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Factors affecting clinical decision-making in inflammatory bowel disease and the role of point-of-care calprotectin

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Abstract

Objectives: Patient-reported symptoms correlate poorly with mucosal inflammation. Clinical decision-making may, therefore, not be based on objective evidence of disease activity. We conducted a study to determine factors associated with clinical decision-making in a secondary care inflammatory bowel disease (IBD) population, using a cross-sectional design.

Methods: Decisions to request investigations or escalate medical therapy were recorded from outpatient clinic encounters in a cohort of 276 patients with ulcerative colitis (UC) or Crohn's disease (CD). Disease activity was assessed using clinical indices, self-reported flare or faecal calprotectin ≥ 250 µg/g. Demographic, disease-related and psychological factors were assessed using validated questionnaires. Logistic regression was performed to determine the association between clinical decision-making and symptoms, mucosal inflammation and psychological comorbidity.

Results: Self-reported flare was associated with requesting investigations in CD [odds ratio (OR) 5.57; 95% confidence interval (CI) 1.84–17.0] and UC (OR 10.8; 95% CI 1.8–64.3), but mucosal inflammation was not (OR 1.62; 95% CI 0.49–5.39; and OR 0.21; 95% CI 0.21–1.05, respectively). Self-reported flare (OR 7.96; 95% CI 1.84–34.4), but not mucosal inflammation (OR 1.67; 95% CI 0.46–6.13) in CD, and clinical disease activity (OR 10.36; 95% CI 2.47–43.5) and mucosal inflammation (OR 4.26; 95% CI 1.28–14.2) in UC were associated with escalation of medical therapy. Almost 60% of patients referred for investigation had no evidence of mucosal inflammation.

Conclusions: Apart from escalation of medical therapy in UC, clinical decision-making was not associated with mucosal inflammation in IBD. The use of point-of-care calprotectin testing may aid clinical decision-making, improve resource allocation and reduce costs in IBD.

Keywords: biomarkers, Crohn's disease, ulcerative colitis, calprotectin

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal (GI) tract, collectively known as the inflammatory bowel diseases (IBD). The combined prevalence of these conditions in Western populations is 450 per 100,000.[1] To date, their aetiology is uncertain, but it is thought that they occur as a consequence of a combination of host genetic and environment factors, including dysregulation of the enteric immune system and alterations in the intestinal microbiome.[2,3]

The natural history of IBD is that of quiescence, interspersed with episodic flares of disease activity. Maintenance of glucocorticosteroid-free remission and the avoidance of surgical intervention are the principal aims of medical management. Evaluation of longitudinal disease activity, traditionally centred on patient-reported symptoms, forms the

mainstay of outpatient disease activity assessment, with those with symptoms suggestive of clinically active disease likely to undergo endoscopic and radiological investigations to confirm this. Despite this, the correlation between symptom reporting and the presence of mucosal inflammation is poor, particularly in CD.[4,5]

GI symptoms arising in the absence of inflammation, which are reported to affect up to 40% of patients with IBD,[6] may lead to uncertainty in disease activity assessment when based on patient-reported symptoms alone. Moreover, the presence of somatoform behaviour, which is independently associated with the reporting of irritable bowel syndrome (IBS)-type symptoms,[7] may complicate this situation. Therefore reliance on symptom reporting alone could result in over-investigation and overtreatment of patients, leading to significant financial implications, a potential for adverse events, and diminishing beneficial returns in terms of disease outcome,[8] while neglecting asymptomatic patients with ongoing occult inflammatory activity.

Faecal biomarkers of intestinal inflammation, including faecal calprotectin (FC), provide a quantifiable, noninvasive and relatively inexpensive measure of mucosal inflammation. Their use is advocated in the differentiation of organic and functional disease[9] and, more recently, has been recommended for the monitoring of disease activity in IBD.[10–12] When compared with endoscopic disease activity assessment in IBD, FC outperforms both clinical disease activity assessment and serum markers of inflammation, including C-reactive protein (CRP),[13,14] and has a sensitivity and specificity for the identification of active inflammation at endoscopy of 93.5% and 79.2%, respectively.[15]

Based on our previous findings,[4] where the association between clinical disease activity scores and the presence of mucosal inflammation, as defined by FC, was poor, our hypothesis was that there would be no association between clinical decision-making and the presence of mucosal inflammation defined using an FC $\geq$ 250 μg/g, particularly in patients with CD. If proven, this may support the routine use of point-of-care FC testing as a cost-effective method of disease assessment, which may improve clinical decision-making, facilitate appropriate allocation of scarce resources, and reduce the costs of managing outpatients with IBD. We aimed to compare the cost of investigation requesting based on the current system of physician global assessment with a novel hypothetical model where any patient being considered for investigation would undergo point-of-care FC testing, with endoscopic or radiological investigations subsequently requested only in those with evidence of mucosal inflammation.

Materials and methods

Participants and setting

The study was conducted at St James's University Hospital, Leeds, UK, which serves a local population of 800,000 people. Consecutive individuals aged over 16 years with an established radiological, histological or endoscopic diagnosis of CD or UC who were attending the IBD clinic were approached about the study. Exclusion criteria were an inability to understand written English, a diagnosis of IBD unclassified, and anyone with an end ileostomy or colostomy, due to the difficulties in assessing disease activity indices in these patients. Patients who had undergone radiological or endoscopic investigations in the preceding 90 days were also excluded as the results of these investigations were deemed likely to have affected any subsequent clinical decision-making. Finally, those with isolated upper GI or isolated fistulising perianal CD were also excluded, as the utility of FC in these subsets of patients is uncertain. At the clinic attendance, prior to the consultation with a gastroenterologist, individuals were presented with an information sheet explaining the nature of the study. Those who agreed to take part provided written informed consent at this visit. The study was approved by the Yorkshire and Humber research ethics committee in November 2012 (12/YH/0443), and data collection continued until June 2015. Questionnaire outcomes and FC results were not available to the consulting physician at any time. Once the study questionnaires were completed, patients proceeded to clinic consultation as normal without any intervention from the study investigators.

Data collection and synthesis

Demographic data and disease characteristics. Once informed consent was obtained, demographic data including sex, age, ethnicity,

marital status, educational level, tobacco and alcohol use, weight (kg) and height (m), which were used to calculate body mass index (BMI), were collected. Medication history, including current use of 5 aminosalicylates (5-ASAs), glucocorticosteroids, immunosuppressants (including thiopurines, methotrexate or mycophenolate mofetil) or biological therapies (infliximab, adalimumab or certolizumab) was noted. Disease distribution and behaviour, as defined by the Montreal classification,[16] and any previous intestinal resection related to CD were also recorded.

Definition and assessment of decision to request investigation or escalate treatment. Clinic letters were reviewed to determine clinician decision-making regarding investigation requesting or escalation of treatment in response to patient symptoms. Relevant investigations included in this definition were computed tomography enterography, magnetic resonance enterography, small bowel meal, colonoscopy, flexible sigmoidoscopy or wireless capsule endoscopy for CD and colonoscopy or sigmoidoscopy for UC. Colonoscopies requested solely for routine colitis surveillance were not included.[17] Routine investigations requested for annual disease assessment in patients treated with anti-tumour necrosis factor α (TNFα) drugs were not included, nor were initial investigations requested to assess the extent of disease in patients with newly diagnosed IBD. Escalation of treatment was defined as either the addition of a new treatment or an increase in dosage of a current medication. Medications included in this definition were 5-ASAs, glucocorticosteroids, immunomodulators and biological therapies.

