ORIGINAL ARTICLE

Finding the needle in the haystack: the diagnostic accuracy of the faecal immunochemical test for colorectal cancer in younger symptomatic patients

Nigel D'Souza^{1,2,3} | Kevin Monahan^{3,4} | Sally C. Benton⁵ | Lisa Wilde⁶ | Muti Abulafi¹ | the NICE FIT Steering Group*

¹Croydon University Hospital, Croydon, UK

²University Hospital Southampton, Southampton, UK

³Imperial College London, London, UK

⁴St Mark's Hospital, Harrow, UK

⁵Royal Surrey County Hospital, Guildford, UK

⁶Bowel Cancer UK, London, UK

Correspondence

Muti Abulafi, Consultant Colorectal Surgeon, Croydon University Hospital, London Road, Croydon CR7 7YE, UK.
Email: muti.abulafi@nhs.net

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Abstract

Aim: Detection of early onset colorectal cancer is challenging, and remains a rare diagnosis amongst younger people with gastrointestinal symptoms. We investigated whether faecal immunochemical testing (FIT) could identify younger patients at higher risk of colorectal cancer or serious bowel disease including colorectal cancer, inflammatory bowel disease or advanced adenomas.

Methods: A subgroup analysis was performed of symptomatic patients under 50 years of age (<50) from the NICE FIT study, a multicentre, prospective diagnostic accuracy study of FIT conducted between October 2017 and December 2019. The diagnostic accuracy of FIT for colorectal cancer and serious bowel disease was investigated in younger patients at different faecal haemoglobin (f-Hb) cut-offs of 2, 10 and 150 µg blood/g faeces (µg/g).

Results: Early onset colorectal cancer was diagnosed in 1.5% (16/1103) of younger symptomatic patients. The sensitivity of FIT for younger patients aged <50 was 87.5% (95% CI 61.7%–98.4%), 81.3% (54.4%–96.0%) and 68.8% (41.3%–89.0%) at f-Hb cut-offs of 2, 10 and 150 µg/g, respectively. The positive predictive value for colorectal cancer increased from 4.2% (2.3%–6.9%) to 11.5% (5.9%–19.6%) at cut-offs of 2 and 150 µg/g, while the positive predictive value for serious bowel disease increased from 31.3% (26.3%–36.5%) to 65.6% (55.2%–75.0%) at the same cut-offs. The negative predictive value of FIT for colorectal cancer remained above 99.5% at all cut-offs.

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Conclusion: Detectable f-Hb on FIT in symptomatic younger patients may indicate referral for investigation of colorectal cancer and serious bowel disease.

KEYWORDS

colonoscopy, colorectal neoplasms, diagnostic accuracy, faecal immunochemical test, FIT

INTRODUCTION

The identification of younger people at risk of colorectal cancer (CRC) represents a significant challenge in primary and secondary care. Whilst the absolute prevalence of CRC in younger people remains low, the disease incidence in this population is unfortunately increasing. Accurate risk assessment remains elusive given the poor predictive value of symptoms in younger people and as such novel approaches to risk stratification may be of significant clinical utility.

The incidence of early onset colorectal cancer (EOCRC), defined as a diagnosis of CRC under age 50 years, has significantly increased in recent years [1–6]. A contemporary global analysis [1] has reported an increase in the incidence of EOCRC in 19 out of 36 countries confirming similar data previously reported from countries including the UK [7], USA [3], Norway [4], Australia [5] and Canada [6]. Although the incidence of EOCRC is increasing, the absolute risk of CRC in this population remains low, with an incidence rate of 7.6 per 100 000 in patients in England aged between 30 and 39, or 2.8 per 100 000 in patients aged between 20 and 29 compared to 165.9 per 100 000 in patients aged between 60 and 69 [8].

