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Application of NICE guideline NG12 to the initial assessment of patients with lower gastrointestinal symptoms: not FIT for purpose?

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Keywords

Adenoma, colorectal cancer, inflammatory bowel disease, faecal immunochemical test, faecal occult blood test

Abstract

Background: The National Institute for Health and Care Excellence (NICE) published NG12 in 2015. The referral criteria for suspected colorectal cancer (CRC) caused controversy, because tests for occult blood in faeces were recommended. Faecal immunochemical tests for haemoglobin (FIT), which estimate faecal haemoglobin concentrations (f-Hb), **might more than fulfil** the intentions. **Our** aim was to compare the utility of f-Hb **as the initial investigation** with the NICE NG12 **symptom-based** guidelines**.**

Methods: Data from three **studies were** included. Patients had **sex, age,** symptoms, f-Hb and colonoscopy and histology data recorded. Sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of f-Hb and NG12 were calculated for all significant colorectal disease (SCD: CRC, higher-risk adenoma and inflammatory bowel disease). **Overall** diagnostic accuracy was also estimated by the area under the receiver operating characteristic curve (AUC).

Results: 1514 patients were included. **At a cut-off of ≥10 µg Hb/g faeces,** the sensitivity of f-Hb for CRC was 93.3% (95% confidence interval (CI): 80.7-98.3) with NPV of 99.7% (95%CI: 99.2-99.9). The sensitivity and NPV for SCD were 63.2% (95%CI: 56.6-69.4) and 96.0% (95%CI: 91.4-94.4) respectively. The NG12 sensitivity and NPV for SCD were 58.4% (95%CI: 51.8-64.8) and 87.6% (95%CI: 85.0-89.8) respectively. The AUC for CRC was 0.85 (95% CI 0.87-0.90) for f-Hb versus 0.65 (95%CI 0.58-0.73) for NG12 ($p<0.005$). For SCD, the AUC was 0.73 (95%CI: 0.69-0.77) for f-Hb versus 0.56 (95%CI: 0.52-0.60) for NG12 ($p<0.0005$).

Conclusion: f-Hb provides a good rule-out test for SCD and has significantly higher overall diagnostic accuracy than NG12.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer related death in the UK, accounting for about 10% of all such deaths.[1] Patients with CRC may present with various lower gastrointestinal (GI) symptoms, such as change in bowel habit, rectal bleeding, lower abdominal pain, abdominal mass, anaemia, or unexplained weight loss. These symptoms are sometimes referred to as "alarm" or "red flag" symptoms and, in a patient who reports any of these, urgent referral for lower GI endoscopy to exclude CRC is usual current practice. However, such symptoms are also common in patients with non-malignant lower GI disease and, as a result, their diagnostic accuracy for CRC has been demonstrated to be poor.[2,,3] Referral guidelines for suspected cancer were published for the National Health Service in England in 2011 (CG27)[4] and subsequently in 2015 (NG12) by the National Institute for Health and Care Excellence (NICE).[5] Current **NG12** criteria that should stimulate urgent referral are **listed** in Table 1. The **older** NICE CG27 guideline has been the most widely used and evaluated referral guidance, but has a low specificity and variable sensitivity,[6] and it was recognised that symptoms have a poor positive predictive value (PPV) for CRC of only 3–4%.[4] A detailed review and meta-analysis also concluded that symptoms alone are poor predictors of underlying pathology.[3] Further, although risk prediction models which combine multiple risk factors and symptoms might have the potential to improve timely diagnosis,[7] **many** patients continue to be referred to secondary care for investigation in the absence of any reliable **first-line** predictor of significant colorectal disease (SCD), namely CRC plus higher-risk adenoma (HRA)[8] plus inflammatory bowel disease (IBD: Crohn's disease and ulcerative colitis).

NICE published NG12 in June 2015.[5] These guidelines caused much controversy when published in both draft and final formats. In particular, the recommendation of a "test for occult blood in faeces", which was **initially** interpreted by most as a recommendation for the traditional guaiac-based faecal occult blood test (gFOBT), was very controversial and became the subject of some concern and debate.[9-11] Previously published authoritative guidelines from NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and the British Society of

