INTRODUCTION

Crohn’s disease (CD) is a chronic disorder characterized by transmural inflammation and patchy distribution in the GI tract. The importance of assessing ongoing GI mucosal inflammation in this condition lies in the fact that it helps predict course of disease, response to therapy, advent of complications, need for hospitalization and surgery. To this effect, various studies have shown mucosal healing to be the best predictor of positive long-term outcomes. Endoscopy is currently regarded as the gold standard test for assessment of mucosal healing. However, it is expensive, invasive, associated with patient discomfort and has an associated small risk of serious complications, thus making it an unfeasible modality for frequent monitoring. Biochemical markers like CRP are inexpensive but have moderate diagnostic accuracy with a specificity of 0.92 (95% CI, 0.72–0.96) but a sensitivity of only...
0.49 (95% CI, 0.34–0.64),\(^9\) hence limiting its use as a disease biomarker.

Since the acutely inflamed intestinal mucosa is deemed to be neutrophil–rich, fecal tests based on neutrophil-derived markers are a realistic option for assessing mucosal inflammation. Among the various fecal markers of intestinal inflammation; fecal calprotectin (FC) is the one most commonly used in clinical practice.\(^10\) FC has a sensitivity of 87% and specificity of 67% when used to detect endoscopic activity in symptomatic CD.\(^9\) It accurately predicts the response to therapy as well as 1-year risk of relapse.\(^11,13\) There are though conflicting reports on whether the diagnostic accuracy in CD is influenced by disease location. FC has been shown to have a lower specificity in CD than in UC and this might be driven through the different disease locations.\(^14-16\) Some studies report that the FC level is lower in small bowel (SB) disease location compared to large bowel (LB) location,\(^17,18\) while others did not observe any difference.\(^14,19\) We feel this is an important matter that could potentially either change practice or serve as a basis for downstream research. We thus aimed to undertake a systematic review of published literature and discuss the effect of disease location on the sensitivity and specificity of FC to accurately measure disease activity in CD.

**METHODS**

1. **Criteria for Inclusion and Exclusion**

   Case control and cohort studies that provided data on FC separately by SB and LB locations were selected. Only those studies which had clearly mentioned the use of endoscopy, MRI, CT or a combination of these modalities as reference standard to assess disease activity were included.\(^8,20\) The subjects included both adult and pediatric patients who had been diagnosed with CD on the basis of their clinical symptoms and supporting investigations (endoscopy, biopsies, imaging, blood and stool tests). We also included studies in which healthy volunteers and subjects with irritable bowel syndrome were recruited as controls. We excluded studies focusing only on SB-CD and studies where the reference standard for activity used was based on clinical or biochemical criteria. We also excluded studies specifically dealing with postoperative CD as it would not have been possible to define the disease location as SB or LB if the recurrence was limited to the anastomosis.

2. **Search Strategy**

   Our search included Medline, Embase, Web of Science and Cochrane Library from inception up to November 8, 2016 with the help of a senior librarian to obtain the appropriate studies. There were no language or publication restrictions applied while searching. Details of the search strategy are provided in the Supplementary Material 1.

   Conference proceedings from Digestive Diseases Week, United European Gastroenterology Week, European Crohn’s and Colitis Organisation (ECCO) and British Society of Gastroenterology annual meetings over the past 12 years (2005–2016) were also searched for relevant additional studies. We performed a manual search from references in the included studies and pertinent review articles. We also searched the Grey Literature Database OpenGrey to check for eligible studies.

3. **Selection**

   The selected studies were initially screened for eligibility by 3 authors (E.G.S., R.W., and A.A.T.). The abstracts were reviewed and those eligible were included for full text review. The full manuscripts were independently assessed (E.G.S. and G.W.M.) as per the inclusion criteria. If there were any disagreements, these were resolved by discussion and consensus with the other authors (S.S., R.W., and A.A.T.). Studies published only in abstract format were included as long as inclusion criteria were satisfied.

