by measuring the haemoglobin concentration in the blood. The World Health Organisation's definition of anaemia is a haemoglobin concentration of below 120 g/l in women and below 130 g/l in men.[82]

There are several serum markers for iron deficiency: serum ferritin, transferrin saturation, serum iron, iron-binding capacity and iron saturation (calculated by dividing serum iron with iron binding capacity). Microcytosis and hypochromia of the red blood cells can also be signs of iron deficiency. Low serum ferritin levels, which indicate iron deficiency, can rise to normal or high levels if there is also an inflammation present.[83] This complicates the evaluation of serum ferritin values.

Normocytic anaemia and anaemia with normal to high serum ferritin levels can also be connected to CRC. A study on fast-track patients found no significant difference in the CRC yield between those with microcytic and normocytic anaemia, and CRC was found in cases with and without low serum ferritin.[84]

In patients with IBD, the anaemia can be caused by iron deficiency as well as be a result of chronic disease.[81, 85]

The diagnostic process and strategies

In general practice, common symptoms mostly have benign explanations. Occasionally though, a common symptom is caused by a serious disease. The suspicion of cancer has been described as arising from practicing basic knowledge, being alert in consultations, intuitive knowing and fear of cancer.[86] In a study in Norway, 12.4% of primary care patients presented with warning signs of cancer and doctors suspected cancer in 24% of these cases.[87, 88] A Danish study found the PPV of primary care doctors' suspicion of serious disease to be 3.1% for cancer within six months.[89]

The diagnostic process of primary care doctors can be described as having three stages: 1) initiation of diagnostic hypotheses, 2) refinement, and 3) defining the final diagnosis.[90] In each of these stages there are different

strategies. Strategies in the first stage include: spot diagnosis, self labelling (by the patient), the presenting complaint as trigger, and pattern recognition trigger. Strategies in the second stage include: restricted rule outs (ruling out the most serious diagnoses), stepwise refinement of the diagnosis, probabilistic reasoning, pattern recognition fit, and use of clinical prediction rules. Strategies in the third stage include: known diagnosis, requesting further tests, test of treatment, test of time, and no label applied (with safety-netting, further investigations, or referral).

In the first stage, self labelling (self diagnosis) can be of help but it can also obscure the doctor's thoughts.[91] For instance, in response to the question "Do you have you any ideas what it might be?" the patient may reveal a fear of cancer or present a plausible (but perhaps incorrect) diagnosis.

In the second stage, tests can be of help. Probabilistic reasoning can be used when test results are evaluated.[92] It can also be used when deciding if it is worthwhile to request another test. Reasons for requesting tests can be influenced by many factors, for example routines, tolerance of diagnostic uncertainty, desire to reassure patients and pressure from specialists.[93] Interpretation of abnormal test results might be influenced by doctors' pre-test estimation of the probability of disease.[94]

In the third stage, safety-netting is often used especially if the diagnosis is uncertain.[95] The patient can be urged to come back if certain symptoms continue, or be scheduled for a re-visit.

In the diagnostic process, primary care doctors also use rules of thumb.[96] A rule of thumb can be described as a practical way of deciding or doing something in a certain situation, without having to reflect, and seems to work as a link between theory and practice.[97]

Gut feeling is a familiar concept to primary care doctors. Two types of gut feelings have been identified, a sense of reassurance and a sense of alarm.[98] A recent study found the PPV of cancer-related gut feelings to be 35% for cancer.[99]

Continuity of care is generally thought of as good and desirable.[100] However, a study concerning patient-doctor continuity and diagnosis of cancer showed no benefit from better continuity.[101] Possibly familiarity with the patient gives the doctor a less open mind to new diagnoses, and patients may be too worried to disturb the doctor.[102]

Guidelines on referral upon suspicion of colorectal cancer

When we performed the studies on which this thesis is based, there were no **Swedish** guidelines on referral for further investigation when CRC was suspected. In December 2015 the guideline "Standardiserat vårdförlopp för tjock- och ändtarmscancer" (Standardised care pathway for colorectal cancer) was introduced.[103] This guideline states that CRC should be suspected when patients present with change in bowel habits, rectal bleeding or anaemia, alone or in combination. Patients are to be referred for colonoscopy in cases with change in bowel habits for more than four weeks in patients of >40 years old, when rectal bleeding is not explained by other findings or has not resolved in four weeks, or when there is no explanation for IDA. The use of FOBTs is not included in the guideline.

In the **United Kingdom**, national guidance on recognition and referral of suspected colorectal cancer has been in use for more than ten years and was updated in 2015.[104] This guideline states that FOBTs can be offered to certain patients who are not subject to urgent referral and have no rectal bleeding. The criteria for offering FOBTs are: a) patients of ≥50 years old with unexplained abdominal pain or weight loss, b) patients of <60 years old with change in their bowel habits or IDA, or c) patients of ≥60 years old with anaemia even in the absence of iron deficiency.

According to the **Danish** national guidelines, FITs are to be used only in secondary care in cases when bowel habits are changed but sigmoidoscopy is normal.[105]

The Swedish Cancer Registry

In Sweden, it is mandatory for doctors as well as pathologists to report all cases of CRC and adenomas with HGD to the Swedish Cancer Registry. The coverage of this register is almost complete.[106] Cancer statistics are published annually by the Swedish National Board of Health and Welfare.[27]

Aims of the dissertation

The overall aim was to explore how doctors in primary care investigate patients with suspected colorectal cancer, the value of faecal immunochemical tests, symptoms and presence of anaemia in diagnosing colorectal cancer and adenomas in primary care, and whether faecal calprotectin tests could contribute to diagnosis.

Objectives of the papers included:

Paper I: To evaluate the use and value of faecal immunochemical tests (FITs) requested in primary care, in patients diagnosed with colorectal cancer (CRC).

Paper II: To investigate patients' symptoms when FITs and/or faecal calprotectin (FC) tests are requested as diagnostic aids in primary care, and to compare these to symptoms perceived by doctors, to FIT results and to diagnoses of CRC, inflammatory bowel disease (IBD) and adenomas with high grade dysplasia (HGD) or low grade dysplasia (LGD) of ≥1cm.

Paper III: To investigate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of a FIT, an FC test and anaemia alone and combined, when requested as diagnostic aids in primary care in the diagnosis of CRC, IBD and adenomas with HGD or with LGD of ≥1cm.

Paper IV: To explore what makes primary care doctors suspect CRC and their practices in terms of investigation and referral, with particular attention paid to their use of FITs.

Materials and methods

The four papers in this thesis are based on three different studies. An overview of the papers and studies is presented in table 2.

Setting

The Region Jämtland Härjedalen (formerly the county of Jämtland, the name was changed in 2015) is a sparsely populated region in northern Sweden. It is slightly larger than the Netherlands in geographical size and has around 127.000 inhabitants.

Twenty-eight primary care health centres are spread throughout the region (Figure 1), 23 of which are run by the regional authorities and five of which are private; all are tax-funded. The health centres are staffed with primary care doctors that are specialists in family medicine, nurses, laboratory nurses, administrative personnel, and also other health care professionals such as health visitors, midwifes, physiotherapists, and teams with psychiatric competence. Health centre laboratories are well equipped and POC FITs and rectoscopies are performed at all health centres.

There is one hospital centrally located in the only major town Östersund, where all endoscopies and surgical treatments for CRC and adenomas are performed. The primary care doctors refer directly to the hospital's endoscopy or radiology departments for bowel imaging.

At the time of the studies there was no screening programme for CRC, and no national or local guidelines on the use of FITs. Neither was there any national guidelines concerning referral of suspected colorectal cancer at the time.

Medical records

Health centres and the hospital in the Region Jämtland Härjedalen share the same electronic medical record system, and patients' medical records are available to all the region's caregivers. The medical records include results from all laboratory tests for the patients. When the studies started, the record system Vårdadministrativt System (VAS) (Tieto, Espoo, Finland) was in use. In April 2015, the medical records were transferred to Cambio COSMIC (Cambio, Linköping, Sweden).

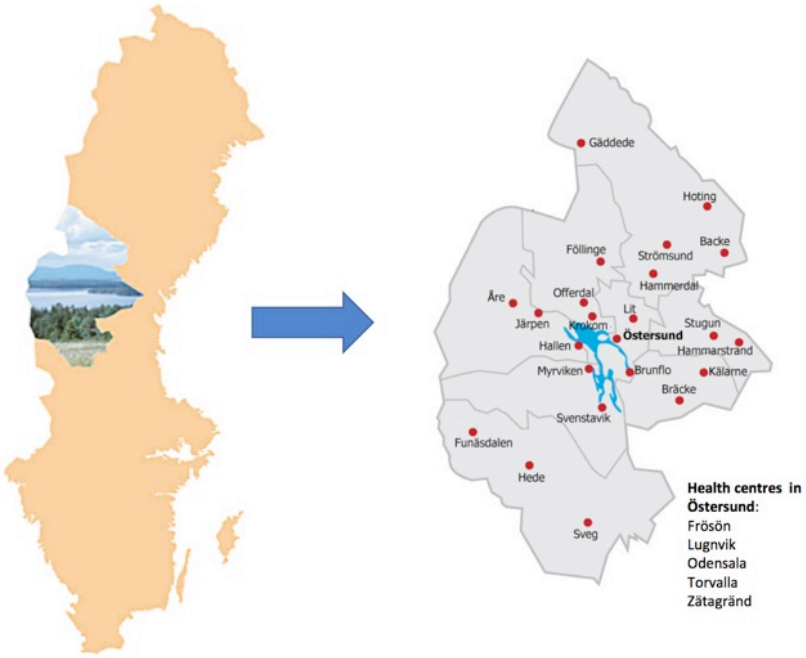


Figure 1. The Region Jämtland Härjedalen and location of 28 health centres (2 in Strömsund).

Definitions of colorectal disease

CRC, adenomas with HGD, adenomas with LGD, and IBD were diagnosed by experienced pathologists.

High risk adenomas (HRA) were defined as adenomas with HGD or adenomas with LGD and a diameter of ≥1 cm.

Significant colorectal disease was defined as CRC, HRA or IBD.

Table 2. Overview of studies and papers included in the thesis.

	Study			
	1	**2**		**3**
	Paper			
	I	**II**	**III**	**IV**
Design	Retrospective population-based study	Prospective cohort study		Qualitative study
Setting	The Region Jämtland Härjedalen, Sweden	Four health centres in the Region Jämtland Härjedalen, Sweden		Nine health centres in the Region Jämtland Härjedalen, Sweden
Period	CRC and adenomas with HGD diagnosed 1st Jan 2005 – 31st Dec 2009	Inclusion period 30th Jan 2013 – 31st May 2014, follow-up until 31st May 2016		Interviews performed 6th Nov 2013 – 27th May 2014
Study partici-pants	323 patients with CRC or adenomas with HGD that initially consulted primary care.	Consecutive symptomatic patients, where FITs and/or FC tests were requested by primary care doctors. 377 patients returned a questionnaire and/or both the FIT and the FC test. Bowel imaging was performed, or patients were followed for two years.		Strategic selection of eleven primary care doctors.
		364 patients that returned a questionnaire.	373 patients that returned both the FIT and the FC test.	
Data collection method	Data retrieved from the Swedish Cancer Registry and from the region's electronic medical record system.	Data retrieved from patients' electronic medical records, and questionnaires to patients and doctors.	Data retrieved from patients' electronic medical records, and questionnaires to doctors.	Semi-structured face-to-face interviews
Primary outcome measures	FIT results. Time from investigation start to diagnosis.	Symptoms and findings reported by patients and doctors alone and in combination, correlated to FIT results and the diagnoses of CRC, IBD and HRAs.	Results of FITs, FC tests, haemoglobin and iron deficiency tests, alone and in combinations, correlated to the diagnoses of CRC, IBD and HRAs.	The factors which make primary care doctors suspect CRC, and their practices with particular attention to their use of FITs.

CRC: colorectal cancer
FC: faecal calprotectin
FIT: faecal immunochemical test
HGD: high-grade dysplasia
HRA: high-risk adenoma
IBD: inflammatory bowel disease

Faecal immunochemical test

The FIT used in the studies was Actim Faecal Blood (Oy Medix Biochemica Ab, Finland), which was the faecal occult blood test used throughout the Region Jämtland Härjedalen at the time. This is a visually read, qualitative, dip-stick test with a sensitivity of 50 ng haemoglobin/ml of faecal solution. With an expected mass of 10 - 20 mg of faeces in each sample, and a volume of the buffering solution of 10 ml, this corresponds to 25 - 50 μg haemoglobin/g faeces according to the manufacturer. The range given is due to possible variations in the amount of faeces collected.[107] It is customary in the region to collect three samples from three consecutive bowel movements for one test. The FIT was regarded positive when one or more of the collected samples for each test showed a positive result. The FITs were analysed by experienced laboratory staff at each health centre.

Faecal calprotectin test

The FC test used in the prospective study was the CALPRO® Calprotectin ELISA Test (Calpro AS, Norway). The samples were analysed at the accredited Department of Laboratory Medicine, Umeå University Hospital. The lower limit of detection was 20 μg/g, higher results were reported as quantitative results. The FC test was considered negative when the result was <100 μg/g, as recommended by the manufacturer.[108]

Anaemia and iron deficiency

The blood samples were analysed at the central laboratory at Östersund Hospital (accredited under SS-EN ISO/EC 17025:2005). Anaemia and iron deficiency were defined by the lower limits of the normal ranges for this laboratory. Anaemia was defined as a haemoglobin concentration of <117 g/l in women and <134 g/l in men. Iron saturation was calculated by dividing the serum iron by the total iron binding capacity. Iron deficiency was defined as an iron saturation value of <0.10 in women up to 50 years old, <0.15 in women of 50 years and older and in men, or a serum ferritin value of <12μg/l in women and <20μg/l in men.

Population and methods – Study 1

This was a retrospective population-based study evaluating the potential value and risk of FITs requested in primary care for patients diagnosed with CRC and adenomas with HGD.

Study population

Patients aged 18 and older residing in the Region Jämtland Härjedalen with a diagnosis of CRC or adenoma with HGD reported from 2005 to 2009, and where investigation started in primary care, were included in the study. The patients were identified from the Regional Cancer Registry.[109] Adenomas with HGD were included as they are important precursors to CRC.[110]

Data collection, definitions

I extracted data from patients' electronic medical records.

