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ORIGINAL ARTICLE

'Low' faecal immunochemical test (FIT) colorectal cancer: a 4-year comparison of the Nottingham '4F' protocol with FIT10 in symptomatic patients

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Abstract

Aim: The aim of this work was to evaluate colorectal cancer (CRC) outcomes after 'low' (sub-threshold) faecal immunochemical test (FIT) results in symptomatic patients tested in primary care.

Method: This work comprised a retrospective audit of 35 289 patients with FIT results who had consulted their general practitioner with lower gastrointestinal symptoms and had subsequent CRC diagnoses.

The Rapid Colorectal Cancer Diagnosis pathway was introduced in November 2017 to allow incorporation of FIT into clinical practice. The local '4F' protocol combined FIT results with blood tests and digital rectal examination (DRE): FIT, full blood count, ferritin and finger [DRE]. The outcome used was detection rates of CRC, missed CRC and time to diagnosis in local 4F protocols for patients with a subthreshold faecal haemoglobin (fHb) result compared with thresholds of 10 and 20 μg Hb/g faeces.

Results: A single threshold of 10 μg Hb/g faeces identifies a population in whom the risk of CRC is 0.2%, but this would have missed 63 (10.5%) of 599 CRCs in this population. The Nottingham 4F protocol would have missed fewer CRCs [42 of 599 (7%)] despite using a threshold of 20 μg Hb/g faeces for patients with normal blood tests. Subthreshold FIT results in patients subsequently diagnosed with a palpable rectal tumour yielded the longest delays in diagnosis.

Conclusion: A combination of FIT with blood results and DRE (the 4F protocol) reduced the risk of missed or delayed diagnosis. Further studies on the impact of such protocols on the diagnostic accuracy of FIT are expected. The value of adding blood tests to FIT may be restricted to specific parts of the fHb results spectrum.

KEYWORDS
blood tests, colorectal cancer, digital rectal examination, Faecal immunochemical testing

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer death in the UK, with over 42000 diagnoses a year [1]. Stage is the most significant predictor of survival. Asymptomatic screening identifies more CRCs at an earlier stage [2], but improvements in early stage diagnosis for symptomatic patients have remained elusive despite efforts such as the two-week-wait (2WW) pathway. National guidelines have focused on age and symptom-based criteria to identify patients who require investigation [3], but there is no evidence that this has achieved favourable stage migration. Furthermore, these guidelines have increased pressure on diagnostic services, precluding the optimization of Bowel Cancer Screening Programme (BCSP) sensitivity.

The evidence for faecal immunochemical testing (FIT), which detects blood in faeces, in symptomatic patients has grown rapidly since the National Institute for Health and Care Excellence (NICE) 2015 guidelines for urgent referral [3, 4]. Recent guidelines from speciality associations and NICE endorse the use of FIT in symptomatic patients, with faecal haemoglobin (fHb) ≥10 μg Hb/g faeces triggering 2WW referral and consideration of other pathways below this threshold [5, 6]. A pooled analysis of 15 studies including 48872 patients tested in primary care yielded a sensitivity of 87.2% (95% CI 81.0%–91.6%) and a specificity of 84.4% (95% CI 79.4%–88.3%) at ≥10 μg Hb/g faeces for CRC [7]. A threshold of ≥20 μg Hb/g faeces missed less than one additional CRC per 1000 patients. Several studies have observed optimal FIT thresholds of 20 μg Hb/g faeces or higher [8, 9], which may reduce the number needed to scope for each CRC for a more efficient service; however, the potential of missing 13% of CRCs that might otherwise be referred urgently raises understandable concerns. Safety-netting remains pivotal to successful roll out of symptomatic FIT pathways.

