ABSTRACT

Objectives We sought to investigate if duplicate faecal immunochemical testing (FIT) sampling improves the negative and positive predictive value of patients thought to be at risk of colorectal cancer (CRC). Specifically, we aimed to investigate whether the proportion of FIT-negative CRC missed by a single FIT test in symptomatic patients could be reduced by duplicate FIT testing.

Design A retrospective service evaluation cohort study of the diagnostic accuracy of duplicate FIT testing.

Setting Patients referred from primary care with suspected CRC to four secondary care trusts in North-West England.

Participants 28,622 patients over 18-years-old with lower gastrointestinal symptoms suggestive of CRC who completed two FIT samples.

Primary and secondary outcome measures The performance of duplicate FIT for detecting CRC at a threshold of 10 µgHb/g.

Results The sensitivity if either test was >10 µgHb/g was 0.978 (0.955–0.989), specificity was 0.662 (0.657–0.668), positive predictive value 0.031 (0.028–0.035) and negative predictive value 1.00 (0.999–1.00). Despite two-thirds of patients (18,952) being negative following two tests, at this threshold only seven CRC were missed over a 26-month period. All seven patients had other high-risk features which should have prompted investigation.

Conclusions This study suggests that in routine NHS practice, a duplicate FIT sample strategy together with clinical evaluation for evidence of anaemia and weight loss is superior to a single FIT sample alone and would allow symptomatic patients to be managed in primary care without the need for urgent referral to secondary care for urgent colonic imaging.

INTRODUCTION

The SARS-CoV-2 pandemic has placed a significant strain on endoscopy services in the UK, with a 92% reduction in the volume of colonoscopies performed in April 2020 compared with April 2019. It has been estimated that it would be necessary to increase UK endoscopy capacity by approximately one-third to eliminate the backlog of cases by June 2022. This has compounded existing challenges faced by endoscopy services where prior to the pandemic almost half of units were failing to comply with colorectal cancer (CRC) diagnostic standards in the UK and referrals for suspected CRC were inexorably increasing. At the same time, over 90% of patients referred with suspected CRC do not have cancer, reflecting the poor predictive value of symptoms for CRC.

In 2017 the National Institute of Health and Care Excellence (NICE) recommended faecal immunochemical testing (FIT) for the detection of CRC in patients with low risk symptoms. Subsequently, several large trials have suggested that FIT also performs well in patients with high-risk symptoms for CRC, suggesting that FIT may be a suitable cost-saving alternative to colonoscopy in some settings. However, given the prevalence of CRC in patients presenting to primary care, up to 10% of patients with CRC will not be detected at a threshold of 10 µgHb/g, raising concerns about how
the risk associated with managing this group of patients should be managed.

To mitigate the risk of missing CRC diagnosis during the first wave of the pandemic, NHS England published guidance on the use of FIT to prioritise investigation and imaging modality for all patients with suspected CRC. This approach, based on preliminary data from three large studies, recommended that patients without iron deficiency anaemia or a palpable mass and with a FIT <10 µgHb/g did not need investigation, but recommended safety netting to mitigate the potential risk of missed CRC diagnosis.

Several strategies have been proposed to mitigate the risk of missing CRC including reducing the threshold for a positive FIT test to <4 µgHb/g or being more cautious in the application of FIT in groups where it is recognised to perform poorly such as in patients with iron deficiency anaemia. However, in contrast to blood, faeces is well documented to be an imperfect biological material with a risk of sampling error, especially as patients themselves are collecting their own sample for FIT.

Therefore, we sought to investigate if there was a role for duplicate FIT samples as a strategy to reduce sampling error and thereby support safety netting in primary care. We aimed to investigate whether the risk of being diagnosed with CRC in patients with two negative FITs was sufficiently low enough to enable more routine referral of these patients, rather than referral on an urgent suspected cancer pathway. This would work alongside other elements of clinical safety netting, such as rectal bleeding, obstructive symptoms, palpable abdominal mass or anaemia, as detailed in the NHS England guidance.

