AGA CLINICAL PRACTICE GUIDELINE ON THE ROLE OF BIOMARKERS FOR THE MANAGEMENT OF CROHN’S DISEASE

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ONLINE SUPPLEMENT
**Table 1.** Systematic literature review on the role of biomarkers in inflammatory bowel diseases

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<th>November 10, 2021</th>
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**Cochrane**

1. MeSH descriptor: [Inflammatory Bowel Diseases] this term only
2. MeSH descriptor: [Colitis, Ulcerative] explode all trees
3. MeSH descriptor: [Crohn Disease] explode all trees
4. ("cleron disease" or "colitis ulcerativa" or "colitis ulcerosa" or "crohn disease" or "crohn's disease" or "Crohn's Enteritis" or "Granulomatous Colitis" or "Granulomatous Enteritis" or "Idiopathic Proctocolitis" or Ileocolitis or "Inflammatory Bowel Disease" or IBD or "morbus crohn" or "mucosal colitis" or "regional enterocolitis" or "Regional Enteritis" or "Regional Ileitides" or "Regional Ileitis" or "Terminal Ileitis" or "ulcerative colitis" or "ulcerative colorectitis" or "ulcerative procto colitis" or "ulcerative proctocolitis" or "ulcerous colitis"):ti,ab,kw
5. {OR #1-#4}
6. MeSH descriptor: [Lactoferrin] explode all trees
7. MeSH descriptor: [Leukocyte L1 Antigen Complex] explode all trees
8. (lactoferrin or calprotectin or lactotransferrin or (("calcium-binding" or "calcium binding") NEAR/1 "myeloid protein") or calgranulin or calprotectin or "Migratory Inhibitory Factor-Related Protein" or "Migratory Inhibitory Factor Related Protein" or ((L1 or 27E10) NEAR/2 antigen) or fCal or fLac):ti,ab,kw
9. MeSH descriptor: [C-Reactive Protein] explode all trees
10. ("c-reactive protein" or "c reactive protein" or CRP or hsCRP or "hs-CRP"):ti,ab,kw
11. MeSH descriptor: [Blood Sedimentation] explode all trees
12. ("blood sedimentation" or "erythrocyte sedimentation" or ESR):ti,ab,kw
13. ("mucosal healing" or MHI or Monitor):ti,ab,kw
14. MeSH descriptor: [Biomarkers] this term only
15. ((biochemical or biologic or biological or clinical or immune or immunologic or laboratory or serum or viral) NEAR/1 marker*:):ti,ab,kw
16. (surrogate NEAR/1 (endpoint* or *end point** or "end-point"* or marker*)):ti,ab,kw
17. (biomarker*:):ti,ab,kw
18. {OR #6-#17}
19. #5 AND #18
20. MeSH descriptor: [Sensitivity and Specificity] explode all trees
21. (sensitivity):ti,ab,kw
22. (specificity):ti,ab,kw
23. ((pre-test or pretest) NEAR/1 probability):ti,ab,kw
24. ("post-test probability"):ti,ab,kw
25. ("predictive value**"):ti,ab,kw
26. ("likelihood ratio**"):ti,ab,kw
27. (((disease* or lesion* or endocop*) NEAR/3 (activit* or scor*)) or (severity NEAR/3 (illness* or disease* or index))):ti,ab,kw
28. MeSH descriptor: [Severity of Illness Index] explode all trees
29. MeSH descriptor: [Predictive Value of Tests] explode all trees
30. MeSH descriptor: [Severity of Illness Index] this term only
31. {OR #20-#30}
32. #19 AND #31
33. MeSH descriptor: [Evidence-Based Medicine] explode all trees
34. MeSH descriptor: [Meta-Analysis] explode all trees
35. MeSH descriptor: [Systematic Review] explode all trees
36. MeSH descriptor: [Practice Guideline] explode all trees
37. MeSH descriptor: [Systematic Reviews as Topic] explode all trees
38. MeSH descriptor: [Meta-Analysis as Topic] explode all trees
39. MeSH descriptor: [Technology Assessment, Biomedical] explode all trees
40. MeSH descriptor: [Network Meta-Analysis] explode all trees
41. MeSH descriptor: [Practice Guidelines as Topic] explode all trees
42. MeSH descriptor: [Randomized Controlled Trial] explode all trees
43. MeSH descriptor: [Placebo Effect] explode all trees
44. MeSH descriptor: [Placebos] explode all trees
45. MeSH descriptor: [Comparative Study] explode all trees
46. MeSH descriptor: [Clinical Trial] explode all trees
47. MeSH descriptor: [Cross-Sectional Studies] explode all trees
48. MeSH descriptor: [Cohort Studies] explode all trees
49. MeSH descriptor: [Longitudinal Studies] explode all trees
50. MeSH descriptor: [Retrospective Studies] explode all trees
51. MeSH descriptor: [Prospective Studies] explode all trees
52. MeSH descriptor: [Observational Study] explode all trees
53. MeSH descriptor: [Clinical Study] this term only
54. MeSH descriptor: [Evaluation Study] explode all trees
55. MeSH descriptor: [Validation Study] explode all trees
56. MeSH descriptor: [Case-Control Studies] explode all trees
57. MeSH descriptor: [Confidence Intervals] explode all trees
58. MeSH descriptor: [Multivariate Analysis] explode all trees
59. ((evidence NEAR/1 based) or (meta NEAR/1 analy*) or metaanalys* or (systematic* NEAR/3 review*) or
guideline* or (control* NEAR/3 study) or (control* NEAR/3 trial) or (randomized NEAR/3 study) or (randomized
NEAR/3 trial) or (randomised NEAR/3 study) or (randomised NEAR/3 trial) or "pragmatic clinical trial" or (random*
NEAR/1 allocat*) or (doubl* NEAR/1 blind*) or (doubl* NEAR/1 mask*) or (singl* NEAR/1 blind*) or (singl* NEAR/1
mask*) or (trip* NEAR/1 blind*) or (trip* NEAR/1 mask*) or (trebl* NEAR/1 blind*) or (trebl* NEAR/1 mask*) or
"latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or
"comparative analysis" or (intervention* NEAR/2 study) or (intervention* NEAR/2 trial) or "cross-sectional study" or
"cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or
"prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or
"disease frequency survey" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or
"longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") NEAR/3 (study or survey or analysis
or design)) or retrospective* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv*
or "concurrent study" or "concurrent survey" or "concurrent analysis" or ("(follow-up" or followup) NEAR/1 (stud* or
survey or analysis)) or ((observation or observational) NEAR/1 (study or survey or analysis)) or "clinical study" or
"clinical trial" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "validation study" or "validation
survey" or "validation analysis" or "case control study" or "case base study" or "case referent study" or "case
referent study" or "case referent study" or "case compere study" or "case comparison study" or "matched case
control" or "multicenter study" or "multi-center study" or study or trial or "odds ratio" or "confidence interval" or
"change analysis" or ((study or trial or random* or control*) and compar*)):ti,ab,kw
60. {OR #33-#59}
61. #32 AND #60
62. MeSH descriptor: [Animals] explode all trees
63. MeSH descriptor: [Humans] explode all trees
Embase