Assessment of IBD activity and mucosal inflammation. Assessment of clinical IBD activity was performed using the Harvey–Bradshaw Index (HBI) for CD,[18] and the Simple Clinical Colitis Activity Index (SCCAI) for UC,[19] with a score of 5 used to define clinically active disease for both, as previously recommended.[20,21] Patients completed these questionnaires prior to consultation, and the results were not available to the reviewing physician. In addition to this, participants were asked to report whether, in their own opinion, they were attending with a flare of disease activity, and to provide stool for quantitative FC analysis by enzyme-linked immunosorbent assay (Immundiagnostik, Bensheim, Germany), as an objective marker of mucosal inflammation. We used a cut-off of ≥250 μg/g of stool to define evidence of mucosal inflammation, in line with the European Crohn's and Colitis Organisation consensus on the use of FC to measure disease activity,[22] which other investigators have employed.[5,23,24] FC was requested at the time of clinic attendance and, for inclusion in the study, was returned within 7 days of this date. FC results were not available at the clinic visit, and FC testing was not routinely available to clinicians for disease monitoring in our centre at the time this study was conducted.

Reference standard used to define the presence of IBS-type symptoms. The presence or absence of IBS-type symptoms was assessed *via* the Rome III criteria,[25] according to the scoring algorithm proposed for use with the Rome III diagnostic questionnaire for the adult functional GI disorders. IBS-type symptoms were defined as present when an individual reported abdominal discomfort or pain with a frequency of 3 days per month over the last 3 months, with the onset of discomfort 6 months previously, associated with two or more of the following: an improvement in pain or discomfort with the passage of stool, more or less frequent bowel movements, or looser or harder stools.

Definition of anxiety or depression. Anxiety and depression data were collected using the Hospital Anxiety and Depression Scale (HADS).[26] This 14-item questionnaire consists of seven questions screening for the presence of anxiety symptoms, and seven for depression symptoms, with a four-point response for each item, ranging from 0 to 3. The total HADS score ranges from a minimum of 0 to a maximum of 21 for both anxiety and depression. Severity was categorised, according to total HADS score, into normal (total HADS depression or anxiety score 0–7), borderline normal (8–10) and abnormal (⩾11).[26]

Definition of somatisation severity using the Patient Health Questionnaire 15. Somatisation data were collected using the Patient Health Questionnaire 15 (PHQ-15), which is derived from the validated full PHQ.[27,28] The PHQ-15 enquires about the presence of 15 somatic symptoms (or symptom clusters) over the last 4 weeks, which contribute to over 90% of physical complaints reported in the outpatient environment.[29] Each individual was asked to rate the severity of each symptom as 'not bothered at all' (scored as 0), 'bothered a little' (scored as 1) or 'bothered a lot' (scored as 2). Therefore the total PHQ-15 score ranges from a

minimum of 0 to a maximum of 30. Somatisation severity was categorized, using the total PHQ-15 score, into high (total PHQ-15 ⩾15), medium (10–14), low (5–9) and minimal (⩽4) levels of somatisation severity.

Statistical analysis

Patients were dichotomised into those who were or were not referred for investigations, those who received or did not receive escalation of medical therapy, and those who received either referral for investigation or escalation of medical therapy, or those who received neither. We compared baseline demographic and disease-related characteristics, clinical disease activity indices, the presence or absence of symptoms meeting Rome III criteria for IBS, FC levels, the presence or absence of a self-reported flare of disease activity, as well as anxiety, depression and somatisation scores in patients with CD and UC separately, for each of these grouping variables. A χ^2 test was used for categorical data and an independent samples t test for continuous data. Due to multiple comparisons a two-tailed p value of less than 0.01 was considered significant for these analyses.

Independent factors associated with decisions to request investigations, escalate therapy, or request investigations and escalate medical therapy were determined for all patients with CD and UC separately by performing multivariate logistic regression to control for all demographic, disease-related and psychological variables. Results of multivariate logistic regression were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

We applied National Health Service (NHS) reference costs from 2015 in order to calculate the overall cost of potentially unnecessary investigations requested in patients with CD and UC without objective evidence of mucosal inflammation (defined by FC <250 μg/g). We compared the mean cost per patient referred for investigation based on physician global assessment with that of a hypothetical investigation requesting pathway when radiology and endoscopy investigations were only deemed necessary in patients with a FC ≥ 250 μg/g (Figure 1). In this hypothetical model, the cost of point-of-care FC analysis was applied to every patient who was referred for investigation, but only the cost of investigations performed in patients with evidence of mucosal inflammation after FC testing was included. An independent samples t test was used with a two-tailed p value less than 0.05 considered significant for these analyses. The cost of medication escalation was not included, due to the uncertainty regarding length of treatment.

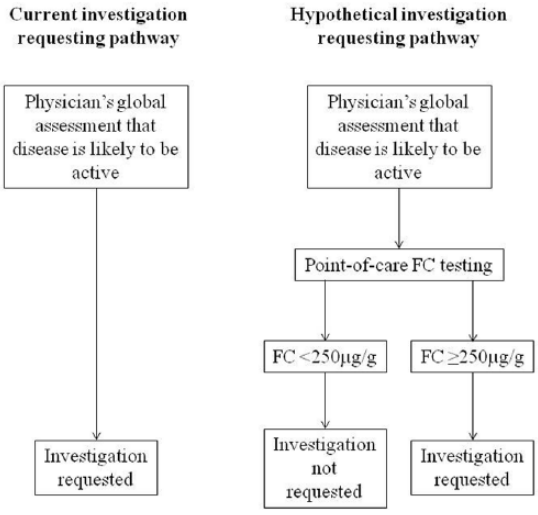

Figure 1. Current and hypothetical investigation requesting pathways. FC, faecal calprotectin.

Results

In total, 276 patients with IBD fulfilling our inclusion criteria consented to participate, had complete HBI or SCCAI data, and returned a FC sample for analysis within 7 days of their clinic attendance. Of these, 150 (54.3%) had confirmed CD and 126 (45.7%) UC.

Characteristics of patients with IBD according to decision to request investigations

Of the 150 patients with CD, 28 (18.7%) had an investigation requested. Fifteen (55.6%) of 28 patients in whom an investigation was requested self-reported a flare of disease activity, compared with 19 (15.6%) of 122 in whom investigation was not deemed necessary ($p < 0.001$). Investigation requesting was associated with the presence of clinically active CD, defined by HBI of 5, but no other demographic, disease-related or psychological factors. Specifically, the presence of mucosal inflammation, as defined by FC, was not associated with investigation requesting in CD (Table 1).

Table 1. Relationship between clinician investigation requests and personal and disease characteristics in Crohn's disease and ulcerative colitis.

