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# Faecal immunochemical testing for adults with symptoms of colorectal cancer attending English primary care: a retrospective cohort study of 14 487 consecutive test requests

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## Summary

**Background:** Faecal immunochemical testing (FIT) is recommended by the National Institute for Health and Care Excellence (NICE) to triage symptomatic primary care patients for further investigation of colorectal cancer.

**Aim:** To ascertain the diagnostic performance of FIT in symptomatic adult primary care patients.

**Methods:** Faecal samples from routine primary care practice in Oxfordshire, UK were analysed using the HM-JACKarc FIT method between March 2017 and March 2020. Clinical details were recorded. Patients were followed for up to 36 months in linked hospital records for evidence of benign and serious (colorectal cancer, high-risk adenomas and bowel inflammation) colorectal disease. The diagnostic accuracy of FIT is reported by gender, age group and FIT threshold.

**Results:** In 9896 adult patients with at least 6-month follow-up, a FIT result ≥10 μg Hb/g faeces had a sensitivity for colorectal cancer of 90.5% (95% CI 84.9%-96.1%), specificity 91.3% (90.8%-91.9%), positive predictive value (PPV) 10.1% (8.15%-12.0%) and negative predictive value (NPV) 99.9% (99.8%-100.0%). The PPV and specificity for serious colorectal disease were higher and the sensitivity and NPV lower than for colorectal cancer alone. The area under the curve for all adults did not change substantially by gender or by increasing the minimum age of testing. Using ≥10 μg Hb/g faeces, 10% of adults would be investigated to detect 91% of cancers, a number needed to scope of ten to detect one cancer. Using ≥7, ≥50 and ≥150 μg Hb/g faeces, 11%, 4% and 3% of adults would be investigated, and 91%, 74% and 54% cancers detected, respectively.

**Conclusion:** A FIT threshold of ≥10 μg Hb/g faeces would be appropriate to triage adult patients presenting to primary care with symptoms of serious colorectal disease. FIT may be used to reprioritise patients referred with colorectal cancer symptoms whose investigations have been delayed by the COVID-19 pandemic.

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## 1 | INTRODUCTION

Since July 2017 the faecal immunochemical test (FIT) has been recommended by the National Institute for Health and Care Excellence (NICE) DG30 guidelines 'to guide referral for suspected colorectal cancer in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway'.[1] Guidance on faecal testing has generated significant debate.[2,3] Concerns have been raised about delayed cancer diagnosis due to false negatives and the potential to increase demand on already stretched endoscopy service due to false positives.[4-6] FIT is an immunoassay-based method that measures the globin component of human haemoglobin and its early degradation products.[7,8] FIT does not require dietary restriction, is specific to lower gastrointestinal (GI) cancers as upper GI enzymes degrade human globin, and is less affected by concomitant medication use than the guaiac method to detect faecal occult blood (gFOB).[7,9] Accordingly, three times fewer false-positive tests are reported when FIT is compared to gFOB in samples sent to the laboratory for symptomatic patients.[10] The adoption of FIT in primary care has been slow with notable variation in uptake and implementation across England,[5] low awareness of the NICE guidance[11] and low confidence in the accuracy of FIT amongst general practitioners (GPs).[12] The public report a preference for FIT over colonoscopy if no additional cancers are missed.[13]

NICE DG30 recommends a quantitative FIT threshold of 10 μg Hb/g faeces should trigger referral for colonoscopy.[1] The NHS England Bowel Cancer Screening Programme (BCSP) currently uses a threshold of 120 μg Hb/g faeces. Colorectal cancer screening studies have consistently demonstrated improved performance of FIT compared to gFOB at a high analytical threshold.[9,14,15] However, NICE expressed concerns about the applicability of all ten of the studies used to underpin their DG30 recommendation: none reported data on patients with low-risk symptoms of colorectal cancer and only one study[16] was conducted in primary care.[1,17]

Evidence has since been published in support the use of low-threshold FIT in symptomatic primary care patients.[5,18-25] A Danish study concluded that FIT may be used as a supplementary diagnostic test in individuals with non-alarm symptoms of colorectal cancer to diagnose serious bowel disease (colorectal cancer, high-risk adenoma and inflammatory bowel disease).[24] Authors of a Scottish study strongly recommended FIT should become integral to the assessment of all patients presenting to primary care with new bowel symptoms, to objectively determine the risk of underlying serious bowel disease.[20] Despite these important studies, data from symptomatic primary care patients prior to referral are lacking.[6] Unanswered questions remain: does FIT perform similarly in men and women, across age-groups and what is the optimal FIT threshold to detect colorectal cancer and significant lower GI disease?[6,26]

The COVID-19 pandemic has introduced a new urgency to identify non-invasive approaches to triage for patients with symptoms of serious colorectal disease requiring further investigation. The large backlog of endoscopy created by the COVID-19 pandemic means that low cut-off FIT will be required to risk stratify patients referred with possible cancer symptoms into groups for urgent and less urgent endoscopy immediately after the pandemic has passed. Understanding the performance of FIT at a range of thresholds in symptomatic patients is therefore a priority.

The Oxford University Hospitals Trust (OUH) adopted FIT prior to the DG30 guidance to comply with the 2015 NG12 NICE guidance for suspected cancer.[6] This coincided with a desire from the clinical laboratory to move away from gFOB. FIT was commissioned by Oxfordshire Clinical Commissioning Group (OCCG) as a direct access test for GPs in 2016.[5] We conducted a diagnostic accuracy study using linked electronic hospital records data to ascertain the diagnostic performance of FIT to detect serious bowel disease in the context of the NICE DG30 guidelines in England. We considered the diagnostic performance of FIT by age-group, gender and FIT threshold, and documented FIT negative cases of colorectal cancer.

