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*TOPIC HIGHLIGHT*

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# Disease monitoring in inflammatory bowel disease

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## Abstract

The optimal method for monitoring quiescent disease in patients with Crohn's disease (CD) and ulcerative colitis is yet to be determined. Endoscopic evaluation with ileocolonoscopy is the gold standard but is invasive, costly, and time-consuming. There are many commercially available biomarkers that may be used in clinical practice to evaluate disease status in patients with inflammatory bowel disease (IBD), but the most widely adopted biomarkers are C-reactive protein (CRP) and fecal calprotectin (FC). This review summarizes the evidence for utilizing CRP and FC for monitoring IBD during clinical remission and after surgical resection. Endoscopic correlation with CRP and FC is evaluated in each disease state. Advantages and drawbacks of each biomarker are discussed with special consideration of isolated ileal CD. Fecal immunochemical testing, traditionally used for colorectal cancer screening, is mentioned as a potential new alternative assay in the evaluation of IBD. Based on a mixture of information gleaned from biomarkers, clinical status, and endoscopic evaluation, the best treatment decisions can be made for the patient with IBD.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Fecal calprotectin; C-reactive protein; Fecal immunochemical test; Biomarkers; Remission; Postoperative recurrence

**Core tip:** C-reactive protein (CRP) is not specific for intestinal inflammation but does have modest correlation with clinical and endoscopic findings in inflammatory bowel disease patients. CRP can be falsely low despite active mucosal inflammation and is more reliable in cases of transmural inflammation. Fecal calprotectin (FC) is more specific than CRP for intestinal inflammation, except in isolated ileal disease. FC better correlates with endoscopic findings than CRP and is useful in monitoring Crohn's patients for postoperative recurrence. Optimal FC cutoffs are still being determined.

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## INTRODUCTION

The clinical course of inflammatory bowel disease (IBD) varies widely from patient to patient. Whereas some patients are able to stay in remission for years with minimal treatment, other patients have a chronic, relapsing course with frequent flares despite aggressive therapy[1]. Twenty percent of Crohn's patients will relapse yearly, and 67% of Crohn's patients cycle between relapse and remission in the first 8 years after diagnosis. In ulcerative colitis (UC), there is a 9% to 21% 10-year cumulative risk of colectomy[2]. Given the known risk of disease progression in IBD, it is important to monitor for active disease and optimize treatment plans accordingly.

In the past, physicians have focused on clinical symptoms and clinical remission to guide treatment. However, it has been established that a patient's clinical symptoms, particularly with Crohn's disease (CD), are frequently inconsistent with endoscopic findings[3]. More recently, the goal of mucosal healing has emerged as the new treatment target[4]. In multiple trials, mucosal healing has been shown to improve long-term outcomes such as avoidance of surgery and fewer hospitalizations[5-7]. While endoscopic evaluation is the gold standard for assessment of mucosal inflammation, less invasive and less time-consuming modalities for assessing inflammation are valuable in day-to-day management.

Relapses are often difficult to predict. The goal of disease monitoring is to identify patients at risk for relapse in order to treat earlier, with the hope of maintaining remission and avoiding irreversible bowel damage such as fistulas and strictures that may lead to surgery.

The optimal method for monitoring disease activity in CD and UC is still being defined. Current modalities for assessing disease activity include colonoscopy, clinical assessment tools, serum biomarkers, fecal biomarkers, and imaging examinations such as CT enterography, small bowel follow-through, and MR enterography.

Many quantifiable laboratory assessments have been studied for evaluation of disease activity in IBD. Examples of commonly available serum lab assays include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), leukocytes, platelets, ferritin, haptoglobin, ceruloplasmin, α-1-antitrypsin, plasminogen, complement factors, and fibrinogen[8]. More experimental serum assays that are not widely commercially available include orosomucoid (α-1-acid glycoprotein), interleukin 6 (IL-6), sialic acid, and serum amyloid A. Stool assays for detecting inflammation include fecal calprotectin (FC), lactoferrin, polymorphonuclear elastase, myeloperoxidase, metall-oproteinase-9, and neopterin. MicroRNA species[9] and proteomic profiles[10], available only in research settings, have also been shown to differentiate active *vs* inactive IBD.

