Accepted Manuscript

British Journal of General Practice

The Fast Track FIT study: diagnostic accuracy of faecal immunochemical test for haemoglobin in patients with suspected colorectal cancer

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DOI: https://doi.org/10.3399/BJGP.2020.1098

To access the most recent version of this article, please click the DOI URL in the line above.

Received 09 December 2020
Revised 21 February 2021
Accepted 24 March 2021

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Running title: Fast Track FIT

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Abstract

Background

The faecal immunochemical test (FIT) is now available to support clinicians in the assessment of patients at low risk of colorectal cancer (CRC) and within the Bowel Cancer Screening Programme.

Aim

To determine the diagnostic accuracy of FIT for CRC and clinically significant disease in patients referred because they were judged by their GP to fulfil NICE NG12 criteria for suspected CRC.

Design and Setting

Patients referred from primary care with suspected CRC, meeting NG12 criteria, to 12 secondary care providers in Yorkshire and Humber were asked to complete a FIT prior to investigation.

Method

The diagnostic accuracy of FIT based upon final diagnosis was evaluated using receiver operating characteristics analysis. This permitted a statistically optimal cut-off value for FIT to be determined based on the maximisation of sensitivity and specificity. Clinicians and patients were blinded to the FIT results.

Results

5040 patients were fully evaluated and CRC was detected in 151 (3%).

An optimal cut-off value of 19 μg Hb/g faeces for CRC was determined, giving a sensitivity of 85.4% (78.8-90.6%) and specificity of 85.2% (84.1-86.2%). The negative predictive value at this cut-off value was 99.5% (99.2-99.7%) and the positive predictive value 15.1% (12.8-17.7%).

Sensitivity and specificity of FIT for CRC and significant premalignant polyps at this cut-off value were 62.9% (57.5-68.0%) and 86.4% (85.4-87.4%) respectively and when including all organic enteric disease were 35.7% (32.9-38.5%) and 88.6% (87.5-89.6%).

Conclusions

FIT used in patients fulfilling NICE NG12 criteria should allow for a more personalised CRC risk assessment. FIT should permit effective, patient-centred decision-making to inform the need for, type and timing of further investigation.

Authorship Statement:

JLT is the guarantor of the article. JLT was the chief investigator, directed the study and wrote the first draft. LJ, AG and TH undertook the laboratory analysis. MH managed the study, data collation and assisted in the preparation of the manuscript. DC provided primary care oversight, support for the study with training and communication and advice to JLT. AM, AK and JLT have carried out the statistical analysis. DT provided laboratory oversight, advice to JLT and assisted in the preparation of the manuscript. The final version is approved by all the authors.

Acknowledgements

We thankfully acknowledge the research teams at the following sites:

York Teaching Hospitals NHS Foundation Trust; Barnsley Hospital NHS Foundation Trust; The Rotherham NHS Foundation Trust; North Lincolnshire and Goole NHS Foundation Trust; Airedale NHS Foundation Trust; The Mid Yorkshire Hospitals NHS Foundation Trust; Calderdale and Huddersfield NHS Foundation Trust; Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust; Harrogate and District NHS Foundation Trust; Leeds Teaching Hospitals NHS Foundation Trust; Sheffield Teaching Hospitals NHS Foundation Trust; Bradford Teaching Hospitals NHS Foundation Trust.

Study funding/potential conflicts of interest

This study has been funded by the Humber Coast Vale Cancer Alliance. It was supported by Alpha Laboratories Ltd, Eastleigh SO50 4NU, who provided the HM-JACKarc analyser and supplied collection devices and reagents free of charge or at a discounted price.

JLT has given a presentation on FIT at a Digestive Diseases Day held by Alpha Laboratories Ltd in November 2017. AK is a member of the York Teaching Hospital NHS Foundation Trust Research and Development Group. All other authors have no conflicts of interest.