The poor predictive value of gastrointestinal symptoms provides an additional challenge in this population. Bowel symptoms in younger patients may be attributed by clinicians to common benign colorectal disease, such as rectal bleeding from haemorrhoids or abdominal pain from irritable bowel syndrome [9–11]. Unfortunately, younger patients who report non-specific symptoms but who have an underlying CRC may require multiple visits before referral for investigation, resulting in longer time to diagnosis [12–15]. A survey of EOCRC patients in the UK reported that 43% of patients required three or more visits to their primary care physician (PCP) before referral to secondary care for further investigation, and that 65% were initially given an incorrect diagnosis [11]. Patients themselves may not suspect their bowel symptoms may be due to cancer: in the same survey, 75% of patients did not suspect their symptoms were due to CRC, and 30% delayed seeing their PCP for up to 3 months [11]. The interval from referral to diagnosis in younger patients is significantly longer in younger patients in national UK data, probably due to an absence of criteria indicating urgent referral for suspected cancer [12]. National cohort data also report that EOCRC more commonly presents as an emergency, at a more advanced stage of diagnosis [12, 14, 16, 17], although younger patients tend to have better survival than older patients [18, 19]. It has been suggested that advanced-stage disease at presentation in younger patients may be due to delay in diagnosis, but there is also evidence that this may be due to a higher prevalence of biologically 'aggressive' tumours [16].

What does this paper add to the literature?

The faecal immunochemical test may indicate urgent investigation of younger patients with bowel symptoms; higher faecal haemoglobin concentrations (above 150 µg/g) confer a 12% risk of colorectal cancer but also a 66% risk of serious bowel disease, including colorectal cancer, advanced adenomas and inflammatory bowel disease.

Thus the diagnosis of CRC in younger patients is difficult, and improvements in early diagnosis in this population may improve outcomes. We postulate that faecal immunochemical testing (FIT) may assist PCPs to identify which younger patients with higher risk symptoms may require colonoscopy or other diagnostics. FIT is a non-invasive, quantitative immunoassay which detects the globin moiety of haemoglobin in faeces and can reliably measure the faecal haemoglobin concentration (f-Hb) to the nearest microgram of haemoglobin per gram of faeces (µg/g). To our knowledge, there are no published data specifically evaluating the diagnostic accuracy of FIT in younger patients referred urgently with suspected CRC symptoms.

METHODS

The primary end-point of this analysis was to establish the sensitivity of FIT for CRC in younger patients with symptoms of suspected CRC. The secondary end-points were to establish the diagnostic accuracy of FIT for CRC, advanced neoplasia (AN) (i.e., CRC and advanced adenoma [AA]) and serious bowel disease (SBD) (CRC, AA and inflammatory bowel disease [IBD]) in younger patients.

The NICE FIT study was a multicentre, ethically approved, diagnostic accuracy study of FIT in English patients referred urgently from primary care with symptoms of suspected CRC that were investigated with colonoscopy [20]. The study was designed with patient and public involvement, according to the standards of reporting of diagnostic studies (STARD) guidelines [21] and was registered prospectively (ISRCTN 49676259) after ethical approval by the National Research Ethics Committee on 23 January 2017 (reference 16/LO/2174). Patients were recruited at 50 National Health Service hospitals across England and took part in the study with informed consent. Symptom criteria for an urgent referral described by the National Institute for Health and Care Excellence (NICE) NG12 and DG30 criteria include change in bowel habit, iron deficiency anaemia, abdominal or rectal mass, and rectal bleeding [22, 23]. When patients were referred

with multiple symptoms, a previously reported hierarchy was used to match each patient to one symptom [20]. We defined younger patients as those referred urgently with symptoms under the age of 50 years ('<50'), with a comparator population ('≥50') of patients referred aged 50 years or older in line with published epidemiological data [2, 3, 5].

The f-Hb results on FIT measured on an HM-Jack analyser (Hitachi Chemical Diagnostics Systems Co. Ltd, Tokyo, Japan, supplied by Alpha Labs Ltd, Eastleigh, Hants, UK) were compared to colonoscopy findings. Data on patient demographics (age, sex, ethnicity, deprivation), serum haemoglobin and ferritin measurements and pathology results including tumour stage were also captured. AAs were defined in the study protocol as adenomas greater than 10 mm, adenomas of any size with high grade dysplasia, and serrated polyps in the right colon. Patients with multiple findings at colonoscopy were re-categorized with one diagnosis in a hierarchy: CRC ranked highest followed by AAs and then IBD, followed by non-malignant findings. The diagnostic accuracy of FIT was calculated for CRC, AN and SBD. A full description of the methodology for the index test, reference standard, hierarchy of findings at colonoscopy and sample size calculation has been published previously [20].