The Nottingham Colorectal Service introduced FIT into its urgent symptomatic pathway in November 2017 [10]. Digital rectal examination (DRE) is recommended on every 'negative' FIT result. Anaemia or thrombocytosis prompts a lower cut-off of 4 μg Hb/g faeces for 2WW investigation. Ferritin was added in 2018. In early 2020 the cut-off for patients with normal bloods was raised to 20 μg Hb/g faeces, based on continuous audit (Appendix S1). In combination, FIT, DRE ('finger'), full blood count (FBC) and ferritin constitute our '4F' protocol in symptomatic patients. Here we present a retrospective analysis of CRC outcomes after the introduction of FIT in the 4 years between November 2017 and December 2021, focusing on patients with a FIT result below the threshold of investigation. Our 4F protocol is compared with single cut-offs of 10 μg Hb/g faeces (FIT10) and 20 μg Hb/g faeces (FIT20) in patients without rectal bleeding or palpable rectal mass.

What does this paper add to the literature?

Combining the faecal immunochemical test (FIT) with blood results and rectal examination for patients presenting to primary care with symptoms suggestive of bowel cancer can reduce the risk of missed cancers compared with a single threshold for 'negative' FIT.

METHOD

Rapid colorectal cancer diagnosis pathway (RCCD)

When a patient presents to primary care with symptoms that may be suggestive of bowel cancer, the general practitioner (GP) is advised to request a FIT and perform DRE, the result of which is used to guide referral to secondary care. The Nottingham pathway incorporates FIT as a triage tool for all referral criteria (except rectal bleeding and palpable mass, described elsewhere) (Appendix S1) [11–13]. FIT and FBC (and ferritin from November 2018 onwards) were mandated irrespective of symptoms or age by local agreement with primary care and used to prioritize access to urgent investigations, with iterative changes guided by the latest evidence (Appendix S2). This study describes the CRC outcomes for all FITs requested in primary care 4 years after introduction, focusing on patients returning a 'low' or 'negative' FIT.

FIT requests and testing

FIT requests in primary care are made on an electronic system that prompts blood tests where indicated. Results are via the same system with guidance on interpretation and subsequent actions. FIT dispatch and return are by post, with analysis using the OC-Sensor™ platform (Eiken Chemical Co., Tokyo, Japan) by our accredited BCSP hub laboratory (Appendix S3) [13].

Results and advice

Patients with a FIT result <4 μg Hb/g faeces, or ≥4 but <20 μg Hb/g faeces with normal Hb (≥130 g/L in men and ≥120 g/L in women), ferritin (25–349 ng/ml) and platelet count $<400\times10^9$/L are considered 'negative' or 'low', with low CRC risk. For these patients, GPs are advised on safety-netting: consideration of an alternative pathway, routine referral or repeat FIT, alongside watchful waiting if their concerns are assuaged by FIT, with a prompt to undertake DRE if not completed.

Patients with FIT results >4 μg Hb/g faeces (or 20 μg Hb/g faeces with normal bloods) are advised to be referred urgently on a suspected cancer pathway. FIT results ≥100 μg Hb/g faeces are flagged to the RCCD vetting team who initiate patient contact for immediate investigation via OSCARS (one-stop surgical assessment, colonoscopy and radiological staging). OSCARS endoscopy lists are delivered by accredited colorectal surgeons with dedicated radiology slots, enabling patients to receive a likely diagnosis, staging and outline of possible management options in one visit.

Cohort and data collection

All patients referred to the Nottingham Colorectal Service on an RCCD form are logged prospectively. Cancer Outcomes and Services Datasets (COSDs) are used to evaluate diagnoses of CRC recorded using ICD codes C18–C20 (excluding C18.1, see the Appendix) with a censor date of 31 December 2021. Trust data and electronic patient records and databases were used for cross-checking and diagnostic validation for all patients sent a FIT between November 2017 and 31 October 2021. This is described in depth elsewhere [14, 15]. Ethical was approval granted locally (NUH registration number 20-135C).

Statistical analysis

Histograms were used to assess normality. Continuous variables were compared using Student's *t*-test and analysis of variance if normally distributed, with Tukey's multiple comparison test for multiple groups. Mann–Whitney *U*, Kruskal–Wallis and Dunn's multiple comparison tests were used for nonparametric data. Comparisons were made between categorical data using the chi-square test.

