"Low FIT" Colorectal Cancer: A four-year comparison of the Nottingham "4F" protocol with FIT10 in symptomatic patients.

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Abstract

Aim:

To evaluate colorectal cancer outcomes after “low” (sub-threshold) Faecal Immunochemical Test (FIT) results in symptomatic patients tested in primary care.

Method:

Retrospective audit of 35,289 patients with FIT results, having consulted their general practitioner with lower gastrointestinal symptoms, and subsequent colorectal cancer (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 (FBC), Ferritin and Finger.

Outcome: Detection rates of CRC, missed CRC and time to diagnosis in local “4F” protocols for patients with a sub-threshold faecal Haemoglobin (fHb) result compared to thresholds of 10 and 20 µgHb/g Faeces.

Results:

A single threshold of 10 µgHb/g Faeces identifies a population in whom the risk of CRC is 0.2% but 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 µgHb/g Faeces for patients with normal blood tests. Sub-threshold FIT results in patients subsequently diagnosed with a palpable rectal tumour yielded the longest delays.

Conclusion:

Combination of FIT with blood results and DRE (“4F”) 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 result spectrum.

What does this paper add to the literature?

Combining 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 to a single threshold for “negative” FIT.

Introduction

Colorectal cancer (CRC) is the second commonest cause of cancer death in the UK, with over 42,000 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 requiring 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 optimisation 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). Specialty association and recent NICE guidelines endorse the use of FIT in symptomatic patients, with fHb ≥10 µgHb/g faeces triggering 2WW referral and consideration of other pathways below this threshold(5, 6). A pooled analysis of 15 studies including 48,872 patients tested in Primary Care yielded, for CRC, 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 µgHb/g faeces(7). A threshold of ≥20 µgHb/g faeces missed less than one additional CRC per 1000 patients. Several studies have observed optimal FIT thresholds of 20 µgHb/g faeces or higher(8, 9), which may reduce the number needed to scope for each CRC for an 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.

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 µgHb/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 µgHb/g faeces, based on continuous audit (Appendix I). 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 introduction of FIT in the 4 years between November 2017 and December 2021, focussing on patients with a FIT result below the threshold of investigation. Our “4F” protocol is compared to single cut-offs of 10 (FIT10) and 20 (FIT20) µgHb/g faeces in patients without rectal bleeding or palpable rectal mass.

Methods

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 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 1)(11-13). FIT, FBC (and Ferritin from November 2018 onwards) were mandated irrespective of symptoms or age by local agreement with Primary Care and used to prioritise access to urgent investigations, with iterative changes guided by the latest evidence (Appendix II). This study describes the CRC outcomes for all FITs requested in Primary Care 4 years after introduction, focussing 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 is postal, with analysis using the OC-Sensor™ platform (Eiken Chemical Co., Tokyo, Japan) by our accredited BCSP Hub laboratory (Appendix III)(13).

Results and advice

Patients with a FIT result <4 µgHb/g faeces, or ≥4 but <20 µgHb/g faeces with normal Haemoglobin (≥130g/l in men; ≥120g/l in women), Ferritin (25-349) and Platelet count <400x10^9/l are considered "negative" or "low", with low CRC risk. For these patients, General Practitioners (GPs) are advised on safety-netting: consideration of an alternate pathway, routine referral or repeat FIT, alongside watchful wait if their concerns are assuaged by FIT, with a prompt to undertake DRE if not completed.

Patients with FIT results above 4 (or 20 µgHb/g faeces with normal bloods) are advised to be referred urgently on a suspected cancer pathway. FIT results ≥100 µgHb/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 & Services Datasets (COSD) are used to evaluate diagnoses of CRC recorded using ICD codes C18-C20 (excluding C18.1 Appendix) with a censor date of 31st December 2021. Trust, electronic patient records and databases were used for cross-checking and diagnosis validation for all patients sent a FIT between November 2017 and 31st October 2021. This is described in depth elsewhere(14, 15). Ethical approval granted locally (NUH Registration Number: 20-135C).

Statistical analysis

Histograms were used to assess normality. Continuous variables were compared using the students t-test and ANOVA if normally distributed, with Tukey's multiple comparison test for multiple groups. Mann Whitney U, Kruskal Wallis and Dunn's multiple comparison test were used for non-parametric data. Comparisons were made between categorical data using Chi-Squared.

Data was 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 µgHb/g faeces), with further segmentation for sub-analysis of results between 4 and 99.9 µgHb/g faeces at 10 µgHb/g bands.

In the context of local protocols and the literature, fHb <20 µgHb/g faeces was considered "low FIT"(7, 16, 17), 20 – 99.9 µgHb/g faeces "intermediate FIT"(18) and ≥100 µgHb/g faeces "high FIT". Time to diagnosis was considered the time in days from FIT result to histological CRC diagnosis. A patient was considered "4F positive" if they had a "low" FIT result of 4-19.9 with abnormal bloods tests or DRE.