Categorical data were compared with χ^2 tests; the Kruskal-Wallis test was used for ordinal or quantitative non-normal variables. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value were reported for each f-Hb cut-off, with 95% confidence intervals. Receiver operating characteristic (ROC) curves were plotted for f-Hb. These were done using an initial threshold of 0.1 to calculate sensitivity and specificity, and then recalculated with increments of 0.1 to plot the ROC curve. In every statistical analysis, $P < 0.05$ was considered significant. All analyses were performed using Stata® 15 (StataCorp 2017, Stata Statistical Software, Release 15; StataCorp LLC, College Station, Texas, USA).

Role of the funding sources

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RESULTS

In total, 9822 patients who underwent FIT for gastrointestinal symptoms were included in the final analysis, of whom 1103 were <50 years. The study flow is reported in Figure 1 and has been reported previously [20].

Population description

Patient demographics are reported in Table 1. The median age of patients in the <50 group was 44 years, and the median age in the ≥50 group was 67 years. Women constituted 59.8% of patients <50 and 54.3% of patients ≥50. Patients <50 were more ethnically diverse. Although the median index of deprivation was 6 in both groups, younger patients had a lower mean index of deprivation (5.7 vs. 6.3, $P < 0.001$) and were significantly more likely to have a lower index of deprivation.

Diagnostic yield at colonoscopy

The findings at colonoscopy are reported in Table 2. The most common finding in all age groups was a normal colonoscopy (51.3% of patients <50, 28.8% of patients ≥50). CRC was significantly less commonly diagnosed in younger patients (1.5% of patients <50 vs. 3.6% of patients ≥50, $P < 0.001$), as were AAs (2.6% of patients <50, 4.5% of patients ≥50, $P = 0.004$) and lower risk adenomas (13.1% of patients <50, 25% of patients ≥50, $P < 0.001$). IBD was significantly more commonly found in younger patients (7.9% of patients <50, 3.9% of patients ≥50, $P < 0.001$) and as a result there was no overall difference in the incidence of significant bowel disease (SBD = IBD + AA + CRC), which was present in 12.0% (132/1103 vs. 1045/8719) in both populations.

Diagnostic accuracy of FIT for CRC

The diagnostic accuracy of FIT for CRC is reported in Table 3. The characteristics of all patients <50 diagnosed with CRC in this study are reported in Appendix S1. The sensitivity of FIT for patients aged <50 was 87.5% (95% CI 61.7%–98.4%), 81.3% (54.4%–96.0%) and 68.8% (41.3%–89.0%) at cut-offs of 2, 10 and 150 µg/g, respectively. The PPV for CRC increased from 4.2% (2.3%–6.9%) to 11.5% (5.9%–19.6%) at cut-offs of 2 and 150 µg/g. The sensitivity of FIT for patients aged ≥50 was 97.4% (95.0%–98.9%), 91.4% (87.7%–94.2%) and 70.9% (65.6%–75.9%) at cut-offs of 2, 10 and 150 µg/g, respectively.

The number needed to scope (NNS) to detect one CRC ranged from 23.8 in patients with detectable f-Hb (above the 2 µg/g cut-off) to one CRC per 8.8 colonoscopies with f-Hb measured above the 150 µg/g cut-off in patients <50. At the same FIT thresholds, the NNS was 10.9 and 2.9 in patients ≥50.

When f-Hb was undetectable (<2 µg/g), CRC prevalence (PPV) was less than 0.4% in all age groups, and the NNS ranged from 250 to 1000.

On ROC curve analysis (Figure 2), the area under the curve (AUC) was 0.86 (0.76–0.97) in patients <50 and 0.94 (0.93–0.95) for patients ≥50.

FIGURE 1 Study flow diagram. Ineligible index test: FIT performed after colonoscopy, FIT sample inadequate, FIT sample >14 days old. Ineligible reference standard: incomplete colonoscopy, underwent other investigations, cancelled colonoscopy, withdrew from study or missing data

Diagnostic accuracy of FIT for AN

The diagnostic accuracy of FIT for AN is reported in Table 4. The sensitivity of FIT for patients with AN aged <50 was 77.8% (62.9%–88.8%), 64.4% (48.8%–78.1%) and 48.9% (33.7%–64.2%) at cut-offs of 2, 10 and 150 µg/g, respectively. The PPV for AN increased from 10.4% (7.4%–14.2%) to 22.9% (15.0%–32.6%) at cut-offs of 2 and 150 µg/g. The sensitivity of FIT for patients aged ≥50 was 79.6% (76.4%–82.5%), 65.4% (61.7%–68.9%) and 43.1% (39.4%–46.9%) at cut-offs of 2, 10 and 150 µg/g, respectively.