Data were segmented and analysed by fHb according to the cut-offs used in our pathway as described above (<4, 4–19.9, 20–99.9 and ≥100 μg Hb/g faeces), with further segmentation for subanalysis of results between 4 and 99.9 μg Hb/g faeces at 10 μg Hb/g bands.

In the context of local protocols and the literature, fHb <20 μg Hb/g faeces was considered 'low FIT' [7, 8, 16], 20–99.9 μg Hb/g faeces 'intermediate FIT' [17] and ≥100 μg Hb/g faeces 'high FIT'. Time to diagnosis was considered the time in days from the FIT result to histological diagnosis of CRC. A patient was considered '4F positive' if they had a low FIT result of 4–19.9 μg Hb/g faeces with abnormal bloods tests or DRE.

Funding

The pathway was commissioned locally; all four local clinical commissioning groups approved and jointly funded this pathway. The cost of each FIT was agreed at £17.50 per sample, including postage, analysis and administration.

RESULTS

FIT usage and cohort cancer detection

We received 49 166 FIT requests during the evaluation period. Of these 8349 (17.0%) were repeat tests from 6640 patients, with a total population of 40 817 individuals. Analysable results were available for 38 920 patients (Figure 1). This population is described in detail elsewhere [14]. A total of 599 CRCs were detected (1.5%), the majority (58.6%) followed a FIT result of ≥100 μg Hb/g faeces. Thirty-eight CRCs (6.3%) were detected in the population that did not return their first FIT. Sixty-two of the 599 CRCs (10.3%) detected arose in the 6640 patients who returned more than one FIT test – a detection rate of 0.9% in the repeat test population.

FIT usage has steadily increased since its introduction into primary care, except for a dip with the arrival of COVID-19 (Figure S1). The number of CRCs diagnosed after FIT flattened out after steadily increasing during the first 12 months (Figure S1). CRC detection rates peaked with the dip in FIT requests during the first wave of the pandemic, with a decline thereafter to pre-pandemic levels, likely reflecting increased testing of a lower-risk population (Figure S1).

The CRC risk was 0.1% in those with fHb <4 μg Hb/g faeces, 0.2% <10 μg Hb/g faeces and 0.3% <20 μg Hb/g faeces (Figure 2).

CRC after low FIT (all <20 μg Hb/g faeces)

Eighty-eight patients were diagnosed with CRC after an initial FIT <20 μg Hb/g faeces, representing 14.7% of all CRCs (Table 1). There were no significant differences in the demographics of subsets defined by FIT result (<4, 4–9.9 and 10–19.9 μg Hb/g faeces). Of these, 48 (54.5%) were right-sided cancers (proximal to the splenic flexure, Table S1) and 14 (82.3%) of 17 rectal cancers subsequently diagnosed in this cohort were palpable on DRE in secondary care (despite being an exclusion for FIT). Over half of CRCs were Stage I or II. Twenty-three patients (26.1%) had an interval from FIT result to diagnosis of more than 180 days. Nine had repeat FIT, which was positive in seven, prompting referral. Other reasons for delay included patient choice and nonreferral despite eligibility. In the delayed group, eight (34.8%) patients were diagnosed at Stage I, four (17.4%) at Stage II, six (26.1%) at Stage III and four (17.4%) at Stage IV; staging was unavailable in one patient.

CRC <4 μg Hb/g faeces

Twenty-six patients with an initial FIT <4 μg Hb/g faeces were subsequently found to have CRC (Table 1) diagnosed via other pathways. Four patients had a subsequent positive FIT prompting referral. Sixteen (61.5%) patients had either abnormal blood tests or a palpable rectal mass. The median number of days from FIT result to diagnosis was 83.9 [interquartile range (IQR) 41.6–419.4] with a maximum of 1023 days. Three patients had a palpable rectal mass; this group had the longest delays to diagnosis (128–1009 days).