How this fits in

The role of FIT in the assessment of patients at high risk of colorectal cancer is uncertain. FIT has a high sensitivity and specificity for colorectal cancer with an area under the curve of 0.89. Some patients in whom FIT sufficiently alters their risk should no longer be investigated within the 'two week wait' pathway. However FIT is an imperfect diagnostic test for colorectal disease and will miss some patients, currently referred, who have CRC, other significant premalignant polyps, inflammatory bowel disease and other non-colorectal cancer. FIT should be used in all patients at high risk of colorectal cancer to inform the need for, and type and timing of further investigation. Studies are needed to understand how best to optimise the benefits of FIT in the clinical context of patients fulfilling NICE NG12 referral criteria for suspected colorectal cancer.

Introduction

The National Institute for Health and Care Excellence (NICE) has issued guidance to help GPs identify those patients at increased risk of colorectal cancer (CRC) (NICE NG12).[1] These recommendations are largely symptom based, modified by age. The guidance is underpinned by a 'two week wait' referral pathway to secondary care and other national targets for timeliness in treatment.[2] Delivering these diagnostic and treatment targets has proved very challenging for secondary care providers.[3-6] There has been a yearly increase in 'two week wait' referrals of patients with suspected CRC but, despite this, the number of CRC cases detected through this pathway has changed little.[7] Since the prevalence of CRC in this cohort of patients is 3-5% large numbers of often elderly and frail patients undergo unnecessary, invasive, unpleasant and expensive investigations, which are not without risk of complication.[8] Because investigative capacity (notably colonoscopy and computed tomography (CT) scans) is constrained, the investigative burden placed on secondary care by NG12 has had the indirect effect of limiting the availability of investigative resource to support other CRC diagnostic pathways.[9-11]

Faecal immunochemical test (FIT), a quantitative test for human haemoglobin in faeces has been recommended to guide referral of patients who are considered to be at 'low risk' of CRC.[12-14] A FIT ≥10 µg Hb/g faeces escalates the patient into the 'two week wait' pathway. FIT is also used in the Bowel Cancer Screening Programme (BCSP) where the cut-off value is set higher, at 120 µg Hb/g faeces.[15] There is increasing interest in whether FIT has a role in decision making for all patients fulfilling NICE NG12 criteria. It has been postulated in previous studies that FIT might refine and improve the diagnostic pathway for CRC in these patients. Initial studies suggested that FIT has a sensitivity and specificity of 84.6% and 88.5% respectively for CRC in the context of patients fulfilling the NG12 referral guidance.[16]

We undertook a diagnostic accuracy study of FIT in patients referred through the 'two week wait' pathway with suspected CRC. FIT was provided prior to secondary care investigation and assessed against final diagnosis for CRC (primary outcome) and for CRC, significant premalignant polyps, inflammatory bowel disease (IBD) and other organic enteric disease (OED) combined (secondary outcomes). Additionally, we sought to identify all clinically significant disease detected in those referred patients in order to obtain a true picture of the benefits of the current NG12 guidance.

Methods

Study design

Ethical approval (REC14/EM/0217) was obtained to conduct a prospective, blinded multi-centre diagnostic accuracy study of FIT for clinical outcomes in patients referred with suspected CRC within the 'two week wait' pathway from 25/04/2018 to 31/12/2019**.**

Participants

Twelve secondary care providers across Yorkshire and Humber were involved in this study. It was conducted following the STAndards for the Reporting of Diagnostic accuracy studies guidelines.[17] A referral proforma containing the NICE NG12 referral criteria was used by GP to access the 'two week wait'. At each site a convenience series of patients attending dedicated 'two week wait' colorectal outpatient or telephone clinics were consented for the study by a research nurse. The 'convenience' related to the availability of the research nurse rather than any patient characteristics. Patient symptoms and relevant medical history were recorded. Whilst GP were guided by the NICE NG12 referral criteria, a formal assessment of compliance was deliberately not undertaken to ensure that the study was representative of the population currently being referred.