	Crohn's disease ($n = 150$)			Ulcerative colitis ($n = 126$)		
	No investigation requested ($n = 122$)	Investigation requested ($n = 28$)	*p* value*	No investigation requested ($n = 105$)	Investigation requested ($n = 21$)	*p* value*
Mean age in years (SD)	46.0 (17.2)	47.9 (14.5)	0.59	50.7 (16.9)	52.0 (15.9)	0.75
Female sex (%)	78 (63.9)	15 (53.6)	0.31	56 (53.3)	14 (66.7)	0.26
Married or cohabiting (%)	74 (60.7)	20 (74.1)	0.19	76 (72.4)	16 (76.2)	0.72
University/postgraduate (%)	31 (25.6)	7 (25.0)	0.95	30 (29.1)	6 (28.6)	0.96
Mean BMI (SD)	26.7 (5.9)	26.6 (5.5)	0.92	26.4 (4.8)	28.8 (5.8)	0.06
Tobacco user (%)	22 (18.0)	8 (28.6)	0.21	6 (5.7)	1 (4.8)	0.86
Alcohol user (%)	74 (6.7)	17 (60.7)	1.00	76 (72.4)	13 (61.9)	0.34
Crohn's disease location (%)						
Ileal	28 (23.0)	7 (25.0)		N/A	N/A	
Colonic	38 (31.1)	5 (17.9)		N/A	N/A	
Ileocolonic	56 (45.9)	16 (57.1)	0.36	N/A	N/A	N/A
Crohn's disease behaviour (%)						
Nonstricturing, nonpenetrating	105 (86.1)	24 (85.7)		N/A	N/A	
Stricturing	12 (9.8)	3 (10.1)		N/A	N/A	
Penetrating	5 (4.1)	1 (3.6)	0.98	N/A	N/A	N/A
Perianal Crohn's disease (%)	12 (9.8)	2 (7.1)	0.66	N/A	N/A	N/A
Ulcerative colitis extent (%)						
Proctitis	N/A	N/A		33 (31.4)	5 (23.8)	
Left sided	N/A	N/A		47 (44.8)	11 (52.4)	
Extensive	N/A	N/A	N/A	25 (23.8)	5 (23.8)	0.76
5-ASA use (%)	33 (27.0)	9 (32.1)	0.59	83 (79.0)	18 (85.7)	0.48
Immunomodulator use (%)	53 (43.4)	13 (46.4)	0.77	21 (20.0)	4 (19.0)	0.92
Anti TNFα use (%)	35 (28.7)	4 (14.3)	0.12	2 (1.9)	0 (0.0)	0.52
Glucocorticosteroid use (%)	11 (9.0)	5 (17.9)	0.17	9 (8.6)	5 (23.8)	0.04
Previous intestinal resection (%)	40 (32.8)	13 (46.4)	0.17	N/A	N/A	N/A
Rome III IBS criteria fulfilled (%)	49 (40.2)	16 (57.1)	0.10	29 (27.6)	7 (33.3)	0.60
Self-reported flare (%)	19 (15.6)	15 (55.6)	<0.001	27 (25.7)	16 (76.2)	<0.001
Mean HBI/SCCAI score (SD)	4.1 (3.5)	5.9 (4.1)	0.02	3.7 (3.1)	6.5 (3.0)	<0.001
HBI ⩾5 (%)	41 (33.6)	17 (60.7)	0.008	N/A	N/A	N/A
Poor general wellbeing (%)	23 (18.9)	11 (39.3)	0.02	N/A	N/A	N/A
Moderate abdominal pain (%)	24 (19.7)	9 (32.1)	0.15	N/A	N/A	N/A
⩾3 stools/day (%)	41 (33.6)	14 (50.0)	0.10	N/A	N/A	N/A

(Continued)

Table 1. (Continued)

	Crohn's disease ($n = 150$)			Ulcerative colitis ($n = 126$)		
	No investigation requested ($n = 122$)	**Investigation requested ($n = 28$)**	***p* value***	**No investigation requested ($n = 105$)**	**Investigation requested ($n = 21$)**	***p* value***
Definite abdominal mass (%)	5 (4.1)	2 (7.1)	0.49	N/A	N/A	N/A
⩾1 associated condition (%)	28 (23.0)	7 (25.0)	0.82	N/A	N/A	N/A
SCCAI ⩾5 (%)	N/A	N/A	N/A	37 (35.2)	16 (76.2)	0.001
⩾4 stools/day (%)	N/A	N/A	N/A	33 (31.4)	12 (57.1)	0.03
⩾1 stool/night (%)	N/A	N/A	N/A	30 (28.6)	10 (47.6)	0.09
Urgency (%)	N/A	N/A	N/A	71 (67.6)	20 (95.2)	0.01
Rectal bleeding (%)	N/A	N/A	N/A	53 (50.5)	18 (85.7)	0.003
Poor or worse general wellbeing (%)	N/A	N/A	N/A	11 (10.5)	5 (23.8)	0.09
⩾1 associated condition (%)	N/A	N/A	N/A	15 (14.3)	3 (14.3)	1.00
Mean FC (SD)	445 (788)	712 (1082)	0.14	494 (681)	766 (1195)	0.15
FC ⩾250 µg/g (%)	47 (38.5)	12 (42.9)	0.67	46 (43.8)	8 (38.1)	0.63
Mean HADS anxiety score (SD)	7.5 (4.4)	7.5 (5.1)	0.97	7.5 (4.9)	8.1 (4.3)	0.61
Anxiety categories (%)						
Normal	68 (55.7)	15 (53.6)		54 (51.4)	11 (52.4)	
Borderline abnormal	23 (18.9)	5 (17.9)		23 (21.9)	4 (19.0)	
Abnormal	31 (25.4)	8 (28.6)	0.94	28 (26.7)	6 (28.6)	0.95
Mean HADS depression score (SD)	4.9 (4.2)	5.5 (4.3)	0.49	4.7 (4.3)	6.1 (3.9)	0.17
Depression categories (%)						
Normal	88 (72.1)	19 (67.9)		87 (83.7)	15 (71.4)	
Borderline abnormal	20 (16.4)	5 (17.9)		5 (4.8)	2 (9.5)	
Abnormal	14 (11.5)	4 (14.3)	0.89	12 (11.5)	4 (19.0)	0.41
Mean PHQ-15 score (SD)	9.9 (4.6)	11.8 (4.0)	0.04	8.7 (5.1)	12.0 (5.5)	0.009
PHQ-15 somatisation categories (%)						
Mild	14 (12.1)	0 (0.0)		20 (19.6)	1 (10.0)	
Low	42 (36.2)	9 (33.3)		33 (32.4)	4 (20.0)	
Medium	44 (37.9)	11 (40.7)		33 (32.4)	6 (30.0)	
High	16 (13.8)	7 (25.9)	0.15	16 (15.7)	8 (40.0)	0.08

*Independent samples *t*-test for comparison of continuous data and χ^2 test for comparison of categorical data.
5-ASA, 5 aminosalicylate; BMI, body mass index; FC, faecal calprotectin; HADS, Hospital Anxiety and Depression Scale; HBI, Harvey–Bradshaw Index; IBS, irritable bowel syndrome; N/A, not applicable; PHQ-15, Patient Health Questionnaire 15; SCCAI, Simple Clinical Colitis Activity Index; SD, standard deviation; TNF, tumour necrosis factor.

