Fecal Immunochemical Testing in Patients With Low-Risk Symptoms of Colorectal Cancer: A Diagnostic Accuracy Study

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ABSTRACT

Background: The fecal immunochemical test (FIT) is recommended for triaging primary care patients in England with low-risk symptoms of colorectal cancer (CRC). The evidence underpinning recommendations by the National Institute for Health and Care Excellence had limitations, with a paucity of primary care evidence. This study examines the diagnostic accuracy of FIT in a defined low-risk symptom primary care population. **Patients and Methods:** Consecutive symptomatic adult patients referred for a FIT between October and December 2019 were included. Patients were derived from 225 primary care practices in England. Serious colorectal diseases (CRC, high-risk polyps, and inflammatory bowel disease [IBD]) were identified through patient follow-up over 18 months, using both primary and secondary healthcare records. Performance characteristics of FIT are reported according to differing thresholds, including the currently recommended threshold of ≥10 μg hemoglobin per gram of feces (μg/g). **Results:** A total of 3,506 patients were included in the final analysis. Of these, 708 had a positive FIT result (≥10 μg/g). The prevalence of CRC was 1.3%. FIT positivity declined from 20.2% to 5.8% and 4.5% at cutoffs of 10, 80, and 120 μg/g, respectively. The sensitivity of FIT at ≥10 μg/g to detect CRC was 91.1% (95% CI, 77.9%–97.1%); its specificity was 80.7% (95% CI, 79.3%–82.0%); the positive predictive value (PPV) was 5.8% (95% CI, 4.2%–7.8%); and the negative predictive value (NPV) was 99.9% (95% CI, 99.6%–99.95%). The area under the receiver operating characteristic curve was 0.93 (0.91–0.96). PPV and specificity increased, whereas sensitivity and NPV decreased when serious colorectal diseases (CRC, high-risk polyps, and IBD) were combined. Age, sex, socioeconomic deprivation, and anemia did not significantly influence FIT sensitivity on subgroup analysis. **Conclusions:** Utilization of FIT at a threshold ≥10 μg/g can safely triage patients with low-risk symptoms in primary care, with negative results effectively ruling out CRC.

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Background

Abdominal symptoms are a common cause for consultation in primary care.[1] Although potentially indicative of an underlying malignancy, the vast majority are of benign origin, which poses challenges regarding investigations and referrals.[1,2] In 2017, the National Institute for Health and Care Excellence Diagnostic Guidelines 30 (NICE DG30) recommended the fecal immunochemical test (FIT) for triaging patients with low-risk symptoms of colorectal cancer (CRC) in England.[3] This low-risk symptom group comprised patients aged >50 years with abdominal pain or weight loss, patients aged <60 years with change in bowel habit or iron deficiency anemia, or patients aged >60 years with non–iron deficiency anemia, in whom CRC risk was <3%.[4]

FIT detects the globin component of human hemoglobin by immunoassay.[3] It is widely used in asymptomatic (bowel cancer screening) populations; however, its role internationally in symptomatic patients remains limited.[5] The quantitative FIT threshold recommended by NICE was 10 μg/g, which is lower than the 120 μg/g threshold used in the Bowel Cancer Screening Program.[3]

The evidence underpinning NICE guidance was recognized to have limitations; only 1 of the 10 studies included were within primary care and none specifically evaluated low-risk symptom populations.[6] This led to recommendations for further diagnostic cohort studies assessing FIT within primary care, which has been reaffirmed in recent systematic reviews.[5,6] Uncertainty existed about how patient-level variables influence FIT.[7–10] This study investigates the diagnostic accuracy of FIT in a defined low-risk symptom primary care population and examines relevant patient-level factors.

Patients and Methods

Study Design

This study met Standards for Reporting of Diagnostic Accuracy (STARD) guidelines.[11] Ethics and study approval were granted from the UK Health Research Authority (IRAS 291908) and Sheffield Teaching Hospitals (STH21340). This


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study describes a cohort of consecutive, symptomatic patients who were managed in primary care in accordance with the NICE DG30 low-risk symptom pathway.[3] The diagnostic accuracy of FIT to detect CRC at a threshold of 10 μg/g is the primary outcome measure.