Funding

The pathway was commissioned locally; all four local CCGs 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. 8349 (17.0%) were repeat tests from 6640 patients, with a total population of 40,817 individuals. 38,920 patients had analysable results (Figure 1). This population is described in detail elsewhere(14). 599 CRCs were detected (1.5%), the majority (58.6%) followed a FIT ≥100 µgHb/g faeces. 38 CRCs (6.3% of CRCs) were detected in the population that did not return their first FIT. 62 of the 599 CRCs (10.3%) detected arose in the 6640 patients that returned more than one FIT test – a 0.9% detection rate in the repeat test population.

FIT usage steadily increased since its introduction in Primary Care, except a dip with the arrival of COVID-19 (Supplementary Figure 1a). The number of CRC's diagnosed after FIT flattened out after steadily increasing during the first 12 months (Supplementary Figure 1b). CRC detection rates peaked with the dip in FIT requests during the first wave of the pandemic, with a decline thereafter to levels below pre-pandemic, likely reflecting increased testing of a lower-risk population (Supplementary Figure 1c).

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

CRC after "low FIT" (all <20 µgHb/g faeces)

88 patients were diagnosed with CRC after an initial FIT <20 µgHb/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 µgHb/g faeces. 48 (54.5%) were right-sided cancers (proximal to splenic flexure, Supplementary Table 1). 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. 23 patients (26.1%) had an interval from FIT result to diagnosis over 180 days. 9 had repeat FIT, positive in 7, prompting referral. Other reasons for delay included patient choice and non-referral despite eligibility. In the delayed group, 8 (34.8%) patients were diagnosed at Stage I, 4 (17.4%) Stage II, 6 (26.1%) Stage III, 4 (17.4%) Stage IV and in one staging was unavailable.

CRC <4 µgHb/g faeces

26 patients with an initial FIT <4 µgHb/g faeces were subsequently found to have CRC (Table 1), diagnosed via other pathways. 4 patients had a subsequent positive FIT prompting referral. 16 (61.5%) patients had either abnormal blood tests or palpable rectal mass. The median number of days from FIT result to diagnosis was 83.9 days (IQR 41.6-419.4) with a maximum of 1023 days. 3 patients had a palpable rectal mass; this group had the longest delays to diagnosis (128 to 1009 days).

CRC 4-9.9 µgHb/g faeces

37 CRCs were diagnosed after initial FIT of 4-9.9 µgHb/g faeces (Table 1), two after subsequent FIT and one at another Trust. 27 (73.0%) patients had either abnormal blood tests or palpable rectal mass. Median time from FIT to diagnosis was 82.5 days (IQR 47.5-156.4), but over 1000 days in 3 patients, in which two were a breach of protocol and one due to clinical decision (Table 1 footnote).

CRC 10-19.9 µgHb/g faeces

25 patients had CRC after FIT 10-19.9 µgHb/g faeces. The threshold for 2WW referral in patients with normal bloods was raised from 10 to 20 µgHb/g faeces in March 2020. 16 (64%) patients had either a palpable rectal mass or abnormal blood results, with median time from FIT result to diagnosis 41.3 days (28.5-75.5, Table 1).

Nottingham 4F: FIT, FBC, Ferritin and Finger (DRE) compared to FIT10 and FIT20

A single cut-off of 10 µgHb/g faeces (FIT10) would have missed 63 CRC's, a sub-threshold (false-negative) rate of 10.5%. Effective DRE might have identified 9 of these, leaving 54 CRC's (9.0%). A single cut-off of 20 µgHb/g (FIT20) would have missed 88 CRC's, a sub-threshold 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 misses 23 CRCs (3.8%) after an initial fHb <4 µgHb/g faeces, including 3 palpable tumours and 13 patients with abnormal bloods. The lower threshold of 4 µgHb/g faeces for those with abnormal bloods, or palpable rectal mass, prompted referral and detection of 27 patients with CRC that would be missed by FIT10. In the cohort with fHb 10-19.9 µgHb/g faeces, the 4F protocol detected 16 but missed 9

CRC's. The 4F protocol detected a net 18 additional CRC's compared to "FIT10" and 46 compared to "FIT20" (Table 2).

CRC detection rates over time

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

Discussion

This dataset describes 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 "finger" shows almost 25% fewer missed CRCs than FIT at 10 µgHb/g faeces alone, despite "4F" using 20 µgHb/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(19) suggests that FIT's sensitivity is higher in rectal bleeding, suggesting that our false-negative rate should be higher than reported elsewhere.

The additional value of blood tests at the lower end of the fHb spectrum is consistent with other studies(20, 21), such as presence of anaemia demonstrated in Glasgow(20), and Hb and microcytosis demonstrated in Tayside(21). 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(22). The extremes of fHb have very strong predictive values (Figure 2), whereas the low and intermediate ranges leave room for considerable improvement(18), where 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 µgHb/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(23, 24); 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 Stage I or II, despite the impact of false reassurance or diagnostic delays in some. We now recommend a second FIT more strongly for those with fHb between 4 and 19.9 µgHb/g

faeces, based on our findings and those from other centres(23, 24). 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(25). 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 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 µgHb/g faeces for standardisation and ease of implementation in areas without established pathways(6). This identifies a group in whom in the risk of CRC is just 2 in 1000, well below the 3% threshold for urgent referral defined by NICE. Raising the threshold to 20 µgHb/g faeces would miss only one additional CRC per thousand patients tested(26); this can be offset by combining FIT with blood tests and DRE - the latter key to avoiding long delays.