Gastroenterology (BSG) did state that there was no role for such gFOBT in assessment of patients presenting in primary care with lower GI symptoms, or in the investigation of iron deficiency anaemia.[12] In consequence, gFOBT were eliminated from the repertoires of many laboratories and its use in clinical settings other than screening very much discouraged.[12] Indeed, NICE did note that the new 2015 NG12 recommendation to test for occult blood in faeces in patients at low risk of CRC would necessitate a change in practice, because such tests were not currently available.[5] However, realisation **quickly** grew that faecal immunochemical tests for haemoglobin (FIT), which are able to quantitate faecal haemoglobin concentrations (f-Hb), could **well** more than fulfil the intentions of NG12.[10] It was recognised by NICE that some evidence did exist to suggest that FIT might have applicability in triaging patients presenting in primary care.[9] FIT, a newer type of test for the detection of occult blood in faeces, use antibodies specific to human haemoglobin. They have been developed as a significant improvement on gFOBT, which are based on the pseudo-peroxidase activity of the haem component of haemoglobin and produce a blue colour change on the test card if positive. Sometimes, this colour change occurs because of moieties with peroxidase activity in the diet, or with medicines being taken, leading to false positive test results. Because FIT are designed to specifically detect human haemoglobin, they do not suffer from interference from dietary constituents. Moreover, FIT target the globin component of haemoglobin, which degrades as it travels through the GI tract, so FIT are less likely to detect globin from upper GI bleeding.[13] In addition, FIT are analytically much more sensitive than gFOBT and so detect smaller amounts of blood in faeces.

There is now significant evidence that FIT do have applicability **as the initial approach** to the assessment of symptomatic patients presenting in primary care, including those who warrant urgent referral. It has been shown that use of f-Hb performs better than previous high-risk symptom-based strategies from NICE and SIGN for fast-tracking suspected CRC referrals.[6,12,14-19] Moreover and, most importantly, f-Hb with very low cut-off concentration has very high NPV for the detection of SCD in this clinical setting.[10] In consequence, a “negative”

test result provides considerable reassurance that **referral for** colonoscopy is not required urgently or even at all. There is no doubt that f-Hb measurements have considerable potential to contribute to reducing unnecessary colonoscopy for the majority of symptomatic patients. However, the question remains of whether f-Hb, **a laboratory-based investigation, is better** than the recent NG12 **symptom-based** referral guidelines **as the initial approach in primary care to rule in CRC (the purpose of NG12) or rule out SCD**. **We did not aim to examine the diagnostic accuracy of the groups detailed in NG12 as shown in Table 1 since this was comprehensively documented in the guideline.[5]** The aim of this study was to undertake such a comparison, **particularly investigating sensitivity as a measure of goodness as a rule in test and NPV as a good estimate of utility as rule out test, for both CRC and SCD.**

Methods

Data from three studies conducted in Scotland were included in our analysis; these are described in detail in the relevant peer-reviewed publications, **and are summarised below**.[17-19] The studies, on the role of f-Hb in assessment of patients presenting in primary care with lower GI symptoms, were conducted between 2010 and 2015 and included only patients with **sex, age, details of symptoms leading to referral for lower GI endoscopy, f-Hb and complete colonoscopy data with histology where applicable. The referrals were done as described in the publications and did not follow the NG12 criteria.** Reasons for referral **were based on** symptoms including rectal bleeding, change in bowel habit, iron deficiency anaemia, abdominal pain, bloating, polyp/colorectal cancer surveillance, family history and assessment of IBD. A f-Hb of greater $\geq$10 µg Hb/g faeces was deemed a positive test result. Results were collated from the three study databases. Referral symptoms were reviewed and categorised as in keeping with NG12 referral criteria or not.

Study one (FITS)[17] was an investigation on diagnostic accuracy based on a consecutive series of participants; no intervention was made based on the f-Hb concentration. Patients who had

been referred from primary care for endoscopic examination of the lower GI tract in NHS Tayside from February 2010 to March 2012 were invited by a colorectal specialist research nurse to participate in the study by completing a single sample faecal collection for f-Hb. The returned samples were analysed for f-Hb using one of two OC-Sensor Diana automated immunoturbidimetric analysers (Eiken Chemical Co., Ltd, Tokyo, Japan). Analyses were carried out in the Scottish Bowel Screening Centre Laboratory.

Study two (FITS2)[19] aimed to determine whether patients with lower abdominal symptoms can be investigated quickly using results of f-Hb and whether this investigation could form part of a diagnostic pathway for SCD. Participants referred from primary care for colonoscopy in NHS Lanarkshire from June 2013 to December 2013 inclusive were recruited by sending one faecal specimen collection device with the appointment for endoscopy and the bowel cleansing materials. The returned samples were analysed for f-Hb using one HM-JACKarc analyser (Kyowa-Medex Co., Ltd., Tokyo, Japan).

