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BJS Open, 2021, zraa056
DOI: 10.1093/bjsopen/zraa056
Original Article

Faecal immunochemical testing and blood tests for prioritization of urgent colorectal cancer referrals in symptomatic patients: a 2-year evaluation

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Abstract

Background: A novel pathway incorporating faecal immunochemical testing (FIT) for rapid colorectal cancer diagnosis (RCCD) was introduced in 2017. This paper reports on the service evaluation after 2 years of pathway implementation.

Methods: The RCCD protocol was based on FIT, blood results and symptoms to stratify adult patients in primary care. Two-week-wait (2WW) investigation was indicated for patients with rectal bleeding, rectal mass and faecal haemoglobin (fHb) level of 10 μg Hb/g faeces or above or 4 μg Hb/g faeces or more in the presence of anaemia, low ferritin or thrombocytosis, in all other symptom groups. Patients with 100 μg Hb/g faeces or above had expedited investigation . A retrospective audit of colorectal cancer detected between 2017 and 2019 was conducted, fHb thresholds were reviewed and critically assessed for cancer diagnoses.

Results: In 2 years, 14788 FIT tests were dispatched with 13361 (90.4 per cent) completed returns. Overall, fHb was less than 4 μg Hb/g faeces in 9208 results (68.9 per cent), 4–9.9 μg Hb/g in 1583 (11.8 per cent), 10–99.9 μg Hb/g in 1850 (13.8 per cent) and 100 μg Hb/g faeces or above in 720 (5.4 per cent). During follow-up (median 10.4 months), 227 colorectal cancers were diagnosed. The cancer detection rate was 0.1 per cent in patients with fHb below 4 μg Hb/g faeces, 0.6 per cent in those with fHb 4–9.9 μg Hb/g faeces, 3.3 per cent for fHb 10–99.9 μg Hb/g faeces and 20.7 per cent for fHb 100 μg Hb/g faeces or above. The detection rate in the cohort with 10–19.9 μg Hb/g faeces was 1.4 per cent, below the National Institute for Health and Care Excellence threshold for urgent referral. The colorectal cancer rate in patients with fHb below 20 μg Hb/g faeces was less than 0.3 per cent.

Conclusion: Use of FIT to "rule out" urgent referral from primary care misses a small number of cases. The threshold for referral may be adjusted with blood results to improve stratification .

Introduction

Colorectal cancer is a common cancer diagnosis with over 40 000 new diagnoses each year, and is the second commonest cause of cancer death in the UK[1]. Improving outcomes remains a key healthcare policy aim[2]. Current criteria for urgent referral to secondary care are largely based on age and symptoms[3], but the UK bowel cancer screening programme (BCSP) has demonstrated that colorectal cancer, and particularly in its early stage, is often asymptomatic[4]. Faecal immunochemical testing (FIT) has replaced guaiac-based faecal occult blood testing in the screening programme across the UK. The thresholds for positivity in the screening programme in England (120 μg haemoglobin (Hb)/g faeces) and Wales (150 μg Hb/g faeces) are higher (less sensitive) than those in Scotland (80 μg Hb/g faeces or above) and many other countries around the world, and have been chosen to mitigate the demand on overburdened diagnostic capacity in the NHS[5].

FIT has been shown to have value in patients with symptoms[6–15], and in 2015 National Institute for Health and Care Excellence (NICE) guidance recommended testing for occult blood in faeces in low-risk patients[3], and subsequently recommended a threshold of 10 μg Hb/g faeces specifically in this context[16]. In September 2016, a locally commissioned year-long pilot of FIT in the 2-week-wait (2WW) population (excluding those with rectal bleeding) was introduced, and demonstrated clear stratification value in all symptom groups judged to be 'high risk' by local primary care colleagues[9]. The value of simple measures such as stratification of anaemia[17–19] and thrombocytosis[20,21] from a full blood count (FBC) has been also confirmed in the same local population. In November 2017, a rapid colorectal cancer

Received: July 31, 2020. **Accepted:** November 15, 2020

diagnosis (RCCD) pathway incorporating direct general practitioner (GP) access to FIT and the use of FIT, FBC and ferritin results for 'rule in', 'rule out' and 'first test' selection in secondary care was introduced[11]. This study aimed to evaluate the colorectal cancer diagnoses from the first 2 years of this pathway, stratified by FIT level[22].

