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ORIGINAL ARTICLE

Evaluation of 13,466 Fecal Immunochemical Tests in Patients Attending Primary Care for High- and Low-Risk Gastrointestinal Symptoms of Colorectal Cancer

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Abstract

Aim/Objective Quantitative fecal immunochemical tests (FIT) were recommended by NICE for patients in primary care presenting with low-risk symptoms of colorectal cancer (CRC). FIT is more accurate in the detection of CRC than symptom criteria. Despite this, CRC still occurs with a negative FIT and the importance of safety netting for patients with severe or persistent symptoms is paramount. We aimed to evaluate the utilization and accuracy of FIT for CRC in low and high-risk symptom groups presenting to primary care, the effectiveness of safety netting in primary care, referral practices with FIT utilization for symptomatic patients and the clinical features of FIT negative patients with CRC.

Materials and Methods Medical records and databases of all patients undertaking a FIT sample in the Herts Valleys CCG between June 2019 and November 2021 were reviewed. 13,466 consecutive FIT samples were requested for 12,231 patients between June 2019 and November 2021.

Results Analysis of diagnostic accuracy was undertaken for the first 5341 patients with a minimum of 12 months follow up. Sensitivity for CRC, in FIT ≥ 4 µg Hb/g, ≥ 10 µg Hb/g and ≥ 100 µg Hb/g was 93% (95% CI 85–98%), 91% (95% CI 82–96%) and 72% (95% CI 60–81%) with a number needed to investigate of 36, 19 and 6, respectively.

Conclusion A FIT ≥ 10 µg Hb/g in conjunction with ongoing GP clinical concern within 8 weeks had a sensitivity for CRC of 97% (95% CI 90–100%), a PPV of 3.6% (95% CI 3.4–3.7%) and a number needed to investigate to detect one CRC of 28.

Keywords Colorectal cancer · Colonoscopy · Colorectal cancer screening · Quantitative fecal immunochemical tests (FIT) · Safety netting · Anemia

Background

The fecal immunochemical test (FIT) is a non-invasive quantitative test which measures occult blood in feces (fecal hemoglobin, fHb). In the United Kingdom (UK), FIT has been used as a diagnostic tool to include patients at risk of colorectal cancer (CRC) in screening populations. Patients with symptoms suggestive of CRC were risk stratified based on clinical criteria outlined in The National Institute for Health and Care Excellence (NICE) NG12 guidance [1]. Patients meeting NG12 symptom criteria were recommended for referral on an urgent 2-week wait (2WW) cancer pathway (Fig. 1). In 2017, FIT were recommended by NICE for patients in primary care presenting with low-risk symptoms (DG30) (Fig. 1) [2]. DG30 guidance was incorporated into the NG12 guidance regarding urgent cancer pathway referral in 2021. A FIT result of ≥ 10 µg Hb/g is considered positive and urgent cancer pathway referral is recommended. British Society of Gastroenterology recently published the use of FIT for all patients with symptoms suggestive of CRC other than rectal or anal mass or ulceration [3]. This guidance states that patients with symptoms of suspected CRC may be managed in primary care if fHb < 10 µg Hb/g provided appropriate safety netting is in place.

In June 2019 Herts Valleys CCG in alliance with the Hertfordshire and West Essex STP implemented FIT for

