Table 1. Focused questions and corresponding PICO questions addressed in these guidelines

#	Focused question	Patients	Intervention (threshold?)	Comparator	Outcome
PATIENTS WITH ULCERATIVE COLITIS IN SYMPTOMATIC REMISSION					
1	In patients with UC in symptomatic remission, is interval biomarker-based monitoring strategy superior to symptom-based monitoring to improve long-term outcomes?	Patients with established UC in symptomatic remission	• Interval biomarker-based monitoring	• Interval symptom-based monitoring	• Maintaining clinical remission at 12 months and beyond
2	In patients with UC in symptomatic remission, at what fecal calprotectin, fecal lactoferrin and serum C-reactive protein cut-off can we accurately rule out active inflammation, obviating *routine* endoscopic assessment?	Patients with established UC in symptomatic remission, or with mild symptoms in whom fecal calprotectin, fecal lactoferrin and serum CRP was measured	• Fecal calprotectin <50μg/g, <150μg/g or <250μg/g • Normal fecal lactoferrin (<7.25μg/g) • Normal CRP (<5mg/L)	• Fecal calprotectin >50μg/g, >150μg/g or >250μg/g • Elevated fecal lactoferrin (>7.25μg/g) • Elevated CRP (>5mg/L)	Beneficial: For detection of endoscopic inflammation, • True positive rate • True negative rate Harms: • False negative rate (false reassurance that inflammation has resolved, leading to increased risk of flares due to undertreatment) • False positive rate (excess endoscopic procedures to rule out inflammation)
PATIENTS WITH SYMPTOMATICALLY ACTIVE ULCERATIVE COLITIS					
3	In patients with symptomatically active UC, is an evaluation strategy that combines biomarkers and symptoms superior to symptom-based evaluation for making treatment adjustments?	Patients with symptomatically active UC	• Biomarker-based evaluation	• Symptom-based evaluation	Beneficial: For detection of endoscopic inflammation, • True positive rate • True negative rate Harms: • False negative rate (failure to recognize flare leading to undertreatment/mistreatment, and patient morbidity) • False positive rate (overdiagnosis, leading to unnecessary treatment adjustment and risk of treatment-related complications)
4	In patients with symptomatically active UC, at what fecal calprotectin, fecal	Patients with established UC with typical symptoms suggestive of flare or mild	• Fecal calprotectin >50μg/g,	• Fecal calprotectin <50μg/g, <150μg/g or <250μg/g	Beneficial: For detection of endoscopic inflammation, • True positive rate

	lactoferrin and serum C-reactive protein cut-off can we accurately diagnose active inflammation, obviating *routine* endoscopic assessment for treatment decisions?	symptoms in whom fecal calprotectin, fecal lactoferrin and serum CRP was measured	>150μg/g or >250μg/g • Elevated fecal lactoferrin (>7.25μg/g) • Elevated CRP (>5mg/L)	• Normal fecal lactoferrin (<7.25μg/g) • Normal CRP (<5mg/L)	• True negative rate Harms: • False negative rate (failure to recognize flare leading to undertreatment/mistreatment, and patient morbidity) • False positive rate (overdiagnosis, leading to unnecessary treatment adjustment and risk of treatment-related complications)
TREAT-TO-TARGET STRATEGIES FOR ULCERATIVE COLITIS					
5	In patients with established UC, is interval biomarker-based monitoring strategy superior to interval endoscopy-based monitoring strategy to improve long-term outcomes?	Patients with UC in symptomatic remission	• Interval biomarker-based monitoring	• Interval endoscopy-based monitoring	• Maintaining clinical remission at 12 months and beyond