CRC 4–9.9 μg Hb/g faeces

Thirty-seven CRCs were diagnosed after initial FIT of 4–9.9 μg Hb/g faeces (Table 1), two after subsequent FIT and one at another

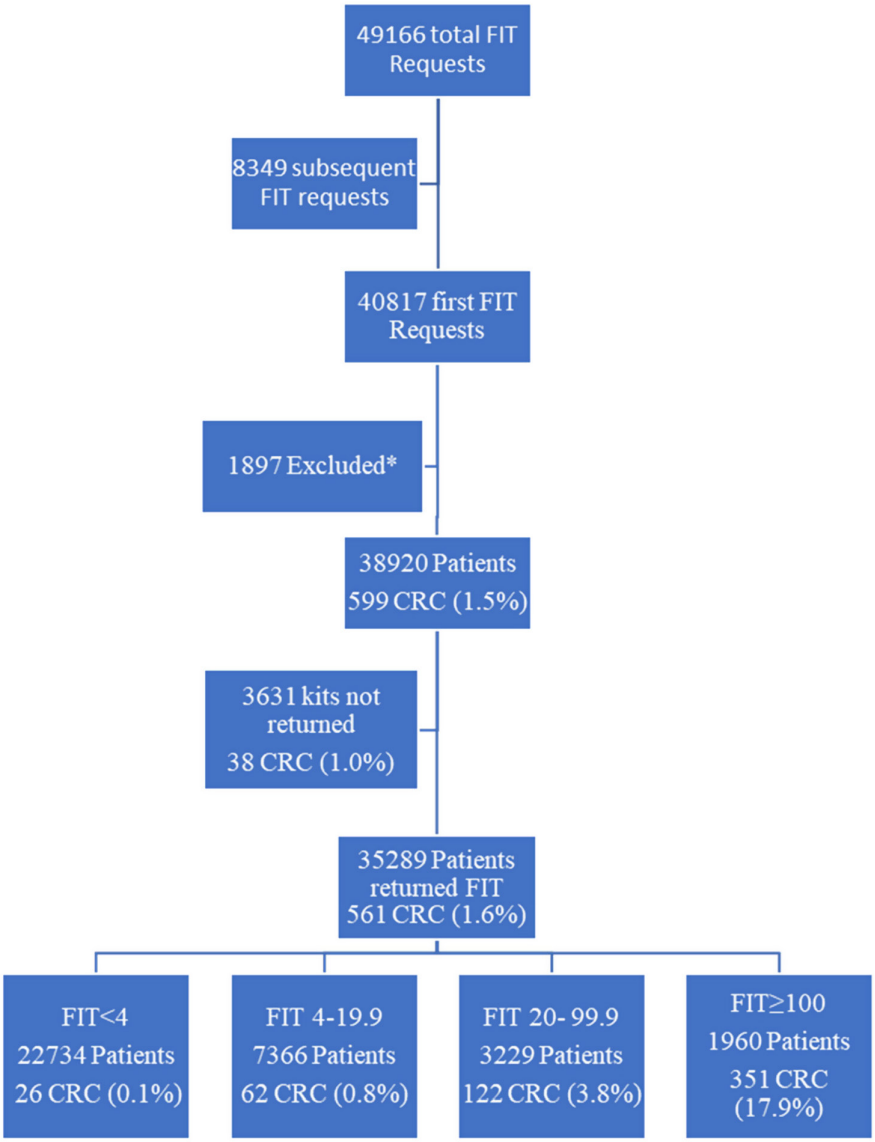


FIGURE 1 Patients with faecal immunochemical test (FIT) requests, from referral to colorectal cancer (CRC) diagnosis.

hospital trust. Twenty-seven (73.0%) patients had either abnormal blood tests or a palpable rectal mass. The median time from FIT to diagnosis was 82.5 days (IQR 47.5–156.4) but in three patients the delay was over 1000 days (two were a breach of protocol and one was due to clinical decision) (see Table 1 footnote 'b').

