Original article

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Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using faecal immunochemical testing in Nottingham

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Abstract

Aim We introduced primary care access to faecal immunochemical testing (FIT) as a stratification tool for symptomatic patients considered to be at risk of colorectal cancer (CRC) prior to urgent referral. We aimed to evaluate clinical and pathway outcomes during the first 6 months of this novel approach.

Method FIT was recommended for all patients who consulted their general practitioner with lower gastrointestinal symptoms other than rectal bleeding and rectal mass. We undertook a retrospective audit of the results of FIT, related clinical outcomes and resource utilization on prospectively logged cases between November 2017 and May 2018.

Results Of the 1862 FIT kits dispatched by post 91.4% were returned, with a median return time of 7 days (range 2–110 days); however, 1.3% of returned kits could not be analysed. FIT results ≥ 150.0 μg haemoglobin (Hb)/g faeces identified patients with a significantly higher risk of CRC (30.9% *vs* 1.4%, chi-square 167.1, $P < 0.0001$). FIT results ≥ 10.0 μg Hb/g faeces identified patients with significantly higher risk of significant noncancer bowel pathology (24.1% *vs* 4.9%, chi-square 73.6, $P < 0.0001$) and FIT results < 4.0 μg Hb/g faeces identified a group more likely to have non-CRC pathology (5.1% *vs* 2.4%, chi-square 3.9, $P < 0.05$). The CRC detection rate in 531 patients investigated after a FIT result of < 4.0 μg Hb/g faeces was 0.2%. In 899 investigated patients, a FIT result with a threshold of 4.0 μg Hb/g faeces had sensitivity 97.2% (85.5–99.9% CI), specificity 61.4% (58.1–64.7% CI), negative predictive value 99.8% (98.7–100.0% CI) and positive predictive value 9.5% (8.7–10.4% CI).

Conclusion A symptomatic pathway incorporating FIT is feasible and appears more clinically effective than pathways based on age and symptoms alone.

Keywords Colorectal cancer, diagnosis, stratification of cancer risk, Faecal immunochemical test (FIT)

What does this paper add to the literature?
This is the first clinical pathway to incorporate faecal immunochemical testing (FIT) into English 2-week-wait practice. FIT appears to improve detection rates of colorectal cancer and significant bowel pathology, whilst also signposting general practitioners to other pathology when readings are very low. FIT might improve clinical outcomes by enabling stage migration in diagnosed cancers.

Introduction

Colorectal cancer (CRC) is the fourth most common cancer diagnosis in the UK and the second most common cause of cancer-related death [1]. The introduction of the 2-week-wait (2WW) pathway in 2000 has had limited beneficial impact on clinical outcomes for CRC [2–5]. National Institute of Health and Care Excellence (NICE) guidance broadening the referral criteria (NG12) [6] has increased activity but with no evidence of increased detection rates or earlier stage at diagnosis. Timely investigation and treatment might improve the patient experience but has not improved 2WW pathway detection rates or stage at diagnosis, which is unsurprising as many symptoms prompting urgent referral lack specificity and are often caused by

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larger (more advanced) tumours. Early CRC (Stage I), which has the best clinical outcome, is often asymptomatic and more frequently diagnosed in the Bowel Cancer Screening Programme (BCSP). The detection rate after positive screening with guaiac faecal occult blood testing (gFOBT) is also sometimes higher than in 2WW pathways despite the poor sensitivity of this test [7].

New referral criteria (NG12) also recommend FOBT in low-risk groups, and subsequent guidance has recommended that faecal immunochemical testing (FIT) should be used [8]. The BCSP has also affirmed an intention to switch to FIT [9]. However, questions persist around the reliability of FIT as a 'rule out' test in symptomatic patients and the thresholds at which it should be used. In clinical practice, referral criteria such as 'change in bowel habit' may fail to meet the 3% threshold that NICE defines as necessary for urgent referral, and many referred patients are not actually fit for (or willing to undergo) invasive investigations [7].

The CRC 2WW pathway consumes huge diagnostic capacity at great cost, and pressure continues to grow. FIT has been shown to outperform traditional referral criteria [10]. UK research studies have demonstrated its potential, but FIT used alone misses some CRC diagnoses [11,12]. We piloted the use of FIT within 2WW clinical practice and found that combining FIT with referral criteria and anaemia could potentially minimize the risk of missed diagnosis but also identify high-risk groups most likely to benefit from rapid investigation [13,14]. Furthermore, we confirmed that FIT had significant stratification value even in patients considered to have 'high-risk' symptoms, and those patients with very low levels of faecal haemoglobin (f-Hb) had CRC detection rates well below NICE's 3% threshold. In November 2017 we introduced a rapid colorectal cancer pathway (RCCD) incorporating FIT with local agreement from our commissioning partners. We present an evaluation of clinical outcomes and pathway performance during the first 6 months of this novel pathway.