We believe FIT's potential benefits outweigh 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 re-purposing diagnostic capacity is key, but will not be enough unless FIT is optimised for symptoms, without missing early-stage CRC with low fHb. We believe optimisation 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.

Figure 1 Patients with FIT requests, from referral to Colorectal Cancer (CRC) diagnosis.

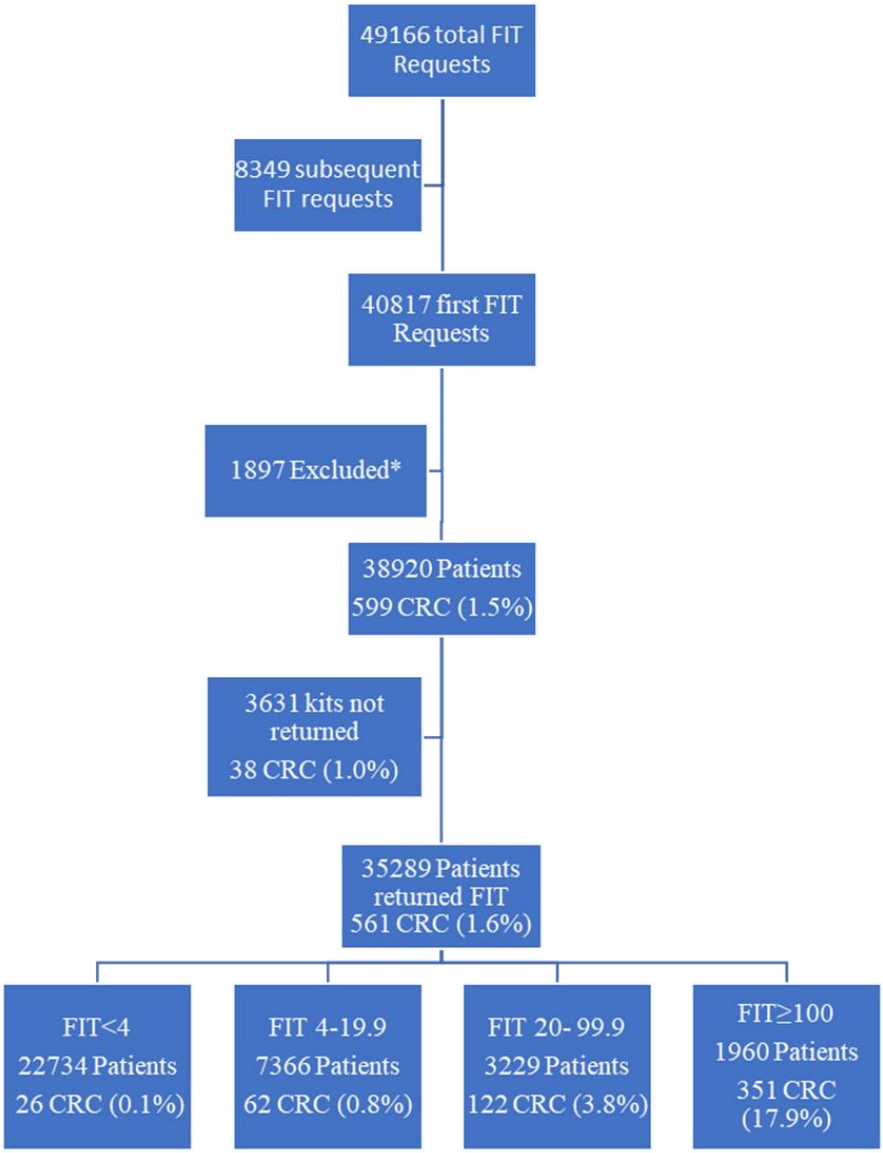
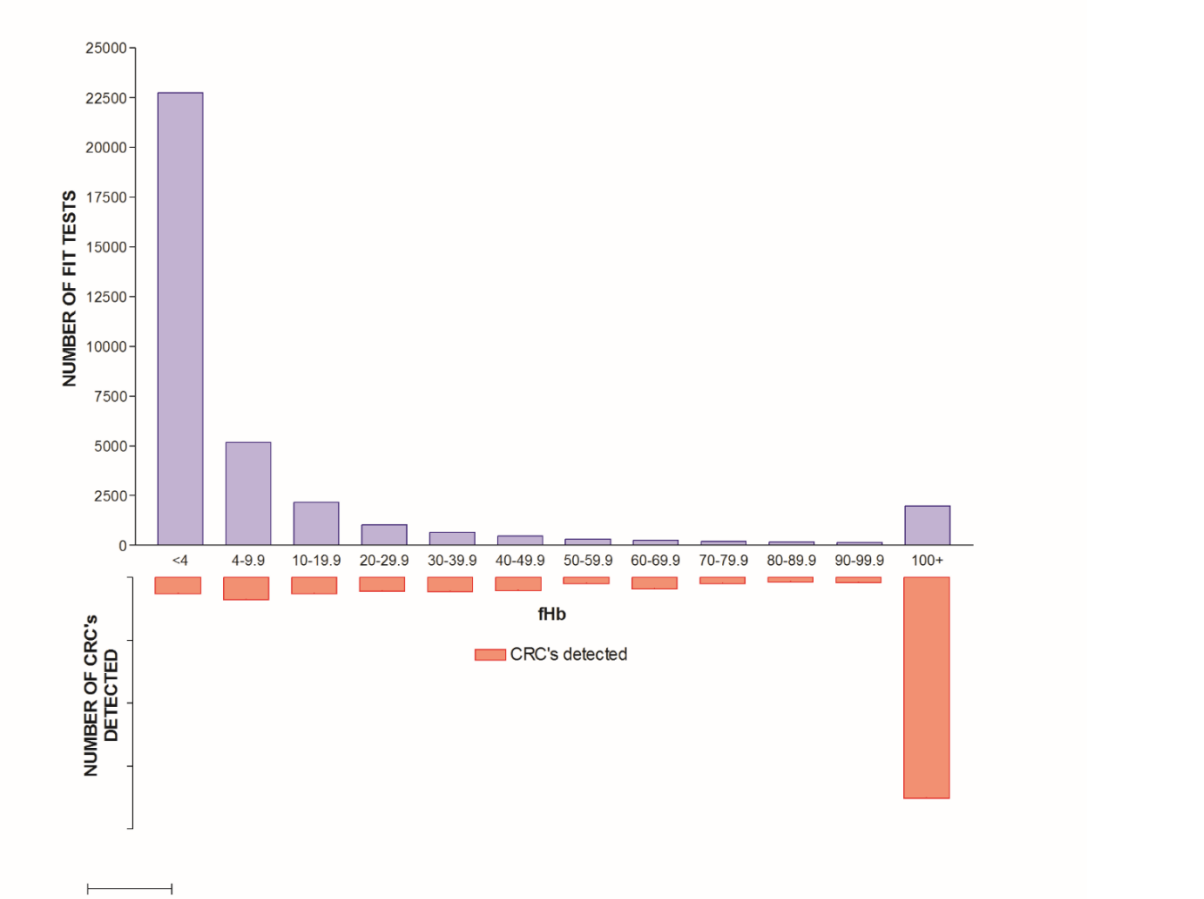