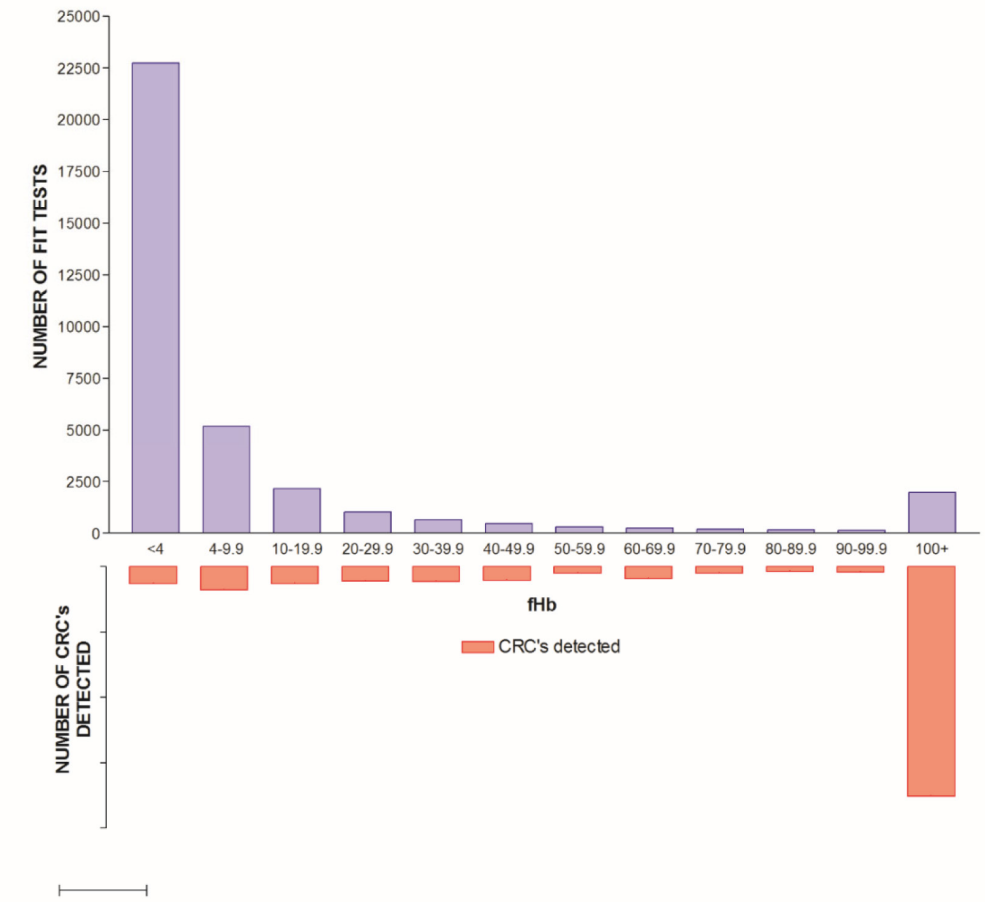
CRC 10–19.9 μg Hb/g faeces

Twenty-five patients had CRC after a FIT result of 10–19.9 μg Hb/g faeces. The threshold for 2WW referral in patients with normal bloods was raised from 10 to 20 μg Hb/g faeces in March 2020. Sixteen (64%) patients had either a palpable rectal mass or abnormal blood results, with a median time from FIT result to diagnosis of 41.3 days (IQR 28.5–75.5; Table 1).

Nottingham 4F: FIT, FBC, ferritin and finger (DRE) compared with FIT10 and FIT20

A single cut-off of 10 μg Hb/g faeces (FIT10) would have missed 63 CRCs, a subthreshold (false-negative) rate of 10.5%. Effective DRE might have identified nine of these, leaving 54 CRCs (9.0%). A single cut-off of 20 μg Hb/g (FIT20) would have missed 88 CRCs, a

FIGURE 2 Distribution of first faecal immunochemical test (FIT) result and corresponding colorectal cancers (CRCs) detected. CRC detection rate above and below chosen cut-offs, and in each stratum of faecal haemoglobin (fHb). CRC detection rates within each fHb stratum did not reach the National Institute of Health and Care Excellence (NICE) 3% threshold below 30 μg Hb/g faeces. The overall positive predictive value did reach 3% at a threshold of 4 μg Hb/g faeces, but this was driven by the high detection rate above 100 μg Hb/g faeces. *Values combined to avoid cells <10.