Method

Integration of FIT and the 2WW pathway

We have previously described our straight to test (STT) pathway [7] and our FIT pilot [13]. A number of locally agreed modifications were required to integrate FIT into clinical pathways (Appendix S1 in the online Supporting Information):

1 Primary care colleagues had direct access to FIT. General practitioners (GPs) were able to access the test via a computerized requesting system commonly used for diagnostic tests (ICE). GPs were advised to avoid FIT in patients with overt rectal bleeding or a palpable rectal mass. A full blood count (FBC), estimated glomerular filtration rate and ferritin were required if such tests had not been undertaken in the 3 months prior to the request for FIT. An ICE request for FIT automatically prompted the dispatch of a FIT kit from our BCSP hub and also prompted associated blood tests;
2 GPs were able to request FIT independently and follow up on the result as they would do with any other test (primary pathway). Each FIT result was notified to the GP by ICE with clear guidance on the interpretation of results and guidance on subsequent actions depending on FIT and FBC results (Appendix S2);
3 GPs were also able to submit a RCCD pathway referral form to secondary care at the same time as requesting a FIT (secondary pathway). Secondary care held these forms in a 'window' for 12 working days to allow return and analysis of dispatched FIT kits and also collection of mandatory blood tests. Completion of the dataset triggered a 2WW clock and secondary care assessment of the referral as per standing protocols. An incomplete dataset after 12 working days also triggered a 2WW clock with subsequent investigation as deemed appropriate. The 'window' was introduced to allay concerns that:
   - patients might not return FIT kits and might not consult again
   - GPs might not act on FIT results per protocol
   - using FIT might cause 'breaches' in 14- and 62-day national targets;
4 It was agreed that any FIT result ≥ 150.0 μg Hb/g faeces would prompt immediate patient contact by the Nottingham Colorectal Service STT team with a view to arranging rapid investigation, irrespective of the pathway by which the GP had requested the FIT test. All such results are electronically notified to the STT team by the BCSP hub as soon as they are analysed. This threshold was used in our pilot to identify those patients with the highest risk of CRC and this cut-off was preselected for our previous pilot as an approximate equivalent to a positive gFOBT – the only alternative in clinical practice at the time [13];
5 It was agreed that the care of patients with 'negative' results (see below) would be returned to primary care for further follow-up unless patients had proven iron deficiency anaemia (IDA), significant weight loss or abdominal mass;
6 Referrals for rectal bleeding and rectal mass were also made on the RCCD form and patients were

investigated as 2WW referrals with an immediate clock start as normal.

FIT analysis

All patients referred for FIT were posted a faecal sample collection device (OC-Sensor™ Eiken Chemical Co., Tokyo, Japan) as previously described [13]. Participants were asked to sample their faeces according to enclosed instructions, date the sampling device, and return by post within 14 days. Returned samples were logged prospectively, stored and analysed for f-Hb using the automated OC-Sensor™-iO (Eiken Chemical Co.) according to the manufacturer's protocols, alongside f-Hb controls and with regular calibration as described elsewhere (Appendix S4) [13].

Analyses were carried out in our United Kingdom Accreditation Service-accredited (ISO 15189) laboratories located at the Eastern Bowel Cancer Screening Hub, Nottingham, UK. These laboratories also take part in the UK National External Quality Assessment Service external quality assessment schemes.

Cohort and data collection

All primary care practices in the four Nottingham clinical commissioning groups had access to the pathway from 7 November 2017. All patients who had a FIT result between 7 November 2017 and 10 May 2018 on ICE were logged prospectively in our BCSP hub in order to ensure clinical governance of this novel pathway.

Patients referred to the Nottingham Colorectal Service STT team on an RCCD form between these dates were logged prospectively in our NUhCLEUS database that supports our STT pathway. Clinical outcomes were retrieved by one author (AB) from our electronic patient records systems using 31 August 2018 as a censor date for further activity – only investigations related to the luminal gastrointestinal tract were documented. Cancer diagnoses at sites other than the colon and rectum were recorded but the related investigations were not. Cancer Outcomes and Services datasets, Nottingham University Hospitals NHS Trust data and NUhCLEUS data were used for cross-checking and data validation.