1. inflammatory bowel disease/
2. enteritis/
3. exp ulcerative colitis/
4. exp Crohn disease/
5. ("cleron disease" or "colitis ulcerativa" or "colitis ulcerosa" or "crohn disease" or "crohn's disease" or "Crohn's Enteritis" or "Granulomatous Colitis" or "Granulomatous Enteritis" or "Idiopathic Proctocolitis" or Ileocolitis or "Inflammatory Bowel Disease" or IBD or "morbus crohn" or "mucosal colitis" or "regional enterocolitis" or "Regional Enteritis" or "Regional Ileitides" or "Regional Ileitis" or "Terminal Ileitis" or "ulcerative colitis" or "ulcerative colorectis" or "ulcerative procto colitis" or "ulcerative proctocolitis" or "ulcerous colitis").tw,kw.
6. or/1-5
7. exp lactoferrin/
8. exp calgranulin/
9. (lactoferrin or calprotectin or lactotransferrin or ("calcium-binding" or "calcium binding") adj1 "myeloid protein") or calgranulin or calprotectin or "Migratory Inhibitory Factor-Related Protein" or ((L1 or 27E10) adj2 antigen) or fCal or fLac).tw,kw.
10. exp C reactive protein/
11. ("c-reactive protein" or "c reactive protein" or CRP or hsCRP or "hs-CRP").tw,kw.
12. exp erythrocyte sedimentation rate/
13. ("blood sedimentation" or "erythrocyte sedimentation" or ESR).tw,kw.
14. ("mucosal healing" or MHI or Monitr).tw,kw.
15. biological marker/
16. ((biochemical or biologic or biological or clinical or immune or immunologic or laboratory or serum or viral) adj1 marker$).tw,kw.
17. (surrogate adj1 (endpoint$ or "end point$" or "end-point$" or marker$)).tw,kw.
18. biomarker$.tw,kw.
19. or/7-18
20. 6 and 19
21. exp "sensitivity and specificity"/
22. sensitivity.tw,hw,kw.
23. specificity.tw,hw,kw.
24. ((pre-test or pretest) adj probability).tw,hw,kw.
25. post-test probability.tw,hw,kw.
26. predictive value$.tw,hw,kw.
27. likelihood ratio$.tw,hw,kw.
28. (((disease* or lesion* or endocop*) adj3 (activit* or scor*)) or (severity adj3 (illness* or disease* or index))).ti,ab,hw,kw.
29. exp "severity of illness index"/
30. exp predictive value/
31. disease severity/
32. or/21-31
33. 20 and 32
34. exp evidence based medicine/
35. exp meta analysis/
36. exp "systematic review"/
37. exp practice guideline/
38. exp practice guideline/
39. exp controlled study/
40. exp randomized controlled trial/
41. exp triple blind procedure/
42. exp double blind procedure/
43. exp single blind procedure/
44. exp Latin square design/
45. exp placebo effect/ or exp placebo/
46. exp comparative study/
47. exp intervention study/
48. exp cross-sectional study/
49. exp cohort analysis/
50. exp longitudinal study/
51. exp retrospective study/
52. exp prospective study/
53. exp population research/
54. exp observational study/
55. exp clinical trial/
56. clinical study/
57. exp evaluation study/
58. exp validation study/
59. exp correlational study/
60. exp case control study/
61. exp confidence interval/
62. exp multivariate analysis/
63. ((evidence adj based) or (meta adj analy*) or metaanalys* or (systematic* adj3 review*) or guideline* or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (random* adj1 allocat*) or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospective* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or (("follow-up" or followup) adj (stud* or survey or analysis)) or ((observation or observational) adj (study or survey or analysis)) or "clinical study" or "clinical trial" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "validation study" or "validation survey" or "validation analysis" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case compere study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or study or trial or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*)).mp.pt.
64. or/34-63
65. 33 and 66
66. case report.ti.
67. 65 not 66
68. exp animal/
69. exp human/
70. 68 not 69
71. 67 not 70

