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TITLE PAGE

Title: Poor Predictive Value of Lower Gastrointestinal Alarm Features in the Diagnosis of Colorectal Cancer in 1981 Patients in Secondary Care.

Short "running" head: Lower GI Alarm Features and Colorectal Cancer.

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Abbreviations:

BMI	body mass index
CRC	colorectal cancer
CI	confidence interval
GI	gastrointestinal
IBD	inflammatory bowel disease
NICE	National Institute for Health and Care Excellence

NPV	negative predictive value
PPV	positive predictive value
SD	standard deviation

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SUMMARY

Background: Clinicians are advised to refer patients with lower gastrointestinal (GI) alarm features for urgent colonoscopy to exclude colorectal cancer (CRC). However, the utility of alarm features is debated.

Aims: To assess whether performance of alarm features is improved by using a symptom frequency threshold to trigger referral, or by combining them into composite variables, including minimum age thresholds, as recommended by the National Institute for Health and Care Excellence (NICE).

Methods: We collected data prospectively from 1981 consecutive adults with lower GI symptoms. Assessors were blinded to symptom status. The reference standard to define CRC was histopathological confirmation of adenocarcinoma in biopsy specimens from a malignant-looking colorectal lesion. Controls were patients without CRC. Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values were calculated for individual alarm features, as well as combinations of these.

Results: In identifying 47 (2.4%) patients with CRC, individual alarm features had sensitivities ranging from 11.1% (family history of CRC) to 66.0% (loose stools), and specificities from 30.5% (loose stools) to 75.6% (family history of CRC). Using higher symptom frequency thresholds improved specificity, but to the detriment of sensitivity. NICE referral criteria also had higher specificities and lower sensitivity, with PPVs above 4.8%. More than 80% of those with CRC met at least one of the NICE referral criteria.

Conclusions: Using higher symptom frequency thresholds for alarm features improved specificity, but sensitivity was low. NICE referral criteria had PPVs above 4.8%, but sensitivities ranged from 2.2% to 32.6%, meaning many cancers would be missed.

INTRODUCTION

In 2012 colorectal cancer (CRC) was the second most common cause of new cases of cancer in women, and the third in men, worldwide. (1) It was also the third commonest cause of cancer death in women, and fourth commonest in men, responsible for the loss of almost 700,000 lives. (1) Timely diagnosis is therefore imperative and, in order to achieve this, many developed nations have instituted screening programmes for CRC, using a variety of methods including lower gastrointestinal (GI) endoscopy or faecal occult blood or immunochemical testing. (2-6) Although programmes such as these are directed towards detection of early CRC in healthy asymptomatic individuals, the majority of patients are symptomatic at the time of diagnosis. (7, 8)

Patients with CRC may present with various lower GI or systemic symptoms, such as a change in bowel habit, rectal bleeding, lower abdominal pain, anaemia, or weight loss. These symptoms are referred to as alarm features, or "red flag" symptoms, and in a patient who reports them, urgent referral for lower GI endoscopy to exclude CRC is recommended. However, these symptoms are also common in patients with non-malignant lower GI disease, (9-12) and as a result their accuracy in predicting a diagnosis of CRC has been shown to be poor. (10)

Recently, in the UK, the National Institute for Health and Care Excellence (NICE) outlined a series of criteria that should trigger a definite referral from primary care, via the urgent referral pathway for suspected CRC. Criteria definitely requiring urgent referral included: ≥40 years of age with weight loss and abdominal pain; ≥50 years of age with rectal bleeding; ≥60 years of age with anaemia; and ≥60 years of age with a change in bowel habit in the last year. (13) Other criteria proposed by the guideline development group where physicians were encouraged to consider a referral included: <50 years of age with rectal bleeding and abdominal pain; <50 years of age with rectal bleeding and a change in bowel

habit; <50 years of age with rectal bleeding and weight loss; and <50 years of age with rectal bleeding and anaemia.

The NICE guidelines development group recognised that, in the production of criteria for referral, a balance must be found between the advantages and disadvantages of investigation via colonoscopy. In finding this balance they declared positive predictive value (PPV) to be the most important statistical measure, and proposed a PPV >3% to underpin any recommendations concerning which symptoms required referral for investigation. (14) However, the performance of these referral criteria has yet to be studied. We therefore sought to investigate the diagnostic accuracy of all proposed alarm features and referral criteria for CRC, via the analysis of a large prospective database of patients in secondary care.