Study three (FITS+)[18] assessed the diagnostic accuracies of quantitative f-Hb and faecal calprotectin tests in patients presenting to primary care with lower GI symptoms who were then referred for investigation. All adult patients referred in NHS Tayside over a six-month period from October 2013 to March 2014 were eligible. Estimates of f-Hb were generated using one OC-Sensor io analyser (Eiken Chemical Co., Ltd., Tokyo, Japan).

Statistical Analysis

To determine differences in **clinical performance** between f-Hb and NG12 referral criteria **as an initial investigation**, we performed the following analyses. Sensitivity, specificity, PPV and NPV (all with 95%CI) were calculated **using a cut-off of ≥10 g Hb/g faeces for CRC, HRA, advanced neoplasia (AN = CRC plus HRA), IBD and SCD**. Receiver operating characteristic (ROC) curves for CRC and SCD were constructed and the area under the curve (AUC), with 95%CI, was determined as **a simple easy to understand** estimate of **overall** diagnostic accuracy. AUC were calculated overall and separately for the three analytical systems used,

for men and women and for those aged <50 years and ≥50 years. AUC were compared using VassarStats: Website for Statistical Computation (http://vassarstats.net/roc_comp.html). Associations between categorical variables were examined using chi-squared tests for linear trend unless otherwise specified. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Patient population

1514 patients were included in our analysis. Patient sex and age, **two variables proven to affect f-Hb,**[20] presenting symptoms, f-Hb and final diagnosis following investigation were recorded in the study specific databases: 280 patients were recruited to the FITS study, 484 patients to FITS2 and 750 patients to FITS+. CRC was found in 45 patients (3.0%), HRA in 95 (6.3%), **AN in 140 (9.3%), IBD in 91 (6.0%) and SCD in 231** (15.3%). **The number who would be directly referred in all three studies for colonoscopy following NG12 guidelines was 731 (48.3%) and the number who would be referred for testing for occult blood in faeces was 485 (32.0%). The criterion used for a positive outcome from f-Hb in those who would have been referred for testing for occult blood using NG12 was f-Hb ≥10µg Hb/g faeces. A total of 1216 (79.7%) would have a further action taken as a result of the NICE NG12 guidelines. No gFOBT was done on the last three groups in Table 1 in any of the three studies because the patient had been referred for endoscopy based solely on *a priori* clinical assessment in primary care and gFOBT were unavailable in both NHS Tayside and NHS Lanarkshire.**

Comparison of the three FIT analytical systems

The three different FIT analytical systems were assessed cumulatively and as individual studies and a simple comparison undertaken **using the AUC as a simple indicator of overall diagnostic accuracy**. **There was no observed differences between the OC-Sensor Diana, HM-JACKarc and the OC-Sensor io systems (Table 2).** Specifically, the AUC for

CRC were 0.87 (95%CI: 0.78-0.94), 0.89 (95%CI: 0.84-0.93) and 0.84 (95%CI: 0.77-0.91) for the three analysers respectively. The AUC for SCD were 0.73 (95%CI: 0.65-0.81), 0.73 (95%CI: 0.65-0.81) and 0.73 (95%CI: 0.67-0.78) respectively.

Clinical characteristics of faecal haemoglobin concentration (f-Hb)

The sensitivity, specificity, PPV and NPV of f-Hb for CRC, HRA, AN, IBD and SCD are summarised in Table 3. The sensitivity, **a good measure of the utility of the investigation as a rule in test, for** CRC, HRA, AN, IBD and SCD was 93.3% (95%CI: 80.7-98.3), 50.5% (95%CI: 40.1-60.9), 64.3% (95%CI: 55.7-72.1), 61.5% (95%CI: 50.7-71.4) and 63.2% (95%CI: 56.6-69.4) respectively. **NPV, the most relevant characteristic to assess f-Hb** as a rule out test was 99.7% (95%CI: 99.2-99.9), 95.9% (95%CI: 94.5-96.9), 95.6% (95%CI: 94.2-96.7), 96.9% (95%CI: 95.7-97.8) and 93.1% (95%CI: 91.4-94.4) respectively.

Clinical characteristics of f-Hb by sex

Differences were observed in sensitivity, specificity, PPV and NPV between men and women, although the AUC was not significantly different in CRC, HRA, AN, IBD or SCD between the two groups (Table 3; $p>0.05$). Sensitivity for CRC, HRA, AN, IBD and SCD was higher in men than women **and specificity lower**. NPV was similar between men and women for CRC, HRA, AN, IBD and SCD.