Patient Selection

The primary care population was derived from 225 primary care practices in South Yorkshire, Bassetlaw, and North Derbyshire, United Kingdom. These 225 practices serve a population of 2 million people, with adult secondary care provided by 8 hospitals. Consecutive symptomatic patients who underwent FIT in primary care between October 1, 2019, and December 31, 2019, were included. These dates were 2 years beyond the adoption of FIT into local low-symptomatic patient pathways, thereby minimizing the risk of spectrum bias.

Index Test and Reference Standard

Patients considered to fulfill NICE DG30 criteria and eligible for FIT were provided with a fecal sample collection device (OC-Sensor sample bottles; Eiken Chemical Company). Individuals were asked to collect a sample of their feces according to instructions, date the sampling device, and return the specimen to the laboratory within 7 days. All received samples were logged and analyzed for fecal hemoglobin within 3 working days (Department of Immunology, Sheffield) using the automated OC-Sensor Pledia analyzer (Eiken Chemical Company).

A fecal hemoglobin cutoff of 10 μg/g was used in accordance with the NICE DG30 threshold. When more than one sample result was available for a single patient, any positive result was considered preferentially, because this finding would prompt a secondary care referral.

Lower gastrointestinal tract (LGI) investigations were the reference standard. Colonoscopy exists as the gold standard test in all centers. Use of CT imaging (CT pneumocolon, CT colon with long oral bowel preparation, and plain abdominal CT) and colon capsule endoscopy were restricted to those declining colonoscopy, or where previous colonoscopy examinations had been incomplete. Endoscopists and radiologists performing these reference standard examinations had access to patient's symptoms and FIT results in advance of procedures as part of routine clinical care.

Data Collection

Clinical data were extracted from the Sheffield Immunology laboratory database in March 2021. This included FIT performance date, FIT result, indication, sex, age, postcode, and hospital numbers. This was subsequently used to identify information in primary and secondary healthcare records. For primary care records, this included a review of symptoms that instigated FIT testing and comparisons with NICE criteria, outcomes of individuals with negative FIT results, and an assessment of individuals who had a positive FIT result and were subsequently not referred. Histologic, endoscopic, and radiologic outcomes were acquired from secondary care databases, and examined up to 18 months following FIT performance.

Data Analysis

Patients having numerous findings at LGI investigations were reclassified with one finding after discussions between members of the research team. Classification was based on a ranking system whereby CRC ranked highest, followed by high-risk polyps, and then inflammatory bowel disease (IBD). This was followed by low-risk polyps, which were ranked above benign diseases that included diverticular disease, microscopic colitis, angiodysplasia, and perianal disease (hemorrhoids, anal fissures). High-risk polyps were defined using the recent British Society of Gastroenterology (BSG) polyp surveillance guidelines.[12]

Anemia was defined as a serum hemoglobin concentration <120 g/L for women and <130 g/L for men in blood tests performed in the 3 months immediately preceding FIT testing. Iron deficiency with and without anemia were defined using BSG guidelines.[13] Postcodes are used to assess socioeconomic deprivation using the Index of Multiple Deprivation 2019 (IMD2019).[14] The IMD2019 ranks every neighborhood in England from 1 (most deprived area) to 32,844 (least deprived area) using 7 different socioeconomic deprivation measures and weightings. The socioeconomic deprivation data are presented as decile values of the 32,844 ranked neighborhoods, with decile 1 being the most deprived and decile 10 being the least deprived.

Statistical analysis was performed using SPSS Statistics, version 25 (IBM Corp), with significance level set at $P<.05$. Categorical variables are summarized using descriptive statistics, including total numbers and percentages, with comparisons between groups performed using the chi-square or Fisher exact test. Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) are reported for each fecal hemoglobin threshold, with 95% confidence intervals provided. Receiver operating characteristics (ROC) are plotted for FIT against CRC diagnosis.