Test methods

The consenting process was independent of any decision by the responsible clinician to investigate the patient. Symptomatology, patient demographics and index for multiple deprivation, use of non-steroidal anti-inflammatory drugs (NSAID), antiplatelet or anticoagulant therapy, relevant personal and family history and baseline blood tests were recorded. The decision to investigate was made on clinical grounds at the discretion of the responsible clinician. Patients and clinicians were blinded to the FIT result throughout. Only patients undergoing full colonoscopy or CT colonography or a lesser investigation (such as CT abdomen/pelvis with contrast or flexible sigmoidoscopy) to the identification of pathology were included in the data analysis.[18] Relevant data and final diagnoses accessed from patient management systems were stored anonymously on an electronic Case Report Form. Significant premalignant polyps are defined as adenomatous or hyperplastic lesions with high-grade dysplasia or when ≥10mm or if ≥5 subcentimetre polyps (excluding hyperplastic rectal polyps).[19] OED includes IBD, microscopic colitis, radiation proctopathy and those cases where the responsible clinician judged the referral diagnosis to be diverticular disease. IBD is reported separately from other OED in some statistical analysis. Asymptomatic, moderate diverticulosis or that described as minor or mild was not included within OED. When no CRC, significant polyp or OED diagnosis was made, the diagnosis was reported as irritable bowel syndrome (IBS), haemorrhoidal bleeding or iron deficiency, no cause found, as appropriate. For the purposes of the study we have grouped this cohort as 'other functional diagnoses'.

FIT analysis

Consenting patients collected a single faecal sample using an EXTEL HEMO-AUTO MC collection device between their out-patient consultation and subsequent investigation. FIT analysis was performed using an automated turbidometric system, HM-JACKarc (Kyowa-Medex Co., Ltd, supplied by Alpha Laboratories Ltd, Eastleigh SO50 4NU). Calibration was

performed in line with the manufacturer's instructions and internal quality control samples provided by the manufacturer were analysed in each batch. The analytical co-efficient of variation (% CV) between batch was 4.6% at a concentration of 27 µg Hb/g faeces and 3.6% at a concentration of 102 µg Hb/g faeces. External Quality Assessment samples from UK NEQAS were analysed regularly. The manufacturer's quoted limit of quantitation of 7 µg Hb/g faeces (imprecision <10% CV), analytical range of 7-400 µg Hb/g faeces and limit of detection of 2 µg Hb/g faeces were used in this study.

Sample size

Using an expected CRC incidence of 3-5% we aimed to recruit a minimum of 5000 patients in order to achieve a representative sample for this diagnostic accuracy study.[14]

Statistical analysis

For the purposes of this study, the primary diagnostic accuracy analyses of FIT in detecting CRC and the secondary clinical outcomes were derived using receiver operating characteristics (ROC) curves. The point on the ROC curve that maximises both sensitivity and specificity was used to determine a statistically optimal cut-off value. Estimates of the area under the curve (AUC), sensitivity, specificity, negative (NPV) and positive (PPV) predictive values were calculated (using the optimal cut-off value for the latter four measures) and presented alongside 95% confidence intervals (CI).

Since the optimisation of FIT may ultimately be determined by a composite of clinical factors beyond Youden's index, the sensitivity, specificity, NPV and PPV of FIT were, in addition, calculated for cut-offs of 2 (the limits of detection), 10, 30, 100 and 300 µg Hb/g faeces.

The proportion of disease cases versus non-disease cases within different ranges of FIT were explored graphically.

Results

Participants

In total, 5153 patients were recruited (Figure 1 & Supplementary Table S1). The mean age was 67.4 (SD 11.7) years and 2852 (55.3%) of the patients were female. The most common presenting symptoms were diarrhoea (1872; 36.3%), abdominal pain (1746; 33.9%) and fresh rectal bleeding (1721; 33.4%). Approximately 10% of patients had a family history of colorectal cancer, with 1389 (27.0%) using either antiplatelet therapy, anticoagulants or NSAIDs (Supplementary Table S1 and S2). Of the 5153 recruited patients, 113 (2.2%) either declined or were not offered any formal investigations and were excluded from the primary and secondary analyses (Supplementary Tables S3 and S4). The most common investigations were colonoscopy (3857; 76.5%), CT colonography (751; 14.9%) and CT of the abdomen or pelvis (1086; 21.5%) (Supplementary Table S5). Final diagnoses were 3% CRC (n=151), 4% significant polyps (n=206), 2% IBD (n=100), 15% OED (n=771), 14% diminutive colorectal polyps (n=682), 8% significant non-enteric disease (n=418) and 54% other functional diagnoses (n=2712) (Supplementary Table S6).

