

AGA CLINICAL PRACTICE GUIDELINE ON THE ROLE OF BIOMARKERS FOR THE MANAGEMENT OF ULCERATIVE COLITIS

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ONLINE SUPPLEMENT

eTable 1. Systematic literature review on the role of biomarkers in inflammatory bowel diseases

Database specifics	November 10, 2021
Cochrane Library via Wiley	1162
Embase Classic+Embase	10569
Global Index Medicus	279
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)	3792
PubMed	5101
Scopus	6878
Web of Science	3122

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 coloproctitis" 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 Monitr):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 analys*) 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 (tripl* NEAR/1 blind*) or (tripl* 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 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) 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 compeer 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
64. #62 NOT #63
65. #61 NOT #64

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 coloproctitis" 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 "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 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 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 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 "validation analysis" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case compeer 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 64
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 "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 coloproctitis" OR "ulcerative procto colitis" OR "ulcerative proctocolitis" OR "ulcerous colitis")) AND ((tw:(lactoferrin OR calprotectin OR lactotransferrin OR ("calcium-binding" OR "calcium binding") AND "myeloid protein") OR calgranulin OR calprotectin OR "Migratory Inhibitory Factor-Related Protein" OR "Migratory Inhibitory Factor Related Protein" OR ((L1 OR 27E10) AND antigen) OR fCal OR fLac)) OR (tw:("c-reactive protein" OR "c reactive protein" OR CRP OR hsCRP OR "hs-CRP") OR (tw:("blood sedimentation" OR "erythrocyte sedimentation" OR ESR) OR ("mucosal healing" OR MHI OR Monitr))) OR (tw:((biochemical OR biologic OR biological OR clinical OR immune OR immunologic OR laboratory OR serum OR viral) AND marker*)) OR (tw:(surrogate AND (endpoint* OR "end point*" OR "end-point*" OR marker*)) OR (tw:(biomarker*)) AND (tw:(sensitivity OR specificity OR ((pre-test OR pretest) AND probability) OR "post-test probability" OR "predictive value*" OR "likelihood ratio*" OR (((disease* OR lesion* OR endocop*) AND (activit* OR scor*)) OR (severity AND (illness* OR disease* OR index)))))) AND (tw:(evidence AND based) OR (meta AND analys*) OR metaanalys* OR (systematic* AND review*) OR guideline* OR (control* AND study) OR (control* AND trial) OR (randomized

AND study) OR (randomized AND trial) OR (randomised AND study) OR (randomised AND trial) OR "pragmatic clinical trial" OR (random* AND allocat*) OR (doubl* AND blind*) OR (doubl* AND mask*) OR (singl* AND blind*) OR (singl* AND mask*) OR (tripl* AND blind*) OR (tripl* AND mask*) OR (trebl* AND blind*) OR (trebl* AND mask*) OR "latin square" OR placebo* OR nocebo* OR multivariate OR "comparative study" OR "comparative survey" OR "comparative analysis" OR (intervention* AND study) OR (intervention* AND 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 ((retrospective OR "ex post facto") AND (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) AND (stud* OR survey OR analysis)) OR ((observation OR observational) AND (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 compeer 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*))

Ovid Medline

1. Inflammatory Bowel Disease/
2. exp "Colitis, Ulcerative"/
3. exp "Crohn Disease"/
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 coloproctitis" or "ulcerative procto colitis" or "ulcerative proctocolitis" or "ulcerous colitis").tw,kw.
5. or/1-4
6. exp Lactoferrin/
7. exp "Leukocyte L1 Antigen Complex"/
8. (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 "Migratory Inhibitory Factor Related Protein" or ((L1 or 27E10) adj2 antigen) or fCal or fLac).tw,kw.
9. exp C-Reactive Protein/
10. ("c-reactive protein" or "c reactive protein" or CRP or hsCRP or "hs-CRP").tw,kw.
11. exp Blood Sedimentation/
12. ("blood sedimentation" or "erythrocyte sedimentation" or ESR).tw,kw.
13. ("mucosal healing" or MHI or Monitr).tw,kw.
14. Biomarkers/
15. ((biochemical or biologic or biological or clinical or immune or immunologic or laboratory or serum or viral) adj1 marker\$).tw,kw.
16. (surrogate adj1 (endpoint\$ or "end point\$" or "end-point\$" or marker\$)).tw,kw.
17. biomarker\$.tw,kw.
18. or/6-17
19. 5 and 18
20. exp "Sensitivity and Specificity"/
21. sensitivity.tw,hw,kw.
22. 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 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 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 "validation analysis" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case compeer 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.

62. or/33-61

63. 32 and 62

64. case report.ti.