4. **Data Extraction**

   Two authors (E.G.S. and G.W.M.) independently completed the data extraction forms for studies in the final selection list. The following data was collated: general information (journal, year, author, title), publication type (full paper or abstract), location, number of centers involved, study design (prospective/cross-sectional), total number of CD subjects and stratification based on disease location, age group (adult/pediatric/both), follow up period in months, FC levels with cutoff, clinical disease activity index, relevant reference standard (with appropriate disease activity score if provided), number of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) and miscellaneous details. If any of the selected studies had missing data or needed clarification, multiple attempts through electronic mail were made to contact the authors to furnish the same.

5. **Risk of Bias**

   To assess the risk of bias, QUADAS-2 was used (Supplementary Material 2). This is a research tool to check the quality of systematic reviews of diagnostic accuracy studies.\(^21\) This was
assessed independently by 2 authors (E.G.S. and G.W.M.) while any disagreement was resolved by consensus with co-authors (S.S., R.W., and A.A.T).

6. Data Synthesis
Sensitivity and specificity in the SB and LB locations were separately derived by calculation from the information provided (i.e., TP, TN, FP, and FN) or as reported in the published literature.

RESULTS
The electronic data base search on November 8, 2016 identified 5,619 results. After the removal of 2,098 duplicates, 3,521 records were screened for inclusion. From the latter, 61 studies were deemed to be relevant and subjected to full text review. Thereafter, 45 studies were excluded either because the numerical data on FC at SB and LB locations were not separately available or because the reference standards used did not conform to inclusion criteria. Finally, 16 studies were included in the qualitative review (Fig. 1) involving 328 patients with SB-CD and 332 patients with LB disease location.

![Fig. 1. PRISMA flow diagram. Sixteen studies, numerical data not available for fecal calprotectin (FC) at large bowel and small bowel locations separately; 16 studies, reference standards for assessment of disease activity were different from those mentioned in inclusion criteria; 13 studies, both numerical data for FC at the 2 locations were not separately available and reference standards used for assessment of disease activity were different from those mentioned in inclusion criteria. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.](image)

Table 1. Study Characteristics

| Study            | Design         | Patient spectrum                  | SB Crohn’s | LB Crohn’s | Reference standard/scoring system used |
|------------------|----------------|-----------------------------------|------------|------------|----------------------------------------|
| af Björkestén    | Prospective    | Anti-TNF treated luminal Crohn’s   | 33         | 50         | SES-CD                                 |
| Faubion          | Cross-sectional| Crohn's cohort on follow-up       | 22         | 12         | ICO-CTE score                          |
| Gece             | Cross-sectional| Crohn’s undergoing ileocolonoscopy| 9          | 20         | SES-CD                                 |
| Jensen           | Cross-sectional| Suspected Crohn’s under evaluation| 13         | 16         | Endoscopy/capsule/surgery              |
| Jones            | Cross-sectional| Crohn’s undergoing ileocolonoscopy| 53         | 40         | SES-CD                                 |
| Lobatón          | Cross-sectional| Crohn’s undergoing ileocolonoscopy| 26         | 45         | CDEIS                                  |
| Makanyanga       | Cross-sectional| Crohn’s cohort on follow-up       | 18         | 15         | MEGS                                   |
| Maltz            | Cross-sectional| Crohn’s cohort on follow-up       | 9          | 18         | Endoscopy                              |
| Schoepfer        | Cross-sectional| Crohn’s undergoing ileocolonoscopy| 35         | 20         | SES-CD                                 |
| Sipponen         | Cross-sectional| Crohn’s undergoing ileocolonoscopy| 16         | 17         | SES-CD                                 |
| Sipponen         | Cross-sectional| Crohn’s undergoing ileocolonoscopy| 19         | 14         | CDEIS                                  |
| Stawczyk-Eder    | Cross-sectional| Hospitalized Crohn’s              | 44         | 22         | SES-CD                                 |
| Zittan           | Cross-sectional| Crohn’s cohort on follow-up       | 14         | 23         | SES-CD, MaRIA                          |
| Moniuszko        | Cross-sectional| Hospitalized Crohn’s              | NA         | NA         | SES-CD, CT enteroclysis                |
| Goutorbe         | Cross-sectional| Crohn’s undergoing ileocolonoscopy| 13         | 12         | CDEIS                                  |
| Lin              | Prospective    | Crohn’s cohort on follow-up       | 4          | 8          | CDEIS                                  |