- The start of an investigation was defined as when a patient with symptoms first consulted a primary care doctor, or when a doctor first initiated an investigation because of an abnormal finding, leading to the diagnosis of CRC or adenoma with HGD.
- Symptoms were recorded and classified as gastrointestinal (change in bowel habits, diarrhoea, constipation, and/or abdominal pain) with or without rectal bleeding, and/or other symptoms. Rectal bleeding was defined as visible blood in the stools and/or on toilet paper.
- Abnormal rectal findings were registered.
- The presence of anaemia was recorded.
- The date of clinical diagnosis was defined as when the CRC or adenoma with HGD was diagnosed through bowel imaging or surgery.
- Whether the patient had planned treatment after referral or was diagnosed after emergency admission was registered.
- Data concerning the patients' FITs from two years before the clinical diagnosis were registered. Patients with at first negative and at later consultations positive sets of FITs were regarded as negative.
- The number of patients that had FITs analysed during 2008 and 2009, as well as FIT results, was extracted from the region's electronic medical records.

The results of this study were used in **Paper I**.

Population and methods – Study 2

This was a prospective cohort study evaluating patients' symptoms and test results when a POC FIT and/or an FC test was requested by primary care doctors.

Study population

Patients aged 20 years and over where primary care doctors requested POC FITs or FC tests, at four health centres (total population 29.000), between 30th January 2013 and 31st May 2014. The health centres were situated at a distance of 3, 17, 20 and 74 kilometres from the hospital in Östersund.

Data collection, definitions

Nurses invited consecutive patients to participate and instructed patients to collect one sample from each of three consecutive stools for a FIT, and to sample one of the stools for an FC test. Blood samples were collected for a full blood count, serum iron, total iron-binding capacity and serum ferritin. Patients and doctors were requested to answer questionnaires, as described below. Doctors were instructed to refer patients with a positive FIT or FC test for colonoscopy and otherwise to act at their own discretion. Colonoscopy findings were recorded in the regional electronic medical records. Patients that agreed to participate were followed for two years; those not examined with bowel imaging and not diagnosed with CRC or IBD during this time were considered free from these diseases. Data on bowel imaging and clinical outcomes were collected from medical records.

Questionnaires

Patients
The validated Gastrointestinal Symptom Rating Scale for irritable bowel syndrome (GSRS-IBS) was used, with the addition of five questions from the former GSRS about symptoms from the upper gastrointestinal tract.[111, 112, 113] These eighteen questions used a 7-point (0-6) Likert scale and asked about symptoms during the previous week with a grading from "no discomfort" to "very severe discomfort". Five questions to be answered with "yes" or "no" about rectal blood on paper or in toilet, black stools, change in bowel habits and weight loss during the previous year were added at the end of the GSRS-IBS. (Appendix A)

The GSRS-IBS answers were grouped in seven clusters: abdominal pain, constipation, diarrhoea, reflux symptoms, bloating, satiety and dyspepsia. This grouping has been used in previous studies.[113, 114, 115] For each cluster the

result of the question with the highest numerical value was registered. The questions regarding incomplete bowel evacuation and urgency were treated separately.

Doctors
A questionnaire with twelve questions was constructed for doctors. The questions concerned the symptoms and findings at the patient's consultation that were regarded as the most relevant to the diagnoses of CRC and IBD. Six questions corresponded to the symptom clusters and questions in the patients' questionnaire, four questions to the patients' questions about rectal bleeding, black stools, change in bowel habits and weight loss, and two questions to examination findings. The answer alternatives were "yes", "no", or "unknown/not examined". (Appendix B)

The results of patients' and doctors´ questionnaires, FIT results and clinical outcome data were used in **Paper II**.

FIT, FC test and blood sample results, the results of doctors' questionnaires and clinical outcome data were used in **Paper III.**

Population and methods – Study 3

This was a qualitative study of interviews with primary care doctors. We explored what made them suspect CRC, and their practices regarding investigation and referral with particular attention to their use of FITs.

Study population

Eight primary care doctors were purposely selected, with the aim of having diversity in gender, length of professional experience and distance from their work-place to the hospital. Six doctors were specialists in family medicine and two were registrars. Once these interviews had been analysed, we saw the need for more interviews to confirm the findings. Another three specialists in family medicine were then invited and interviewed. In total, the interviewees represented nine health centres, four of which are located at a distance of more than 25 kilometres from the hospital (mean distance 36 kilometres). Four of the specialists had less than ten years of work experience as a specialist and five had more than ten years; the registrars had a mean professional experience of 3.5 years after graduation.

Data collection

I performed and recorded individual interviews face-to face, and transcribed the interviews verbatim. The interviews lasted for 20 to 49 (mean 37) minutes. A semi-structured interview topic guide was used; it was revised after the first and second interviews (Appendix C). By the eleventh interview data saturation seemed to be reached, to confirm this I conducted supplementary telephone interviews with two of the first eight interviewees.

Analysis

Qualitative content analysis with an inductive approach was used, as described by Graneheim and Lundman.[116] In this analytical process, meaning units were identified, condensed, coded, and sorted into categories that were refined throughout the process. We included naïve reading of the interviews to obtain a sense of the whole and enable interpretation of the latent content of the interviews. Each interview was separately coded by myself and one other author. A consensus on the interpretation of the material and the analysis was reached through group discussions with all authors.

The results from this study were used in **Paper IV**.

Statistics

We used IBM SPSS Statistics, versions 18 – 24, for calculations in Papers I, II, and III (IBM, Armonk, NY, USA).

Study 1

To calculate sensitivity, specificity, PPV and NPV, we used the total number of patients that had FITs analysed at the region's primary care health centres during 2008 and 2009. The Kruskal Wallis test was used to test for differences in time from start of investigation to diagnosis between patients with positive FITs, negative FITs, and no FITs analysed. An ANCOVA was performed to adjust for age and sex.

Calculations of positive likelihood ratio (LR+) and negative likelihood ratio (LR-) have been added.

Study 2

We calculated the sample size based on the hypothesis that there would be a significant difference in the sensitivity between the FIT and the FC test for detecting CRC and HRAs. To estimate the prevalence of CRC and HRAs and FIT results we used data from Study 1 and a previous study at a health centre in the region.[117] Assuming a prevalence of CRC and HRAs of 4.1% and a sum of true positive and true negative FITs of 75%, it was estimated that a sample size of 330 patients would provide a power of 10% difference at the 5% significance level.

We calculated sensitivity, specificity, PPV and NPV for FIT results, FC test results at cut-offs of ≥20 μg/g, ≥50 μg/g and ≥100 μg/g, anaemia, and iron deficiency; alone and in combination. We also calculated PPV and NPV for recorded rectal bleeding alone and in combination with FIT results. These calculations were made for the diagnoses of CRC, HRAs and IBD, with the exception that NPVs were not calculated for HRAs, as HRAs can plausibly be asymptomatic and not all participants underwent bowel imaging.

Comparisons were made using Pearson's Chi-square test with Yate's continuity correction or Fischer's exact test, as appropriate. A p-value of <0.05 was considered significant.

Logistic regression was used to explore the relation between patient-recorded symptoms, FIT results and diagnoses.

Calculations of the positive likelihood ratio (LR+) and the negative likelihood ratio (LR-) for FIT results have been added.

Ethical considerations

Ethical approval for the studies was obtained from the Regional Ethical Review Board, Umeå (2010-358-31M, 2012-391-31M, 2013/326-31).

In Study 1, the information that was extracted from patients' electronic medical records was anonymised before registration and analysis.

In Study 2 patients were informed in an invitation letter as well as verbally by laboratory nursing staff. One reminder letter was sent out, patients who did not return the tests or the questionnaire after this were understood as not wanting to participate in the respective part of the study. Test results were handled by primary care doctors according to established practice.

In Study 3 the interviewees were informed about the study in an invitation letter and by telephone before their decision on participation. They could end the interview at any time, they read their transcribed interviews, and were invited to make corrections and additions. The transcribed interviews were anonymous.

Results

In this chapter the results from paper I-IV are summarised, and presented together with additional data.

Study 1

FIT results, anaemia, and time to diagnosis in patients with colorectal cancer and adenomas with high-grade dysplasia, that initially consulted primary care (Paper I)

During the period 2005 to 2009, 472 cases of CRC and 66 cases of adenomas with HGD were recorded from Region Jämtland Härjedalen in the Regional Cancer Registry. The studied population that started their investigation in primary care consisted of 294 patients with CRC and 29 patients with adenomas with HGD (48% women, mean age 71.3 (33-96) years).

At the start of investigations in primary care, 116 (39.5%) patients with CRC had a history of rectal bleeding, 145 (49.3%) had other symptoms and 33 (11.2%) had anaemia found en passant without symptoms. In total 124 (42.2%) had anaemia, 93 (31.6%) had IDA.

FITs were analysed in 198 (67.3%) patients with CRC and 17 (58.6%) patients with adenomas with HGD. Of patients with CRC 23 (11.6%) had negative FITs, and of patients with adenomas with HDG two (11.8%) had negative FITs. Patients with negative FITs had CRCs in all locations, including the rectum, but more frequently in the right-side colon where 18.6% of FITs were negative.

Twenty-three patients with CRC had negative FITs and CRC, of which 15 (65.2%) had anaemia. In 34 cases, 33 of which with CRC, FITs were performed because anaemia was found en passant, and no gastrointestinal symptoms were mentioned. Of these, ten (30.3%) patients with CRC had negative FITs, with a mean haemoglobin value of 103 g/l (eight IDA, two unspecific anaemia).

The time from investigation start to the diagnosis of CRC or adenomas with HGD was significantly longer for patients with negative FITs. This was most obvious in cases with anaemia without any other symptoms. Adjustment for age and sex did not change the results.

For the estimation of FIT results in relation to the diagnoses of CRC and adenomas with HGD, please see table 3. This also shows a comparison of results from Study 1 and Study 2.

Table 3. Faecal immunochemical test results related to diagnoses of colorectal cancer and adenomas with high-grade dysplasia, in Study 1 and Study 2 respectively.

	Study 1 (retrospective)		Study 2 (prospective)	
	CRC + Adenomas HGD n=215	CRC n=198	CRC + Adenomas HGD** n=13	CRC n=9
True positives	190	175	11	8
False negatives	25	23	2	1
False positives	2653*	2668*	117	120
True negatives	7380*	7382*	247	248
PPV %	6.7	6.2	8.6	6.3
NPV %	99.7	99.7	99.2	99.6
Sensitivity %	88.4	88.4	84.6	88.9
Specificity %	73.6	73.3	67.6	67.4
LR+	3.35	3.31	2.61	2.73
LR-	0.16	0.16	0.23	0.16

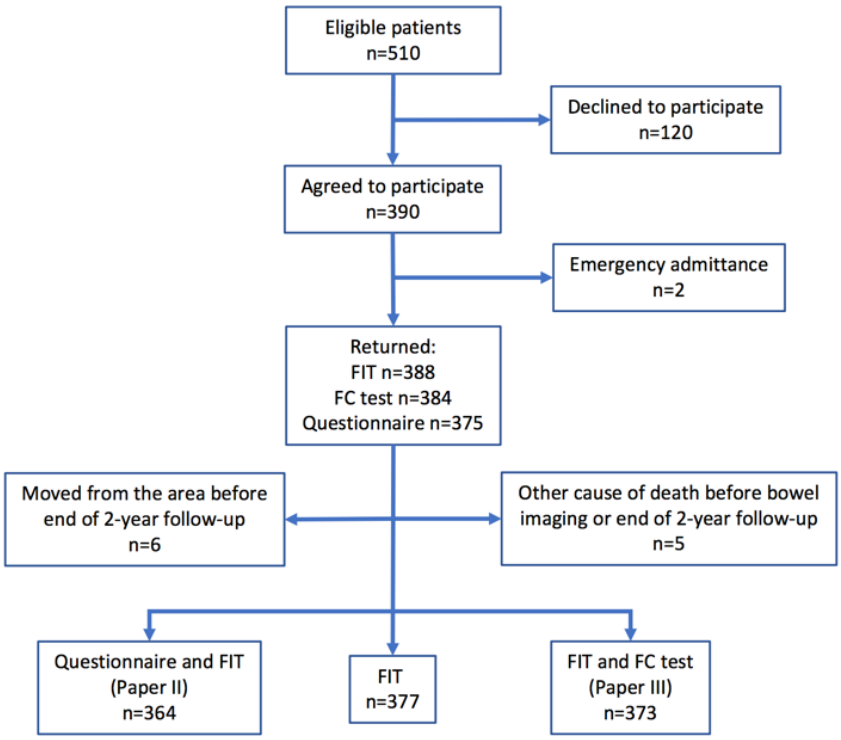
*Estimated from the number of patients who had FITs analysed at the region's primary care health centres during 2008 – 2009.

** In this study, all patients were not examined with bowel imaging and some adenomas with HGD may have been missed.

Study 2

Of 510 eligible patients, 120 (65.8% women, median age 65 years) declined to participate (Figure 2). In total 377 patients were included in the study. All delivered FITs, 128 of which were positive. Of the nine patients diagnosed with CRC four had anaemia, three of these had IDA.

(In the study flow diagram in Paper III, numbers for "Declined to participate" and "Agreed to participate" are incorrectly reported as 119 and 391 respectively, this should be 120 and 390 respectively. Also, the number for "FC not returned" is incorrectly reported as 5, this should be 4.)



FC: faecal calprotectin
FIT: faecal immunochemical test

Figure 2. Study flow diagram for Study 2.

Results of patients' and doctors' questionnaires related to each other, FIT results, significant colorectal disease, and colorectal cancer and inflammatory bowel disease (Paper II)

The analysis included 364 patients (64.3% women, median age 64 years). The doctors' questionnaire was returned in 356 cases. All patients provided samples for a FIT. Bowel imaging was performed on 182 patients. Bowel imaging was performed on 85/151 (56.3%) of the patients who had recorded rectal bleeding, and on 108/125 (86.4%) of the patients with positive FITs. Additionally, rectoscopy was performed on eleven patients who recorded rectal bleeding.

Significant colorectal disease was diagnosed in 27 patients: CRC in nine, adenomas with HGD in four, adenomas with LGD in four, and IBD in ten patients.

Of the symptoms that were graded by patients using the 7-point-scale, abdominal pain was the most common followed by diarrhoea. A summary of the answers from doctors and patients, when patients graded symptoms as "moderate discomfort or more", is shown in table 4.

Table 4. Symptoms recorded by patients and doctors respectively, when a faecal immunochemical test and/or a faecal calprotectin test was requested in primary care, and symptoms were graded as moderate discomfort or more by patients.