65. 63 not 64

66. exp animals/ not exp humans/

67. 65 not 66

68. remove duplicates from 67

PubMed

("Inflammatory Bowel Diseases"[Mesh:NoExp] OR "Colitis, Ulcerative"[Mesh] OR "Crohn Disease"[Mesh] OR ("cleron disease"[tw] OR "colitis ulcerativa"[tw] OR "colitis ulcerosa"[tw] OR "crohn disease"[tw] OR "crohn's disease"[tw] OR "Crohn's Enteritis"[tw] OR "Granulomatous Colitis"[tw] OR "Granulomatous Enteritis"[tw] OR "Idiopathic Proctocolitis"[tw] OR Ileocolitis[tw] OR "Inflammatory Bowel Disease"[tw] OR IBD[tw] OR "morbus crohn"[tw] OR "mucosal colitis"[tw] OR "regional enterocolitis"[tw] OR "Regional Enteritis"[tw] OR "Regional Ileitides"[tw] OR "Regional Ileitis"[tw] OR "Terminal Ileitis"[tw] OR "ulcerative colitis"[tw] OR "ulcerative coloproctitis"[tw] OR "ulcerative procto colitis"[tw] OR "ulcerative proctocolitis"[tw] OR "ulcerous colitis"[tw])) AND ("Lactoferrin"[Mesh] OR "Leukocyte L1 Antigen Complex"[Mesh] OR (lactoferrin[tw] OR calprotectin[tw] OR lactotransferrin[tw] OR (("calcium-binding"[tw] OR "calcium binding") AND "myeloid protein"))[tw] OR calgranulin[tw] OR calprotectin[tw] OR "Migratory Inhibitory Factor-Related Protein"[tw] OR "Migratory Inhibitory Factor Related Protein"[tw] OR ((L1[tw] OR 27E10) AND antigen)[tw] OR fCal[tw] OR fLac[tw]) OR "C-Reactive Protein"[Mesh] OR ("c-reactive protein"[tw] OR "c reactive protein"[tw] OR CRP[tw] OR hsCRP[tw] OR "hs-CRP"[tw] OR "Blood Sedimentation"[Mesh] OR ("blood sedimentation"[tw] OR "erythrocyte sedimentation"[tw] OR ESR[tw] OR ("mucosal healing"[tw] OR MHI[tw] OR Monitr[tw]) OR "Biomarkers"[Mesh:NoExp] OR ((biochemical[tw] OR biologic[tw] OR biological[tw] OR clinical[tw] OR immune[tw] OR immunologic[tw] OR laboratory[tw] OR serum[tw] OR viral[tw]) AND marker*[tw]) OR (surrogate[tw] AND (endpoint*[tw] OR "end point"*[tw] OR "end-point"*[tw] OR marker*[tw])) OR biomarker*[tw]) AND ("Sensitivity and Specificity"[Mesh] OR sensitivity[tw] OR specificity[tw] OR ((pre-test[tw] OR pretest[tw]) AND probability[tw]) OR "post-test probability"[tw] OR "predictive value"*[tw] OR "likelihood ratio"*[tw] OR (((disease*[tw] OR lesion*[tw] OR endocop*[tw]) AND (activit*[tw] OR scor*[tw]))) OR (severity[tw] AND (illness*[tw] OR disease*[tw] OR index[tw]))) OR "Severity of Illness Index"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "disease severity"[Mesh:NoExp]) AND ("Evidence-Based Medicine"[Mesh] OR "Meta-Analysis"[Mesh] OR "Systematic Review"[Mesh] OR "Practice Guideline"[Mesh] OR "Systematic Reviews as Topic"[Mesh] OR "Meta-Analysis as Topic"[Mesh] OR "Technology Assessment, Biomedical"[Mesh] OR "Network Meta-Analysis"[Mesh] OR "systematic review"[pt] OR "meta-analysis"[pt] OR "practice guidelines as topic"[Mesh] OR "randomized controlled trial"[Mesh] OR "placebo effect"[Mesh] OR "placebos"[Mesh] OR "comparative study"[Mesh] OR "intervention studies"[Mesh] OR "cross-sectional studies"[Mesh] OR "cohort analysis"[Mesh] OR "longitudinal study"[Mesh] OR "retrospective study"[Mesh] OR "prospective study"[Mesh] OR "observational study"[Mesh] OR "clinical trial"[Mesh] OR "clinical study"[Mesh:NoExp] OR "evaluation study"[Mesh] OR "validation study"[Mesh] OR "case-control studies"[Mesh] OR "confidence intervals"[Mesh] OR "multivariate analysis"[Mesh] OR ((evidence[tw] AND based)[tw] OR (meta[tw] AND analys*[tw]) OR metaanalys*[tw] OR (systematic*[tw] AND review*[tw]) OR guideline*[tw] OR (control*[tw] AND study[tw]) OR (control*[tw] AND trial[tw]) OR (randomized[tw] AND study[tw]) OR (randomized[tw] AND trial[tw]) OR (randomised[tw] AND study[tw]) OR (randomised[tw] AND trial[tw]) OR "pragmatic clinical trial"[tw] OR (random*[tw] AND allocat*[tw]) OR (doubl*[tw] AND blind*[tw]) OR (doubl*[tw] AND mask*[tw]) OR (singl*[tw] AND blind*[tw]) OR (singl*[tw] AND mask*[tw]) OR (tripl*[tw] AND blind*[tw]) OR (tripl*[tw] AND mask*[tw]) OR (trebl*[tw] AND blind*[tw]) OR (trebl*[tw] AND mask*[tw]) OR "latin square"[tw] OR placebo*[tw] OR nocebo*[tw] OR multivariate[tw] OR "comparative study"[tw] OR "comparative survey"[tw]