Forty-five per cent of CRC 2WW referrals made in our area were managed by an independent provider at a diagnostic treatment centre and they were unable to implement this new pathway. Our upper gastrointestinal (UGI) cancer pathway also receives referrals for IDA but no changes were made in this pathway during this evaluation period. It was accepted that patients in these pathways would be seen and investigated as before.

Data analysis

Exposure and covariates

Faecal Hb concentrations were determined and categorized as ≥ 150.0 μg Hb/g faeces (high risk positive – rapid), 10.0–149.9 μg Hb/g faeces (standard risk – 2WW), 4.0–9.9 μg Hb/g faeces with anaemia (standard risk – 2WW) and without anaemia (negative), and < 4.0 μg Hb/g faeces (negative) as per our 'Getting FIT' pilot [13]. A result of 4.0 μg Hb/g faeces represents the limit of quantification in our laboratory, i.e. the lowest amount of f-Hb that could be reliably measured. Anaemia was defined as previously described [13,14].

Outcome definition

Colorectal cancer diagnoses, and other diagnoses, were determined from investigation outcomes: endoscopy, radiology, histology and multidisciplinary team (MDT) reports were reviewed for diagnoses. The most significant pathology was recorded as the primary diagnosis (Appendix S3). Squamous cell carcinoma of the anus was considered 'other', as typical symptoms of rectal mass and bleeding were exclusion criteria for FIT testing.

Right colon was defined as the caecum to the splenic flexure, left colon was defined as the splenic flexure to the rectum and rectum was defined as the last 15 cm of the lower gastrointestinal tract.

Significant bowel pathology (SBP) was defined as those pathologies requiring secondary care input: inflammatory bowel disease (IBD), microscopic colitis, complicated diverticular disease, adenomas requiring endoscopic follow-up (one adenoma > 1 cm or three or more confirmed adenomas) and lesions requiring MDT assessment and urgent removal: suspicious polyps and early colorectal cancer (SPECC); lesions subsequently proven to be malignant were included in the CRC group. Other recorded diagnoses included cancer at other sites, low-risk adenomas that did not require follow-up, UGI tract benign pathology and significant extra-colonic pathology on CT scan requiring further activity. Normal examinations, hyperplastic polyps, uncomplicated diverticular disease and haemorrhoids were considered as no significant pathology (NSP) in the context of an urgent cancer pathway.

Investigations and cost

The initial investigations undertaken for CRC diagnosis were documented. Subsequent repeat investigations and staging investigations were not recorded. The following locally agreed tariffs were attributed to each diagnostic test: colonoscopy £419, oesophagogastroduodenoscopy

£341, flexible sigmoidoscopy £322, CT colonography £204 and CT (with or without intravenous contrast) £104.

The cost of outpatient clinics, FIT, histopathology and administration were not recorded or evaluated.

Statistical analysis

Data were assessed for normality using histograms and a Shapiro–Wilk test. Comparisons were made between continuous variables using the Student's *t*-test (or Tukey's multiple comparison test) if normally distributed or Mann–Whitney if not normally distributed. Categorical data were summarized using frequencies and percentages. Comparisons were made between categorical data using chi-square tests. All statistics were performed using GRAPHPAD PRISM (GraphPad Software, San Diego, California, USA). Tests were considered significant if a *P*-value of < 0.05 was obtained.

Results

FIT and results

We evaluated 1947 FIT requests between 7 November 2017 and 10 May 2018, representing 1934 patients with a mean age of 66.3 (±0.3 SEM) years, 44.4% of whom were men. The return rate was 91.4% and median time to kit return was 7 days (range 2–110 days). Twenty-two kits were unsuitable for analysis (Fig. 1a). Those not returning their kit were significantly younger than the cohort that did (62.7 ± 1.1 *vs* 67.1 ± 0.3 years, unpaired *t*-test $P < 0.01$). Thirteen patients returned more than one kit with an analysable sample: eleven had both results < 4.0 μg Hb/g faeces, one had both results between 4.0 and 10.0 μg Hb/g faeces without anaemia and one had discrepant results with one kit reading 'negative' and a subsequent reading positive after the evaluation period.