	Patients		Doctors*			Both patient and doctor*	
Symptoms	N	Moderate discomfort or more (%)	N	Yes (%)	Unknown (%)	N	Agreeing positive answers
Abdominal pain	364	220 (60.4)	356	201 (56.5)	6 (1.7)	356	156
Diarrhoea	361	173 (47.9)	356	151 (42.4)	14 (3.9)	353	110
Urgency	360	146 (40.6)	356	72 (20.2)	35 (9.8)	352	59
Constipation	359	147 (40.9)	356	94 (26.4)	16 (4.5)	351	67
Incomplete evacuation	361	162 (44.9)	356	55 (15.4)	48 (13.5)	353	41
Reflux	362	76 (21.0)	356	44 (12.4)	50 (14.0)	354	20

*Doctors' questions answered with yes/no/unknown.

Change in bowel habits was the most common symptom among the questions that were answered by both patients and doctors with yes or no. A summary of the answers to these questions are presented in table 5.

Table 5. Symptoms recorded by patients and doctors respectively, when a faecal immunochemical test and/or a faecal calprotectin test was requested in primary care.

	Patients*		Doctors**			Both patient* and doctor**	
Symptoms	**N**	**Yes (%)**	**N**	**Yes (%)**	**Unknown (%)**	**N**	**Agreeing positive answers**
Change in bowel habits	342	164 (48.0)	356	158 (44.4)	10 (2.8)	335	98
Rectal bleeding	347	151 (43.5)	356	91 (25.6)	20 (5.6)	339	84
Black stools	338	72 (21.3)	356	20 (5.6)	19 (5.3)	330	16
Weight loss	343	65 (19.0)	356	45 (12.6)	23 (6.5)	335	35

*Patients' questions answered with yes/no.
**Doctors' questions answered with yes/no/unknown.

In this study, the only symptom related to significant colorectal disease was rectal bleeding, both when reported by doctors and by patients.

Rectal bleeding was recorded by 43.5% of patients and 25.6% of doctors that answered questionnaires; FITs were negative in 58.9% and 52.7% of these cases respectively. PPVs for rectal bleeding and FITs alone and in combination are presented in table 6. The combination of rectal bleeding recorded by patients or doctors with a negative FIT result, resulted in an NPV for CRC and IBD of 98.9% and 100% respectively.

When relating the patient-reported symptoms and the FIT results to the diagnoses of CRC and IBD, a positive FIT gave an odds ratio (OR) of 16.8 (95% CI 3.8 – 75.1) and rectal bleeding an OR of 4.0 (95% CI 1.3 – 12.9), whereas diarrhoea was not significant with an OR of 2.4 (95% CI 0.9 – 7.0).

Table 6. Positive predictive values of rectal bleeding and faecal immunochemical tests (FITs) for significant colorectal disease, in patients where primary care doctors requested a FIT and/or a faecal calprotectin test and patients and doctors answered questionnaires. N=364.

Symptom or finding	Number with symptom or finding	PPV for significant colorectal disease (%) (n=27)	PPV for CRC+ IBD (%) (n=19)	PPV for CRC+ adenomas HGD (%) (n=13)	PPV for CRC (%) (n=9)
Abdominal pain (patient-recorded)*	220	6.4	4.5	2.3	1.8
Abdominal pain (doctor-recorded)	201	7.0	4.0	3.5	2.0
Diarrhoea (patient-recorded)*	173	9.2	7.5	4.6	4.0
Diarrhoea (doctor-recorded)	151	11.3	7.9	4.6	3.3
Constipation (patient-recorded)*	147	8.8	6.1	4.8	2.7
Constipation (doctor-recorded)	94	5.3	3.2	0.0	0.0
Change in bowel habits (patient-recorded)	164	8.5	6.1	4.3	2.4
Change in bowel habits (doctor-recorded)	158	8.9	5.7	4.4	2.5
Weight loss (patient-recorded)	65	12.3	10.8	4.6	4.6
Weight loss (doctor-recorded)	45	6.7	4.4	4.4	4.4
Rectal bleeding (patient-recorded)	151	12.6	9.9	6.6	5.3
Rectal bleeding (doctor-recorded)	91	13.2	12.1	6.6	5.5
FIT positive	125	19.2	13.6	8.8	6.4
FIT positive, no rectal bleeding (patient-recorded)	56	12.5	5.4	5.4	1.8
FIT positive, no rectal bleeding (doctor-recorded)	72	16.7	8.3	8.3	4.2
FIT positive, rectal bleeding (patient-recorded)	62	27.4	22.6	12.9	11.3
FIT positive, rectal bleeding (doctor-recorded)	43	25.6	25.6	11.6	11.6

*Symptoms graded as “moderate discomfort or more”.
FIT: faecal immunochemical test.
PPV: positive predictive value
CRC: colorectal cancer
Adenomas with HGD: adenomas with high grade dysplasia
IBD: inflammatory bowel disease
Significant colorectal disease: CRC + adenomas with HGD + adenomas with low-grade dysplasia ≥1 cm + IBD

Results of FITs, FC tests and haemoglobin values, alone and in combination, related to significant colorectal disease, colorectal cancer and inflammatory bowel disease (Paper III)

The analysis included 373 patients (64.6% women, median age 63.0 years). Bowel imaging was performed on 127 (85.2%) of 149 patients with a positive FIT/and or FC test, and on 58 (25.9%) of 224 patients with negative tests.

Significant colorectal disease was diagnosed in 26 patients: CRC in eight, adenomas with HGD in three, adenomas with LGD in five and IBD in ten patients.

Anaemia was found in 16.6% of all patients. Iron deficiency anaemia (IDA) was present in 6.2% and iron deficiency without anaemia in 6.8%.

The best test for detecting CRC and IBD was the combination of a positive FIT and/or anaemia with sensitivity, specificity, PPV, NPV, LR+ and LR- of 100%, 61.7%, 11.7%, 100%, 2.61 and 0 respectively. Including HRAs also, the PPV was 16.9%. Combining a positive FIT and/or iron deficiency with or without anaemia gave the same sensitivity of 100%, a lower specificity of 56.4%, and a PPV of 10.5% for CRC and IBD.

The FC test at the cut-off of ≥100 μg/g detected a smaller proportion of CRCs and IBDs than the FIT: 61.1% versus 88.9%. With the cut-off of ≥50 μg/g the FC test detected the same number of CRCs and IBDs as the FIT, but fewer HRAs. With the cut-off of ≥20 μg/g the FC test detected all CRCs and IBDs but with a low specificity of 53.0%. The combination of a positive FIT and/or an FC test of ≥100 μg/g showed no better result than the FIT alone. The combination of a positive FIT and/or an FC test of ≥20 μg/g showed no better result than the combination of a positive FIT and anaemia.

The FIT had a higher sensitivity for IBD than the FC test at the cut-off of 100 μg/g faeces, while the sensitivity was the same for both tests at the FC cut-off of 50μg/g.

Study 3

Factors raising primary care doctors' suspicion of colorectal cancer, their procedures, diagnostic thinking, and use of diagnostic aids (Paper IV)

We identified four categories, as described below. These are illustrated with quotes from the interviewees.

1. Careful listening – with awareness of the pitfalls

Attentive listening, a thorough medical history, use of basic knowledge about CRC symptoms, and background knowledge about the patient was thought important. New symptoms aroused suspicion, and if patients considered for example bowel habits to be changed, they were considered as changed.

> *"It's the patient that knows how things were. … If something brings the patient to me because he or she feels that something is different, then there is in fact a change."* (Specialist 2)

However, attentive listening also involved a risk of being misled by patients' explanations and previous medical history. Continuity of care could be helpful but also a risk.

> *"This group of patients that are nervous and contact us very often, they live a little dangerously, because if they did develop something malignant, then there is a big risk that things would be delayed."* (Specialist 6)

2. Tests can help – the FIT can also complicate the diagnosis

All used FITs and other laboratory tests, and they initially ordered a personal standard battery of tests. Anaemia was considered an important finding. There were different opinions on the usefulness of FITs; ranging from their being considered as of great help to not being so useful in reality.

> *"Yes, they are of huge help, yes. … They're of crucial importance."* (Specialist 6)
> *"Yes, they serve as an indication."* (Specialist 8)
> *"In reality, they're not so useful. … They don't help me very much."* (Specialist 5)

The handling of FIT results varied. Three positive samples generally resulted in a referral. Three negative samples could encourage watchful waiting but were not thought conclusive. With one positive sample out of three, there was a grey area. Some considered it as a positive test, and others sometimes repeated the FIT. If the repeated FIT was negative and the patient's history benign, the doctor could then decide not to refer.

With rectal bleeding in the history, rectoscopy was performed as a rule. Some used FITs to verify the bleeding, others found it unnecessary. Both with positive and with negative FITs, haemorrhoids could sometimes suffice as an explanation for the bleeding. However, many found this a difficult decision.

> *"If I have positive FITs, then I'd like to know why this is the case … and in those cases a rectoscopy may suffice, if I find something that's bleeding there."* (Registrar 1)

3. To refer or not to refer – safety margins are necessary

Uncertainty was described as more or less constantly present in the work situation, and it was deemed be helpful to discuss with colleagues and to reflect for some time before decision. It was also considered important to involve the patient in the decision on referral.

> *"This is probably the hardest part. When things are vague, when to leave it. The conversation with the patient is really important in order to sense where he or she stands psychologically in all this."* (Specialist 4)

Generally, doctors thought themselves to be generous with referrals, but at the same time they said that there should be reasonable ground for the referrals.

> *"Most of what we investigate turn out to be nothing. … You have to draw the line somewhere and keep a cool head and wait a while."* (Specialist 7)

The doctors also described acting as advocates for their patients when resources for colonoscopy were limited and when patients needed help with laxation. When patients were not referred, different levels of safety netting were used, and the tool of time was found important.

4. Growing more confident – but also more humble

The doctors described becoming more confident in decisions with time and that they had learnt to live with uncertainty. Gut feelings was described by the doctors with longer work experience and was thought to be based on experience and change over time. However, with greater knowledge and longer experience they also became more cautious and aware of possible pitfalls.

> *"You don't always feel more confident just because you have more information. … I've become more uncertain about things like FITs, for example. … I used to think those tests were a lot more help than I do these days."* (Specialist 4)

They cared less than earlier about what hospital specialists thought of their referrals even if they valued dialogue with secondary care. They were also more humble and focused on their patients.

The primary care doctor's path to decision on referral, when CRC is suspected, can be illustrated as in Figure 4.

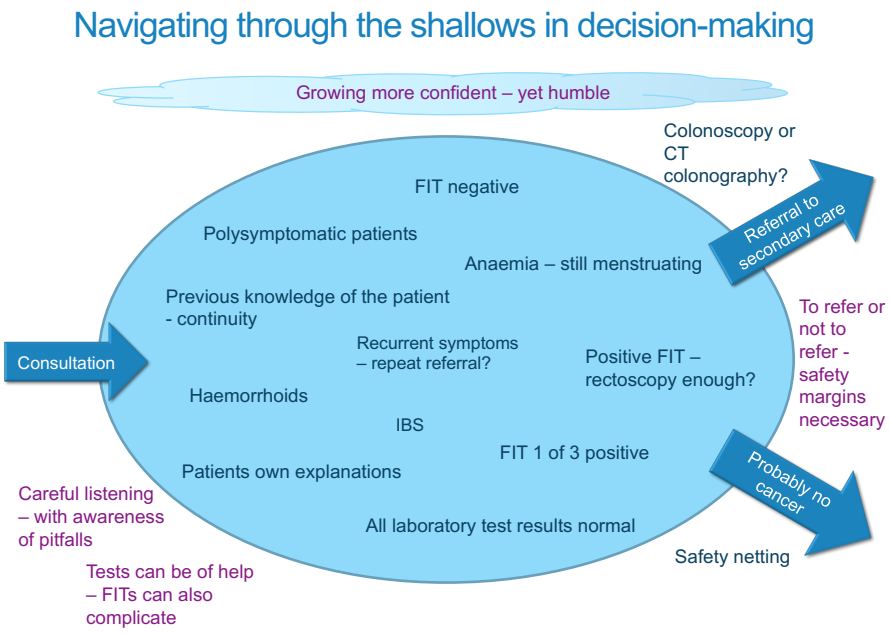


Figure 3. The patient and the doctor together enter the sea of consultation. The doctor has to navigate through the shallows belonging to category 1 and category 2. The doctor and the patient together arrive at the decision to refer to secondary care or not, category 3. The cloud of experience is present throughout the journey, category 4.

Discussion

Findings in relation to aims

Two-thirds of patients diagnosed with CRC initially consulted primary care. Two-thirds of these patients had FITs analysed. Tests were negative in 12% of cases where FITs were analysed. All CRC patients that presented with anaemia found en passant had FITs analysed, and one-third had negative FITs. A longer diagnostic delay was observed in cases with negative FITs (**Paper I**).

In the prospective study, there was a generally low concordance between symptoms recorded by the patient and what the doctor perceived at the consultation. Almost half of the patients recorded rectal bleeding. When a doctor ordered a FIT and the FIT gave a negative result, CRC and IBD could be ruled out with a high degree of certainty. This was also true for patients with a history of rectal bleeding and a negative FIT (**Paper II**). The best test for detecting CRC and IBD was the combination of the FIT and the haemoglobin concentration. The combination of the FIT and the FC test showed no improvement over the FIT alone (**Paper III**).

Careful listening to the patients was essential for prompting primary care doctors to be suspicious of CRC. FITs were frequently used to support decisions about which patients to refer, but there were different views on the helpfulness of FITs, and a considerable variation in the handling of the FIT results (**Paper IV**).

Methodological considerations

Representativeness of the population and the health centres

The population in the Region Jämtland Härjedalen is older than the average in Sweden, with 23.0% 65 years and older versus 19.8% in the whole of Sweden.[118] The age-standardised (for the world) incidence of colorectal and anal cancer in the region in 2013 – 2014 was 26.1 - 28.1/100 000 men and 26.2 - 25.0/100 000 women, compared to 33.0 - 32.2/100 000 men and 26.8 - 25.9/100 000 women in Sweden as a whole.[119]

Health centres in the region are well-equipped with a high standard in the whole region, and they have at least the same standard as in the rest of Sweden. At the time of Study 2, the health centres included in this study were well staffed. In Sweden, rectoscopies are generally performed by

primary care doctors at health centres, as was the case in these studies. POC FITs are also generally performed at Swedish health centres, just as in this region.