Clinical characteristics of f-Hb by age

In those aged less than 50 years, the sensitivity for detecting CRC, HRA, AN, IBD and SCD **was higher than in those older than 50 years.** The NPV for CRC, HRA, AN, IBD and SCD were 100.0% (95%CI: 98.1-1.0), 97.6% (95%CI: 94.7-99.0), 97.6% (95%CI: 94.7-99.0), 95.3% (95%CI: 91.7-97.4) and 92.9% (95%CI: 88.8-95.6) respectively in those less than 50 years compared to 99.7% (95%CI: 96.0-98.3), 95.4% (95%CI: 93.7-96.6), 95.3% (95%CI: 93.3-96.3), 97.4% (95%CI: 96.0-98.3) and 92.4% (95%CI: 90.4-94.0) respectively in those aged older than 50 years. The AUC for f-Hb was not significantly different for CRC, HRA, AN, IBD

and SCD in those participants less than 50 years of age and in those equal to or older than 50 years (Table 3; p>0.05).

Overall diagnostic accuracy of f-Hb and NG12 compared

Overall, f-Hb had statistically significantly higher diagnostic accuracy than NG12 for all of CRC, HRA, AN, IBD and SCD (p<0.0005) as shown in Table 3. For both CRC and SCD, the AUC was significantly higher for f-Hb than NG12 (p<0.0005).

Number of cases missed using f-Hb and NG12

As shown in Table 4, three cases of CRC would be potentially missed using f-Hb with a ≥10 µg Hb/g faeces cut-off. All three cases had detectable f-Hb, but with a concentration below the lower limit of the analytical working range as reported by the manufacturer of 10 µg Hb/g faeces, and were recruited to the FITS+ study. Two of these patients would have met the NG12 criteria. In contrast, 10 patients with CRC would be missed by NG12 criteria of which nine had a positive f-Hb test result >10 µg Hb/g faeces. Use of f-Hb missed overall fewer cases of AN (50 v 53), IBD (35 v 43) and SCD (85 v 96) as compared to NG12.

Discussion

NG12 uses the terminology "a test for occult blood in faeces" and this could be interpreted as gFOBT or FIT: no studies such as ours have investigated gFOBT, an obsolete investigation,[12] and no patient in any of the three studies from which data were obtained had gFOBT performed. Most importantly, the high NPV of f-Hb for all SCD confirm the high utility of f-Hb as a rule-out test. In addition, the results demonstrate that f-Hb with a cut-off for referral of ≥10 µg Hb/g faeces, a laboratory-based investigation, has significantly higher overall diagnostic accuracy than the symptom-based NICE NG12 guidelines and would therefore be more reliable as an indication for referral for further investigation than NG12. The results add to the growing body of

evidence supporting the use of FIT as the first-line investigation in in the assessment of patients presenting in primary (and secondary) care with lower GI symptoms, as recently argued.[21]

There are now several studies including a meta-analysis that have evaluated the diagnostic performance of FIT in symptomatic and high-risk populations, suggesting high sensitivity and specificity for CRC.[3, 7] A Spanish study of 787 patients referred for colonoscopy showed that FIT was more accurate in detecting CRC than the previous 2011 NICE or the SIGN referral criteria.[6] Similar to the results observed in this study, they demonstrated that, in a high risk population, using a f-Hb cut-off of ≥20 µg Hb/g faeces, 20% fewer colonoscopies would have been required to detect 42% more CRC. A further study done in a different region of Spain confirmed these results: NICE and SIGN guidelines detected 46.7% and 43.3% of cases of CRC while f-Hb ≥15 µg Hb/g faeces detected 96.7% of cases.[16] In other studies investigating the use of f-Hb for detection of CRC in symptomatic patients, sensitivity has ranged from 67% to 100% and specificity from 71% to 93% dependent on the f-Hb cut-off used.[6, 15, 17-19] As in this study, inspection of the NPV in particular demonstrates that the results of these studies provide telling evidence that the f-Hb has the potential to be a good rule-out test for SCD and could therefore reduce the number of unnecessary referrals for colonoscopy, easing the pressure on already over-subscribed services. To allow comparison between studies, we used ≥10 µg Hb/g faeces as the f-Hb cut-off, exactly in keeping with latest draft NICE guideline in development (GID-DG10005) on quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care.[21]