Of these diverse assays, CRP and FC are the most widely adopted in clinical practice for disease monitoring in IBD. This is a review of the current medical literature regarding the use of these two commonly utilized biomarkers for monitoring of disease to predict relapse in patients in clinical remission and in the postoperative setting.

## CRP

C-reactive protein was first described in 1930 by Tillet and Francis[11]. Patients with pneumonia were noted to have serum that precipitated when brought in contact with bacterial "Fraction C" substance in the supernatant. This precipitant was no longer present in serum after the pneumonia resolved but was persistently present in lethal cases.

CRP is a pentameric, acute-phase protein made by hepatocytes[12]. The half-life of CRP is 19 hours, which allows for rapid rising and falling of levels with onset of and resolution of inflammatory states, respectively. Healthy individuals have low levels of CRP in circulation, usually less than 1 mg/L, but levels can rise 100-fold in periods of acute inflammation[13].

CRP is not a specific marker for intestinal inflammation. Measurements of CRP may be elevated for other reasons such as infection or extraintestinal inflammation. CRP has been studied outside of gastroenterology to predict disease outcomes after myocardial infarction and diagnosis of multiple myeloma[14,15]. In IBD, CRP has been significantly associated with other biomarkers of inflammation including ESR, thrombocytosis, anemia, and hypoal-buminemia[16]. As a biomarker, CRP is appealing because it is inexpensive, minimally invasive, and quick to result.

## CRP CORRELATION WITH ENDOSCOPY

CRP is often used to monitor for occult internal inflammation when patients are clinically asymptomatic. In general, CRP is more frequently elevated in active transmural CD than in mild to moderate mucosal inflammation associated with UC[17-20]. Though not always accurate or specific, clinical disease activity in adults and children with CD has been shown to correlate with CRP level[16,21,22]. However, 20%-25% of CD patients having flares do not exhibit increased CRP due to genetic single nucleotide polymorphisms in the CRP gene, which affects CRP production[23].

Several studies have reported good correlation

**Table 1  Endoscopic score correlation with C-reactive protein**

| Ref. | Disease | Endoscopic tool | Correlation | *P* value |
|---|---|---|---|---|
| Sipponen *et al*[88] | CD | CDEIS | $r = 0.608$ | < 0.001 |
| Schoepfer *et al*[77] | CD | CDEIS | $r = 0.75$ | < 0.010 |
| af Björkesten *et al*[25] | CD | SES-CD | $r = 0.56$ | < 0.001 |
| Lobatón *et al*[48] | UC | Mayo | $r = 0.307$ | < 0.001 |

CDEIS: Crohn's disease endoscopic index of severity; SES-CD: Simple endoscopic score for Crohn's disease; *r*: Spearman's rank correlation coefficient.

between CRP levels and findings seen during endoscopy[16,24,25] (Table 1). Solem *et al*[16] reported a retrospective cohort of 104 CD patients. CRP was found to be normal in 75% of the CD patients with normal ileocolonoscopy. On the other hand, CRP elevations were significantly associated with active mucosal inflammation on colonoscopy (OR = 3.5, 95%CI: 1.4-8.9) defined as erosions, ulcerations, spontaneous bleeding, exudate, friability, granularity, cobblestoning, extensive erythema, inflammatory-appearing nodularity, and masses. CRP elevations (> 0.8 mg/dL) were significantly associated with moderate to severe clinical activity (OR = 4.5, 95%CI: 1.1-18.3) as defined by ACG clinical practice guidelines[26] (Table 2). Notably, in this study, there was no significant correlation between abnormal small bowel imaging and CRP elevation, suggesting that CRP could be normal in patients with isolated small bowel CD, but there was no subgroup analysis of isolated endoscopic ileitis in relation to CRP.

Henriksen *et al*[27] studied CRP levels according to disease subtype in 176 Crohn's patients and 371 UC patients. For CD, there were no significant differences in CRP levels based on disease localization (ileitis, colitis, or ileocolitis), showing that isolated ileal disease also caused a rise in CRP. For both UC and CD, CRP responses increased based on extent of disease. However, the mean and median levels of CRP in UC were within the normal range for CRP (< 10 mg/L) for all disease subgroups, making CRP less informative in UC disease monitoring.

