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Faecal calprotectin in patients with suspected colorectal cancer:

a diagnostic accuracy study

Abstract

Background
NICE guidance exists for the use of faecal calprotectin (FC) when irritable bowel syndrome or inflammatory bowel disease are suspected. Often, however, colorectal cancer is considered within the differential. Should FC have a high diagnostic accuracy for colorectal cancer, it may be applicable as a primary care screening test for all patients with lower gastrointestinal symptoms.

Aim
To determine the negative and positive predictive value (NPV/PPV) of FC in patients referred from primary care with suspected colorectal cancer.

Design and setting
A diagnostic accuracy study conducted at a single secondary care site

Method
Consenting patients referred with suspected colorectal cancer within the '2-week wait' pathway provided a stool sample for FC prior to investigation. FC levels were reconciled with end diagnoses: cancer, adenomatous polyps ≥10 mm, and all enteric organic disease.

Results
A total of 654 patients completed the evaluation; median age 69 years, female 56%. The NPV for colorectal cancer was 98.6% and 97.2% when including polyps ≥10 mm. The PPV for all organic enteric disease was 32.7%. The diagnostic yield for cancer based on clinical suspicion was 6.3%. By altering the FC cut-off to fix the NPV at 97.0%, the PPV for cancer increased from 8.7% to 13.3%.

Conclusion
FC has a high NPV for colorectal cancer and significant polyps in patients with suspected cancer. In total, 27.8% of patients had a normal FC and could safely have been spared a '2-week wait' referral. The addition of FC testing into the current symptom-based assessment has the potential to increase colorectal cancer detection rate yet be clinically and cost effective.

Keywords
calprotectin; colorectal cancer; diagnostic accuracy; primary care.

INTRODUCTION

Levels of faecal calprotectin (FC), a mucosal neutrophil degradation product, correlate well with intestinal inflammation.[1,2] Because a range of intestinal diseases have an inflammatory component it is a non-specific test. However, should it be sufficiently sensitive, FC might differentiate much organic enteric disease from functional disorders, such as irritable bowel syndrome (IBS).[1–4] This would empower the expectant treatment of low-risk patients and the cost-effective identification of those requiring urgent investigation.

Recognising this, the National Institute for Health and Care Excellence (NICE) has produced guidance (DG11) for the use of FC when IBS or inflammatory bowel disease (IBD) are suspected.[5] But it does not apply when colorectal cancer is suspected.[6,7] Instead, patients fulfilling symptomatic criteria are referred urgently. The assessment and investigation of these '2-week wait' patients represents a significant healthcare burden for the NHS. Currently, colorectal cancer is diagnosed in only 8% of those referred.[8] Yet many patients continue to be diagnosed outside this pathway. In an attempt to improve cancer diagnosis, the NICE guidance has been updated (NG12) and faecal occult blood (FOB) testing introduced.[9,10] Currently, however, FOB is not widely available within the symptomatic service.

From a clinical perspective, an ideal faecal biomarker should be safe (that is, missing very few colorectal cancers), be effective, picking up significant pre-malignant colorectal polyps and all organic enteric disease, and have utility (that is, a better positive predictive value (PPV) than current clinical practice). From a laboratory perspective, it should be stable, and easy and cheap to assay. The authors postulated that there would be a sufficient inflammatory component in patients symptomatic of colorectal cancer resulting in a raised FC. A study was thus undertaken to determine the diagnostic accuracy of FC in patients referred with suspected colorectal cancer, both for clinically significant colorectal neoplasia and for all organic enteric disease.