OR "comparative analysis"[tw] OR (intervention*[tw] AND study[tw]) OR (intervention*[tw] AND trial[tw]) OR "cross-sectional study"[tw] OR "cross-sectional analysis"[tw] OR "cross-sectional survey"[tw] OR "cross-sectional design"[tw] OR "prevalence study"[tw] OR "prevalence analysis"[tw] OR "prevalence survey"[tw] OR "disease frequency study"[tw] OR "disease frequency analysis"[tw] OR "disease frequency survey"[tw] OR cohort*[tw] OR "longitudinal study"[tw] OR "longitudinal survey"[tw] OR "longitudinal analysis"[tw] OR "longitudinal evaluation"[tw] OR ((retrospective[tw] OR "ex post facto"[tw]) AND (study[tw] OR survey[tw] OR analysis[tw] OR design[tw])) OR retrospectiv*[tw] OR "prospective study"[tw] OR "prospective survey"[tw] OR "prospective analysis"[tw] OR "concurrent study"[tw] OR "concurrent survey"[tw] OR "concurrent analysis"[tw] OR (("follow-up"[tw] OR followup[tw]) AND (stud*[tw] OR survey[tw] OR analysis[tw])) OR ((observation[tw] OR observational[tw]) AND (study[tw] OR survey[tw] OR analysis[tw])) OR "clinical study"[tw] OR "clinical trial"[tw] OR "evaluation study"[tw] OR "evaluation survey"[tw] OR "evaluation analysis"[tw] OR "validation study"[tw] OR "validation survey"[tw] OR "validation analysis"[tw] OR "case control study"[tw] OR "case base study"[tw] OR "case referent study"[tw] OR "case referent study"[tw] OR "case referent study"[tw] OR "case compeer study"[tw] OR "case comparison study"[tw] OR "matched case control"[tw] OR "multicenter study"[tw] OR "multi-center study"[tw] OR study[tw] OR trial[tw] OR "odds ratio"[tw] OR "confidence interval"[tw] OR "change analysis"[tw] OR ((study[tw] OR trial[tw] OR random*[tw] OR control*[tw]) AND compar*[tw])) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

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(((INDEXTERMS ("inflammatory bowel disease") OR INDEXTERMS ("enteritis") OR INDEXTERMS ("ulcerative colitis") OR INDEXTERMS ("Colitis, Ulcerative") OR INDEXTERMS ("Crohn disease") OR TITLE-ABS-KEY ("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 coloproctitis" 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 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 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 endocop*) 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 (doubl* AND w/1blind*) OR (doubl* 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 "latin square" OR placebo* OR nocebo* OR multivariate 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 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) 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 compeer 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"))