In a prospective study of 64 CD patients on anti-TNF therapy, endoscopic SES-CD activity score correlated better with CRP ($r = 0.56$, $P < 0.001$) than with clinical indices including the CD Activity Index (CDAI) ($r = 0.40$, $P < 0.001$) and the Harvey Bradshaw Index (HBI) ($r = 0.32$, $P < 0.001$)[25]. However, CRP was not reliable in predicting endoscopic remission; the CRP was falsely negative (< 3 mg/L) nearly twice as often as the SES-CD indicated endoscopic remission.

Mosli *et al*[28] completed a meta-analysis comprised of 19 studies (*n* = 2499 IBD patients) to characterize CRP correlation with endoscopic disease activity. For IBD, CRP levels had a pooled sensitivity and specificity of 49% and 92%, respectively. There were

an insufficient number of studies to calculate separate CRP performance metrics for UC and CD. The authors suggested a CRP cutoff of greater than 5mg/dL to indicate active endoscopic disease.

## PREDICTION OF RELAPSE USING CRP

High CRP levels correlate with clinical relapse in both short-term and long-term follow up[29-32]. Various studies have reported an increased risk of relapse with the relative risk ranging from 3 to 58[30-32]. In severe UC flares, high CRP, combined with high stool frequency and low serum albumin, has been associated with higher likelihood of failure to respond to medical therapy[33,34]. There is also a 6-times higher risk of hospitalization (OR = 6.82, 95%CI: 2.5-18.58; *P* < 0.0001) with elevated CRP in CD patients[35].

In analysis of the GETAID trial, 71 CD patients in medically-induced clinical remission had CRP, complete blood count, erythrocyte sedimentation rate (ESR), alpha-1 antitrypsin, and orosomucoid, checked every 6 wk[32]. Thirty-eight patients clinically relapsed, defined as a CDAI greater than 150 or increase of at least 100 points from baseline, after a median of 31 wk. Only ESR greater than 15 mm and CRP greater than 20 mg/L predicted clinical relapse. Levels of CRP were noted to rise 4 to 6 mo prior to clinical relapse, suggesting that routine measurement of biomarkers every 3-4 mo could alert the clinician that an alteration in therapy may be necessary.

Achieving not only clinical remission but also mucosal healing may lead to higher rates of long-term response or remission. In post-hoc analysis for the ACCENT-1 trial, 137 CD patients in clinical remission had CRP levels measured after induction with infliximab. At week 14, 56.6% of patients with a CRP less than 0.5 mg/dL *vs* 37.2% of patients with a CRP greater than 0.5 mg/dL maintained response to infliximab through 54 wk (*P* = 0.005)[36].

Rapid normalization of CRP levels correlates with sustained long-term response to infliximab[37] and adalimumab[24]. Jurgens *et al*[37] evaluated 268 CD patients who had responded to infliximab induction. Of these patients, 197 patients (73.5%) had increased CRP levels at baseline. Ninety-two patients (46.7%) had CRP normalization (< 3 mg/L) at week 4, and another 29 (14.7%) had CRP normalization after 10 wk. Kaplan-Meier curves indicated that CRP normalization after 4 wk of therapy had long-term benefit (*P* < 0.001) out to 5 years with a PPV of 63%. Karmiris *et al*[38] reported similar findings for CD patients with baseline elevated CRP and normalization of CRP (< 3 mg/L) at both weeks 4 and 12 predicting less frequent discontinuation of adalimumab and longer sustained clinical benefit up to 2 years of follow up. Kiss *et al*[24] reported low CRP at week 12 (< 10 mg/L) as being a predictor of clinical remission at 52 wk (OR = 4.61, *P* < 0.001) during the first year of