Figure 2 Distribution of first FIT result and corresponding CRCs detected. CRC detection rate above and below chosen cut-offs, and in each stratum of fHb.



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 µgHb/g faeces, stratified by bloods results/DRE to "4F positive" or "4F negative".

Patients with CRC	Number (% of CRC fHb <20)	Mean Age (years, SD)	Male (%)	Median (IQR) days to diagnosis
All <20µgHb/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)**
<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 <20µgHb/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)*	73.0 (12.8)	<10	162.9 (52.7 – 457.6)

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

***3 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 CTC which was not removed given the patient's age and frailty and presented with cancer 3 years later.*

DRE= digital rectal examination

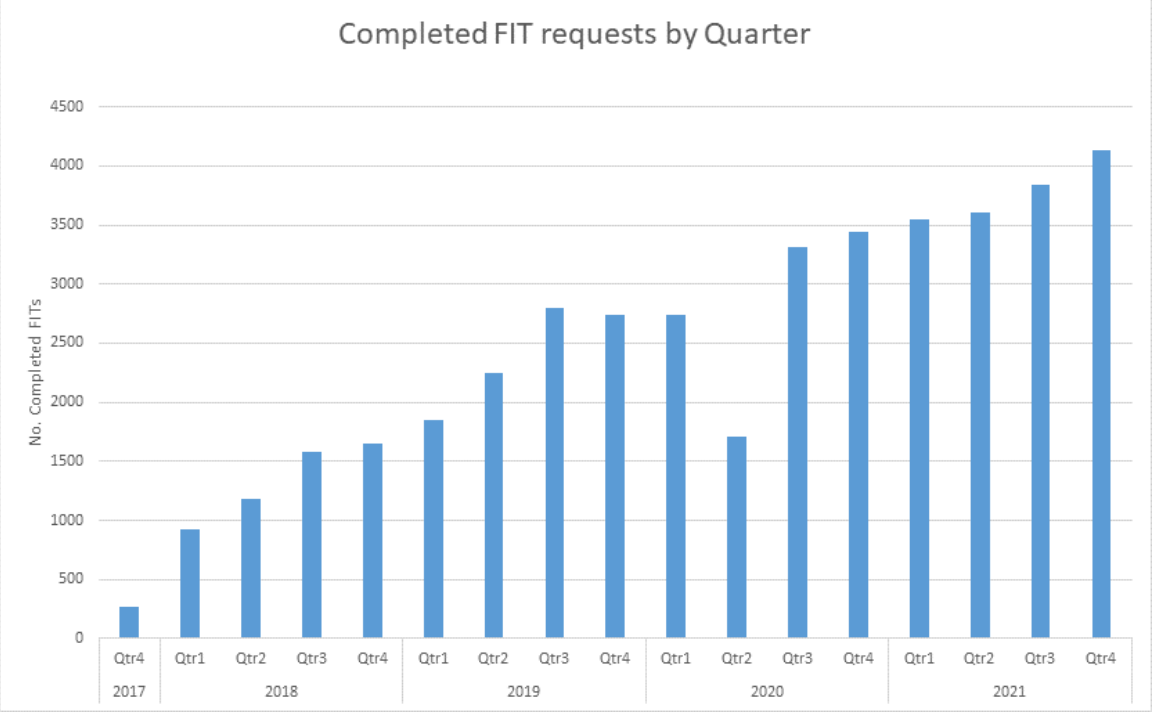
All cells with values less than 10 reported as <10.