There are no national guidelines in Sweden or local guidelines in Jämtland Härjedalen on when and how to use FITs, and to my knowledge no local guidelines exist in other parts of Sweden. However, it is likely that the use of FITs is similar in the whole of Region Jämtland Härjedalen, as it is a small region with good communication and cooperation between health centres. It also seems likely that the use of FITs in the rest of Sweden is similar to Region Jämtland Härjedalen, as Sweden is a comparatively small country with medical schools at only six universities at the time of the study, and doctors participating in the study were educated at several of these.

Paper I

Study 1 was retrospective, and FITs were not analysed in more than 67% of cases. It is probable that among patients where no FIT was performed, there was a higher proportion with more evident symptoms and that these patients were referred to the hospital without further investigations in primary care.

Symptoms were retrieved from patients' medical records, and the symptoms recorded there were probably not the entirety of the symptoms that patients experienced or mentioned, a presumption which is supported by the findings in Study 2. It is also possible that doctors did not record all symptoms they had knowledge of in the medical records. However, it is likely that they registered what they considered most important for their decisions.

There was no validation of the data extraction, and it is possible that there were inconsistencies in the registration. However, all records were analysed by myself during a limited time period, which should have reduced this risk.

To calculate the sensitivity, specificity, PPV and NPV we used the region's FIT results from only two of the five years included in the study, as the process of obtaining this information was very time-consuming. This might make these figures more uncertain. However, to my knowledge the FIT routines and registration of test results were unchanged during the five-year period. The results were also similar to those in Study 2.

There are also several strengths in the study. The coverage of the Swedish Cancer Registry is almost complete,[106] and the study population included almost all registered cases of CRC and adenomas with HGD in a well defined area. Further, computerised medical records were kept in the same system for the whole region, which facilitated the data extraction. The date of diagnosis was exact as it was retrieved directly from the medical records. Finally, the health centres are well organised and of high standard, and all have laboratories with laboratory nurses.

Papers II and III

Study 2 only included cases where doctors requested FITs or FC tests. Here, different doctors may have had different routines regarding the use of FITs, which is implied by the findings in Study 3. Patients may have been referred to the hospital without previous tests, and these patients may have had symptoms or findings that were more severe or obvious for CRC. On the other hand, the patients eligible for the study were those where doctors more likely needed a diagnostic aid.

The fact that there was an ongoing study may have influenced doctors to request more or fewer tests than usual. However, patients were invited to take part by laboratory nurses and not by doctors, which should have reduced this influence.

73.9% of the eligible patients were included in the study, which is an acceptable proportion. The median age and sex distribution were similar among patients that declined to take part and those included in the study.

In the patients' questionnaire, the eighteen questions from the GSRS-IBS asked about symptoms during the previous week.[112, 113] The five questions we added after the GSRS-IBS about blood on the toilet paper or in the toilet, melena, change in bowel habits and weight loss asked about symptoms during the previous year. We chose this longer time span for these symptoms as they are considered important for CRC and we did not want to miss any patients with symptoms. Weight loss also takes time to evolve. Additionally, twelve months was the time period used in a previous Danish study about self-reported symptoms.[40]

In each symptom cluster, the answer with the highest numerical value was recorded. An alternative could have been to use the mean value in each cluster, but this would have diminished the value for patients who recorded a high value for one symptom in a cluster and a low value for another, for example "very severe discomfort" for question 1 (abdominal pain) and "no discomfort" for question 2 (pain or discomfort that is relieved by emptying bowels).

Patients' and doctors' questionnaires were not the same, which made them less easy to compare. The GSRS-IBS questions were designed for patients´ evaluation of their symptoms and were not suitable for doctors, we therefore constructed six questions for doctors based on the symptom clusters and questions of the GSRS-IBS. As we considered it to be difficult and of less importance for doctors to grade the patients' symptoms, the possible answers to doctors' questions were yes/no/unknown or not examined.

We used the number where both patients and doctors had confirmed the symptom to evaluate the agreement between patients' and doctors' answers,

as we deemed the identification of symptoms to be important in decisions on referral.

For comparisons of patients' and doctors' answers correlated to FIT results and diagnoses we used patients' grading of symptoms as "moderate discomfort or more". One could argue that "mild discomfort" should be enough for doctors to react upon, however from experience and intuitively we beleive mild discomfort is something patients mostly find normal and do not seek medical advice for.

It is a weakness that not all patients underwent bowel imaging. As all patients, who were not examined with bowel imaging, were followed for two years, it is unlikely that any cases of CRC or IBD were missed. However, there may have been cases of adenomas with HGD or LGD of ≥1 cm among those not examined with bowel imaging, both with positive and negative FITs/FC tests. As a consequence, only PPVs could be calculated for the tests when adenomas were included and not sensitivity, specificity or NPVs.

Paper IV

The concepts credibility, dependability, confirmability and transferability can be used to assess the scientific rigour of qualitative studies.[116, 120]

Credibility is of importance both concerning data collection and the analysis. To obtain as rich data as possible, we took care to include doctors of varying age, sex, workplace distance to hospital and length of experience. Only two of the invited doctors declined to take part in the study, in their places we invited and interviewed two doctors with matching characteristics. The interviewees were invited to read their transcribed interview and to make corrections. We discussed focus groups as a possible alternative to collecting data but decided on individual interviews, as we thought this would enable the interviewees to speak more freely about their practices. Open-ended questions and an open approach were also means to obtain credibility in the data. We used a well-structured methodology in the analysis and were careful to include all data in the categories that emerged.

Dependability has been described as "the degree to which data change over time, and alterations made in the researcher's decisions during the analysis process".[116] The first eight interviews took place over a period of three months. Once we had analysed these, we saw the need for more interviews to confirm our findings and included three more doctors. These interviews were completed in another three months. The time span that elapsed gave us the possibility to reflect on questions and on the follow-up of topics where we thought more data was needed.

Confirmability corresponds to objectivity in quantitative research .[120] We sought to achieve this by having two researchers coding each interview

independently, and through group discussions throughout the analysis. We also asked other researchers to read and comment on the results.

Transferability deals with whether the results are possible to apply in another context.[116] The geographical area covered and the number of participants in the study was limited. To make judgements of transferability possible for others, we sought to clearly describe the context and the study participants.

I conducted the interviews and also made the transcriptions. This provided a good picture and thorough understanding of the material, which was useful in the analytical process. Being a primary care doctor myself could be both an advantage and a disadvantage in the interview situation as well as in the analysis. In the interviews, as a primary care doctor working in the region I shared experiences with the interviewees and could easily understand their situation and problems. In the analysis, it was helpful to be able to relate to background knowledge. However, there was also a risk of influencing the interviewees and of being misled in the analysis by preconceptions. In an effort to become aware of my own preconceptions and diminish their influence, I performed a "self-interview" before the first interview. In this I wrote down answers to the questions I wanted to bring up, sorted them into topics and constructed a matrix where I added columns for feelings, knowledge from previous studies I had carried out, and what to note especially during the interviews. I found this to be valuable in preparing for the interviews and analysis.

Patients´symptoms, colorectal cancer and inflammatory bowel disease

In Study 3 doctors described that they found it essential to listen carefully to the patient's history. This was also a finding in a Norwegian study in primary care.[86] Doctors recorded largely the same symptom pattern for patients diagnosed with CRC and with IBD in Study 2, which is in line with previous findings.[121] For primary care doctors, it is of less importance to distinguish the onset symptoms of CRC from IBD, as both diseases require referral to secondary care.

NICE guidelines on suspected cancer uses a 3% PPV threshold value for recommendations in cancer pathway referrals.[104] That is, when 3% or more of patients with a symptom are expected to be diagnosed with cancer, patients with this symptom should be subjected to a cancer pathway referral. As most studies concerning symptoms and colorectal neoplasms use CRC as an outcome measure, I here choose to compare PPVs for CRC, even though the number of CRCs in our study was small. (For PPVs, see also Table 6).

Rectal bleeding

This was the only symptom significantly related to CRC and IBD in Study 2. The PPV of patient-reported and doctor-reported rectal bleeding for CRC was 5.3% and 5.5 % respectively (table 6). Other studies in primary care in European countries have found a PPV of rectal bleeding for CRC ranging from 2.0% (women) to 7.0% (table 1).[35 - 39, 42, 45, 47, 122] One of these studies also registered proctocolitis and found the PPV of rectal bleeding to be 1.9% for this.[122] Our study included only patients where doctors requested FITs and/or FC tests. Patients with rectal bleeding may have been referred without previous FITs, or may not have been investigated further at all, which makes it difficult to compare the PPVs. However, our study included a considerable number of patients that reported rectal bleeding, and the PPV for CRC resembles PPVs found in other studies.

Irrespective of whether blood was recorded by the patient as seen on the paper or in the toilet, the PPVs and NPVs for CRC and IBD in our study were similar. According to this it seems unnecessary to distinguish between different locations of blood. This is in line with findings in some previous studies.[122, 123]

Change in bowel habits

We did not find that change in bowel habits was related to CRC or IBD in Study 2. The PPV of doctor-reported change in bowel habits for CRC and IBD was 2.5%. Three other studies in primary care have shown a higher risk of CRC in patients with change in bowel habits with PPVs of 6.89% men/2.42% women (aged 60-69 years), 3.9% (male aged ≥80 years) and 14% respectively.[45, 47, 124] The highest figure comes from a study with patients where primary care doctors had already decided on referral and where 14.6% of patients were diagnosed with CRC.

There is a possibility that the connotation of the expression “change in bowel habits” varies between languages which might make comparisons between countries uncertain. Perhaps there is also a difference between doctors and patients in how this phrase is interpreted. An alternative could be to use the concepts diarrhoea/loose stools and constipation.

I have found **diarrhoea** examined separately in three primary care studies. There was again a wide span in the PPVs for CRC: 0.94%, 1.2% (male aged ≥80 years) and 11.8%.[37, 47, 124] In Study 2 the PPV of doctor-reported diarrhoea for CRC was 3.3%. There was also an indication that diarrhoea could be related to significant colorectal disease (the sum of CRC, IBD and HRA), but this was not significant.

Constipation had no relation to CRC or IBD in our study. This finding is supported by previous studies.[125, 126] Also, one review found no increase in the prevalence of CRC in people with constipation.[44]

Weight loss

Weight loss was the symptom registered by the lowest number of patients in Study 2. I have found information about the PPV of weight loss (analysed separately) for CRC in four other primary care-based studies.[37, 42, 47, 124] These report PPVs of 1.2%, 1.0%, 0.8% (male aged ≥80 years) and 35.7% respectively. The highest figure is again from the study mentioned above where 14.6% of patients were diagnosed with CRC.

Combinations of symptoms

Combinations of symptoms can give higher PPVs. However, there are few studies that report on symptom combinations. One review has reported that a change in bowel habits increased the risk of CRC above that of rectal bleeding, with an estimated PPV of 11.8%.[41] Study 2 was too small to explore symptom combinations.

Risk assessment tools have been developed in England and in Sweden and could be of assistance to primary care doctors in decisions on which patients to refer.[42, 46] The tools use PPVs of pairs of symptoms (also including anaemia) and of two consultations for the same symptom. In the English version, the combination of rectal bleeding and diarrhoea notes a PPV of 3.4% for CRC, and in the Swedish version the combination of rectal bleeding and a change in bowel habits a PPV of 13.7%.

Concordance between patients' and doctors' answers

In spite of doctors expressing it essential to listen carefully to the patients, the concordance between patients' recorded symptoms and what doctors perceived at consultations was generally low. For example, the concordance of positive answers for rectal bleeding was as low as 56.8%. This can have several potential explanations: other symptoms may have dominated, the bleeding may have been interpreted as caused by unimportant haemorrhoids, patients may be less willing to talk about rectal issues, and doctors may have forgotten to ask about bleeding. A previous study on differences in symptom reports of patients and doctors, showed that patients

and doctors disagreed on what triggered the consultation in one-third of cases, and that disagreement was more likely when symptoms had existed for a longer time and when they were less intense.[127]

The low concordance shows the difficulty of comparing results from studies with patients' questionnaires to results from studies with doctors' questionnaires.

In spite of the low concordance, PPVs for CRC and IBD were similar for most symptoms whether they were recorded by doctors or patients (Table 6).

In summary, no single symptom or combination of symptoms, whether recorded by the doctor or by the patient, seem to be useful for ruling in or ruling out CRC in clinical practice in primary care.

Laboratory tests as diagnostic aids

Our studies confirm that laboratory tests were commonly used as diagnostic aids by primary care doctors in Region Jämtland Härjedalen when CRC was suspected. Opinions on the usefulness of FITs varied.

Faecal immunochemical test

Previous studies on symptomatic patients have been performed after referral.[63 - 69, 78, 128 – 134] (Table 7.) To my knowledge, Study 2 in this thesis is the first study with patients where primary care doctors have requested FITs as diagnostic aids before decisions on referral.

Table 7: Sensitivity, specificity and positive predictive values of faecal immunochemical tests for colorectal cancer in other studies.