**Table 2  C-reactive protein values and correlating endoscopic scores**

| Ref. | Disease | Endoscopic tool | Endoscopic score (descriptor) | Calculation | CRP scores |
| --- | --- | --- | --- | --- | --- |
| Falvey *et al*[71] | CD | SES-CD | 0-2 (inactive) | Mean (95%CI) | 2.9 mg/L (1.8-4.6) |
| | | | 3-6 (mild) | | 4.0 mg/L (2.6-6.1) |
| | | | 7-15 (moderate) | | 5.1 mg/L (3.0-9.0) |
| | | | > 16 (severe) | | 22 mg/L (12.5-38.9) |
| Sipponen *et al*[88] | CD | CDEIS | < 3 (inactive) | Median (95%CI) | 0.0 mg/L (0-21) |
| | | | 3-9 (mild) | | 0.0 mg/L (0-26) |
| | | | 9-12 (moderate) | | 8.5 mg/L (0-85) |
| | | | ≥ 12 (severe) | | 16.5 mg/L (0-211) |
| Schoepfer *et al*[77] | CD | SES-CD | 0-3 (inactive) | Mean (range) | 12 mg/L (3-94) |
| | | | 4-10 (mild) | | 8 mg/L (3-53) |
| | | | 11-19 (moderate) | | 23 mg/L (3-172) |
| | | | ≥ 20 (high) | | 40 mg/L (5-121) |

CDEIS: Crohn's disease endoscopic index of severity; SES-CD: Simple endoscopic score for Crohn's disease.

adalimumab therapy.

Conversely, CRP levels are frequently elevated in patients who lose response to biologics[37]. Elevated CRP may be a sign of low drug level and a harbinger of ensuing loss of response and clinical relapse. In Jurgens *et al*[37], 57 CD patients who were responders to induction with infliximab had CRP and infliximab levels evaluated at week 14. In 75% of the patients who had clinical response after induction, a decrease in infliximab levels preceded loss of response by week 54. In 60% to 80% of patients with elevated CRP greater than 5 mg/L, the infliximab level was less than 1 μg/mL. CRP has also been shown to correlate better with low infliximab levels (< 1 μg/mL) than with clinical assessment using CDAI[39].

Higher CRP levels are also associated with an increased risk of surgery. In a Norwegian study, UC patients with a CRP above 23 mg/L at diagnosis were 4.8 times more likely to have surgery in the future (95%CI: 1.5-15.1, *P* = 0.02). At 1 year, UC patients with a CRP level greater than 10 mg/L were 3 times more likely to require surgery in the next 4 years (95%CI: 1.1-7.8, *P* = 0.02)[27]. CD patients with terminal ileitis were 6 times more likely to need future surgery if CRP levels at diagnosis were above 53 mg/L (95%CI: 1.1-31.9, *P* = 0.03).

## PREDICTING POSTOPERATIVE RECURRENCE WITH CRP

Postoperative recurrence of CD is common. Up to 80% of CD patients will require surgery during their lifetime, and 70% of these patients will need a second surgery[40]. Predicting recurrence of CD after intestinal resection for strictures and fistulizing disease is difficult. Half of patients in clinical remission have ileocolonic ulcerations on endoscopic examination[41]. Treatment is tailored to the individual patient based on his or her risk of recurrence. The best biomarker for determining which postoperative CD patients are at highest risk of recurrence is not known. There are few studies dedicated solely to the evaluation of CRP and postoperative CD recurrence.

Previous studies report mixed results regarding the use of CRP for monitoring for postoperative recurrence in CD. Regueiro *et al*[42] reported a prospective cohort of 25 postoperative CD patients with CRP levels measured prior to surgery and then at 54 wk postoperatively. At 54 wk, there was no significant increase in CRP in patients who relapsed as compared to patients remaining in remission. CRP also did not correlate significantly with endoscopic scores in this study.

A smaller study has shown correlation between CRP and postoperative recurrence[43]. In 12 postoperative CD patients on infliximab without endoscopic or clinical recurrence after 3 years, infliximab was stopped; ten of 12 patients had endoscopic recurrence after 16 wk (Rutgeerts score > i2). After cessation of infliximab, CRP increased significantly in all patients compared to baseline (12.5 ± 4 mg/L *vs* 3.0 ± 1.4 mg/L, *P* < 0.001)[43]. Once infliximab was resumed in a dose-dependent fashion (1 to 3 mg/kg), the CRP significantly decreased (*P* < 0.0001). In this study, CRP significantly correlated with postoperative endoscopic recurrence, but again, the main limitation of this study is the small sample size. A recent study of 86 CD patients who underwent ileocolonic resection found a weak but significant difference in high sensitivity CRP (hsCRP) concentrations between patients in endoscopic remission and patients with recurrence (3.0 ± 0.7 mg/L *vs* 8.5 ± 1.4 mg/L; *P* = 0.0014)[44].