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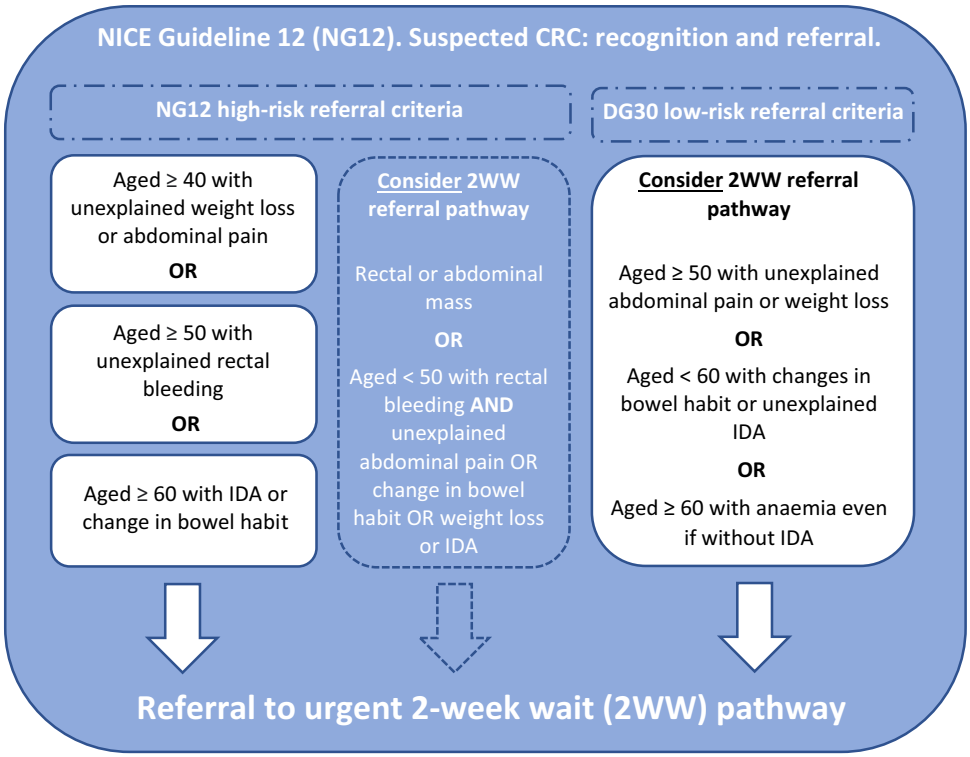

Fig. 1 Current NICE guidelines for suspected CRC. *IDA* iron deficiency anemia

the investigation of patients with gastrointestinal symptoms of CRC. Prior agreement by network consensus (including patient and non-patient public representatives) and cancer board approval implemented the use of FIT for patients meeting NICE DG30 (low risk) criteria and for some of the higher risk NG12 criteria including: patients 60 years or over with change in bowel habit and patients 40 years or over with abdominal pain and weight loss. FIT was not implemented for patients with iron deficiency anemia (IDA), rectal bleeding, or rectal or abdominal masses due to the higher positive predictive value (PPV) for CRC for patients with these symptoms and the national guidance at that time.

Studies have evaluated FIT in patients meeting both low and high-risk criteria [4–6]. FIT is more accurate in the detection of CRC than symptom criteria [7, 8]. Despite this, CRC can still occur with a negative FIT and other significant bowel pathology can be missed. The importance of safety netting for patients with severe or persistent symptoms is paramount [9, 10]. Previous studies have also suggested the presence of anemia as an additional risk factor that may impact on the interpretation of FIT results for triaging patients for urgent investigation [4, 8, 11]. The COVID-19 pandemic has introduced a new urgency to identify approaches to triage for patients with symptoms of serious colorectal disease requiring further investigation [12].

Evaluations of FIT have not demonstrated differences in the use of FIT between patients with DG30 or NG12 symptom criteria. However, these studies were undertaken in secondary care after decision for referral and triage to colonoscopy. An evaluation of FIT in primary care in the UK was previously undertaken for patients with low-risk symptoms [12]. There are few data describing the experience and outcomes of patients undertaking FIT in primary care for both low and high-risk symptom criteria. There is also a paucity of data describing referral and safety netting practices in primary care and their effectiveness following a negative FIT result.