Author, publication year	Patients N (CRC, %), patients' characteristics	FIT type, cut-off, number of samples	RB* N	Sensi-tivity %	Speci-ficity %	PPV %
Smith, et al. 2006[128]	161 (7, 4.3%) Scheduled for diagnostic colonoscopy.	Qual, cut-off ?, 2	0	100	80.5**	18.9**
Levi, et al. 2007[129]	1000 (17, 1.7%) Referred for colonoscopy, of which 47.1% symptomatic patients.	Quant, 75 ng/ml, 3	0	94.1	87.5	11.9**

Author, publication year	Patients N (CRC, %) patients' characteristics	FIT type, cut-off, number of samples	RB* N	Sensi-tivity %	Speci-ficity %	PPV %
Kok, et al. 2012[63]	382 (19, 5.0%) Referred by GPs because of lower abdominal complaints suggestive of organic bowel disease.	Qual, 6 µg/g, 1	141	84		
Parente, et al. 2012[64]	280 (47, 16.8%) Symptomatic patients aged 50-80 years attending gastroenterology clinics.	Quant, 100 ng/ml, 1	73	61.7	88.8	52.7
Turenhout, et al. 2012[130]	3014 (105, 3.5%) All referrals (of which screening and surveillance 38%).	Quant, 50 ng/ml, 1	418	91.4	83.7	
Kaul, et al. 2013[65]	126 (17, 13.5%) Referred for urgent investigation.	Qual, 40 ng/ml, 1	16	100	86.3	56.6
McDonald, et al. 2013[66]	280 (6, 2.1%) Referred from primary care.	Quant, 50 ng/ml = 10 µg/g, 1	yes	100	93.9	7.6
Cubiella, et al. 2014[67]	787 (97, 12.3%) Referred with gastrointestinal symptoms.	Quant, 100 ng/ml, 1	504	87.6	77.4	35.3
Rodriguez, et al. 2015[131]	1003 (30, 3.0%) Referred for diagnostic colonoscopy.	Quant, 15 µg/g, 1	343	96.7	83.1	15.0
Mowat, et al. 2016[68]	755 (28, 3.7%) Symptomatic patients referred from primary care.	Quant, 10 µg/g, 1	258	89.3	79.1	14.2
Godber, et al. 2016[69]	484 (11, 2.3%) Referred from primary care for colonoscopy.	Quant, 10 µg/g , 1	yes	100	76.5**	9.0**
Cubiella, et al. 2016[132]	1572 (214, 13.6%) Referred with gastrointestinal symptoms.	Quant, 20 µg/g, 1	942	Not presented		
Elias, et al. 2016[134]	810 (37, 4.6%) Referred by GPs because of lower abdominal complaints suggestive of organic bowel disease.	Qual, 6µg/g, 1	43.6%	Not presented		
Auge, et al. 2016[133]	208 (2, 1.0%) Colonoscpy for investigation of lower abdominal symptoms or colonic polyp surveillance.	Quant, 0.6, 10, 20, 30 µg/g, 2	0	Calculated for the sum of CRC and high-risk adenomas.		
Widlak, et al. 2017[78]	430 (24+1HGD, 5.8%) Symptomatic patients referred urgently through "two week wait" pathway.	Quant, 7 µg/g, 1	185	84	93	44

*RB: patients with rectal bleeding
**calculated from figures in the article
Qual: qualitative test
Quant: quantitative test

Difficulties in comparing FIT results

There are several difficulties in comparing studies concerning FIT results.

Studies use different cut-off values. There are many FIT products with varying cut-off values. In screening situations it can be desirable to have higher cut-off values, which result in fewer false positive tests, if colonoscopy capacity is limited.[135]

FITs can be analysed using different methods. They can be qualitative and visually read as positive/negative, or quantitative and usually instrument-read with numerical values. Qualitative tests are mostly dip-stick tests similar to home pregnancy tests. These are less exact than quantitative tests and test results can be influenced by inter-reader variations.[58] Each manufacturer of qualitative FITs sets their own cut-off level which can differ considerably. Further, cut-off levels for qualitative tests cannot be set as low as for quantitative tests.

Further, FIT products from different manufacturers are difficult to compare to each other. Differences in the antibodies and the buffers used may influence the diagnostic performance. Both qualitative and quantitative FIT products with the same numerical cut-off can give different positivity rates and have different PPVs for CRC.[136 - 139]

There are also sex differences in physiological faecal haemoglobin concentrations with higher concentrations in men.[140, 141] A study in a screening situation showed a significantly higher positivity rate among men compared to women, with a higher false positivity rate as well as a higher detection rate for adenomas and CRC.[142] Studies have also shown that PPVs of FITs for adenomas and CRC in screening situations do not seem to differ in men and women.[140, 142]

FIT results also vary with different ages. Higher age is connected to higher faecal haemoglobin content, but also to a higher risk of CRC.[138, 139]

FITs can use different numbers of samples per test. Reasons to use more than one sample can include variations in test performance and the risk of intermittent bleeding from CRCs. Screening with gFOBTs often analyses six samples per test.[2] Traditionally in Sweden, at least three and sometimes six samples have been used for gFOBTs. FITs are more sensitive and specific than gFOBTs, and screening with FITs often analyses 1-sample tests.[2]

Standardisation of cut-off values

Cut-off values have been presented by manufacturers as ng haemoglobin/ml buffer solution. As FIT products collect different amounts of faeces and vary in buffer volume, these values are not comparable between brands. A calculation of μg haemoglobin/g faeces is now mostly used.[59] It has been

suggested that the unit should instead more correctly be µg haemoglobin/ml faeces (the volume collected for the sample).[143]

Comparison of sensitivities and specificities

The FIT used in our studies was a qualitative dip-stick test with a cut off value of 25 - 50 µg/g with three samples analysed for each FIT. The number of CRCs in Study 2 was small which makes statistical comparisons uncertain. Keeping this in mind, the PPVs (6.2% versus 6.3%), NPVs (99.7% versus 99.6%) and sensitivities (88.4% versus 88.9%) for CRC were very similar in Studies 1 and 2 (table 3). Specificity was higher in Study 1 (73.3% versus 67.4%). It is possible that doctors in the prospective Study 2 were reminded of the option to request FITs, and so ordered these more frequently.

In Study 2, the proportion of patients diagnosed with CRC was 2.4%. In twelve previous studies with patients in secondary care, the proportion of patients diagnosed with CRC was between 1.7% and 16.8% (table 7).[63 – 69, 78, 128 - 131] The sensitivity of FITs for CRC in these studies ranged from 61.7% to 100% and the specificity from 76.5% to 93.9%. Cut-off values are difficult to compare, as five studies presented these in ng haemoglobin/ml, and six studies in µg haemoglobin/g and almost all studies used a different cut-off level. (In one study the cut-off level was not presented.) In four studies with symptomatic patients, the proportion of patients diagnosed with CRC was 4% or lower,[66, 68, 69, 131] presumably populations in these studies most resembled the population in Study 2. Here sensitivities were from 89.3% to 100% and specificities from 76.5% to 93.9%, which are of the same magnitudes as in our studies. These four studies all used quantitative FITs with cut-offs from 10–15µg Hb/g faeces; it seems likely that these tests could be at least somewhat more sensitive than the FIT we used. On the other hand, these studies analysed 1-sample FITs while our study used a 3-sample FIT.

A cut-off of as low as possible, that is at the level of detectable blood, has been used as an alternative in two studies. One study showed 100% sensitivity and 43.4% specificity for CRC.[68] In the other study only two cases of CRC were detected and results were presented for the sum of CRCs and high-risk adenomas with a sensitivity of 91.7% for women and 100% for men and a specificity of 10.6%.[133] Thus, a high number of people without serious disease will be subjected to endoscopy if a very low cut-off is used.

Number of samples

It seems reasonable that as FITs are more sensitive and specific than gFOBTs, fewer samples than for gFOBT should suffice. However, with the use of a one-sample FIT there may be a risk of missing CRCs with intermittent bleeding. Studies have shown that 2-sample and 3-sample FITs detect more cases of CRC than 1-sample FITs.[144 - 146] Another study suggested that a 1-sample FIT was preferable to a 2-sample FIT for screening.[147] A post-hoc analysis of data from Study 1 showed that the use of one sample instead of three samples for a FIT would have resulted in missing one tenth of symptomatic CRCs and adenomas with HGD.

FITs and rectal bleeding

Generally rectal bleeding is considered as a symptom that warrants further examination. It is also common in patients contacting primary care. In Study 2, over 50% of cases with rectal bleeding had negative FITs, irrespective of if the bleeding was recorded by the patient or the doctor. In cases where doctors recorded rectal bleeding and FITs were negative, no patients were diagnosed with CRC or IBD. Two other studies have reported similar findings: One study found that 34.0% of patients with rectal bleeding had negative FITs with an undetectable blood level, and a 3.4% incidence of significant bowel disease (CRC, IBD or HRA) among these patients.[68] Another study found that 65.6% of patients with rectal bleeding had negative POC FITs, and that a diagnostic model including a FIT had value also in patients with rectal bleeding.[134]

When only rectal bleeding was considered, the PPV for CRC and IBD was 9.9% for patients' reports and 12.1% for doctors' reports (table 6). When rectal bleeding was combined with a positive FIT, the PPV for CRC and IBD increased to 22.6% and 25.6% respectively. With a combination of rectal bleeding and a negative FIT, the NPV for CRC and IBD was 98.9% and 100% respectively. A positive FIT, regardless of whether there was rectal bleeding or not, showed a PPV of 13.6% for CRC and IBD. This indicates that the result of a FIT requested by a primary care doctor could be better than a history of rectal bleeding as an aid in selecting which patients to refer for further investigation. With both a history of rectal bleeding and a positive FIT, colonoscopy appears to be warranted.

The findings in Study 3 show that, as there were no guidelines, doctors had found their own ways to handle FIT results. Interestingly, FITs could be used in cases with rectal bleeding and if the FIT was negative it could reinforce a decision not to refer for colonoscopy. Thus, the findings in Study 2 are in line with what primary care doctors already practiced.

FITs for home-use are now commercially available.[148] It is important to note that the high NPV of negative FITs in cases of rectal bleeding for CRC/IBD found in this study may not be applicable to self-testing. This is because people in this study consulted primary care, and they were the patients for which primary care doctors considered it appropriate to order FITs as diagnostic aids.

FITs and IBD

Tests for FC are recommended when IBD is suspected.[72] In Study 2, the FIT had a higher sensitivity for IBD than the FC test at the recommended FC test cut-off of 100 µg/g faeces, while the sensitivity was the same for both tests at the FC cut-off of 50µg/g. A previous study has shown that FITs had a similar accuracy to FC tests for detecting IBD.[149] A study has also shown that FITs may be useful for surveillance of ulcerative colitis.[150] Further studies are needed to determine if FITs can be used instead of FC tests for these purposes in the future.

Negative FITs and CRC

In Study 1, the more proximal the CRCs were located, the greater proportion of FITs were negative: 18.6% in the right-side colon, 7.6% in the left-side colon and 3.6% in the rectum. It seems plausible that the reason is degradation of haemoglobin during the bowel passage. There is also a possibility that right-sided tumours are different from left-sided and bleed less.

The majority (15/23) of patients with negative FITs in Study 1 had anaemia. Ten of these had no symptoms although the mean haemoglobin value was as low as 103 g/l. It appears that extra care is warranted when ruling out CRC in patients with anaemia and no other symptoms.

For patients with negative FITs there was a significantly longer diagnostic delay. It seems plausible that negative FITs gave patients a false reassurance that there was no CRC.[151, 152] Doctors were probably also misled. Safety-netting at different levels could have an important role in reducing the risk of delay. Safety-netting was also described by doctors in Study 3.

Test for anaemia and iron deficiency

Cut-offs for haemoglobin values vary between laboratories. The tests that are used to diagnose iron deficiency and their cut-offs also vary. This complicates the comparison of results between studies. For example in one study, on the outcome after attendance at an iron deficiency anaemia clinic, the definition of IDA was microcytic anaemia (no mean corpuscular volume (MCV) mentioned) with a serum ferritin of <30 ng/l.[153] In another study, on the result of fast track investigations, the definition was anaemia with an MCV of <80 fl together with a serum ferritin of <20 ng/l or serum iron of <10 µmol/l.[84]

In Study 1 42.2% of patients diagnosed with CRC had anaemia, 31.6% had IDA. In Study 2, in total 44.4% of patients diagnosed with CRC had anaemia, 33.3% had IDA. These numbers are in line with previous findings.[79] The above-mentioned study at the iron deficiency anaemia clinic found that patients with anaemia and normal serum ferritin values had a similar incidence of CRC to patients with IDA.[153] Thus, it seems reasonable that CRC should also be suspected in patients with anaemia without iron deficiency.

Faecal calprotectin test

In Study 2, the sensitivity of the FC test at the recommended cut-off of 100 µg/g faeces was 50.0% for detecting CRC. This is too low for it to be useful as a diagnostic aid on its own. With a cut-off of 50 µg/g, the sensitivity and specificity of 87.5% and 72.1% respectively were similar to the FIT.

Other studies concerning the diagnostic value of FC tests including the diagnosis of CRC, have mostly applied a cut-off of 50 µg/g (table 8). They all concern patients referred to secondary care. In two studies using only FC tests, the sensitivity for CRC was 85% - 92.7% and the specificity 58% - 35.2%.[77, 154] In four studies comparing FC tests and FITs, FC tests had sensitivities from 68% to 95%, and specificities from 38.8% to 84% for CRC.[63, 64, 68, 78] Three of the studies also reported the FC tests' sensitivities and specificities for IBD, these were 70% to 90.6% and 39.3% to 91% respectively.[63, 68, 78] It is possible that the variation in the reported sensitivities and specificities is due to differences in the studied populations with for example varying proportions of urgent referrals. No study found the FC test to be superior to the FIT.

Table 8: Sensitivity, specificity and positive predictive values of faecal calprotectin for colorectal cancer in other studies.

Author, publication year	Patients N (CRC, %) Patients' characteristics	Calprotectin cut-off	Sensitivity %	Specificity %	PPV %
Meucci, et al. 2010[154]	870 (34, 3,9%) Outpatients referred for colonoscopy (of which 36% surveillance or screening).	50 mg/dl	85	58	6
Kok, et al. 2012[63]	382 (19, 5,0%) Referred by GPs because of lower abdominal complaints suggestive of organic bowel disease.	ELISA test: 50 µg/g POC test: 50 µg/g	ELISA: 95 POC: 79		
Parente, et al. 2012[64]	280 (47, 16,8%) Symptomatic patients aged 50-80 years attending gastroenterology clinics	50 µg/g	85.7	39.7	22.2
Mowat, et al. 2016[68]	755 (28, 3.7%) Symptomatic patients referred from primary care	50 µg/g 200 µg/g	82.1 46.4	38.8 74.9	5.1 6.9
Turvill, et al. 2016[77]	654 (39, 6.0%) Patients referred urgently through "two week wait" pathway	50 µg/g	92.7	35.2	8.7
Widlak, et al. 2017[78]	430 (24+1HGD, 5.8%) Patients referred urgently through "two week wait" pathway"	50 µg/g	68	84	21

ELISA: enzyme-linked immunosorbent assay
HGD: high-grade dysplasia
GP: general practitioner
POC: point of care
PPV: positive predictive value

Combinations of tests

As a primary care doctor, I want diagnostic aids to safely rule out serious diseases such as CRC, that is tests need to have a high sensitivity and NPV. At the same time, I want to avoid unnecessary referrals for colonoscopy, as this is a troublesome procedure for patients and endoscopy resources are limited. This means that tests should also have as high specificity and PPV as possible.

