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ORIGINAL ARTICLE

Utility of panenteric capsule endoscopy for the detection of small-bowel Crohn's disease in patients with a normal magnetic resonance enterography: A prospective observational pilot study

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Abstract

Background and Aim: Capsule endoscopy allows the direct visualization of the small bowel. We examined the diagnostic utility of a new modality, namely panenteric Crohn's capsule endoscopy (CE), in detecting active small-bowel Crohn's disease (CD) in those with normal magnetic resonance enterography (MRE).
Methods: We prospectively recruited patients with a diagnosis of CD or suspected small-bowel CD in whom the MRE was normal. Inclusion criteria included abdominal symptoms and abnormal serum or fecal biomarkers. The primary outcome was the detection of active small-bowel CD (measured through the Lewis score [LS]). Secondary outcomes included change in Montreal classification for those with a pre-existing CD diagnosis, change in medical therapy, clinical activity, and biomarkers at baseline and 6 months, and quality-of-life measures.
Results: A total of 22 patients with a diagnosis of CD or suspected new diagnosis were recruited, with CE complete to the caecum in 21 and 18/21 (86%) showing evidence of active small-bowel CD (LS > 135). Of the patients with a pre-existing diagnosis of CD, 9/11 (82%) had a change in Montreal classification. At 6 months following CE, 17/18 (94%) had clinician-directed change in therapy. This correlated with an improvement in the quality of life ($P < 0.05$ as per the Short Inflammatory Bowel Disease Questionnaire), a reduction in the Harvey Bradshaw index (median: 7–4, $P < 0.001$), and favorable CRP and albumin response.
Conclusion: Crohn's CE is a useful diagnostic test for assessing active small-bowel CD when imaging is normal but clinical suspicion is high. Crohn's CE should be integrated into the diagnostic algorithm for small-bowel CD.

Introduction

Crohn's disease (CD), with an incidence of over 300 per 100 000 persons,[1–3] affects the small bowel in up to 70% of patients. Manifestations in the small bowel vary from mucosal inflammation to ulceration and transmural inflammation. Delays in treatment result in stricturing and penetrating complications.[4,5] Current therapies for CD[6] work best if commenced early, before the onset of complications.

Diagnosis and disease activity assessments rely on ileocolonoscopy, cross-sectional imaging such as magnetic resonance enterography (MRE), and noninvasive fecal and serum biomarkers,[7–11] but all of these modalities have limitations in the small bowel. Ileocolonoscopy is limited to views of the distal terminal ileum[8]; balloon enteroscopy requires technical expertise[12]; and MRE can be poorly tolerated because of the high volumes of oral contrast and positioning requirements[13] as well as reduced sensitivity in mucosal CD.[14,15]

Capsule endoscopy (CE) has demonstrated its capability in detecting active CD within the small bowel.[12] More recently, multiple panenteric CE systems have been developed, including the recent Pillcam Crohn's capsule system.[16] Compared with its predecessor models, the Pillcam Crohn's capsule system has both an improved frame rate, which increases the number of frames captured per second from 4 to 35, and a wider viewing angle with dual camera function, in an effort to enhance the diagnostic capabilities of this device.

Currently, there are limited data comparing the efficacy of panenteric CE in CD, particularly in comparison to MRE, and the magnitude of benefit of this additional modality in the management and outcomes of patients with CD.[17,18] Yet, anecdotally, there are many patients in whom small-bowel CD is highly suspected clinically and biochemically but MRE and/or other modalities yield a negative result.

Hence, this observational pilot study was designed to explore the diagnostic utility and safety of panenteric CE (PillCam Crohn's capsule) in the detection of small-bowel CD in patients with an established CD diagnosis and/or those with suspected yet undiagnosed CD unable to be substantiated on the basis of standard diagnostic modalities including MRE. We also aim to assess the impact of CE on therapeutic decision making and the impact of CE-diagnosed small-bowel CD on patients' quality of life and productivity.