FIT stratum (µgHb/g faeces)	Patients with first FIT results in stratum	Number of CRC diagnoses	CRC detection rate within stratum (%)	CRC miss rate below lower limit of stratum (%)	CRC detection rate above lower limit of stratum (%)
<4	22734	26	0.1	-	-
4-9.9	5190	37	0.7	0.1	4.3
10-19.9	2176	25	1.1	0.2	6.8
20-29.9	1031	22	2.1	0.3	9.1
30-39.9	646	23	3.6	0.4	10.8
40-49.9	477	21	4.4	0.4	12.2
50-59.9	315	10	3.2	0.5	13.4
60-69.9	252	19	7.5	0.5	14.6
70-79.9	192	10	5.2	0.6	15.3
80-89.9	164	17*	4.9	0.6	16.2
90-99.9	152		5.9	0.6	17.0
≥100	1960	351	17.9	0.6	17.9
Did not return	3631	38	1.0		

CRC detection rates within fHb stratum did not reach NICE's 3% threshold below 30 µgHb/g faeces. The overall positive predictive value did reach 3% at a threshold of 4 µgHb/g faeces but this was driven by the high detection rate above 100 µgHb/g faeces. *Values combined to avoid cells <10.

TABLE 1 Characteristics and time to diagnosis in 88 patients diagnosed with CRC after a FIT result <20 μg Hb/g faeces, stratified by blood results/DRE to '4F positive' or '4F negative'.

Patients with CRC	Number (% of CRCs fHb <20)	Mean age (years, SD)	Male (%)	Median (IQR) days to diagnosis
All <20 μgHb/g faeces	88	74.8 (11.1)	51 (58.0)	64.9 (35.1–204.7)
10–19.9 μgHb/g faeces	25 (28.0)	72.5 (12.0)	15 (60.0)	41.3 (28.5–75.5)
4–9.9 μgHb/g faeces	37 (42.0)	76.5 (10.2)	18 (48.6)	82.5 (47.5–156.4)[a]
<4 μgHb/g faeces	26 (30.0)	74.8 (11.7)	18 (69.2)	83.9 (41.6–419.4)
Bloods/DRE abnormal ("4F positive" if FIT ≥4 μgHb/g faeces)				
All <20 μgHb/g faeces	59 (67.0)	75.0 (11.6)	32 (54.2)	66.3 (35.3–176.4)
10–19.9 μgHb/g faeces	16 (18.2)	72.4 (13.1)	11 (68.8)	42.8 (27.7–86.5)
4–9.9 μgHb/g faeces	27 (30.7)	76.0 (11.1)	11 (40.7)	107.5 (44.9–192.9)
<4 μgHb/g faeces	16 (18.2)	75.9 (11.2)	10 (62.5)	59.8 (37.6–252.1)
Bloods/DRE normal ("4F negative")				
All <20 μgHb/g faeces	29 (33.0)	74.5 (10.3)	19 (65.5)	63.5 (34.5–241.3)
10–19.9 μgHb/g faeces	<10	72.7 (10.3)	<10	34.5 (31.5–72.5)
4–9.9 μgHb/g faeces	10 (11.4)	77.7 (7.3)	<10	59.4 (50.9–93.5)
<4 μgHb/g faeces	10 (11.4)[b]	73.0 (12.8)	<10	162.9 (52.7–457.6)

Note: All cells with values less than 10 reported as <10.

Abbreviations: CRC, colorectal cancer; DRE, digital rectal examination; FIT, faecal immunochemical test; Hb, haemoglobin; IQR, interquartile range; 4F, FIT, full blood count, ferritin and finger [DRE].

[a]Three patients had greatly delayed diagnosis in this group. Of these, one had a palpable mass and no DRE. One was not referred despite being eligible due to abnormal blood tests but was referred after repeat FIT 3 years later. One had a polyp on CT colonography which was not removed given the patient's age and frailty and they presented with cancer 3 years later.