Methods

Rapid colorectal cancer diagnosis pathway

This local pathway was designed to incorporate FIT as a triage tool for all referral criteria in adult patients of any age, except those with rectal bleeding and rectal mass, as described elsewhere[11,22], presenting to local GP practices within the authors' catchment area. GPs were able to request FIT (and blood tests) independently and to act on the result, or, if clinical suspicion was high, they could submit an RCCD referral form contemporaneously. In the latter pathway, the form was held for 12 working days in a 'window' and the 62-day clock started only either on receipt of FIT (and blood) results or on expiry of the window. The outcomes from this pathway have been evaluated prospectively, and in June 2019 the window was no longer required after local agreement that GPs were familiar with the pathway and contemporaneous audit data supported this change (*Appendix S1*).

The pathway was commissioned locally to allow direct access to FIT for local GPs, and all four local clinical commissioning groups (CCGs) (Nottingham City, Nottingham North and East, Nottingham West and Rushcliffe) approved and jointly funded the pathway. The cost of each faecal immunochemical test was agreed as £17.50 (approximately €20) per sample to CCGs; this included postage, analysis and administration costs.

Faecal immunochemical testing requests and testing

FIT requests in primary care were made on an electronic request system (ICE) that also prompted requests for blood tests, where indicated. Results were notified on the same electronic system with text guidance on how to interpret results and subsequent actions. An electronic guidance system F12 (SystmOne; The Phoenix Partnership, Leeds, UK) was also used to guide GPs on the use of FIT and the new pathway in practices that used this system, with direct links to the relevant referral form where appropriate. FIT dispatch and return were entirely postal, and kits were analysed according to the manufacturer's protocols as described elsewhere by an accredited BCSP hub laboratory (*Appendix S2*)[9,11,22]. The OC-Sensor™ platform (Eiken Chemical, Tokyo, Japan) was used as described previously[9].

Patients referred with a rectal mass were not subject to FIT, but were seen in a one-stop flexible sigmoidoscopy clinic. Patients with rectal bleeding, no other symptoms and no anaemia were also seen in a one-stop clinic, as well as some patients with rectal bleeding deemed unlikely to be fit for colonoscopy at straight-to-test (STT) vetting of referrals[23]. Patients diagnosed with cancer in this one-stop pathway could have CT colonography as part of their staging to exclude synchronous lesions, if appropriate. This pathway has traditionally excluded rectal bleeding because the colorectal cancer detection rate approaches 10 per cent in this group locally, and the use of flexible sigmoidoscopy mitigates colonoscopy demand.

FIT, FBC and ferritin (or iron studies) were mandated for all other referrals, irrespective of symptoms or age, by local agreement with partners in primary care.

'Rule in'

Between November 2017 and June 2019, patients with a FIT result of 150 μg Hb/g faeces or above were considered 'high risk' positive, and the result was notified directly by BCSP to the Nottingham Colorectal Service STT team, as well as to the GP, irrespective of whether an RCCD form had been submitted. The STT team contacted these patients directly for vetting and appropriate investigation on a 'rapid' pathway, according to local protocols. This threshold was lowered to 100 μg Hb/g faeces or above in June 2019 as prospective evaluation demonstrated significant colorectal cancer detection rates at this threshold. Patients with a faecal Hb (fHb) level of 10 μg Hb/g faeces or above or 4 μg Hb/g faeces or above in the presence of anaemia, low ferritin or thrombocytosis were also considered positive, and were investigated on a 2WW pathway.

'Rule out'

Patients with a FIT result below 4 μg Hb/g faeces were considered to have a 'negative' FIT test result and to be at low risk for colorectal cancer. Patients with a FIT result of 4 μg Hb/g faeces or above but below 10 μg Hb/g faeces were also considered to have a negative result if their Hb level was normal (at least 130 g/l in men and 120 g/l in women), ferritin concentration was normal, and platelet count was less than 400×10^9/l). GPs were advised that patients with negative FIT tests had a low risk of colorectal cancer, and management options were to consider an alternative urgent pathway, routine referral, or repeat FIT.