Limited data are available on the diagnostic accuracy of f-Hb for non-neoplastic SCD, particularly IBD. We have previously demonstrated that, in a population of symptomatic patients referred for endoscopy from primary care, CRC, HRA and IBD had significantly higher median f-Hb than those with less clinically important findings.[17] Using a cut-off of ≥10 µg Hb/g faeces, the current study has demonstrated a sensitivity, specificity and PPV and NPV of f-Hb for CRC of 93.3% (95%CI: 80.7-98.3), 77.3 (95%CI: 75.1-79.4), 11.2% (95%CI: 8.3-14.9) and

99.7% (95%CI: 99.2-99.9) respectively. 1283 (84.7%) of our patient cohort had non-significant colonic findings – normal bowel (933 patients; 61.6%), and less significant pathology such as haemorrhoids, hyperplastic polyps and simple diverticular disease (397 patients; 26.2%). Using f-Hb as a triage investigation in this cohort would potentially have avoided a referral and subsequent invasive investigations in the 82.2% of patients without serious pathology. **NG12 is concerned with the detection of lower GI cancer and therefore does not have such a broad clinical aim as the published concepts from Scotland on the application of f-Hb. As expected, f-Hb missed overall fewer cases of AN, IBD and SCD. However, in spite of missing some cases, the high NPV demonstrates that this approach of investigating all patients with lower GI symptoms with an initial f-Hb is most appropriate for use as a rule-out test for SCD, but with robust safety-netting procedures in place.** This interpretation is in agreement with previous studies utilising FIT for assessment of symptomatic populations.[2, 18, 19]

We observed that 229 patients (15.1%) who had f-Hb ≥10 µg Hb/g faeces had no significant pathology as compared with 603 (40.0%) patients referred following NG12 guidelines. The concern from clinical specialists that using f-Hb in primary care to triage suspected colorectal cancer referrals could result in unnecessary colonoscopy referrals is not confirmed by this study. In addition, the number of false-positive test results that occur when using f-Hb **to diagnose CRC, as shown by the PPV,** would be partially offset by detecting other **important and** treatable bowel diseases, particularly HRA and IBD. Positive FIT should be viewed as a marker of potential SCD, irrespective of symptoms.

The strengths of this study include the large sample size, with 1514 patients providing **age, sex,** complete symptom data, as well as f-Hb and final diagnoses. In addition, the unselected nature of the patients referred from primary care increases the applicability of the findings to those working to identify cases of SCD in primary and secondary care. A limitation of our study is that the location of the CRC and HRA was not recorded and therefore cannot be assessed in terms of predictive value of disease detection. **This will be very interesting to**

study further if f-Hb is rolled out into routine clinical practice, as will studies on the health economic benefits of introducing this test and potential cost savings through reduction in referrals and number of colonoscopic (and possibly imaging) procedures undertaken. A further limitation is that it might be considered invalid to evaluate referral criteria in referred patients only. The NG12 guidelines were unavailable when these studies were done: interestingly, the Scottish referral guidelines for suspected cancer[23] are much less prescriptive than NG12, but f-Hb is now seen to have significant potential as the first-line investigation in assessment of patients presenting in primary care with lower abdominal sysmptoms.[24]

In conclusion, **we have demonstrated that, in the primary care setting, the reliability of f-Hb to rule-out most SCD is high and we believe that our results are widely applicable. In addition, f-Hb has significantly higher overall diagnostic accuracy than NG12 referral criteria for CRC detection.** Although we do not have any data on the acceptability of FIT to patients presenting in primary care with lower GI symptoms, the need for only one faecal sample, collected in an easy to use, hygienic device, should encourage completion of the test.

Conflict of interest

CGF has undertaken consultancy with Immunostics Inc., Ocean, NJ, USA, and Kyowa-Medex Co., Ltd, Tokyo, Japan, and received assistance for travel and attendance at meetings from Alpha Labs Ltd, Eastleigh, Hants, UK. All other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The FITS study was approved by Tayside Research Ethics Committee, the FITS2 study by the West of Scotland ethics service and the FITS+ study by the East of Scotland REC.

Guarantor

CGF

Contributorship

CGF, RJCS and AJQ conceived and planned the study. AJQ, CGF, JD and RJCS performed the data analysis. JD, RJCS, JAS, CM, PJMcD, FAC, IMG, HBY and CGF were investigators on the three component studies. AJQ and CGF prepared drafts of the manuscript. All authors contributed significantly to the writing of the paper.