MATERIALS AND METHODS

Participants and Setting

Demographic data and alarm feature status were collected from consecutive, unselected patients newly referred with GI symptoms from primary care to two secondary care centres over a 4-year period. The McMaster University Medical Center and St. Joseph's Healthcare together provide secondary care services to a local population of 520,000. The Hamilton Health Sciences and McMaster University research ethics board approved this study in January 2008 and recruitment continued until December 2012. The minimum age for inclusion in the study was 16 years. The only other requirement was an understanding of written English, so as to enable prospective participants to self-administer the symptom questionnaire. Informed consent was obtained at the initial clinic visit by providing patients with a study information sheet prior to completion of the questionnaire. We have published other studies from this large dataset, which examine the utility of symptoms in predicting a diagnosis of irritable bowel syndrome, functional dyspepsia, and inflammatory bowel disease (IBD), as well as characteristics of patients with functional GI disorders. (9, 15-21)

Data Collection and Synthesis

Demographic and Symptom Data

All demographic and symptom data were collected prospectively at the initial clinic visit, prior to referral for colonoscopy. Age, gender, ethnicity, marital status, educational level, lifestyle (tobacco and alcohol use), height (in metres), and weight (in kilograms), which were used to calculate body mass index (BMI), were recorded. Symptom data were collected using the Rome III diagnostic questionnaire for the adult functional GI disorders, a 93-item

instrument, which has been validated previously. (22) All questionnaire data were entered into a database by a trained researcher who was not involved with the clinical care of the patient, thus ensuring assessors were blinded to symptom status.

We used any symptom item included within this questionnaire that could be a potential presenting feature of CRC, and is accepted as an alarm feature. These included: presence of rectal bleeding; whether the patient had been told by a doctor that they were anaemic; a family history of CRC; any change in bowel habit within the last 12 months; presence of unintentional weight loss; passage of ≥4 stools per day; passage of <3 stools per week; presence of loose stools; and presence of hard stools.

Based on our previous meta-analysis, which demonstrated a poor predictive value of many alarm features for the diagnosis of CRC, (10) we studied whether the frequency at which these symptoms were reported, as well as the amount of weight lost, improved their diagnostic accuracy. In addition, in light of the updated referral guidelines for suspected cancer from NICE, (13) we used our dataset to create composite variables that reflected the alarm features recommended in these guidelines for use in prioritising urgent referral with suspected CRC (Table 1).

Colonoscopic and Histopathological Data

All patients included in this study underwent complete colonoscopy to the caecum or terminal ileum, as part of routine clinical practice, using Pentax colonoscopes (Pentax Canada, Inc) and following standard bowel preparation, using either polyethylene glycol or sodium picosulfate (depending on patient and physician preference). Endoscopists performing colonoscopy were blinded to the questionnaire data for each patient. Endoscopic findings were recorded using the endoPRO reporting system (Pentax Canada, Inc), which was

accessed by the study investigators in order to record the ultimate colonoscopic diagnosis for each included patient.

Experienced GI histopathologists, who were also blinded to the questionnaire data of the patient, interpreted biopsy specimens. These were obtained at the discretion of the endoscopist. Histopathological findings were recorded using the MEDITECH Healthcare Reporting System (Medical Information Technology Inc, Westwood, MA), which was accessed by the study investigators in order to record the ultimate histopathological diagnosis.

The reference standard to define patients with CRC was after histopathological confirmation of adenocarcinoma in biopsy specimens taken from a suspected malignant colorectal lesion. Patients with functional lower GI symptoms with normal colonoscopy and normal histology, or those with any other organic lower GI disease at either colonoscopy (including suspected IBD, benign colonic stricture, evidence of radiation-induced colorectal disease, colorectal adenoma, or haemorrhoids), or on examination of biopsy specimens (ulcerative colitis, Crohn's disease, IBD-unclassifiable, microscopic colitis, ischaemic colitis, radiation enteropathy, or neuroendocrine tumour) served as controls without CRC.