We evaluate the first 13,466 consecutive FIT samples requested in primary care in Herts Valleys CCG from patients with both low and high-risk symptoms. All patients with a FIT result were included. We describe the accuracy of FIT for CRC for low and high-risk symptom groups as well as the accuracy of FIT use with varying clinical strategies. We discuss features of FIT negative cancers and referral and investigation behaviors in primary care associated with the incorporation of FIT for high and low-risk patients into the 2WW pathway and the effectiveness of safety netting of patients in primary care following a negative FIT result.

Methods

Samples were collected in FIT sample tubes (Eiken Chemical Co., Tokyo, Japan) in primary care and delivered to the Laboratory of West Hertfordshire Hospitals NHS Trust, daily. FIT analysis was performed using a single OC-Sensor

IO analyzer (Eiken Chemical Co., Tokyo, Japan). The OC sensor IO analyzer FIT method has a working range of 0–200 µg Hb/g and between day imprecision of 4%. The limit of detection is 2 µg Hb/g and the limit of quantification is 4 µg Hb/g.

FIT results that ≥ 10 µg Hb/g or for patients meeting NG12 criteria that were ≥ 4 µg Hb/g and < 10 µg Hb/g in the context of anemia (< 130 g/l for men or < 120 g/l for women) were considered positive. Safety netting for patients with severe or persistent symptoms with negative FIT results is advised with review of all patients with FIT results in primary care at day 12 after FIT is requested and consideration for referral and investigation within 8 weeks if ongoing clinical concern.

The FIT patient database is cross referenced quarterly with the trust cancer database to ensure capture of all CRCs for patients that have submitted a FIT sample. Cancer site and staging for all detected cancers are subsequently verified on review of medical records. For the initial 18 months of FIT service all patient records were individually assessed prospectively. For these 5341 patients symptoms on presentation were reviewed from test request clinical information and medical records in secondary care where available. Thereafter prospectively, data is updated on all FIT requests every quarter from hospital databases at West Hertfordshire Hospitals NHS Trust.

Analysis of diagnostic accuracy was undertaken for the first 5341 patients where a minimum of 12 months follow up was available to account for any potentially delayed cancer diagnoses. fHb cut offs of ≥ 4 µg Hb/g, ≥ 10 µg Hb/g, ≥ 100 µg Hb/g were taken to assess sensitivity, specificity and predictive values. The number needed to scope was defined as previously described as the number of persons undergoing a colonoscopy to detect one person with CRC as a reciprocal of the PPV (NNTScope = 1/PPV) [13]. χ^2 was used to calculate differences between categorical variables. MedCalc® statistical software was used for all calculations.

Results

Between June 2019 and November 2021, 13,466 consecutive FIT samples were requested for 12,231 patients. The median age was 61 years (IQR 55–77 years). 57% of patients were female. No result was returned in 2% of samples. The median time from request to report was 7 days (IQR 4–11 days). 23% of returned FIT results were ≥ 10 µg Hb/g. 16% of patients under 60 years compared with 27% 60 and over returned FIT results ≥ 10 µg Hb/g ($p < 0.01$). 19% of women compared with 29% of men returned FIT results ≥ 10 µg Hb/g ($p < 0.01$). 129 Patients were diagnosed with CRC after a FIT result.

15 Patients with CRC had a FIT result < 10 µg Hb/g (0.15% of all patients with a FIT < 10 µg Hb/g). Eight patients had a FIT result that was < 4 µg Hb/g. Thirteen of these patients met NG12 criteria. Five had anemia, two of these with iron deficiency. Eight patients were found to have right sided colon cancer, one in the left colon and four rectal cancer. Nine patients with a diagnosis of CRC and a FIT result < 10 µg Hb/g, had stage 1 or 2 disease at diagnosis (60%) and 5 stage III or IV disease (33%). Twelve patients with a diagnosis of CRC after a negative FIT result were referred to secondary care less than 2 months from the date of a FIT result and nine were diagnosed within 2 months of receiving a FIT result. For patients with a diagnosis of CRC after a negative FIT result the median number of days from FIT result to diagnosis was 51 days (IQR 36.5–174.5 days).