[b]One rectal neuroendocrine tumour included in the numbers of CRC with FIT <4, included here in the bloods/DRE normal group.

TABLE 2 A comparison of single cut-offs (FIT20, FIT10), a single threshold of 10 combined with bloods and DRE, with the Nottingham 4F protocol for CRC detection in 30 100 patients in whom the first FIT result was below 20 μg Hb/g faeces.

	No, of CRCs missed per protocol (%)	No. of CRCs picked up by lowering the threshold or adding bloods/DRE compared with FIT20
FIT20	88 (14.7)	NA
FIT10	63 (10.5)	25 (4.2)
FIT10 and bloods/DRE	33 (5.5)	55 (9.2)
Nottingham 4F	42 (7.0)	46 (7.7)

Abbreviations: CRC, colorectal cancer; DRE, digital rectal examination; FIT, faecal immunochemical test; FIT10 (20), cut-off of 10 (20) μg Hb/g faeces in patients without rectal bleeding or palpable rectal mass; Hb, haemoglobin; NA, not applicable; 4F, FIT, full blood count, ferritin and finger [DRE].

subthreshold rate of 14.7% (12.3% if DRE excluded those with palpable rectal mass).

The Nottingham 4F protocol would have missed 42 CRCs, a false-negative rate of 7.0% (Table 2), assuming all palpable rectal cancers would be detectable at initial DRE. The 4F protocol missed 23 CRCs (3.8%) after an initial fHb <4 μg Hb/g faeces, including three palpable tumours and 13 patients with abnormal bloods. The lower threshold of 4 μg Hb/g faeces for those with abnormal bloods, or palpable rectal mass, prompted referral and detection of 27 patients with CRC who would be missed by FIT10. In the cohort with fHb 10–19.9 μg Hb/g faeces, the 4F protocol detected 16 but missed 9 CRCs. The 4F protocol detected a net 18 additional CRCs compared with FIT10 and 46 compared with FIT20 (Table 2).

CRC detection rates over time

Table S2 compares CRC detection rates at 2 and 4 years [13]. The CRC detection rate for <4 μg Hb/g faeces has risen with longer follow-up, but this does not reach significance. CRC detection rates for >100 μg Hb/g faeces fell significantly over time ($p < 0.0001$).

DISCUSSION

These data describe CRC outcomes in those with low FIT following access to FIT in primary care for symptomatic patients since 2017. The Nottingham 4F protocol based on FIT, FBC, ferritin and DRE shows almost 25% fewer missed CRCs than FIT at 10 μg Hb/g faeces

alone, despite 4F using 20 μg Hb/g faeces for those without blood or DRE abnormalities. 4F is more complex than a single threshold, but our large numbers and increasing usage demonstrate that multiple thresholds can be implemented effectively. Our FIT10 results are consistent with published data on the sensitivity and specificity of FIT, even with the exclusion of rectal bleeding and mass. Indeed, the pooled analysis of Saw et al. [16] suggests that the sensitivity of FIT is higher in rectal bleeding, suggesting that our false-negative rate should be higher than in other reports.

The additional value of blood tests at the lower end of the fHb spectrum is consistent with other studies [18, 19], such as presence of anaemia demonstrated in Glasgow [18] and Hb and microcytosis demonstrated in Tayside [19]. We have not assessed microcytosis, but our dataset provides unique insight on the additional stratification value of DRE, thrombocytosis and ferritin when FIT is used in an English 2WW setting. Colleagues in Oxford have not demonstrated stratification value in Hb results in primary care when using FIT, but this may be due to differences in pathways and populations [20]. The extremes of fHb have very strong predictive values (Figure 2), whereas the low and intermediate ranges leave room for considerable improvement [17], and here additional stratification tools (blood tests or otherwise) may have benefit, but outcomes of the COLOFIT study should provide insight. We have demonstrated that CRC risk in the intermediate range fell below NICE's 3% actuarial threshold in this cohort, depending on age and blood results [15].