Of the 126 patients with UC, 21 (16.7%) had an investigation requested. Self-reported flare, clinical disease activity, the presence of rectal bleeding, and elevated mean PHQ-15 somatisation score were associated with investigation requesting. Again, the presence of mucosal inflammation was

Table 2. Relationship between clinician investigation requests and personal and disease characteristics in Crohn's disease and ulcerative colitis after logistic regression.

	Crohn's disease and investigation requesting OR (95%CI)	Ulcerative colitis and investigation requesting OR (95%CI)
Female sex	0.24 (0.07–0.80)	2.31 (0.47–11.36)
Age (per year)	1.00 (0.96–1.05)	1.01 (0.96–1.06)
Married or cohabiting	2.08 (0.62–7.00)	1.86 (0.33–10.5)
University/postgraduate	1.00 (0.24–4.07)	1.58 (0.25–9.90)
BMI (per kg/m^2)	1.01 (0.92–1.11)	1.13 (0.98–1.31)
Tobacco use	4.85 (1.19–19.8)	3.62 (0.20–66.9)
Alcohol use	1.77 (0.53–5.92)	2.49 (0.46–13.6)
5-ASA use	0.89 (0.24–3.27)	3.61 (0.36–36.6)
Immunomodulator use	0.97 (0.31–3.06)	0.89 (0.14–5.64)
Anti-TNFα use	0.60 (0.15–2.42)	N/A†
Glucocorticosteroid use	2.23 (0.45–11.1)	0.46 (0.06–3.29)
Previous intestinal resection	0.85 (0.26–2.78)	N/A
Rome III IBS criteria fulfilled	1.24 (0.37–4.10)	0.65 (0.11–3.76)
Self-reported flare	5.75 (1.84–17.0)	10.8 (1.80–64.3)
Total HBI ⩾5	1.87 (0.51–6.84)	N/A
Total SCCAI ⩾5	N/A	4.01 (0.77–21.1)
FC ⩾250 μg/g	1.62 (0.49–5.39)	0.21 (0.04–1.05)
Anxiety (per one-point change on HADS anxiety score)	0.89 (0.74–1.06)	0.70 (0.53–0.92)
Depression (per one-point change on HADS depression score)	0.98 (0.80–1.19)	1.38 (0.99–1.91)
Somatisation (per one-point change on PHQ-15 score)	1.16 (0.95–1.42)	1.11 (0.91–1.36)

*The use of anti-TNFα drugs for maintenance therapy in UC was approved by the National Institute of Health and Care Excellence in 2015. The number of UC anti-TNFα users in this cohort is therefore small. This variable has been excluded from multivariate analysis in UC.
5-ASA, 5 aminosalicylate; BMI, body mass index; CI, confidence interval; FC, faecal calprotectin; HADS, Hospital Anxiety and Depression Scale; HBI, Harvey–Bradshaw Index; IBS, irritable bowel syndrome; N/A, not applicable; OR, odds ratio; PHQ-15, Patient Health Questionnaire 15; SCCAI, Simple Clinical Colitis Activity Index; TNF, tumour necrosis factor; UC, ulcerative colitis.

not associated with investigation requesting in UC (Table 1).

After multivariate logistic regression, male sex, tobacco use and self-reported flare of disease activity were associated with investigation requesting in CD. Self-reported flare of disease activity and lower mean HADS anxiety scores were associated with investigation requesting in UC (Table 2).

Characteristics of patients with IBD according to decision to escalate medical treatment

Of the 150 patients with CD, 21 (14.0%) underwent escalation of medical treatment. Current glucocorticosteroid use, self-reported flare of disease activity, and two of the constituent items from the HBI score (poor or worse general health, and moderate or worse abdominal pain), but not a total HBI score of 5, were associated with escalation of medical treatment. The presence of

mucosal inflammation was not associated with clinician decisions to escalate medical treatment. Ten (47.6%) of 21 patients with CD who underwent escalation of medical therapy had no evidence of mucosal inflammation, as defined by FC (Table 3).

Of the 126 patients with UC, 35 (27.8%) underwent escalation of medical treatment. Younger age, self-reported flare, SCCAI score of 5, the passage of four or more stools per day, nocturnal passage of stools, urgency, rectal bleeding, higher mean somatisation scores, and the presence of mucosal inflammation were associated with escalation of medical treatment in UC. Eleven (31.5%) of 35 patients with UC who underwent escalation of medical therapy had no evidence of mucosal inflammation defined by FC (Table 3).

After multivariate logistic regression, younger age and self-reported flare, but not the presence of mucosal inflammation, were associated with escalation of medical therapy in CD. In UC, clinically active disease defined by total SCCAI score of 5 and the presence of mucosal inflammation were both associated with the decision to escalate medical treatment (Table 4).

Characteristics of patients with IBD according to decision to request investigations or escalate medical treatment

Of the 150 patients with CD, 44 (29.3%) were referred for an investigation or underwent escalation of medical treatment. In univariate analyses, self-reported flare, anti-TNFα use, and clinically active disease, including poor general wellbeing and abdominal pain, were associated with the clinical decision to request investigations or escalate treatment in these patients. There was no difference in mean FC between patients with CD being referred for investigations or receiving escalation of medical treatment compared with those who were not (570 *versus* 464; $p = 0.49$). In total, 39 (36.8%) of 106 patients with CD who were neither referred for investigation nor had their medical therapy escalated had evidence of mucosal inflammation defined by FC ≥ 250 μg/g (Table 5).

Of the 126 patients with UC, 47 (37.3%) were referred for an investigation or underwent escalation of medical treatment. Glucocorticosteroid use, self-reported flare of disease activity, clinically active disease defined by SCCAI score of 5, as well as the passage of four or more stools per day, nocturnal passage of stools, urgency and rectal bleeding were associated with referral for investigation or escalation of medical treatment. Mean FC results (901 *versus* 323; $p < 0.001$) and mean somatisation scores (11.1 *versus* 8.1; $p = 0.002$) were significantly higher in patients with UC being referred for investigations or receiving escalation of medical treatment compared with those who were not. In total, 27 (34.2%) of 79 patients with UC who were neither referred for investigation nor had their medical treatment escalated had evidence of mucosal inflammation defined by FC ≥250 μg/g (Table 5).

After multivariate logistic regression, being married or cohabiting, and a self-reported flare of disease activity, but not the presence of mucosal inflammation, were associated with investigation requesting or escalation of medical treatment in CD. In UC, self-reported flare and clinically active disease defined by SCCAI score ≥ 5 were associated with these clinical decisions, but again not the presence of mucosal inflammation (Table 6).