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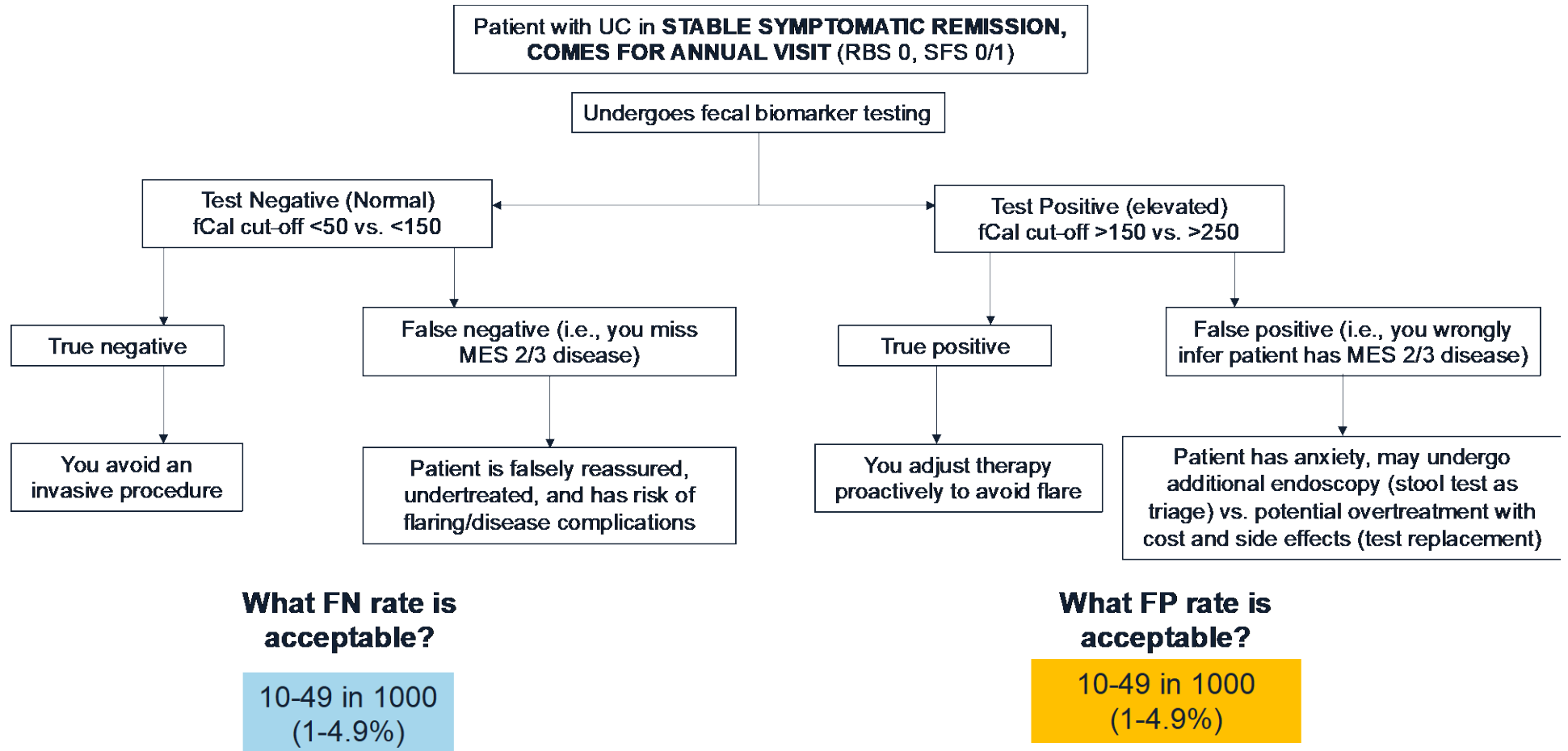
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2. TS=(lactoferrin or calprotectin or lactotransferrin or (("calcium-binding" or "calcium binding") NEAR/1 "myeloid protein") or calgranulin or calprotectin or "Migratory Inhibitory Factor-Related Protein" or "Migratory Inhibitory Factor Related Protein" or ((L1 or 27E10) NEAR/2 antigen) or fCal or fLac 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 analys*) 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* 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 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 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 referrent study" or "case referent study" or "case referent study" or "case referent study" or "case compeer 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

eTable 2. Prevalence of moderate to severe inflammation on endoscopy (MES 2 or 3) by patient-reported outcomes in clinical trials of biologic agents and tofacitinib for moderate-severe ulcerative colitis, post-induction therapy (6-8 weeks) and during maintenance therapy (week 30-54)