Global Index Medicus
(tw:"cleron disease" OR "colitis ulcerativa" OR "colitis ulcerosa" OR "crohn disease" OR "crohn's disease" OR "Crohn's Enteritis" OR "Granulomatous Colitis" OR "Granulomatous Enteritis" OR "Idiopathic Proctocolitis" OR Ileocolitis OR "Inflammatory Bowel Disease" OR IBD OR "morbis crohn" OR "mucosal colitis" OR "regional enterocolitis" OR "Regional Enteritis" OR "Regional Ileitides" OR "Regional Ileitis" OR "Terminal Ileitis" OR "ulcerative colitis" OR "ulcerative colorectitis" OR "ulcerative procto colitis" OR "ulcerative proctocolitis" OR "ulcerous colitis") AND ((tw:(lactoferrin OR
specificity.tw, hw, kw.
23. ((pre-test or pretest) adj probability).tw, hw, kw.
24. post-test probability.tw, hw, kw.
25. predictive value$.tw, hw, kw.
26. likelihood ratio$.tw, hw, kw.
27. (((disease* or lesion* or endocop*) adj3 (activit* or scor*)) or (severity adj3 (illness* or disease* or
index))).ti, ab, hw, kw.
28. exp "Severity of Illness Index"/
29. exp "Predictive Value of Tests"/
30. disease severity/
31. or/20-30
32. 19 and 31
33. exp Evidence-Based Medicine/
34. exp Meta-Analysis/
35. exp "Systematic Review"/
36. exp Practice Guideline/
37. exp Systematic Reviews as Topic/
38. exp Meta-Analysis as Topic/
39. exp Technology Assessment, Biomedical/
40. exp Network Meta-Analysis/
41. systematic review.pt.
42. meta-analysis.pt.
43. exp practice guideline/
44. exp randomized controlled trial/
45. exp placebo effect/ or exp placebo/
46. exp comparative study/
47. exp intervention study/
48. exp cross-sectional study/
49. exp cohort analysis/
50. exp longitudinal study/
51. exp retrospective study/
52. exp prospective study/
53. exp observational study/
54. exp clinical trial/
55. clinical study/
56. exp evaluation study/
57. exp validation study/
58. exp case control study/
59. exp confidence interval/
60. exp multivariate analysis/
61. ((evidence adj based) or (meta adj analys*) or metaanalys* or (systematic* adj3 review*) or guideline* or (control*
adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study)
or (randomised adj3 trial) or "pragmatic clinical trial" or (random* adj1 allocat*) or (doubl* adj blind*) or (doubl* adj
mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or
(trebl* adj mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative
survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study"
or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence
analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease
discovery survey" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or
"longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or
design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or
"concurrent study" or "concurrent survey" or "concurrent analysis" or ("follow-up" or followup) adj (stud* or survey
or analysis)) or (observation or observational) adj (study or survey or analysis) or "clinical study" or "clinical
trial" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "validation study" or "validation
survey" or
Scopus