Methods

Study design and population. Patients with known (or suspected) CD from two tertiary inflammatory bowel disease (IBD) centres in Australia between January 2021 to August 2022 were referred by their treating clinician for inclusion in this study and for being assessed by the Pillcam Crohn's capsule based upon clinical suspicion of ongoing active small-bowel CD for further diagnosis (Fig. 1). The inclusion criteria included (i) age ≥18 years; (ii) performance of an MRE within 6 months of referral for screening with no features of active CD as reported by a qualified, experienced radiologist; (iii) no change(s) to therapy effected since the performance of MRE, (iv) the presence of at least one gastrointestinal symptom as reported by the patient (i.e., abdominal pain, diarrhea, bloating); and (v) one or more abnormal blood or feces biomarkers from the following performed at the time of referral to the study: elevated fecal calprotectin (FC) >50 μg/g; iron deficiency, defined as a serum ferritin <30 μg/L; anemia, defined as a hemoglobin <115 g/L; hypoalbuminemia, defined as a serum albumin <35 g/L; and C-reactive protein (CRP), defined as CRP level >5 mg/L). Exclusion criteria were (i) the use of nonsteroid anti-inflammatory drugs or aspirin in the 3 months prior to MRE and CE (if proceeding into study), (ii) presence of strictures on MRE, or (iii) a change in medical management between screening and CE.

Initial screening was performed by the lead investigator (A.B.). Patients who met the screening criteria had their MRE reviewed at an IBD multidisciplinary meeting with gastroenterologists, colorectal surgeons, and an experienced abdominal radiologist who performed a second review of the MRE to confirm disease inactivity and absence of small intestinal strictures. Patients were subsequently referred for the CE procedure.

The recorded baseline characteristics included the presence of clinical symptoms, hemoglobin, serum albumin, ferritin and CRP, fecal calprotectin, Harvey Bradshaw index (HBI), Montreal classification for CD (if applicable), and current CD therapy (if applicable). Patients completed the Short inflammatory bowel disease Questionnaire (sIBDQ) and the Workplace Productivity and Activity Impairment Questionnaire for General Health (WPAI-GH) at baseline. The WPAI questionnaire contains six questions measuring absenteeism, presenteeism, and the impairment of activities including work over a 7-day period.[19] SIBQ is a validated questionnaire in patients with IBD measuring quality across four domains (bowel symptoms, social function, emotional well-being, and systemic function) tested through 10 questions.[20] SIBDQ was used under license from McMaster University. These parameters were repeated at routine outpatient clinical follow-up 6 months following CE to capture any change in symptoms, diagnosis, biochemical markers, therapy, and quality of life. Any change in therapy was solely at the discretion of the treating clinician, which was independent of this study.

Capsule endoscopy protocol. The PillCam Crohn's capsule (Medtronic, Dublin, Ireland) was used in this study, and reporting was done with the Rapid PillCam Reader v.9.0 software (Medtronic). The presence of active CD was reported via the Lewis Score (LS), described previously by Gralnek *et al.*[21] The LS is based on three main CE variables in three tertile segments of the small bowel calculated by the determination of CE transit time, villous appearance, ulcers, and stenosis. A total score is created as follows: high tertile score (villous parameter × extent × descriptor) + (ulcer parameter × extent × size) for tertile 1, 2, or 3 depending on the tertile score + stenosis score (stenosis number × ulcerated × traversed). A score <135 is deemed normal, a score between 135 and 790 denotes mildly active CD, and a score ≥790 is defined as moderate to severely active CD.[21] TI was defined as the last 10 min of the CE video before entering the caecum, consistent with previous studies.[17]

In addition, the quality of CE images of the small bowel was evaluated using a previously published methodology.[22] They were categorized as excellent (>90% of the mucosa can be visualized), good (≥75% can be visualized), fair (50–75% of the mucosa can be visualized), or poor (<50% of the mucosa can be