Statistical Analysis

In order to assess whether those who underwent colonoscopy were representative of all patients seen in the two GI outpatient clinics demographic data were compared between those undergoing colonoscopy who completed the symptom questionnaire, and those who completed the symptom questionnaire but did not undergo colonoscopy, using a χ^2 test for categorical data, and an independent samples t-test for continuous data, with a mean and standard deviation (SD). We also compared the prevalence of individual lower GI alarm features between these two groups using a χ^2 test. Due to multiple comparisons, a 2-tailed P

value of <0.01 was considered statistically significant for these analyses, which were performed using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL, USA).

The aim of the study was to describe the performance of individual alarm features, at different symptom frequencies, as well as combinations of these as composite variables as proposed by NICE, (13) in predicting the presence of CRC versus the reference standard. The sensitivity, specificity, PPV, and negative predictive value (NPV) were calculated for each of these using a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA), and their 95% confidence intervals (CIs) confirmed using StatsDirect version 2.7.7 (StatsDirect Ltd, Sale, Cheshire, England).

RESULTS

In total, 4224 consecutive patients gave informed consent and were recruited into the study between January 2008 and December 2012. The mean age of all recruited subjects was 47.6 years (range 16 to 93 years) and 2617 (62.0%) were female. Of these, 1981 (46.9%) subjects underwent complete colonoscopic evaluation for their lower GI symptoms. The other 2243 patients were either consulting with other GI symptoms, or a colonoscopy was not felt to be necessary by the responsible physician in order to facilitate a diagnosis. Demographic data of the patients who had complete colonoscopy were compared with the 2243 subjects who did not (Supplementary Table 1). Those undergoing colonoscopy were slightly older (49.3 years vs. 46.1 years), of higher BMI (27.3kg/m^2 vs. 26.7kg/m^2), and were more likely to be White Caucasian (90.2% vs. 85.5%).

Compared with those who did not undergo colonoscopy, the frequency of reporting of all the individual lower GI alarm features considered was significantly higher among those patients undergoing colonoscopy, with the exception of anaemia, weight loss, passage of <3 stools per week, or passage of hard or lumpy stools (Supplementary Table 2). Greater proportions of subjects undergoing colonoscopy also met the referral criteria recommended by NICE, with the exception of the combination of ≥60 years of age and anaemia.

Of those colonoscoped, 1289 (65.1%) had colonic or rectal biopsies taken. In total, there were 47 (2.4%) patients diagnosed with CRC, according to the reference standard, among the 1981 individuals undergoing colonoscopy (Figure 1). There were a further 302 (15.2%) patients found to have IBD, 104 (5.2%) with ulcerative colitis, 147 (7.4%) with Crohn's disease, and 51 (2.6%) with IBD-unclassifiable, as well as 468 (23.6%) with adenomatous or hyperplastic polyps, 162 (8.2%) with haemorrhoids, 33 (1.7%) with microscopic colitis, 15 (0.8%) with angiodysplasia, 10 (0.5%) with radiation enteropathy, and 897 (45.3%) with no organic cause for their lower GI symptoms who had a normal

colonoscopy, with normal colonic biopsies, where obtained. Patients with CRC were older (mean age 62.5 years versus 49.0 years, P<0.001), and more likely to be married, cohabiting or widowed (P = 0.002), but there were no other significant differences in demographics or baseline characteristics (Table 2).

Performance of Lower GI Alarm features in Predicting CRC

The performance of individual alarm features in predicting a diagnosis of CRC is summarised in Table 3. In terms of sensitivity, only a change in bowel habit in the last year and the passage of ≥4 stools per day exceeded 50%. Specificity was also modest for almost all variables, with only anaemia and a family history of CRC in excess of 75%. Specificity of individual symptom items such as weight loss, stool number, and stool consistency increased to 90% or above with an increasing amount of weight loss, or a higher symptom frequency, but this was at the expense of sensitivity, which fell to 11% or less for all alarm features. NPVs for all alarm features were excellent, in excess of 95%, meaning that if absent CRC was extremely unlikely. However, PPVs were extremely poor, with less than 5% of individuals reporting these ultimately found to have CRC. The only exception to this was weight loss of ≥20kg, where PPV rose to 9.8%.