A weakness is that most patients tested did not undergo whole colon investigation, and some patients with CRC may have presented elsewhere; therefore we have not assessed diagnostic accuracy. Any ascertainment bias would apply to both 4F and the use of 10 or 20 μg Hb/g faeces, thus allowing consistent comparisons between approaches. It does assume full compliance with protocols, which does not always occur. It is also possible that more cancers would be palpable in secondary care when examined by trained colorectal surgeons. In the absence of strong evidence, repeat FIT for those with initially negative results is inconsistent. Some benefited from repeat FIT in line with emerging data from other groups [21, 22]; a route to diagnosis in 10% of the patients with CRC but with repeat test detection rates <1%. Low FIT appears to detect early stage CRC in this dataset, over half with Stage I or II, despite the impact of false reassurance or diagnostic delays in some. We now recommend more strongly a second FIT for those with fHb between 4 and 19.9 μg Hb/g faeces based on our findings and those from other centres [21, 22]. These areas require further study and validation.

We have not experienced a reduction in 2WW diagnostic demand since the introduction of FIT in primary care [12]. One explanation may be exclusion of rectal bleeding. Since November 2021, we have modified our pathway to include FIT in rectal bleeding. Historically, around half of CRCs diagnosed after GP referral were via routine or non-CRC 2WW pathways. We previously demonstrated that the introduction of FIT yielded a swing of CRC diagnosis towards 2WW pathways [12]. However, this inevitably diverts a 'false-positive' population towards the urgent pathway, which may explain why demand has not reduced. Recent analysis of our cohort shows that the CRC risk is often <3% even above our thresholds [15], highlighting the need to consider adjuncts to FIT.

New NICE FIT guidelines represent a major step forward, pragmatically choosing a single cut-off of 10 μg Hb/g faeces for standardization and ease of implementation in areas without established pathways [6]. This identifies a group in whom in the risk of CRC is just two in 1000, well below the 3% threshold for urgent referral defined by NICE. Raising the threshold to 20 μg Hb/g faeces would miss only one additional CRC per 1000 patients tested [23]; this can be offset by combining FIT with blood tests and DRE – the latter being key to avoiding long delays.

We believe that the potential benefits of FIT outweigh the risks, and we support its use despite not seeing a reduction in 2WW demand. The aspiration to increase early diagnosis by broadening access and lowering thresholds in the BSCP remains a cornerstone of improving outcomes. Increasing and repurposing diagnostic capacity is key but will not be enough unless FIT is optimized for symptoms, without missing early stage CRC with low fHb. We believe that optimization of FIT requires adjuncts, such as blood tests, with the dual benefit of improving FIT performance in both symptomatic and asymptomatic pathways – key to improving early diagnosis of CRC in a constrained system.

AUTHOR CONTRIBUTIONS

A. J. Morton: Conceptualization; writing – original draft; methodology; visualization; writing – review and editing; software; formal analysis; project administration; data curation; investigation; validation. **J. A. Bailey:** Conceptualization; investigation; writing – original draft; methodology; visualization; formal analysis; project administration; data curation. **J. Jones:** Conceptualization; methodology; data curation; software; formal analysis; project administration; visualization; investigation; resources. **C. J. Chapman:** Conceptualization; investigation; writing – review and editing; methodology; validation; software; formal analysis; project administration; data curation; resources. **S. Oliver:** Conceptualization; investigation; methodology; validation; visualization; software; project administration; resources. **J. R. Morling:** Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; validation; visualization; formal analysis; project administration; supervision. **H. Patel:** Conceptualization; investigation; methodology; validation; software; visualization. **D. J. Humes:** Conceptualization; investigation; writing – review and editing; writing – original draft; methodology; validation; visualization; resources; supervision; data curation; software; formal analysis; project administration. **A. Banerjea:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; supervision; resources; data curation; software; formal analysis; project administration.

FUNDING INFORMATION

No external funding was gained for this work.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

Ethical approval gained locally (NUH registration number 20-135C).

CONSENT

All work using routinely collected data, no new data required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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