METHOD

This pragmatic, blinded, observational study was performed at York Hospital, following the STAndards for the Reporting of Diagnostic accuracy studies (STARD) guidelines.[11] All patients referred urgently as '2-week wait' for suspected colorectal cancer from primary care were eligible

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How this fits in

Symptoms in colorectal cancer are often non-specific. This represents a major clinical and cost effectiveness challenge. In patients suspected by their GP of having colorectal cancer, faecal calprotectin has a negative predictive value of 98.6%. A normal faecal calprotectin would safely permit the expectant management of 27.8% of patients currently referred urgently (as 'two week wait' patients). Faecal calprotectin can be used to develop a needs-based rather than symptom-based approach to referral for the future.

for the study. Patients entered dedicated '2-week wait' colorectal clinics, the GP indicating the criterion for referral. NICE guidance CG27 criteria were used,[12] because the study pre-dated the publication of NICE guidance NG12.[9]

Consenting patients provided a stool sample for the blinded determination of FC before any investigations were undertaken. All investigations were arranged on clinical grounds at the discretion of the responsible clinician. The majority of investigations were performed within 2 weeks of referral. The stool sample was delivered to the Department of Clinical Biochemistry at York Hospital on the same day that it was passed.[13] Samples were stored at <4°C prior to extraction (weighing method). Extracts were stored at –20°C and then analysed in batches. The stool extract was analysed using a monoclonal enzyme-linked immunosorbent assay (EK-CAL Calprotectin ELISA, Bühlmann, supplied by Alpha Laboratories Ltd, Eastleigh, UK) to determine the FC level. The normal cut-off is taken to be <50 mcg/g in line with the manufacturer's guidance. A quality control sample set at a level of 150 was present in every test batch, the coefficient of variation being 5%. The upper limit of linearity for the assay is 600 mcg/g and samples giving results above this level were subject to further dilutions to provide a quantitative result.

The hospital Core Patient Database was accessed to identify the referral proforma, the consultation records, and all correspondence, investigations, and clinical outcomes. Relevant data and clinical outcomes were then stored anonymously. Clinical outcomes were recorded as primary, secondary, or incidental diagnoses. The primary diagnosis recorded, which accounted for the symptomatic presentation, was that made by the responsible clinician. This included some cases of diverticulosis. Sometimes the clinician added a secondary diagnosis that was contributing to symptoms. For the purposes of this study, symptomatic disease included iron deficiency anaemia. Significant colorectal neoplasia was judged to include colorectal polyps ≥10 mm.[14] Asymptomatic, moderate diverticulosis was recorded as incidental. Diverticulosis described as minor or mild was ignored. Some incidental disease was significant, however, and is presented in the results section. When no organic enteric diagnosis was made, the responsible clinician reported the diagnosis as IBS, haemorrhoidal bleeding, iron deficiency, no cause found, as appropriate. For the purposes of the study, this cohort was included and grouped as 'other functional diagnoses'. Inevitably, some patients were referred to the '2-week wait' colorectal clinic because their GP suspected colorectal cancer but in whom the '2-week wait' referral guidelines were not strictly fulfilled. These were managed no differently from other study patients. However, in recording fulfilment of the '2-week wait' guidelines, the judgement of both the GP and the responsible clinician had to concur.

Sample size estimation

It was expected that around 100 '2-week wait' patients per month would be referred to York Hospital, and it was estimated that 10% would have significant colonic neoplasia. With a sensitivity for FC of 95%, it was estimated that recruiting 800 patients would allow the sensitivity and specificity to be calculated to within ±5%, based on 95% confidence.

Statistical analysis

Negative predictive value (NPV), PPV, sensitivity, and specificity were estimated with their corresponding confidence intervals (95%).

RESULTS

Demographics

Of the 1250 patients attending the dedicated '2-week wait' colorectal clinics between September 2014 and September 2015, 777 patients consented to enter the study. Ultimately, 654 both provided a stool sample and completed all investigations, and their data are presented below. Of these patients, 56% were female and the median age was 69 years; 480 patients fulfilled historic fast-track criteria CG27, whereas 603 fulfilled the new guidance NG12 (Table 1) and 537 patients underwent full colonic evaluation in