Cohort and data collection

All patients who were subject to a FIT request between 7 November 2017 and 5 November 2019 were logged prospectively in the BCSP hub to ensure clinical governance of this novel pathway. All patients referred to the Nottingham Colorectal Service STT team on an RCCD form between these dates were logged prospectively in NUhCLEUS database (a locally created software programme), which supports the STT pathway. Cancer Outcomes and Services Data sets (COSD) were used to evaluate diagnoses of colorectal cancer recorded using ICD codes C18-C20 (excluding C18.1) with a censor date of 31 December 2019. Nottingham University Hospitals NHS Trust data, electronic patient records, and NUhCLEUS data were used for cross-checking and validation of diagnosis data. Cancer diagnoses were related to any previous patient episodes that started from a FIT result, and are presented in that context. Further details of patients who had repeat FIT testing are presented in *Fig. 1* and *Appendix S3*.

Statistical analysis

Histograms were used to check for normal distribution. Comparisons were made between continuous variables using Student's *t* test and ANOVA if normally distributed, with Tukey's multiple comparison test for multiple groups. Categorical data were summarized using frequencies and percentages. Comparisons were made between categorical data using χ^2 tests. All statistical analyses were performed using GraphPad Prism® (GraphPad Software, San Diego, CA, USA). Tests of significance were considered significant when $P < 0.050$ was obtained.

Data were segmented and analysed by fHb according to the cut-offs used during a pilot study[9] and subsequent iterations of pathway, as described above and elsewhere[11,18]. For the primary analyses, fHb below 4, 4–9.9, 10–99.9 and 100 μg Hb/g faeces or above were used. The latter group was further segmented into 100–149.9 and 150 μg Hb/g faeces or more (original cut-off for