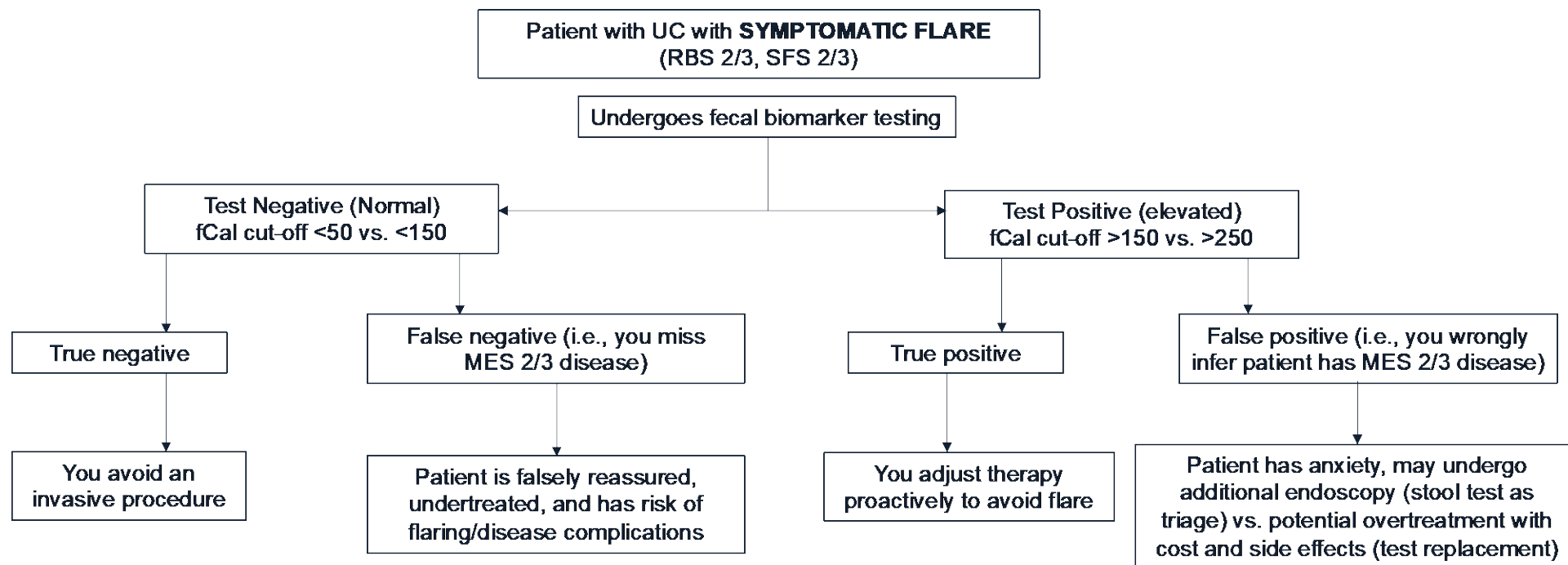
PRO measure	Pre-test probability of MES 2 or 3	INDUCTION (week 6-8)	MAINTENANCE (week 30-54)	Assumptions used in current evidence synthesis
RBS 0 + SFS 0/1	Low	25%	12%	15%
RBS 0 + SFS 2/3	Intermediate	65%	55%	50%
RBS 2/3 + SFS 2/3	High	90%	85%	85%

Abbreviations: RBS: rectal bleeding score; SFS: stool frequency score; PRO: patient reported outcome

eFigure 1. Clinical scenario for implementing the use of biomarkers in patients with ulcerative colitis in symptomatic remission



eFigure 2. Clinical scenario for implementing the use of biomarkers in patients with symptomatically active ulcerative colitis



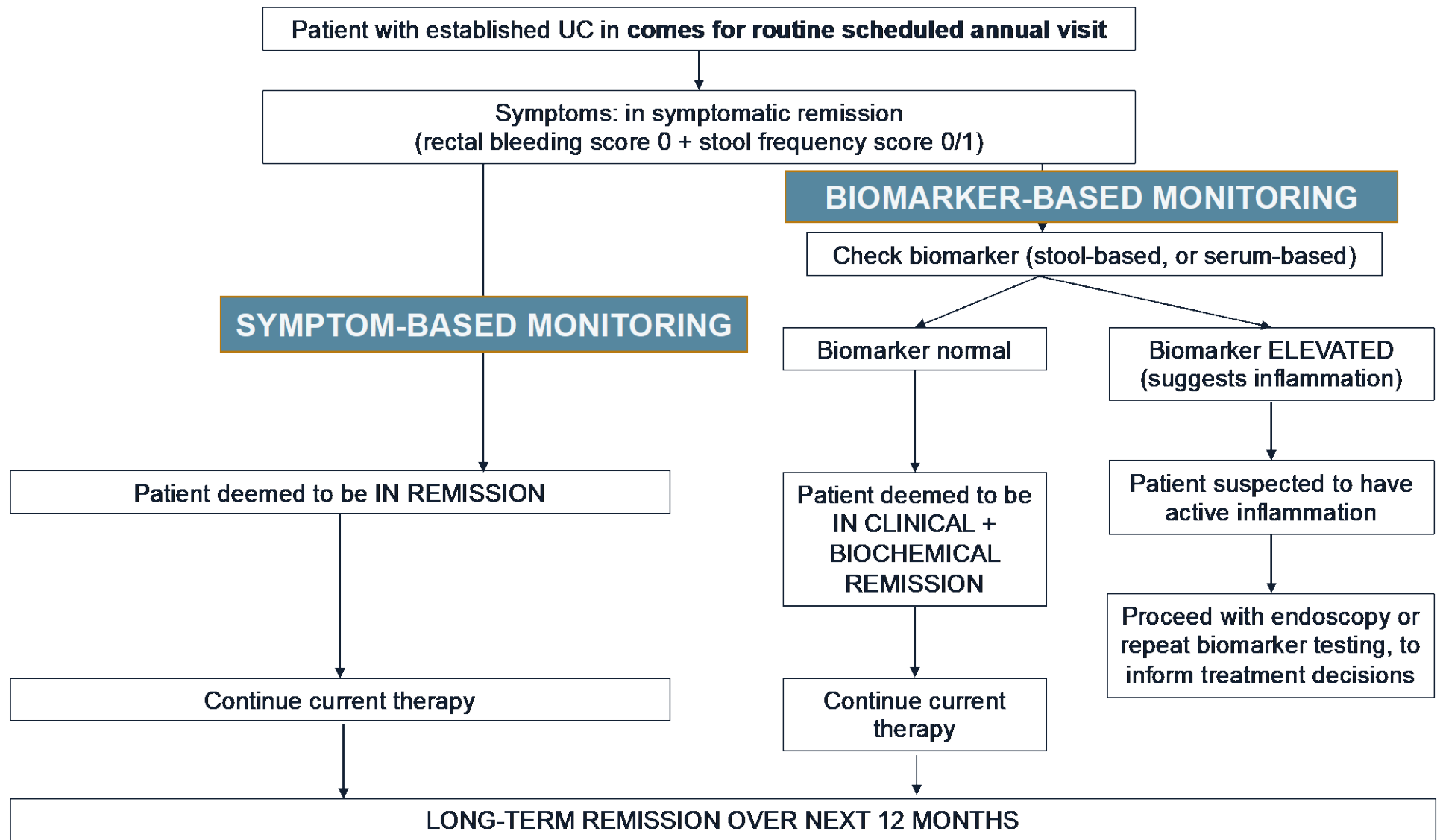
What FN rate is acceptable?