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All those who assisted us in the FITS, FITS2 and FITS+ studies are acknowledged in the relevant papers on the studies.

References

1. CRUK. 2015. Bowel Cancer Statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer. Accessed Feb 2017.

2. Vega P, Valentin F and Cubiella J. Colorectal cancer diagnosis: Pitfalls and opportunities. *World J Gastrointest Oncol*. 2015; 7: 422-33.

3. Jellema P, van der Windt DA, Bruinvels DJ, et al. Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis. *BMJ*. 2010; 340: c1269.

4. NICE. Referral guidelines for suspected cancer CG27. 2005. https://www.nice.org.uk/guidance/cg27. Accessed Feb 2017

5. NICE. NG12 Suspected Cancer: Recognition and Referral. Colorectal Cancer. https://www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer#lower-gastrointestinal-tract-cancers. Accessed Feb 2017

6. Cubiella J, Salve M, Diaz-Ondina M, et al. Diagnostic accuracy of the faecal immunochemical test for colorectal cancer in symptomatic patients: comparison with NICE and SIGN referral criteria. *Colorectal Dis*. 2014; 16: O273-82.

7. Williams TG, Cubiella J, Griffin SJ, Walter FM and Usher-Smith JA. Risk prediction models for colorectal cancer in people with symptoms: a systematic review. *BMC Gastroenterol*. 2016; 16: 63.

8. Atkin WS and Saunders BP. Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut*. 2002; 51 Suppl 5: V6-9.

9. Steele R, Forgacs I, McCreanor G, et al. Use of faecal occult blood tests in symptomatic patients. *BMJ*. 2015; 351: h4256.

10. Fraser CG and Strachan JA. A nicer approach to the use of 'faecal occult blood tests' in assessment of the symptomatic. *Ann Clin Biochem*. 2016; 53: 5-6.

11. Benton S, Steele R, Logan R, Djedovic N, Smith S and Addison C. NICE referral guidelines for suspected cancer: colorectal cancer and faecal occult blood testing. *Ann Clin Biochem*. 2016; 53: 7-9.

12. Fraser CG. A future for faecal haemoglobin measurements in the medical laboratory. *Ann Clin Biochem*. 2012; 49: 518-26.

13. Allison JE, Fraser CG, Halloran SP and Young GP. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). *Gut Liver*. 2014; 8: 117-30.

14. Widlak MM, Thomas CL, Thomas MG, et al. Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and adenoma in symptomatic patients. *Aliment Pharmacol Ther*. 2017; 45: 354-63.

15. Auge JM, Fraser CG, Rodriguez C, et al. Clinical utility of one versus two faecal immunochemical test samples in the detection of advanced colorectal neoplasia in symptomatic patients. *Clin Chem Lab Med*. 2016; 54: 125-32.

16. Rodriguez-Alonso L, Rodriguez-Moranta F, Ruiz-Cerulla A, et al. An urgent referral strategy for symptomatic patients with suspected colorectal cancer based on a quantitative immunochemical faecal occult blood test. *Dig Liver Dis*. 2015; 47: 797-804.

17. McDonald PJ, Digby J, Innes C, et al. Low faecal haemoglobin concentration potentially rules out significant colorectal disease. *Colorectal Dis*. 2013; 15: e151-9.

18. Mowat C, Digby J, Strachan JA, et al. Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms. *Gut*. 2016; 65: 1463-9.

19. Godber IM, Todd LM, Fraser CG, MacDonald LR and Younes HB. Use of a faecal immunochemical test for haemoglobin can aid in the investigation of patients with lower abdominal symptoms. *Clin Chem Lab Med*. 2016; 54: 595-602.

20. Fraser CG, Rubeca T, Rapi S, Chen LS, Chen HH. Faecal haemoglobin concentrations vary with sex and age, but data are not transferable across geography for colorectal cancer screening. *Clin Chem Lab Med* 2014; 52: 1211-6.

21. Fraser CG. Diagnostic work-up of patients presenting in primary care with lower abdominal symptoms: which faecal test and triage strategy should be used? *BMC Med* 2016; 14:139.

22. NICE. GID-DG10005. 2017. https://www.nice.org.uk/guidance/indevelopment/gid-dg10005. Accessed Feb 2017

23. Scottish Cancer Referral Guidelines. http://www.cancerreferral.scot.nhs.uk/. Accessed March 2017.

24. Scottish Government. Redesign of key cancer services. https://news.gov.scot/news/redesign-of-key-cancer-services. Accessed March 2017.