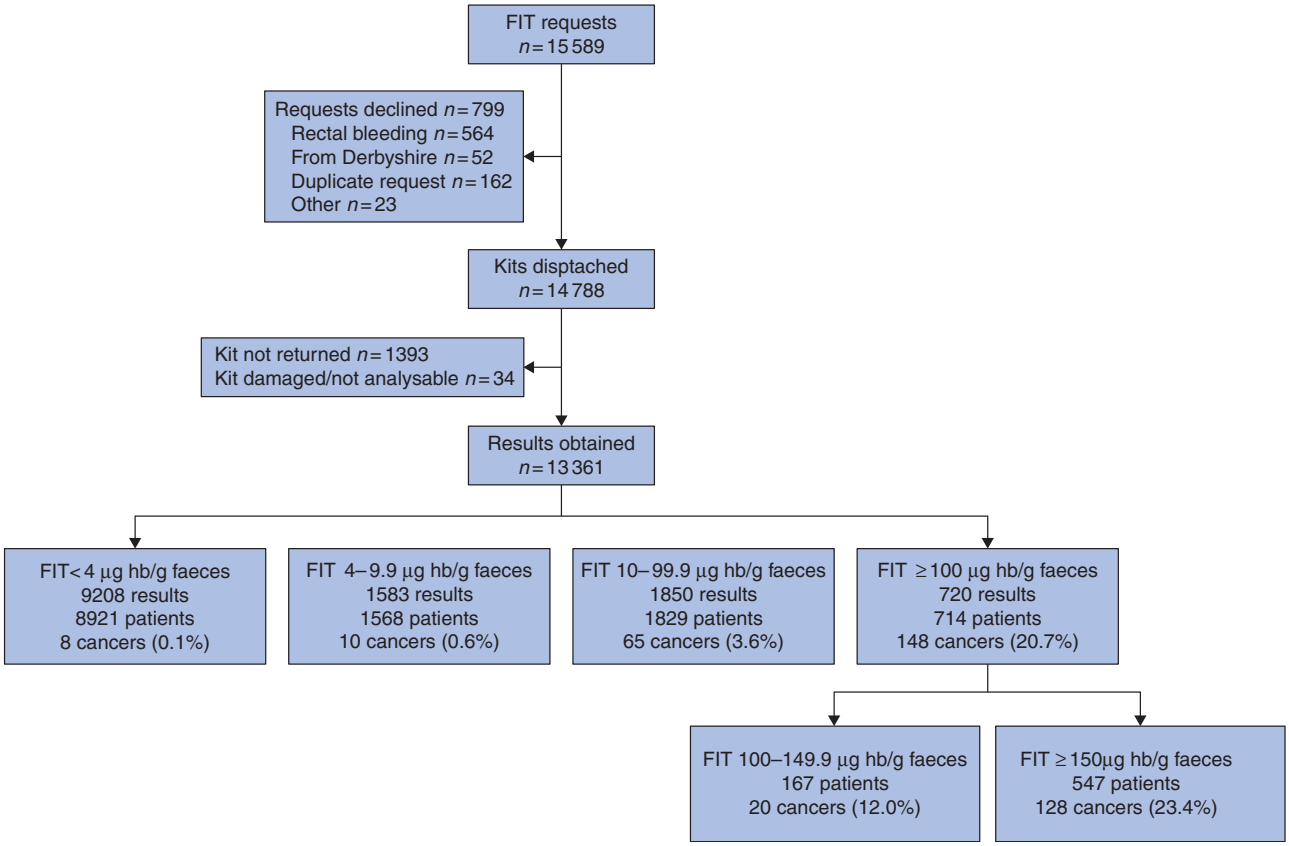

Fig. 1 Flow diagram of patients with faecal immunochemical testing requests from referral to colorectal cancer diagnosis

Numbers of patients lower than number of results in each stratum reflects repeat tests within one stratum. For additional data see *Appendix S3*. FIT, faecal immunochemical testing; Hb, haemoglobin.

high-risk positivity). Further segmentation for subanalysis of results between 10 and 99.9 µg Hb/g faeces was chosen empirically as follows: 10–19.9, 20–39.9, 40–59.9, 60–79.9 and 80–99.9 µg Hb/g faeces.

Results

Faecal immunochemical test requests and results

In total 15 589 FIT requests were made during the evaluation period (*Fig. 1*). Some 564 requests (3.6 per cent) were rejected as clinical details mentioned rectal bleeding as a symptom. There were 162 duplicate requests (1.0 per cent) and 75 requests (0.5 per cent) were declined for other reasons. A total of 14788 kits were dispatched, and 13395 kits were returned within 14 days (90.6 per cent), 34 kits were spoiled on return or not suitable for analysis (0.2 per cent).

Overall, 13361 FIT results were available, of which 9208 (68.9 per cent) were less than 4 µg Hb/g faeces, 1583 (11.8 per cent) were 4–9.9 µg Hb/g faeces, 1850 (13.8 per cent) were 10–99.9 µg Hb/g faeces, and 720 (5.4 per cent) were 100 µg Hb/g faeces or above. *Table 1* shows the patient demographic characteristics in each subgroup. The majority (67.8 per cent) of FIT occurred in symptomatic patients over the age of 60 years who met the current NICE guidance for referral[3]. Some 505 FIT results (3.8 per cent) were from patients under the age of 40 years and 81.6 per cent (412 of 505) yielded fHb below 4 µg Hb/g faeces. The mean age of patients with lower levels of fHb was significantly lower than that for the higher strata of fHb ($P<0.0001$, ANOVA; $P<0.01$, Tukey's multiple comparison test). The cohort diagnosed with colorectal cancer was significantly older than those without ($P<0.001$, unpaired *t* test). There were significantly more men in the cohort with fHb 100 µg Hb/g faeces or above compared with those with lower fHb levels (53.1 *versus* 43.5 per cent respectively; $\chi^2 = 25.2$, $P<0.001$), and also in patients diagnosed with colorectal cancer compared with those without that diagnosis (59.5 *versus* 43.7 per cent; $\chi^2 = 22.4$, $P<0.001$).