(((INDEXTERMS("inflammatory bowel disease") OR INDEXTERMS("enteritis")) OR INDEXTERMS("ulcerative colitis")) OR INDEXTERMS("Colitis, Ulcerative") OR INDEXTERMS("Crohn disease") OR TITLE-ABS-KEY("clerion disease") OR "colitis ulcerativa" OR "colitis ulcerosa" OR "crohn disease" OR "crohn's disease" OR "Crohn's Enteritis" OR "Granulomatous Colitis" OR "Granulomatous Enteritis" OR "Idiopathic Proctocolitis" OR ileocolitis OR "Inflammatory Bowel Disease" OR ibd OR "morbus crohn" OR "mucosal colitis" OR "regional enterocolitis" OR "Regional Enteritis" OR "Regional Ileitides" OR "Regional Ileitis" OR "Terminal ileitis" OR "ulcerative colitis" OR ulcerative colerectitis OR "ulcerative procto colitis" OR "ulcerative proctocolitis" OR "ulcerous colitis")) AND ((INDEXTERMS("lactoferrin") OR INDEXTERMS("calgranulin") OR INDEXTERMS("Leukocyte L1 Antigen Complex")) OR TITLE-ABS-KEY("lactoferrin" OR calprotectin OR lactotransferrin OR (("calcium-binding" OR "calcium binding") W/1 "myeloid protein") OR calgranulin OR calprotectin OR "Migratory Inhibitory Factor-Related Protein" OR "Migratory Inhibitory Factor Related Protein" OR ((11 OR 27e10) W/2 antigen) OR fcal OR flac) OR INDEXTERMS("C reactive protein") OR INDEXTERMS("C-Reactive Protein") OR TITLE-ABS-KEY("c-reactive protein" OR "c reactive protein" OR "c reactive protein" OR crp OR hscrp OR "hs-CRP") OR INDEXTERMS("erythrocyte sedimentation rate") OR INDEXTERMS("Blood Sedimentation") OR TITLE-ABS-KEY("blood sedimentation") OR "erythrocyte sedimentation" OR esr) OR TITLE-ABS-KEY("mucosal healing" OR mhi OR monitr) OR INDEXTERMS("biological marker") OR INDEXTERMS("Biomarkers") OR TITLE-ABS-KEY(((biochemical OR biologic OR biological OR clinical OR immune OR immunologic OR laboratory OR serum OR viral) W/1 marker) OR TITLE-ABS-KEY (surrogate W/1 (endpoint OR "end point" OR "end point" OR "end point" OR marker)) OR TITLE-ABS-KEY(biomarker*) AND ((INDEXTERMS("sensitivity and specificity") OR TITLE-ABS-KEY("sensitivity") OR TITLE-ABS-KEY("specificity") OR TITLE-ABS-KEY((pre-test OR pretest) W/1 probability)) OR TITLE-ABS-KEY("post-test probability") OR TITLE-ABS-KEY("predictive value") OR TITLE-ABS-KEY("likelihood ratio") OR TITLE-ABS-KEY ((disease OR lesion OR endocap) W/3 (activit OR scor)) OR TITLE-ABS-KEY(severity W/3 (illness OR disease OR index)) OR INDEXTERMS("severity of illness index") OR INDEXTERMS("predictive value") OR INDEXTERMS("disease severity") AND ((INDEXTERMS("evidence based medicine") OR INDEXTERMS("meta-analysis") OR INDEXTERMS("systematic review") OR INDEXTERMS("practice guideline") OR INDEXTERMS("systematic review as topic") OR INDEXTERMS("meta-analysis as topic") OR INDEXTERMS("practice guideline as topic") OR INDEXTERMS("controlled study") OR INDEXTERMS("randomized controlled trial") OR INDEXTERMS("triple blind procedure") OR INDEXTERMS("double blind procedure") OR INDEXTERMS("single blind procedure") OR INDEXTERMS("Latin square design") OR INDEXTERMS("placebo effect") OR INDEXTERMS("placebos") OR INDEXTERMS("comparative study") OR INDEXTERMS("intervention study") OR INDEXTERMS("cross-sectional study") OR INDEXTERMS("cohort analysis") OR INDEXTERMS("longitudinal study") OR INDEXTERMS("retrospective