FIT result ≥ 150 μg Hb/g faeces

Eighty-one (4.8%) patients with a FIT result ≥ 150 μg Hb/g faeces were investigated on our 'rapid' or high-risk pathway (Fig. 1b). There were significantly more men in this cohort (61.7% *vs* 43.3%, chi-square 10.5, $P = 0.001$; Table 1). The CRC detection rate was significantly higher than in other FIT strata (30.9% *vs* 1.4%, chi-square 167.1, $P < 0.0001$). The mean age of patients diagnosed with CRC was 72.4 years (±2.6 SEM) and without a CRC diagnosis it was 68.4 years (±2.0 SEM; NS).

Nine patients had rectal cancer (36.0%), nine patients had left-sided colon cancer (36.0%) and seven patients had right-sided cancer (28.0%). Six patients (24.0%) had Stage I, eight patients Stage II (32.0%), three patients Stage III (12.0%) and eight patients Stage IV disease (32.0%). Six of 81 (7.4%) patients declined, did not attend (DNA) or were unable to complete investigation (Table 2). The median time from FIT result to first test in this group was 13 days (range 1–146 days). In patients diagnosed with CRC the median time to first test was 14 days (range 3−33 days) and the median time to tissue diagnosis where available was 27 days (range 5–61 days).

The total cost of initial investigations in these patients (not including the cost of FIT, clinic visits, histopathology, staging or repeat testing) was estimated to be £36 380. The cost per CRC diagnosis was £1456 and per SBP diagnosis £2022, lower than the equivalent costs in all other strata (Table 3).

FIT result 10.0–149.9 μg Hb/g faeces

Two hundred and twenty-two patients (98 men, 44.1%) had FIT results of 10.0–149.9 μg Hb/g faeces (Fig. 1c), of these 191 (86.0%) were referred on 2WW pathways, 11 (5.0%) on other secondary care pathways and 20 (9.0%) were tested by GPs in the primary pathway but not subsequently referred. Nine patients (4.1%) were diagnosed with CRC – four rectal cancers (44.4%), two left-sided cancers (22.2%) and three right-sided colonic cancers (33.3%). One had Stage I (11.1%), two Stage II (22.2%) and six patients (66.7%) had Stage IV disease. The detection rate for SBP was significantly higher in this group than in groups with lower FIT results (24.1% *vs* 4.9%, chi-square 73.6, $P < 0.0001$; Table 3).

Four of nine patients with CRC had FIT results ≥ 100.0 μg Hb/g faeces, representing a CRC detection rate of 22.2% between 100.0 and 149.9 μg Hb/g faeces (18 patients). The detection rate between 4.0 and 99.9 μg Hb/g faeces was 2.5% (five cancers in 204 patients). In four patients with FIT results < 80.0 μg Hb/g faeces, three had one or more objective markers of risk: anaemia, thrombocytosis or palpable mass on digital rectal examination. Twenty-one patients (9.5%) DNA, declined or did not complete planned investigations.

The median time from FIT result to first test in this group was 21 days (range 0–142 days) – the 'window' pathway and investigation on other pathways allowed some patients to be investigated before a FIT result was available – and this was significantly longer than in our 'rapid' pathway (Mann–Whitney *U*, $P < 0.001$). In those diagnosed with CRC, the median time to first test was also longer at 18 days (range 10–91 days) and the median time to tissue diagnosis where available was