SB, small bowel; LB, large bowel; SES-CD, Simple Endoscopic Score for Crohn’s Disease; ICO-CTE, ileocolonoscopy and CT enterography; CDEIS, Crohn’s Disease Endoscopic Index of Severity; MEGS, MRI enterography global score; MaRIA, magnetic resonance index of activity; NA, not available.
1. Study Demographics

Fourteen relevant cross-sectional and 2 prospective studies were published between 2008 and 2016 (Table 1). Four of the 16 studies were published as conference abstracts, although 1 of these was subsequently published as a full text article. Almost all the studies were single/dual-center based other than the studies by Faubion et al. and Lin et al. which were multi-center. All the studies were performed in Europe and North America apart from a single study originating from Asia. The majority of the studies involved adult subjects. The study by Jones et al. included 23 subjects who were less than 16 years while the youngest subject in the study by Jensen et al. was 16 years. With regard to the reference standards utilized; 11 studies used endoscopy, 2 used endoscopy and CT in combination while there was one each for MRI alone, endoscopy and MRI in combination and a composite assessment of endoscopy/capsule endoscopy/surgery (Table 1).

2. Risk of Bias Assessment

With regard to QUADAS-2 risk assessments of the selected studies (Table 2), only a single study scored low in all 4 domains of risk of bias and the domain of concern for applicability. There were again just 3 studies by which scored low in 3 domains of risk of bias. Most studies had an unclear risk of bias in patient selection. With respect to the index test, there were 3 studies that had high risk while one was unclear. The studies were almost evenly distributed between low and unclear risk with regard to the reference standard. Eight studies had either high or unclear risk of bias under subject flow and selection. There were just 6 studies which had low concern for applicability under subject selection.

3. Sensitivity and Specificity of FC by Location

The data on the effect of disease location on FC is heterogeneous (Table 3). Some studies showed that the FC was significantly higher in LB vs SB location while others did not corroborate this finding, though absolute values have limited value. The studies by Jones et al., Sipponen et al., and Zittan et al. showed that FC significantly correlated with the reference standard only at the LB location but not at the SB location while the other 2 studies showed that FC correlated with the reference standard at both the locations (Table 4). The reference standard used in these studies was endoscopy with the scor-

Table 2. QUADAS-2 Risk Assessment for the Selected Studies

| Study          | Subject selection | Index test | Reference standard | Flow and timing | Subject selection | Index test | Reference standard |
|----------------|-------------------|------------|--------------------|-----------------|-------------------|------------|--------------------|
| af Björkesten  | Low               | Low        | Low                | Low             | High              | NC         | NC                 |
| Faubion        | Unclear           | Low        | Unclear            | Unclear         | High              | NC         | NC                 |
| Gecse          | High              | Low        | Unclear            | Low             | Unclear           | NC         | NC                 |
| Jensen         | Unclear           | Low        | Unclear            | High            | High              | NC         | NC                 |
| Jones          | Unclear           | Low        | Low                | Low             | Low               | NC         | NC                 |
| Lobatón        | Low               | High       | Low                | High            | Low               | NC         | NC                 |
| Makanyanga     | Unclear           | High       | Low                | Unclear         | High              | NC         | NC                 |
| Maltz          | Unclear           | Unclear    | Unclear            | Low             | Unclear           | NC         | NC                 |
| Schoepfer      | High              | Low        | Unclear            | Low             | Low               | NC         | NC                 |
| Sipponen       | Unclear           | Low        | Low                | Low             | Unclear           | NC         | NC                 |
| Sipponen       | Unclear           | Low        | Unclear            | Unclear         | Unclear           | NC         | NC                 |
| Stawczyk-Eder  | Unclear           | High       | Low                | Low             | Low               | NC         | NC                 |
| Zittan         | Unclear           | Low        | Unclear            | Unclear         | Unclear           | NC         | NC                 |
| Moniuszko      | Unclear           | Low        | Unclear            | Unclear         | Unclear           | NC         | NC                 |
| Goutorbe       | Low               | Low        | Low                | Low             | Low               | NC         | NC                 |
| Lin            | Unclear           | Low        | Low                | Low             | Low               | NC         | NC                 |