10-49 in 1000
(1-4.9%)

What FP rate is acceptable?

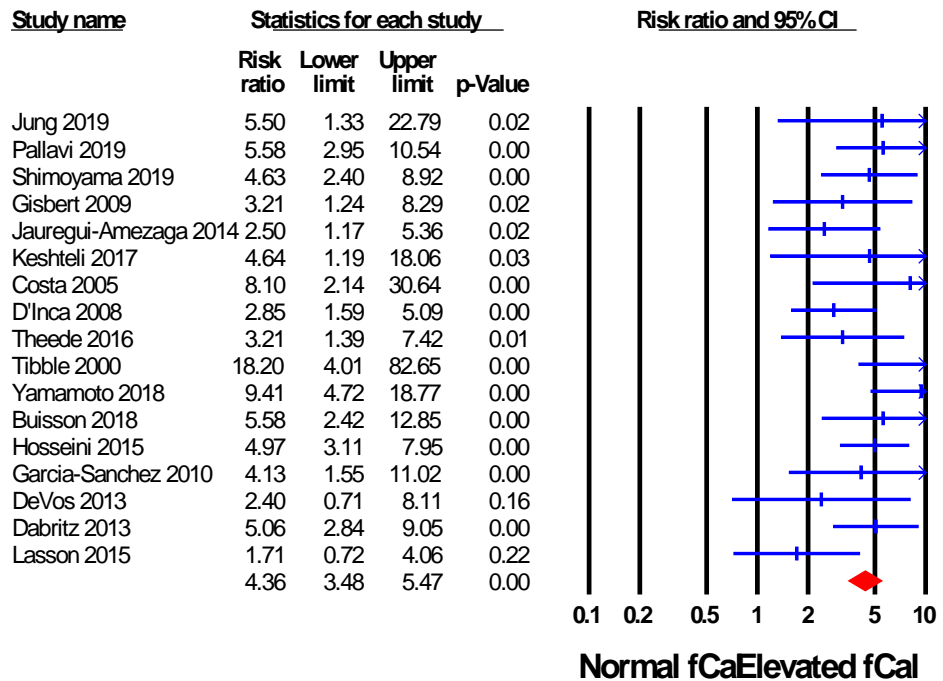
10-49 in 1000
(1-4.9%)

eFigure 3. Schema for proposed comparison of a biomarker-based monitoring strategy vs. symptom-based monitoring strategy in patients with ulcerative colitis in symptomatic remission