Results

FIT Returns and Patient Characteristics

Between October 1, 2019, and December 31, 2019, a total of 4,219 FIT requests were received from primary care. Of these, 599 (14.2%) tests were not analyzed due to inadequate sampling, insufficient clinical details, or insufficient patient identification, or because the tests were older than 7 days. Twenty-nine (0.8%) of the 3,620

samples analyzed were repeated tests on the same individual. Medical records and 18 months of follow-up were available for 3,506 (97.6%) of the eligible 3,591 patients. A study flow diagram (adapted from STARD) is shown in Figure 1, with patient demographics for the 3,506 individuals summarized in Table 1.

Median patient age in this cohort was 64 years (range, 14–106 years), and 55.3% were female. The mean [SD] index of socioeconomic deprivation decile score was 5.05 [2.96]. Although 3,506 patients were managed according to the low-risk symptom pathway within primary care, a subsequent review of patient records suggested that 614 (17.5%) may have fulfilled NICE NG12 high-risk or medium-risk symptom criteria.[4] We continued to include these patients within our analyses.

FIT Results, Referrals, and Investigation Outcomes

Of the 3,506 patients tested, 708 (20.2%) had positive FIT results (fecal hemoglobin cutoff values ≥10 μg/g), of which 366 (51.7%) were female and 622 (87.8%) were subsequently referred to secondary care. Patient choice, alternative diagnoses to CRC, recent gastrointestinal investigations, and advanced comorbidities were factors for nonreferral in reviewed primary care records (n=86). Of the 2,798 patients with a negative FIT result, 406 (14.5%) were also referred to secondary care within 3 months of FIT performance (total referred to secondary care = 1,028). Most of these 1,028 patients (n=701; 68.1%) underwent LGI endoscopic investigations (696 colonoscopies, 5 flexible sigmoidoscopies). Alternative or additional LGI investigations that occurred in the referred cohort included CT pneumocolon (virtual colonoscopy) examinations (n=107), CT colon scans with long oral bowel preparation (n=50), colon capsule endoscopy (n=2), and CT abdomen scans (n=300).

Findings from the LGI investigations are shown in Table 2 (n=1,009). The most prevalent finding was a normal examination of the colon (64.8%). CRC was identified in 45 (4.5%) patients, with other serious colorectal diseases (ie, high-risk polyps, IBD) detected in 104 (10.3%). Non-CRCs were seen in 32 (3.2%) patients. These non-CRCs were identified through diagnostic examinations performed in secondary care, with lung cancer the most common malignancy identified (34.4%; 11/32) (Table 3).

Performance Characteristics of FIT

The diagnostic accuracy of FIT for CRC detection at differing cutoff values is summarized in Table 4. At the currently adopted threshold of 10 μg/g, the sensitivity of FIT was 91.1% (95% CI, 77.9%–97.1%). This decreased to 62.2% (95% CI, 46.5%–75.8%) at a threshold of 120 μg/g. In women, the sensitivity decreased from 100.0% (95% CI, 80.0%–100.0%) at 10 μg/g to 65.0% (95% CI, 40.9%–83.7%) at 120 μg/g (Table 5). For men, sensitivity decreased from 84.0% (95% CI, 63.1%–94.7%) to 60.0% (95% CI, 38.9%–78.2%) using the same thresholds.

The PPV for all adults was 5.8% (95% CI, 4.2%–7.8%) at 10 μg/g (5.5% for women, 6.1% for men). This increased to 17.6% (95% CI, 12.2%–24.6%) when the 120 μg/g threshold was applied (18.3% for women, 17.0% for men). The NPV for all adults at a threshold of 10 μg/g and 120 μg/g was 99.9% (95% CI, 99.6%–99.95%) and 99.5% (95% CI,