Table 1. Patient demographics, presenting symptom complexes, colonic evaluations, and prescribed medicines implicated in gastrointestinal bleeding (*n* = 654)

	n	%
Median age, years (interquartile range)	69 (62–77)	
Female	368	56
Presenting symptoms and signs		
Fulfil fast-track criteria CG27	480	74
Change of bowel habit and bleeding >40 years	96	15
Rectal bleeding >60 years	51	8
Change of bowel habit >60 years	290	45
Right abdominal mass	22	3
Rectal mass	25	4
Iron deficiency anaemia	26	4
Fulfil fast-track criteria NG12	603	92
Colonic evaluation		
Full evaluation	537	82
Colonoscopy	373	57
CT colonography	126	19
Barium enema	38	6
CT abdomen and pelvis	138	21
Flexible sigmoidoscopy	161	25
Prescribed medicines implicated in GI bleeding		
None	494	76
Aspirin	65	10
NSAID	28	4
Warfarin	32	5
NOAC	12	1.5
Anti-platelet therapy	27	4

GI = gastrointestinal. NOAC = new oral anticoagulant. NSAID = nonsteroidal anti-inflammatory drug.

the form of colonoscopy, CT colonography, or barium enema. Others had CT abdomen and pelvis and flexible sigmoidoscopy because of their frailty. Gastroscopy or MRI were also performed as indicated. A total of 164 patients were on aspirin, anticoagulants, antiplatelet therapy, or NSAIDs.

Clinical outcome

In total, 39 patients had colorectal cancer, and two further upper gastrointestinal cancers were detected (which were included in the analysis). This gave a colorectal cancer diagnostic yield of 6.3% of referrals. All patients with colorectal cancer had a raised FC, except one low rectal cancer and two cancers arising from polyps, one of which was asymptomatic.

An additional 33 significant neoplastic polyps were identified, 13 of which were incidental. Three patients with neoplastic polyps had a normal FC, one of which was a high-grade dysplastic tubulovillous adenoma. Typical of clinical practice, a range of other organic enteric diseases was diagnosed. For some patients more than one diagnosis was entered (Table 2).

Diagnostic accuracy

The median FC result and the NPV, PPV, sensitivity, and specificity using an FC cut-off value of <50 mcg/g for colorectal cancer, significant neoplasia, and all organic enteric disease are presented below (the two upper gastrointestinal cancers were included in the analysis) (Table 3).

Similar results were found when looking exclusively at those patients who underwent colonoscopy: 98.4% (95% confidence interval [CI] = 94 to 100) NPV; 12.6% (95% CI = 9 to 18) PPV; 93.9% (95% CI = 78 to 99) sensitivity; and 36.2% (95% CI = 31 to 42) specificity. Of those diagnosed with functional disease,

Table 2. Incidence of colorectal cancer, adenomatous polyps ≥10 mm, organic enteric disease, and 'functional disease' in patients referred with suspected colorectal cancer (*n* = 656[a])

GI diagnoses	*n*	%
Neoplasia	74	11
All gastrointestinal cancers	41	6
Colorectal cancer	39	
Other GI cancer		
Oesophageal	1	
Ampulla of Vater	1	
All colorectal polyps ≥10 mm	33	5
High-grade dysplasia		
Tubulovillous	3	
Low-grade dysplasia		
Tubulovillous	23	
Tubular	7	
Non-neoplastic organic enteric disease	99	15
Ulcerative colitis	16	2
Crohn's disease	6	
Microscopic colitis	18	3
Symptomatic diverticular disease	43	7
Pancreatic insufficiency	3	
Radiation proctopathy	4	
Non-specific colitis	2	
Gastroenteritis	1	
Ischaemic colitis	1	
Solitary rectal ulcer syndrome	1	
Gastric ulcer	1	
Coeliac disease	1	
Hypothyroidism	1	
Appendicitis	1	
Other 'functional' diagnoses		
IBS	387	58
Haemorrhoidal bleeding	74	11
Iron deficiency, no cause found	30	5

[a]*In two patients there were two diagnoses. GI = gastrointestinal. IBS = irritable bowel syndrome.*

reassurance and simple guidance were given to the patients, who were then discharged. A total of 182 patients (27.8% of the study group) had a normal FC. Six-month follow-up data is now available, accessed from the hospital Core Patient Database, on 354 of the patients who entered the trial.