## 2 | METHODS

This retrospective cohort study included consecutive FIT samples sent to OUH clinical biochemistry laboratory from primary care for adults (≥18 years old) during the period March 2017 to March 2020. The laboratory serves all primary care clinicians in the county of Oxfordshire with a population of approximately 660 000. Based at the John Radcliffe Hospital, it is one of the largest laboratories in the United Kingdom, performing over 8 million tests a year using an in house laboratory information management system based on Intersystems Caché. This study was registered as a service evaluation on the OUH Datix register (CSS-BIO-3 4730). We followed STARD reporting guidelines.[27]

Leading up to the study period, the change in NICE guidance and the indications for FIT testing were communicated to GPs in Oxfordshire by email and newsletter from the OCCG. Samples were collected into standard collection pots by patients in primary care and analysed for FIT using the HM-JACKarc analyser (Hitachi Chemical Diagnostics Systems Co., Ltd) a method that has been independently evaluated with respect to analytical performance[16] and is recommended in the context of use for samples from primary care.[1] The method had a calibration range of 7-450 μg Hb/g faeces and immunoassay reproducibility, assessed across 12 months was between 4.5% and 8.7% when expressed as a percentage coefficient of variation. Sample preparation prior to analysis on the FIT instrument utilized the Extel Hemo-Auto MC device, a process which introduced additional variation, with overall analytical imprecision observed to be between 7.0% and 13.5% when specimens had been homogenised and sampled by laboratory staff. The selection of the faecal Hb concentration considered positive was made before the NICE recommendation to use 10 μg Hb/g faeces and was based on the methods lowest calibrant value of 7 μg Hb/g faeces and agreed with the OCCG based on initial method verification data.[10] Results were reported electronically to the requesting GP as either positive or negative. In selecting the approach to faecal sample handling we balanced two competing pre-analytical sources of error: the requirements to minimize sampling errors if undertaken by the patient,

which may give rise to false negatives if the collection device was inadequately filled; and specimen degradation concerns if sampling is undertaken in the laboratory due to delays between specimen collection and stabilisation in the collection device buffer. We have highlighted the balancing of these risks in our contribution to the NICE DG30 FIT adoption resource.[1] Where more than one sample result was available for any individual patient, any positive result within those samples tested was considered a positive outcome on the basis that a single positive would trigger referral.

To confirm the presence or absence of disease, OUHT clinical and diagnostic databases were searched for evidence of cellular pathology for up to 36 months following the FIT test for all patients. Histology, endoscopy and CT colonoscopy reports were retrieved by searching by both hospital and NHS number. Patients were classified individually then by discussion between members of the research team (BS, BN, TJ, JE) having colorectal cancer, normal cellular pathology findings, colorectal polyps, inflammation of the colon or no further follow-up investigation for between 6 and 36 months. Patients who had no further investigation were categorised as negative for serious pathology as any serious pathology would be expected to have presented to secondary care within this time period. Serious disease was a combination of any of: colorectal cancer, large polyp or high-grade dysplasia, or inflammation of the colon.

The diagnostic accuracy of FIT in relation to a diagnosis of cancer within 6 months confirmed within the linked hospital record was summarised using sensitivity, specificity, negative and positive predictive values, the area under the curve (AUC) and exact 95% confidence intervals. We used the sensitivity and specificity and prevalence of colorectal cancer from this analysis to derive estimates of positive and negative FIT tests in relation to cancer and serious colorectal disease outcomes per 1000 patients tested. In addition, the clinical details of patients with a negative FIT were collated. A sensitivity analysis investigated the effect of using follow-up periods of 3, 6 and 12 months.

**TABLE 1** Clinical details of patients tested with FIT

| | Women N (% FIT ≥7 μg Hb/g faeces) | Men N (% FIT ≥7 μg Hb/g faeces) |
|---|---|---|
| Age group (y) | | |
| 18-39 | 459 (7.4) | 334 (10.8) |
| 40-49 | 891 (6.1) | 509 (9) |
| 50-59 | 1681 (6.7) | 1068 (9.7) |
| 60-69 | 947 (7.4) | 704 (11.4) |
| 70-79 | 1047 (12.7) | 821 (16.1) |
| ≥80 | 770 (18.8) | 665 (22.7) |
| Clinical features | | |
| Abdominal pain | 1488 (7.0) | 1013 (9.2) |
| Anaemia | 1587 (12.3) | 1204 (17.4) |
| Blood in stools | 805 (17.0) | 672 (22.9) |
| Change in bowel habit | 3000 (6.7) | 2011 (9.0) |
| Inflammation | 114 (17.5) | 59 (20.3) |
| Iron deficiency | 772 (10.1) | 436 (14.4) |
| Thrombocytosis | 99 (6.1) | 35 (14.3) |
| Tired all the time | 33 (6.1) | 33 (9.1) |
| Weight loss | 488 (9.6) | 463 (12.1) |
| Outcome | | |
| Colorectal cancer | 40 (90.0) | 65 (92.3) |
| Benign disease (polyp <10 mm/diverticulosis) | 40 (15.0) | 40 (30.0) |
| Bowel inflammation | 116 (27.6) | 88 (47.7) |
| High-risk adenoma (polyp >10 mm or high-grade dysplasia) | 186 (40.3) | 187 (42.8) |
| No significant pathology | 255 (14.9) | 163 (18.4) |
| No further investigation | 5158 (7.0) | 3558 (9.1) |
| Total | 5795 (9.5) | 4101 (13.4) |

## 3 | RESULTS

A total of 14 487 consecutive FITs were conducted for 12 509 patients during the study period. A total of 9896 patients had at least 6 months of follow-up and were retained in the primary analysis. The median age was 60 years (range 18-101 years, inter-quartile range 51-74 years). 5795 (58.6%) were women (59 years [18-101 years] [51-74 years]) and 4101 (41.4%) were men (62 years [18-99 years] [52-76 years]). A larger proportion of FITs were positive (≥7 μg Hb/g faeces) in men (13.4%) than women (9.6%), and in older patients (eg 18.8% of women aged ≥80 years compared to 8.7% aged 18-39 years) (Table 1).

### 3.1 | Clinical details and outcomes

FIT requests included a range of clinical features (symptoms, signs, test results) that gave rise to a concern about serious colorectal pathology. Patients commonly presented with combinations of clinical features (Table 1). The most common clinical features were change in bowel habit (included in 50.6% of requests), anaemia (28.2%), abdominal pain (25.2%), blood in stools (19.7%) and iron deficiency (12.2%). Significant colorectal disease was detected in 682 (6.9%) of patients tested, 105 (1.1%) were diagnosed with colorectal cancer, 373 (3.8%) large >10 mm or high-grade dysplastic polyps and 204 (2.1%) patients who had bowel inflammation (Table 1). Figure 1 shows the FIT values according to outcome group and gender.