Of the laboratory tests we examined, the best test for detecting CRC and IBD was a combination of the FIT and the haemoglobin value with 100% sensitivity, 61.7% specificity, 11.7% PPV and 100% NPV. Iron deficiency should be expected to appear in patients before they get IDA, and so tests for iron deficiency ought to enable an earlier diagnosis. Perhaps the

combination of a FIT, the testing of haemoglobin concentration and an iron deficiency test is an even better test for excluding CRC and IBD. A population-based study has found a five times higher risk of gastrointestinal malignancy among men and postmenopausal women with iron deficiency without anaemia which could support this.[155] However, including iron deficiency tests would probably result in a lower specificity.

The combination of a FIT and an FC test in Study 2 showed no improvement over the FIT alone and does not appear to be more valuable as a diagnostic aid. This has also been the conclusion in other studies evaluating this combination.[64, 68, 78, 134]

Different prediction models that include laboratory tests have been proposed for use as aids when deciding upon further investigation of suspected CRC.[156] Some prediction models include many variables, making them complicated to use.[132, 134, 157] Two articles have proposed a score based on a FIT result, age and gender.[131, 158] To my knowledge, none of these prediction models have been tested in primary care and their ability to rule in or rule out CRC in a primary care setting is thus unknown.

The diagnostic process and strategies

In study 3 the doctors gave many examples of their use of the diagnostic strategies that are described in the background chapter.[90]

For the first stage (initiation of diagnostic hypotheses) they described the presenting complaint as a trigger, the pattern recognition trigger and also the risk of self labelling by the patient.

For the second stage (refinement) they described stepwise refinement of the diagnosis, probabilistic reasoning and pattern recognition fit.

For the third stage (defining the final diagnosis) they described known diagnosis, requesting further tests, test of time, and no label applied with safety-netting or referral.

They also told about rules of thumb. Two examples can be worded like this: “When there is rectal bleeding, always determine the source”, and “always come to an agreement with the patient”.

The role of gut feeling was described by doctors with longer work experience. Gut feeling was thought to be based on experience and thus changed with time.

Continuity of care was thought to be both an advantage and a disadvantage. Previous knowledge of patients was mostly considered helpful but patients

with frequent consultations were thought to be at risk of delayed referral and diagnosis. Other studies have also found that continuity of care can be both positive and negative. In two qualitative studies, with primary care staff interviews, continuity was described as a positive factor.[86, 159] On the other hand, a cohort study found that greater former knowledge of the patient may be related to a longer system delay, and a medical record study found that increased continuity was related to a small increase of delay in the diagnosis of colorectal cancer.[101, 160] Patients may also have different views on continuity of care; primary care doctor continuity is desirable for many, while rapid access can be more important to others.[100, 102]

Deciding on whether to refer or not includes management of uncertainty, which is an essential part of the work as a primary care doctor.[161] The interviewees described different methods for dealing with this, and decision-making seemed to be easier with increasing experience. This has also been described previously.[162] However, longer experience did not seem to result in less uncertainty but instead greater cautiousness and humility.

In the absence of guidelines, primary care doctors seem to have found practical ways to handle the use of FITs and the test results. As rectal bleeding is the symptom with the most evident connection to CRC it would seem reasonable to refer all persons with this symptom for bowel imaging. However, rectal bleeding mostly has benign explanations, and doctors were aware that if all patients presenting with rectal bleeding were referred it would outrun the resources for bowel imaging. A negative FIT, perhaps in combination with a normal proctoscopy or rectoscopy, could encourage watchful waiting.

Implications for clinical practice

FITs requested by primary care doctors seem to be useful as diagnostic aids when CRC is suspected, and this may also be true in patients with rectal bleeding. FITs may also be useful when IBD is suspected. Patients, at least over the age of 50, with unexplained anaemia should be suspected of having CRC also if FITs are negative. In patients with negative FITs and no anaemia or iron deficiency the risk of CRC seems to be small.

Implications for future research

To confirm the results of the studies in this thesis, more and larger studies are needed.

Analysis methods for quantitative POC FITs are now being developed and will probably improve possibilities to use FITs as diagnostic aids in primary care.

For future use of FITs as diagnostic aids, the optimal cut-off value for symptomatic patients needs to be established in prospective studies. Studies should also include haemoglobin values and tests for iron deficiency to evaluate the combination of these with FITs. Patients with rectal bleeding should be included in the studies.

There is also a need for standardisation of FITs, in order for different brands to be comparable.

Risk assessment tools might be useful as aids in selecting the patients for which to request FITs. This could also be a subject for future research.

Conclusions

- Primary care was important in the detection of symptomatic CRC, as the majority of patients with this diagnosis initially consulted primary care.

- Rectal bleeding was the only symptom with a significant relation to CRC and IBD in patients where doctors requested FITs and/or FC tests. Change in bowel habits had no relation to CRC or IBD. Instead, diarrhoea may be more connected to the onset of CRC and IBD.

- The FIT showed a better PPV for CRC and IBD than rectal bleeding.

- In cases with rectal bleeding, a negative FIT requested by a primary care doctor could exclude CRC and IBD with a high degree of safety.

- With negative FITs there was however also a risk of delay of the diagnosis of CRC, especially in cases with asymptomatic anaemia.

- The best test for detecting CRC and IBD was the combination of a positive FIT and/or anaemia.

- The FC test had no additional value to the FIT alone.

- FITs were frequently used as support in decisions about which patients to refer, but with considerable variation in the handling of the results.

- The diagnostic process can be described as navigating uncertain waters with safety margins, striving to keep the patient's best interests in mind.

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References

1. International Agency for Research on Cancer [Internet]. Cancer Today [cited 20/3 2017]. Available from: http://gco.iarc.fr/today/home
2. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64:1637-49.
3. Hallifax R, Lacey M, Bevis P, Borley NR, Brooklyn T, Wheeler JM. Slipping through the bowel cancer screening programme. Colorectal Dis. 2012;14:844-7.
4. Moreno CC, Mittal PK, Sullivan PS, Rutherford R, Staley CA, Cardona K, et al. Colorectal cancer initial diagnosis: Screening colonoscopy, diagnostic colonoscopy, or emergent surgery, and tumor stage and size at initial presentation. Clin Colorectal Cancer. 2016;15:67-73.
5. Torring ML, Frydenberg M, Hamilton W, Hansen RP, Lautrup MD, Vedsted P. Diagnostic interval and mortality in colorectal cancer: U-shaped association demonstrated for three different datasets. J Clin Epidemiol. 2012;65:669-78.
6. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer. 2015;112:S92-107.
7. Månsson J, Björkelund C, Hultborn R. Symptom pattern and diagnostic work-up of malignancy at first symptom presentation as related to level of care. A retrospective study from the primary health care centre area of Kungsbacka, Sweden. Neoplasma. 1999;46:93-9.
8. Högberg C, Karling P, Rutegård J, Lilja M, Ljung T. Immunochemical faecal occult blood tests in primary care and the risk of delay in the diagnosis of colorectal cancer. Scand J Prim Health Care. 2013;31:209-14.
9. Barrett J, Jiwa M, Rose P, Hamilton W. Pathways to the diagnosis of colorectal cancer: an observational study in three UK cities. Family Practice. 2006;23:15-9.
10. Sheringham JR, Georghiou T, Chitnis XA, Bardsley M. Comparing primary and secondary health-care use between diagnostic routes before a colorectal cancer diagnosis: cohort study using linked data. Br J Cancer. 2014;111:1490-9.
11. Tidig upptäckt av symtomgivande cancer. En systematisk litteraturöversikt. Stockholm: Statens beredning för medicinsk utvärdering (SBU) [Swedish Council on Health Technology Assessment] In Swedish. 2014;222.

12. Rasmussen S, Larsen PV, Sondergaard J, Elnegaard S, Svendsen RP, Jarbol DE. Specific and non-specific symptoms of colorectal cancer and contact to general practice. Family Practice. 2015;32:387-94.
13. Talley NJ, Jones M. Self-reported rectal bleeding in a United States community: prevalence, risk factors, and health care seeking. Am J Gastroenterol. 1998;93:2179-83.
14. Svendsen RP, Stovring H, Hansen BL, Kragstrup J, Sondergaard J, Jarbol DE. Prevalence of cancer alarm symptoms: A population-based cross-sectional study. Scand J Prim Health Care. 2010;28:132-7.
15. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. New Engl J Med. 1992;326:658-62.
16. Jellema P, van Tulder MW, van der Horst HE, Florie J, Mulder CJ, van der Windt DA. Inflammatory bowel disease: a systematic review on the value of diagnostic testing in primary care. Colorectal Dis. 2011;13:239-54.
17. Gibson JA, Odze RD. Pathology of premalignant colorectal neoplasia. Dig Endosc. 2016;28:312-23.
18. Langner C. Serrated and non-serrated precursor lesions of colorectal cancer. Dig Dis. 2015;33:28-37.
19. Hassan C, Quintero E, Dumonceau JM, Regula J, Brandao C, Chaussade S, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2013;45:842-51.
20. Snover DC AD, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman FT, Carneiro F, Hruban RH, et al, editors. WHO classification of tumours of the digestive system. Lyon, France: IARC; 2010.
21. O'Connell BM, Crockett SD. The clinical impact of serrated colorectal polyps. Clin Epidemiol. 2017;9:113-25.
22. Warschkow R, Sulz MC, Marti L, Tarantino I, Schmied BM, Cerny T, et al. Better survival in right-sided versus left-sided stage I - III colon cancer patients. BMC Cancer. 2016;16:554.
23. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383:1490-502.
24. Rosty C, Hewett DG, Brown IS, Leggett BA, Whitehall VL. Serrated polyps of the large intestine: current understanding of diagnosis, pathogenesis, and clinical management. J Gastroenterol. 2013;48:287-302.
25. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380:1606-19.
26. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380:1590-605.

27. Socialstyrelsen (National Board of Health and Welfare) [Internet]. Statistics on Cancer Incidence 2015. 2017 [cited 20/3 2017]. Available from: http://www.socialstyrelsen.se/publikationer2017/2017-1-20
28. NORDCAN, Association of the Nordic Cancer Registries [Internet]. Cancer fact sheets 2016. [cited 20/3 2017]. Available from: http://www-dep.iarc.fr/NORDCAN/English/frame.asp
29. Sjöberg D, Holmström T, Larsson M, Nielsen AL, Holmquist L, Ekbom A, et al. Inidence and clinical course of Crohn's disease during the first year - results from the IBD Cohort of the Uppsala Region (ICURE) of Sweden 2005-2009. J Crohns Colitis. 2014;8:215-22.
30. Sjöberg D, Holmström T, Larsson M, Nielsen AL, Holmquist L, Ekbom A, et al. Incidence and natural history of ulcerative colitis in the Uppsala Region of Sweden 2005-2009 - results from the IBD cohort of the Uppsala Region (ICURE). J Crohns Colitis. 2013;7:e351-7.
31. Thörn M, Sjöberg D, Ekbom A, Holmström T, Larsson M, Nielsen AL, et al. Microscopic colitis in Uppsala health region, a population-based prospective study 2005-2009. Scand J Gastroenterol. 2013;48:825-30.
32. Gisbert JP, Chaparro M. Systematic review with meta-analysis: inflammatory bowel disease in the elderly. Aliment Pharmacol Ther. 2014;39:459-77.
33. Hou JK, Feagins LA, Waljee AK. Characteristics and behavior of elderly-onset inflammatory bowel disease: A multi-center US study. Inflamm Bowel Dis. 2016;22:2200-5.
34. Del Giudice ME, Vella ET, Hey A, Simunovic M, Harris W, Levitt C. Systematic review of clinical features of suspected colorectal cancer in primary care. Can Fam Physician. 2014;60:717-23.
35. Fijten GH, Starmans R, Muris JW, Schouten HJ, Blijham GH, Knottnerus JA. Predictive value of signs and symptoms for colorectal cancer in patients with rectal bleeding in general practice. Fam Pract. 1995;12:279-86.
36. Wauters H, Van Casteren V, Buntinx F. Rectal bleeding and colorectal cancer in general practice: diagnostic study. BMJ. 2000;321:998-9.
37. Hamilton W, Round A, Sharp D, Peters TJ. Clinical features of colorectal cancer before diagnosis: a population-based case-control study. Br J Cancer. 2005;93:399-405.
38. du Toit J, Hamilton W, Barraclough K. Risk in primary care of colorectal cancer from new onset rectal bleeding: 10 year prospective study. BMJ. 2006;333:69-70.
39. Jones R, Latinovic R, Charlton J, Gulliford MC. Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database. BMJ. 2007;334:1040.

40. Bjerregaard NC, Tøttrup A, Sørensen HT, Laurberg S. Diagnostic value of self-reported symptoms in Danish outpatients referred with symptoms consistent with colorectal cancer. Colorectal Dis. 2007;9:443-51.
41. Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. Br J Gen Pract. 2011;61:e231-43.
42. Ewing M, Naredi P, Zhang C, Månsson J. Identification of patients with non-metastatic colorectal cancer in primary care: a case-control study. Br J Gen Pract. 2016;66:e880-6.
43. Park JY, Mitrou PN, Luben R, Khaw KT, Bingham SA. Is bowel habit linked to colorectal cancer? - Results from the EPIC-Norfolk study. Eur J Cancer. 2009;45:139-45.
44. Power AM, Talley NJ, Ford AC. Association between constipation and colorectal cancer: systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2013;108:894-903.
45. Lawrenson R, Logie J, Marks C. Risk of colorectal cancer in general practice patients presenting with rectal bleeding, change in bowel habit or anaemia. Eur J Cancer Care. 2006;15:267-71.
46. Hamilton W, Green T, Martins T, Elliott K, Rubin G, Macleod U. Evaluation of risk assessment tools for suspected cancer in general practice: a cohort study. Br J Gen Pract. 2013;63:e30-6.
47. Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng K, Marshall T. The risk of colorectal cancer with symptoms at different ages and between the sexes: a case-control study. BMC Med. 2009;7:17.
48. Boas I. Diseases of the stomach. Philadelphia: FA Davis Company; 1908.
49. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med. 1993;328:1365-71.
50. Kewenter J, Brevinge H, Engarás B, Haglind E, Ährén C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing: Results for 68,308 Subjects. Scand J Gastroenterol. 1994;29:468-73.
51. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348:1472-7.
52. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348:1467-71.
53. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev. 2007(1):CD001216.