Table 2. Executive summary of recommendations

Recommendation	Strength of recommendation	Certainty of evidence
PATIENTS WITH ULCERATIVE COLITIS IN SYMPTOMATIC REMISSION		
1. In patients with UC in symptomatic remission, the AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone **Comment:** Patients who place high value in avoiding burden of biomarker testing, over a potentially higher risk of flare or overtreatment, may reasonably choose interval symptom-based monitoring **Implementation considerations:** a. Biomarker testing, particularly stool-based testing, may be inconvenient, contribute to anxiety, have implications for downstream consequences (including repeat testing or endoscopy and associated costs). b. Fecal-based biomarkers (fecal calprotectin or fecal lactoferrin) may be optimal for monitoring. It may be particularly useful in patients where biomarkers have historically correlated with endoscopic disease activity. c. Interval biomarker monitoring may be performed every 6-12 months.	**Conditional**	**Moderate**
2. In patients with UC in symptomatic remission, the AGA suggests using fecal calprotectin <150μg/g, normal fecal lactoferrin or normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease activity **Implementation considerations:** *a.* In patients who have recently achieved symptomatic remission after treatment adjustment in the preceding 1-3 months, fecal calprotectin <50μg/g may be preferred over <150μg/g. *b.* Normal CRP may be less informative in patients with UC in symptomatic remission, particularly in patients who have recently achieved symptomatic remission after treatment adjustment. However, if the CRP was elevated at time of initial flare, then normalization of CRP may suggest absence of moderate to severe endoscopic activity.	**Conditional**	**Low** (fecal calprotectin and fecal lactoferrin) **to very low** (CRP)
3. In patients with UC in symptomatic remission but elevated stool or serum markers of inflammation (fecal calprotectin >150μg/g, elevated fecal lactoferrin, elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment **Implementation consideration:** a. Repeat measurement of biomarkers (in 3-6 months) may be a reasonable alternative to endoscopic assessment. If biomarkers are elevated on repeat evaluation, then endoscopic assessment may be warranted.	**Conditional**	**Very low**

PATIENTS WITH SYMPTOMATICALLY ACTIVE ULCERATIVE COLITIS		
4. In patients with symptomatically active UC, the AGA suggests an evaluation strategy that combines biomarkers and symptoms, rather than symptoms alone to inform treatment adjustments **Comment:** Patients, particularly those with severe symptoms, who place high value in avoiding burden of biomarker testing, over a potentially higher risk of inappropriate overtreatment, may reasonably choose symptom-informed treatment decision-making.	**Conditional**	**Low**
5. In patients with UC with mild symptoms, with normal stool or serum markers of inflammation (fecal calprotectin <150μg/g, normal fecal lactoferrin, normal CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment **Implementation consideration:** a. In patients with UC with mild symptoms (for example, slight increase in stool frequency and/or infrequent rectal bleeding), it may be reasonable to proceed directly with endoscopic assessment b. In patients with UC with normal biomarkers of inflammation, who prefer to avoid endoscopic assessment or empiric treatment escalation, repeat measurement of biomarkers (in 3-6 months) may be a reasonable alternative	**Conditional**	**Very low**
6. In patients with UC with mild symptoms, with elevated stool or serum markers of inflammation (fecal calprotectin >150μg/g, elevated fecal lactoferrin or elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment **Implementation consideration:** a. In patients with UC who underwent recent adjustment of treatment in response to moderate to severe symptomatic flare, and now have mild residual symptoms, elevated stool or serum markers of inflammation may be used to inform treatment adjustments	**Conditional**	**Very low**
7. In patients with UC with moderate to severe symptoms suggestive of flare, the AGA suggests using fecal calprotectin >150μg/g, elevated fecal lactoferrin or elevated CRP to rule in active inflammation and inform treatment adjustment and avoid routine endoscopic assessment of disease activity **Comment:** In patients who place greater value in confirming inflammation, particularly when making significant treatment decisions (such as starting or switching immunosuppressive therapies) and lesser value on the inconvenience of endoscopy, may choose to pursue endoscopic evaluation prior to treatment adjustment.	**Conditional**	**Moderate** (CRP)**, low** (fecal calprotectin) **to very low** (fecal lactoferrin)

TREAT-TO-TARGET STRATEGIES FOR ULCERATIVE COLITIS		
8. In patients with UC, the AGA makes no recommendation in favor of, or against, a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy to improve long-term outcomes	**No recommendation**	**Knowledge gap**