Costs of investigation requesting in IBD

Of the 28 patients with CD who were referred for investigations, 16 (57.1%) had no evidence of mucosal inflammation, defined by FC < 250 μg/g. In UC, the corresponding figure was 13 (61.9%) of 21 patients referred for investigations. The cost of these potentially unnecessary investigations is described in Supplementary Table 1. In both CD and UC, the mean cost of investigation per patient using the current investigation requesting pathway was significantly more expensive than when the hypothetical investigation requesting pathway (Figure 1) was used (£297.77 *versus* £195.71; $p = 0.004$ and £404.29 *versus* £171.44; $p < 0.001$, respectively).

Discussion

In this study we have demonstrated that the presence of active mucosal inflammation was not associated with investigation requesting for disease activity assessment in IBD. In this instance, self-reported flare of disease activity was the most consistent factor associated with a clinician's

Table 3. Relationship between clinician decisions to escalate treatment and personal and disease characteristics in Crohn's disease and ulcerative colitis.

	Crohn's disease ($n = 150$)			Ulcerative colitis ($n = 126$)		
	No escalation ($n = 129$)	Escalation ($n = 21$)	*p* value*	No escalation ($n = 91$)	Escalation ($n = 35$)	*p* value*
Mean age in years (SD)	47.0 (16.7)	42.8 (16.5)	0.29	53.4 (16.5)	44.4 (15.3)	0.006
Female sex (%)	78 (60.5)	15 (71.4)	0.34	49 (53.8)	21 (60.0)	0.53
Married or cohabiting (%)	77 (60.2)	17 (81.0)	0.07	66 (72.5)	26 (74.3)	0.84
University/postgraduate (%)	31 (24.2)	7 (33.3)	0.37	23 (25.8)	13 (37.1)	0.21
Mean BMI (SD)	26.6 (5.6)	27.0 (7.2)	0.76	26.5 (5.2)	27.6 (4.8)	0.30
Tobacco user (%)	26 (20.2)	4 (19.0)	0.91	4 (4.4)	3 (8.6)	0.36
Alcohol user (%)	81 (62.8)	10 (47.6)	0.19	65 (71.4)	24 (68.6)	0.75
Crohn's disease location (%)						
Ileal	27 (20.9)	8 (38.1)		N/A	N/A	
Colonic	40 (31.0)	3 (14.3)		N/A	N/A	
Ileocolonic	62 (48.1)	10 (47.6)	0.13	N/A	N/A	N/A
Crohn's disease behaviour (%)						
Nonstricturing, nonpenetrating	109 (84.5)	20 (95.2)		N/A	N/A	
Stricturing	14 (10.9)	1 (4.8)		N/A	N/A	
Penetrating	6 (4.7)	0 (0.0)	0.39	N/A	N/A	N/A
Perianal Crohn's disease (%)	12 (9.3)	2 (9.5)	0.97	N/A	N/A	N/A
Ulcerative colitis extent (%)						
Proctitis	N/A	N/A		24 (26.4)	14 (40.0)	
Left sided	N/A	N/A		44 (48.4)	14 (40.0)	
Extensive	N/A	N/A	N/A	23 (25.3)	7 (20.0)	0.33
5-ASA use (%)	34 (26.4)	8 (38.1)	0.27	73 (80.2)	28 (80.0)	0.98
Immunomodulator use (%)	59 (45.7)	7 (33.3)	0.29	19 (20.9)	6 (17.1)	0.64
Anti TNFα use (%)	37 (28.7)	2 (9.5)	0.06	2 (2.2)	0 (0.0)	0.38
Glucocorticosteroid use (%)	10 (7.8)	6 (28.6)	0.004	7 (7.7)	7 (20.0)	0.05
Previous intestinal resection (%)	48 (37.2)	5 (23.8)	0.23	N/A	N/A	N/A
Rome III IBS criteria fulfilled (%)	57 (44.2)	8 (38.1)	0.60	23 (25.3)	13 (37.1)	0.19
Self-reported flare (%)	22 (17.2)	12 (57.1)	<0.001	20 (22.0)	23 (65.7)	<0.001
Mean HBI/SCCAI score (SD)	4.1 (3.6)	6.2 (3.7)	0.02	3.1 (2.8)	6.8 (2.7)	<0.001
HBI ⩾5 (%)	46 (35.7)	12 (57.1)	0.06	N/A	N/A	N/A
Poor general wellbeing (%)	(18.6)	10 (47.6)	0.003	N/A	N/A	N/A
Moderate abdominal pain (%)	22 (17.1)	11 (52.4)	<0.001	N/A	N/A	N/A
⩾3 stools/day (%)	45 (34.9)	10 (47.6)	0.26	N/A	N/A	N/A
Definite abdominal mass (%)	6 (4.7)	1 (4.8)	0.98	N/A	N/A	N/A

(Continued)

Table 3. (Continued)

	Crohn's disease ($n = 150$)			Ulcerative colitis ($n = 126$)		
	No escalation ($n = 129$)	Escalation ($n = 21$)	*p* value*	No escalation ($n = 91$)	Escalation ($n = 35$)	*p* value*
⩾1 associated condition (%)	28 (21.7)	7 (33.3)	0.24	N/A	N/A	N/A
SCCAI ⩾5 (%)	N/A	N/A	N/A	25 (27.5)	28 (80.0)	<0.001
⩾4 stools/day (%)	N/A	N/A	N/A	22 (24.2)	23 (65.7)	<0.001
⩾1 stool/night (%)	N/A	N/A	N/A	22 (24.2)	18 (51.4)	0.003
Urgency (%)	N/A	N/A	N/A	58 (63.7)	33 (94.3)	0.001
Rectal bleeding (%)	N/A	N/A	N/A	41 (45.1)	30 (85.7)	<0.001
Poor or worse general wellbeing (%)	N/A	N/A	N/A	8 (8.8)	8 (22.9)	0.03
⩾1 associated condition (%)	N/A	N/A	N/A	14 (15.4)	4 (11.4)	0.57
Mean FC (SD)	472 (805)	638 (1114)	0.41	375 (656)	965 (947)	<0.001
FC ⩾250 µg/g (%)	48 (37.2)	11 (52.4)	0.19	30 (33.0)	24 (68.6)	<0.001
Mean HADS anxiety score (SD)	7.4 (4.5)	7.6 (4.8)	0.90	7.0 (4.7)	8.9 (5.1)	0.05
Anxiety categories (%)						
Normal	71 (55.0)	12 (57.1)		49 (53.8)	16 (45.7)	
Borderline abnormal	25 (19.4)	3 (14.3)		22 (24.2)	5 (14.3)	
Abnormal	33 (25.6)	6 (28.6)	0.85	20 (22.0)	14 (40.0)	0.10
Mean HADS depression score (SD)	4.9 (4.3)	5.3 (3.8)	0.69	4.5 (4.1)	5.9 (4.5)	0.10
Depression categories (%)						
Normal	92 (71.3)	15 (71.4)		77 (85.6)	25 (71.4)	
Borderline abnormal	21 (16.3)	4 (19.0)		4 (4.4)	3 (8.6)	
Abnormal	16 (12.4)	2 (9.5)	0.90	9 (10.0)	7 (20.0)	0.19
Mean PHQ-15 score (SD)	10.1 (4.6)	11.1 (4.0)	0.37	8.4 (5.2)	11.5 (4.7)	0.003
PHQ-15 somatisation categories (%)						
Mild	13 (10.7)	1 (4.8)		20 (22.5)	2 (6.1)	
Low	42 (34.4)	9 (42.9)		29 (32.6)	8 (24.2)	
Medium	50 (41.0)	5 (23.8)		27 (30.0)	12 (36.4)	
High	17 (13.9)	6 (28.6)	0.19	13 (14.6)	11 (33.3)	0.03