Primary analysis:

Diagnostic accuracy of FIT for colorectal cancer

CRC was detected in 151 (3.0%) of the 5040 patients evaluated. An optimal cut-off value of 19 μg Hb/g faeces was determined giving a sensitivity of 85.4% (78.8-90.6%) and specificity of 85.2% (84.1-86.2%), a PPV of 15.1% (12.8-17.7%) and NPV of 99.5% (99.2-99.7%) (Table 1 and Supplementary Table S7). The AUC was estimated to be 0.89 (0.86-0.92) (Supplementary Figure S1). Using this threshold, 854 (16.9%) patients were considered to have a positive FIT and of whom 129 had CRC whilst 4186 patients (85.4%) were considered to have a negative FIT with 22 (14.6%) having CRC. The location of the CRC, whether right or left sided or rectal did not alter the diagnostic accuracy of FIT. The sensitivity, specificity, PPV and NPV of FIT for CRC at 5 different fixed positivity thresholds from 2 to 300 μg

Hb/g faeces was determined and the proportion of CRC based on different FIT ranges is presented graphically (Table 2 and Figure 2). An exploratory analysis of the tumour stage of the TNM Classification of Malignant Tumours was available on 114 patients with CRC. Of the 19 patients with CRC and FIT ≤18 μg Hb/g faeces 30.8% were T1, 19.4% T2, 10.2% T3 and 19.0% T4 (Supplementary Table S6).

Subgroup analyses: symptoms, demographics and drugs

Subgroup analyses were performed across a range of demographics, symptoms and the use of drugs to identify subgroup specific FIT optimal cut-off values (Table 1 and Supplementary Table S7). There were no differences in the sensitivity of FIT in the subgroup analyses. However the specificity of FIT differed in the following subgroups: change in bowel habit, constipation, abdominal pain and drug use.

Secondary analyses:

Diagnostic accuracy of FIT for CRC, significant polyps, IBD and all OED

In total, 342 (6.8%) patients had the secondary outcome of having either CRC or significant premalignant polyps, while 1147 (22.8%) had the secondary outcome of having either CRC, significant premalignant polyps, IBD or OED (Supplementary Table S6). The diagnostic accuracy of FIT in this setting was poorer and is presented both at the optimal cut-off value for each secondary analysis group and at 19 μg Hb/g faeces (Table 3). Here 717 patients with secondary diagnoses (72.1%) were 'FIT negative'. This represents 59.6% of the patients with significant premalignant polyps and 36% of the patients with IBD. The proportion of CRC or one of these secondary diagnoses based on the FIT range is presented graphically (Figure 3).

Opportunistic and non-enteric diagnoses

Of the 206 patients with significant premalignant polyps, only 43% had symptoms of rectal bleeding or rectal mass, the remainder should be considered opportunistic findings. A further 682 patients were found to have opportunistic, low risk premalignant polyps, 84.0% of whom

had a FIT below 19µg Hb/g faeces. Significant non-enteric disease that required onward medical management was found in 418 (8.3%) additional patients, of whom 83 had non-colorectal cancers (Supplementary Table S6).