NC, not a concern.
Table 3. Comparison of Mean or Median Levels in the 2 Locations

| Study          | SB Crohn’s | LB Crohn’s | Reference standard/scoring system used | Key result | Inference                              |
|----------------|------------|------------|----------------------------------------|------------|----------------------------------------|
| af Björksten14 | 33         | 50         | SES-CD                                 | Median FC level in SB: 86 µg/g | No difference between both locations |
| Geese17        | 9          | 20         | SES-CD                                 | Mean FC level in SB: 297±81 mg/g | Higher in LB location                |
| Jensen19       | 13         | 16         | Endoscopy/capsule/surgery              | Median FC level in SB: 890 mg/kg | No difference between both locations  |
| Lobatón67      | 26         | 45         | CDEIS                                  | Median FC level in SB: 420.5 µg/g | Higher in LB location                |
| Makanyanga68   | 18         | 15         | MEGS                                   | Mean FC level in SB: 319.1 µg/g | No difference between both locations  |
| Maltz69        | 9          | 18         | Endoscopy                              | Median FC level in SB: 442 µg/g | Higher in LB location                |
| Schoepfer70    | 35         | 20         | SES-CD                                 | Mean FC level in SB: 287±279 µg/g | No difference between both locations  |
| Sipponen18     | 19         | 14         | CDEIS                                  | Median FC level in SB: 180 µg/g | Higher in LB location                |
| Moniuszko74    | NA         | NA         | SES-CD, CT enteroclysis               | Median FC level in SB: 195 µg/g | No difference between both locations  |
| Goutorbe75     | 13         | 12         | CDEIS                                  | Median FC level in SB: 841 µg/g | No difference between both locations  |
| Lin76          | 4          | 8          | CDEIS                                  | Median FC level in SB: 2,693 µg/g | No difference between both locations  |

SB, small bowel; LB, large bowel; SES-CD, Simple Endoscopic Score for Crohn’s Disease; FC, fecal calprotectin; CDEIS, Crohn’s Disease Endoscopic Index of Severity; MEGS, MRI enterography global score; NA, not available.

Table 4. Correlation between Fecal Calprotectin and Reference Standard at Respective Locations

| Study          | SB Crohn’s | LB Crohn’s | Reference standard/scoring system used | Key result | Comment                              |
|----------------|------------|------------|----------------------------------------|------------|----------------------------------------|
| Jones44        | 53         | 40         | SES-CD                                 | Correlation in SB: -0.01 (NS) | Correlation noted only at LB location |
| Lobatón67      | 26         | 45         | CDEIS                                  | Correlation in SB: 0.437 (P=0.016) | -                                    |
| Sipponen71     | 16         | 17         | SES-CD                                 | Correlation in SB: 0.317 (NS) | Correlation noted only at LB location |
| Stawczyk-Eder72 | 44         | 22         | SES-CD                                 | Correlation with SES-CD in SB: 0.78 | -                                    |
| Zittan73       | 14         | 23         | SES-CD, MaRIA                          | Correlation in SB: 0.4 (P=NS) | Correlation noted only at LB location |

SB, small bowel; LB, large bowel; SES-CD, Simple Endoscopic Score for Crohn’s Disease; CDEIS, Crohn’s Disease Endoscopic Index of Severity; MaRIA, magnetic resonance index of activity.
The data represented here is heterogeneous with varying gold-standards. There are only 5 studies in the published literature with the primary aim of investigating the effect of disease location on the sensitivity and specificity of FC.\textsuperscript{17,18,72–74} In the remaining eleven studies, this information was expressed as a sub-analysis. Moreover, apart from the published data, raw data to calculate sensitivity and specificity was only available in 5 small studies. These data did not pertain to all the cohorts published but only relevant to smaller sub-groups.\textsuperscript{14,17,65,74,75} One might speculate that LB disease location is within reach of colonoscopy and hence is more commonly validated with a gold-standard investigation. As for SB disease location, unless the disease is in the terminal ileum this might not be as accurately located though the sensitivities and specificities of MRI to measure disease activity is widely published.\textsuperscript{77} A possible reason for the effect of disease location on the specificity of FC might be that other common disease of the colon such as diverticulitis, microscopic colitis or infectious enteritides might raise FC other than LB-CD. The same might not be said for SB inflammation in cohort studies undertaken in the Western Hemisphere where CD is the commonest cause for ileal inflammation. Effectively, this systematic analysis highlights the need of properly designed prospective studies to answer this important question.