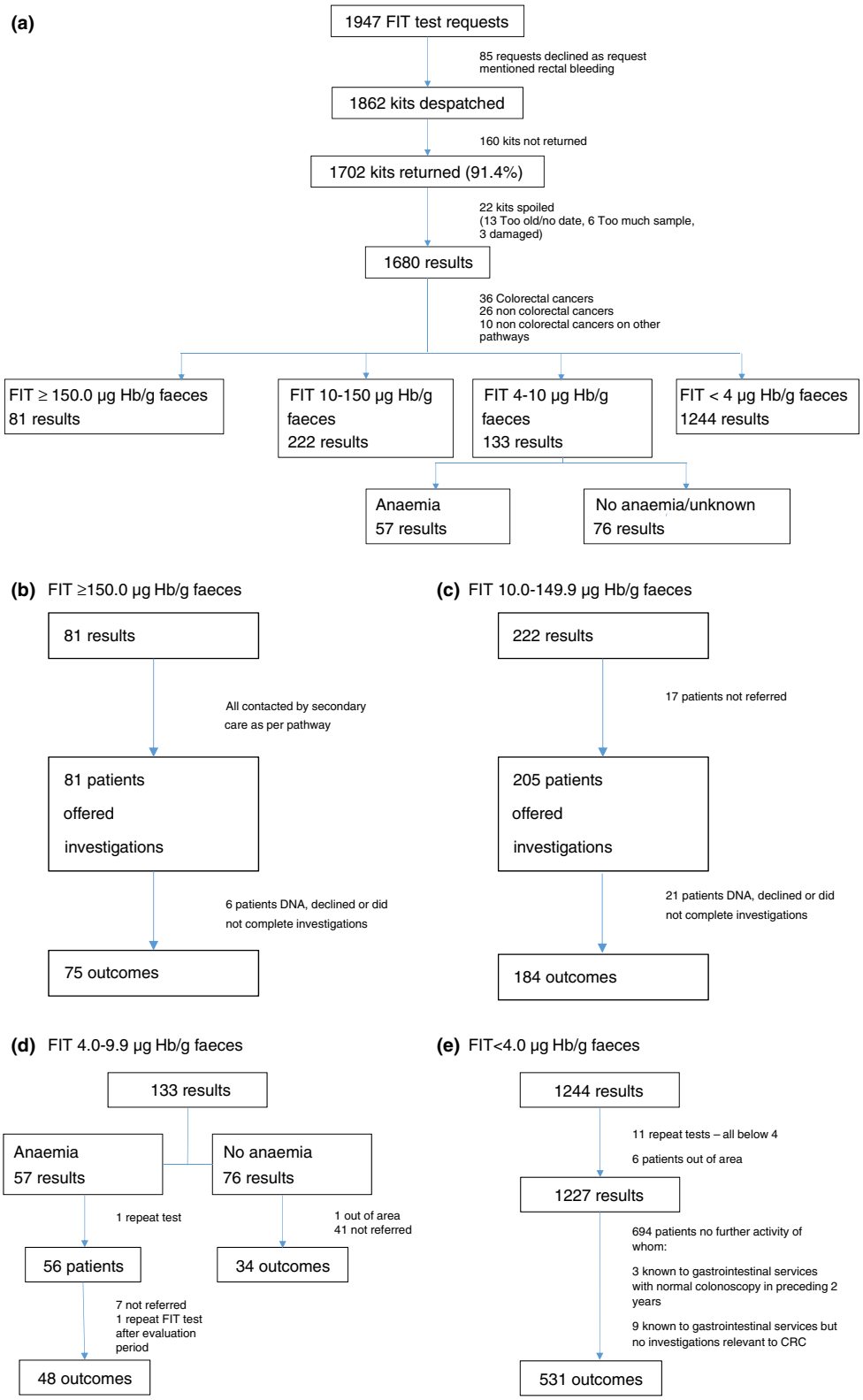

Figure 1 Breakdown of all FIT results and subsequent subsets for stratification.

Table 1 Patient demographics stratified by FIT results.

	All results	FIT ≥ 150.0 μg Hb/g faeces	FIT 10.0–149.9 μg Hb/g faeces	FIT 4.0–9.9 μg Hb/g faeces (with anaemia)	FIT 4.0–9.9 μg Hb/g faeces (without anaemia)	FIT < 4.0 μg Hb/g faeces	
Patients	1668	81	222	56	76	1233	
FIT results	1680	81	222	57	76	1244	
M:F (%)	738:930 (44.2:55.8)	50:31* (61.7:38.3)	98:124 (44.1:55.9)	28:28 (50.0:50.0)	23:53 (30.3:69.7)	538:695 (43.6:56.4)	Chi square 10.5, $P = 0.001$*
Mean age (years) (±SEM)	67.1 (±0.3)	70.6 (±1.6)	72.1 (±0.9)	75.5 (±1.4)	69.4 (±1.4)	66.5 (±0.6)	$P < 0.05$ (Tukey's)
Proportion of all FIT results (%)		4.8	13.2	3.4	4.5	74.0	
Patients followed up (*n*)		81	222	56	75	1227	
Patients undergoing subsequent secondary care activity (%)		81 (100)	205 (92.3)	48 (85.7)	34 (45.3)	531 (43.3)	
Patients who were eligible for 2WW referral not seen in any secondary care pathway (%)		0	17 (7.7)	8 (14.3)	0	26† (9.7)	

*There were significantly more men in the group with a FIT result ≥ 150 μg Hb/g faeces.
†Two hundred and sixty-nine patients were deemed acceptable for 2WW referral for iron deficiency anaemia, of whom 26 were not seen.

23 days (range 13–47 days), but these differences were not statistically significant.