In summary, an elevated CRP has been shown to positively correlate with endoscopic disease activity and may predict ensuing relapse while a patient is in clinical remission. Therefore, a persistently elevated CRP in both CD and UC should prompt further investigation with further blood work, stool studies for infection, and endoscopic evaluation to evaluate for active disease. On the other hand, normal CRP levels in UC patients should be interpreted with caution as endoscopic disease may still be present. For predicting postoperative recurrence of CD, there is not strong data supporting the use of CRP or hsCRP.

**Table 3  Endoscopic score correlation with fecal calprotectin**

| Ref. | Disease | Endoscopic tool | Correlation | *P* value |
|---|---|---|---|---|
| af Björkesten *et al*[25] | CD | SES-CD | r = 0.560 | < 0.001 |
| Sipponen *et al*[88] | CD | CDEIS | r = 0.831 | < 0.001 |
| Sipponen *et al*[49] | CD | SES-CD | r = 0.642 | < 0.001 |
| Sipponen *et al*[62] | CD | CDEIS | r = 0.729 | < 0.001 |
| Schoepfer *et al*[77] | CD | SES-CD | r = 0.530 | < 0.010 |
| Lobatón *et al*[74] | CD | CDEIS | r = 0.722[1] | < 0.001 |
| | | | r = 0.769[2] | < 0.001 |
| Lobatón *et al*[48] | UC | Mayo | r = 0.741[1] | < 0.001 |
| | | | r = 0.727[2] | < 0.001 |
| Takashima *et al*[67] | UC | Mayo | r = 0.580 | < 0.0001 |
| Røseth *et al*[66] | UC | Mayo | r = 0.570 | < 0.0001 |
| D'Haens *et al*[64] | UC | Mayo | r = 0.623 | < 0.001 |
| | CD | CDEIS | r = 0.419 | < 0.001 |
| | CD | SES-CD | r = 0.490 | < 0.001 |

[1]FC-ELISA; [2]FC Q-POCT (quantitative-point-of-care test). CDEIS: Crohn's disease endoscopic index of severity; SES-CD: Simple endoscopic score for Crohn's disease; r: Spearman's rank correlation coefficient.

## FC

First described in 1980, calprotectin is a 36 kilodalton inflammatory protein found in the cytosol of human neutrophils, macrophages, and monocytes[45,46]. Calprotectin comprises up to 60% of neutrophil cystolic proteins. The presence of calprotectin in the feces is directly proportional to neutrophil migration into the gastrointestinal tract during times of inflammation[12].

FC is a stable marker, resistant to degradation, that can be detected in stool for more than one week at room temperature[47]. Two FC assays are currently available: ELISA and a quantitative point-of-care-test (FC-QPOCT)[48]. Fecal lactoferrin, another stool neutrophil protein, is frequently paired with FC in clinical studies and generally has similar to slightly lower sensitivity and specificity when compared to FC[49-52].

Many gastrointestinal conditions can lead to elevations in FC concentrations including IBD, pouchitis, diverticulitis, malignancy, infections, nonsteroidal anti-inflammatory drug (NSAID) enteropathy, celiac disease, and microscopic colitis[53-55]. Though calprotectin is nonspecific and may be elevated in other gastrointestinal conditions, there is a substantial body of evidence supporting the use of FC in management of IBD.

Calprotectin levels have been reported to have low day-to-day variability in CD. Naismith *et al*[56] measured three consecutive days of FC levels in 98 patients with CD in clinical remission. An intraclass correlation (ICC) of 0.84 (95%CI: 0.79-0.89), low variability across patient samples, was reported. On the other hand, FC levels in UC patients have been shown to have high within-day variability[57]. Sampling the first bowel movement of the morning has been suggested to avoid falsely low measurements[58].

To further complicate matters, variations exist in FC levels depending on age. FC levels have been shown

positively correlate with age in 320 normal adult subjects, ages 50 to 70[59]. Likewise, normal volunteers 60 years or older had higher FC levels than patients aged 10 to 59[60]. However, infants[61] and children less than 10 years old[60] have higher FC levels than adults.