Discussion

Summary

This diagnostic accuracy study, recruiting over 5000 patients in a convenience series represents as closely as pragmatically possible, the population of adults seen within primary care with symptoms judged to be high-risk for CRC. The index for multiple deprivation seen across the 12 NHS Hospital Trusts in Yorkshire and Humber in this study broadly mirrors that in England and includes a number of large conurbations with an ethnic diversity. Colonoscopy, CTC or flexible sigmoidoscopy and abdomino-pelvic CT were performed on 92% of patients.[19] Only 33 patients were excluded from the evaluation as they underwent no secondary care investigation. This likely reflects the current clinical imperative of secondary care to investigate patients referred with suspected CRC. A statistically optimal cut-off value of 19 µg Hb/g faeces for CRC was determined using ROC curves, giving a sensitivity of 85.4% (78.8-90.6%) and specificity of 85.2% (84.1-86.2%). The negative predictive value at this cut-off value was 99.5% (99.2-99.7%) and the positive predictive value 15.1% (12.8-17.7%).

Comparisons with existing literature

Previous smaller diagnostic accuracy studies quoted a sensitivity for CRC of very close to 100% for FIT.[20,21] Subsequently it became clear that, dependent upon the cut off chosen, FIT will miss between 7-15% of patients with CRC.[22-24] The sensitivity and specificity of FIT for CRC in our study aligns with the smaller studies that recruited patients fulfilling NICE NG12 criteria.[16,25] Our previous study determined the optimal cut-off value for FIT to be ≥12 µg Hb/g faeces. However in that study, faecal sampling into collection devices was performed in

the laboratory instead of by the patient and this may have resulted in some pre-analytic haemoglobin degradation.[26,27] The published study most comparable by design, since it too recruited patients exclusively referred through the 'two week wait' for CRC and used an HM-JACKarc analyser, found a similar sensitivity and specificity of 84% and 93% respectively.[25] In Scotland, where the Scottish Intercollegiate Guidance Network guidance produces a different referral population from NICE, FIT has a similar diagnostic accuracy to this study.[28,21,29,30] A similar sensitivity and specificity are obtained in the two other large diagnostic accuracy studies that have been conducted in England, the NICE FIT study and qFIT pilot study. The NICE FIT study, recently published, reports an AUC for CRC of 0.93 (0.92–0.95) and an optimal cut-off value for FIT of 38 μg Hb/g faeces.[31,32]

Strengths and limitations

This diagnostic accuracy study presents its findings in terms of the statistical optimisation of the sensitivity and specificity of FIT. The use of a statistically optimal cut-off value highlights the need for FIT to be considered as a tool by which to both minimise the risk of missing CRC and to optimise the use of investigative resource within a constrained healthcare system. There is an inevitable trade-off between the two. Reconciling that trade-off is a major healthcare challenge. Ultimately a detailed and comprehensive health economic analysis is required to determine the true clinical utility of FIT. This is beyond the scope of our study but, recognising the complexity of this task, the data have also been presented with a range of cut-off values from 2 (the limits of detection), 10, 30, 100 and 300 μg Hb/g faeces. Very little is yet known of the response of symptomatic patients and their clinicians to a FIT based assessment and the savings of investigative resource that might result. We judged therefore that using a statistical measure represented the appropriate starting point for that risk analysis. Using this approach a high sensitivity and specificity for FIT is retained across age and sex, symptoms and signs, medicines use and anaemia. The optimal cut-off value for

people ≥60 years (19 µg Hb/g faeces) is lower than for those <60 years (37 µg Hb/g faeces) and for women (16 µg Hb/g faeces) rather than men (21 µg Hb/g faeces).[33,16,34,35] Interestingly and contrary to NICE DG30 guidance, we found that FIT retained a high diagnostic accuracy in those with rectal bleeding, although the optimal cut-off value was higher in those with (37 µg Hb/g faeces) than without (10 µg Hb/g faeces) bleeding. It had previously been our experience with faecal calprotectin that the diagnostic accuracy of a faecal biomarker was preserved in the context of rectal bleeding.[36] We speculated that anal canal bleeding might coat rather than impregnate the faeces and thus not interfere with sampling from the centre of a formed faecal sample. Previous studies have also suggested that the diagnostic accuracy of FIT is lower in patients with anaemia but we did not find this to be the case in iron deficiency or iron deficiency anaemia.[21,23] In line with the qFIT pilot study the optimal cut-off value for those patients with abdominal pain was set lower at 10 µg Hb/g faeces.[32] Lastly only in the small subgroup of patients who had an abdominal mass did FIT achieve a sensitivity of 100%. Otherwise FIT inevitably misses CRC in a small number of patients. Alternative approaches to using FIT, such as applying the lowest possible cut-off, either the limit of quantitation (7 µg Hb/g faeces) or limit of detection (2 µg Hb/g faeces) are unlikely to be effective in preventing missed CRC. They will improve the NPV of FIT by 0.1% at the cost of an inferior PPV and so will more than double the burden imposed on investigative resource. This trade-off also applies at the cut-off value 10 µg Hb/g faeces, as currently recommended by NHS E in its specialty guides for patient management during the coronavirus pandemic.[37] The imperfect nature of FIT at whatever cut-off value chosen reinforces the need for a formal, contextualised health economic analysis to determine a clinically, rather than necessarily statistically, optimal FIT cut-off value.[38]