Colorectal cancer diagnoses after faecal immunochemical testing

The median follow-up in this cohort was 10.4 (i.q.r. 5.7–16.3) months (*Table 1*). In total, 227 colorectal cancers were diagnosed after FIT (1.7 per cent of the 13 361 tests performed). Eight cancers were diagnosed in 8920 patients (0.1 per cent) after a FIT result with fHb below 4 µg Hb/g faeces during follow-up, 10 cancers in 1568 patients (0.6 per cent) with fHb 4–9.9 µg Hb/g faeces, 61 in 1840 patients (3.3 per cent) with fHb 10–99.9 µg Hb/g faeces, and 148 cancers (20.7 per cent) in 714 patients with fHb 100 µg Hb/g faeces or above. The known colorectal cancer detection rates were significantly lower in the group with fHb below 4 µg Hb/g faeces than in the rest of the cohort (0.1 *versus* 5.3 per cent respectively; $\chi^2 = 449.7$, $P<0.001$) and in the group with fHb below 10 µg Hb/g faeces (0.2 *versus* 8.2 per cent respectively; $\chi^2 = 770.8$, $P<0.001$). The known colorectal cancer detection rate was significantly higher in the cohort with fHb 100 µg Hb/g faeces or above, compared to less those with fHb less than 100 µg Hb/g faeces (20.7 per cent *versus* 0.6 per cent; $\chi^2 = 1592.4$, $P<0.001$). Three diagnoses of colorectal cancer were related to repeat FIT in

Table 1 Demographics of all patients with a faecal immunochemical test result and colorectal cancer diagnoses stratified by faecal haemoglobin and age

FIT stratum (μg Hb/g faeces)	Median follow-up (months)	Patients with FIT results	Sex ratio (M : F)	Age (years)			
				Mean(s.e.m.)	≤ 49†	50–59†	≥ 60†,‡
Total	**10.4 (5.7–16.3)**	**13 042**	**5740 : 7302**	**66.3(0.2)**	**1658 (12.7)**	**2546 (19.5)**	**8838 (67.8)**
Total cancers diagnosed		227 (1.7)	135 : 92§	74.1(1.2)¶			
< 4	10.6 (5.8–16.5)	8920	3850 : 5070	64.5(0.1)¶	1329 (14.9)	2003 (22.5)	5588 (62.6)
Cancers diagnosed		8 (0.1)§	6 : 2	77.4(3.1)	0 (0)	0 (0)	8 (0.1)
4–9.9	10.6 (5.0–15.0)	1568	656 : 912	69.0(0.3)¶	146 (9.3)	224 (14.3)	1198 (76.4)
Cancers diagnosed		10 (0.6)§	5 : 5	75.0(3.6)	1 (0.7)	0 (0)	9 (0.7)
10–99.9	9.9 (5.7–15.8)	1840	855 : 985	71.4(0.3)¶	129 (7.0)	234 (12.7)	1477 (80.3)
Cancers diagnosed		61 (3.3)§	34 : 27	74.6(1.4)	1 (0.8)	7 (3.0)	53 (3.6)
≥ 100	10.3 (5.9–16.2)	714	379 : 335§	71.5(0.5)¶	54 (7.6)	85 (11.9)	575 (80.5)
Cancers diagnosed		148 (20.7)§	90 : 58	73.7(0.9)	7(13)	14 (16)	127 (22.1)

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.); †percentage values are of stratum. ‡Patients aged 60 years or more with symptoms commonly eligible for urgent referral according to National Institute for Health and Care Excellence guidance[3]. FIT, faecal immunochemical test; Hb, haemoglobin. §$P < 0.001$ (χ^2 tests comparing FIT strata by gender, and colorectal cancer diagnosis by gender); ¶$P < 0.001$ (ANOVA comparing patient age by FIT strata).

229 patients with sequential fHb results in different strata (*Appendix S3*).

Overall, 86.8 per cent (197 of 227) of colorectal cancers were diagnosed in patients over the age of 60 years. One patient aged under 40 years was diagnosed with cancer with a fHb result of 100 μg Hb/g faeces or above, and 29 cancers were diagnosed in those aged 40–59 years.

Colorectal cancer diagnoses after a negative test result

Eight of 227 CRCs (3.5 per cent) were diagnosed after a fHb reported as less than 4 μg Hb/g faeces (*Table S1*). These patients were identified via referral through other pathways: three had CT arranged by the upper gastrointestinal team, two were seen by the medical gastroenterology team, two were diagnosed in routine colorectal clinics, and one presented as an emergency with acute bowel obstruction. The median time from a negative FIT result to colorectal cancer diagnosis was 41.5 (i.q.r. 31–72.3) days. One sample was analysed after 17 days, and the patient should have had repeat FIT due to risk of a false-negative result[24]. In the population with fHb 4–9.9 μg Hb/g faeces, all patients but one satisfied the Nottingham protocol whereby an abnormal blood parameter (anaemia, thrombocytosis or low ferritin (or iron)) reduces the threshold to investigate to 4 μg Hb/g faeces (*Table S1*). The other patient had an abnormally high ferritin level but was considered 'negative' according to local protocol at the time of testing.