There was a fourfold increase in the number of FIT samples received per month between the first and last 6-month periods. This may in part have been due to national guidance during the COVID-19 pandemic. In the same period, patients referred on a colorectal 2WW pathway increased by 70% (Fig. 2). 44% of 12,231 patients were referred to secondary care. 29% were referred on a 2WW pathway. 32% of patients with a FIT result < 10 µg Hb/g were referred to secondary care; 50% of these on a 2WW pathway. 39% of patients underwent any investigation. 9% of patients with a FIT < 10 µg Hb/g underwent a colonoscopy.

Analysis of 5341 patients with a minimum of 12 months follow up between June 2019 and November 2020 found 58% of patients met NICE NG12 criteria. 68% of patients had a presenting symptom of change in bowel habit. Despite local guidance 9% of patients had rectal bleeding and 2% IDA. 30% of FIT samples were ≥ 10 µg Hb/g in patients meeting NG12 criteria compared with 14.5% in those meeting DG30 criteria ($p < 0.01$, Table 1).

Seventy four of 5341 patients with a minimum of 12 months follow up after a FIT result, were diagnosed with CRC. 3.3% of all patients referred to secondary care following a FIT result were diagnosed with CRC. 77% of patients with CRC were referred on a CRC pathway, 9% on a non-cancer referral pathway and 5% presented as an emergency. 30% of post FIT CRC were in the left colon, 39% in the right colon and 27% in the rectum. 28% of CRC post FIT were stage 1 and 55% were stage I or II at diagnosis. 7% of CRC post FIT were stage 4 at diagnosis.

Analysis of diagnostic accuracy was undertaken for 5341 patients with a minimum of 12 months follow up. The diagnostic accuracy of FIT for CRC at fHb cut offs of ≥ 4 µg Hb/g, ≥ 10 µg Hb/g and ≥ 100 µg Hb/g are summarized in Table 2. 43% of samples returned results below the limit of detection; 56% ≥ 4 µg Hb/g, 23% ≥ 10 µg Hb/g, 6% ≥ 100 µg Hb/g. At the same cut offs the PPV for CRC increased from 2.8% (95% CI 2.6–3.0%) to 5.2% (95% CI 4.8–5.7%) and 17% (95% CI 14.6–19.8%) respectively, but the sensitivity