Implications for research and/or practice

Whatever acceptable balance of risk is ultimately arrived at, we believe that FIT must primarily be used to 'democratise' the CRC risk assessment.[39] We believe that a personalised, optimal FIT cut-off value can, in future, be generated as a 'risk score' for an individual patient, based on sex, age, symptoms and signs, drug history and blood parameters. GP electronic requesting systems can be used to capture clinical indications for FIT requests and this can be linked together with demographic data, other blood results and FIT results in the laboratory information system. This data could be used in future by an automated algorithm to generate a personalised risk score to accompany or replace the numerical FIT result and this risk score could then be reported along with recommendations on referral or management based upon that risk score.

That personalised CRC risk next needs to be incorporated into a personalised clinical assessment of the patient. This is the challenge. This study demonstrates that 'FIT negative' patients with NICE NG12 criteria for suspected CRC have a CRC risk of less than 0.5%. This may be lower than the prevalent risk of CRC in an equivalently aged asymptomatic population.[40,41] But more than one in five of the patients referred had an OED that required prompt diagnosis and management, even if not within the 'two week wait' timeframe. This includes 14.2% of the 'FIT negative' patients, such as those with IBD, where early diagnosis has been shown to minimise complications and the need for surgery.[42,43] In addition, another 8.3% of patients had significant non-enteric disease including other cancers, such as ovarian, pancreatic and renal cancer. In total, non-CRC malignancies accounted for 35.5% of all the cancer diagnoses in this study.[44] The opportunistic diagnosis of diminutive premalignant colorectal polyps represents a further cohort, currently undefined, of screening benefit for the population. Lastly, many of those with on-going functional symptoms and haemorrhoidal bleeding will remain symptomatic within a population previously considered high-risk for CRC. In England initial symptomatic treatment strategies are not currently offered in these

patients as they are in Scotland.[45-48] Whilst only 16.9% of 'two week wait' patients referred in this study had a 'positive FIT', this will not represent the proportion of patients ultimately referred to secondary care in any future FIT based pathway. We have previously estimated that 25% might be spared investigation by the use of a faecal biomarker and the resolution of symptoms.[49]

FIT can reduce CRC risk well below the 3% threshold upon which the NICE NG12 guidelines were devised. However, currently it is not known what alternative management strategies are required to support optimal patient and clinician decision-making on the need for, and type and timing of investigations.[50-53] Investigation is not risk free and for many frail patients that risk will now exceed any benefit that could be derived from early diagnosis of disease.[54,55] If FIT could spare unnecessary investigation and re-direct resource to other diagnostic pathways, such as the BCSP, there could be a net significant health economic benefit for the wider population.[9-11] Those NG12 patients with CRC missed because of a 'negative FIT' would be offset by the increased number of detected participants with CRC within the BCSP.