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

	Number of CRCs missed per protocol (%)	Number of CRCs picked up by lowering threshold or adding bloods/digital rectal examination compared to FIT20
FIT 20	88 (14.7)	NA
FIT 10	63 (10.5)	25 (4.2)
FIT 10 and bloods/DRE	33 (5.5)	55 (9.2)
Nottingham 4F	42 (7.0)	46 (7.7)

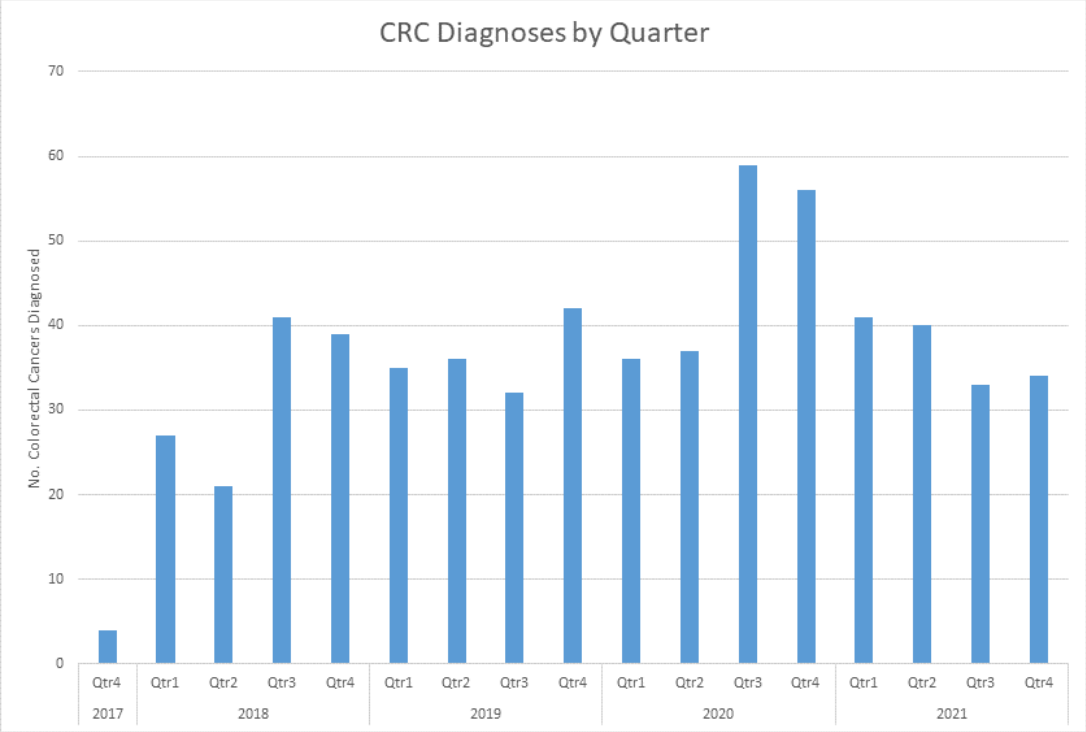
Supplementary Figure 1: Trends in FIT usage and CRC detection rates between November 2017 and November 2021.