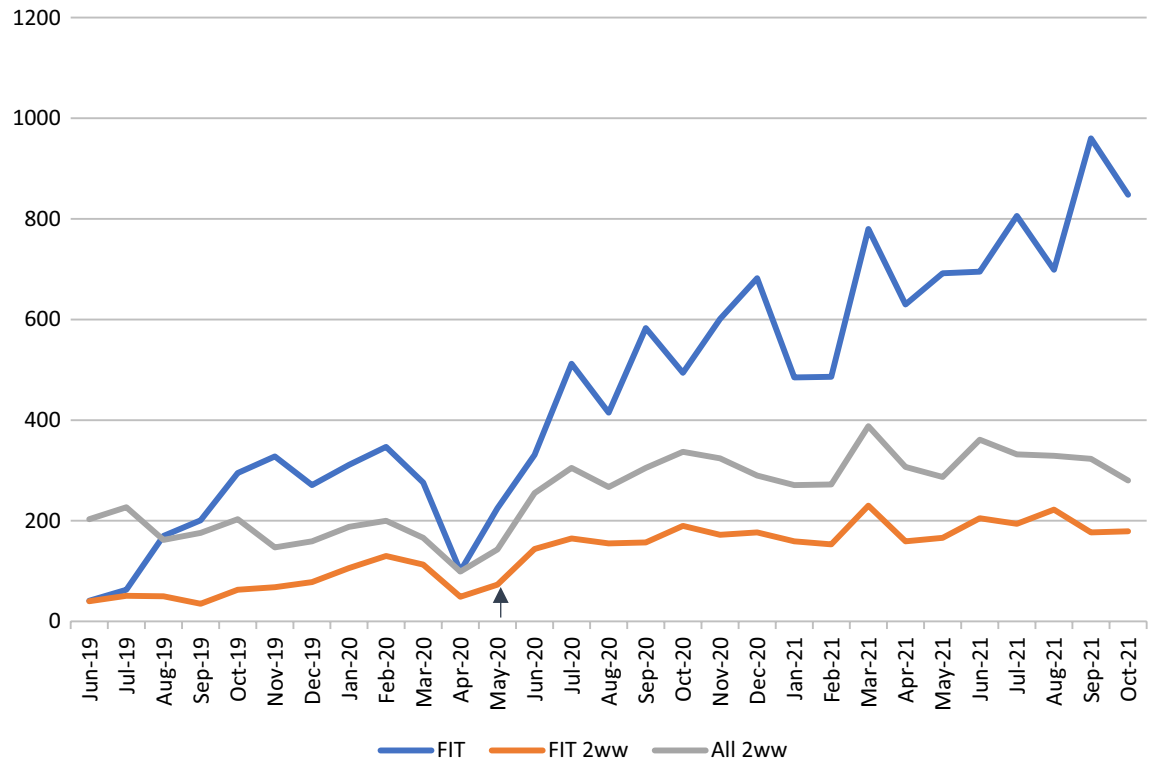

Fig. 2 Graph showing monthly FIT requests for patients with lower gastrointestinal symptoms and 2WW referrals with and without FIT results between June 2019 and October 2021. Arrow highlights timing of NHS England publication promoting use of FIT during COVID-19 pandemic [18]. May 20

Table 1 Patient demographics

	Total (12,231)		FIT ≥ 10 µg Hb/g		CRC	
	N	%	*N*	%	*N*	%
Male	5234	43	1519	29	80	1.5
Female	6997	57	1305	19	49	0.7
< 60 years	4216	34	674	16	20	0.5
> 60 years	8015	66	2185	27	109	0.8
	Total with 12 months follow up (5341)		FIT ≥ 10 µg Hb/g		CRC	
	N	%	*N*	%	*N*	%
IDA	115	2	41	36	8	7.0
Rectal bleeding	508	9	231	45	19	3.7
Diarrhea	1267	24	402	32	25	2.0
Any CIBH	3855	72	807	21	41	1.1
Pain AND weight loss	118	2	32	27	1	0.8
Pain OR weight loss	600	11	86	14	5	0.8
Anemia (non IDA) > 60 years	231	4	65	28	0	0
	Total (5341)		FIT ≥ 10 µg Hb/g		CRC	
	N	%	*N*	%	*N*	%
Meeting NG12 criteria	3098	58	957	30	61	1.9
Meeting DG30 criteria	2243	42	326	14.5	13	0.6

NB: Symptoms not mutually exclusive

Table 2 Diagnostic accuracy by FIT threshold

Cut off µg Hb/g	Positivity (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	NNS
FIT ≥ 4 µg Hb/g	56	93 (84.9–97.8)	56 (54.8–57.4)	2.8 (2.6–3)	99.8 (99.6–99.9)	36
FIT ≥ 10 µg Hb/g	23	90.5 (81.5–96.1)	78 (76.7–78.9)	5.2 (4.8–5.7)	99.8 (99.7–99.9)	19
FIT ≥ 100 µg Hb/g	6	71.6 (60.0–81.5)	95 (94.7–95.8)	17 (14.6–19.8)	99.6 (99.4–99.7)	6

for CRC declined from 93% (95% CI 84.9–97.8%) to 90.5% (95% CI 81.5–96.1%) and 71.6% (95% CI 60.0–81.5%). The number needed to scope (the number requiring colonoscopy to detect 1 CRC) was 36, 19 and 6 for a cut off ≥ 4 µg Hb/g, ≥ 10 µg Hb/g and ≥ 100 µg Hb/g, respectively.