When we applied the composite variables, created to reflect current recommendations from NICE, the results were similar (Table 4). Sensitivity ranged from 2.2% for age <50 years with rectal bleeding and anaemia, to 32.6% for either age ≥40 years with weight loss and abdominal pain, or ≥60 years with a change in bowel habit in the last year. Specificity ranged from 85% to 95% for all of these composite variables, with the exception of age <50 years with rectal bleeding and abdominal pain, with a specificity of 82.0%. Again, NPVs were in excess of 95%, but PPVs ranged from 0.8% for age <50 years with rectal bleeding and anaemia, to 11.4% for age ≥60 years with anaemia. More than 80% of those with CRC

met at least one of the NICE referral criteria, but because 1026 (52.8%) of 1944 individuals without CRC also met these criteria, the PPV was only 3.5%.

DISCUSSION

This study builds on previous reports outlining the limited utility of individual items from the clinical history in predicting CRC. Individual symptoms and signs demonstrated generally poor sensitivities and PPVs, with modest specificities, and high NPVs. Due to the poor sensitivities and PPVs, using their presence as criteria for referral would result in large numbers of patients being investigated in order to detect only a small number of cancers, even in a secondary care population such as this. Some quantified variables showed improvements in PPV, such as weight loss ≥20kg, which had a PPV of 9.8% compared with 3.5% for any amount of weight loss. However, as the PPV rose for greater quantities of weight loss, the sensitivity fell, suggesting that using higher thresholds for referral would result in greater numbers of CRCs being missed. Other quantified variables such as <3 stools per week or hard stools demonstrated lower PPVs at greater symptom frequencies, suggesting, as we have shown previously, (23) that constipation-type symptoms are negatively associated with CRC. The composite variables constructed to reflect NICE referral criteria showed modest sensitivities and good specificities, with PPVs in excess of 3%, but the NICE criteria for which clinicians are encouraged to 'consider' a referral showed poor sensitivities and low PPVs. Finally, although more than 80% of patients with CRC met at least one of these referral criteria, the PPV remained at 3.5% due to the large number of individuals without CRC who also met these criteria.

Strengths of this study include the large sample size, with 1981 patients providing complete symptom data, as well as final diagnoses. In addition, the prospective and consecutive sampling of patients, and the blinding of endoscopists to symptom status, reduces the potential for selection bias within the study. The use of patient-reported symptoms increases the applicability of this study to the real-world setting, where patients with various complaints, including alarm features, will consult with physicians about their own

experiences. Finally, the unselected nature of the patients, which included those with other organic as well as functional diseases, increases the generalisability of the findings to clinicians working to identify cases of CRC within a cohort of mixed lower GI pathologies in secondary care.

The use of colonoscopy with histopathology as a proxy for definitive presence of CRC is a limitation of this study. Despite the fact that it is accepted as the gold standard diagnostic tool for CRC, audits have reported miss rates of up to 3.5%, (24) although all physicians performing colonoscopy in this study were experienced consultant gastroenterologists. In addition, not all patients enrolled in this study had a colonoscopy performed. This could have resulted in a small number of asymptomatic cancers being missed among those who were not colonoscoped, which may have improved the performance of the variables being studied. The caveat to this limitation is, of course, that to perform colonoscopies in patients in whom there was no clinical indication to do so would be both inefficient and unethical. Further limitations of this study concern the nature of the cohort being studied. We applied alarm features and NICE referral criteria to a cohort of patients in secondary care, which may not necessarily reflect the demographic composition of those presenting to primary care. This setting is where the NICE guidance, in particular, is intended to be applied. However, in primary care, where the prevalence of CRC is likely to be even lower than the 2.4% we observed, the performance of both alarm features and current NICE referral criteria would be even worse. (25)

The PPVs of individual symptoms we observed were generally lower than those reported in previous studies, (26-28) and the PPV of anaemia in this study was also lower than in a previous study by Hamilton et al. (29) These differences may relate to the lower prevalence of CRC within the cohort we studied, as well as our use of patient-reported symptoms and signs. Other studies have used variations in recorded weights from clinic visits