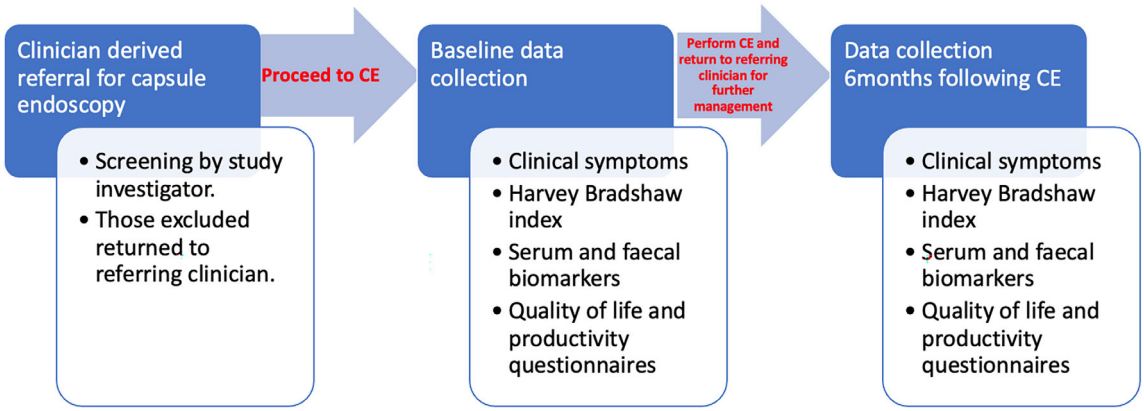

Figure 1 Observational study flow diagram.

evaluated). Given that this study focused on the assessment of the small bowel, no bowel preparation was necessary; however, ingestion of the capsule was done with water plus simethicone (80 mg) to reduce intestinal bubbles. All patients had undergone an ileocolonoscopy within 12 months preceding CE, with no active colonic CD observed. All CE images were read by a single reader (D.V.L.), who was recognized by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy in Australia, and was blinded to clinical and biomarker assessment data. The single reader (D.V.L.) had over 12 years of experience in reading CE images with more than 1000 cases previously reported. The reader provided a formal report back to the original referrer who, independent of this study, had the sole responsibility for any therapeutic changes arising from the results.

Study outcomes

Primary outcome. The primary outcome was the detection of small-bowel CD on CE (defined as a Lewis score >135) in a cohort of patients with established or suspected CD, but with normal MRE.

Secondary outcomes. Secondary endpoints included assessment of the safety and effect of panenteric CE, by measuring (i) CE completion and capsule retention rates, (ii) the impact of panenteric capsule on CD therapy, clinical and biomarker changes at 6 months following CE, (iii) comparison of disease location via Montreal classification before and after CE, (iv) correlation of disease activity on CE with contemporaneously measured clinical and biochemical markers of activity, and (v) change in sIBDQ and WPAI from baseline to 6 months following CE to determine the impact of CE-related outcomes on the quality of life and workplace productivity.

Statistical analysis. Continuous and categorical variables are reported as median (±interquartile range [IQR]) and frequency (%), respectively. Differences in the CD and suspected CD groups were measured with the Wilcoxon rank-sum test and the Fisher exact test (significance level $P < 0.05$). Differences before CE and 6 months after CE were compared using the paired-sample Wilcoxon test (significance level $P < 0.05$). The performance of clinical activity scores and biomarkers in the prediction of CD activity on CE is reported as the sensitivity. All statistical analyses were performed using GraphPad Prism version 9.0 (San Diego, CA, USA).

Results

Between January 2021 and August 2022, 30 patients were screened for inclusion who were referred from clinicians across two tertiary IBD centres. Eight patients failed screening because of failure to meet inclusion criteria or meeting the exclusion criteria, and one patient failed the CE procedure due to capsule retention. Thus 21 patients were included in the final analysis. Of the 21 patients, 10 (48%) were suspected to have CD and 11 (52%) had a known diagnosis of CD. Of those with known CD, eight (73%) had L1 distribution, one (9%) had L2 distribution, two (18%) had L3 distribution, and none (0%) had known L4 disease.

The most common symptom in the 11 patients with a diagnosis of CD was diarrhea in 9 (82%) patients and abdominal pain in 9/10 (90%) patients with suspected CD. An elevated FC (>50 μg/g) was the most frequent abnormal biomarker in both confirmed CD and suspected CD (64% and 50%, respectively) (Tables 1 and 3).