The rate of re-referral for lower gastrointestinal symptoms during this time was 4.0%. A 10 mm low-grade tubular adenoma was identified in one elderly patient whose FC had been 62 mcg/g but who had not previously had a full colonic evaluation. No other significant disease was diagnosed among those re-referred.

In Table 4, the diagnostic accuracy of FC is presented according to each of the criteria for '2-week wait' patient referral. Strict

Table 3. Diagnostic accuracy of faecal calprotectin for colorectal cancer, significant neoplasia, and organic enteric disease

	FC, mcg/g		NPV		PPV		Sensitivity		Specificity	
	Median	IQR	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
Neoplasia										
Cancer	227	94.5 to 496	98.6	95.7 to 99.6	8.7	6.3 to 11.9	92.7	79 to 98	35.2	31.5 to 39.2
Cancer and polyps	189.5	88 to 494	97.2	93.8 to 98.9	15.6	12.4 to 19.4	91.9	82.6 to 96.7	36.4	32.5 to 40.5
Organic enteric disease	232	79 to 580	89.4	84.3 to 93	32.7	28.4 to 37.4	86.1	79.7 to 90.8	39.8	35.4 to 44.3

IFC = faecal calprotectin. QR = interquartile range. NPV = negative predictive value. PPV = positive predictive value.

Table 4. Diagnostic accuracy of faecal calprotectin, based on criteria for suspected colorectal cancer referral

	n	Diagnosis	NPV, %	PPV, %	Sensitivity, %	Specificity, %
2WW guidance CG27	480	CRC	98	11	92	33
		Neoplasia	96	19	91	34
		OED	89	38	89	39
Bleeding and diarrhoea >40 years	96	CRC	100	19	100	40
		Neoplasia	97	30	95	42
		OED	94	56	95	53
Diarrhoea >60 years	288	CRC	99	7	93	32
		Neoplasia	97	13	90	33
		OED	88	33	86	36
Bleeding >60 years	50	CRC	92	14	83	27
		Neoplasia	92	30	92	32
		OED	85	46	89	35
Right abdominal mass	22	CRC	100	26	10	36
		Neoplasia	100	57	100	57
		OED	100	64	100	62
Rectal mass	24	CRC	83	44	89	33
		Neoplasia	83	78	93	56
		OED	83	78	93	56
Iron deficiency anaemia	26	CRC	100	22	100	14
		Neoplasia	100	22	100	14
		OED	100	26	100	15
2WW guidance NG12	603	CRC	98	9	93	35
		Neoplasia	97	16	92	36
		OED	91	34	88	40
Not within 2WW guidance	161	CRC	100	2	100	40
		Neoplasia	100	5	100	40
		OED	97	11	85	41

2WW = 2-week wait. CRC = colorectal cancer. OED = organic enteric disease. NPV = negative predictive value. PPV = positive predictive value.

adherence in referral practice to both CG27 and NG12 suspected cancer guidelines retained a high NPV and improved the PPV. Only five patients presented with colorectal neoplasia outside referral guidance, all of whom had an FC >100 mcg/g.

There were 24 (4%) patients who fulfilled NICE guidance NG12, section 1.3.4, where FOB testing is offered to lower-risk patients. Here, FC had an NPV of 100% and PPV of 5.3% for colorectal neoplasia.

Non-enteric and incidental disease

Referral into the '2-week wait' colorectal clinic resulted in the diagnosis of additional significant non-enteric disease and low-grade dysplastic sub-centimetre polyps (Table 5).

Manipulation of the FC cut-off to improve PPV for colorectal cancer and neoplasia

Current symptom-based referral guidelines accept a 3% risk of missing colorectal cancer. Accepting this risk, the FC cut-off can be altered to fix the NPV for colorectal cancer to 97% (Table 6).