as a proxy for weight loss, (30) or haemoglobin levels as a measure of anaemia. (31) However, the use of patient-reported symptoms and signs as alarm features in our study, although opening up the results to the possibility of recall bias, also make them more applicable to a real-world setting. In addition, the PPV of patient-reported anaemia of 3.8% we observed was higher than many of the other alarm features we studied, suggesting it may still be useful for clinicians to enquire about a patient's knowledge of anaemia as a presenting feature. The composite variable recommended by NICE of ≥60 years of age with anaemia produced a PPV of 11.4%, the highest of any of the variables in this analysis. Although the relatively high PPV suggests that this combination may have diagnostic value, it should be remembered that anaemia is a later presenting feature of CRC. (32) There is also growing evidence that the incidence of colorectal cancers in younger individuals is increasing, (33) with up to 10% occurring in those aged under 50 years of age, (34) and these individuals may present with more advanced lesions, suggesting that application of such age thresholds is unwarranted. In general, the criteria which the NICE guideline development group recommended should definitely trigger an urgent referral had higher PPVs than those which only warrant consideration of a referral.

This study builds on previous reports which have highlighted the problem that although CRC is a relatively rare diagnosis in primary care, the alarm features that supposedly indicate its presence are very common among the general population. (35) This in turn limits their ability to predict a diagnosis of CRC accurately. A recent UK-based study has suggested that up to 20% of individuals with an "emergency" index presentation with colorectal cancer may have reported "alarm" symptoms in the previous 12 months, (36) leading to much criticism of general practitioners in the media for "missing" the diagnosis in these patients. However, our data highlight the poor predictive value of the majority of alarm features, although attempts in this study to improve their performance through quantification

and categorisation have, in some instances such as weight loss, shown an improvement in the PPV, but to the detriment of sensitivity, suggesting that although implementing stricter criteria for urgent referral may increase the proportion of patients with a detected cancer, it will also result in many cancers being missed by the pathway.

Although current NICE criteria for referral with suspected CRC performed satisfactorily with a PPV of >3%, the benchmark proposed by the guideline development group, it should be remembered that the patient cohort in our study will likely have a higher prevalence of CRC than a primary care population, and that the diagnostic value of these referral criteria are therefore probably overestimations. Developments in the broader field of CRC diagnosis and management such as new routes of screening, (37) or combining symptoms with biomarkers, (38) and increased evidence for the efficacy of some chemopreventive agents, (39) as well as both primary and secondary prevention at the public health level, may prove more effective methods to reduce both the human and economic cost of CRC at the population level.

AUTHORSHIP

Guarantor of the article: ACF is guarantor.

Specific author contributions: SJS, MIP-S, PM, PB, DGM, CB, and ACF conceived and drafted the study. ACF, CB, and MIP-S collected all data. SJS and ACF analysed and interpreted the data. PM provided statistical advice and support. SJS and ACF drafted the manuscript. All authors have approved the final draft of the manuscript.

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Table 1. NICE Recommendations for Urgent Referral for Suspected CRC. (13)

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they:	Are aged ≥40 with unexplained weight loss and abdominal pain
	Are aged ≥50 with unexplained rectal bleeding
	Are aged ≥60 with anaemia
	Are aged ≥60 with changes in their bowel habit
Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in adults aged <50 with rectal bleeding and any of the following unexplained symptoms or findings:	Abdominal pain
	Change in bowel habit
	Weight loss
	Anaemia

Table 2. Demographics and Baseline Characteristics of Patients with CRC Compared with Patients without CRC.

	Individuals with CRC (n = 47)	**Individuals without CRC (n = 1934)**	**P value***
Mean age (SD)	62.5 (16.3)	49.0 (17.0)	<0.001
Mean BMI (SD)	25.9 (6.2)	27.3 (6.0)	0.12
Male gender (%)	21 (44.7)	709 (36.7)	0.26
Tobacco user (%)	5 (10.6)	404 (20.9)	0.22
Alcohol user (%)	23 (48.9)	1142 (59.0)	0.27
Marital status (%)			
Married of cohabiting	31 (66.0)	1181 (61.1)	
Divorced or separated	3 (6.4)	224 (11.6)	
Never married	4 (8.5)	425 (22.0)	
Widowed	7 (14.9)	83 (4.3)	0.002
Educational Level (%)			
Elementary	5 (10.6)	90 (4.7)	
High school	16 (34.0)	556 (28.7)	
Technical school/college	15 (31.9)	576 (29.8)	
University	8 (17.0)	496 (25.6)	
Postgraduate	3 (6.4)	179 (9.3)	0.23

Ethnicity (%)			
White Caucasian	42 (89.4)	1745 (90.2)	
South Asian	0 (0)	22 (1.1)	
Middle-Eastern	0 (0)	21 (1.1)	
North American	0 (0)	21 (1.1)	
Aboriginal			
African	1 (2.1)	20 (1.0)	
South East Asian	1 (2.1)	13 (0.7)	
Latin-American	0 (0)	13 (0.7)	
Other	2 (4.3)	41 (2.1)	0.69

*P value for independent samples t-test for continuous data and Pearson χ^2 for comparison of categorical data.