### 3.2 | Overall diagnostic accuracy—gender and age

Table 2 presents AUCs by age cut-off for men and for women for a diagnosis of colorectal cancer and for significant colorectal disease. Increasing the lower age-limit for FIT testing made no substantial difference to the overall AUC for colorectal cancer with poorer

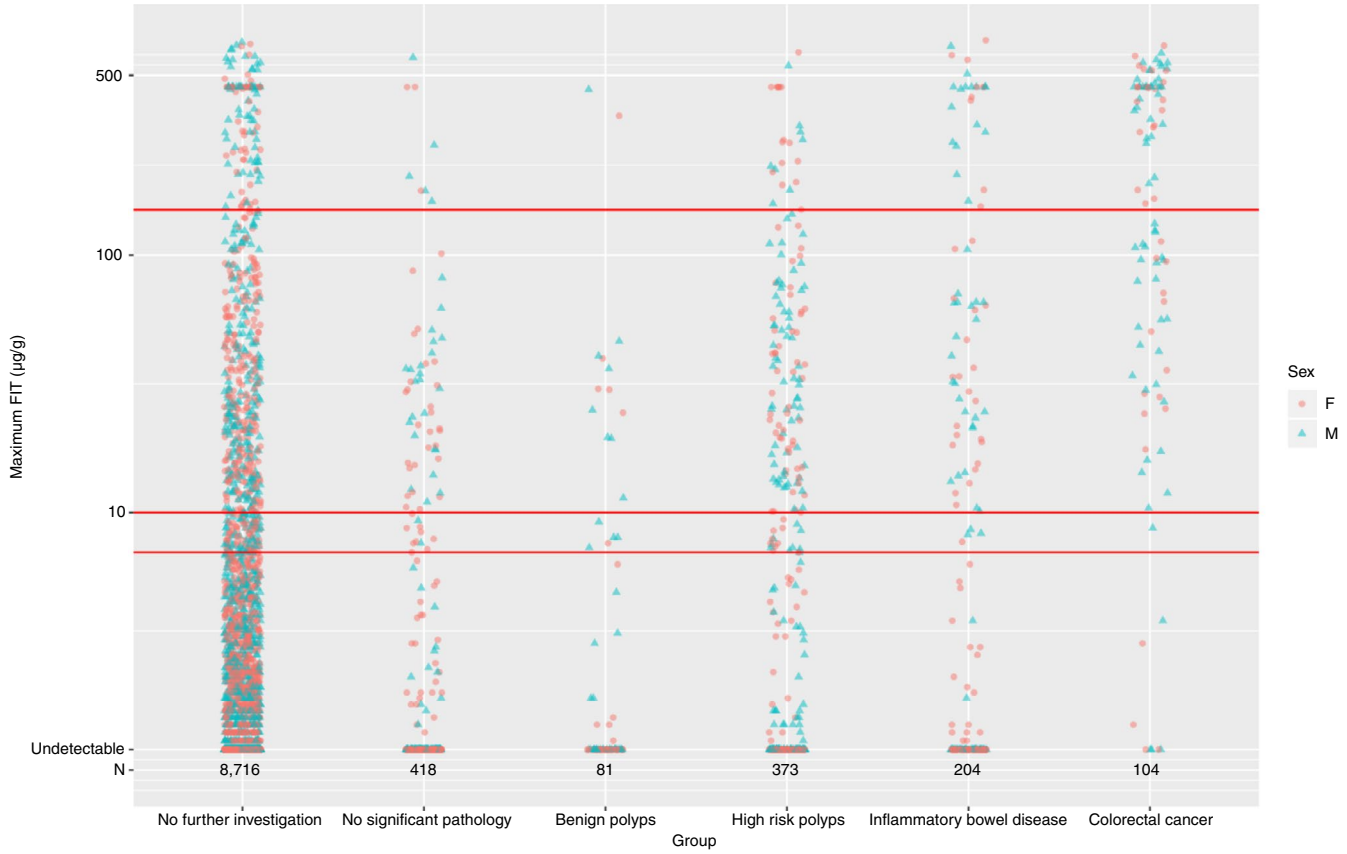


**FIGURE 1** Quantitative FIT results by outcome category and gender. F, female; M, male; µg/g, µg Hb/g faeces

discrimination noted when using a higher cut-off. The AUC for colorectal cancer was 0.941 (0.914-0.968) ranging from 0.886 (0.805-0.967) in men aged ≥80 years to 0.933 (0.898-0.969) in men aged ≥18 years, and 0.881 (0.693-1.000) in women aged ≥80 years to 0.948 (0.907-0.989) in women aged ≥18 years.

## 3.3 | Diagnostic accuracy by FIT threshold

For a colorectal cancer diagnosis in adults, the sensitivity of FIT decreased from 91.4% (05% CI 86.1%-96.8%) at a cut-off of 7 µg Hb/g faeces to 54.3% (44.8%-63.8%) at 150 µg Hb/g faeces (Figure 2; Table S1). In women, the sensitivity decreased from 90.0% (80.7%-99.3%) at 7 µg Hb/g faeces to 60.0% (44.8%-75.2%) at 150 µg Hb/g faeces (Figure 2, Table 3). For men, sensitivity was 92.3% (85.8%-98.8%) at 7 µg Hb/g faeces decreasing to 50.8% (38.6%-62.9%) at 150 µg Hb/g faeces. Specificity in adults increased from 89.8% (89.2%-90.4%) at 7 µg Hb/g faeces to 98.1% (97.8%-98.4%) at 150 µg Hb/g faeces, in women from 91.1% (90.3%-91.8%) to 98.5% (98.2%-98.8%), and in men from 87.9% (86.9%-88.9%) at 7 µg Hb/g faeces to 97.5% (97.1%-98.0%) at 150 µg Hb/g faeces in men.