Table 3. Key considerations when using biomarkers for monitoring in UC

1. ***Considerations of test performance and specificity of biomarkers:*** *CRP, fecal calprotectin and fecal lactoferrin may be elevated because of non-intestinal sources of infection or inflammation. In patients with UC who present with elevated biomarkers and disease-related symptoms, stool testing for C. difficile and other enteric pathogens is important to help rule out other sources of GI infections.*
2. ***Role of endoscopic evaluation for other indications:*** *Biomarkers of inflammation have no role in dysplasia detection and surveillance and ruling out cytomegalovirus colitis, and endoscopic evaluation is the main strategy for evaluating these. Endoscopic evaluation may be useful for prognostication in patients hospitalized with acute severe UC.*
3. ***Association between treatment target and biomarker performance:*** *Test performance of all biomarkers in this guideline reflect their ability to rule out moderate to severe endoscopic inflammation (MES 2 or 3 [or equivalent]). Biomarkers may be suboptimal for detecting more rigorous treatment targets such as endoscopic remission (MES 0) or histologic remission. Biomarkers may also be suboptimal in detecting the presence of mild endoscopic activity (MES 1) in patients with mild symptoms.*
4. ***Influence of disease extent on biomarker performance:*** *Biomarkers may be less accurate in detecting endoscopic inflammation in patients with ulcerative proctitis or limited segmental disease.*
5. ***Interpreting biomarker performance for low-risk vs. high-risk treatment adjustments:*** *Application of all biomarkers in clinical practice should be guided by downstream implications, including risk of consequent treatment decisions (low-risk treatment adjustment vs. high-risk treatment adjustment). Test performance thresholds (acceptable false positive and false negative rates) may vary for patient-provider teams depending on what treatment adjustment is being considered.* .
6. ***Inter- and intra-assay test variability:*** *Fecal calprotectin assays may not be interchangeable and the same assay should be used for a given patient to compare results over time. Since there can be substantial within-stool, and within-day variation of fecal calprotectin measurements from a single patient, confidence in any single measurement may be limited. Hence, if there is uncertainty of results (such as borderline or unexpected results), repeat fecal calprotectin testing or endoscopic evaluation for confirmation may be required.*
7. ***Inter-individual heterogeneity in biomarkers responsiveness:*** *There are inter-individual differences in biomarker elevation in patients with intestinal inflammation, and in a subset of patients, biomarkers may correlate poorly with endoscopic activity. The overall performance and confidence in the use of biomarkers for treatment decisions in a particular patient may be higher when these biomarkers have been longitudinally observed to correlate with the patient's endoscopic disease activity (both active disease and remission).*

Table 4. Consequences of diagnostic test results on patient-important outcomes

True positives	Patients correctly diagnosed as having moderate to severe endoscopic activity would be eligible to undergo treatment adjustment, which may improve symptoms and decrease risk of disease-related complications and morbidity, without being subject to risk, invasiveness and cost of endoscopic assessment.
False positives	Patients incorrectly labeled as having moderate to severe endoscopic activity, when actually they are in endoscopic remission or have only mild endoscopic activity may undergo unnecessary testing (endoscopy) and/or treatment adjustment, and have avoidable anxiety, potential testing- or treatment-related complications and increased resource utilization.
True negatives	Patients correctly diagnosed as being in endoscopic remission or having only mild endoscopic activity would be reassured and obviate the need for invasive testing with endoscopy, although they may need to undergo serial assessment of biomarker at periodic intervals.
False negatives	Patients incorrectly labeled as being in endoscopic remission or having only mild endoscopic activity, when actually they have moderate to severe endoscopic activity would be falsely reassured, may have avoidable anxiety about unexplained symptoms, and may not receive appropriate treatment adjustment, potentially leading to increased disease related complications, morbidity and mortality.

Table 5. GRADE Evidence Profile for PICO #1, comparing outcomes with interval biomarker-based monitoring vs. symptom-based monitoring to improve long-term outcomes in patients with ulcerative colitis in symptomatic remission

Q1. What is the risk of relapse in patients with UC in symptomatic remission with elevated vs. normal fecal calprotectin during routine follow-up?