study") OR INDEXTERMS("prospective study") OR INDEXTERMS("population research") OR INDEXTERMS("observational study") OR INDEXTERMS("clinical trial") OR INDEXTERMS("clinical study") OR INDEXTERMS("evaluation study") OR INDEXTERMS("validation study") OR INDEXTERMS("correlational study") OR INDEXTERMS("case control study") OR INDEXTERMS("confidence interval") OR INDEXTERMS("multivariate analysis") OR TITLE-ABS-KEY(("evidence AND w/1based") OR (meta AND w/1analys*) OR metaanalys* OR (systematic* W/3 review*) OR guideline* OR (control W/3 study) OR (control W/3 trial) OR (randomized W/3 study) OR (randomized W/3 trial) OR (randomised W/3 study) OR (randomised W/3 trial) OR (pragmatic clinical trial OR (random* W/1 allocat) OR (double* AND W/1blind*) OR (double* AND W/1mask*) OR (singl* AND W/1blind*) OR (singl* AND W/1mask*) OR (tripl* AND W/1blind*) OR (tripl* AND W/1mask*) OR (trebl* AND W/1blind*) OR (trebl* AND W/1mask*) OR (tripl* AND W/1mask*) OR (tripl* AND W/1blind*) OR (tripl* AND W/1mask*) OR (tripl* AND W/1blind*) OR (tripl* AND W/1mask*) OR (lati* OR placebo* OR nocebo* OR multicvariate OR comparative study) OR "comparative survey" OR "comparative analysis" OR "intervention" W/2 study) OR (intervention* W/2 trial) OR "cross-sectional study" OR "cross-sectional analysis" OR "cross-sectional survey" OR "cross-sectional design" OR "prevalence study" OR "prevalence analysis" OR "prevalence survey" OR "disease frequency study" OR "disease frequency analysis" OR "disease frequency survey" OR cohort* OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "longitudinal evaluation" OR longitudinal* OR ((retrospective OR "ex post facto") W/3 (study OR survey OR analysis OR design)) OR retrospective* OR "prospective study" OR "prospective survey" OR "prospective analysis" OR prospectiv* OR "concurrent study" OR "concurrent survey" OR "current analysis" OR (("follow-up" OR followup) W/1 (stud* OR survey OR analysis)) OR (observation OR observational) W/1 (study OR survey OR analysis)) OR "clinical study" OR "clinical trial" OR "evaluation study" OR "evaluation survey" OR "evaluation analysis" OR "validation study" OR "validation survey" OR "validation analysis" OR "case control study" OR "case base study" OR "case referrent study" OR "case referent study" OR "case referent study" OR "case compleer study" OR "case comparison study" OR "matched case control" OR "multicenter study" OR "multi-center study" OR study OR trial OR "odds ratio" OR "confidence interval" OR "change analysis" OR ((study OR trial OR random* OR control*) AND compar*)))))) AND NOT (INDEXTERMS("Animals") AND NOT INDEXTERMS("Humans"))
1. TS="("cleron disease" or "colitis ulcerativa" or "colitis ulcerosa" or "crohn disease" or "crohn's disease" or "Crohn's Enteritis" or "Granulomatous Colitis" or "Granulomatous Enteritis" or "Idiopathic Proctocolitis" or Ileocolitis or "Inflammatory Bowel Disease" or IBD or "morbus crohn" or "mucosal colitis" or "regional enterocolitis" or "Regional Enteritis" or "Regional Ileitides" or "Regional ileitis" or "Terminal ileitis" or "ulcerative colitis" or "ulcerative colorectitis" or "ulcerative procto colitis" or "ulcerative proctocolitis" or "ulcerous colitis")