Primary outcome. Of the total cohort ($n = 21$), 18 (86%) patients with normal MRE had active CD (LS > 135) based on the PillCam Crohn's CE. Of the 11 patients with a pre-existing diagnosis of CD, 2 (18%) had a normal CE (LS < 135), 5 (45%) had mild CD (LS 135–790), and 4 (36%) had moderate CD (LS > 790). One patient (9%) with known CD had findings of a stenosis (Fig. 2) in the CE, but the remainder had no stenosis detected. Of the 10 patients with suspected CD, one (10%) had a normal CE, 6 (60%) had mild CD (LS 135–790), and 3 (30%) had moderate CD (LS > 790). Collectively, 6 (33%) patients had an LS determined from active CD found in tertile 2, while the remaining 12 (67%) had an LS determined from activity in tertile 3. These findings are summarized in Table 2.

Table 1 Baseline population details of included patients

	Known Crohn's disease ($n = 11$)	Suspected Crohn's disease ($n = 10$)	*P*-value
Age (median ± IQR)	52 ± 16	37.5 ± 31	0.15
Female sex (%)	8 (73%)	6 (60%)	0.66
Abdominal symptom frequency			
Abdominal pain	8 (73%)	9 (90%)	0.59
Diarrhea	9 (82%)	7 (70%)	0.64
Bloating	4 (36%)	1 (10%)	0.31
Vomiting	0 (0%)	4 (40%)	0.10
Prevalence of abnormal biomarker			
Elevated fecal calprotectin (>50 μg/g)	7 (64%)	5 (50%)	0.66
Iron deficiency (serum ferritin <30 μg/L)	4 (36%)	3 (30%)	1.00
Anemia (Hb < 115 g/L)	4 (36%)	2 (20%)	0.64
Hypoalbuminemia (serum albumin <35 g/L)	4 (36%)	1 (10%)	0.31
C-reactive protein >5 mg/L	3 (27%)	4 (40%)	0.66

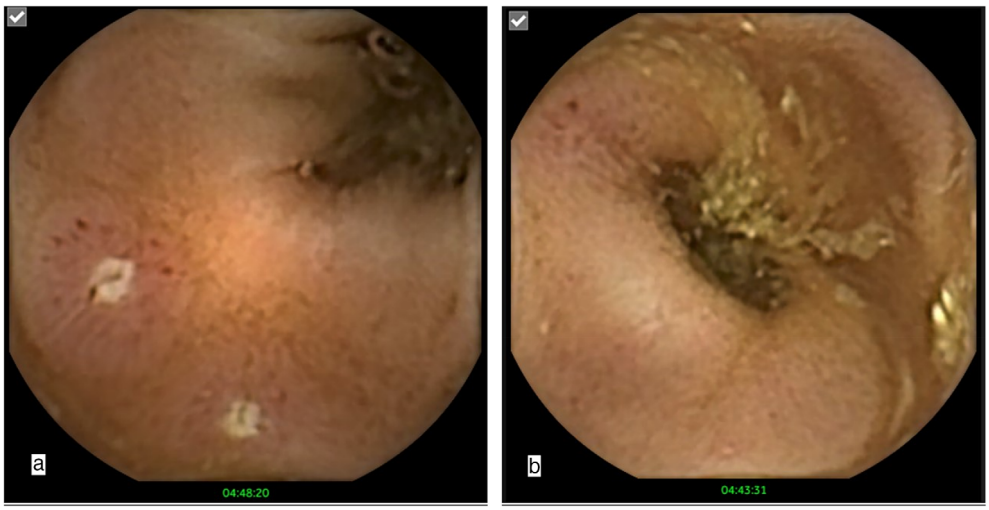

Figure 2 A 72-year-old, iron-deficient female with Crohn's disease. (a) Mid-small-bowel ulceration with mild surrounding erythema. (b) Mid-small-bowel stricture.