We assessed the diagnostic accuracy for CRC with different strategies, combining clinical criteria and fHb thresholds (summarized in Table 3). The first strategy comprised patients meeting high-risk NG12 criteria regardless of FIT result **and** patients meeting low risk (DG30) criteria with a FIT ≥ 10 µg Hb/g (NICE 2021 guidance). Strategy 2 included patients meeting high-risk NG12 criteria alone (NICE 2015 guidance). Strategy 3 included patients with a FIT ≥ 10 µg Hb/g as well as those with a FIT between 4 and 9.9 µg Hb/g with anemia (2). Strategy 4 included patients meeting high-risk NG12 criteria with a FIT ≥ 4 µg Hb/g as well as patients with low-risk criteria and a FIT ≥ 10 µg Hb/g (4) and strategy 5 included all patients with a FIT ≥ 10 µg Hb/g **and** those meeting high-risk NG12 criteria safety netted with a referral to secondary care within 2 months due to ongoing clinical concern (Table 3).

The sensitivity for CRC was highest for strategy 1; 100% (95% CI 95.1–100%), with a PPV of 2.1% (95% CI 2.0–2.1%) and a NNS of 48. Strategy 5 had a sensitivity for CRC of 97% (95% CI 90.6–99.7%) with a PPV of 3.6% (95% CI 3.4–3.7%) and a NNS of 28. Strategy 4 had a sensitivity for CRC of 93% with a PPV of 2.9% and a NNS of 34. Strategy 3 had a sensitivity of 90.5% with a PPV of 4% and NNS of 24. Strategy 2 had a sensitivity of 82% with a PPV of 1.9% and a NNS of 53.

Discussion

We have evaluated the experience of FIT for a large population of patients presenting with gastrointestinal symptoms in primary care in Herts Valleys CCG. We report the increasing uptake of FIT in primary care since implementation and concomitant increases in secondary care referrals and investigations. We demonstrated the diagnostic accuracy of FIT for detection of CRC in over 5000 patients with at least 12 months follow up performed with cross reference with the local cancer database.

At a cut off of ≥ 10 µg Hb/g, FIT has a sensitivity of 90.5%. The sensitivity of FIT for CRC is in keeping with that of previous studies [4–6]. However, previous studies assessing the diagnostic performance of FIT for both low and high-risk symptoms have predominantly been conducted

Table 3 Diagnostic accuracy by FIT strategy

Strategy	Cut off µg Hb/g	Positivity (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	NNS
Strategy 1	NG12 (2021 update)	64	100 (95.1–100)	36 (35.1–37.6)	2.1 (2.0–2.1)	100	48
Strategy 2	NG12 (2015)	58	82 (71.8–90.3)	42 (40.7–43.4)	1.9 (1.7–2.1)	99.4 (99.1–99.7)	53
Strategy 3	FIT ≥ 10 µg Hb/g + FIT 4–9.9 µg Hb/g with anemia	29	90.5 (81.5–96.1)	72 (70.5–72.9)	4.2 (3.8–4.5)	99.8 (99.6–99.9)	24
Strategy 4	NG12 (2015) FIT ≥ 4 µg Hb/g + DG30 FIT ≥ 10 µg Hb/g	42	93 (84.9–97.8)	58 (56.7–59.4)	2.9 (2.7–3.1)	99.8 (99.6–99.9)	34
Strategy 5	FIT ≥ 10 µg Hb/g + FIT < 10 µg Hb/g with ongoing clinical concern for colorectal cancer investigated within 8 weeks of FIT result	37	97 (90.6–99.7)	64 (63–65.6)	3.6 (3.4–3.7)	99.9 (99.8–100)	28