**MATERIALS AND METHODS**

**Settings**
The Lancashire and South Cumbria Cancer Alliance (LSCCA) encompasses four secondary care trusts: Lancashire Teaching Hospitals NHS Foundation Trust, University Hospitals of Morecambe Bay NHS Foundation Trust, East Lancashire Hospitals NHS Trust and Blackpool Teaching Hospitals NHS Foundation Trust, serving a population of 1.8 million people.

**Inclusion criteria**
All adult patients referred from primary care with suspected CRC with low-risk symptoms defined by NICE DG30 criteria were asked to complete two FIT samples on different bowel motions between August 2017 and June 2020 prior to clinical assessment in secondary care. After June 2020 all patients, including those with higher risk symptoms defined by NICE NG12 criteria, were included to facilitate decision-making and risk stratification for colonic imaging by hospital specialists during the SARS-CoV-2 pandemic. Some Trusts included in the study do test patients with FIT if they have rectal bleeding, whereas other Trusts do not. Patients with rectal bleeding were not delayed in their referral as urgent referral was made simultaneously to FIT requests.

**Measures**
FIT samples were analysed at the Royal Preston Hospital, Royal Blackburn Teaching Hospital and Royal Lancaster Infirmary using the OC-Sensor FIT-Screening System (Mast Group Ltd, Bootle, UK) using a threshold of 10 µgHg/g to denote a positive test. Cancer registries were interrogated for all diagnosis of CRC following completion of the second FIT test. The NHS numbers of patients extracted from the laboratory information system were cross referenced with the Somerset Cancer Registry to check for lower GI cancer diagnosis. All patients who completed two FIT samples between January 2019 and February 2021 were included in this analysis. Patients who did not provide two samples, completed an inadequate sample, or for whom it was not possible to analyse one of the samples were excluded from the analysis. Demographic characteristics and clinical information were obtained from electronic patient records that were populated as part of routine patient care.

**Sub-group analysis**
We have compared subgroups of our data with regard to temporal analysis prepandemic and postpandemic (April 2019–February 2020 and April 2020–February 2021) to assess the impact of low and high risk symptoms on our data. We have also analysed subgroups of data with regard to whether the Trust from which the FIT request originated from included patients with rectal bleeding or not.

**Statistical analysis**
Statistical analysis was undertaken using GraphPad Prism V.9 for Windows (GraphPad Software, San Diego, California, USA). A contingency table was used to calculate sensitivity, specificity, NPV and PPV. Sensitivity was defined as true positive cases/true positive plus false negative cases, specificity was defined as true negative cases/true negative plus false positive cases, NPV was defined as true negative cases/true negative plus false negative cases and PPV was defined as true positive/true positive plus false positive cases. The Wilson-Brown method was used to calculate 95% CI. The proportion of patients with CRC with a negative FIT result was calculated. Fisher’s exact test was used to calculate differences for subgroup analyses.

This study used data collected as part of routine patient clinical care and was therefore exempt from specific NHS research ethics committee approval. It was, however, approved by the Research and Innovation committee at the Lancashire Teaching Hospitals NHS Foundation Trust. All local and national guidelines on research and information governance were adhered to.

**Patient and public involvement**
Patients and public were not involved in the design, conduct or dissemination of the details of is study.
However, patient groups were involved in approving the patient information leaflet for sample collection.

RESULTS
Of note, 30,104 patients completed FIT samples between January 2019 and February 2021 across LSCCA (see figure 1 to visualise flow); 28,622 (95%) patients completed two FIT samples as directed and were included in the analysis. The median age was 66 (range 16–103), 56% female; 317 (1.1%) patients were subsequently diagnosed with colorectal adenocarcinoma following interrogation of cancer registries (table 1). The median age of patients diagnosed with cancer was 73 (range 35–94), 188 of 319 cancers (59%) were in males.

The requirement to complete two positive FIT tests had an impact on the performance of FIT. The sensitivity, specificity, NPV, PPV and likelihood ratio after two FIT results at a threshold of 10 µgHb/g are reported in table 2.

Notably, more than 18,000 patients had two FIT results <10 µgHb/g, 7 of whom were subsequently diagnosed with CRC over the 26-month follow-up period (0.04%). The characteristics of these seven patients were congruent with the published literature with six of them having right-sided tumours (the only exception had an obstructing sigmoid tumour). All seven patients suffered from iron deficiency anaemia (table 3).