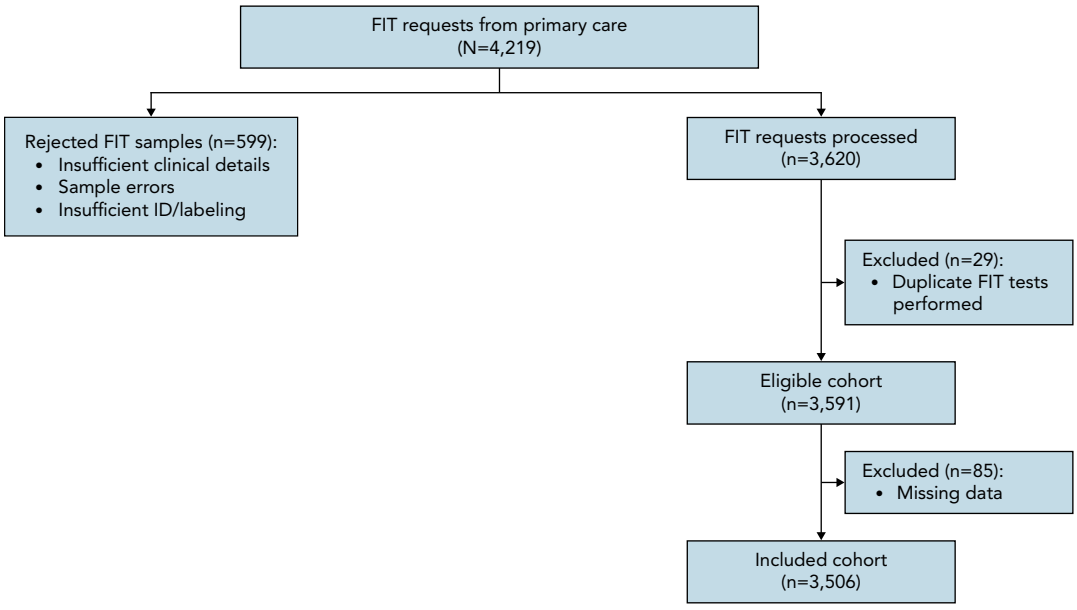

Figure 1. Study flow diagram. The cohort was derived from 225 general practitioner practices within 7 comprehensive cancer groups.
Abbreviations: FIT, fecal immunochemical test; ID, identification.

Table 1. Patient Demographics

Characteristic	n (%)
Total	3,506 (100)
Sex	
Women	1,940 (55.3)
Men	1,566 (44.7)
Age, y	
Mean [SD]	63.5 [14.4]
Median (range)	64 (14–106)
Age group	
≤40 y	219 (6.2)
41–50 y	436 (12.4)
51–60 y	838 (23.9)
61–70 y	777 (22.2)
71–80 y	771 (22.0)
>80 y	465 (13.3)
Index of socioeconomic deprivation[a]	
Mean [SD]	5.05 [2.96]
Median	5
Symptom risk category	
High	104 (3.0)
Medium	510 (14.5)
Low	2,617 (74.6)
Other[b]	275 (7.8)
FIT result	
Positive	708 (20.2)
Negative	2,798 (79.8)

Abbreviation: FIT, fecal immunochemical test.
[a]1 = most deprivation; 10 = least deprivation.
[b]Patients referred with symptoms not meeting NG12 or DG30 criteria.

Table 2. Findings Following Lower Gastrointestinal Investigations (n=1,009)

Diagnosis	n (%)
Normal	654 (64.8)
Diverticular disease	220 (21.8)
Low-risk polyp	153 (15.2)
High-risk polyp	83 (8.2)
Perianal disease[a]	79 (7.8)
Colorectal cancer	45 (4.5)
Inflammatory bowel disease	21 (2.1)
Microscopic colitis	7 (0.7)
Angioectasia	4 (0.4)

[a]Hemorrhoids, anal fissure, anal fistula, solitary rectal ulcer.

99.1%–99.6%), respectively. When CRC was grouped with other serious colorectal disorders, the sensitivity was lower across all thresholds (supplemental eTable 1, available with this article at JNCCN.org), varying from 84.1% (95% CI, 76.9%–89.4%) at the 10 μg/g threshold to 38.6% (95% CI, 30.8%–47.1%) at 120 μg/g. On ROC curve analysis (Figure 2), the area under the curve (AUC) for CRC was 0.93 (0.91–0.96). Youden's index, which maximizes the sum of sensitivity and specificity, was 18 μg/g.