Table 2 Findings from Crohn's capsule endoscopy

	Known Crohn's disease (CD) ($n = 11$)	Suspected CD ($n = 10$)
Normal/Lewis score <135	2 (18%)	1 (10%)
Mild CD/Lewis score between 135 and 790	5 (46%)	6 (60%)
Moderate CD/Lewis score ≥790	4 (36%)	3 (30%)

Table 3 Change in clinical and other biomarkers at 6 months following capsule endoscopy (CE)

	Before CE	6 months after CE
Montreal location classification		
No disease	10	1
L1	8	15
L2	1	1
L3	2	3
+L4	0	15
Crohn's disease therapy	$n = 11$	$n = 18$
Nil	5 (45%)	1 (6%)
Corticosteroid	0 (0%)	17 (94%)
Thiopurine	3 (27%)	10 (56%)
Biologic	3 (27%)	11 (61%)

Secondary outcomes

Effect of CE on Montreal classification, therapy change, and clinical and biomarker change at 6 months following CE. Following CE, nine (82%) patients with a prior diagnosis of CD had a change in Montreal classification, with all nine patients with known CD adding L4 disease to their pre-existing Montreal classification. From the entire cohort (known and suspected CD) following CE, 12/21 (57%) patients were classified to L1 + L4 disease, 3/21 (9.5%) to L3 + L4 disease, and 3/21 (9.5%) to isolated L1 disease.

Therapy modifications were made for 18/21 patients in the 6 months following CE (one declined). Of these, 17 (94%) had received a course of corticosteroid (either budesonide or prednisolone), 7(39%) were commenced on a thiopurine, and 8 (44%) on a biologic agent (3 started on adalimumab, 3 on ustekinumab, and 2 on infliximab). Of those already on a biologic, one was switched to ustekinumab from vedolizumab, and another had the frequency of vedolizumab increased from 8 to 4 weekly.

Of the 18 patients with active disease as confirmed by CE, a significant change from baseline was seen in the following measures at 6 months: HBI (median: from 7 to 4, $P < 0.001$), serum CRP (median: from 4.7 to 1.95 mg/L, $P = 0.032$), and serum albumin (median: from 38 to 39.5 g/L, $P = 0.047$). No significant changes in plasma hemoglobin, serum ferritin, and fecal calprotectin were observed.

Change in quality of life and workplace productivity due to therapy change from CE. Health-related quality of life was measured with sIBDQ. There was a significant ($P < 0.05$) improvement in all four domains of SIBDQ up to 6 months following CE (Table 4). The effect of health problems on the ability to perform work and regular activities was measured with WPAI-GH. At the time of enrolment, 14/21 (67%) patients were on paid employment. There was no significant difference between absenteeism and hours worked before and after CE (absenteeism: $P = 0.63$, hours worked: $P = 0.13$). Presenteeism was not evaluated, as it was not required for this study. There was no significant difference in workplace productivity before and after CE ($P = 0.44$); however, a significant reduction in the impact of symptoms on the ability of perform non-employment/regular activities was observed before and after CE ($P = 0.001$).

Sensitivity of individual baseline clinical activity and biomarkers in detecting active disease. HBI showed the highest sensitivity of 83% for detecting active CD on CE (Table 5). The highest objective biomarker sensitivity of 73% was demonstrated with a baseline FC > 50 μg/g. Other assessed biomarkers such as CRP (>5 mg/L), serum albumin (<35 g/L), hemoglobin (<115 g/L), and serum ferritin (<30 μg/L) all had poor sensitivity (<40%) in detecting active CD on CE. With only three patients showing inactive CD on CE, specificity was not calculated, as it was likely to be inaccurate with only a few patients with inactive disease.

Capsule completion rate and colon cleansing level. All but one capsule (95%) achieved transit of the entire small bowel during the recording period. One patient was excluded from the study because of the lack of progression of the capsule beyond a segment of proximal small bowel during the recording period. On follow-up abdominal X-ray performed 2 weeks after the CE, there was no evidence of capsule retention. Of the 21 completed procedures, all had images that were rated as of excellent or good quality throughout the recording period.