Table 3. Sensitivity, Specificity, and Positive and Negative Predictive Values for Lower GI Alarm Features in Predicting a Diagnosis of CRC.

	No. with CRC reporting	Total no. with CRC	No. without CRC reporting	Total no. without CRC	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Rectal bleeding	20	47	676	1900	42.6% (29.5% - 56.7%	64.4% (62.2% - 66.5%)	2.9% (1.9% - 4.5%)	97.8% (96.9%- 98.5%)
Anaemia	18	43	462	1865	41.9% (28.4% - 56.7%)	75.2% (73.2% - 77.1%)	3.8% (2.4% - 5.9%)	98.3% (97.4% - 98.8%)
Family history of colorectal cancer	6	46	433	1812	11.1% (4.8% - 23.5%)	75.6% (73.5% - 77.6%)	1.2% (0.5% - 2.7%)	97.0% (96.0% - 97.8%)
Change in bowel habit in the last year	27	47	971	1887	57.5% (43.3% - 70.5%)	48.5% (46.3% - 50.8%)	2.7% (1.9% - 3.9%)	97.9% (96.7% - 98.6%)

Weight loss								
Any	22	44	602	1888	50.0% (35.8% - 64.2%)	68.1% (66.0% - 70.2%)	3.5% (2.3% - 5.3%)	98.3% (97.5% - 98.9%)
≥5kg	13	44	373	1859	29.6% (18.2% - 44.2%)	79.9% (78.1% - 81.7%)	3.4% (2.0% - 5.5%)	98.0% (97.1% - 98.6%)
≥10kg	10	44	161	1859	22.7% (12.8% - 37.0%)	91.3% (90.0% - 92.5%)	5.9% (0.3% - 10.4%)	98.0% (97.3% - 98.6%)
≥15kg	7	72	72	1859	15.9% (7.9% - 29.4%)	96.1% (95.2% - 97.0%)	8.9% (4.4% - 17.2%)	98.0% (97.2% - 98.5%)
≥20kg	5	46	46	1859	11.4% (5.0% - 24.0%)	97.5% (96.7% - 98.1%)	9.8% (4.3% - 21.0%)	97.9% (97.1% - 98.5%)

<3 stools per week								
Sometimes or more	17	45	508	1910	37.8% (25.1% - 52.4%)	73.4% (71.4% - 75.3%)	3.2% (2.0% - 5.1%)	98.0% (97.2% - 98.6%)
Often or more	7	45	249	1910	15.6% (7.8% - 28.8%)	87.0% (85.4% - 88.4%)	2.7% (1.3% - 5.5%)	97.8% (96.9% - 98.4%)
Most of the time or more	2	45	146	1910	4.4% (1.2% - 14.8%)	92.4% (91.1% - 93.5%)	1.4% (0.4% - 4.8%)	97.6% (96.8% - 98.2%)
Always	0	45	68	1910	0% (0% - 7.9%)	96.4% (95.5% - 97.2%)	0% (0.0% - 5.4%)	97.6% (96.8% - 98.2%)
Hard stools								
25% of the time or more	22	46	992	1904	47.8% (34.1% - 61.9%)	47.9% (45.7% - 50.2%)	2.2% (1.4% - 3.3%)	97.4% (96.2% - 98.3%)
50% of the time or more	10	46	443	1904	21.7% (12.3% - 35.6%)	76.7% (74.8% - 78.6%)	2.2% (1.2% - 4.0%)	97.6% (96.7% - 98.3%)
75% of the time or more	3	46	214	1904	6.5% (2.2% - 17.5%)	88.8% (87.3% - 90.1%)	1.4% (0.5% - 4.0%)	97.5% (96.7% - 98.2%)
100% of the time	0	46	55	1904	0% (0% - 7.7%)	97.1% (96.3% - 97.8%)	0% (0.0% - 6.5%)	97.6% (96.8% - 98.2%)