The NNS to detect one AN ranged from 9.6 in patients with detectable f-Hb (above the 2 µg/g cut-off) to one AN per 4.4 colonoscopies with f-Hb measured above the 150 µg/g cut-off in patients <50. At the same FIT thresholds, the NNS was 5.9 and 2.1 in patients ≥50. On ROC curve analysis (Figure 3), the AUC of FIT for AN was 0.80 (0.72–0.87) in patients <50 and 0.80 (0.79–0.82) for patients ≥50.

Diagnostic accuracy of FIT for SBD

The diagnostic accuracy of FIT for SBD is reported in Table 5. The PPV for SBD in patients <50 increased from 31.3% (26.3%–36.5%) to 65.6% (55.2%–75.0%) at cut-offs of 2 and 150 µg/g. The PPV for SBD in patients ≥50 increased from 24.2% (22.7%–25.7%) to 64.3% (60.5%–68.0%) at the same cut-offs. The NNS to detect one case of SBD ranged from 3.2 in patients with detectable f-Hb (above the 2 µg/g cut-off) to 1.5 with f-Hb measured above the 150 µg/g cut-off in patients <50. At the same cut-offs the NNS was 4.1 and 1.6 in patients ≥50.

In all age groups, when f-Hb was undetectable (<2 µg/g), SBD prevalence (PPV) was less than 4.5% in all age groups, and the NNS ranged from 22.2 to 28.6. On ROC curve analysis (Figure 4), the AUC of FIT for SBD was 0.83 (0.79–0.88) in patients <50 and 0.80 (0.78–0.81) for patients ≥50.

TABLE 1 Patient characteristics

		<50 years		≥50 years		P
		n	%	n	%	
Total		1 103	100	8 719	100	
Age (years)	Mean	42		66.7		
	Standard deviation (SD)	6.5		9.16		
	Minimum	17		50		
	Median	44		67		
	Maximum	49		97		
Sex	Women	659	59.8	4 735	54.3	0.001
	Men	444	40.2	3 984	45.7	
Ethnicity	White	685	68.4	6 768	79	<0.001
	Asian	104	9.8	510	5.95	<0.001
	Black	57	5.4	308	3.6	0.007
	Mixed	12	1.1	46	0.5	0.02
	Chinese	12	1.2	29	0.3	<0.001
	Other ^a	192	18.1	911	10.6	<0.001
	Missing	49	4.4	138	1.4	<0.001
Index of deprivation	Mean	5.7		6.3		<0.001
	Standard deviation (SD)	2.6		2.6		
	Median	6		6		
Referral symptom						
Mass		30	2.7	147	1.7	0.02
Iron deficiency anaemia		65	5.9	414	4.8	0.10
Rectal bleeding		510	46.2	2 536	29.1	<0.001
Change in bowel habit		231	20.9	4 018	46.1	<0.001
Abdominal pain and/or weight loss		88	8.0	646	7.4	0.50
Anaemia (non-iron deficiency)		21	1.9	482	5.5	<0.001
Other		158	14.3	476	5.5	<0.001

^aOther ethnicity: any other ethnic group, not specified.

DISCUSSION

This is the first study to specifically report on the diagnostic accuracy of FIT for CRC in younger patients with suspected bowel cancer symptoms. The negative predictive value of FIT for CRC in our data is very high due to the low CRC prevalence in younger patients of 1.5%. The sensitivity of FIT for CRC was moderate at lower cut-offs of 2 and 10 µg/g, but the prevalence (i.e., PPV) was 11.5% at the highest cut-off of 150 µg/g. However, FIT was associated with a high prevalence of SBD of 46.1% at the 10 µg/g cut-off recommended by NICE DG30. Even at a lower cut-off of detectable f-Hb (>2 µg/g), the prevalence of SBD was 31.3%, rising to 65.6% at a cut-off of 150 µg/g. This suggests that the presence of blood in faeces on FIT may indicate urgent investigation of symptomatic younger patients, particularly when f-Hb measures above 150 µg/g. Although our data may not support the use of FIT as a test to rule out CRC in younger patients, it can help clinicians in primary care to identify patients who require urgent referral and investigation for SBD, potentially an

important application given the poor predictive value of symptoms alone for the identification of high risk patients. FIT at the time of initial presentation of younger patients with non-specific symptoms may also prevent delayed diagnosis due to further repeated attendances in primary care.