This is in contrast to patients who had one positive and one negative FIT, in whom only 32% had anaemia (table 4), although some have red flag clinical presentations, rectal bleeding (14%), palpable mass (9%) and strong clinical suspicion (4.5%).

Although the PPV is excellent whether only one FIT or both FITs are positive, both the PPV and the likelihood ratio are higher if both FITs are positive than if only one test is positive. Having two FIT results can give enriched information on the likelihood of the patient having a CRC diagnosis (table 5). If a patient has two positive FITs rather than one positive FIT, the chance of having cancer increased from 0.5% to 5.5% and if a patient has two FITs over 100 µgHb/g rather than two FITs over 10 µgHb/g, the chance is 14% rather than 5.5% (table 5 and figure 2).

Sub-group analysis
Subgroup analysis of the postpandemic group, including higher risk NG12 patients shows that the performance of FIT remains excellent (online supplemental table). Compared with the prepandemic cohort (April 2019 to February 2020), there were no differences in patient demographics nor the proportion of patients with two negative FITs who had a CRC diagnosis (p>0.999, Fisher’s exact test).

Subgroup analysis of patients based on whether FIT was (or was not) recommended in the presence of overt rectal bleeding groups also showed no significant difference between the proportion of patients with two negative FITs who had a diagnosis of CRC (p>0.999, Fisher’s exact test).

Table 1  Number of colorectal cancers detected, according to one or two FIT positive tests

| FIT result | Colorectal cancer negative | Colorectal cancer positive |
|------------|-----------------------------|----------------------------|
| 10 µgHb/g threshold | 19,952                      | 7 (0.04%, 95% CI 0.01% to 0.08%) |
| 2 negative tests | 19,952                      | 7 (0.04%, 95% CI 0.01% to 0.08%) |
| 1 positive, 1 negative test | 4392                      | 22 (0.5%, 95 CI 0.3% to 0.7%) |
| 2 positive tests | 5278                      | 290 (5.2%, 95% CI 4.6% to 5.8%) |

FIT, faecal immunochemical testing.
a clinical trial. Over 96% of patients were able to provide two samples as directed in the patient information leaflet and consequently 28,622 were included in the analysis. Our study suggests that a two-sample strategy is highly sensitive if the patient is investigated if either test is positive at a threshold of 10 µg Hb/g, while still returning negative results for two-thirds of patients. The proportion of CRC that were negative (2.2%) were significantly less than those in the reported literature, and the incidence of missed CRC was extremely low (0.04%). Our results are congruent with the published literature in that most FIT negative CRC patients had iron deficiency anaemia and right-sided cancers. As all the patients who were subsequently diagnosed with CRC following two negative tests were subsequently found to have anaemia, if FIT was performed in combination with a FBC, it is possible that almost all patients with CRC could be identified using a minimally invasive approach. This supports the strategies of combining negative FIT and lack of anaemia described by the Nottingham and Glasgow groups. While the validity of this approach will require robust evaluation, this raises the possibility that a significant proportion of symptomatic patients who are currently referred as suspected cancer patients to secondary care for colonoscopy could potentially avoid urgent referral. Since patients with two negative FIT results have such a low chance of having a diagnosis of CRC, this provides excellent reassurance for primary care physicians and patients. In future, using a two-test strategy could potentially be used to safely and cost-effectively manage patients in the community, providing clinical safety netting and monitoring mechanisms are established. By contrast, a one-sample FIT strategy at a threshold of 10 µg Hb/g with safety-netting for patients with anaemia and abdominal pain would result in a failure to detect 5.5% of CRC and would require 44% of patients to have colonic imaging. We suggest that a two-sample FIT strategy is likely to be both safer and more cost-effective than a one-sample FIT strategy with safety netting.