Colorectal Cancers

Characteristics of the 45 CRCs diagnosed are summarized in Table 6. Of these cancers, 4 (8.9%) were diagnosed following a negative FIT; all were T2 cancers found in the proximal colon (cecum, n=2; ascending colon, n=1; transverse colon, n=1), and 3 of these cancers fulfilled NICE NG12 medium-risk symptom criteria, which should have negated the need for a FIT in advance of referral. The final case was a 41-year-old man who had a change in bowel habits and iron deficiency anemia (hemoglobin, 78 g/L; ferritin, 2 μg/L). No significant variation was seen in the ability of FIT to detect CRC using age, sex, socioeconomic deprivation, or anemia.

Had restriction of this tested cohort been to individuals only strictly fulfilling low-risk NICE DG30 criteria (n=2,892), then a lower CRC prevalence of 0.59% (17/2,892) would have been identified. Adopting the 10 μg/g threshold in this would have led to a sensitivity, specificity, PPV, and NPV of 94.1% (95% CI, 69.2%–99.6%), 85.4% (95% CI, 84.1%–86.7%), 3.7% (95% CI, 2.2%–6.1%), and 99.95% (95% CI, 97.4%–99.99%), respectively.

Discussion

This study reports the diagnostic accuracy of the OC-Sensor quantitative FIT in a cohort of symptomatic primary care patients, managed in accordance with the low-risk symptom CRC pathway. In this defined low-risk primary care population, a CRC prevalence of 1.3% was identified. Both patient symptoms and outcomes have been validated using both primary and secondary healthcare records.

The sensitivity and specificity of FIT to detect CRC at ≥10 μg/g was 91.1% and 80.7%, respectively. Using this threshold, the PPV and NPV was 5.8% and 99.9%, respectively. No significant difference in FIT sensitivity was found on subgroup analysis by age, sex, or socioeconomic deprivation. FIT-negative CRCs were more likely to originate in the proximal colon and have an earlier stage. It is plausible that proximal and smaller lesions bleed less, and hence why detection using FIT was suboptimal. Higher cutoffs for FIT increased the PPV but at the expense of FIT sensitivity and CRC detection.

The strengths of this study are its primary care setting (where FIT is performed), follow-up duration following FIT performance, and the assessment of both primary and

Table 3. Non-CRCs Detected via the Low-Risk LGI Pathway (n=32)

Non-CRC Site	n (%)	FIT Cutoff <10 μg/g	FIT Cutoff ≥10 μg/g
Lung	11 (34.4)	6	5
Pancreatic	5 (15.6)	4	1
Prostate	3 (9.4)	2	1
Renal	3 (9.4)	1	2
Hematologic	3 (9.4)	2	2
Ovarian	2 (6.3)	2	0
Disseminated disease/ unknown primary	2 (6.3)	2	0
Stomach	2 (6.3)	0	2
Duodenum	1 (3.1)	0	1

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; LGI, lower gastrointestinal tract.

secondary care health records. Use of a single laboratory and the same FIT (OC-Sensor) ensured uniformity of the testing within the studied cohort. The CRC prevalence of 1.3% is another reassuring finding of our work, as it falls within the 1% to 3% pretest probability range (PPV), which NICE assumed for low-risk symptom populations.[4] Reassurances are also provided from the median age of our patients (64 years), which lies close to the peak age for CRC diagnosis (65–69 years),[15] suggesting appropriate testing of relevant at-risk individuals within primary care.

The main limitation of our study is that many patients with a negative FIT did not undergo colonoscopy or have alternative LGI investigations. This introduces a potential for verification bias, where a lower-bound value of CRC prevalence could lead to an overestimation of FIT sensitivity. Instead, patients were followed up for 18 months using both hospital and primary care records, and using local endoscopy, radiology, and pathology databases. This approach considered that cancer and IBD symptoms are usually progressive or persistent, which would have likely led to further investigations during follow-up, including individuals having potentially false-negative FIT results. Another limitation is that although all patients were managed on a low-risk pathway, a minority had NICE NG12–defined high-risk or medium-risk symptoms following assessment of their primary care records. We continued to include these high- or medium-risk individuals within our analysis, as it is recognized that alarm symptoms may be variable and subject to interpretation by differing primary care physicians, with a possibility that lower-risk features existed for these tested individuals.[16] Although no differences were seen in the ability of FIT to detect CRC using age, sex, socioeconomic deprivation, or anemia, it is recognized that the total number of CRC cases was low in our cohort, raising the possibility of a type 2 error in the reporting of these outcomes.