Table 1. Summary of NICE NG12 guidelines for suspected gastrointestinal cancer and number of study participants fulfilling the individual criteria for referral

	Criteria	**Number (%) of study participants satisfying criteria**
Refer adults using a suspected cancer pathway referral (for an appointment within 2weeks) for colorectal cancer if:	They are aged 40 and over with unexplained weight loss and abdominal pain **or**	14 (0.9)
	They are aged 50 and over with unexplained rectal bleeding **or**	313 (21.7)
	They are aged 60 and over with: iron deficiency anaemia **or** changes in their bowel habit **or** tests show occult blood in their faeces.	371 (24.5)
Consider a suspected cancer pathway referral for colorectal cancer in adults with	Rectal or abdominal mass	0 (0)
Consider a suspected cancer pathway referral for colorectal cancer in adults aged under 50 with rectal bleeding **and** any of the following unexplained symptoms or findings:	Abdominal pain	13 (0.9)
	Change in bowel habit	18 (1.2)
	Weight loss	1 (0.1)
	Iron deficiency anaemia	1 (0.1)
Offer testing for occult blood in faeces to assess for colorectal cancer in adults **without** rectal bleeding who:	Are aged 50 **or** over with unexplained abdominal pain or weight loss **or**	220 (14.5)
	Over aged 60 with: changes in their bowels **or** iron deficiency anaemia **or**	183 (12.1)
	Are aged 60 and over and have anaemia even in the absence of iron deficiency.	82 (5.4)

Table 2. Comparison of overall diagnostic accuracy assessed by the Area under the Receiver Operating Characteristic Curve (AUC), with 95% CI, for faecal haemoglobin concentration, overall, and by FIT analyser and study, and for the NICE NG12 guidelines for colorectal cancer

	Faecal haemoglobin concentration				NICE NG12
Disease	**Overall**	**OC-Sensor Diana (FITS)**	**HM-JACKarc (FITS2)**	**OC-Sensor io (FITS+)**	
Colorectal cancer (CRC)	0.85 (0.87-0.90)	0.87 (0.78-0.94)	0.89 (0.84-0.93)	0.84 (0.77-0.91)	0.65 (0.58-0.73)
Higher risk adenoma (HRA)	0.64 (0.56-0.70)	0.72 (0.62-0.82)	0.65 (0.51-0.78)	0.59 (0.50-0.67)	0.54 (0.47-0.60)
All neoplasia (CRC + HRA)	0.72 (0.67-0.77)	0.76 (0.67-0.85)	0.74 (0.64-0.84)	0.69 (0.62-0.82)	0.58 (0.53-0.63)
Inflammatory bowel disease (IBD)	0.70 (0.64-0.76)	0.63 (0.52-0.75)	0.69 (0.57-0.81)	0.74 (0.65-0.82)	0.52 (0.46-0.59)
Significant colorectal disease (CRC + HRA + IBD)	0.73 (0.69-0.77)	0.73 (0.65-0.81)	0.73 (0.65-0.81)	0.73 (0.67-0.78)	0.56 (0.52-0.60)

Table 3. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), as percentages, and area under the ROC curve (AUC), with 95% CI, of faecal haemoglobin concentration (f-Hb) overall and by sex and age, **using a cut-off of ≥10 µg Hb/g faeces.**