This allows for an uplift in PPV and permits FC cut-off levels to be further modified according to specific patient symptomatology.[9]

DISCUSSION

Summary

The diagnosis of colorectal cancer is a major challenge for primary care. Gastrointestinal disorders account for ≥7.8% of all GP consultations, yet only one case of colorectal cancer a year will be seen by a GP.[15] Symptoms are non-specific.[9] It may be difficult for the GP to interpret referral guidance strictly and to respond to the concerns of an individual patient. Once the '2-week wait'

Table 5. Significant incidental non-enteric disease and diminutive polyps diagnosed after suspected colorectal cancer referral

	n
Cancer	
Renal cell	2
Peritoneal	1
Lung	1
Gynaecological	1
Prostate	1
Breast	1
Bladder	1
Colorectal polyps, mm	49
<5	27
5 to <9	22
Other	
Uterine fibroids	2
Ovarian cyst	1
Adrenal adenomata	1
Barrett's oesophagus	1
Mesenteric panniculitis	1
Gall stones	9
Chronic liver disease	2
Benign pancreatic disease	3
Lung disease	2
Abdominal aortic aneurysm	3
Benign renal tract disease	4

Table 6. The faecal calprotectin (FC) (mcg/g) can be manipulated, based on referral criteria to increase the PPV, assuming an NPV of 97%

Patient group	FC cut-off to achieve NPV of 97%, mcg/g	PPV, %
All	<110	10.8
Any change of bowel habit	<161	11.8
Looser and/or more frequent stools	<101	10.8
Rectal bleeding	<67	13.3

NPV = negative predictive value. PPV = positive predictive value.

referral is initiated, invasive investigative and treatment targets are imposed that consume secondary care clinical time, and endoscopic and radiological resource. Yet the rate of colorectal cancer diagnosis is only 6.3% in this study. Clearly, if a patient is symptomatic, a diagnosis needs to be made. But can resources be used safely and more cost effectively than at present? On the one hand, NICE guidance NG12 is set in the context of 50% of patients presenting with colorectal cancer outwith the '2-week wait' referral pathway. On the other hand, if criteria for suspected cancer are fulfilled, there is no opportunity for expectant care; this, despite 75% of patients proving to have functional disease. IBS is common in the elderly and responds well to simple therapies.

A more responsive model of care is needed that identifies risk of colorectal cancer and organic enteric disease, irrespective of the current '2-week wait' criteria; which identifies low-risk patients who can be managed expectantly in the first instance, those remaining symptomatic being referred routinely for assessment thereafter; and which directs the GP to consider non-enteric causes of the patient's symptoms. FC already has a number of benefits for use as a risk assessment tool. First, guidance already exists for its use, and it is increasingly becoming incorporated into primary care practice, albeit not where colorectal cancer is suspected.[16–18] Next, FC has a diagnostic accuracy across a range of organic enteric diseases and so offers the ideal of being a single, common tool for use. FC is relatively stable in stool, more so than haemoglobin. Lastly, a quantitative assay for FC allows for the customisation of the positivity threshold and so the promise of risk assessment stratification. In lower-risk patients it may be safe to raise the cut-off for FC from 50 mcg/g to 100 or 150, while it can be reduced below 50 mcg/g to further improve the NPV.[4,16–18]

Strengths and limitations

The primary aim of this study has been to determine the diagnostic accuracy of FC in patients with suspected colorectal cancer. This single-site observational study has been pragmatic in design, looking at the problem from the perspective of the GP. All patients referred with suspected colorectal cancer ('2-week wait') were eligible, so minimising selection bias. Investigations were arranged at the discretion of the responsible clinician who was blinded to the FC result. The stool sample was provided within the days prior to investigation. Typical of clinical practice, some patients were frail and investigations had to be couched appropriately. All significant organic enteric disease was recorded. Of the 1250 patients who attended the '2-week wait' colorectal clinics, 654 consented to enter and completed the study. Many patients attending this clinic were extremely anxious and it is believed that it was largely for this reason that some declined to enter into the study. There is no reason to consider selection bias. In 654 patients, FC has an NPV of 98.6% for colorectal cancer. This is the same as in the subpopulation who underwent colonoscopy. The authors judge this to be sufficiently accurate to make FC a safe risk assessment tool. Of the false-negative cancers, one was detected on per rectum examination, where there will have been insufficient mixing of calprotectin. The other two were polyp cancers. Over one-quarter of patients referred had a normal FC, the colorectal cancer risk for each being <2%; these patients might have been treated expectantly in the first place. Most patients within this group were successfully treated symptomatically once reassured.[17]