The role of heritable factors in EOCRC patients has been moderately well characterized, and provides significant opportunities for cancer prevention. However, the majority of EOCRC cannot currently be accounted for by known genetic syndromes, as pathogenic predisposition gene variants have been identified in only 15%–20% of patients [24]. In addition, only a minority of people with high risk conditions such as Lynch syndrome have been identified. A national CRC screening programme which incorporates all younger patients may not be feasible given the rarity of the disease in this population. While the American Cancer Society guidelines have advocated lowering the national screening age for CRC to 45 [25], this is based on an assumed increased CRC risk due to birth cohort effects that is not yet seen in real-world data. Furthermore, according to modelling

TABLE 2 Findings at colonoscopy by age group

Diagnosis	<50	≥50	P	Total
Normal	566 (51.3%)	2 513 (28.8%)	<0.001	3079
Lower risk adenoma	144 (13.1%)	2 177 (25.0%)	<0.001	2321
Diverticular disease	80 (7.3%)	2 214 (25.4%)	<0.001	2294
Perianal disease	166 (15.1%)	557 (6.4%)	<0.001	723
Microscopic colitis	9 (0.8%)	143 (1.6%)	0.04	152
Miscellaneous	6 (0.5%)	47 (0.5%)	0.98	53
Angiodysplasia	0	23 (0.3%)	0.09	23
Inflammatory bowel disease	87 (7.9%)	340 (3.9%)	<0.001	427
Advanced adenoma	29 (2.6%)	392 (4.5%)	0.004	421
Colorectal cancer	16 (1.5%)	313 (3.6%)	<0.001	329
SBD (IBD + AA + CRC)	132 (12.0%)	1 045 (12.0%)	0.99	1177
Total	1 103	8 719		9822

Abbreviations: AA, advanced adenoma; CRC, colorectal cancer; IBD, inflammatory bowel disease; SBD, serious bowel disease.

^aPerianal disease: anal fissure, anal fistula, haemorrhoids, solitary rectal ulcer. Miscellaneous: lipoma, melanosis coli, parasites.

TABLE 3 Diagnostic accuracy of FIT for CRC by age group

Age group	Cut-off (µg/g)	FIT positivity	CRC per cut-off ^b	NNS	Sensitivity	Specificity	PPV	NPV
<50 years	None ^a		16/16	68.9	–	–	–	–
	<2	69.5	02/16	333.3	12.5 (1.6–38.3)	29.6 (26.9–32.4)	0.3 (0.0–0.9)	95.8 (93.1–97.7)
	≥2	38.1	14/16	23.8	87.5 (61.7–98.4)	70.4 (67.6–73.1)	4.2 (2.3–6.9)	99.7 (99.1–100.0)
	≥10	19.2	13/16	14.7	81.3 (54.4–96.0)	83.6 (81.3–85.5)	6.8 (3.7–11.4)	99.7 (99.0–99.9)
	≥150	7.5	11/16	8.7	68.8 (41.3–89.0)	92.2 (90.4–93.7)	11.5 (5.9–19.6)	99.5 (98.8–99.8)
≥50 years	None ^a		313/313	27.9	–	–	–	–
	<2	61.9	8/313	1000	2.6 (1.1–5.0)	35.9 (34.8–36.9)	0.1 (0.1–0.3)	90.8 (89.8–91.8)
	≥2	38.1	305/313	10.9	97.4 (95.0–98.9)	64.1 (63.1–65.2)	9.2 (8.2–10.2)	99.9 (99.7–99.9)
	≥10	19.2	286/313	5.8	91.4 (87.7–94.2)	83.5 (82.7–84.3)	17.1 (15.3–19.0)	99.6 (99.4–99.7)
	≥150	7.5	222/313	2.9	70.9 (65.6–75.9)	94.9 (94.4–95.3)	34 (30.4–37.8)	98.9 (98.6–99.1)

Note: 95% confidence interval within parentheses.

Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; NNS, number needed to scope; NPV, negative predictive value; PPV, positive predictive value, or prevalence.

^aNone is no FIT, i.e., all patients < or ≥ 50 years.

^bNumber of CRC detected at cut-off/number of CRC diagnosed in age group.

estimates, as the population screening age is lowered the relative risk of complications from colonoscopy increases alongside diminishing efficacy [26]. Pragmatically, many countries and populations

do not have the endoscopy or financial resources to adopt such a screening strategy. The vast majority of EOCRC may most likely be diagnosed after presentation with symptoms.