Three recent and comparable studies have examined FIT in symptomatic primary care populations. The first is a Danish study of 3,462 patients aged ≥30 years having "nonalarm" symptoms.[16] The definition of nonalarm symptoms was left to the discretion of the general practitioner as opposed to formal criteria, and included patients with irritable bowel syndrome. Of those included, 540 (15.6%) had a positive FIT at a threshold ≥10 μg/g, with a PPV of 9.4% for CRC detection during 3 months of follow-up. In a large UK study from Oxfordshire (n=9,896), Nicholson et al[17] followed up primary care patients for at least 6 months who underwent FIT testing using the HM-JACKarc FIT system (Alpha Laboratories). The sensitivity for CRC at a threshold ≥10 μg/g was 90.5% (84.9%–96.1%) and PPV was 10.1% (8.2%–12%); however, inclusion criteria did not match NICE criteria, and included patients with rectal bleeding (19.7% of cases). In a recent study from the southwest of England, Bailey et al[18] reviewed outcomes of 3,890 patients with low-risk symptoms, in accordance with NICE criteria, and followed them for 12 months. Using the HM-JACKarc FIT method they identified a CRC prevalence of 1.3%,

Table 4. Diagnostic Accuracy of FIT for CRC Detection at Differing Fecal Hemoglobin Cutoff Values

Cutoff (μg/g)	Positivity n (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	TP n	FN n	FP n	TN n
10	708 (20.2)	91.1 (77.9–97.1)	80.7 (79.3–82.0)	5.8 (4.2–7.8)	99.9 (99.6–99.95)	41	4	667	2,794
20	479 (13.7)	86.7 (72.5–94.5)	87.3 (86.1–88.4)	8.1 (5.9–11.1)	99.8 (99.5–99.9)	39	6	440	3,021
50	277 (7.9)	73.3 (57.8–84.9)	93.0 (92.0–93.8)	11.9 (8.4–16.4)	99.6 (99.3–99.8)	33	12	244	3,217
80	204 (5.8)	66.7 (50.9–79.6)	94.9 (94.2–95.7)	14.7 (10.3–20.4)	99.5 (99.2–99.7)	30	15	174	3,287
100	176 (5.0)	66.7 (50.9–79.6)	95.8 (95.0–96.4)	17.0 (12.0–23.6)	99.5 (99.2–99.7)	30	15	146	3,315
120	159 (4.5)	62.2 (46.5–75.8)	96.2 (95.5–96.8)	17.6 (12.2–24.6)	99.5 (99.1–99.6)	28	17	131	3,330
150	131 (3.7)	53.3 (38.0–68.1)	96.9 (96.3–97.4)	18.3 (12.3–26.2)	99.4 (99.0–99.6)	24	21	107	3,461

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; FN, false-negative; FP, false-positive; NPV, negative predictive value; PPV, positive predictive value; TN, true-negative; TP, true-positive.

Table 5. Comparison of FIT for CRC Detection by Sex

Outcome	Cutoff (μg/g)	Female				Male			
		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
CRC	10	100 (80.0–100.0)	82 (80.2–83.7)	5.5 (3.5–8.5)	100 (99.7–100.0)	84 (63.1–94.7)	79.2 (77.0–81.2)	6.1 (3.9–9.3)	99.7 (99.1–99.9)
	20	95 (73.1–99.7)	88.8 (87.2–90.2)	8.1 (5.1–12.6)	99.9 (99.6–99.9)	80 (58.7–92.4)	85.4 (83.5–87.1)	8.4 (8.2–8.6)	99.6 (99.0–99.9)
	50	80 (55.7–93.3)	94.1 (92.9–95.1)	12.3 (7.4–19.5)	99.8 (99.4–99.9)	68 (46.4–84.3)	91.6 (90.0–92.9)	11.6 (7.1–18.1)	99.4 (98.8–99.7)
	80	70 (45.7–87.2)	95.8 (94.8–96.6)	14.9 (8.7–24.1)	99.7 (99.3–99.9)	64 (42.6–81.3)	93.9 (92.6–95.0)	14.5 (8.8–22.8)	99.4 (98.8–99.7)
	100	70 (45.7–87.2)	96.7 (95.8–97.4)	18.2 (10.6–29.0)	99.7 (99.2–99.9)	64 (42.6–81.3)	94.6 (93.3–95.7)	16.2 (9.8–25.2)	99.4 (98.8–99.7)
	120	65 (40.9–83.7)	97 (96.1–97.7)	18.3 (10.5–29.6)	99.6 (99.2–99.8)	60 (38.9–78.2)	95.2 (94.0–96.2)	17 (10.1–26.9)	99.3 (98.7–99.7)
	150	55 (32.0–76.2)	97.3 (96.5–98.0)	17.7 (9.6–29.9)	99.5 (99.0–99.8)	52 (31.8–71.7)	96.4 (95.3–97.2)	18.8 (10.8–30.4)	99.2 (98.6–99.6)