Conclusion

FIT has a high diagnostic accuracy for CRC and should be used in the clinical assessment of all patients fulfilling NICE NG 12 criteria for suspected CRC.[37,56,57] Patients in whom FIT sufficiently alters that risk assessment should no longer be investigated within the 'two week wait'. However it is important to recognise that FIT will miss some patients with CRC, OED and non-GI pathology currently identified using NG12 criteria. FIT allows for a re-design of the current, largely symptom based, referral process defined in NG12 into a novel, risk based decision-making pathway for the care for patients with abdominal symptoms. If properly developed and applied the net benefit of using FIT as an alternative to a symptom based

referral criteria could be the optimised early diagnosis of CRC and reduced morbidity and mortality for the whole population.

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Tables

	N	cases, n (%)	optimal cut-off, µg/g	sensitivity (95% CI), %	specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %	AUC (95% CI)
Primary outcome								
All participants with formal investigations	5040	151 (3.0)	19	85.4 (78.8-90.6)	85.2 (84.1-86.2)	15.1 (12.8-17.7)	99.5 (99.2-99.7)	0.89 (0.86-0.92)
Subgroup analyses								
Age								
<60	1217	30 (2.5)	37	90.0 (73.5-97.9)	87.4 (85.4-89.3)	15.3 (10.4-21.5)	99.7 (99.2-99.9)	0.92 (0.88-0.96)
≥60	3823	121 (3.2)	19	83.5 (75.6-89.6)	85.4 (84.2-86.5)	15.7 (13.0-18.8)	99.4 (99.0-99.6)	0.88 (0.85-0.92)
Sex								
Male	2242	89 (4.0)	21	85.4 (76.3-92.0)	83.7 (82.0-85.2)	17.8 (14.3-21.7)	99.3 (98.8-99.6)	0.89 (0.86-0.93)
Female	2798	62 (2.2)	16	87.1 (76.1-94.3)	85.6 (84.2-86.9)	12.0 (9.2-15.4)	99.7 (99.3-99.9)	0.88 (0.82-0.93)
Change in bowel habit								
Yes	3467	89 (2.6)	16	85.4 (76.3-92.0)	85.8 (84.5-86.9)	13.6 (10.9-16.8)	99.6 (99.2-99.8)	0.89 (0.85-0.93)
No	1573	62 (3.9)	21	87.1 (76.1-94.3)	82.3 (80.2-84.2)	16.8 (12.9-21.3)	99.4 (98.7-99.7)	0.89 (0.84-0.93)
Rectal bleeding								
Yes	1912	77 (4.0)	37	90.9 (82.2-96.3)	83.2 (81.4-84.8)	18.5 (14.7-22.7)	99.5 (99.1-99.8)	0.90 (0.87-0.93)
No	3128	74 (2.4)	10	79.7 (68.8-88.2)	84.0 (82.6-85.3)	10.8 (8.3-13.7)	99.4 (99.0-99.7)	0.87 (0.82-0.92)
Abdominal pain								
Yes	1722	47 (2.7)	10	85.1 (71.7-93.8)	82.5 (80.6-84.3)	12.0 (8.7-16.0)	99.5 (99.0-99.8)	0.88 (0.83-0.93)
No	3318	104 (3.1)	37	85.6 (77.3-91.7)	88.4 (87.2-89.5)	19.2 (15.7-23.1)	99.5 (99.1-99.7)	0.90 (0.86-0.93)
Weight loss								
Yes	1093	38 (3.5)	13	89.5 (75.2-97.1)	83.1 (80.7-85.3)	16.0 (11.4-21.7)	99.5 (98.8-99.9)	0.88 (0.82-0.94)
No	3947	113 (2.9)	19	85.8 (78.0-91.7)	85.0 (83.8-86.1)	14.4 (11.9-17.3)	99.5 (99.2-99.7)	0.89 (0.86-0.93)
ID anaemia[†]								
Yes	559	34 (6.1)	21	82.4 (65.5-93.2)	81.5 (77.9-84.8)	22.4 (15.4-30.7)	98.6 (97.0-99.5)	0.87 (0.80-0.93)
No	3582	101 (2.8)	19	88.1 (80.2-93.7)	85.3 (84.0-86.4)	14.8 (12.0-17.9)	99.6 (99.3-99.8)	0.90 (0.87-0.93)

Table 1: Primary outcome analysis and subgroup analyses. †Number of patients and cases do not add up to 5040 and 151 respectively due to missing anaemia and ID status.