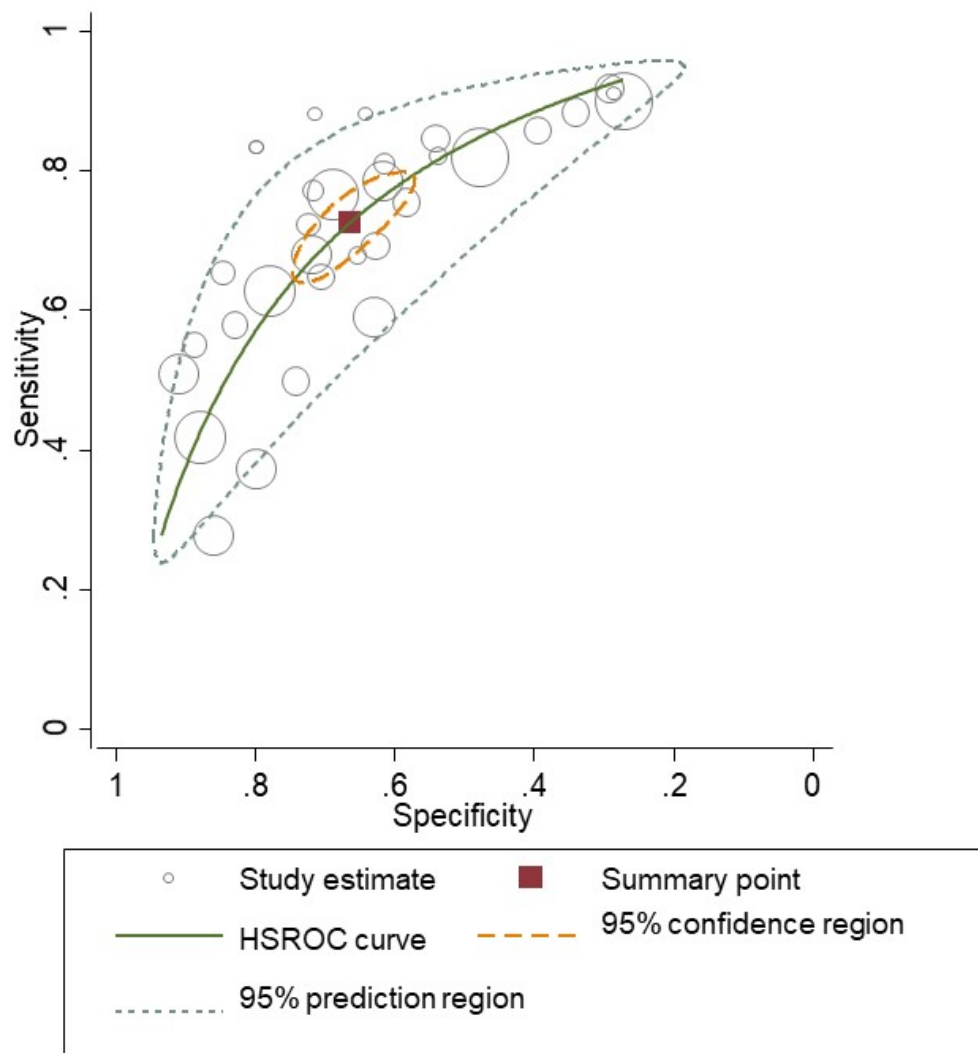


eFigure 4. Meta-analysis comparing risk of relapse in patients with ulcerative colitis in symptomatic remission with elevated fecal calprotectin vs. normal calprotectin