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test.

with a sensitivity for CRC at a threshold ≥10 μg/g of 84.3% (95% CI, 71.4%–93.0%) and a PPV of 7.0% (95% CI, 5.1%–9.3%). This CRC prevalence is identical to our studied cohort. A limitation in their study was that symptom data were not verified in those included. Our analysis of primary care records allowed symptom data verification, alongside investigation relevant patient variables such as age, sex, socioeconomic deprivation, cancer stage, and anemia.

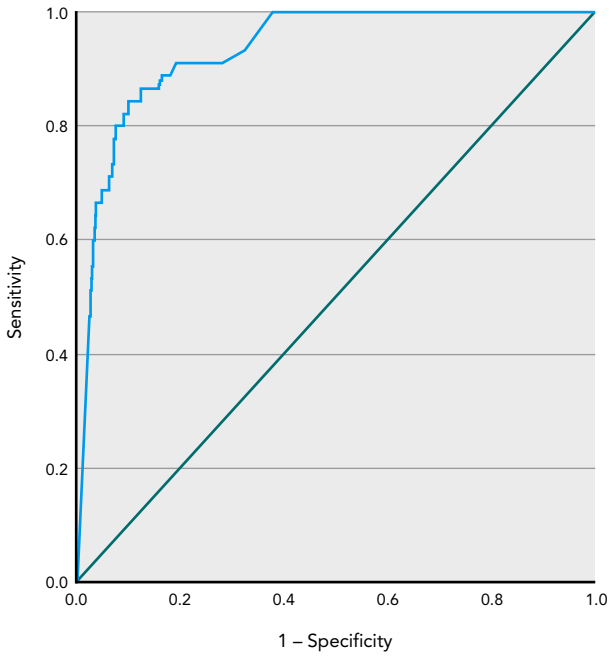

Figure 2. ROC curve of FIT for CRC detection.
Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; ROC, receiver operating characteristic.

Conclusions

The evidence provided in our study supports using FIT at a threshold ≥10 μg/g in low-risk symptom populations. Although CRC prevalence is low (1.3%), reassurances are provided to patients, clinicians, and commissioners of colorectal services that FIT can safely cancer triage within this population. The timely investigation of patients with false-negative FIT results is also reassuring, highlighting the judicious referral of a select number of patients from primary care, where continued strong clinical suspicion and/or evidence of anemia exists. Our study also demonstrates a low prevalence of non-CRCs (0.9%) within this low-risk population. These findings may support additional tests being performed within primary care to exclude non-CRCs if FIT or LGI investigations are negative, and when persistent concerning symptoms are present.

Future research should focus on combining FIT with other clinical information, including blood and fecal tests in primary care settings. Assessment of FIT thresholds, patient acceptability, and health economic outcomes could inform optimal pathways for detection of CRC and improve PPV. Indeed, a higher FIT threshold is supported by our work (Youden Index of 18 μg/g), with 227 fewer people requiring investigations when a 20 μg/g threshold is applied (PPV, 8.1%; NPV, 99.8%). There has also been increasing interest in FIT use in high-risk populations.[19] This adoption outside of current NICE guidance has generated controversy and been used to mitigate pressure on endoscopic and radiologic resources, which have been impacted by the COVID-19 pandemic.[20] Future work needs to evaluate this evolving use of FIT to ensure appropriate triaging and prioritization of symptomatic primary care patients, while considering