2. TS="("calcium-binding" or "calcium binding") NEAR/1 "myeloid protein") or calgranulin or calprotectin or "Migratory Inhibitory Factor Related Protein" or "Migratory Inhibitory Factor Related Protein" or ((L1 or 27E10) NEAR/2 antigen) or fCal or fLac OR "c-reactive protein" or "c reactive protein" or CRP or hscRP OR "hs-CRP" OR "blood sedimentation" or "erythrocyte sedimentation" or ESR OR "mucosal healing" or MHI or Monitr OR ((biochemical or biologic or biological or clinical or immune or immunologic or laboratory or serum or viral) NEAR/1 marker*) OR (surrogate NEAR/1 (endpoint* or "end point"* or "end-point"* or marker*)) OR biomarker*)

3. TS=(sensitivity OR specificity OR ((pre-test or pretest) NEXT probability) OR "post-test probability" OR "predictive value"* OR "likelihood ratio"* OR (((disease* or lesion* or endocop*) NEAR/3 (activit* or scor*)) or (severity NEAR/3 (illness* or disease* or index)))

4. TS=((evidence NEXT based) or (meta NEXT analy*) or metaanaly* or (systematic* NEAR/3 review*) or guideline* or (control* NEAR/3 study) or (control* NEAR/3 trial) or (randomized NEAR/3 study) or (randomized NEAR/3 trial) or (randomised NEAR/3 study) or (randomised NEAR/3 trial) or "pragmatic clinical trial" or (random* NEAR/1 allocat*) or (doubl* NEXT blind*) or (doubl* NEXT mask*) or (singl* NEXT blind*) or (singl* NEXT mask*) or (tripl* NEXT blind*) or (tripl* NEXT mask*) or (trebl* NEXT blind*) or (trebl* NEXT mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative analysis" or "comparative survey" or "comparative survey" or (intervention* NEAR/2 study) or (intervention* NEAR/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") NEAR/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or (("follow-up" or followup) NEXT (stud* or survey or analysis)) or ("observation or observational" NEXT (study or survey or analysis)) or "clinical study" or "clinical trial" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "validation study" or "validation survey" or "validation analysis" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case report study" or "case compar is study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or study or trial or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*))

5. #1 AND #2 AND #3 AND #4
eFigure 1. Clinical scenario for implementing the use of biomarkers in patients with Crohn's disease in symptomatic remission

Patient with CD in SYMPTOMATIC REMISSION (PRO2 <8 or PRO3 <13)

Undergoes biomarker testing

Test Negative (Normal)  
fCal cut-off <50 vs. <150  
CRP normal

True negative  
You avoid an invasive procedure

False negative (i.e., you miss endoscopically active disease)  
Patient is falsely reassured, undertreated, and has risk of flaring/disease complications

Test Positive (elevated)  
fCal cut-off >150 vs. >250  
CRP elevated

True positive  
You adjust therapy proactively to avoid flare

False positive (i.e., you wrongly infer patient has endoscopically active disease)  
Patient has anxiety, may undergo additional endoscopy (stool test as triage) vs. potential overtreatment with cost and side effects (test replacement)

What FN rate is acceptable?  
10-49 in 1000 (1-4.9%)

What FP rate is acceptable?  
10-49 in 1000 (1-4.9%)
**eFigure 2. Clinical scenario for implementing the use of biomarkers in patients with symptomatically active Crohn’s disease**

**Patient with SYMPTOMATICALLY ACTIVE CD (PRO2 >8 or PRO3 >12)**

**Test Negative (Normal)**
- fCal cut-off <50 vs. <150, or normal CRP
  - **True negative**
    - You avoid an invasive procedure
  - **False negative** (i.e., you miss endoscopically active disease)
    - Patient is falsely reassured, undertreated, and has risk of flaring/disease complications