54. Leicester RJ, Lightfoot A, Millar J, Colin-Jones DG, Hunt RH. Accuracy and value of the Hemoccult test in symptomatic patients. Br Med J (Clin Res Ed). 1983;286:673-4.
55. Gillberg A, Ericsson E, Granström F, Olsson LI. A population-based audit of the clinical use of faecal occult blood testing in primary care for colorectal cancer. Colorectal Dis. 2012;14:e539-46.
56. Peacock O, Watts ES, Hanna N, Kerr K, Goddard AF, Lund JN. Inappropriate use of the faecal occult blood test outside of the National Health Service colorectal cancer screening programme. Eur J Gastroenterol Hepatol. 2012;24:1270-5.
57. Barrows GH, Burton RM, Jarrett DD, Russell GG, Alford MD, Songster CL. Immunochemical detection of human blood in feces. Am J Clin Pathol. 1978;69:342-6.
58. Brenner H, Haug U, Hundt S. Inter-test agreement and quantitative cross-validation of immunochromatographical fecal occult blood tests. Int J Cancer. 2010;127:1643-9.
59. Fraser CG, Allison JE, Halloran SP, Young GP. A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. J Natl Cancer Inst. 2012;104:810-4.
60. Segnan N, Patnick J, von Karsa L, editors. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Luxembourg: European Union; 2010. [cited 20/3 2017]. Available from: https://bookshop.europa.eu/en/european-guidelines-for-quality-assurance-in-colorectal-cancer-screening-and-diagnosis-pbND3210390/
61. Robertson DJ, Lee JK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, et al. Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: A consensus statement by the US Multi-Society Task Force on colorectal cancer. Am J Gastroenterol. 2017;112:37-53.
62. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med. 2014;160:171.
63. Kok L, Elias SG, Witteman BJ, Goedhard JG, Muris JW, Moons KG, et al. Diagnostic accuracy of point-of-care fecal calprotectin and immunochemical occult blood tests for diagnosis of organic bowel disease in primary care: the Cost-Effectiveness of a Decision Rule for Abdominal Complaints in Primary Care (CEDAR) study. Clin Chem. 2012;58:989-98.

64. Parente F, Marino B, Ilardo A, Fracasso P, Zullo A, Hassan C, et al. A combination of faecal tests for the detection of colon cancer: a new strategy for an appropriate selection of referrals to colonoscopy? A prospective multicentre Italian study. Eur J Gastroenterol Hepatol. 2012;24:1145-52.
65. Kaul A, Shah A, Magill FH, Hawkins SA, Skaife P. Immunological faecal occult blood testing: a discriminatory test to identify colorectal cancer in symptomatic patients. Int J Surg. 2013;11:329-31.
66. McDonald PJ, Digby J, Innes C, Strachan JA, Carey FA, Steele RJC, et al. Low faecal haemoglobin concentration potentially rules out significant colorectal disease. Colorectal Dis. 2013;15:e151-9.
67. Cubiella J, Salve M, Diaz-Ondina M, Vega P, Alves MT, Iglesias F, et al. Diagnostic accuracy of the faecal immunochemical test for colorectal cancer in symptomatic patients: comparison with NICE and SIGN referral criteria. Colorectal Dis. 2014;16:O273-82.
68. Mowat C, Digby J, Strachan JA, Wilson R, Carey FA, Fraser CG, et al. Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms. Gut. 2016;65:1463-9.
69. Godber IM, Todd LM, Fraser CG, MacDonald LR, Younes HB. Use of a faecal immunochemical test for haemoglobin can aid in the investigation of patients with lower abdominal symptoms. Clin Chem Lab Med. 2016;54:595-602.
70. Røseth AG, Fagerhol MK, Aadland E, Schjønsby H. Assessment of the neutrophil dominating protein calprotectin in feces: A methodologic study. Scand J Gastroenterol. 1992;27:793-8.
71. Tøn H, Brandsnes Ø, Dale S, Holtlund J, Skuibina E, Schjønsby H, et al. Improved assay for fecal calprotectin. Clin Chim Acta. 2000;292:41-54.
72. NICE diagnostic guidance. Faecal calprotectin diagnostic tests for inflammatory disease of the bowel. 2013 [cited 20/32017]. Available from: https://www.nice.org.uk/guidance/dg11.
73. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ. 2010;341:c3369.
74. Sipponen T, Kolho KL. Fecal calprotectin in diagnosis and clinical assessment of inflammatory bowel disease. Scand J Gastroenterol. 2015;50:74-80.
75. Røseth AG, Kristinsson J, Fagerhol MK, Schjønsby H, Aadland E, Nygaard K, et al. Faecal Calprotectin: A Novel Test for the Diagnosis of Colorectal Cancer? Scand J Gastroenterol. 1993;28:1073-6.

76. Tibble J, Sigthorsson G, Foster R, Sherwood R, Fagerhol M, Bjarnason I. Faecal calprotectin and faecal occult blood tests in the diagnosis of colorectal carcinoma and adenoma. Gut. 2001;49:402-8.
77. Turvill J, Aghahoseini A, Sivarajasingham N, Abbas K, Choudhry M, Polyzois K, et al. Faecal calprotectin in patients with suspected colorectal cancer: a diagnostic accuracy study. Br J Gen Pract. 2016;66:e499-506.
78. Widlak MM, Thomas CL, Thomas MG, Tomkins C, Smith S, O'Connell N, et al. Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and adenoma in symptomatic patients. Aliment Pharmacol Ther. 2017;45:354-63.
79. Acher PL, Al-Mishlab T, Rahman M, Bates T. Iron-deficiency anaemia and delay in the diagnosis of colorectal cancer. Colorectal Dis. 2003;5:145-8.
80. Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng KK, Marshall T. The importance of anaemia in diagnosing colorectal cancer: a case-control study using electronic primary care records. Br J Cancer. 2008;98:323-7.
81. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. Am J Med. 2004;116 Suppl 7A:44S-9S.
82. World Health Organisation (WHO) [Internet]. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011 [cited 20/3 2017]. Available from: http://apps.who.int/iris/bitstream/10665/85839/3/WHO_NMH_NHD_MNM_11.1_eng.pdf?ua=1
83. Goddard AF, James MW, McIntyre AS, Scott BB, British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. Gut. 2011;60:1309-16.
84. Panagiotopoulou IG, Fitzrol D, Parker RA, Kuzhively J, Luscombe N, Wells AD, et al. The yield of colorectal cancer among fast track patients with normocytic and microcytic anaemia. Ann R Coll Surg Eng. 2014;96:289-93.
85. Bager P, Befrits R, Wikman O, Lindgren S, Moum B, Hjortswang H, et al. The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. Scand J Gastroenterol. 2011;46:304-9.
86. Johansen ML, Holtedahl KA, Rudebeck CE. How does the thought of cancer arise in a general practice consultation? Interviews with GPs. Scand J Prim Health Care. 2012;30:135-40.
87. Ingebrigtsen SG, Scheel BI, Hart B, Thorsen T, Holtedahl K. Frequency of 'warning signs of cancer' in Norwegian general practice, with prospective recording of subsequent cancer. Fam Pract. 2013;30:153-60.

88. Scheel BI, Ingebrigtsen SG, Thorsen T, Holtedahl K. Cancer suspicion in general practice: the role of symptoms and patient characteristics, and their association with subsequent cancer. Br J Gen Pract. 2013;63:627-35.
89. Hjertholm P, Moth G, Ingeman ML, Vedsted P. Predictive values of GPs' suspicion of serious disease: a population-based follow-up study. Br J Gen Pract. 2014;64:e346-53.
90. Heneghan C, Glasziou P, Thompson M, Rose P, Balla J, Lasserson D, et al. Diagnostic strategies used in primary care. BMJ. 2009;338:b946.
91. Goyder C, McPherson A, Glasziou P. Diagnosis in general practice. Self diagnosis. BMJ. 2009;339:b4418.
92. Doust J. Diagnosis in General Practice. Using probabilistic reasoning. BMJ. 2009;339:b3823.
93. van der Weijden T, van Bokhoven MA, Dinant GJ, van Hasselt CM, Grol RP. Understanding laboratory testing in diagnostic uncertainty: a qualitative study in general practice. Br J Gen Pract. 2002;52:974-80.
94. Houben PH, van der Weijden T, Winkens B, Winkens RA, Grol RP. Pretest expectations strongly influence interpretation of abnormal laboratory results and further management. BMC Fam Pract. 2010;11:13.
95. Almond S, Mant D, Thompson M. Diagnostic safety-netting. Br J Gen Pract. 2009;59:872-4; discussion 4.
96. André M, Borgquist L, Foldevi M, Mölstad S. Asking for 'rules of thumb': a way to discover tacit knowledge in general practice. Fam Pract. 2002;19:617-22.
97. André M, Borgquist L, Mölstad S. Use of rules of thumb in the consultation in general practice - an act of balance between the individual and the general perspective. Fam Pract. 2003;20:514-9.
98. Stolper E, van Bokhoven M, Houben P, Van Royen P, van de Wiel M, van der Weijden T, et al. The diagnostic role of gut feelings in general practice. A focus group study of the concept and its determinants. BMC Fam Pract. 2009;10:17.
99. Donker GA, Wiersma E, van der Hoek L, Heins M. Determinants of general practitioner's cancer-related gut feelings-a prospective cohort study. BMJ open. 2016;6:e012511.
100. Guthrie B, Wyke S. Personal continuity and access in UK general practice: a qualitative study of general practitioners' and patients' perceptions of when and how they matter. BMC Fam Pract. 2006;7:11.
101. Ridd MJ, Ferreira DL, Montgomery AA, Salisbury C, Hamilton W. Patient-doctor continuity and diagnosis of cancer: electronic medical records study in general practice. Br J Gen Pract. 2015;65:e305-11.

102. Bain NS, Campbell NC, Ritchie LD, Cassidy, J. Striking the right balance in colorectal cancer care—a qualitative study of rural and urban patients. Fam Pract. 2002;19:369-74.
103. Regionala cancer centrum i samverkan (RCC) [Internet]. Standardiserat vårdförlopp för tjock- och ändtarmscancer. 2016 [cited 20/3 2017]. Available from: https://www.cancercentrum.se/globalassets/cancerdiagnoser/tjock--och-andtarm-anal/vardforlopp/standardiserat_vardforlopp_tjock-andtarm_20151221.pdf
104. NICE guidelines [Internet]. Suspected cancer: recognition and referral. 2015 [cited 20/3 2017]. Available from: https://www.nice.org.uk/guidance/ng12
105. Sundhetsstyrelsen (Danish Health Authority) [Internet]. Pakkeforløb for kræft i tyk- og endetarm. 2012 [cited 20/3 2017]. Available from: https://www.sst.dk/da/sygdom-og-behandling/kraeft/pakkeforloeb/beskrivelser
106. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48:27-33.
107. Oy Medix Biochemica Ab [Internet]. [Cited 20/3 2017.] Available from: www.medixbiochemica.com
108. Calpro AS [Internet].[Cited 20/3 2017.] Available from: https://calpro.no/products/calprotectin-elisa-test
109. Regionalt cancercentrum norr [Internet]. [Cited 20/3 2017.] Available from: www.cancercentrum.se/norr
110. Podolsky DK, Camilleri M, Fitz JG, Kalloo AN, Shanahan F, Wang TC (editors). Yamada's Textbook of Gastroenterology, 6th ed. London: Wiley; 2015.
111. Svedlund J, Sjödin I, Dotevall G. GSRS – A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33:129-34.
112. Dimenäs E, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Quality of life in patients with upper gastrointestinal symptoms: An improved evaluation of treatment regimens? Scand J Gastroenterol. 1993;28:681-7.
113. Wiklund IK, Fullerton S, Hawkey CJ, Jones RH, Longstreth GF, Mayer EA, et al. An irritable bowel syndrome-specific symptom questionnaire: Development and validation. Scand J Gastroenterol. 2003;38:947-54.
114. Dimenäs E, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol. 1995;30:1046-52.

115. Lundgren D, Rutegård J, Eklöf V, Palmqvist R, Karling P. Patients with longstanding ulcerative colitis in remission do not have more irritable bowel syndrome-like symptoms than controls. BMC Gastroenterol. 2016;16:139.
116. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today. 2004;24:105-12.
117. Högberg C, Asplund R. [Small benefit of many feces-Hb tests. Low diagnostic value of the immunochemical method according to a primary health care study]. In Swedish. Läkartidningen. 2010;107:1372-5.
118. Regionfakta [Internet]. [Cited 20/3 2017] Available from: www.regionfakta.com
119. Statistikdatabas för cancer (Swedish Cancer Registry) [Internet]. National Board of Health and Welfare. Available from: http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer
120. Hamberg K, Johansson E, Lindgren G, Westman G. Scientific rigour in qualitative research - examples from a study in women's health in family practice. Fam Pract. 1994;11:176-81.
121. Jones R, Charlton J, Latinovic R, Gulliford MC. Alarm symptoms and identification of non-cancer diagnoses in primary care: cohort study. BMJ. 2009;339:b3094.
122. Ellis BG, Thompson MR. Factors identifying higher risk rectal bleeding in general practice. Br J Gen Pract. 2005;55:949-55.
123. Robertson R, Campbell C, Weller DP, Elton R, Mant D, Primrose J, et al. Predicting colorectal cancer risk in patients with rectal bleeding. Br J Gen Pract. 2006;56:763-7.
124. Panzuto F, Chiriatti A, Bevilacqua S, Giovannetti P, Russo G, Impinna S, et al. Symptom-based approach to colorectal cancer: survey of primary care physicians in Italy. Dig Liver Dis. 2003;35:869-75.
125. Selvachandran SN, Hodder RJ, Ballal MS, Jones P, Cade D. Prediction of colorectal cancer by a patient consultation questionnaire and scoring system: a prospective study. Lancet. 2002;360:278-83.
126. Huang L, Wang X, Gong W, Huang Y, Jiang B. The comparison of the clinical manifestations and risk factors of colorectal cancer and adenomas: results from a colonoscopy-based study in southern Chinese. In J Colorectal Dis. 2010;25:1343-1351.
127. Scheuer E, Steurer J, Buddeberg C. Predictors of differences in symptom perception of older patients and their doctors. Fam Pract. 2002;19:357-61.