FIGURE 2 ROC curve analysis of FIT for CRC. Left: Patients aged <50 years. Right: Patients aged ≥50 years

TABLE 4 Diagnostic accuracy of FIT for AN by age group

Age group	Cut-off (μg/g)	FIT positivity	AN per cut-off ^b	NNS	Sensitivity	Specificity	PPV	NPV
<50 years	None ^a		45/45	24.5	–	–	–	–
	<2	69.5	10/45	76.7	22.2 (11.2–37.1)	28.4 (25.7–31.3)	1.3 (0.6–2.4)	89.6 (85.8–92.6)
	≥2	30.5	35/45	9.6	77.8 (62.9–88.8)	71.6 (68.7–74.3)	10.4 (7.4–14.2)	98.7 (97.6–99.4)
	≥10	17.3	29/45	6.6	64.4 (48.8–78.1)	84.7 (82.4–86.8)	15.2 (10.4–21.1)	98.2 (97.2–99.0)
	≥150	8.7	22/45	4.4	48.9 (33.7–64.2)	93.0 (91.3–94.5)	22.9 (15.0–32.6)	97.7 (96.6–98.5)
≥50 years	None ^a		705/705	12.3	–	–	–	–
	<2	61.9	144/705	37.5	20.4 (17.5–23.6)	34.4 (33.4–35.5)	2.7 (2.3–3.1)	83.1 (81.8–84.4)
	≥2	38.1	561/705	5.9	79.6 (76.4–82.5)	65.6 (64.5–66.6)	16.9 (15.6–18.2)	97.3 (96.9–97.7)
	≥10	19.1	461/705	3.6	65.4 (61.7–68.9)	84.9 (84.1–85.7)	27.6 (25.5–29.8)	96.5 (96.1–97.0)
	≥150	7.5	304/705	2.1	43.1 (39.4–46.9)	95.6 (95.2–96.1)	46.6 (42.7–50.5)	95.0 (94.5–95.5)

Note: 95% confidence interval within parentheses.

Abbreviations: AN, advanced neoplasia; FIT, faecal immunochemical test; NNS, number needed to scope; NPV, negative predictive value; PPV, positive predictive value, or prevalence.

^aNone is no FIT, i.e., all patients < or ≥ 50 years.

^bNumber of AN detected at cut-off/number of AN diagnosed in age group.

Colonoscopy remains the gold standard investigation of gastrointestinal symptoms and is increasingly employed in younger patients, predominantly to investigate symptoms [27]. Through identification and excision of adenomas and other precursors it is also an effective CRC preventative intervention [28]. In contrast, FIT is associated with a lower adenoma detection rate than

colonoscopy, and thus is better designed to identify CRC rather than AA, as confirmed by our data where the false negative rate for AA was 54.6% at 10 μg/g [29]. The sensitivity of FIT for AN, with both CRC and AA, remained low in both younger and older patients in our data as a result of its low sensitivity to AA. As such there is only a moderate estimated benefit of colonoscopy as a

FIGURE 3 ROC curve analysis of FIT for AN. Left: Patients aged <50 years. Right: Patients aged ≥50 years

TABLE 5 Diagnostic accuracy of FIT for SBD by age group

Age group	Cut-off (μg/g)	FIT positivity	SBD per cut-off ^b	NNS	Sensitivity	Specificity	PPV	NPV
<50 years	None ^a		132/132	8.4	–	–	–	–
	<2	69.5	27/132	28.6	20.5 (13.9–28.3)	23.8 (21.1–26.6)	3.5 (2.3–5.1)	68.8 (63.5–73.7)
	≥2	30.5	105/132	3.2	79.5 (71.7–86.1)	76.2 (73.4–78.9)	31.3 (26.3–36.5)	96.5 (94.9–97.9)
	≥10	17.3	88/132	2.2	66.7 (57.9–74.6)	89.4 (87.3–91.3)	46.1 (38.9–53.4)	95.2 (93.6–96.5)
	≥150	8.7	62/132	1.5	47.7 (39.0–56.6)	96.6 (95.3–97.6)	65.6 (55.2–75.0)	93.1 (91.4–94.6)
	None ^a		1045/1045	8.3	–	–	–	–
≥50 years	<2	61.9	242/1045	22.2	23.2 (20.6–25.8)	32.8 (31.7–33.8)	4.5 (3.9–5.1)	75.8 (74.3–77.3)
	≥2	38.1	803/1045	4.1	76.8 (74.2–79.4)	67.2 (66.2–68.3)	24.2 (22.7–25.7)	95.5 (94.9–96.1)
	≥10	19.2	649/1045	2.6	62.1 (59.1–65.1)	86.7 (85.9–87.4)	38.8 (36.5–41.2)	94.4 (93.8–94.9)
	≥150	7.5	420/1045	1.6	40.2 (37.2–43.2)	97 (96.6–97.3)	64.3 (60.5–68.0)	92.3 (91.6–92.8)
	None ^a		1045/1045	8.3	–	–	–	–