While this large, real-world, retrospective study represents important early data on the acceptability, safety, and potential utility of a two-sample FIT strategy in routine NHS clinical practice, there are important limitations. Significantly, the inclusive and pragmatic nature of this study has inevitably resulted in a heterogeneous cohort of high-risk and low-risk symptomatic patients with a range of demographic characteristics and comorbidities. Importantly, as the diagnosis we obtained were based on interrogation of cancer registries and not scrutiny of individual patient colonoscopy reports it is feasible that patients with CRC may have been missed if hospital episodes were incorrectly coded or they did not subsequently have diagnostic tests performed because of comorbidities, they left the area or they are still awaiting investigation as a consequence of the SARS-CoV-2 pandemic. Despite the limitations of this study, however, the recognised problems associated with individual sample FIT testing and the pressing challenges faced by diagnostic services for CRC necessitate comparison of strategies to optimise the use of FIT. This should include comparison and combination of two-sample FIT testing with strategies to modify referral pathways to account for patients in whom FIT is known to perform poorly, and alteration of the threshold for a positive FIT result. It is reassuring that the power of two negative FITs remains even when higher risk NG12 patients are being tested in addition to patients who meet DG30 clinical criteria deemed at lower risk.

Our groups are currently undertaking a decision analytical approach encompassing cost-effectiveness and budget impact analysis to address this problem.

Table 3: Clinical characteristics of colorectal cancers with two negative FIT tests

| Age | Gender | FIT 1 µg Hb/g | FIT 2 µg Hb/g | Presenting Symptoms | Hb G/L | MCV fL | Ferritin µg/L | Platelets | Diagnosis |
|-----|--------|-------------|-------------|-------------------|-------|-------|-------------|----------|-----------|
| Male | 80–89  | 8.8         | 7.2         | Anaemia           | 122   | 85.1  | 9           | 235      | Adenocarcinoma of caecum |
| Male | 80–89  | <5          | <5          | Right-sided abdominal pain | 122   | 82.6  | 80          | 418      | Adenocarcinoma of ascending colon |
| Female | 70–79 | <5          | 6           | Right-sided abdominal pain and weight loss | 114   | 79.5  | 35          | 322      | Adenocarcinoma of caecum |
| Female | 60–69 | 6.4         | <5          | Abdominal pain weight loss, vomiting | 100   | 66.6  | 8           | 389      | Adenocarcinoma of ascending colon |
| Female | 60–69 | <5          | <5          | Abdominal pain weight loss, diarrhoea | 102   | 80    | –           | 376      | Adenocarcinoma of caecum |
| Male | 70–79  | 7.8         | 7           | Oedema and anaemia | 101   | 73.5  | 11          | 288      | Adenocarcinoma of ascending colon |
| Male | 70–79  | <5          | 9           | Abdominal pain, mass | 95    | 77.7  | 639         | 172      | Adenocarcinoma of sigmoid colon |

FIT, faecal immunochemical testing; MCV, mean corpuscular volume.
Supporting existing literature

The utility of a two-sample FIT strategy has previously been evaluated in the literature. While it has been suggested that it may be a useful tool for clinicians to risk stratify patients referred for urgent colonoscopy, other groups suggest that the performance of FIT is not improved with repeated sampling. Some of this evidence is from asymptomatic patients in screening.