Blood results and palpable rectal mass

Detection rates for different strata of fHb within the range 10–99.9 μg Hb/g faeces are shown in *Table 2*. The colorectal cancer detection rate in the group with fHb 10–19.9 μg Hb/g faeces was 1.4 per cent, and was below the NICE 3 per cent threshold for urgent referral. These patients were all eligible for 2WW referral and investigation in the local protocol. Eight of 10 colorectal cancers detected in this stratum had abnormal blood parameters or abnormal digital rectal examination before referral (*Table S1*). Forty-seven of 61 patients with cancer (77 per cent) detected after fHb result of 10–99.9 μg Hb/g faeces had one or more abnormal blood test results or a palpable rectal mass (latter not mentioned on referral from primary care). Six cancers were detected in 11 194 patients with fHb below 20 μg Hb/g faeces in whom there was no evidence of abnormal blood results or palpable rectal mass.

Discussion

This is a large English data set on primary care access to FIT in symptomatic patients for all symptoms and all age groups. In previous studies, a colorectal cancer diagnosis rate of 0.2 per cent in patients undergoing 2WW investigation with fHb below 4 μg Hb/g faeces was documented[9,11,22]. Data from Scotland suggest a similar 'miss rate' with longer follow-up in patients with unquantifiable fHb levels on a different manufacturer's platform[10]. The colorectal cancer diagnosis rate of 0.1 per cent after a 'negative' FIT test (as per local definition) in this population is consistent with these data, and appears well below the NICE threshold of 3 per cent, despite including the NG12 'high risk' population[3]. Other strengths of this study include a large data set with optimal return rates and a 'real-world' analysis of FIT usage in a clinical setting. Use of a prospectively recorded database to log cancer diagnoses validates the accuracy of the retrospective study.

In evaluating this pathway, it is important to stress that FIT should not be compared to colonoscopy, because, in the UK and many other countries, GPs do not have direct access to colonoscopy. Instead, 2WW pathways that use FIT in primary care should be compared with those that do not. Indeed, the 'miss rate' of age- and symptom-based criteria in primary care (the number of cancers detected in symptomatic patients after routine referral) was historically around 50 per cent on average[21], and even a standard investigation such as colonoscopy is known to miss diagnoses of colorectal cancer[25].

Overall, 5588 patients aged 60 years or more with fHb below 4 μg Hb/g faeces were tested by GPs. This would have equated to more than 230 additional referrals per month over 2 years (if FIT had not been used for 'rule out') to detect eight colorectal cancers.

However, this methodology does not identify patients diagnosed with colorectal cancer at other trusts, which is a relative weakness. Concomitant analysis across the Cancer Alliance is ongoing, and analysis of East Midlands Cancer Network data has not yet demonstrated additional cases of 'post- negative FIT colorectal cancer', although this scenario may arise. In addition, most patients have not been investigated after a 'negative' FIT result,

Table 2 Colorectal cancers diagnosed in patients stratified by faecal haemoglobin result and detection rates above and below each lower limit

FIT stratum (μg Hb/g faeces)	Patients with FIT results in stratum	Cancer diagnoses	Cancer detection rate within stratum (%)	Cancer miss rate below lower limit of stratum (%)	Cancer detection rate above lower limit of stratum (%)
< 10	10 488	18	0.2		
10–19.9	706	10	1.4	0.2	8.2
20–39.9	543	22	4.1	0.3	10.8
40–59.9	303	8	2.6	0.4	13.6
60–79.9	168	13	7.7	0.5	16.9
80–99.9	120	8	6.7	0.6	18.7
≥ 100	714	148	20.7	0.6	20.7

FIT, faecal immunochemical test. This study used faecal immunochemical testing and simple blood test results to stratify the risk of colorectal cancer in symptomatic patients for over 2 years. Outcome data from a service evaluation demonstrated clinical effectiveness and safety. This strategy may be crucial to overcoming the effects of the coronavirus pandemic on 2-week-wait and urgent pathways.

and some may yet present with colorectal cancer with ongoing follow-up.