Discussion

To our knowledge, this prospective pilot study is the first panenteric CE study evaluating the diagnostic utility of CE for the detection of small-bowel CD in a cohort of patients with pre-existing or suspected CD and with normal MRE. Conventional diagnostic modalities in small-bowel CD such as ileocolonoscopy and MRE are, of course, effective and remain the standard of care. Yet, these may fail to capture activity in those with more subtle and/or non-stricturing, non-penetrating phenotypes of small-bowel CD, particularly proximal to the terminal

Table 4 Change in clinical and other biomarkers at 6 months following capsule endoscopy (CE) ($n = 18$)

	Baseline (pre-CE) (median ± IQR)	Post-CE with therapy change (median ± IQR)	*P*-value
Clinical activity			
Harvey Bradshaw index	7 ± 3	4 ± 3	<0.0001
Serum biomarkers			
CRP (mg/L)	4.7 ± 18	1.95 ± 2	0.032
Albumin (g/L)	38 ± 8	39.5 ± 5	0.047
Hemoglobin (g/L)	131.5 ± 30	129.5 ± 21	0.45
Ferritin (μg/L)	64 ± 156	78 ± 87	0.74
Fecal calprotectin (μg/g)	95 ± 116	63.5 ± 61	0.49
SIBDQ domains			
Bowel (questions 4, 6, and 9)	13 ± 4	17.5 ± 4	<0.0001
Systemic (questions 1 and 7)	10 ± 2	12 ± 4	0.002
Social (questions 2 and 3)	8 ± 5	12.5 ± 2	0.0002
Emotional (questions 5, 8, and10)	15 ± 4	16 ± 3	0.043
WPAI			
Absenteeism (h) (question 2)	0 ± 10	0 ± 0	0.63
Hours worked (question 4)	40 ± 0	40 ± 0	0.13
Workplace productivity (question 5)	4.5 ± 5	2 ± 5	0.44
Non-work/regular activity productivity (question 6)	5 ± 4	2 ± 2	0.001

WPAI, Workplace Productivity and Activity Impairment.

ileum.[8,23–26] This study has demonstrated the clear benefits of performing CE in this clinical context, where there is a high index of clinical suspicion based upon symptoms, abnormal biochemistry, and/or fecal calprotectin.

In this cohort, the high probability of identifying small-bowel CD on CE was demonstrated, with active disease (LS > 135) found in over 80% of patients. Moreover, the finding of active CD on CE culminated in a change in CD therapy in over 90%. In turn, over the 6 months following CE, a significant improvement in HBI, serum biomarkers such as CRP and albumin, and even the quality of life ensued. Another valuable aspect of performing CE in this context was exemplified by the finding that 15 patients in this cohort were reclassified as having Montreal L4 disease location (i.e., upper gastrointestinal disease, including the proximal two-thirds of the ileum) with CE. This is highly important, as CD with L4 location tends to be more refractory to medical treatment and is more likely require surgery for the management of CD than other phenotypes and locations of CD. Hence, accurate classification with CE potentially allows for earlier introduction, or escalation, of therapy to prevent complications of untreated small-bowel disease.[27]

Serum biomarkers, including albumin, CRP, ferritin, and hemoglobin, had poor sensitivity in predicting active small-bowel CD compared to CE (<40% for all serum biomarkers). In our study, FC demonstrated a sensitivity of 73% in predicting active small-bowel CD, which is similar to previous meta-analyses.[28,29] HBI showed a high sensitivity of 83%; however, previous studies showed a less impressive association between HBI and active small-bowel CD.[30] Our study excluded asymptomatic patients, which was not the case in previous studies, which likely explains this discrepancy.

Previous systematic reviews have shown a capsule retention rate of 2.6% in those with established CD.[31] In our study, CE appeared to be safe in these patients, with no capsule retention observed. One patient had delayed capsule transit, but on follow-up abdominal X-ray, it was found to have passed. We chose not to perform patency CE but instead mandated that an MRE be performed prior to capsule ingestion to stratify the risk of retention, and those with suspected or confirmed small-bowel strictures were excluded.