Abbreviations: ID: iron deficiency.

	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
FIT ≥ 2 µg /g	92.7 (87.3-96.3)	60.7 (59.3-62.1)	6.8 (5.7-8.0)	99.6 (99.3-99.8)
FIT ≥ 10 µg/g	87.4 (81.0-92.3)	80.9 (79.7-81.9)	12.4 (10.4-14.5)	99.5 (99.3-99.7)
FIT ≥ 30 µg/g	80.1 (72.9-86.2)	87.7 (86.8-88.6)	16.8 (14.1-19.7)	99.3 (99.0-99.5)
FIT ≥ 100 µg/g	66.2 (58.1-73.7)	92.7 (91.9-93.4)	21.8 (18.1-25.8)	98.9 (98.5-99.2)
FIT ≥ 300 µg/g	53.0 (44.7-61.1)	95.1 (94.5-95.7)	25.2 (20.5-30.3)	98.5 (98.1-98.8)

Table 2: Diagnostic accuracy of FIT in detecting the primary outcome of colorectal cancer at thresholds of 2, 10, 30, 100 and 300 µg Hb/g faeces. Abbreviations: µg/g: µg Hb/g faeces

	N	cases, n (%)	optimal cut-off, µg/g	sensitivity (95% CI), %	specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %	AUC (95% CI)
Secondary outcomes								
CRC or sig. polyps	5040	342 (6.8)	7	69.6 (64.4-75.4)	78.9 (77.7-80.0)	19.3 (17.2-21.7)	97.3 (96.7-97.8)	0.79 (0.76-0.82)
CRC, sig. polyps or IBD*	5040	442 (8.8)	6	69.9 (65.4-74.2)	78.6 (77.4-79.8)	23.9 (21.6-26.4)	96.5 (95.8-97.0)	0.80 (0.77-0.82)
CRC, sig. polyps, IBD or OED	5040	1147 (22.8)	2	56.7 (53.7-59.6)	63.8 (62.2-65.3)	31.6 (29.5-33.6)	83.3 (81.9-84.6)	0.64 (0.62-0.66)
Diagnostic accuracy of FIT in detecting each secondary outcome using a cut-off of 19 µg Hb/g faeces								
CRC or sig. Polyps*				62.9 (57.5-68.0)	86.4 (85.4-87.4)	25.2 (22.3-28.2)	97.0 (96.4-97.5)	
CRC, sig. polyps or IBD*				63.1 (58.4-67.6)	87.5 (86.5-88.4)	32.7 (29.5-35.9)	96.1 (95.5-96.7)	
CRC, sig. polyps, IBD or OED*				35.7 (32.9-38.5)	88.6 (87.5-89.6)	47.9 (44.5-51.3)	82.4 (81.1-83.5)	

Table 3: Secondary outcome analyses. *Exploratory analysis; Abbreviations: CRC: colorectal cancer, sig. polyps: significant premalignant polyps, IBD: inflammatory bowel disease, OED: organic enteric disease, µg/g: µg Hb/g faeces

Figures

Figure 1: Flow of participants from attendance in 'two week wait clinics for suspected CRC through to formal evaluation.

Figure 2: Proportion of CRC at different FIT level (µg Hb/g faeces) ranges. Footnote: Each data point represents the midpoint of consecutive FIT level ranges. Readings below 2 are represented by a value of 1 and readings of 400 and above are represented by a value of 400. Lines represent automatically fitted power trendlines.

Figure 3: Proportion of disease cases (CRC with significant premalignant polyps, IBD and all OED) at different FIT level (µg Hb/g faeces) ranges. Footnote: Each data point represents the midpoint of consecutive FIT level ranges. Readings below 2 are represented by a value of 1 and readings of 400 and above are represented by a value of 400. Lines represent automatically fitted power trendlines.