Supplementary Material

<table>
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<th>Title</th>
<th>C-Reactive Protein, Fecal Calprotectin, And Stool Lactoferrin For Detection Of Endoscopic Activity In Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review And Meta-Analysis</th>
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</thead>
</table>
| List of Supplementary Material                                      | Supplementary Material 1: Preliminary Search Strategies  
Supplementary Material 2: Assessment of Methodological Quality: QUADAS-2  
Supplementary Table 1: Methodological quality summary; review authors' judgements about each methodological quality item for each included study.  
Supplementary Figure 1: Summary receiver operator characteristics plots of all tests |

This supplementary material has been provided by the authors to give readers additional information about their work.

**Supplementary Material 1) Preliminary Search Strategies**

**MEDLINE – SEARCH STRATEGY**

1. Crohn's Disease.mp. or exp Crohn Disease/
2. Ulcerative Colitis.mp. or exp Colitis, Ulcerative/
3. Inflammatory Bowel Disease.mp. or exp Inflammatory Bowel Diseases/
4. 1 or 2 or 3
5. exp "Severity of Illness Index"/ or disease activity.mp.
6. limit 5 to humans
7. C-reactive protein.mp. or exp C-Reactive Protein/
8. lactoferrin.mp. or exp Lactoferrin/
9. calprotectin.mp. or exp Leukocyte L1 Antigen Complex/
10. 7 or 8 or 9
11. 4 and 6 and 10
EMBASE – SEARCH STRATEGY

1. Crohn's Disease.mp. or exp Crohn disease/
2. Ulcerative Colitis.mp. or exp ulcerative colitis/
3. Inflammatory Bowel Disease.mp. or exp enteritis/
4. 1 or 2 or 3
5. disease activity.mp. or exp disease activity/
6. limit 5 to human
7. C-reactive protein.mp. or exp C reactive protein/
8. calprotectin.mp. or exp calgranulin/
9. lactoferrin.mp. or exp lactoferrin/
10. 7 or 8 or 9
11. 4 and 6 and 10

Cochrane Library (CENTRAL) – SEARCH STRATEGY

1. “Inflammatory Bowel Disease” or “Ulcerative Colitis” OR “Crohn’s Disease”
2. “disease activity”
3. “C-reactive protein” OR calprotectin OR lactoferrin

ISI Web of Knowledge - SEARCH STRATEGY

1. “ulcerative colitis” OR “Crohn’s disease” OR “inflammatory bowel disease”.
2. “disease activity”
3. “c-reactive protein” OR “CRP” OR lactoferrin OR calprotectin

Supplementary Material 2): Assessment of Methodological Quality: QUADAS-2

Domain 1: Patient Selection
Risk of bias: Could the selection of patients have introduced bias?
Signalling question 1: Was a consecutive or random sample of patients enrolled?
We will score ‘yes’ if the study enrolled a consecutive or random sample of eligible patients; ‘no’ if the study selected patients by convenience; and ‘unclear’ if the study did
not report the manner of patient selection.

**Signalling question 2: Was a case-control design avoided?** We will score 'yes' if a case-control design was avoided; 'no' if a case-control design was used; and 'unclear' if insufficient information was reported to allow a judgement.

**Signalling question 3: Did the study avoid inappropriate exclusions?** We will score 'yes' if the study avoided inappropriate exclusions; 'no' if the study did not avoid inappropriate exclusions (e.g. only patients with severe disease included); and 'unclear' if insufficient information was reported to allow a judgement.

**Risk of bias** will be scored as ‘low concern’ if selection was done in a random or consecutive manner and the study avoided inappropriate exclusions; ‘high concern’ if selection was by convenience or the study had inappropriate exclusions; and ‘unclear concern’ if the manner of participant selection was unclear and no clinical information was provided.

**Applicability: Are there concerns that the included patients and setting do not match the review question?** We are interested in diagnosing disease activity in patients with established IBD. We will score 'low concern' for applicability if the patients clearly have established IBD and 'high' concern if it is possible that the sample includes patients with their first presentation of IBD. We will judge applicability to be of ‘unclear concern’ if the study does not provide enough clinical information to make a judgement about applicability.

**Domain 2: Index Test**

**Risk of bias: Could the conduct or interpretation of the index test have introduced bias?**

**Signalling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?** We will not score this signalling question, as it is not applicable to our review. The index tests for this review include serum CRP, SL and FC. These are objective tests based on laboratory results, which would not be influenced by blinding the test interpreter to the results of the reference standard.