Supp. Figure 1a Number of FIT requests in Primary care by quarter

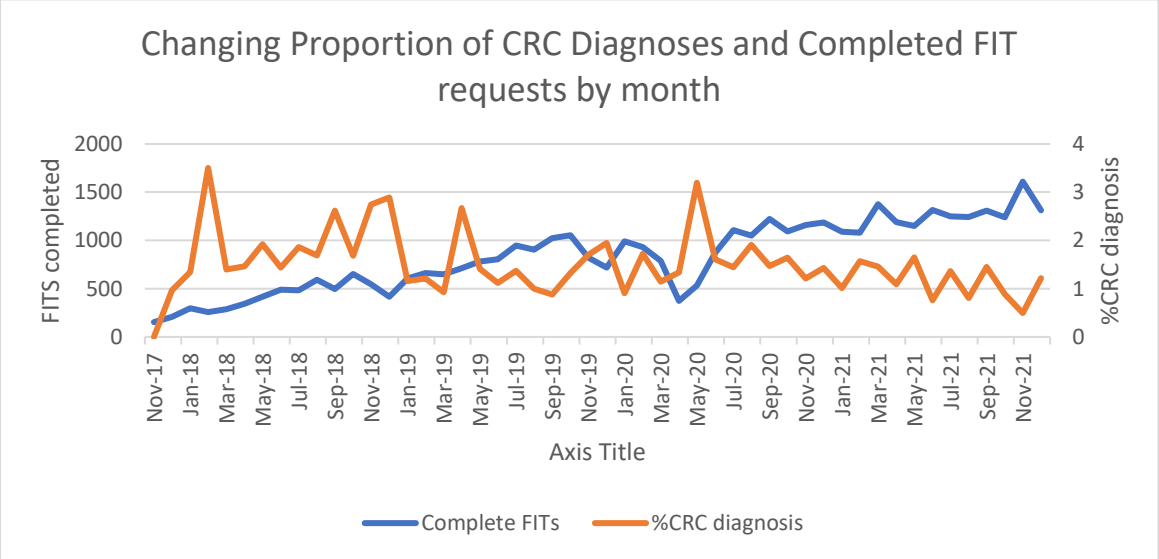


Quarters taken per calendar year (eg Q1 represents 1st January to 31st March inclusive).

Supp. Figure 1b Number of CRC diagnoses after a FIT result by quarter



Supp. Figure 1c CRC detection rate by month over time.



Supplementary Table 1: Detailed breakdown of 88 patients diagnosed with CRC after a FIT <20µg Hb/g faeces.

Cancers	n	Mean Age (y)	M:F	Stage I:II:III:IV	Abnormal bloods*	Palpable on Digital rectal examination
All cancers fHb <20 µgHb/g faeces	88	74.8	51:37	26:17:24:17 (4 UK**)	45	14
All cancers with fHb <4 µgHb/g faeces	26	74.8	18:<10		13	<10
Male	18	73.2			10	
Female	<10	78.4			<10	
Right	16	76.1	<10		<10	
Left	<10	77.9	<10		<10	
Rectum	<10	61.0	<10		<10	
All cancers with fHb 4-9.9 µgHb/g faeces	37	76.5	18:19		21	<10
Male	18	78.9			<10	
Female	19	74.1			12	
Right	19	76.2	<10		16	
Left	<10	76.8	<10		<10	
Rectum	<10	76.8	<10		<10	
All cancers with fHb 10-19.9 µgHb/g faeces	25	72.5	15:10		11	<10
Male	15	72.7			<10	

Female	10	72.2			<10	
Right	13	72.8	<10		<10	
Left	<10	72.1	<10		<10	
Rectum	<10	72.0	<10		<10	

Right is defined as cancers proximal to the splenic flexure, and left from splenic flexure distally

*For this analysis this group only includes those without a palpable rectal mass on DRE.

**UK = unknown – not formally staged (including one rectal submucosal neuroendocrine tumour).

All cells with individual values less than 10 are reported as <10 according to local data practices (meaning stage cannot be broken down for each FIT subgroup).

Supplementary Table 2 A comparison of colorectal cancer detection rates for fHb thresholds as reported at 2 years and 4 years of service evaluation.