Patient or population: Patients with UC in symptomatic remission
Setting: Cohort
Exposure: Elevated fecal calprotectin (generally >150μg/g)
Comparison: Normal fecal calprotectin

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of evidence
		Normal fecal calprotectin	**Elevated fecal calprotectin**	**Difference**	
Risk of relapse at 12m № of participants: 1286 (17 cohorts)	**RR 4.36** (3.48 to 5.47)	**Pooled relapse rate**			⊕⊕⊕◯ MODERATE*
		15%	**65.4%** (52.2% to 82%)	**50.4% more** (37.2% more to 67% more)	

*Evidence rated down for risk of bias based on QUIPS tool and slight variability in fecal calprotectin cut-offs

Table 6. GRADE Evidence Profile for PICO #2, comparing cut-offs for (A) fecal calprotectin, (B) fecal lactoferrin and (C) serum C-reactive protein in patients with ulcerative colitis without symptoms (low pretest probability) or with mild symptoms (intermediate pretest probability)

A. Fecal calprotectin

Q2A. In patients with UC in symptomatic remission, how accurate is fecal calprotectin cut-off of <50μg/g vs. <150μg/g vs. <250μg/g for ruling out moderate to severe endoscopically active disease (Mayo endoscopy score 2/3), obviating the need for routine endoscopic assessment?

Population/Setting: Patients with UC in symptomatic remission – **low pre-test probability/likelihood** of having moderate to severe endoscopically active disease (no rectal bleeding [RBS 0], and normal to mild increase in stool frequency [SFS 0 or 1], under routine maintenance therapy, or having recently achieved symptomatic remission after treatment adjustment) with estimated prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 15%; **intermediate pre-test probability/likelihood** of having moderate to severe endoscopically active disease (patients with mild symptoms of UC, such as infrequent rectal bleeding [RBS 0 or 1] and/or increased stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 50%

Pooled sensitivity/specificity fecal calprotectin with cut-off <50μg/g: Sens 78 (95% CI, 66-86); Spec 57 (95% CI, 40-72), 11 studies |
Pooled sensitivity/specificity fecal calprotectin with cut-off <150μg/g: Sens 71 (95% CI, 62-78); Spec 69 (95% CI, 62-75), 12 studies |
Pooled sensitivity/specificity fecal calprotectin with cut-off <250μg/g: Sens 67 (95% CI, 53-78); Spec 73 (95% CI, 65-80), 9 studies

Reference Test: Lower endoscopy

Test result	Number of results per 1000 patients tested (95% CI)						Comments
	Low-likelihood (Prevalence 15%)			Intermediate-likelihood (Prevalence 50%)			
	fCal <50	fCal <150	fCal<250	fCal <50	fCal <150	fCal <250	
True positives (patients correctly diagnosed as having moderate to severe endoscopic activity)	117 (99 to 129)	107 (93 to 117)	95 (80 to 117)	390 (330 to 430)	355 (310 to 390	315 (265 to 390)	True positives would be eligible to undergo treatment adjustment, which may decrease disease-related complications and morbidity, without being subject to risks and invasive testing with endoscopy.
False negatives (patients incorrectly labeled as being in endoscopic remission or having only mild endoscopic activity, when actually they have moderate to severe endoscopic activity)	**33 (21 to 51)**	**43 (33 to 57)**	**55 (33 to 70)**	**110 (70 to 170)**	**145 (110 to 190)**	**185 (110 to 235)**	False negatives would be falsely reassured, and may be at higher risk of disease complications/flare due to undertreatment.
GRADE Certainty of evidence	LOW[1,2]	LOW[1,2]	VERY LOW[1,3]	VERY LOW[1,3]	VERY LOW[1,3]	VERY LOW[1,3]	

Test result	Number of results per 1000 patients tested (95% CI)						Comments
	Low-likelihood (Prevalence 15%)			Intermediate-likelihood (Prevalence 50%)			
	fCal <50	fCal <150	fCal<250	fCal <50	fCal <150	fCal <250	
True negatives (patients correctly diagnosed as being in endoscopic remission or having only mild endoscopic activity)	484 (340 to 612)	586 (527 to 638	620 (553 to 680)	285 (200 to 360)	345 (310 to 375)	365 (325 to 400)	True negatives would be reassured and obviate the need for invasive testing with endoscopy, although they may need to undergo serial assessment of biomarker at periodic intervals.
False positives (patients incorrectly labeled as having moderate to severe endoscopic activity, when actually they are in endoscopic remission or have only mild endoscopic activity)	**366 (238 to 510)**	**264 (212 to 323)**	**230 (170 to 297)**	**215 (140 to 300)**	**155 (125 to 190)**	**135 (100 to 175)**	False positives may receive unnecessary testing (endoscopy) and/or treatment adjustment, and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.
GRADE Certainty of evidence	VERY LOW[1,4]	VERY LOW[1,4]	VERY LOW[1,4]	VERY LOW[1,4]	VERY LOW[1,4]	VERY LOW[1,4]	