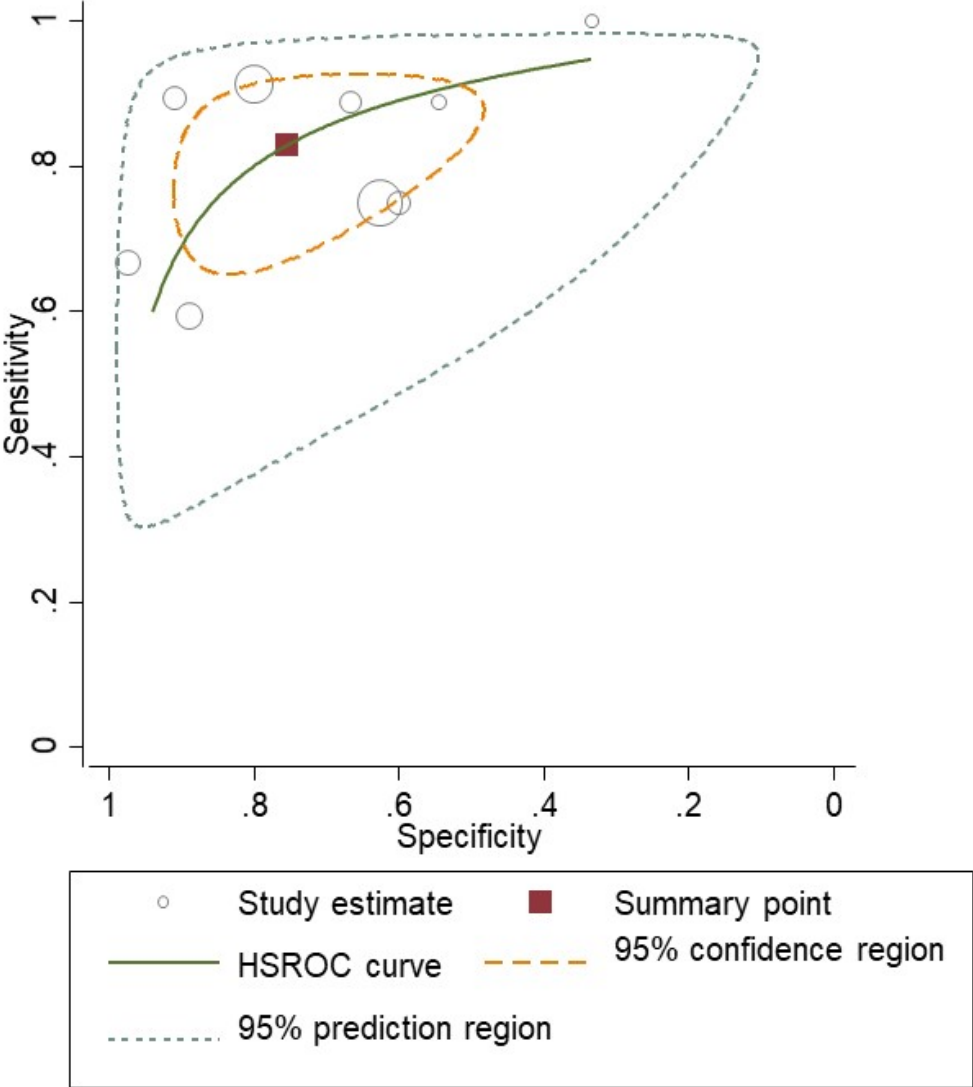
Risk of Relapse by Baseline fCal



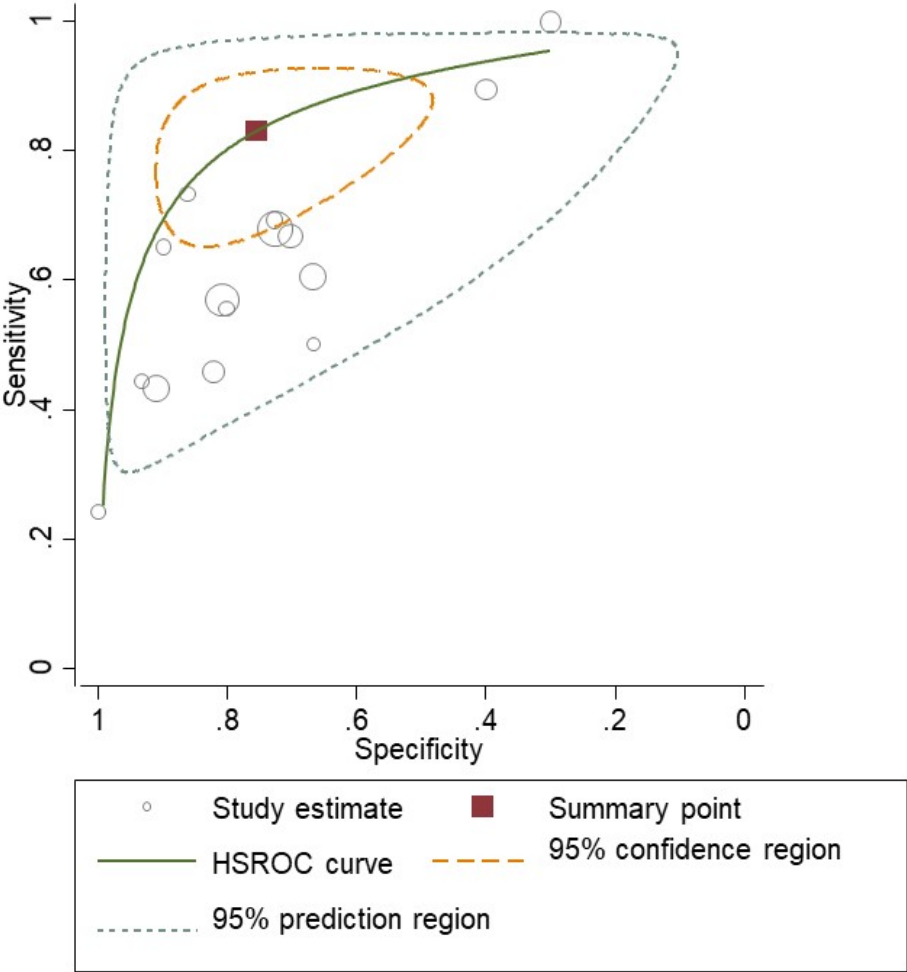
eFigure 5. Diagnostic performance of fecal calprotectin at cut-off 150 μ g/g to detect moderate to severe endoscopic inflammation



eFigure 6. Diagnostic performance of fecal lactoferrin to detect moderate to severe endoscopic inflammation



eFigure 7. Diagnostic performance of serum C-reactive protein to detect moderate to severe endoscopic inflammation



eFigure 8. Schema for proposed comparison of a biomarker-based monitoring strategy vs. endoscopy-based monitoring strategy in patients with ulcerative colitis in symptomatic remission