*Independent samples *t*-test for comparison of continuous data and χ^2 test for comparison of categorical data.
5-ASA, 5 aminosalicylate; BMI, body mass index; FC, faecal calprotectin; HADS, Hospital Anxiety and Depression Scale; HBI, Harvey–Bradshaw Index; IBS, irritable bowel syndrome; N/A, not applicable; PHQ-15, Patient Health Questionnaire 15; SCCAI, Simple Clinical Colitis Activity Index; SD, standard deviation; TNF, tumour necrosis factor.

decision to request investigations in both CD and UC. In CD, there was no association between the presence of mucosal inflammation and clinician decisions to escalate medical treatment. Again, patient self-report of disease activity had the strongest association with a decision to escalate medical treatment. In UC, both the presence of symptoms consistent with clinically active disease, and the presence of mucosal inflammation were associated with escalation of medical

Table 4. Relationship between clinician decisions to escalate treatment and personal and disease characteristics in Crohn's disease and ulcerative colitis after logistic regression.

	Crohn's disease and escalation OR (95%CI)	Ulcerative colitis and escalation OR (95%CI)
Female sex	1.16 (0.29–4.60)	1.54 (0.40–5.93)
Age (per year)	0.94 (0.90–0.99)	0.96 (0.92–1.01)
Married or cohabiting	4.56 (0.92–22.5)	1.19 (0.26–5.31)
University/postgraduate	1.22 (0.30–4.91)	2.26 (0.52–9.86)
BMI (per kg/m^2)	0.99 (0.88–1.12)	1.05 (0.93–1.18)
Tobacco use	0.79 (0.14–4.40)	1.46 (0.09–22.69)
Alcohol use	0.39 (0.10–1.52)	1.14 (0.38–4.59)
5-ASA use	1.07 (0.24–4.82)	0.90 (0.18–4.39)
Immunomodulator use	0.26 (0.06–1.14)	0.41 (0.47–18.68)
Anti-TNFα use	0.64 (0.11–3.84)	N/A[a]
Glucocorticosteroid use	4.23 (0.74–24.1)	2.97 (0.47–18.68)
Previous intestinal resection	0.42 (0.09–1.91)	N/A
Rome III IBS criteria fulfilled	0.68 (0.17–2.73)	1.24 (0.31–5.03)
Self-reported flare	7.96 (1.84–34.4)	2.39 (0.64–8.87)
Total HBI ⩾5	3.53 (0.74–16.89)	N/A
Total SCCAI ⩾5	N/A	10.36 (2.47–43.5)
FC ⩾250 μg/g	1.67 (0.46–6.13)	4.26 (1.28–14.2)
Anxiety (per one-point change on HADS anxiety score)	0.98 (0.80–1.19)	1.04 (0.88–1.25)
Depression (per one-point change on HADS depression score)	1.11 (0.88–1.40)	0.91 (0.73–1.14)
Somatisation (per one-point change on PHQ-15 score)	0.90 (0.71–1.15)	1.01 (0.85–1.21)

*The use of anti-TNFα drugs for maintenance therapy in UC was approved by the National Institute of Health and Care Excellence in 2015. The number of UC anti-TNFα users in this cohort is therefore small. This variable has therefore been excluded from multivariate analysis in UC.
5-ASA, 5 aminosalicylate; BMI, body mass index; CI, confidence interval; FC, faecal calprotectin; HADS, Hospital Anxiety and Depression Scale; HBI, Harvey–Bradshaw Index; IBS, irritable bowel syndrome; N/A, not applicable; OR, odds ratio; PHQ-15, Patient Health Questionnaire 15; SCCAI, Simple Clinical Colitis Activity Index; TNF, tumour necrosis factor; UC, ulcerative colitis.

therapy. After multivariate logistic regression, the presence of functional symptoms and psychological comorbidity, specifically somatisation, was not associated with an increase in investigation requesting or escalation of medical therapy in either CD or UC. Overall, more than one third of patients with CD and UC were neither referred for investigations nor had their medical therapy escalated despite having evidence of occult mucosal inflammation, based on FC results that were not available to the attending physician at the time of clinic visit.

To the best of our knowledge, this is the only study to address the association between demographic, disease-related and psychological factors, and clinical decision-making in IBD, and to explore the impact of these decisions on costs. Strengths of this study include the well characterised group of consecutive, unselected patients

Table 5. Relationship between clinician investigation requests or decisions to escalate treatment and personal and disease characteristics in Crohn's disease and ulcerative colitis.

	Crohn's disease ($n = 150$)			Ulcerative colitis ($n = 126$)		
	No investigation or escalation ($n = 106$)	Investigation or escalation ($n = 44$)	*p* value*	No investigation or escalation ($n = 79$)	Investigation or escalation ($n = 47$)	*p* value*
Mean age in years (SD)	46.3 (17.3)	46.6 (15.4)	0.90	52.9 (16.7)	47.5 (16.1)	0.08
Female sex (%)	65 (61.3)	28 (63.6)	0.79	41 (51.9)	29 (61.7)	0.28
Married or cohabiting (%)	61 (57.5)	33 (76.7)	0.03	57 (72.2)	35 (74.5)	0.78
University/postgraduate (%)	26 (24.8)	12 (27.3)	0.75	18 (23.4)	18 (38.3)	0.08
Mean BMI (SD)	26.4 (5.6)	27.2 (6.4)	0.49	26.3 (5.0)	27.6 (5.1)	0.19
Tobacco user (%)	19 (17.9)	11 (25.0)	0.32	4 (5.1)	3 (6.4)	0.75
Alcohol user (%)	67 (63.2)	24 (54.5)	0.32	58 (73.4)	31 (66.0)	0.37
Crohn's disease location (%)						
Ileal	22 (20.8)	13 (29.5)		N/A	N/A	
Colonic	35 (33.0)	8 (18.2)		N/A	N/A	
Ileocolonic	49 (46.2)	23 (52.3)	0.16	N/A	N/A	N/A
Crohn's disease behaviour (%)						
Nonstricturing, nonpenetrating	90 (84.9)	39 (88.6)		N/A	N/A	
Stricturing	11 (10.4)	4 (9.1)		N/A	N/A	
Penetrating	5 (4.7)	1 (2.3)	0.75	N/A	N/A	N/A
Perianal Crohn's disease (%)	11 (10.4)	3 (6.8)	0.50	N/A	N/A	N/A
Ulcerative colitis extent (%)						
Proctitis	N/A	N/A		23 (29.1)	15 (31.9)	
Left sided	N/A	N/A		36 (45.6)	22 (46.8)	
Extensive	N/A	N/A	N/A	20 (25.3)	10 (21.3)	0.87
5-ASA use (%)	28 (26.4)	14 (31.8)	0.50	63 (79.7)	38 (80.9)	0.88
Immunomodulator use (%)	50 (47.2)	16 (36.4)	0.23	16 (20.3)	9 (19.1)	0.88
Anti TNFα use (%)	34 (32.1)	5 (11.4)	0.008	2 (2.5)	0 (0.0)	0.27
Glucocorticosteroid use (%)	8 (7.5)	8 (18.2)	0.06	4 (5.1)	10 (21.3)	0.005
Previous intestinal resection (%)	36 (34.0)	17 (38.6)	0.59	N/A	N/A	N/A
Rome III IBS criteria fulfilled (%)	42 (39.6)	23 (52.3)	0.16	19 (24.1)	17 (36.2)	0.15
Self-reported flare (%)	12 (11.3)	22 (51.2)	<0.001	11 (13.9)	32 (68.1)	<0.001
Mean HBI/SCCAI score (SD)	3.8 (3.4)	5.8 (3.9)	0.002	2.8 (2.6)	6.5 (2.8)	<0.001
HBI ⩾5 (%)	33 (31.1)	25 (56.8)	0.003	N/A	N/A	N/A
Poor general wellbeing (%)	17 (16.0)	17 (38.6)	0.003	N/A	N/A	N/A
Moderate abdominal pain (%)	16 (15.1)	17 (38.6)	0.002	N/A	N/A	N/A