**Test Positive (elevated)**
- fCal cut-off >150 vs. >250, or elevated CRP
  - **True positive**
    - You adjust therapy proactively to avoid flare
  - **False positive** (i.e., you wrongly infer patient has active disease)
    - Patient has anxiety, may undergo additional endoscopy (stool test as triage) vs. potential overtreatment with cost and side effects (test replacement)

**What FN rate is acceptable?**
- 10-49 in 1000 (1-4.9%)

**What FP rate is acceptable?**
- 10-49 in 1000 (1-4.9%)
eFigure 3. Schema for proposed comparison of a biomarker-based monitoring strategy vs. symptom-based monitoring strategy in patients with Crohn’s disease in symptomatic remission.
**eFigure 4.** Meta-analysis comparing risk of relapse in patients with Crohn’s disease in symptomatic remission with elevated fecal calprotectin vs. normal calprotectin

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Risk ratio and 95% CI</th>
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<tr>
<td>Costa 2005</td>
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<td>0.44</td>
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<td>D'Inca 2008</td>
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<td>Gisbert 2009</td>
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<td>Magro 2022</td>
<td>1.60</td>
<td>1.17</td>
<td>2.17</td>
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</tr>
</tbody>
</table>

Meta Analysis
eFigure 5. Diagnostic performance of fecal calprotectin in patients with luminal Crohn’s disease at cut-off (A) >50\(\mu\)g/g, (B) >150\(\mu\)g/g and (C) >250\(\mu\)g/g to detect endoscopic inflammation

(A) >50mg/g
(B) >150mg/g

Summary point HSROC curve
95% confidence region
95% prediction region
(C)>250mg/g
eFigure 6. Diagnostic performance of serum CRP to detect endoscopic inflammation in patients with luminal Crohn’s disease.
eFigure 7. Diagnostic performance of fecal calprotectin in patients with surgically-induced remission at cut-off (A) >50mg/g, (B) >150mg/g and (C) >250mg/g to detect endoscopic recurrence 6-12 months after surgery

A) > 50mg/g
B) > 150mg/g
C) > 250mg/g

Summary point HSROC curve
95% confidence region
95% prediction region
eFigure 8. Pre-test probabilities of detecting endoscopic recurrence 6-12 months after surgery in asymptomatic patients, based on individual patient factors influencing risk of post-operative recurrence at time of surgery, and use of post-operative pharmacological prophylaxis

<table>
<thead>
<tr>
<th>Higher baseline risk of recurrence</th>
<th>Not post-op prophylaxis</th>
<th>ON post-op prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td>Lower baseline risk of recurrence</td>
<td>30%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Illustrative risk categories for recurrence of CD after surgically-induced remission:
- **Higher risk**: Younger patient (<30y); smoker; ≥2 prior surgeries for penetrating disease, with or without perianal disease
- **Lower risk**: Older patient (>50y); non-smoker; 1st surgery for a short segment of fibrostenotic disease (<10-20cm); disease duration >10 years
**eFigure 9.** Schema for proposed comparison of a biomarker-based monitoring strategy vs. endoscopy-based monitoring strategy in patients with Crohn’s disease in symptomatic remission

Patient with established CD in **comes for routine scheduled annual visit**

**Symptoms:** in symptomatic remission (PRO2 <8 or PRO3 <13)

**BIOMARKER-BASED MONITORING**
- Check biomarker (stool-based, or serum-based)
  - **Biomarker normal**
    - Patient deemed to be **IN CLINICAL + BIOCHEMICAL REMISSION**
    - Continue current therapy
  - **Biomarker ELEVATED** (suggests inflammation)
    - Patient suspected to have active inflammation
    - Proceed with endoscopy or repeat biomarker testing, to inform treatment decisions

**ENDOSCOPY-BASED MONITORING**
- Perform endoscopy
  - **Endoscopy with inflammation**
    - Adjust therapy to target endoscopic remission
  - **Endoscopy with remission**
    - Patient deemed to be **IN CLINICAL + ENDOSCOPIC REMISSION**
    - Continue current therapy

**LONG-TERM REMISSION OVER NEXT 12 MONTHS**