In all adults, the PPV was 8.74% (7.07%-10.4%) at 7 µg Hb/g faeces and 23.4% (18.1%-28.7%) at 150 µg Hb/g faeces (Table S1). The PPV was greater in men than in women, especially at lower thresholds (Table 3). In women, the PPV was 6.56% (4.49%-8.63%) at 7 µg Hb/g faeces compared to 10.9% (8.32%-13.5%) in men. At 150 µg Hb/g faeces the PPV was 21.4% (13.8%-29.0%) in women and 25.0% (17.6%-32.4%) in men. The NPV for colorectal cancer remained ≥99% for men and women at all thresholds studied (Table 3). Increasing the threshold from 7 µg Hb/g faeces to 150 µg Hb/g faeces reduced the NPV from 99.9% (99.8%-100.0%) to 99.5% (99.4%-99.6%) overall. This was similar for women (99.9% [99.8%-100.0%] to 99.7% [99.6%-99.9%]) and men (99.9% [99.7%-100.0%] to 99.2% [98.9%-99.5%]).

For the serious colorectal disease grouping, sensitivity was lower than for colorectal cancer across all thresholds studied, ranging from 55.0% (49.5%-60.6%) at 7 µg Hb/g faeces to 26.9% (21.9%-31.8%) at 150 µg Hb/g faeces (Table S1). The NPV was also lower ranging from 98.4 (98.2%-98.7%) to 97.7% (97.4%-98.0%), whereas the specificity was higher from 90.3% (89.7%-90.9%) to 98.3% (98.1%-98.6%), and the PPV was higher from 15.5% (13.3%-17.6%) to 34.0% (28.1%-40.0%). The sensitivity and PPV were higher and specificity and NPV lower across all thresholds in men compared to women (Table 4).

## 3.4 | Trade-offs per 1000 patients tested

If all patients were referred and received definitive testing for colorectal cancer, using a FIT threshold of ≥10 µg Hb/g faeces would lead to seven patients without cancer referred for each person referred with cancer (Table 5). In women this ratio was 12:1 and for men, 7:1. Fewer patients with a positive FIT of ≥10 µg Hb/g faeces would need to be referred to detect one serious colorectal

**TABLE 2** Area under the curve (AUC) for FIT for a diagnosis of cancer or serious colorectal disease by gender and age-group

| Age group | Women | Men |
|---|---|---|
| Colorectal cancer | | |
| ≥18 y | 0.948 (0.907-0.989) | 0.933 (0.898-0.969) |
| ≥40 y | 0.944 (0.899-0.988) | 0.934 (0.897-0.972) |
| ≥50 y | 0.938 (0.889-0.987) | 0.929 (0.887-0.971) |
| ≥60 y | 0.919 (0.856-0.982) | 0.921 (0.870-0.971) |
| ≥70 y | 0.934 (0.867-1.000) | 0.936 (0.895-0.978) |
| ≥80 y | 0.881 (0.693-1.000) | 0.886 (0.805-0.967) |
| Serious colorectal disease | | |
| ≥18 y | 0.707 (0.663-0.751) | 0.781 (0.738-0.825) |
| ≥40 y | 0.698 (0.652-0.744) | 0.769 (0.723-0.816) |
| ≥50 y | 0.708 (0.658-0.758) | 0.769 (0.719-0.819) |
| ≥60 y | 0.648 (0.586-0.710) | 0.773 (0.712-0.833) |
| ≥70 y | 0.662 (0.581-0.743) | 0.793 (0.722-0.864) |
| ≥80 y | 0.649 (0.508-0.790) | 0.764 (0.655-0.874) |

disease: two to one overall, three to one in women and two to one in men (Table 5). A lower number of patients would be investigated to detect a serious colorectal disease using a FIT threshold of ≥10 μg Hb/g faeces however 53% of the patients with serious colorectal disease would be further investigated compared to 90% of patients with colorectal cancer.

### 3.5 | Colorectal cancers classified as FIT negative

Table 6 details cancers diagnosed following a FIT result less than the current DG30 threshold of 10 μg Hb/g faeces. Nine cancers (7.8%, 9/115) were diagnosed within 6 months of a negative FIT (all within 3 months) Five of these diagnoses followed a change in bowel habit, four patients had anaemia, two had unexpected weight loss and two had abdominal pain. Seven of these cancers were located in the rectum or sigmoid colon, and three presented with obstruction.

### 3.6 | Sensitivity analysis

The sensitivity analysis investigating the effect of alternative follow-up periods of 3, 6 and 12 months showed no change in diagnostic performance for colorectal cancer detection using FIT ≥10 μg Hb/g faeces (Table 7).

## 4 | DISCUSSION

We report a large in-context retrospective cohort study to ascertain the diagnostic performance of FIT used to investigate adult patients presenting to primary care in England with clinical features of colorectal disease. The sensitivity and specificity of FIT were both 91% for colorectal cancer using a FIT cut-off of ≥10 μg Hb/g faeces, the threshold currently recommended by NICE. If investigated further, one in ten patients with a positive FIT would be diagnosed with colorectal cancer. Using a FIT cut-off of ≥10 μg Hb/g faeces, one person with colorectal cancer would not be referred for further investigation for every one thousand patients tested. Selecting a higher threshold would mean that fewer patients without cancer would be eligible for referral for every person with cancer referred but a greater proportion of patients not referred for further investigation would have cancer. For serious colorectal disease, the specificity and PPV of FIT were higher and the sensitivity and NPV were lower than for colorectal cancer.

### 4.1 | Strengths and limitations

We present a large retrospective cohort study of FIT testing of English primary care patients to guide referral for colorectal cancer in the context of NICE DG30 guidelines. We ensured the population studied was relevant to DG30 by only including FIT requests originating in primary care following GP education on the use of FIT in this context. We have assumed that GPs have followed the guidance communicated to them about using FIT to triage 'low-risk' symptomatic patients. Although 'high-risk' symptoms qualifying for urgent colonoscopy were noted in the clinical details, such as weight loss or anaemia, it can be assumed that GPs assessed these cases to be lower risk and not to qualify for fast-track referral and that GPs required additional information to guide their management. This is consistent with previous literature recognising that symptoms and signs of disease form a 'symptom continuum' and that interpretation of alarm symptoms vary between GPs.[24]