(Continued)

Table 5. (Continued)

	Crohn's disease ($n = 150$)			Ulcerative colitis ($n = 126$)		
	No investigation or escalation ($n = 106$)	**Investigation or escalation ($n = 44$)**	***p* value***	**No investigation or escalation ($n = 79$)**	**Investigation or escalation ($n = 47$)**	***p* value***
⩾3 stools/day (%)	34 (32.1)	21 (47.7)	0.07	N/A	N/A	N/A
Definite abdominal mass (%)	4 (3.8)	3 (6.8)	0.42	N/A	N/A	N/A
⩾1 associated condition (%)	23 (21.7)	12 (27.3)	0.46	N/A	N/A	N/A
SCCAI ⩾5 (%)	N/A	N/A	N/A	17 (21.5)	36 (76.6)	<0.001
⩾4 stools/day (%)	N/A	N/A	N/A	16 (20.3)	29 (61.7)	<0.001
⩾1 stool/night (%)	N/A	N/A	N/A	17 (21.5)	23 (48.9)	0.001
Urgency (%)	N/A	N/A	N/A	47 (59.5)	44 (93.6)	<0.001
Rectal bleeding (%)	N/A	N/A	N/A	32 (40.5)	39 (83.0)	<0.001
Poor or worse general wellbeing (%)	N/A	N/A	N/A	6 (7.6)	10 (21.3)	0.03
⩾1 associated condition (%)	N/A	N/A	N/A	11 (13.9)	7 (14.9)	0.88
Mean FC (SD)	464 (831)	570 (909)	0.49	323 (465)	901 (1054)	<0.001
FC ⩾250 µg/g (%)	39 (36.8)	20 (45.5)	0.32	27 (34.2)	27 (57.4)	0.01
Mean HADS anxiety score (SD)	7.3 (4.3)	7.9 (4.9)	0.48	7.1 (4.9)	8.3 (4.7)	0.21
Anxiety categories (%)						
Normal	60 (56.6)	23 (52.3)		41 (51.9)	24 (51.1)	
Borderline abnormal	21 (19.8)	7 (15.9)		19 (24.1)	8 (17.0)	
Abnormal	25 (23.6)	14 (31.8)	0.56	19 (24.1)	15 (31.9)	0.51
Mean HADS depression score (SD)	4.7 (4.3)	5.8 (4.0)	0.14	4.4 (4.2)	5.7 (4.2)	0.10
Depression categories (%)						
Normal	78 (73.6)	29 (65.9)		67 (85.9)	35 (74.5)	
Borderline abnormal	16 (15.1)	9 (20.5)		3 (3.8)	4 (8.5)	
Abnormal	12 (11.3)	6 (13.6)	0.63	8 (10.3)	8 (17.0)	0.27
Mean PHQ-15 score (SD)	9.7 (4.6)	11.5 (4.1)	0.02	8.1 (5.3)	11.1 (4.7)	0.002
PHQ-15 somatisation categories (%)						
Mild	13 (13.0)	1 (2.3)		19 (24.4)	3 (6.8)	
Low	35 (35.0)	16 (37.2)		26 (33.3)	11 (25.0)	
Medium	41 (41.0)	14 (32.6)		22 (28.2)	17 (38.6)	
High	11 (11.0)	12 (27.9)	0.02	11 (14.1)	13 (29.5)	0.02

*Independent samples *t*-test for comparison of continuous data and χ^2 test for comparison of categorical data.
5-ASA, 5 aminosalicylate; BMI, body mass index; FC, faecal calprotectin; HADS, Hospital Anxiety and Depression Scale; HBI, Harvey–Bradshaw Index; IBS, irritable bowel syndrome; N/A, not applicable; PHQ-15, Patient Health Questionnaire 15; SCCAI, Simple Clinical Colitis Activity Index; SD, standard deviation; TNF, tumour necrosis factor.

Table 6. Relationship between clinician investigation requests or decisions to escalate treatment and personal and disease characteristics in Crohn's disease and ulcerative colitis after logistic regression.

	Crohn's disease and investigation or escalation OR (95%CI)	Ulcerative colitis and investigation or escalation OR (95%CI)
Female sex	0.58 (0.21–1.65)	2.66 (0.60–11.7)
Age (per year)	0.99 (0.95–1.02)	0.99 (0.95–1.03)
Married or cohabiting	3.24 (1.09–9.59)	1.48 (0.33–6.74)
University/postgraduate	1.22 (0.38–4.00)	3.74 (0.81–17.3)
BMI (per kg/m^2)	1.03 (0.95–1.11)	1.07 (0.95–1.21)
Tobacco use	2.63 (0.76–9.04)	0.69 (0.03–14.3)
Alcohol use	0.85 (0.30–2.40)	1.64 (0.38–7.04)
5-ASA use	0.81 (0.26–2.56)	0.93 (0.19–4.42)
Immunomodulator use	0.42 (0.15–1.15)	0.55 (0.10–3.05)
Anti-TNFα use	0.43 (0.12–1.55)	N/A†
Glucocorticosteroid use	2.09 (0.47–9.36)	4.17 (0.50–34.5)
Previous intestinal resection	0.67 (0.23–1.91)	N/A
Rome III IBS criteria fulfilled	1.07 (0.37–3.08)	1.50 (0.32–7.09)
Self-reported flare	8.23 (2.69–25.1)	5.63 (1.50–21.2)
Total HBI ⩾5	1.95 (0.62–6.08)	N/A
Total SCCAI ⩾5	N/A	20.2 (4.25–96.5)
FC ⩾250 µg/g	1.53 (0.55–4.25)	2.06 (0.60–7.13)
Anxiety (per one-point change on HADS anxiety score)	0.93 (0.80–1.09)	0.86 (0.71–1.05)
Depression (per one-point change on HADS depression score)	1.05 (0.89–1.24)	1.02 (0.80–1.30)
Somatisation (per one-point change on PHQ-15 score)	1.05(0.88–1.26)	0.99 (0.83–1.19)