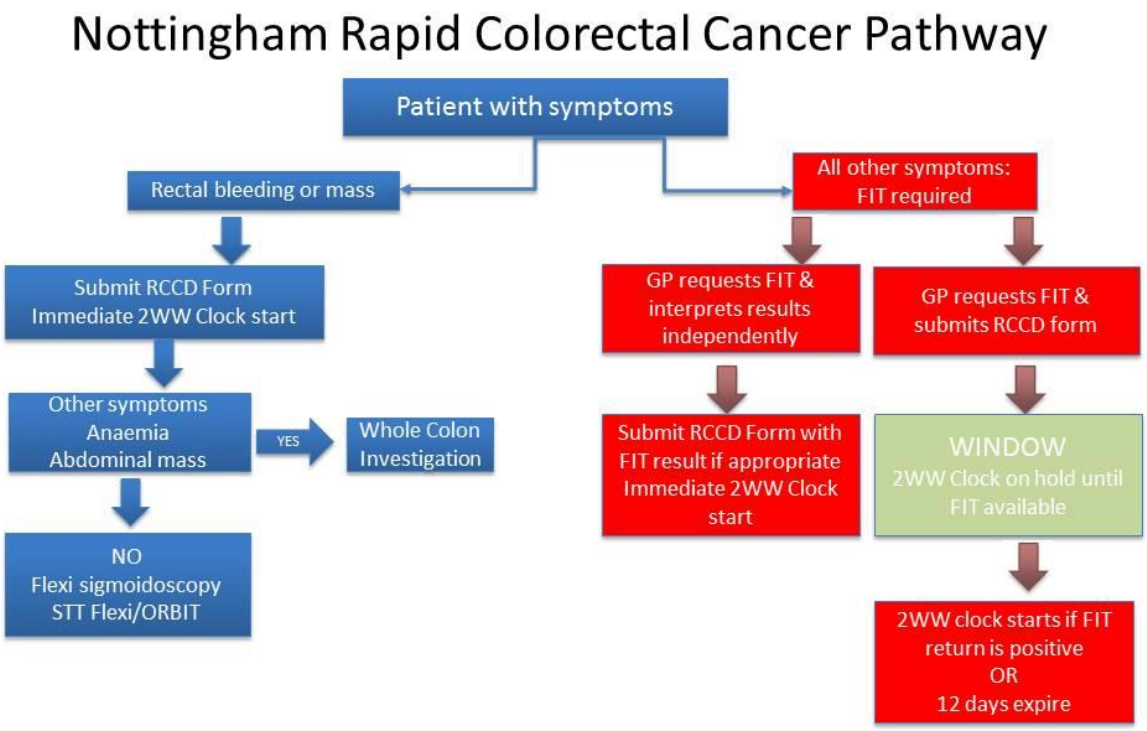
fHb Stratum	**2 years**			**4 years**		
	Patients	**CRC**	**Detection Rate (%)**	**Patients**	**CRC**	**Detection Rate (%)**
<4	**8920**	**<10**	**<0.1**	**22734**	**26**	**0.1**
4-9.9	**1568**	**10**	**0.6**	5190	37	0.7
10-19.9	**706**	**10**	**1.4**	2176	25	1.1
20-99.9	**1134**	**51**	**4.5**	**3229**	**122**	**3.8**
≥100	**714**	**153**	**21.4**	**1960**	**351**	**17.9***

***Chi squared 15.3, p<0.0001**

Numbers of CRC include one rectal neuroendocrine tumour and one patient who had highly suggestive radiological features of cancer who did not have a histological diagnosis (included to avoid understating CRC risk after low FIT).

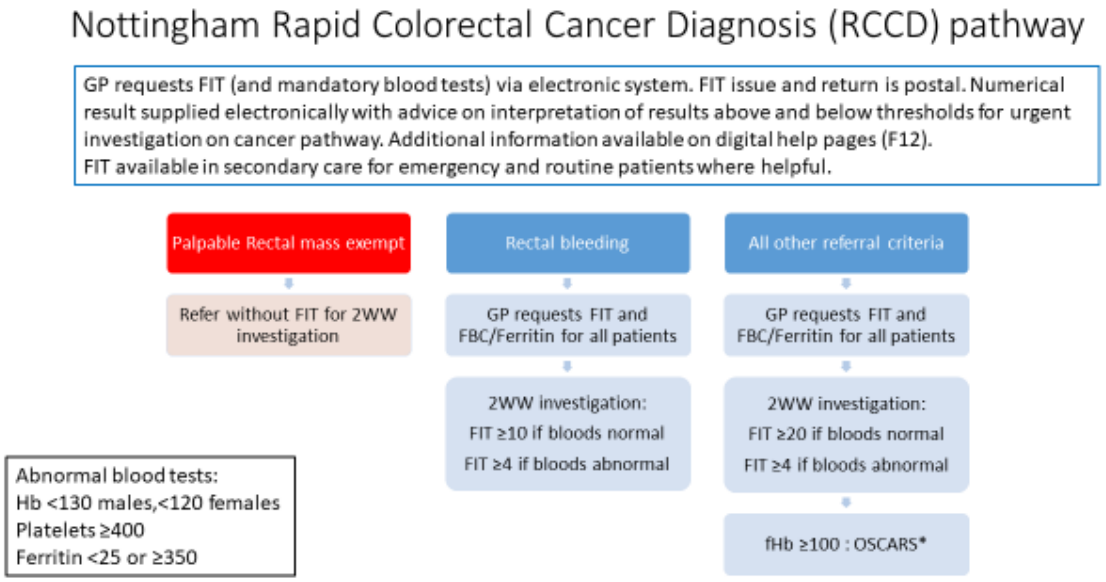
Cells with values less than 10 are reported as <10.