As a retrospective cohort study using routinely collected electronic hospital records data, the majority of patients did not have a gold standard investigation at the time of the FIT test to confirm whether serious colorectal disease was present or absent. All patients were therefore followed up for evidence of subsequent pathology in hospital clinical, laboratory, radiology, endoscopy and pathology database between 6 and 36 months after initial. A potential criticism of this study is the veracity of the follow-up interval chosen. Whilst our primary analysis used 6 months of follow-up, previous studies have used a shorter minimum follow-up period of 3 months reporting similar results.[24] Changing the follow-up period to 3 and 12 months made no difference in our sensitivity analysis. If cancer was the cause of symptoms that prompted a FIT test then these symptoms will persist, evolve and worsen in the following months (even if the FIT test was to be a false negative). Premalignant lesions detected at colonoscopy triggered by a positive FIT would not have caused the presenting symptoms and are therefore likely to represent incidental findings, though their management will contribute to cancer prevention in the years to come. Preventing these cancers might therefore be regarded the result of opportunistic screening for asymptomatic lesions in symptomatic people. A longer follow-up period would therefore

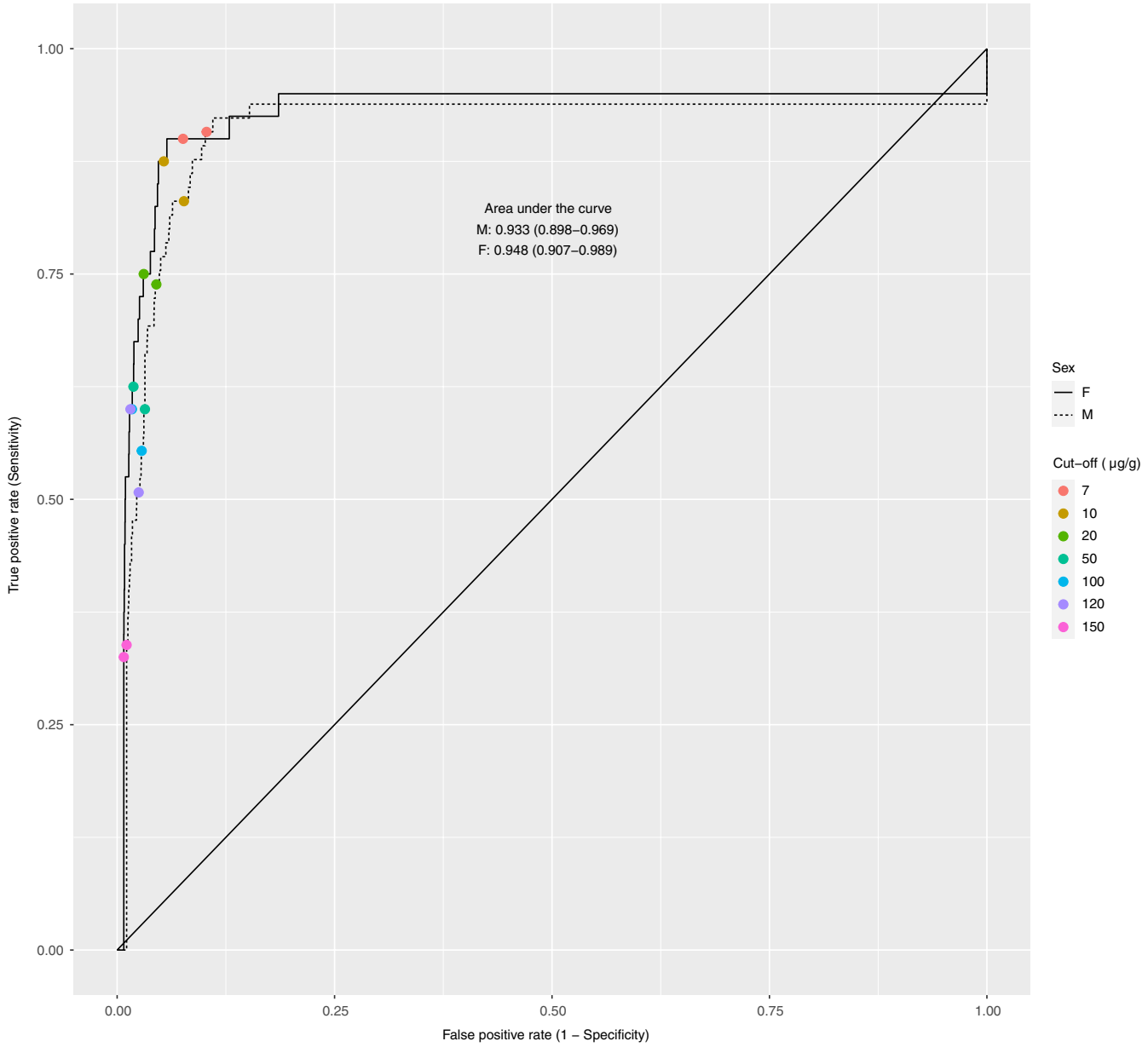


**FIGURE 2** Receiver operating characteristic (ROC) curves of FIT for the detection of colorectal cancer. Coloured symbols correspond to the true-positive/false-positive rate estimates for thresholds of 7, 10, 20, 50, 100, 120 and 150 µg Hb/g faeces. AUC, area under the curve; F, female; M, male; µg/g, µg Hb/g faeces

be necessary to identify any effect of FIT use on cancer stage at diagnosis at a population level. We could have furthered our analysis by linking the data set to Public Health England's National Cancer Registration and Analysis Service (NCRAS). NCRAS uses multiple data sources to compile an accurate description of each cancer reported in England. By linking multiple local data sources for patients tested in a single central laboratory with a clearly defined geographical catchment area we increased the likelihood that serious disease diagnosed during the study period was captured.

Specimen preparation is a critical step in the overall performance of the FIT method.[28,29] The methodological approach used in the present study involved collection of faeces by the patient into a standard sample pot which was then sampled into the FIT collection device by trained staff in the laboratory. This approach was adopted due to local concerns that patients may incorrectly use the collection device: even sampling by laboratory staff shows high imprecision,[10,29] and patient collection into the device precludes concurrent testing for other faecal tests, such as calprotectin. It is possible that, as a consequence of the delay between collection and arrival in the laboratory, some degree of degradation may have occurred and the quantitative FIT value may represent an underestimation of the true haemoglobin concentration.[30] The excellent discriminatory value of FIT (AUC of 0.941) and the low number of false negatives reported in this large in-context cohort indicates that haemoglobin degradation is not a major limitation of clinical performance when using a low threshold of FIT.[29]