In this study, only nine cancers were diagnosed in patients under the age of 50 years, and unsurprisingly the majority had fHb of 100 μg Hb/g faeces or above. The recommendation[16] of a fHb threshold of 10 μg Hb/g faeces for 'low risk' patients appears questionable in this context. A threshold as low as 4 μg Hb/g faeces in patients with anaemia, low ferritin and thrombocytosis was driven by concern around the use of FIT in 'high risk' patients, but is vindicated by the detection of nine such patients with colorectal cancer in the cohort with fHb below 10 μg Hb/g faeces. Interestingly, these data suggest a similar principle may be applicable between 10 and 19.9 μg Hb/g faeces, and perhaps at even higher levels. The utility of anaemia[19] and thrombocytosis[21] in the local 2WW pathway have been evaluated previously, but not that of ferritin. The protocol has hitherto mandated investigation only when ferritin level is low. However, studies have suggested that ferritin may have value when the level is abnormally high[26], and thus there may be value in using high ferritin to improve the sensitivity and specificity of the symptomatic pathway. In the present cohort, only one additional cancer would have been missed if the threshold had been 20 μg Hb/g faeces for patients with normal rectal examination, FBC and ferritin. FIT is a stratification tool, and appears to be most useful when combined with other objective measures. The FAST (Faecal haemoglobin, Age and Sex Test) score[27], combining FIT with age and sex, could be improved[28], and performance characteristics of such scoring systems might increase if FIT were combined with FBC, ferritin and a digital rectal examination. These four Fs appear likely to have greatest combined value as the level of fHb declines towards undetectable.

The use of FIT has been introduced in the English BCSP with a threshold of 120 μg Hb/g faeces. This raises a number of interesting issues in relation to the training, accreditation, and workload of endoscopists. The challenge to reduce the FIT threshold or the screening age in England might be aided by the use of higher FIT thresholds, alongside blood tests, in symptomatic patients as greater diagnostic capacity is freed up. An alternative solution may be to invite screened patients with a FIT result below 120 μg Hb/g faeces to attend their GP for FBC and ferritin testing, and to lower the threshold when such parameters are abnormal. Ultimately, raising symptomatic thresholds and lowering BCSP thresholds may help to yield more coherent and consistent use of FIT in all parts of the population.

Both symptomatic and asymptomatic pathways face unprecedented circumstances in the UK in relation to the coronavirus pandemic. UK diagnostic services that were overstretched before the pandemic will doubtless struggle to cope with a backlog for many months afterwards. Accordingly, FIT results and other objective measures such as blood results should be used to prioritize those individuals most likely to benefit from urgent investigation (*Appendix S4*).

Finally, other large service evaluation studies[10,14] have now demonstrated similar results to those from the present data set, and the recently published NICE FIT study[15] adds high-volume multicentre research data to this consensus. No test is perfect, but there is now a high volume of data to demonstrate that FIT adds significant value to symptoms alone in aiding the decision to refer.

Acknowledgements

For primary care, the authors thank E.. Maddock, H. Patel, M. O'Neil, M. Jelpke and S. Karim and all primary care colleagues who accepted a significant change in working practice, as well as S. Oliver, S. Castle, and all colleagues in local CCGs who facilitated this service development.

For the Nottingham Colorectal Service, the authors thank S. Thomson, B. Harwood, S. Hall, T. Dorn, L. Hamonga, D. Williams, H. Andrews, D. Bradshaw, S. Jamil, R. Bailey, J. Williams, J. Abercrombie, C. Maxwell-Armstrong, A. Acheson, K. Walter, B. Bharathan, K. Mohiuddin, K. Thomas, A. Simpson, A. Siddika, S. Liptrot, H. Zaidi, O. Odofin, and the wider team. They also thank the Nottinghamshire Bowel Cancer Screening Hub and R. Logan.

For IT support, K. Premji and S. Murdock are thanked, as well as O. Ng and NUhCLEUS. Thanks also go to the Departments of Gastroenterology and Radiology, Nottingham University Hospitals, and to Nottingham City Hospital Endoscopy Service.

Supplementary material

Supplementary material is available at *BJS Open* online.

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