| Age | Gender | FIT 1 µg Hb/g | FIT 2 µg Hb/g | Presenting symptoms | Hb G/L | MCV fL | Ferritin µg/L | Platelets | Diagnosis |
|-----|--------|---------------|---------------|---------------------|--------|--------|--------------|-----------|-----------|
| Female | 80–90 | 5 | 15.6 | Change in bowel habit and weight loss | 115 | 83.6 | – | 416 | Adenocarcinoma of caecum |
| Female | 70–79 | 27.6 | 7.8 | Diarrhoea | 128 | 82.4 | – | 263 | Adenocarcinoma of transverse colon |
| Male | 70–79 | 11.2 | 9.6 | Change in bowel habit and palpable mass | 142 | 89.8 | – | 286 | Adenocarcinoma of ascending colon |
| Male | 70–79 | 7.2 | 52 | Change in bowel habit, abdominal pain, weight loss and fatigue | 149 | 87.6 | – | 183 | Adenocarcinoma of rectum |
| Male | 80–89 | 30.4 | 8 | Lower abdominal pain and change in bowel habit | 140 | 83.9 | – | 176 | Adenocarcinoma of splenic flexure |
| Male | 70–79 | <5 | 17.4 | Strong clinical suspicion of malignancy. Weight loss and change in bowel habit | 138 | 78.2 | – | 348 | Adenocarcinoma of ascending colon |
| Female | 80–89 | 37.6 | 8.4 | Left-sided abdominal pain | 102 | 87.7 | – | 329 | Adenocarcinoma of transverse colon |
| Male | 60–69 | 16.2 | <5 | Fatigue | 139 | 81.6 | – | 191 | Adenocarcinoma of caecum |
| Male | 80–89 | <5 | 20.4 | Rectal bleeding | 137 | 92.1 | – | 284 | Adenocarcinoma of anus |
| Female | 70–79 | 7.2 | 451 | Abdominal pain and change in bowel habit | 133 | 107.6 | – | 284 | Adenocarcinoma of overlapping region of rectum, anus and anal canal |
| Female | 80–89 | 10.6 | <5 | Rectal bleeding and change in bowel habit | 148 | 95.5 | – | 218 | Adenocarcinoma of rectum |
| Male | 50–59 | 16.2 | 9.8 | Weight loss, abdominal pain and anaemia | 84 | 64.2 | – | 539 | Adenocarcinoma of ascending colon |
| Male | 80–89 | 19 | 6 | Change in bowel habit | 145 | 97.6 | – | 151 | Adenocarcinoma of colon |
| Male | 80–89 | 82 | 6 | Anaemia | 109 | 93 | – | 274 | Adenocarcinoma of colon |
| Male | 90+ | 38 | 7 | Change in bowel habit | 129 | 94 | – | 261 | Adenocarcinoma of colon |
| Female | 80–89 | 8 | 16 | Anaemia | 100 | 81.9 | – | 310 | Adenocarcinoma of colon |
| Male | 60–69 | 184 | <5 | Rectal bleeding | 148 | 93.8 | – | 275 | Adenocarcinoma of rectum |
| Female | 80–89 | 10 | 7.6 | Change in bowel habit and weight loss | 137 | 97.3 | – | – | Adenocarcinoma of colon |
| Male | 70–79 | 20.4 | 5.2 | Iron deficiency anaemia | 101 | 71.6 | – | – | Adenocarcinoma of rectosigmoid junction |
| Female | 50–59 | <5 | 89.4 | Change in bowel habit and palpable mass | 143 | 104.8 | – | – | Adenocarcinoma of anus and anal canal |
| Female | 70–79 | 8.6 | 12.6 | Change in bowel habit and anaemia | 88 | 74.8 | 8 | – | Adenocarcinoma of caecum |
| Male | 80–89 | 9.4 | 15.4 | Anaemia | 149 | 84.2 | 195 | 417 | Adenocarcinoma of caecum |

FIT, faecal immunochemical testing; MCV, mean corpuscular volume.
In conclusion, this study demonstrates the feasibility of a two-test strategy, in routine NHS practice. It suggests that a two-sample strategy is acceptable to patients and highly sensitive, raising the possibility that a significant proportion of symptomatic patients who are currently referred with suspected CRC to secondary care for colonoscopy could potentially be safely and cost-effectively managed in the community with suitable clinical safety netting.

Two-sample FIT testing may also facilitate individualisation of patient care by expert clinicians according to the relative risk of pathology and complications of investigation according to demographic characteristics, comorbidities and patient preference. The results of more comprehensive decision analytical and economic evaluation of this strategy are urgently awaited.

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### Contributors
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The authors’ contributions are as follows, Study design: NH, MM, CR and RL. Data acquisition: NH, VC, JO and CA. Patient treatment: VC and NS. Statistical analysis: VC and CR. Interpretation of data: NH, CR, JO, SB, RL and MM. Manuscript preparation: CR and NH. Manuscript editing: NH, CR, VC, JO, CA, NS, SB, RL and MM. Manuscript review including revising it critically for important intellectual content and final approval: NH, CR, RL and MM. Project administration: CA. Supervision: MM. Author acting as guarantor: NH.

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### Data availability statement
All data relevant to the study are included in the article or uploaded as supplementary information. The raw data set will be made available upon reasonable request from the corresponding author.

### Supplemental material
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