Despite endoscopy being the gold standard for assessment of disease activity, we also included studies where radiological tests such as CT or MRI were utilized as reference standards to evaluate the SB activity as these have been supported by the ECCO guidelines.\textsuperscript{8,20} However, the lack of a uniform gold standard was a limiting factor. This heterogeneity multiplied by the inter-observer variability for the various investigative

### Table 5. Diagnostic Accuracy of Fecal Calprotectin in CD at SB versus LB Location

| Study               | Sensitivity SB (95% CI) | Sensitivity LB (95% CI) | Specificity SB (95% CI) | Specificity LB (95% CI) | FC cutoff (µg/g) |
|---------------------|------------------------|-------------------------|-------------------------|-------------------------|-----------------|
| Jensen\textsuperscript{19,a} | 92                     | 94                      | NA                      | NA                      | 50              |
| Lobatón\textsuperscript{67,a} | 63                     | 79                      | 100                     | 100                     | 272             |
| Zittan\textsuperscript{73,a}   | 75                     | 100                     | 50                      | 67                      | 100             |
| af Björkesten\textsuperscript{14} | 60.0 (32.9–82.5)       | 78.9 (53.9–93)          | 100 (31.0–100)          | 75.0 (35.6–95.5)       | 100             |
| Faubion\textsuperscript{66}    | 76.9 (46.0–93.8)       | 80.0 (29.9–98.9)        | 75.0 (35.6–95.5)        | 28.6 (5.1–69.7)        | 100             |
| Gece\textsuperscript{17}       | 42.9 (11.8–79.8)       | 100 (78.1–100)          | NA                      | 100 (5.5–100)          | 200             |
| Goutorbe\textsuperscript{75}   | 100 (51.7–100)         | 100 (62.9–100)          | 50.0 (13.9–86.0)        | 33.3 (1.8–87.5)        | 200             |
| Moniuszko\textsuperscript{74}  | 100 (31.0–100)         | 66.7 (30.9–91.0)        | 100 (31.0–100)          | 50.0 (2.7–97.3)        | 238             |

All unit of data is percent.

\textsuperscript{a} Raw data and associated CI are not available.

SB, small bowel; LB, large bowel; FC, fecal calprotectin; NA, not available.

DISCUSSION

A variety of clinical studies have indicated a wide range of sensitivities and specificities for FC in CD at different disease locations.\textsuperscript{14,17–19} We have undertaken a systematic review to objectively appraise the literature. Overall, the sensitivity and specificity of FC in the SB ranged from 42.9% to 100% and from 50% to 100% respectively. The sensitivity and specificity of FC in the LB ranged from 66.7% to 100% and from 28.6% to 100% respectively.

The ing system being either Simple Endoscopic Score for Crohn’s Disease (SES-CD),\textsuperscript{64,71–73} Crohn’s Disease Endoscopic Index of Severity (CDEIS)\textsuperscript{67} although in the study by Zittan et al.,\textsuperscript{73} MR enterography score (MaRIA, magnetic resonance index of activity) was also used in the SB location.

The sensitivity and specificity data were available for 8 studies in total (Table 5). Sensitivities were available in the published literature for just 2 studies\textsuperscript{19,67} while in 1 study,\textsuperscript{73} these were retrospectively provided by the author. For the remaining 5 studies,\textsuperscript{14,17,66,74,75} the relevant authors provided the raw data on the number of TP, TN, FP and FN, from which the sensitivity and specificity values were retrospectively calculated.