**TABLE 3** Comparison of diagnostic accuracy of FIT by cut-off for the detection of colorectal cancer by gender

| Colorectal outcome | FIT cut-off (μg Hb/g faeces) | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
| Cancer | 7 | 90.0 (80.7-99.3) | 91.1 (90.3-91.8) | 6.56 (4.49-8.63) | 99.9 (99.8-100) | 92.3 (85.8-98.8) | 87.9 (86.9-88.9) | 10.9 (8.32-13.5) | 99.9 (99.7-100) |
| | 10 | 90.0 (80.7-99.3) | 92.4 (91.8-93.1) | 7.64 (5.24-10.0) | 99.9 (99.9-100) | 90.8 (83.7-97.8) | 89.8 (88.8-90.7) | 12.5 (9.52-15.5) | 99.8 (99.7-100) |
| | 20 | 87.5 (77.3-97.7) | 94.6 (94.1-95.2) | 10.2 (7.00-13.4) | 99.9 (99.8-100) | 83.1 (74.0-92.2) | 92.3 (91.5-93.2) | 14.9 (11.2-18.5) | 99.7 (99.5-99.9) |
| | 50 | 75.0 (61.6-88.4) | 96.9 (96.5-97.4) | 14.6 (9.75-19.4) | 99.8 (99.7-99.9) | 73.8 (63.2-84.5) | 95.5 (94.9-96.2) | 21.0 (15.7-26.2) | 99.6 (99.4-99.8) |
| | 100 | 62.5 (47.5-77.5) | 98.1 (97.8-98.5) | 18.9 (12.3-25.6) | 99.7 (99.6-99.9) | 60.0 (48.1-71.9) | 96.8 (96.3-97.3) | 23.2 (16.8-29.6) | 99.3 (99.1-99.6) |
| | 120 | 60.0 (44.8-75.2) | 98.3 (98.0-98.6) | 19.8 (12.7-26.9) | 99.7 (99.6-99.9) | 55.4 (43.3-67.5) | 97.2 (96.7-97.7) | 24.0 (17.2-30.8) | 99.3 (99.0-99.5) |
| | 150 | 60.0 (44.8-75.2) | 98.5 (98.2-98.8) | 21.4 (13.8-29.0) | 99.7 (99.6-99.9) | 50.8 (38.6-62.9) | 97.5 (97.1-98.0) | 25.0 (17.6-32.4) | 99.2 (98.9-99.5) |

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

## 4.2 | Comparison with existing literature

A Danish study including 3462 FIT samples from patients aged ≥30 years investigated in primary care for 'low-risk' or 'non-alarm' symptoms including change in bowel habit, abdominal pain, unexplained anaemia and nonspecific symptoms of fatigue and weight loss.[24] 540 (15.6%) were positive at a threshold of 10 μg Hb/g faeces, but sensitivity and specificity were not reported. The PPV for colorectal cancer was 9.4% (95% CI: 7.0%-11.9%) overall, 6.1% (3.2%-8.7%) in women and 13.3% (9.1%-17.5%) in men over 3 months of follow-up. The PPV in our study was similar 10.1% (8.2%-12.0%), 7.64 (5.24-10.0) in women and 12.5 (9.52-15.5) in men, despite the longer follow-up period. The same study reported a PPV for serious colorectal disease (colorectal cancer, high-risk adenoma and inflammatory bowel disease) of 14.7% (10.6%-18.9%) overall and in women 12.2% (8.1-16.2) and men 13.5% (10.6%-16.4%). The PPV for serious colorectal disease was higher in our study, but remained lower for women than for men.

Others have reported the diagnostic accuracy of FIT in patients referred for colorectal investigation. A study from Scotland reported a sensitivity for colorectal cancer of 89.3%, specificity 79.1%, PPV 14.2% and an NPV of 99.5% and for serious colorectal disease sensitivity 68.6%, specificity 83.6%, PPV 39.8% and an NPV of 94.4%.[16] In a Dutch cross-sectional diagnostic accuracy study,[31] 810 patients referred for colonoscopy for suspicion of significant colorectal disease were investigated with point-of-care FIT using a haemoglobin threshold of >6 μg Hb/g faeces. The sensitivity for significant colorectal disease (colorectal cancer, inflammatory bowel disease, diverticulitis or advanced adenoma >1 cm) was 67%; specificity 84%; PPV 47% and NPV 92%. In a further prospective English study of 430 nonconsecutive patients[25] referred for urgent lower GI investigation, the sensitivity for colorectal cancer was 84% and specificity 93%. The difference in performance of FIT in our study most likely reflects the lower risk spectrum of unselected symptomatic primary care patients—the NICE DG30 population.

## 4.3 | Implications for research and practice

FIT could be used to further simplify referral pathways for patients with suspected colorectal cancer. It could also provide a means to reprioritise patients with clinical features of colorectal disease who have had definitive investigation delayed, for example those currently awaiting colonoscopy deferred due to the COVID-19 pandemic. A recent English audit from Nottingham reported that a FIT ≥150 μg Hb/g faeces triggered an immediate patient contact to arrange rapid investigation more expedient than urgent 2-week-wait investigation.[22] Based on our cohort, using a threshold of ≥150 μg Hb/g faeces would lead to 3% of patients FIT tested being rapidly investigated to detect 54% of all undiagnosed colorectal cancer. Reducing the threshold to ≥120 μg Hb/g faeces, the level used by the BCSP would lead to a similar percentage of patients being referred to detect an additional 3% of the underlying cancers. By setting the threshold at ≥10 μg Hb/g faeces, 10% of the tested population would be further investigated to detect 91% of cancers. Furthermore, the PPV of 10% associated with a FIT ≥10 μg Hb/g faeces far exceeds the PPV threshold of ≥3% which NICE NG12 recommends further investigation for cancer in symptomatic patients, and the 8% threshold used in the BCSP. Therefore, symptomatic patients with positive FIT at a low cut off, such as ≥10 μg Hb/g faeces, should be prioritised similarly or even ahead of asymptomatic patients with a positive FIT diagnosed as part of bowel cancer screening.[32]

Use of FIT testing in colorectal low-risk symptom pathways is likely to be controversial as was the introduction of gFOB by NICE