FIT result 4.0–9.9 μg Hb/g faeces

One hundred and thirty-two patients returned 133 kits with a result between 4.0 and 9.9 μg Hb/g faeces (Fig. 1d). Fifty-six patients (42.4%) had anaemia (28 men, 50.0%), 48 (85.7%) of whom were seen in secondary care thereafter, but eight patients (14.3% of those eligible for referral) were not referred. One female patient returned two negative kits within the evaluation period and one man underwent repeat FIT and was investigated after the follow-up period. This anaemic group was significantly older than other groups stratified by FIT result (Tukey's multiple comparison, $P < 0.05$).

Seventy-six patients (57.6%) had no evidence of anaemia (23 men,-30.3%) – one male patient was from another region and no record existed on local systems. Thirty-four patients (44.7%) were seen in secondary care pathways and 41 patients (53.9%) had no evidence of further secondary care activity. Nineteen of the 34 patients (55.9%) were seen on 2WW pathways, nine (26.5%) on routine pathways, four (12.1%) as emergency attendances and two via other routes (6.1%).

One CRC (left colon, Stage I) was detected in this group in a patient with normal Hb but low ferritin levels at the time of referral. Other pathologies detected in this small group are shown in Table 2 and the cost per diagnosis group in Table 3.

FIT result < 4.0 μg Hb/g faeces

One thousand two hundred and forty-four returned kits yielded a result of < 4.0 μg Hb/g faeces (Fig. 1e). Eleven patients had repeat testing with both kits negative and six patients returning kits from outside our area could not be assessed for further activity. One thousand two hundred and seventy-seven patients were assessed for further activity related to the luminal GI tract or cancer. Patients with a FIT result < 4.0 μg Hb/g faeces were significantly younger (66.5 ± 0.6 years) than those with higher FIT results (Table 1; Tukey's multiple comparison $P < 0.05$).

Six hundred and ninety-four patients (56.6%) had no evidence of further activity up to 31 August 2018 with a median follow-up of 5 months (range 3–9 months) – 12 patients were already known to gastroenterology or colorectal services and three of these patients had had normal colonoscopy within the previous 2 years. Five hundred and thirty-one patients (43.3%) underwent investigation after a FIT result of < 4.0 μg Hb/g faeces

Table 2 Clinical outcomes in patients seen in secondary care for each stratum of FIT test result.

Diagnoses	FIT ≥ 150.0 μg Hb/g faeces Percentage of 81 patients seen in secondary care	FIT 10.0–149.9 μg Hb/g faeces Percentage of 205 patients seen in secondary care	FIT 4.0–9.9 μg Hb/g faeces (with anaemia) Percentage of 48 patients seen in secondary care	FIT 4.0–9.9 μg Hb/g faeces (without anaemia) Percentage of 34 patients seen in secondary care	FIT < 4.0 μg Hb/g faeces Percentage of 531 patients seen in secondary care
Colorectal cancer	30.9	4.4	0	2.9	0.2
UGI cancer	0	0	0	0	0.2
Other cancers*	3.7	1.5	2.1	5.9	3.0
IBD	7.4	4.9	0	0	0.4
Microscopic colitis	1.2	4.4	0	0	1.9
UGI inflammation	3.7	8.3	27.1	11.8	10.9
Polyps – no FU required	3.7	6.8	12.5	5.9	6.4
Polyps – BSG FU indicated	11.1	12.7	2.1	0	2.3
SPECC	1.2	2.4	0	0	0
Complicated DD	1.2	0.5		2.9	0.8
NSP	25.9	39.0	39.6	55.9	54.2
DNA or declined ix	7.4	10.2	12.5	11.8	16.2
Other CT findings requiring FU	1.2	4.4	2.1	2.9	2.1
Other	1.2	0.5	2.1	0	1.5

BSG, British Society of Gastroenterology; CT, computed tomography; DD, diverticular disease; DNA, did not attend; FU, follow-up; IBD, inflammatory bowel disease; NSP, no significant pathology; SPECC, significant polyps suspicious for early colorectal cancer; UGI, upper gastrointestinal. Significant bowel pathology = IBD, microscopic colitis, complicated diverticular disease, adenomas requiring endoscopic follow-up (one adenoma > 1 cm or three or more confirmed adenomas) and SPECC.

*Two of the noncolorectal cancers in this group were an anal cancer and a small bowel neuroendocrine tumour. Ten noncolorectal cancers were diagnosed on nongastrointestinal pathways.