≥4 stools per day								
Sometimes or more	22	46	954	1907	47.8% (34.1% - 61.9%)	50.0% (47.7% - 52.2%)	2.3% (1.5% - 3.4%)	97.5% (96.4% - 98.3%)
Often or more	12	46	498	1907	26.1% (15.6% - 40.3%)	73.9% (71.9% - 75.8%)	2.4% (1.4% - 4.1%)	97.6% (96.7% - 98.3%)
Most of the time or more	7	46	287	1907	15.2% (7.6% - 28.2%)	85.0% (83.3% - 86.5%)	2.4% (1.2% - 4.8%)	97.7% (96.8% - 98.3%)
Always	4	46	157	1907	8.7% (3.4% - 20.3%)	91.8% (90.5% - 92.9%)	2.5% (1.0% - 6.2%)	97.7% (96.9% - 98.3%)
Loose stools								
25% of the time or more	31	47	1318	1897	66.0% (51.7% - 77.8%)	30.5% (28.5% - 32.6%)	2.3% (1.6% - 3.3%)	97.3% (95.7% - 98.3%)
50% of the time or more	22	47	809	1897	46.8% (33.3% - 60.8%)	57.4% (55.1% - 59.6%)	2.7% (1.8% - 4.0%)	97.8% (96.7% - 98.5%)
75% of the time or more	8	47	527	1897	17.0% (8.9% - 30.1%)	72.2% (70.2% - 74.2%)	1.5% (0.8% - 2.9%)	97.2% (96.2% - 98.0%)
100% of the time	5	47	192	1897	10.6% (4.6% - 22.6%)	89.9% (88.4% - 91.2%)	2.5% (1.1% - 5.8%)	97.6% (96.8% - 98.2%)

Table 4. Sensitivity, Specificity, and Positive and Negative Predictive Values for NICE Referral Criteria in Predicting a Diagnosis of CRC.

	No. with CRC reporting	Total no. with CRC	No. without CRC reporting	Total no. without CRC	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
≥40 years of age and weight loss and abdominal pain	14	43	245	1900	32.6% (20.5% - 47.5%)	87.1% (85.5% - 88.5%)	5.4% (3.3% - 8.9%)	98.3% (97.5% - 98.8%)
≥50 years of age and rectal bleeding	13	47	259	1913	27.7% (16.9% - 41.8%)	86.5% (84.9% - 87.9%)	4.8% (2.8% - 8.0%)	98.0% (97.2% - 98.6%)
≥60 years of age and anaemia	14	44	109	1907	31.8% (20.0% - 46.6%)	94.3% (93.2% - 95.2%)	11.4% (6.9% - 18.2%)	98.4% (97.7% - 98.9%)
≥60 years of age and a change in bowel habit in the last year	15	46	239	1913	32.6% (20.9% - 47.0%)	87.5% (86.0% - 88.9%)	5.9% (3.6% - 9.5%)	98.2% (97.4% - 98.7%)

<50 years of age, rectal bleeding, and abdominal pain	6	47	344	1913	12.8% (6.0% - 25.2%)	82.0% (80.2% - 83.7%)	1.7% (0.8% - 3.7%)	97.5% (96.6% - 98.1%)
<50 years of age, rectal bleeding, and change in bowel habit	5	47	240	1922	10.6% (4.6% - 22.6%)	87.5% (86.0% - 88.9%)	2.0% (0.9% - 4.7%)	97.6% (96.7% - 98.2%)
<50 years of age, rectal bleeding, and weight loss	6	47	164	1917	12.8% (6.0% - 25.2%)	91.4% (90.1% - 92.6%)	3.8% (1.7% - 7.9%)	97.7% (96.9% - 98.3%)
<50 years of age, rectal bleeding, and anaemia	1	46	122	1917	2.2% (0.4% - 11.3%)	93.6% (92.5% - 94.7%)	0.8% (0.1% - 4.5%)	97.5% (96.7% - 98.1%)
Any of the NICE referral criteria	37	46	1026	1944	80.4% (66.1% - 90.6%)	47.2% (45.0% - 49.5%)	3.5% (2.5% - 4.8%)	99.0% (98.2% - 99.6%)

Figure 1. Flow of Study Participants.