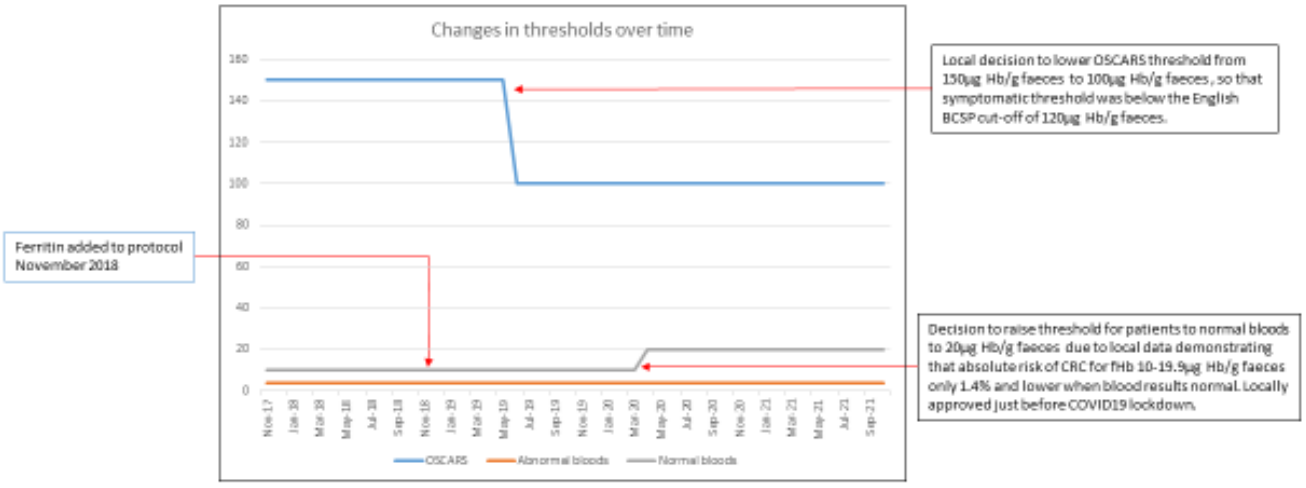
Appendix I: Original pathway introduced in November 2017: FIT used in all groups other than those with rectal bleeding or mass (Blue). All other symptoms eligible for FIT (Red): Primary pathway on left where GPs request and action FIT independently. Secondary pathway on right (in Red) where GP's submit referral and request FIT concomitantly. Referrals were initially held until results were available up to maximum of 12 working days – this was closed with local agreement in June 2019.



Each new referral is vetted by a Colorectal Nurse Practitioner and electronic records of test results and previous investigations are noted. A joint review is then undertaken with a Colorectal consultant surgeon. A pre-defined protocol based on FIT, blood results, age and referral symptoms is used but consultants are allowed to deviate from the protocol. To June 2019 all patients with FIT ≥150 µg Hb/g faeces were electronically notified to the team as soon as the result is available and prioritised for STT Colonoscopy or CT colonography if suitable. After June 2019 this was reduced to FIT ≥100 µg Hb/g faeces. All STT patients are telephoned by a CNP to confirm their suitability and have the process explained if they are deemed fit according to a protocol fitness questionnaire. Those considered unsuitable for STT during telephone assessment or not contactable are offered outpatient assessment (OPA), as were patients deemed not fit during vetting. The protocol further defined that the oldest and most frail patients be seen in consultant clinics, whilst others were directed to CNP-led clinics as before.

Appendix II Current RCCD pathway since modification in November 2021 and summary of changes since introduction.





RCCD pathway based on FIT and FBC based on published evidence, pilot results and local audit. Thrombocytosis incorporated due to available evidence and local data analysis.

OSCARS – One stop Surgical assessment, Colonoscopy and Radiological Staging – dedicated colonoscopy lists with senior surgeons and protected slots for radiology when required.

Appendix III: FITTER Checklist

All patients referred without rectal bleeding were sent (by normal UK Post Office mail system) a faecal sample collection device (OC-Sensor™, Eiken Chemical Co, Tokyo, Japan) within 2 days of the 2WW referral being received. The faecal Haemoglobin (fHb) concentration in the OC-Sensor FIT is determined in nanograms of haemoglobin per millilitre of buffer in the sample tube (ng/ml). Each sample tube contains 2 ml of stabilising sample buffer in which, with the aid of the test-wand, 10 mg of stool sample is suspended. Results are reported in µg Hb/g faeces.

The device was pre-labelled with the patient's name, NHS number, a unique laboratory ID number and a space to add the sample date. An instruction leaflet for using the sampling device, a letter outlining the purpose of the test and clarifying that the results would not be used for diagnostic purposes in isolation, and a prepaid first class return envelope were also included. Participants were asked to sample their faeces according to instructions, date the sampling device, and return it to the laboratory as soon as possible within 14 days of receipt of the letter. The process for kit dispatch and return was entirely postal.

All returned samples were logged prospectively at the receiving laboratory and analysed once for f-Hb using the automated OC-Sensor™ (Eiken Chemical Co., Tokyo, Japan) according to manufacturer's protocols, alongside f-Hb controls. The analyser was calibrated once a month, and 2 levels of controls were validated at the beginning and end of each run. Returned samples were usually analysed on day of receipt otherwise they were stored in a refrigerator at 4°C upon arrival until analysis. All samples were analysed within 1 week of receipt.

If sample values were above the linearity of the assay (200µg Hb/g faeces) they were diluted in OC Calibration Diluent (1 in 10 and 1 in 100) in order to obtain a quantitative result.

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