**TABLE 4** Comparison of diagnostic accuracy of FIT by cut-off for the detection of serious colorectal disease (cancer; high-risk adenoma; bowel inflammation) by gender

| Colorectal outcome | FIT cut-off (μg Hb/g faeces) | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
| Serious colorectal disease | 7 | 43.6 (35.8-51.4) | 91.5 (90.7-92.2) | 12.4 (9.63-15.1) | 98.3 (98.0-98.7) | 66.7 (59.2-74.1) | 88.7 (87.7-89.7) | 18.6 (15.3-21.8) | 98.6 (98.2-99.0) |
| | 10 | 42.9 (35.2-50.7) | 92.8 (92.2-93.5) | 14.2 (11.1-17.4) | 98.3 (98.0-98.7) | 64.1 (56.4-71.7) | 90.5 (89.6-91.4) | 20.8 (17.1-24.4) | 98.5 (98.1-98.9) |
| | 20 | 36.5 (29.0-44.1) | 94.9 (94.4-95.5) | 16.6 (12.7-20.6) | 98.2 (97.8-98.5) | 57.5 (49.7-65.3) | 93.0 (92.2-93.8) | 24.2 (19.8-28.7) | 98.3 (97.8-98.7) |
| | 50 | 28.8 (21.7-36.0) | 97.1 (96.7-97.6) | 21.8 (16.2-27.5) | 98.0 (97.6-98.4) | 47.1 (39.1-55.0) | 96.0 (95.4-96.6) | 31.4 (25.4-37.5) | 97.9 (97.5-98.4) |
| | 100 | 23.7 (17.0-30.4) | 98.3 (98.0-98.7) | 28.0 (20.4-35.7) | 97.9 (97.5-98.3) | 36.6 (29.0-44.2) | 97.2 (96.6-97.7) | 33.3 (26.2-40.5) | 97.5 (97.0-98.0) |
| | 120 | 21.8 (15.3-28.3) | 98.5 (98.1-98.8) | 28.1 (20.1-36.1) | 97.8 (97.5-98.2) | 34.0 (26.5-41.5) | 97.5 (97.0-98.0) | 34.7 (27.1-42.3) | 97.4 (97.0-97.9) |
| | 150 | 21.8 (15.3-28.3) | 98.6 (98.3-98.9) | 30.4 (21.8-38.9) | 97.9 (97.5-98.2) | 32.0 (24.6-39.4) | 97.9 (97.5-98.3) | 37.1 (28.9-45.4) | 97.4 (96.9-97.9) |

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

**TABLE 5** Patients with cancer detected if patients with positive FIT referred expressed by FIT threshold and gender per 1000 patients FIT tested

| | Threshold (μg Hb/g faeces) | Positive FITs n (%) | Negative FITs n (%) | Cancers detected n (%) | Positive FITs to detect one cancer (number needed to scope) | Patients with cancer and a negative FIT (the cancer miss rate per 1000 tests) | Serious disease detected n (%) | Positive FITs to detect one serious colorectal disease (number needed to scope) |
|---|---|---|---|---|---|---|---|---|
| Women | 7 | 95 (9) | 905 (91) | 6 (90) | 15 | 1 | 26 (44) | 4 |
| | 10 | 82 (8) | 918 (92) | 6 (90) | 13 | 1 | 25 (43) | 4 |
| | 20 | 60 (6) | 940 (94) | 6 (88) | 10 | 1 | 22 (37) | 3 |
| | 50 | 36 (4) | 964 (96) | 5 (75) | 7 | 2 | 17 (29) | 3 |
| | 100 | 23 (2) | 977 (98) | 4 (63) | 5 | 3 | 14 (24) | 2 |
| | 120 | 21 (2) | 979 (98) | 4 (60) | 5 | 3 | 13 (22) | 2 |
| | 150 | 19 (2) | 981 (98) | 4 (60) | 5 | 3 | 13 (22) | 2 |
| Men | 7 | 134 (13) | 866 (87) | 15 (92) | 9 | 1 | 55 (67) | 3 |
| | 10 | 115 (11) | 885 (89) | 14 (91) | 8 | 2 | 53 (64) | 3 |
| | 20 | 89 (9) | 911 (91) | 13 (83) | 7 | 3 | 48 (58) | 2 |
| | 50 | 56 (6) | 944 (94) | 12 (74) | 5 | 4 | 39 (47) | 2 |
| | 100 | 41 (4) | 959 (96) | 10 (60) | 4 | 7 | 30 (37) | 2 |
| | 120 | 36 (4) | 964 (96) | 9 (55) | 4 | 7 | 28 (34) | 2 |
| | 150 | 33 (3) | 967 (97) | 8 (51) | 4 | 8 | 42 (51) | 1 |
| All | 7 | 111 (11) | 889 (89) | 10 (91) | 11 | 1 | 38 (55) | 3 |
| | 10 | 96 (10) | 904 (90) | 10 (91) | 10 | 1 | 37 (53) | 3 |
| | 20 | 71 (7) | 929 (93) | 9 (85) | 8 | 2 | 32 (47) | 3 |
| | 50 | 44 (4) | 956 (96) | 8 (74) | 6 | 3 | 26 (38) | 2 |
| | 100 | 30 (3) | 970 (97) | 7 (61) | 5 | 4 | 21 (30) | 2 |
| | 120 | 28 (3) | 972 (97) | 6 (57) | 5 | 5 | 19 (28) | 2 |
| | 150 | 25 (2) | 975 (98) | 6 (54) | 4 | 5 | 19 (27) | 2 |

**TABLE 6** Clinical characteristics of FIT negative cancers <10 μg Hb/g faeces

| Age | Sex | FIT request details | FIT (μg Hb/g faeces) | Delay to laboratory (days) | FIT to diagnosis (days) | Diagnosis |
|---|---|---|---|---|---|---|
| 69 | F | Change in bowel habit | 3.1 | <1 | 6 | 2WW, stenosing rectosigmoid |
| 64 | F | New onset diarrhoea and weight loss | 0.7 | <1 | 10 | 2WW, 20 mm low rectal |
| 69 | M | Microcytic anaemia | 0.1 | 4-5 | 19 | 2WW, rectal |
| 83 | F | Irregular bowel habit | 0.8 | 3-4 | 23 | Obstruction, right hemicolectomy |
| 82 | M | Wind and abdominal pain | 3.8 | <1 | 24 | Obstruction, metastatic to liver |
| 32 | M | Weight loss, iron deficiency anaemia | 8.7 | 3-4 | 26 | 2WW, ascending colon |
| 82 | M | Anaemia | 0 | 3-4 | 28 | 2WW, sigmoid tumour on CT |
| 63 | M | Change bowel habit | 0.1 | 3-4 | 54 | 2WW, rectal tumour on CT |
| 74 | F | Hypertension, change in bowel habit | 1.5 | <1 | 91 | 2WW, rectal tumour |
| 53 | M | Abdominal pain | 0.1 | <1 | 188 | 2WW, terminal ileum NET |
| 48 | F | IDA | 1.7 | <1 | 374 | Obstruction, sigmoid tumour |
| 79 | F | PR bleed | 0.3 | <1 | 407 | 2WW, right hemicolectomy |

Abbreviations: 2WW, 2-week-wait referral; Abdo, abdominal; CIBH, change in bowel habit; CT, computed tomography; IDA, iron deficiency anaemia; NET, neuroendocrine tumour.