in patients referred to secondary care and have demonstrated a higher PPV and lower NNS for CRC than in our evaluation. In the study by Nicholson et al. [12] assessing FIT in primary care, the positive rate at a threshold of ≥ 10 µg Hb/g was 10% compared with 23% in our population. In the Nicholson et al. [12] study patients FIT use in primary care was assumed to be for low-risk patients only. In in our cohort 14.5% of patients with low-risk symptoms returned a FIT result ≥ 10 µg Hb/g. In addition, a slightly older population was seen in our cohort. Only 1% of all patients undertaking FIT were found to have CRC and the PPV for a threshold of ≥ 4 µg Hb/g and of ≥ 10 µg Hb/g are lower than in previous studies [14]. This is likely to be explained by the real-life representation described, as well as the exclusion of patients with rectal bleeding or IDA (both symptoms with a higher risk of CRC) from FIT requesting in our pathway [15, 16].

We also demonstrate the diagnostic performance of FIT incorporating the fHb threshold in conjunction with other clinical categorization. The addition of anemia with detectable FIT in our population did not increase the sensitivity for CRC demonstrated in other studies [4]. Although recent updated 2021 NICE guidance has the greatest sensitivity for CRC, the PPV for this strategy was below the threshold for referral suggested by NICE and had a high NNS to detect a patient with cancer. We demonstrate that a fHb threshold of ≥ 10 µg Hb/g in conjunction with ongoing GP clinical concern has a sensitivity of 97%, with a PPV closest to the 3% threshold suggested by NICE for an urgent suspected cancer pathway referral. This strategy had a higher sensitivity and PPV compared with a FIT ≥ 4 µg Hb/g for patients with high-risk symptoms. Reassuringly, safety netting of patients with a negative FIT appears to have been effective and timely with early referral to secondary care if ongoing concern regarding patients' symptoms.

The strengths of this evaluation are the use of FIT for a large number of patients presenting in primary care with symptoms of CRC and the large number of patients with at least 12 months follow up. The limitations are that not all patients were evaluated with colonoscopy. However, it is assumed that patients presenting with symptoms relating to CRC would be diagnosed within 12 months of presentation due to progression of disease. This is a single center evaluation and it is possible patients developing CRC could have been diagnosed elsewhere. However, it is atypical that practices linked to the hospital laboratory where the FIT samples were analyzed would refer to another hospital. In addition, although in our cohort the majority of patients met NG12 criteria, our pathway excluded those with higher risk symptoms of rectal bleeding and IDA [15–17].

Incorporation of FIT into the diagnostic pathway for patients with symptoms of CRC has not been accompanied by a reduction in referrals to secondary care on a 2WW pathway.

Over the same period a significant increase in referrals was seen although direct causality with the use of FIT in patient assessment is not certain and several other factors could also account for this. However, a large population of symptomatic patients have had access to a test for CRC, that would not otherwise have accessed optical or virtual colonoscopy for their symptoms. This may have led to a low PPV for FIT at a threshold of ≥ 10 µg Hb/g compared with other studies. However, a high proportion of cancers were diagnosed at an early stage and 60% of cancers diagnosed after a negative FIT were stage I/II at diagnosis. This may represent the opportunity FIT offers for wider testing at a lower threshold, leading to earlier diagnosis. However, further analysis and follow up is required to confirm this. In our evaluation a fHb threshold of ≥ 10 µg Hb/g in conjunction with ongoing GP clinical concern appears to safely offer this wide testing opportunity at the threshold for referral according with NICE guidance. The acceptable FIT threshold and strategy for urgent referral balancing available resources and patient acceptability requires ongoing consideration and further national guidance is awaited in 2022.

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Author's contribution JL led the planning and writing of the manuscript. RC and NK collected the data and helped with the writing of the manuscript. BP performed the statistical analysis. PS helped with writing of the manuscript.

Conflict of interest Author declare that there is no conflict of interest from any of the authors in the publication of this manuscript.

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