Table 6. Characteristics of the 45 CRCs Diagnosed

Variable	n (%)	FIT Cutoff		*P* Value
		<10 μg/g	≥10 μg/g	
Sex				.12
Female	20 (44.4)	0	20	
Male	25 (55.6)	4	21	
Age group				.33
≤40 y	0 (0)			
41–50 y	2 (4.4)	1	1	
51–60 y	3 (6.7)	0	3	
61–70 y	10 (22.2)	1	9	
71–80 y	17 (37.8)	1	16	
>80 y	13 (28.9)	1	12	
Index of socioeconomic deprivation				.63
1 (most deprived)	6 (13.3)	0	6	
2	5 (11.1)	0	5	
3	5 (11.1)	0	5	
4	3 (6.7)	0	3	
5	4 (8.9)	0	4	
6	7 (15.6)	1	6	
7	3 (6.7)	0	3	
8	4 (8.9)	1	3	
9	5 (11.1)	1	4	
10 (least deprived)	3 (6.7)	1	2	
Tumor site				.04
Proximal colon				
Cecum	7 (15.6)	2	5	
Ascending colon	6 (13.3)	1	5	
Hepatic flexure	1 (2.2)	0	1	
Transverse colon	4 (8.9)	1	3	
Distal colon				
Splenic flexure	1 (2.2)	0	1	
Descending colon	5 (11.1)	0	5	
Sigmoid colon	9 (20.0)	0	9	
Rectosigmoid	4 (8.9)	0	4	
Rectum	8 (17.8)	0	8	
TNM staging				.01
I	0 (0.0)	0	0	
II	13 (28.9)	4	9	
III	19 (42.2)	0	19	
IV	9 (20.0)	0	9	
Unknown/Missing	4 (8.9)	0	4	
Anemia				.387
Yes	5 (11.1)	1	4	
No	40 (88.9)	3	37	

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test.

resource use and costs. In conclusion, FIT at a threshold ≥10 μg/g safely triages patients with low-risk symptoms within primary care, with negative results effectively ruling out CRC.

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Fecal Immunochemical Testing in Patients With Low-Risk Symptoms of Colorectal Cancer: A Diagnostic Accuracy Study

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eTable 1: Diagnostic Accuracy of FIT for Serious Colorectal Diseases Detection

eTable 1. Diagnostic Accuracy of FIT for Serious Colorectal Diseases Detection

Cutoff (μg/g)	Positivity n (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	TP n	FN n	FP n	TN n
10	708 (20.2)	84.1 (76.9–89.4)	82.6 (81.2–83.8)	17.2 (14.5–20.2)	99.2 (98.7–99.5)	122	23	586	2,775
20	479 (13.7)	70.3 (62.1–77.5)	88.8 (87.7–89.8)	21.3 (17.8–25.3)	98.6 (98.1–99.0)	102	43	377	2,984
50	277 (7.9)	50.3 (42.0–58.7)	93.9 (93.1–94.7)	26.4 (21.3–32.0)	97.8 (97.2–98.2)	73	73	204	3,157
80	204 (5.8)	44.1 (36.0–52.6)	95.8 (95.1–96.5)	31.4 (25.2–38.3)	97.5 (96.9–98.0)	64	81	140	3,221
100	176 (5.0)	42.8 (34.7–51.2)	96.6 (95.9–97.2)	35.2 (28.3–42.8)	97.5 (96.9–97.8)	62	83	114	3,247
120	159 (4.5)	38.6 (30.8–47.1)	96.9 (96.3–97.5)	35.2 (27.9–43.2)	97.3 (96.7–97.8)	56	89	103	3,258
150	131 (3.7)	32.4 (25.0–40.7)	97.5 (96.9–98.0)	35.9 (27.8–44.8)	97.1 (96.5–97.6)	47	98	84	3,277

Abbreviations: FIT, fecal immunochemical test; FN, false-negative; FP, false-positive; NPV, negative predictive value; PPV, positive predictive value; TN, true-negative; TP, true-positive.