[1]High unexplained heterogeneity, selective inclusion of studies reporting cut-offs
[2]Serious imprecision since 95% CI crosses maximal tolerable FN threshold of <5%
[3]Very serious imprecision since point estimate is higher than maximal tolerable FN threshold
[4]Very serious imprecision since point estimate is higher than maximal tolerable FP threshold

B. Fecal lactoferrin

Q2B. In patients with UC in symptomatic remission, how accurate is negative fecal lactoferrin for ruling out moderate to severe endoscopically active disease (Mayo endoscopy score 2/3), obviating the need for routine endoscopic assessment?

Population/Setting: Patients with UC in symptomatic remission – **low pre-test probability/likelihood** of having moderate to severe endoscopically active disease (no rectal bleeding [RBS 0], and normal to mild increase in stool frequency [SFS 0 or 1], under routine maintenance therapy, or having recently achieved symptomatic remission after treatment adjustment) with estimated prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 15%; **intermediate pre-test probability/likelihood** of having moderate to severe endoscopically active disease (patients with mild symptoms of UC, such as infrequent rectal bleeding [RBS 0 or 1] and/or increased stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 50%

Pooled sensitivity/specificity fecal lactoferrin with cut-off <7.25-10μg/g: Sens 83 (95% CI, 72-90); Spec 75 (95% CI, 59-87), 9 studies;

Reference Test: Lower endoscopy

Test result	Number of results per 1000 patients tested (95% CI)		Comments
	Low-likelihood (Prevalence 15%)	Intermediate-likelihood (Prevalence 50%)	
	Negative lactoferrin	Negative lactoferrin	
True positives (patients correctly diagnosed as having moderate to severe endoscopic activity)	124 (108 to 135)	415 (360 to 450)	True positives would be eligible to undergo treatment adjustment, which may decrease disease-related complications and morbidity, without being subject to risks and invasive testing with endoscopy.
False negatives (patients incorrectly labeled as being in endoscopic remission or having only mild endoscopic activity, when actually they have moderate to severe endoscopic activity)	**26 (15 to 42)**	**85 (50 to 140)**	False negatives would be falsely reassured, and may be at higher risk of disease complications/flare due to undertreatment.
GRADE Certainty of evidence	LOW[1]	VERY LOW[1,2]	
True negatives (patients correctly diagnosed as being in endoscopic remission or having only mild endoscopic activity)	638 (501 to 739)	375 (295 to 435)	True negatives would be reassured and obviate the need for invasive testing with endoscopy, although they may need to undergo serial assessment of biomarker at periodic intervals.
False positives (patients incorrectly labeled as having moderate to severe endoscopic activity, when actually they are in endoscopic remission or have only mild endoscopic activity)	**212 (111 to 349)**	**125 (65 to 205)**	False positives may receive unnecessary testing (endoscopy) and/or treatment adjustment, and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.
GRADE Certainty of evidence	VERY LOW[1,3]	VERY LOW[1,3]	

[1]Very serious inconsistency, due to selective reporting of cut-offs in studies optimized for best performance and high heterogeneity for summary sensitivity/specificity

[2]Very serious imprecision since point estimate is higher than maximal tolerable FN threshold

[3]Very serious imprecision since point estimate is higher than maximal tolerable FP threshold

C. Serum C-reactive protein

Q2C. In patients with UC in symptomatic remission, how accurate is normal serum C-reactive protein for ruling out moderate to severe endoscopically active disease (Mayo endoscopy score 2/3), obviating the need for routine endoscopic assessment?