*The use of anti-TNFα drugs for maintenance therapy in UC was approved by the National Institute of Health and Care Excellence in 2015. The number of UC anti-TNFα users in this cohort is therefore small. This variable has therefore been excluded from multivariate analysis in UC.
5-ASA, 5 aminosalicylate; BMI, body mass index; CI, confidence interval; FC, faecal calprotectin; HADS, Hospital Anxiety and Depression Scale; HBI, Harvey–Bradshaw Index; IBS, irritable bowel syndrome; N/A, not applicable; OR, odds ratio; PHQ-15, Patient Health Questionnaire 15; SCCAI, Simple Clinical Colitis Activity Index; TNF, tumour necrosis factor; UC, ulcerative colitis.

who provided complete clinical and psychological data. These patients were recruited from a secondary care population, and the study was conducted alongside routine clinical care, therefore maximising the generalisability of our findings. Our use of validated questionnaires for the assessment of clinical disease activity,[18,19] IBS symptoms,[25] anxiety,[26] depression[26] and somatisation[,28] is also a strength. There are several limitations associated with studies of this nature. First, the cross-sectional design means that the relationship between demographic, disease-related and psychological factors, and clinical decision-making can only be associative, and the relative influence of these individual factors on decisions to investigate or escalate medical treatment cannot be ascertained. Furthermore, the impact of previous consultations on clinician

decision-making is uncertain, but may be substantial, and is not accounted for. We were unable to account for the influence of current glucocorticosteroid use on the decision to escalate medical therapy. Here, it is possible that appropriate escalation of medical therapy to steroid-sparing agents in patients in glucocorticosteroid-induced remission may have led to an overestimate of the proportion of patients exposed to potentially injudicious prescribing. In addition, although investigations included in this study were limited to those requested for the assessment of inflammatory disease activity, we acknowledge that 10% of patients with CD in our cohort had a stricturing disease phenotype, which may have affected symptom reporting and thus influenced clinical decision-making, independent of inflammatory burden. The utility of FC in CD is debated, particularly in ileal disease for which its use is cautioned by some[30] but advocated by others.[31–33] However, in sensitivity analysis when patients with CD and isolated ileal disease were excluded, there remained no association between the presence of mucosal inflammation and clinician decisions to request investigations or escalate medical therapy, while patient self-reported flare remained associated with both. The FC cutoff of 250 μg/g used to define the presence of mucosal inflammation in this study may be contentious. Despite this, the value we used is supported by expert opinion[22] and has been widely used in other studies.[4,5,23,24] Finally, due to the length of time between requesting and the date of investigation, any association between symptom reporting, mucosal inflammation as defined by FC, and endoscopy or radiology investigation outcomes could not be reliably determined.

Our study highlights that the cost of potentially unnecessary investigations is high, and that the incorporation of point-of-care faecal biomarkers of intestinal inflammation into the decision-making process may save money. However, these findings also highlight that 36% of patients with IBD who were neither referred for investigation nor had their medical therapy escalated have evidence of ongoing mucosal inflammation. Our hypothetical pathway for investigation requesting does not address this group of patients, as it relies on a physician's global assessment of disease activity, which failed to identify these cases. That said, whether a 'treat to target' approach, when patients with occult inflammation receive escalation of therapy, leads to better long-term outcomes is currently not fully established and is not advocated by international guidance.[34–37] In addition, roughly 50% of patients who initially consented to participate in our study subsequently failed to provide a stool sample for FC analysis. The reluctance of a secondary care IBD population to provide routine faecal samples is likely to have implications for the benefit of any disease activity assessment pathway that incorporates point-of-care FC, although assessment of the feasibility of implementing any such pathway is beyond the scope of this study.

The sensitivity and specificity of both patient-reported symptoms and the combination of symptoms included in the HBI at predicting mucosal inflammation in CD is poor.[4,5] Despite this, poor general wellbeing and abdominal pain were associated with clinician decisions to escalate medical therapy, and a HBI score of 5 was associated with investigation requesting in CD. Although, after adjusting for confounding variables in multivariate analysis, any significant association between clinical disease activity and clinician decision-making was lost, these findings highlight potential implications of a reliance on patient-reported outcome measures (PROMs) in disease activity assessment. This is of particular relevance given that the use of PROMs as outcome measures in clinical trials in CD has been advocated by the US Food and Drug Administration.[38] Self-reported flare of disease activity was the only factor that was consistently associated with a decision to investigate or escalate medical treatment in patients with CD, despite its poor positive and negative predictive values for predicting FC ≥ 250 μg/g, which were 42.9% and 63.1%, respectively in a previous study.[4]

There was no association between clinical decision-making and mucosal inflammation in CD, thus highlighting the difficulties in assessing disease activity when this is based on patient-reported symptoms alone. Almost half of all patients with CD who underwent escalation of medical treatment did not have evidence of mucosal inflammation, as defined by FC, which is of particular importance given the lack of efficacy of some of these drugs in patients with a limited inflammatory burden.[8] The use of point-of-care FC testing may, in this instance, aid decision-making, improving the appropriateness of

resource allocation, and reducing the risk of adverse events in these patients.

In UC, escalation of medical therapy was associated with the presence of mucosal inflammation and symptoms consistent with clinical disease activity. This is likely to be due to the greater correlation between symptoms and inflammation in UC, as has been described previously.[4,5] Despite this, 31% of patients who underwent escalation of medical therapy did not have evidence of mucosal inflammation, as defined by FC, suggesting that clinical decision-making based solely on a physician's global assessment may be associated with limited effects in terms of disease outcomes, and an increased risk of medication-associated adverse events. After multivariate logistic regression, self-reported flare of disease activity and lower mean HADS anxiety scores were associated with decision to request investigations in UC, suggesting that clinicians avoid investigations in anxious patients, rather than overinvestigating them. Here, the use of point-of-care FC testing may be useful in reducing the number of unnecessary investigations, particularly as 13 (61.9%) of 21 tests were performed in patients with a FC <250 μg/g, at a total cost of £5329.

In summary, self-reported flare was the most consistent factor associated with clinician decision-making in CD, and investigation requesting in UC. The presence of mucosal inflammation, as defined by FC ≥ 250 μg/g, was not associated with the decision to request investigations in either CD or UC, nor was it associated with escalation of medical therapy in CD. Escalation of medical therapy in UC was associated with the presence of mucosal inflammation and raised clinical disease activity indices. Almost 60% of investigations requested for disease activity assessment on the basis of a physician's global assessment could have been avoided. The introduction of routine point-of-care FC testing could, potentially, improve the appropriateness of clinical decision-making, streamline resource allocation, reduce adverse events associated with injudicious use of medications, and reduce costs.

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Conflict of interest statement

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Supplementary Material

Supplementary material is available for this article online.

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