Including data from all the 8 studies, the sensitivity and specificity of FC in the SB ranged from 42.9% to 100% and from 50% to 100% respectively. The sensitivity and specificity of FC in the LB ranged from 66.7% to 100% and from 28.6% to 100% respectively.
modalities used, limited the validity of the reported sensitivities and specificities. The limitations of CT and MRI may include decreased sensitivity to detect early disease that may otherwise be detected on endoscopy. Even in those studies that have used endoscopy as the reference standard, various scoring systems such as the SES-CD and the CDEIS scores were utilized. These scoring systems themselves have limitations such as the endoscopic evaluation being confined to the terminal ileum or colon subject to the reach of the colonoscope and inter-observer variability. Capsule endoscopy is a non-invasive way to evaluate the entire SB. However, its disadvantages include lack of utility when there is a SB stricture as well as subjective nature of reporting.

There are certain limitations in the published literature that need to be highlighted. The FC cutoffs used in all the reported studies are different. The cutoff values can influence the test accuracy and there are different cutoff values for FC depending on the intent of use. The current National Institute for Health and Care Excellence (NICE) guideline indicates that an FC value <50 μg/g suggest no significant GI mucosal inflammation, with a value of >250 μg/g corresponds well with endoscopic and histology activity. The cutoff values used in the studies presented in this systematic review were not uniform. Most of the studies used cutoff of 100 μg/g with just 3 studies using a cutoff value of 50 μg/g. The diagnostic test used to determine the FC levels were not uniform. Most studies used ELISA test while some used the rapid test (Quantum Blue). Stool collection time was not standardized across the studies described in this systematic review. There was a paucity of detail regarding processing of the stool samples across the studies. These factors could also contribute to differences of FC across the studies.

Our systematic review included both pediatric and adult studies though most of the data was from the adult population and the pediatric population appeared under-represented. The specificity of FC appears to improve with patient age. van Rheenen et al. undertook a meta-analysis of 13 studies, obtained a pooled sensitivity of 93% and specificity of 96% in adults and 92% and 76% in children respectively. The larger share of irritable bowel disease with absence of alarm symptoms was thought to overestimate the specificity in the adults subjects compared to children. Henderson et al. undertook a meta-analysis of 8 studies and concluded that the sensitivity and specificity of FC in IBD in the pediatric cohort were 97.8% and 68.2%. Factors that could contribute to the difference in specificity of FC in adult versus pediatric populations include the variation in the disease prevalence and spectrum, variation in the FC threshold to trigger endoscopic evaluation, parental expectation and concerns about missed diagnosis. The pediatric cohort in this systematic review was too small to be able to make any firm conclusions.

We observed that most of the studies originated from the Western Hemisphere except for the study from Taiwan, perhaps indicating that these findings may not be reflective of the situation in the general population worldwide. It would be difficult to get homogenous world-wide data on the accuracy of FC in SB and LB locations due to differences in incidence and prevalence of IBD across regions.

This systematic review has some major strengths. We had undertaken a comprehensive search including important online databases (Medline, Embase, Web of Science, and Cochrane Library). We had no language or publication restrictions. Moreover, relevant conference proceedings were searched since 2005 to ensure no publication bias was introduced within our search. We excluded studies that were merely restricted to SB-CD since we also needed information from the LB in order to compare. We excluded those studies solely describing postoperative cohorts to exclude the effect of non-IBD related anastomotic ulceration on the analysis. Moreover, since the raw figures (i.e., TP, TN, FP and FN in both SB and LB locations) of the selected studies were not provided in the original published manuscripts, electronic communication with relevant study authors was undertaken as part of our data extraction process for this systematic review.

The range of sensitivities and specificities for FC by disease location are variable and incomparable. As the gold standard comparators used in various studies are heterogeneous it has not been possible to pool the data and calculate common variables for FC. Prospective cohort studies with common comparators and similar quantification methodologies for FC are needed to answer this question; in order to better understand the right place for FC as a disease monitoring tool.

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**AUTHOR CONTRIBUTION**

Simon EG: conception & design of the study; data acquisition, analysis & interpretation; drafting and revising the article; final approval. Wardle R, Thi AA, Eldridge J, and Samuel S: data interpretation; revising the article; final approval. Moran GW: conception & design of the study; data interpretation; revising the article; final approval. All authors have approved the final version of the manuscript.