– 300 (57.6%) on 2WW, 198 (37.3%) on routine, 12 (2.3%) on emergency pathways and 23 (4.3%) on other pathways. The median follow-up time of this cohort was 6 months (range 3–9 months). The cohort that was not referred was significantly younger than the cohort that underwent investigation (64.5 ± 0.5 *vs* 66.6 ± 0.6 years, unpaired *t*-test $P < 0.01$). One CRC (left colon, Stage I) was detected in this group in a patient previously referred on our 2WW pathway with a polyp detected that was not followed-up appropriately – this patient had also had their IDA corrected at that time. Twenty-seven cancers at other sites were detected within the follow-up period – 17 within gastrointestinal pathways and 10 on other pathways (Table 2). This higher detection rate for other cancer was significantly higher than in those with a FIT result of > 4.0 μg Hb/g faeces (5.1% *vs* 2.4%, chi-square 3.9, $P < 0.05$).

Test performance

A total of 899 patients underwent secondary care activity after a FIT result. A threshold of 150.0 μg Hb/g faeces yielded a sensitivity of 69.4% (95% CI 51.9–83.6) and a specificity of 93.5% (95% CI 91.7–95.1), with a negative predictive value (NPV) of 98.7% (95% CI 97.8–98.2) and a positive predictive value (PPV) of 30.9% (95% CI 24.2–38.4) in this dataset. A threshold of 4.0 μg Hb/g faeces yielded a sensitivity of 97.2% (95% CI 85.5–99.9), a specificity of 61.4% (95% CI 58.1–64.7), a NPV of 99.8% (95% CI 98.7–100.0) and a PPV of 9.5% (95% CI 8.7–10.4).

Discussion

We demonstrate that clinical introduction of FIT yields acceptable performance characteristics, consistent with the results of our pilot [13]. We acknowledge that the follow-up period for this cohort is short, but 43.1% of patients with a FIT result of < 4.0 μg Hb/g faeces were investigated with only one CRC detected (0.2%). This missed cancer arose in a patient who had already been through our standard 2WW pathway in the previous 2 years – demonstrating that all pathways fail at times. In time we do expect to see patients diagnosed with CRC

Table 3 Investigations and estimated costs thereof in each stratum of FIT result.

Investigations*	FIT ≥ 150.0 µg Hb/g faeces	FIT 10.0–149.9 µg Hb/g faeces	FIT 4.0–9.9 µg Hb/g faeces (with anaemia)	FIT 4.0–9.9 µg Hb/g faeces (without anaemia)	FIT < 4.0 µg Hb/g faeces	Comment
% Colonoscopy	69.1	55.6	33.3	50.0	49.0	
% Flexible sigmoidoscopy	8.6	6.3	8.3	5.9	7.0	
% CT colonography	16.0	18.0	31.2	23.5	18.3	
% CT with/without IV contrast	22.2	21.5	29.2	29.4	21.7	
% OGD	22.2	19.5	37.5	29.4	28.2	
Estimated cost of initial investigations (£)	36 380	77 716	18 646	13 849	203 752	
% CRC detected	30.9”	4.4	0	2.9	0.2	30.9% *vs* 1.4% in FIT < 150.0 µg Hb/g faeces, chi square 167.1, $P < 0.0001$
Cost per CRC diagnosis (£)	1456	8636		13 849	203 752	
% SBP detected	22.2	24.9””	2.1	2.9	5.3	24.1% in FIT ≥ 10.0 µg Hb/g faeces *vs* 4.9% in FIT < 10.0 µg Hb/g faeces, chi-square 73.6, $P < 0.0001$
Cost per SBP diagnosis (£)	2022	1524	18 646	13 849	7277	
Other cancer detected (%)	3.7	1.5	2.1	5.9	5.1†	5.1% in FIT < 4.0 µg Hb/g faeces *vs* 2.4% in FIT ≥ 4.0 µg Hb/g faeces, chi-square 3.9, $P < 0.05$†
Cost per other cancer diagnosis (£)	12 127	25 906	18 646	6925	7547	

Tariffs: colonoscopy £419; flexible sigmoidoscopy £322; computed tomography (CT) colonography £204; CT [with intravenous (IV) contrast]; £104; oesophagogastroduodenoscopy (OGD) £341. SBP, significant bowel pathology.

*Some patients had more than one test.