Importantly, the NPV was also high when significant adenomatous polyps were included in the analysis, this despite 40% being incidental. The cut-off for 'significant polyp' size was set at ≥10 mm.[14] The NPV of FC for all organic enteric disease was lower than is seen in a younger cohort, because of the increased incidence of non-inflammatory enteric disease in the elderly (such as microscopic colitis and pancreatic insufficiency).[4] Diverticulosis in the absence

of inflammation was a diagnosis made on occasion by the responsible clinician.

Having established its safety, the utility of FC next depends on its PPV. With a 50 mcg/g cut-off, the PPV for colorectal cancer was 8.7%; for all significant neoplasia 15.6%; and for organic enteric disease, it was 32.7%. This compares with a cancer diagnostic yield of 6.3% based on clinical judgement and an acceptability of 3% based on current referral guidance.[9] Clearly, the identification of all time-sensitive enteric disease is important, allowing other NICE guidance to be fulfilled, such as that for IBD.[19]

Comparison with existing literature

These findings are similar to other primary care referral or suspected colorectal cancer studies but the authors believe that this study gives a truer picture of the diagnostic challenge for the GP and patient when colorectal cancer is suspected.[20–22] Fewer than 50% of patients evaluated by Mowat *et al* were urgent referrals and the number with suspected cancer is not specified.[21] Two papers looked largely at IBD as the non-neoplastic organic enteric disease of interest but, in the present study, IBD represents only 25% of all organic enteric disease.[20,22]

Faecal immunochemical occult blood testing (FIT) is an important alternative screening technology. This too has a high NPV and the advantage of NICE guidance NG12 to support its use. It does not, however, dovetail as FC does with existing guidance for the screening of benign enteric disease.[5,16,17] Nonetheless, Mowat *et al* found it to be superior to FC; the colorectal cancer NPV for detectable faecal haemoglobin was 100%.[21] However, the resultant PPV was low at 6%. Furthermore, the authors believe the absence of non-IBD organic enteric disease skews the composite PPV as presented, in favour of FIT over FC. Others have found a similar NPV when comparing FC and FIT.[20,22] Currently, FIT is not a widely-available test for the symptomatic population in primary and secondary care.

Implications for research and practice

In the future, should the NPV be judged acceptable, then the utility of faecal biomarkers turns on their re-design of patient pathways of care, bridging safety, clinical effectiveness, and cost effectiveness. It is for this reason that this study has additionally assessed FC in the context of specific symptom complexes, looking at all patients whom GPs suspected of having colorectal cancer, as well as those particularly fulfilling elements of the original or updated NICE guidance. This updated NICE guidance accepts a 3% risk of missing colorectal cancer in setting symptom criteria for referral.[9] The FC level cut-off can be set to fit that risk and then be further modified, dependent upon symptom criteria. In this way, the PPV for colorectal cancer increases to 13.3%.[9] Models incorporating sophisticated risk scores to more efficiently stratify screening have been proposed; such models including symptomatology, age, family history, and biomarker cut-off may improve diagnostic yield.[23,24] Repeating the test might also improve the PPV without impacting the NPV.[25]

FC offers the promise of a risk stratification for all patients with lower gastrointestinal symptoms, rather than the current focus on those with suspected colorectal cancer that distorts clinical thinking and becomes increasingly inefficient as the symptom-based predictive value falls ever lower.[8] Large-scale, primary care based studies are required here. Whether FIT and FC have a synergistic or competing role is not clear.[23] In the meantime, FC may be considered in place of FOB testing to support NICE guidance NG12 in areas where the FIT is not currently available.

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Ethical approval

Ethical approval (REC14/EM/0217) was obtained to perform this study.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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