Population/Setting: Patients with UC in symptomatic remission – **low pre-test probability/likelihood** of having moderate to severe endoscopically active disease (no rectal bleeding [RBS 0], and normal to mild increase in stool frequency [SFS 0 or 1], under routine maintenance therapy, or having recently achieved symptomatic remission after treatment adjustment) with estimated prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 15%; **intermediate pre-test probability/likelihood** of having moderate to severe endoscopically active disease (patients with mild symptoms of UC, such as infrequent rectal bleeding [RBS 0 or 1] and/or increased stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 50%

Pooled sensitivity/specificity CRP with cut-off <5mg/L: Sensitivity = 63 (95% CI, 50-75); Specificity = 77 (95% CI, 67-84); 15 studies

Reference Test: Lower endoscopy

Test result	Number of results per 1000 patients tested (95% CI)		Comments
	Low-likelihood (Prevalence 15%)	Intermediate-likelihood (Prevalence 50%)	
	Normal CRP	Normal CRP	
True positives (patients correctly diagnosed as having moderate to severe endoscopic activity)	95 (75 to 112)	315 (250 to 375)	True positives would be eligible to undergo treatment adjustment, which may decrease disease-related complications and morbidity, without being subject to risks and invasive testing with endoscopy.
False negatives (patients incorrectly labeled as being in endoscopic remission or having only mild endoscopic activity, when actually they have moderate to severe endoscopic activity)	**55 (38 to 75)**	**185 (125 to 250)**	False negatives would be falsely reassured, and may be at higher risk of disease complications/flare due to undertreatment.
GRADE Certainty of evidence	VERY LOW[1,2]	VERY LOW[1,2]	
True negatives (patients correctly diagnosed as being in endoscopic remission or having only mild endoscopic activity)	655 (570 to 714)	385 (335 to 420)	True negatives would be reassured and obviate the need for invasive testing with endoscopy, although they may need to undergo serial assessment of biomarker at periodic intervals.
False positives (patients incorrectly labeled as having moderate to severe endoscopic activity, when actually they are in endoscopic remission or have only mild endoscopic activity)	**195 (136 to 280)**	**115 (80 to 165)**	False positives may receive unnecessary testing (endoscopy) and/or treatment adjustment, and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.
GRADE Certainty of evidence	VERY LOW[1,3]	VERY LOW[1,3]	

[1]High unexplained heterogeneity, selective inclusion of studies reporting cut-offs
[2]Very serious imprecision since point estimate is higher than maximal tolerable FN threshold
[3]Very serious imprecision since point estimate is higher than maximal tolerable FP threshold

Table 7. GRADE Evidence Profile for PICO #3, comparing cut-offs for (A) fecal calprotectin, (B) fecal lactoferrin and (C) serum C-reactive protein in patients with symptomatically active ulcerative colitis with typical symptoms of a flare (high pretest probability) or with mild symptoms (intermediate pretest probability)

A. Fecal calprotectin

Q3A. In patients with symptomatically active UC, how accurate is fecal calprotectin cut-off of >50μg/g vs. >150μg/g vs. >250μg/g for ruling in moderate to severe endoscopically active disease (Mayo endoscopy score 2/3), obviating the need for routine endoscopic assessment?

Population/Setting: Patients with symptomatically active UC – **intermediate pre-test probability** of having moderate to severe endoscopically active disease (patients with mild symptoms of UC, such as infrequent rectal bleeding [RBS 0 or 1] and/or increased stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 50%; **high pre-test probability** of having moderate to severe endoscopically active disease (patients with typical symptoms of UC flare with frequent rectal bleeding [RBS 2 or 3] and significant increase in stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 85%

Pooled sensitivity/specificity fecal calprotectin with cut-off >50μg/g: Sens 78 (95% CI, 66-86); Spec 57 (95% CI, 40-72), 11 studies |

Pooled sensitivity/specificity fecal calprotectin with cut-off >150μg/g: Sens 71 (95% CI, 62-78); Spec 69 (95% CI, 62-75), 12 studies |

Pooled sensitivity/specificity fecal calprotectin with cut-off >250μg/g: Sens 67 (95% CI, 53-78); Spec 73 (95% CI, 65-80), 9 studies