		f-Hb Overall	**Male**	**Female**	**<50 years**	**≥50 years**
Colorectal cancer (CRC)	Sensitivity	93.3% (80.7-98.3)	100.0% (82.2-1.0)	88.0% (67.7-96.8)	100.0% (31.0-1.0)	92.9 (79.4-98.1)
	Specificity	77.3% (75.1-79.4)	73.0% (69.3-76.3)	80.7% (77.8-83.3)	79.8% (75.0-84.1)	76.6% (73.5-78.6)
	PPV	11.2% (8.3-14.9)	11.8% (7.8-17.4)	12.0% (7.8-17.8)	4.5% (1.2-13.4)	12.7% (9.0-16.7)
	NPV	99.7% (99.2-99.9)	100.0% (99.0-1.0)	99.6% (98.6-99.9)	100.0% (98.1-1.0)	99.7% (96.0-98.3)
	AUC	0.85 (0.87-0.90)	0.86 (0.83-0.90)	0.84 (0.75-0.92)	0.90 (0.83-0.97)	0.85 (0.80-0.90)
Higher-risk adenoma (HRA)	Sensitivity	50.5% (40.1-60.9)	56.6% (42.4-69.9)	42.9% (28.1-58.9)	57.1% (29.6-81.2)	49.4% (38.1-60.6)
	Specificity	77.0% (74.7-79.1)	72.8% (69.0-76.2)	80.1% (77.1-82.7)	80.8% (75.8-83.4)	75.9% (73.2-78.4)
	PPV	12.8% (9.7-16.7)	15.4% (10.7-21.4)	10.0% (6.2-15.6)	11.9% (5.7-22.7)	13.0% (9.5-17.4)
	NPV	95.9% (94.5-96.9)	95.0% (92.5-96.7)	96.4% (94.7-97.6)	97.6% (94.7-99.0)	95.4% (93.7-96.6)
	AUC	0.64 (0.56-0.70)	0.65 (0.57-0.73)	0.62 (0.52-0.71)	0.69 (0.53-0.85)	0.62 (0.56-0.69)
All neoplasia (CRC + HRA)	Sensitivity	64.3% (55.7-72.1)	69.7% (58.0-79.4)	59.7% (47.0-71.3)	64.7% (38.6-84.7)	64.2% (55.0-72.5)
	Specificity	79.3% (77.0-81.3)	75.6% (71.9-79.0)	81.9% (79.0-84.5)	81.6% (76.7-85.7)	78.6% (76.0-81.0)
	PPV	24.0% (19.8-28.7)	27.2% (21.2-34.1)	21.9% (16.2-28.7)	16.4 (8.9-27.9)	25.7% (20.9-31.0)
	NPV	95.6% (94.2-96.7)	95.0% (92.5-96.8)	96.0% (94.1-97.3)	97.6% (94.7-99.0)	95.3% (93.3-96.3)
	AUC	0.72 (0.67-0.77)	0.73 (0.66-0.79)	0.70 (0.63-0.77)	0.73 (0.60-0.87)	0.71 (0.66-0.77)
Inflammatory bowel disease (IBD)	Sensitivity	61.5% (50.7-71.4)	66.7% (50.9-79.6)	56.5% (41.2-70.7)	60.0% (40.7-76.8)	62.3% (48.9-74.1)
	Specificity	77.6% (75.3-79.7)	73.1% (69.4-76.6)	81.0% (78.0-83.6	83.2% (78.2-87.2)	76.2% (73.5-78.6)
	PPV	14.9% (11.6-19.0)	15.4% (10.8-21.4)	14.4% (9.8-20.6)	26.9% (17.1-39.3)	12.3% (9.0-16.6)
	NPV	96.9% (95.7-97.8)	96.8% (94.6-98.1)	97.0% (95.4-98.1)	95.3% (91.7-97.4)	97.4% (96.0-98.3)
	AUC	0.70 (0.64-0.76)	0.70 (0.62-0.78)	0.69 (0.60-0.77)	0.72 (0.61-0.82)	0.69 (0.62-0.77)
Significant colorectal disease (CRC + HRA + IBD)	Sensitivity	63.2% (56.6-69.4)	68.6% (91.4-94.4)	57.3% (47.5-66.5)	61.7% (46.4-75.1)	63.6% (56.1-70.4)
	Specificity	83.3% (81.1-85.2)	79.2% (75.4-82.5)	84.3% (81.4-86.8)	86.1% (81.3-90.0)	81.1% (78.4-83.4)
	PPV	38.9% (34.0-44.1)	42.6% (35.6-49.8)	35.0% (28.1-42.5)	43.3% (31.4-55.9)	38.0% (32.6-43.6)
	NPV	93.1% (91.4-94.4)	91.8% (88.8-94.1)	93.0% (28.1-42.5)	92.9% (88.8-95.6)	92.4% (90.4-94.0)
	AUC	0.73 (0.69-0.77)	0.74 (0.69-0.79)	0.71 (0.65-0.77)	0.74 (0.65-0.83)	0.72 (0.68-0.77)

Table 4. Number of patients with colorectal diseases missed using faecal haemoglobin concentration at ≥10 µg Hb/g faeces cut-off and number missed using NICE NG12 guidelines

Disease	**No missed using faecal haemoglobin concentration at 10 µg Hb/g faeces cut-off**	**No missed using NICE NG12 guidelines**
Colorectal cancer (CRC)	3	10
Higher risk adenoma (HRA)	47	43
All neoplasia (CRC + HRA)	50	53
Inflammatory bowel disease (IBD)	35	43
Significant colorectal disease (CRC + HRA + IBD)	85	96