This study has a number of limitations. First, our prospective pilot study comprised a small sample of patients ($n = 22$), so larger studies are needed to confirm the results. Also, there was a potential selection bias given that for study inclusion all patients required both clinical symptoms and abnormal biomarkers. Hence, these data should be extrapolated only to a similar population (i.e., patients with a high index of suspicion of small-bowel disease based on symptoms and biomarkers). Furthermore, in this study the CE image was read by a single experienced reader, therefore we could not assess any interobserver variability. Previous studies have shown that LS has high rates of interobserver agreement, and therefore the impact of a single reader in this cohort may be minimal.[32] Finally, in our pilot study, the findings of active CD on CE were not confirmed by contemporaneous small-bowel enteroscopy, and not all patients had screening gastroscopies at time of the study.

Table 5 Sensitivity of clinical and other biomarkers in predicting active CD on CE ($n = 18$)

Variable	Sensitivity
Harvey Bradshaw index ≥5	83.33%
CRP > 5 mg/L	35.29%
Serum albumin <35 g/L	27.78%
Hemoglobin <115 g/L	27.78%
Serum ferritin <30 μg/L	37.50%
FC > 50 μg/g	73.33%
Composite scoring (clinical and objective biomarker)	
HBI ≥ 5 and/or CRP > 5 mg/L	83.33%
HBI ≥ 5 and/or serum albumin <35 g/L	83.33%
HBI ≥ 5 and/or hemoglobin <115 g/L	83.33%
HBI ≥ 5 and/or serum ferritin <30 μg/L	88.89%
HBI ≥ 5 and/or FC > 50 μg/g	88.89%

CD, Crohn's disease; CE, capsule endoscopy; CRP, C-reactive protein; FC, fecal calprotectin; HBI, Harvey Bradshaw index.

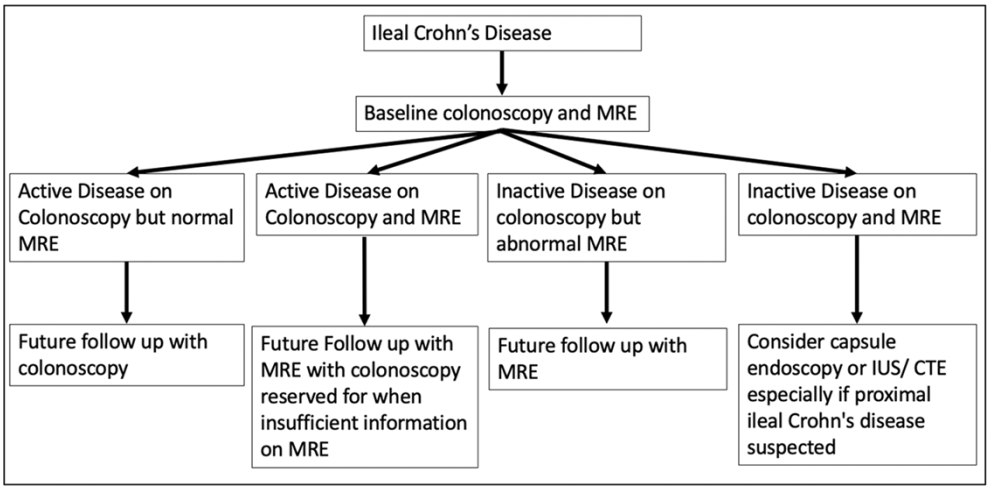

Figure 3 Potential small-bowel Crohn's disease (CD) evaluation strategy. Reproduced with permission from the authors of "Replacing endoscopy with Magnetic Resonance Enterography in Terminal Ileal CD: Are we there yet?"[8]

Conclusion

Panenteric Crohn's CE has an apparent high yield for the detection of small-bowel CD in those with suggestive clinical symptoms and at least one elevated biomarker despite normal conventional diagnostics including small-bowel imaging. Hence, CE should be considered as a useful adjunctive diagnostic tool in established and suspected CD given its potential to achieve earlier diagnosis and more accurate classification of active disease (Fig. 3), in turn enabling earlier therapeutic intervention and improving the patients′ quality of life.

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Ethics and consent statement

The study was approved by the Eastern Health Ethics unit (approval number: E20-013-65 781), and informed consent was obtained from all participants.

Data availability statement. The data underlying this article will be shared on a reasonable request to the corresponding author.

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