**TABLE 7** Effect of adjusting the period of follow-up on diagnostic accuracy measures for colorectal cancer using FIT ≥10 μg Hb/g faeces

| Months follow-up | TP | FP | FN | TN | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|---|
| 3 | 85 | 898 | 9 | 9851 | 90.4 (84.5-96.4) | 91.6 (91.1-92.2) | 8.65 (6.89-10.4) | 99.9 (99.8-100.0) |
| 6 | 95 | 848 | 10 | 8943 | 90.5 (84.9-96.1) | 91.3 (90.8-91.9) | 10.1 (8.15-12.0) | 99.9 (99.8-100.0) |
| 12 | 99 | 740 | 11 | 6931 | 90.0 (84.4-95.6) | 90.4 (89.7-91.0) | 11.8 (9.62-14.0) | 99.8 (99.7-99.9) |

Abbreviations: FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

in 2015.[2,3] However, patients and bowel cancer charities may be reassured by the improved performance of FIT compared to gFOB and with appropriate safety netting allow more rapid definitive testing for the at risk population.[13] Commissioners of colorectal cancer services are likely to support this more efficient use of expensive endoscopic resource to target those at highest risk and to potentially reach underserved populations given the simplicity of the test.[33] There will be large backlogs post-COVID 19 and FIT use might ensure potential cancers are given higher priority as Trust and endoscopy services review deferred cases. Nevertheless, laboratories may find a very substantial increase in FIT workload and will need to consider the logistics of getting FIT kits out to patients and back ideally via post in the COVID-19 pandemic, including making sure the correct clinician in primary or secondary care receives the result. There is likely to be comment by National professional bodies such as the Joint Advisory Group for Endoscopy (JAG), British Society of Gastroenterology, Association of Coloproctoloigists of Great Britain and Ireland on the use of FIT in this way: many societies have been supportive and again recognise that previous ways of using endoscopy services will not be sustainable in the post-COVID environment. Better to target high-quality endoscopy at selected cases than try to carry out large volumes of lower quality colonoscopy. Finally, a FIT threshold of ≥10 μg Hb/g faeces is likely to be welcomed by endoscopists: it will clearly lead to a greater proportion of colonoscopies identifying important pathology or being therapeutic.

Previous research has considered the added value of interpreting FIT in combination with other clinical information, including additional faecal and blood tests. Combining negative FIT with a negative faecal calprotectin or a negative FIT and a normal haemoglobin were reported as safe approaches to ruling-out serious colorectal disease.[16,34] A multivariable model 'COLONPREDICT' was developed in Spain to predict colorectal cancer in patients referred for colonoscopy.[26] It included 12 covariates derived from age, gender, FIT, blood haemoglobin, carcinoembryonic antigen, acetylsalicylic acid treatment, previous colonoscopy, rectal mass, benign anorectal lesion, rectal bleeding and change in bowel habit. The Scottish FAST score combines FIT, age and sex as a single-test result which might indicate individual risk of colorectal cancer or serious colorectal disease.[21] Compared to FIT alone, the AUC for colorectal cancer was 0.92 (0.90-0.94) for COLONPREDICT and 0.87 (0.85-0.89) for FAST.[35] Both of these scores show greater discriminative ability for colorectal cancer than symptom-based referral criteria included in NICE NG12 (0.53 (0.49-0.57).[35] Based on the AUC of FIT alone (0.94 [0.91-0.97]) derived from our cohort

of 9896 English primary care patients tested with FIT for clinical features of colorectal cancer prior to referral, it seems that FIT performs with greater discrimination than more complex approaches. This would allow a simple recommendation for primary care commissioners and clinicians: a FIT result ≥10 μg Hb/g faeces from a patient tested in primary care for suspected colorectal cancer or serious colorectal disease should prompt urgent referral for definitive colorectal investigation.

The risk of a colorectal cancer diagnosis in a primary care patient with a negative FIT was low at one in a thousand patients tested (<0.1% over 6 months and <0.2% over 12 months). The background risk of colorectal cancer over a 2-year period in a 60-year old presenting to primary care without symptoms of colorectal cancer is 0.2% and 0.1%, for men and women respectively.[36] As estimates for a negative FIT are comparable to the cancer risk in asymptomatic patients over a longer period, the risk of colorectal cancer in patients with a negative FIT is similar if not lower than the baseline risk. However, patients with a negative FIT, and persistent, new, or worsening symptoms should be encouraged to re-attend primary care within a defined period of time (eg within 4 weeks) so they are not lost to follow-up. By safety-netting in this way, clinicians may reconsider definitive colorectal investigation, investigation for other serious causes of abdominal symptoms, seeking specialist advice and guidance where necessary.

## 5 | CONCLUSIONS

FIT offers an appropriate triage test for use in primary care to investigate patients with symptoms of serious colorectal disease. A FIT threshold of ≥10 μg Hb/g faeces would lead to 10% of patients tested being recommended for definitive investigation to detect 91% of the underlying cancers. Simple safety netting advice can guard against very infrequent false-negative FIT results for colorectal cancer. FIT could be used to reduce pressure on urgent referral pathways by identifying patients who do not require further investigation for colorectal cancer, thereby controlling colonoscopy demand and reducing costs. FIT could be used in this way to reprioritise patients with lower colorectal cancer symptoms whose tests have been delayed by the COVID-19 pandemic.

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## SUPPORTING INFORMATION

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

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