Note: 95% confidence interval within parentheses.

Abbreviations: FIT, faecal immunochemical test; NNS, number needed to scope; NPV, negative predictive value; PPV, positive predictive value, or prevalence; SBD, serious bowel disease.

^aNone is no FIT, i.e., all patients < or ≥ 50 years.

^bNumber of SBD detected at cut-off/number of SBD diagnosed in age group.

preventative intervention in the younger symptomatic population compared to older individuals where AAs are more prevalent. In our study the absolute prevalence of CRC and AAs is low in symptomatic individuals under 50 years of age; as such FIT may be suitably employed in the identification of prevalent CRCs in this population. FIT may also offer more effective selection of patients

who require colonoscopy, particularly where access to endoscopy may be limited during the COVID-19 pandemic.

Our results illustrate the difficulty in identifying CRC in younger symptomatic patients as only 1.5% of patients <50 were diagnosed with CRC. Symptoms are therefore poorly predictive for CRC in younger patients. Furthermore, it is assumed that only younger

FIGURE 4 ROC curve analysis of FIT for SBD. Left: Patients aged <50 years. Right: Patients aged ≥50 years

patients with the highest risk symptoms have been captured in this study, and that younger patients at even lower risk may have quite reasonably been managed in primary care and not referred for investigations. The primary end-point of the original NICE FIT study was powered to establish the sensitivity of FIT for CRC in patients referred urgently with suspected CRC symptoms and was not age stratified [20]. Consequently, this study is underpowered to detect the diagnostic accuracy of FIT in younger symptomatic patients. The prevalence of CRC may be lower in this group, and it is possible that triage for investigation with FIT may generate more false positive results. However, in the previous analysis of the NICE FIT study, triage of a group with lower risk (DG30) symptoms led to more true negative rather than false positive results [30]. There is no biological reason to suggest that the sensitivity of FIT will diminish in this population and fail to detect cancer. Further adequately powered research in a lower risk population may be required to determine the diagnostic accuracy of FIT for CRC or SBD, and also importantly the specificity and false positive rate, to avoid unnecessary anxiety to patients and unnecessary urgent referrals for investigation.

To establish accurate risk scores for younger symptomatic patients, prospective studies would need to be conducted in primary care to establish an accurate denominator, as only the highest risk patients will be referred on to secondary care. Due to the low prevalence of CRC in an unselected symptomatic younger population in primary care, this would require a very large study size. More objective measures alongside FIT, such as anaemia or thrombocytosis, may help to determine the risk of EOCRC [31, 32]. Further research into further non-invasive biomarkers for CRC such as breath [33] or urinary volatile organic compounds [34], or faecal/serum DNA samples, may help to identify patients at higher risk of CRC. Adding in faecal calprotectin into pathways for diagnosis of SBD may reduce false negative or false positive tests, although the detection of CRC and IBD was optimized by FIT without faecal calprotectin in a previous prospective study in primary care [35].

CRC diagnosis in younger symptomatic patients is difficult and FIT alone is unlikely to solve this problem. However, FIT could provide a diagnostic adjunct for PCPs to risk stratify referred patients in a similar way to how faecal calprotectin is currently being used. The higher prevalence of SBD in patients with elevated f-Hb concentrations of 150 µg/g on FIT should indicate referral in younger patients and suggests that an urgent pathway should be set up for these patients, as this may avoid any delay to diagnosis in primary or secondary care [36].

