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

Siddharth Singh¹,²*, Ashwin N. Ananthakrishnan³*, Nghia H. Nguyen¹, Benjamin L. Cohen⁴, Fernando S. Velayos⁵, Jennifer M. Weiss⁶, Shahnaz Sultan⁷, Shazia M. Siddique⁸,⁹, Jeremy Adler¹⁰, Karen A. Chachu¹¹, on behalf of the AGA Clinical Guidelines Committee

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

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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 Entertitis" 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 Ileitis" 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 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
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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
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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 "Idiopathic Ileocolitis" or "Inflammatory Bowel Disease" or IBD or "morbis crohn" or "mucosal colitis" or "regional enterocolitis" or "Regional Enteritis" or "Regional Enterocolitis" or "Regional Ileitides" or "Regional Ileitis" or "Terminal Ileitis" or "ulcerative colitis" or "ulcerative colitis" or "ulcerative colorectitis" or "ulcerative proct coliitis" 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/
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 "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 "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 "ulceraive colitis" or "ulcerative colitis" 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/
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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 coloreticities" or "ulcerative procto colitis" or "ulcerative proctocolitis" or "ulcerous colitis")

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 metanaanaly* 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 (trip* 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 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 study" or "longitudinal survey" 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 "prospective" OR "concurrent study" OR "concurrent survey" OR "concurrent" 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 "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation 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 "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation 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 "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation analysis" OR "validation study" OR "validation survey" OR "validation analysis") 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" ) )

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)

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

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

Patient with UC in **STABLE SYMPTOMATIC REMISSION, COMES FOR ANNUAL VISIT** (RBS 0, SFS 0/1)

Undergoes fecal biomarker testing

- **Test Negative (Normal)**
  - fCal cut off <50 vs. <150
    - True negative
      - You avoid an invasive procedure
    - False negative (i.e., you miss MES 2/3 disease)
      - Patient is falsely reassured, undertreated, and has risk of flaring/disease complications

- **Test Positive (elevated)**
  - fCal cut off >150 vs. >250
    - True positive
      - You adjust therapy proactively to avoid flare
    - False positive (i.e., you wrongly infer patient has MES 2/3 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 ulcerative colitis

Patient with UC with SYMPTOMATIC FLARE (RBS 2/3, SFS 2/3)

Undergoes fecal biomarker testing

Test Negative (Normal)
- fCal cut-off <50 vs. <150
  - True negative
    - You avoid an invasive procedure
  - False negative (i.e., you miss MES 2/3 disease)
    - Patient is falsely reassured, undertreated, and has risk of flaring/disease complications

Test Positive (elevated)
- fCal cut-off >150 vs. >250
  - True positive
    - You adjust therapy proactively to avoid flare
  - False positive (i.e., you wrongly infer patient has MES 2/3 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 ulcerative colitis in symptomatic remission.
eFigure 4. Meta-analysis comparing risk of relapse in patients with ulcerative colitis in symptomatic remission with elevated fecal calprotecting vs. normal calprotectin

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eFigure 5. Diagnostic performance of fecal calprotectin at cut-off 150µg/g to detect moderate to severe endoscopic inflammation.
eFigure 6. Diagnostic performance of fecal lactoferrin to detect moderate to severe endoscopic inflammation
Figure 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.

1. **Patient with established UC in comes for routine scheduled annual visit**

2. **Symptoms: in symptomatic remission (rectal bleeding score 0 + stool frequency score 0/1)**

3. **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 with inflammation
         - Adjust therapy to target endoscopic remission
       - Endoscopy with remission
         - Patient deemed to be IN CLINICAL + ENDOSCOPIC REMISSION
         - Continue current therapy

4. **Endoscopy-Based Monitoring**
   - Perform endoscopy
     - Endoscopy with inflammation
     - Endoscopy with remission
   - Long-term remission over next 12 months