Reference Test: Lower endoscopy

Test result	Number of results per 1000 patients tested (95% CI)						Comments
	Intermediate-likelihood (Prevalence 50%)			High-likelihood (Prevalence 85%)			
	fCal >50	fCal >150	fCal>250	fCal >50	fCal >150	fCal >250	
True positives (patients with mod-severe endoscopically active disease)	390 (330 to 430)	355 (310 to 390	315 (265 to 390)	663 (561 to 731)	603 (527-663)	536 (451 to 663)	True positives would be eligible to undergo treatment adjustment, which may decrease disease-related complications and morbidity, without being subject to risks and invasive testing with endoscopy.
False negatives (patients incorrectly classified as being in endoscopic remission or having mildly active disease)	**110 (70 to 170)**	**145 (110 to 190)**	**185 (110 to 235)**	**187 (119 to 289)**	**247 (187-323)**	**314 (187 to 399)**	False negatives may be falsely reassured, undertreated or mistreated (as not having UC flare), potentially leading to increased disease related complications and morbidity.
GRADE Certainty of evidence	VERY LOW[1,3]	VERY LOW[1,3]	VERY LOW[1,3]	VERY LOW[1,3]	VERY LOW[1,3]	VERY LOW[1,3]	
True negatives (patients in endoscopic remission or having mildly active disease)	285 (200 to 360)	345 (310 to 375)	365 (325 to 400)	86 (60 to 108)	104 (93-113)	110 (98 to 120)	True negatives would be reassured and obviate the need for invasive testing with endoscopy, although they may need to undergo serial assessment of biomarker at periodic intervals.

Test result	Number of results per 1000 patients tested (95% CI)						Comments
	Intermediate-likelihood (Prevalence 50%)			High-likelihood (Prevalence 85%)			
	fCal >50	fCal >150	fCal>250	fCal >50	fCal >150	fCal >250	
False positives (patients incorrectly classified as having moderate to severe endoscopically active disease)	**215 (140 to 300)**	**155 (125 to 190)**	**135 (100 to 175)**	**64 (42 to 90)**	**46 (37-57)**	**40 (30-52)**	False positives may undergo unnecessary treatment adjustment and have treatment-related complications.
GRADE Certainty of evidence	VERY LOW[1,4]	VERY LOW[1,4]	VERY LOW[1,4]	VERY LOW[1,4]	LOW[1,5]	LOW[1,5]	

[1]High unexplained heterogeneity, selective inclusion of studies reporting cut-offs
[2]Serious imprecision since 95% CI crosses maximal tolerable FN threshold of <5%
[3]Very serious imprecision since point estimate is higher than maximal tolerable FN threshold
[4]Very serious imprecision since point estimate is higher than maximal tolerable FP threshold
[5]Serious imprecision since 95% CI crosses maximal tolerable FP threshold of <5%

B. Fecal lactoferrin

Q3B. In patients with symptomatically active UC, how accurate is positive fecal lactoferrin for ruling in moderate to severe endoscopically active disease (Mayo endoscopy score 2/3), obviating the need for routine endoscopic assessment?

Population/Setting: Patients with symptomatically active UC – **intermediate pre-test probability** of having moderate to severe endoscopically active disease (patients with mild symptoms of UC, such as infrequent rectal bleeding [RBS 0 or 1] and/or increased stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 50%; **high pre-test probability** of having moderate to severe endoscopically active disease (patients with typical symptoms of UC flare with frequent rectal bleeding [RBS 2 or 3] and significant increase in stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 85%

Pooled sensitivity/specificity fecal lactoferrin with cut-off <7.25-10μg/g: Sens 83 (95% CI, 72-90); Spec 75 (95% CI, 59-87), 9 studies;