†Ten noncolorectal cancers diagnosed outside the pathway but within the follow-up period are included.

after a previous ‘negative’ FIT (as defined in our pathway), just as we see CRC in patients with a previous negative colonoscopy now [15], and in future this will be an interesting comparison to make. Notably, patients with ‘negative’ FIT results were more likely to have cancer at alternative sites. This underlines the potential value of FIT in ‘signposting’ GPs to the most appropriate urgent pathway given that most symptoms can be associated with cancer at other sites. We also confirm that a very high concentration of f-Hb detected by FIT identifies a group with significant risk of pathology that truly merits ‘rapid’ investigation, as shown in previous studies [11–13,16]. Clinical implementation of FIT does allow prioritization into pathways that significantly increase detection rates of CRC and SBP, and may help to reduce negative investigation rates (NSP), improve cost-effectiveness and reduce time to first test.

In resource-limited systems such as the UK National Health Service, capacity and cost are obvious drivers for the introduction of FIT. Our data show that FIT may be key to the identification of patients who might be safely reassured but may also be directed to other site-specific urgent or routine pathways, or to more appropriate testing – with CT colonography and standard CT

offering reasonable alternatives – in patients with lower risk of CRC but higher risk of other cancers. This has significant implications for valid consent where FIT might allow a more informed conversation around risks and benefits of investigation in all patients, but particularly the elderly and frail. The high return rate we observe in these symptomatic patients has been consistent since our pathway change and confirms the acceptability of FIT to patients.

In this dataset the proportion of FIT results of < 4.0 μg Hb/g faeces is higher than during our pilot [13], confirming that direct GP access to FIT does enable 'opportunistic screening'. This is further evident in the wide age range of patients who returned a FIT kit, with patients as young as 18 being tested. However, our aim is that local practices will learn to rely more on objective measures such as FIT and FBC and perhaps yield a 'stage migration' in CRC diagnoses. These data suggest this is not unrealistic. The overall detection rates for CRC and SBP in our 'positive' pathways remain as good as in our old STT pathway [7] for FIT results of 4.0–149.9 μg Hb/g faeces, and significantly higher in our rapid pathway for FIT results of ≥ 150.0 μg Hb/g faeces. We have therefore not introduced restrictions on FIT usage but we recognize that scoring systems that incorporate FIT, age and other objective parameters [14,17–19] ultimately hold the most promise for improving specificity whilst maintaining sensitivity [19]. We have stopped investigating patients with FIT results of < 4.0 μg Hb/g faeces with colon-specific tests on 2WW pathways in light of these results, and ongoing evaluation continues.

Our pilot study using FIT within our 2WW pathway [13] preceded NICE guidance on FIT for symptomatic patients (DG30) [20] and the updated NICE guidelines that followed [8]. On the basis of our own pilot data we agreed locally to use FIT in all symptomatic patients, both 'high' and 'low' risk, when we rolled out our RCCD pathway in 2017 and defined our thresholds accordingly. Our pathway and the 'window' process demonstrate one method of allaying concern around the introduction of FIT and minimizing any negative potential impact on NICE's 'high risk' symptom groups [21,22]. Our findings broadly concur with previous research, and in particular outcomes in Scotland where FIT has been used in symptomatic patients for longer – although there are appreciable differences in the way challenges around pathway specifics, FIT analysers and inclusion/exclusion criteria used have been met [11,21–23]. Nevertheless, we show that only 0.2% of patients with the lowest f-Hb concentrations were found to have CRC when investigated, and reassuringly this is the same 'miss rate' reported for very low f-Hb concentrations with longer follow-up in Scotland [23]. This 'miss rate' is an order of magnitude lower than NICE's threshold of a 3% detection rate and should reassure other English centres, and indeed groups elsewhere, that are considering the incorporation of FIT into local 2WW pathways or equivalent. We believe FIT should not be considered as a test for CRC *per se* but rather a risk stratification tool in symptomatic patients. As such, future studies should compare clinical pathways that use FIT with those that do not rather than compare FIT with the 'gold standard' of colonoscopy. These data suggest that a symptomatic pathway that incorporates FIT outperforms pathways based on history and symptoms [10,24]. We should cease to consider symptoms as a primary indicator of risk, and instead we should consider that FIT more effectively categorizes all symptomatic patients into 'high risk' and 'low risk' groups.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Pathway as introduced and during this evaluation.

Appendix S2. All FIT results were returned with automated results and appropriate guidance to GPs for interpretation selected from below.

Appendix S3. Hierarchy of primary diagnoses recorded.

Appendix S4. FIT testing process – additional detail for FITTER checklist.