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Supplementary Material 1

Search strategies:

A. Medline - Search strategy
1. exp Leukocyte L1 Antigen Complex/
2. (calprotectin* or calgranulin*).mp.
3. (S100A8* or S100A9*).mp.
4. "Leukocyte L1 Antigen Complex".mp.
5. (leu#ocyt* adj3 "L1" adj3 antigen* adj3 complex*).mp.
6. 1 or 2 or 3 or 4 or 5
7. exp Biological Markers/
8. (((bio* or lab* or progno* or predict* or fecal* or faecal* or feces* or faeces*) adj2 marker*) or biomarker* or (biologic* adj marker*) or marker* or surrogat*).mp.
9. 7 or 8
10. exp Crohn Disease/
11. crohn*.mp.
12. exp Inflammatory Bowel Diseases/
13. (ibd* or (inflam* adj3 bowel*)).mp.
14. exp Colitis, Ulcerative/
15. (ulcer* adj3 colitis*).mp.
16. 10 or 11 or 12 or 13 or 14 or 15
17. (fecal* or faecal* or feces* or faeces* or excret* or stool*).mp.
18. 6 and 16
19. 9 and 16 and 17
20. 18 or 19

B. Embase - Search strategy
1. exp calgranulin/
2. (calprotectin* or calgranulin*).mp.
3. "Leukocyte L1 Antigen Complex".mp.
4. (leu#ocyt* adj3 "L1" adj3 antigen* adj3 complex*).mp.
5. (S100A8* or S100A9*).mp.
6. 1 or 2 or 3 or 4 or 5
7. exp biological marker/
8. (((bio* or lab* or progno* or predict* or fecal* or faecal* or feces* or faeces*) adj2 marker*) or biomarker* or (biologic* adj marker*) or marker* or surrogat*).mp.
9. 7 or 8
10. exp Crohn disease/
11. exp ulcerative colitis/
12. exp inflammatory bowel disease/
13. crohn*.mp.
14. (ibd* or (inflam* adj3 bowel*)).mp.
15. (ulcer* adj3 colitis*).mp.
16. 10 or 11 or 12 or 13 or 14 or 15
The following criteria were assessed in QUADAS-2:

1. Was a consecutive or random sample of subjects enrolled?
2. Was a case-control design avoided?
3. Did the study avoid inappropriate exclusions?
4. Could the selection of subjects have introduced bias?
5. Is there concern that the included subjects do not match the review question?
6. Were the index test results interpreted without knowledge of the results of the reference standard?
7. If a threshold was used, was it pre-specified?
8. Could the conduct or interpretation of the index test have introduced bias?
9. Is there concern that the index test, its conduct, or its interpretation differ from the review question?
10. Is the reference standard likely to correctly classify the target condition?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Could the reference standard, its conduct, or its interpretation have introduced bias?
13. Is there concern that the target condition as defined by the reference standard does not match the review question?
14. Was there an appropriate interval between index test (s) and reference standard?
15. Did all subjects receive a reference standard?
16. Did subjects receive the same reference standard?
17. Were all subjects included in the analysis?
18. Could the subject flow have introduced bias?

We modified the application of the QUADAS-2 as previously shown. With regard to question 5, “low concern” was scored if the subjects clearly had established CD and “high concern” if the study sample had subjects presenting for the first time with CD. Question 6 was not scored as fecal calprotectin is an objective test based on laboratory result which is not affected by blinding the index test interpreter to the reference standard. The applicability of the index test (question 9) was not a concern for this review despite the variations in the way the index test was performed and interpreted. For question 10, “yes” was scored for all the studies since endoscopy is considered the gold standard for diagnosis of CD while MRI or CT are considered useful in assessment for CD in the small bowel in the most recent European guidelines. Since the gold standards used for assessment of CD were endoscopy, MRI or CT; question 13 (applicability of reference standard) was considered not of concern. The responses for the signalling questions were “yes,” “no” or “unclear” and the risk of bias was marked as “low,” “high” or “unclear.” If all the signalling questions for a particular domain were “yes,” this would indicate a “low” risk of bias while presence of any “no” would raise the concern for bias. When the information was insufficient, “unclear” has been marked.
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