Reference Test: Lower endoscopy

Test result	Number of results per 1000 patients tested (95% CI)		Comments
	Intermediate-likelihood (Prevalence 50%)	High-likelihood (Prevalence 85%)	
	Positive lactoferrin	Positive lactoferrin	
True positives (patients correctly diagnosed as having moderate to severe endoscopic activity)	415 (360 to 450)	705 (612 to 765)	True positives would be eligible to undergo treatment adjustment, which may decrease disease-related complications and morbidity, without being subject to risks and invasive testing with endoscopy.
False negatives (patients incorrectly labeled as being in endoscopic remission or having only mild endoscopic activity, when actually they have moderate to severe endoscopic activity)	**85 (50 to 140)**	**145 (85 to 238)**	False negatives may be falsely reassured, undertreated or mistreated (as not having UC flare), potentially leading to increased disease related complications and morbidity.
GRADE Certainty of evidence	VERY LOW[1,2]	VERY LOW[1,2]	
True negatives (patients correctly diagnosed as being in endoscopic remission or having only mild endoscopic activity)	375 (295 to 435)	113 (89 to 131)	True negatives would be reassured and obviate the need for invasive testing with endoscopy, although they may need to undergo serial assessment of biomarker at periodic intervals.
False positives (patients incorrectly labeled as having moderate to severe endoscopic activity, when actually they are in endoscopic remission or have only mild endoscopic activity)	**125 (65 to 205)**	**37 (19 to 61)**	False positives may undergo unnecessary treatment adjustment and have treatment-related complications.
GRADE Certainty of evidence	VERY LOW[1,3]	VERY LOW[1,4]	

[1]Very serious inconsistency heterogeneity, due to selective reporting of cut-offs in studies optimized for best performance and high heterogeneity for summary sensitivity/specificity

[2]Very serious imprecision since point estimate is higher than maximal tolerable FN threshold

[3]Very serious imprecision since point estimate is higher than maximal tolerable FP threshold

[4]Serious imprecision since 95% CI crosses maximal tolerable FP threshold of <5%

C. Serum C-reactive protein

Q3C. In patients with symptomatically active UC, how accurate is elevated serum C-reactive protein for ruling in moderate to severe endoscopically active disease (Mayo endoscopy score 2/3), obviating the need for routine endoscopic assessment?

Population/Setting: Patients with symptomatically active UC – **intermediate pre-test probability** of having moderate to severe endoscopically active disease (patients with mild symptoms of UC, such as infrequent rectal bleeding [RBS 0 or 1] and/or increased stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 50%; **high pre-test probability** of having moderate to severe endoscopically active disease (patients with typical symptoms of UC flare with frequent rectal bleeding [RBS 2 or 3] and significant increase in stool frequency [SFS 2 or 3]) with observed prevalence of moderate to severe endoscopically active disease (Mayo endoscopy score 2/3) of 85%

Pooled sensitivity/specificity CRP with cut-off <5mg/L: Sensitivity = 63 (95% CI, 50-75); Specificity = 77 (95% CI, 67-84); 15 studies

Reference Test: Lower endoscopy

Test result	Number of results per 1000 patients tested (95% CI)		Comments
	Intermediate-likelihood (Prevalence 50%)	**High-likelihood (Prevalence 85%)**	
	Elevated CRP	**Elevated CRP**	
True positives (patients correctly diagnosed as having moderate to severe endoscopic activity)	315 (250 to 375)	536 (425 to 638)	True positives would be eligible to undergo treatment adjustment, which may decrease disease-related complications and morbidity, without being subject to risks and invasive testing with endoscopy.
False negatives (patients incorrectly labeled as being in endoscopic remission or having only mild endoscopic activity, when actually they have moderate to severe endoscopic activity)	**185 (125 to 250)**	**314 (212 to 425)**	False negatives may be falsely reassured, undertreated or mistreated (as not having UC flare), potentially leading to increased disease related complications and morbidity.
GRADE Certainty of evidence	VERY LOW[1,2]	VERY LOW[1,2]	
True negatives (patients correctly diagnosed as being in endoscopic remission or having only mild endoscopic activity)	385 (335 to 420)	116 (101 to 126)	True negatives would be reassured and obviate the need for invasive testing with endoscopy, although they may need to undergo serial assessment of biomarker at periodic intervals.
False positives (patients incorrectly labeled as having moderate to severe endoscopic activity, when actually they are in endoscopic remission or have only mild endoscopic activity)	**115 (80 to 165)**	**34 (24 to 49)**	False positives may undergo unnecessary treatment adjustment and have treatment-related complications.
GRADE Certainty of evidence	VERY LOW[1,3]	MODERATE[1]	

[1]High unexplained heterogeneity, selective inclusion of studies reporting cut-offs
[2]Very serious imprecision since point estimate is higher than maximal tolerable FN threshold
[3]Very serious imprecision since point estimate is higher than maximal tolerable FP threshold