CONCLUSION

FIT holds promise in the investigation of younger patients with bowel symptoms. Detectable f-Hb should indicate referral for investigation of SBD, which will be detected in one in three patients. Higher f-Hb concentrations above 150 µg/g confer a 12% risk of CRC and a 66% risk of SBD indicating urgent referral for investigation. Further work is required to assess the utility of FIT to risk stratify younger symptomatic patients who are likely to benefit from invasive investigations such as colonoscopy.

AUTHOR CONTRIBUTORS

NDS and MA were responsible for the conception and design of the study. NDS, KM, LW, SB and MA were responsible for data analysis and interpretation, and critical revision of the manuscript. The trial steering group provided oversight of recruitment activity, data analysis and interpretation. All authors were responsible for data acquisition. MA is the guarantor of the study, and affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

Data will be shared with NHS England for further analysis but is not publicly available.

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The NICE FIT steering committee comprised: Theo Georgiou Delisle (Croydon University Hospital); Toni Mitchell (Hammersmith Medical Research); Kevin Monahan (West Middlesex University Hospital). The central study team included Anthonette Dzakupas-Amevor and Christine Nangendo. Principal Investigators: Pasha Nisar (Ashford and St Peter's Hospitals NHS Foundation Trust); Yuksel Gercek (Bedford Hospital NHS Trust); Mark Austin (Brighton and Sussex University Hospitals NHS Trust); Nigel Hall (Cambridge University Hospitals NHS Foundation Trust); Robin Gupta (Chesterfield Royal Hospital NHS Foundation Trust); Rakesh Bhardway (Dartford and Gravesham NHS Trust); Arabis Oglesby (Dorset County Hospital NHS Foundation Trust); Usman Khan (East Cheshire NHS Trust); Nasser Khan (East and North Hertfordshire NHS Trust); Sudhakar Mangam (East Kent Hospitals University NHS Foundation Trust); Alexandra Cope (Frimley Health NHS Foundation Trust); Isobel Thomas (United Lincolnshire Hospitals NHS Trust); John Ramage (Hampshire Hospitals NHS Foundation Trust); Mark Pugh (Isle of Wight NHS Trust); Roshan Lal (James Paget University Hospitals NHS Foundation Trust); Tushar Agarwal, Ian Jenkins (London North West University Healthcare); Mark Hill (Maidstone and Tunbridge Wells NHS Trust); Henk Wegstapel (Medway NHS Foundation Trust); Vimal Hariharan (North West Anglia NHS Foundation Trust); Salim Kurrimboccus (Pennine Acute Hospitals NHS Trust); Andrew Clarke (Poole Hospital NHS Foundation Trust); Tracey Dobson (Portsmouth Hospitals NHS Trust); Joseph Ellul (Princess Royal University Hospital, King's College Hospital NHS Foundation Trust); Hayley Webb (Queen Elizabeth Hospital Kings Lynn NHS Trust); Gemma Faulkner (Bolton NHS Foundation Trust); Sanjaya Wijeyekoon (Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust); Neil Smart (Royal Devon and Exeter NHS Foundation Trust); John Stebbing (Royal Surrey NHS Foundation Trust); Jonathan Epstein (Salford Royal NHS Foundation Trust); Graham Branagan (Salisbury NHS Foundation Trust); Stephen Foley (Sherwood Forest Hospitals

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The NICE FIT Steering Group: Oliver Warren (Chelsea and Westminster Hospital NHS Foundation Trust); Saidyousuf Ahmadi, Theo Georgiou Delisle, Carlene Parchment, Arun Shanmuganandan (Croydon University Hospital); Nicholas West (Epsom and St Helier University Hospitals); Toni Mitchell, Stephen Sah and Nick Jackson (Hammersmith Medical Research); Alistair Myers (Hillingdon Hospitals NHS Foundation Trust); Paul Ziprin (Imperial College Healthcare NHS Trust); Ian Bloom (Kingston Hospital NHS Foundation Trust); Michelle Chen, Stan Kaye (Royal Marsden Partners); Andy Ramwell (St George's University Hospitals NHS Foundation Trust); John T Jenkins (St Mark's Hospital); Kevin Monahan (West Middlesex University Hospital).

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

The study was approved by the National Research Ethics Service Committee, London South East (reference 16/LO/2174), and conducted with patient consent.

ORCID

Nigel D'Souza <https://orcid.org/0000-0002-9614-6113>
Kevin Monahan <https://orcid.org/0000-0002-7918-4003>
Muti Abulafi <https://orcid.org/0000-0001-7088-4292>

TWITTER

Muti Abulafi @muti192

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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