**Signalling question 2: If a threshold was used, was it pre-specified?** We will score 'yes' if the threshold was pre-specified; 'no' if the threshold was not pre-specified; and
'unclear’ if insufficient information was reported to allow a judgement.

Risk of bias will be scored as ‘low concern’ if pre-specified thresholds were used; ‘high concern’ if thresholds were not pre-specified; and ‘unclear concern’ if insufficient information was reported to allow a judgement.

Applicability: Are there concerns that the index test, its conduct, or its interpretation differs from the review question? Although variations in test technology, execution, or interpretation might affect estimates of the diagnostic accuracy of a test, we feel that applicability of the index tests is not a concern for this review.

Domain 3: Reference Standard
Risk of bias: Could the reference standard, its conduct, or its interpretation has introduced bias?
Signalling question 1: Is the reference standard likely to correctly classify the target condition? Endoscopy is considered to be the gold standard for diagnosis of IBD. We will score ‘yes’ for all studies.
Signalling question 2: Were the reference standard results interpreted without knowledge of the results of the index test? We will score ‘yes’ if blinding was explicitly stated, or it was clear that the reference standard was performed at a separate outpatient location or performed by different people. We will score ‘no’ if the study stated that the reference standard result was interpreted with knowledge of index test results. We will score ‘unclear’ if insufficient information was reported to allow a judgement.
Risk of bias will be scored ‘low concern’ if the reference standard results were interpreted without knowledge of the results of the index test; ‘high concern’ if the study explicitly stated the result of the reference standard was interpreted with knowledge of the index test results. We will score ‘unclear concern’ if insufficient information was reported to allow a judgement.
Applicability: Are there concerns that the target condition as defined by the reference standard does not match the question? Endoscopy is considered to be the gold standard for diagnosis of IBD. We feel that applicability of the reference
standard is not a concern for this review.

Domain 4: Flow and Timing

Risk of bias: Could the patient flow have introduced bias?

Signalling question 1: Was there an appropriate interval between the index test and reference standard? In the majority of included studies, we expected specimens for the index tests to be obtained two weeks (or less) before endoscopy. However, even if there were a delay of several days or weeks between index test and reference standard, UC and Crohn's are chronic diseases and we consider misclassification of disease status to be unlikely. We will score 'yes' for studies that report an appropriate interval and 'unclear' for studies that do not report the interval.

Signalling question 2: Did all patients receive a reference standard? We will score 'yes' if all patients received a reference standard; 'no' if some patients did not receive the reference standard; and 'unclear' if insufficient information was reported to allow a judgement.

Signalling question 3: Did all patients receive the same reference standard? We will score 'yes' if it is clear that all patients in the study received the same reference standard; 'no' if it is clear that some patients received a different reference standard (e.g. patients with UC receiving colonoscopy or sigmoidoscopy); and 'unclear' if insufficient information was reported to allow a judgement.

Signalling question 4: Were all patients included in the analysis? We will score 'yes' if the number of patients enrolled matches the number of patients included in the analysis; 'no' if the number of patients enrolled does not match the number of patients included in the analysis; and 'unclear' if insufficient information was reported to allow a judgement.

Risk of bias will be scored 'low concern' if the number of patients enrolled was clearly reported and corresponds to the number of patients in the analysis or if exclusions were adequately described. We will score 'high concern' if there was a high proportion of missing patients or patients excluded from the analysis and there was no explanation given; and 'unclear concern' if insufficient information was reported to allow a judgement (i.e. the number of patients originally enrolled in the study was not explicitly reported).
**Supplementary Table 1**: Methodological quality summary; review authors' judgements about each methodological quality item for each included study.

<table>
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<th>Study</th>
<th>QI1</th>
<th>QI2</th>
<th>QI3</th>
<th>QI4</th>
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QI = Quality item; QI1 = Representative spectrum; QI2 = Acceptable reference standard; QI3 = Acceptable delay between tests; QI4 = Partial verification avoided; QI5 = Differential verification avoided; QI6 = Incorporation avoided; QI7 = Reference standard results blinded; QI8 = Index test results blinded; QI9 = Relevant clinical information; QI10 = Uninterpretable results; QI11 = Withdrawals
Supplementary Figure 1: Summary receiver operator characteristics plots of all tests