128. Smith A, Young GP, Cole SR, Bampton P. Comparison of a brush-fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. Cancer. 2006;107:2152-9.
129. Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med. 2007;146:244-55.
130. van Turenhout ST, van Rossum LG, Oort FA, Laheij RJ, van Rijn AF, Terhaar sive Droste JS, et al. Similar fecal immunochemical test results in screening and referral colorectal cancer. World J Gastroenterol. 2012;18:5397-403.
131. Rodriguez-Alonso L, Rodriguez-Moranta F, Ruiz-Cerulla A, Lobaton T, Arajol C, Binefa G, et al. An urgent referral strategy for symptomatic patients with suspected colorectal cancer based on a quantitative immunochemical faecal occult blood test. Dig Liver Dis. 2015;47:797-804.
132. Cubiella J, Vega P, Salve M, Diaz-Ondina M, Alves MT, Quintero E, et al. Development and external validation of a faecal immunochemical test-based prediction model for colorectal cancer detection in symptomatic patients. BMC Med. 2016;14(1):128.
133. Auge JM, Fraser CG, Rodriguez C, Roset A, Lopez-Ceron M, Grau J, et al. Clinical utility of one versus two faecal immunochemical test samples in the detection of advanced colorectal neoplasia in symptomatic patients. Clin Chem Lab Med. 2016;54:125-32.
134. Elias SG, Kok L, de Wit NJ, Witteman BJ, Goedhard JG, Romberg-Camps MJ, et al. Is there an added value of faecal calprotectin and haemoglobin in the diagnostic work-up for primary care patients suspected of significant colorectal disease? A cross-sectional diagnostic study. BMC Med. 2016;14:141.
135. Wilschut JA, Habbema JD, van Leerdam ME, Hol L, Lansdorp-Vogelaar I, Kuipers EJ, et al. Fecal occult blood testing when colonoscopy capacity is limited. J Natl Cancer Inst. 2011;103:1741-51.
136. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med. 2009;150:162-9.
137. Tannous B, Lee-Lewandrowski E, Sharples C, Brugge W, Bigatello L, Thompson T, et al. Comparison of conventional guaiac to four immunochemical methods for fecal occult blood testing: implications for clinical practice in hospital and outpatient settings. Clin Chim Acta. 2009;400:120-2.

138. Santare D, Kojalo I, Liepniece-Karele I, Kikuste I, Tolmanis I, Polaka I, et al. Comparison of the yield from two faecal immunochemical tests at identical cutoff concentrations - a randomized trial in Latvia. Eur J Gastroenterol Hepatol. 2016;28:904-10.
139. Chiang TH, Chuang SL, Chen SL, Chiu HM, Yen AM, Chiu SY, et al. Difference in performance of fecal immunochemical tests with the same hemoglobin cutoff concentration in a nationwide colorectal cancer screening program. Gastroenterology. 2014;147:1317-26.
140. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol. 2010;105:2457-64.
141. McDonald PJ, Strachan JA, Digby J, Steele RJ, Fraser CG. Faecal haemoglobin concentrations by gender and age: implications for population-based screening for colorectal cancer. Clin Chem Lab Med. 2012;50:935-40.
142. Kapidzic A, van der Meulen MP, Hol L, van Roon AH, Looman CW, Lansdorp-Vogelaar I, et al. Gender differences in fecal immunochemical test performance for early detection of colorectal neoplasia. Clin Gastroenterol Hepatol. 2015;13:1464-71.e4.
143. Fraser CG, Rapi S, Rubeca T. RE: A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. J Natl Cancer Inst. 2016;108(1).
144. Park DI, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol. 2010;105:2017-25.
145. Raginel T, Puvinel J, Ferrand O, Bouvier V, Levillain R, Ruiz A, et al. A population-based comparison of immunochemical fecal occult blood tests for colorectal cancer screening. Gastroenterology. 2013;144:918-25.
146. Wu D, Luo HQ, Zhou WX, Qian JM, Li JN. The performance of three-sample qualitative immunochemical fecal test to detect colorectal adenoma and cancer in gastrointestinal outpatients: an observational study. PloS one. 2014;9:e106648.
147. Kapidzic A, van Roon AH, van Leerdam ME, van Vuuren AJ, van Ballegooijen M, Lansdorp-Vogelaar I, et al. Attendance and diagnostic yield of repeated two-sample faecal immunochemical test screening for colorectal cancer. Gut. 2017;66:118-123
148. Nicholson BD, Thompson M, Price CP, Heneghan C, Pluddemann A. Home-use faecal immunochemical testing: primary care diagnostic technology update. Br J Gen Pract. 2015;65:156-8.

149. Mooiweer E, Fidder HH, Siersema PD, Laheij RJ, Oldenburg B. Fecal hemoglobin and calprotectin are equally effective in identifying patients with inflammatory bowel disease with active endoscopic inflammation. Inflamm Bowel Dis. 2014;20:307-14.
150. Nakarai A, Kato J, Hiraoka S, Takashima S, Takei D, Inokuchi T, et al. Ulcerative colitis patients in clinical remission demonstrate correlations between fecal immunochemical test results, mucosal healing, and risk of relapse. World J Gastroenterol. 2016;22:5079-87.
151. Renzi C, Whitaker KL, Wardle J. Over-reassurance and undersupport after a 'false alarm': a systematic review of the impact on subsequent cancer symptom attribution and help seeking. BMJ Open. 2015;5:e007002.
152. Renzi C, Whitaker KL, Winstanley K, Cromme S, Wardle J. Unintended consequences of an 'all-clear' diagnosis for potential cancer symptoms: a nested qualitative interview study with primary care patients. Br J Gen Pract. 2016;66:e158-70.
153. Pengelly S, Fabricius M, McMenamin D, Wu E, Metzner M, Lewis SJ, et al. Attendance at iron deficiency anaemia clinic: audit of outcomes 5 years on. Colorectal Dis. 2013;15:423-7.
154. Meucci G, D'Inca R, Maieron R, Orzes N, Vecchi M, Visentini D, et al. Diagnostic value of faecal calprotectin in unselected outpatients referred for colonoscopy: A multicenter prospective study. Dig Liver Dis. 2010;42:191-5.
155. Ioannou GN, Rockey DC, Bryson CL, Weiss NS. Iron Deficiency and Gastrointestinal Malignancy: A Population-Based Cohort Study. Am J Med. 2002;113:276-80.
156. Williams TG, Cubiella J, Griffin SJ, Walter FM, Usher-Smith JA. Risk prediction models for colorectal cancer in people with symptoms: a systematic review. BMC Gastroenterol. 2016;16:63.
157. Marshall T, Lancashire R, Sharp D, Peters TJ, Cheng KK, Hamilton W. The diagnostic performance of scoring systems to identify symptomatic colorectal cancer compared to current referral guidance. Gut. 2011;60:1242-8.
158. Cubiella J, Digby J, Rodríguez-Alonso L, Vega P, Salve M, Díaz-Ondina M, et al;. The FAST (Faecal Haemoglobin Concentration, Age and Sex Test) Score: Development and external validation of a simple prediction tool for colorectal cancer detection in symptomatic patients. Int J Cancer. 2017 Feb 10 [Epub ahead of print].
159. Cook N, Thomson G, Dey P. Managing risk in cancer presentation, detection and referral: a qualitative study of primary care staff views. BMJ Open. 2014;4:e004820.

160. Hansen RP, Vedsted P, Sokolowski I, Sondergaard J, Olesen F. General practitioner characteristics and delay in cancer diagnosis. a population-based cohort study. BMC Fam Pract. 2011;12:100.
161. O'Riordan M, Dahinden A, Akturk Z, Bueno Ortiz JM, Dagdeviren N, Elwyn G, et al. Dealing with uncertainty in general practice: an essential skill for the general practitioner. Qual Prim Care. 2011;19:175-81.
162. Nevalainen M, Kuikka L, Pitkälä K. Medical errors and uncertainty in primary healthcare: A comparative study of coping strategies among young and experienced GPs. Scand J Prim Health Care. 2014;32:84-9.

Appendices

Appendix A

Datum ……. Namn …… Personnummer…….

FRÅGOR OM MAGTARM BESVÄR (18 frågor)

Läs detta först: Undersökningen innehåller frågor om hur du mår och hur du haft det den senaste veckan. Markera med ett X det alternativ som bäst passar in på Dig och Din situation.

1. Har Du under den senaste veckan besvärats av ONT I MAGEN ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

2. Har Du under den senaste veckan besvärats av SMÄRTA ELLER OBEHAG I MAGEN SOM BLIR BÄTTRE OM DU TÖMMER TARMEN ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

3. Har Du under den senaste veckan besvärats av EN KÄNSLA AV UPPKÖRDHET I MAGEN ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

4. Har du under den senaste veckan besvärats av ATT DU SLÄPPER UT GASER ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

5. Har du under den senaste veckan besvärats av FÖRSTOPPNING ELLER PROBLEM ATT TÖMMA TARMEN ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

6. Har du under den senaste veckan besvärats av MÅNGA TARMTÖMNINGAR PER DAG ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

7. Har Du under den senaste veckan besvärats av LÖS AVFÖRING ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

8. Har Du under den senaste veckan besvärats av HÅRD AVFÖRING ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

9. Har Du under den senaste veckan besvärats av TRÄNGANDE AVFÖRINGSBEHOV ? (Bråttom till toaletten.)

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

10. Har Du under den senaste veckan besvärats av en KÄNSLA AV ATT DU INTE RIKTIGT KAN TÖMMA TARMEN ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

11. Har Du under den senaste veckan besvärats av att Du KÄNT DIG MÄTT INNAN DU HAR ÄTIT FÄRDIGT? (Blir fort mätt.)

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

12. Har Du under den senaste veckan besvärats av att Du KÄNT DIG MÄTT LÄNGE EFTER ATT DU ÄTIT FÄRDIGT ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

13. Har Du under den senaste veckan besvärats av att MAGEN SVULLNAR SÅ ATT DET SYNS ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

14. Har Du under den senaste veckan besvärats av HALSBRÄNNA ELLER BRÖSTBRÄNNA ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

15. Har Du under den senaste veckan besvärats av SURA UPPSTÖTNINGAR ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

16. Har Du under den senaste veckan besvärats av EN SUGANDE KÄNSLA I ÖVRE DELEN AV MAGEN ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

17. Har Du under den senaste veckan besvärats av ILLAMÅENDE ELLER KRÄKNINGAR ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

18. Har Du under den senaste veckan besvärats av RAPNINGAR ?

Inga besvär alls	
Obetydliga besvär	
Milda besvär	
Måttliga besvär	
Ganska svåra besvär	
Svåra besvär	
Mycket svåra besvär	

Har du det senaste året haft något av följande?

	Ja	Nej
Blod på pappret när du torkar dej?		
Synligt blod eller blodtillblandad avföring när du tittar ner i toalettstolen?		
Svart avföring?		
Ändrade avföringsvanor?		
Ofrivillig viktnedgång?		

Tar du för närvarande något läkemedel som är:

Blodförtunnande eller förebyggande mot blodpropp (t ex Waran, Trombyl, Persantin, Clopidogrel, Heparin)

om ja, vilket/vilka?.....

……..

Mot värk eller inflammation (även receptfria läkemedel)?

om ja, vilket/vilka?.....

……..

Mot högt blodtryck eller för hjärtat?

om ja, vilket/vilka?.....

……..

Tack för din medverkan!

Appendix B

Patient:……..(etikett eller personnr)

Frågor till dig som ordinerat F-Hb eller F-kalprotektin

På tre hälsocentraler i Jämtland pågår en studie i samarbete med Umeå Universitet med syftet att undersöka värdet av anamnes och F-Hb för diagnostik av kolorektalcancer, samt om F-kalprotektin kan förbättra diagnostiken. Studien är godkänd av Regionala etikprövningsnämnden i Umeå och svaren bearbetas kodade. Jag hoppas att du kan besvara nedanstående frågor om en patient du nyligen träffat:

Hade patienten något/några av följande symptom eller undersökningsfynd?

	Ja	**Nej**	**Vet ej/ ej undersökt**
1. Ont i magen?	□	□	□
2. Hård avföring?	□	□	□
3. Lös avföring?	□	□	□
4. Trängningar till avföring (bråttom till toaletten)?	□	□	□
5. Känsla av att inte kunna tömma tarmen?	□	□	□
6. Ändrade avföringsvanor?	□	□	□
7. Halsbränna och/eller sura uppstötningar?	□	□	□
8. Blod på toalettpappret eller i toalettstolen?	□	□	□
9. Svart avföring?	□	□	□
10. Ofrivillig viktnedgång?	□	□	□
11. Palpabel resistens i buken?	□	□	□
12. Anemi?	□	□	□

13. Annat symptom, undersökningsfynd eller provsvar som orsak till ordination av prov?

……..

Lägg den ifyllda enkäten i diktathögen till sekreterarna.

Tack för din medverkan!

Cecilia Högberg, Distriktsläkare, Hälsocentralen Krokom. Tel 0640-16600.

Sekreterare: Lägg enkäten i Cecilia Högbergs postfack.

Appendix C

Intervjuguide

Anställd vid:

Ålder:
Leg läk år:
Spec allmänmedicin år:

Plats:

Datum och tid:

Inledning: Kolorektalcancer vanligt, svår diagnos, bristande kunskaper om diagnostik, F-Hbs roll. Inga rätt eller fel svar finns på frågorna.

Hur funderar du kring diagnostik av kolorektalcancer? Hur gör du? Vad väcker misstanken?

Vilka symptom har störst betydelse? Vad talar för utredning? Mot?
"Ändrade avföringsvanor": Vad beskriver patienten när du använder det begreppet?
Ser du någon skillnad på kvinnor och män när det gäller symptom? Utredning?
Skillnader misstanke/utredning yngre/äldre?

Egna erfarenheter av patienter som fått diagnosen?

Om du tar några prover – vilka prover tar du?
På vilka patienter? Utifrån symptom, ålder, patientens önskemål, hereditet?
Hur värderar du resultat av olika prover?
Vad tycker du att resultatet av F-Hb-prov ger dig för information?
Anemi med negativt F-Hb?

Tankar kring beslut att remittera respektive avstå från utredning?
Vad talar för remiss? Vad talar mot?
Hur tänker du kring restid till sjukhuset? Vad tror du att patienten tycker?
Avstå från utredning trots positivt F-Hb – i så fall när?
Avstå från utredning vid anamnes på rektal blödning samt negativt F-Hb?

Tumregler? (Tankegång som används under konsultationen och som kommer automatiskt) För att börja utredning? För remiss?

Osäkerhet. Hur hanterar du den?

Vad har du för erfarenheter av patienter (egna eller andras) där diagnos blivit fördröjd?

Ändring av praxis över tid?

Hur fungerar utredning av kolorektalcancer i praktiken?
Idealtillstånd? Hur skulle du beskriva det?
Vad skulle förbättra för dig?

Tillägga något mer?