## FC CORRELATION WITH ENDOSCOPY

FC has been used to monitor patients during periods of quiescent disease. There is poor correlation between clinical assessment tools such as the CDAI with endoscopic inflammation in CD patients[3,49,62].

UC patients in clinical remission tend to have FC levels that positively correlate with endoscopic inflammation[63-66]. A study by Schoepfer *et al*[65] reported better correlation of endoscopic activity with FC than with other markers of inflammation including CRP, platelets, and serum leukocytes. In a recent study by Takashima *et al*[67], there was significant correlation of Mayo endoscopic scores with FC (r = 0.58; *P* < 0.0001) in 92 patients with UC.

In the meta-analysis by Mosli *et al*[28], FC predicted endoscopic activity with overall higher sensitivity than CRP, as expected. The pooled sensitivity and specificity of FC for endoscopically active IBD was 88% and 73%, respectively. When UC and CD were considered separately, UC exhibited equivalent sensitivity (88% *vs* 87%, respectively) but superior specificity (73% *vs* 67%) when compared to CD. An optimal FC cutoff of greater than 50 μg/g was calculated to signify endoscopically active disease. Stool lactoferrin had similar sensitivity and specificity (82% and 79%, respectively). A lactoferrin cutoff of greater than 7.25 μg/mL was calculated for endoscopically active disease.

In CD, clinical remission does not consistently correlate with FC levels[68,69]. Detecting subclinical inflammation is a high priority in CD to prevent long-term complications such as fibrostenotic strictures and perianal fistulae. However, endoscopic scores have been shown to correlate with FC levels in adults[25,49,62,64,70,71] and children[72,73] (Tables 3 and 4). In a group of 87 CD patients, D'haens *et al*[64] showed a significant correlation in adults between FC and CDEIS scores (r = 0.419, *P* < 0.001) and SES-CD (r = 0.49, *P* < 0.001) scores. Using receiver operating characteristic (ROC) curves, a cutoff of less than 250 μg/g correlated with endoscopic remission (CDEIS < 3) with high sensitivity (94.1%), moderate specificity (62.2%), and high negative predictive value (96.6%). Roseth *et al*[70] found that 44 out of 45 patients with a FC level < 50 mg/L had completely normal ileocolonoscopies. Moreover, by evaluating 18 of the stool samples from these same patients during previously active disease, the median FC level had been elevated to 3000 mg/L (*P* < 0.0001).

Isolated ileal CD impacts FC correlation with endoscopic scores. In a series of 87 consecutive ileo-colonoscopies, there was a significant correlation with

**Table 4  Fecal calprotectin values and correlating endoscopic scores**

| Ref. | Disease | Endoscopic tool | Endoscopic score (descriptor) | Calculation | Calprotectin scores |
|------|---------|-----------------|-------------------------------|-------------|---------------------|
| Falvey *et al*[71] | CD | SES-CD | 0-2 (inactive) | mean (95%CI) | 55 µg/g (25-123) |
| | | | 3-6 (mild) | | 167 µg/g (97-288) |
| | | | 7-15 (moderate) | | 366 µg/g (192-698) |
| | | | 16+ (severe) | | 732 µg/g (338-1587) |
| Sipponen *et al*[49] | CD | SES-CD | ≤ 3 (inactive-mild) | Median (range) | 37 µg/g (13-166) |
| | | | > 3 (active) | | 686 µg/g (18-15326) |
| Sipponen *et al*[62] | CD | CDEIS | < 3 (inactive) | Median (range) | 63 µg/g (11-869) |
| | | | 3-9 (mild) | | 170 µg/g (17-2440) |
| | | | 9-12 (moderate) | | 1014 µg/g (123-2284) |
| | | | > 12 (severe) | | 2066 µg/g (323-18575) |
| Schoepfer *et al*[77] | CD | SES-CD | 0-3 (inactive) | mean (range) | 104 µg/g (10-725) |
| | | | 4-10 (mild) | | 231 µg/g (12-1009) |
| | | | 11-19 (moderate) | | 395 µg/g (68-912) |
| | | | ≥ 20 (high) | | 718 µg/g (93-1327) |
| Lobatón *et al*[48] | CD | CDEIS | < 3 (endoscopic remission) | Median (range) | 101.8 µg/g (30-1620.9) |
| | | | ≥ 3 (endoscopic activity) | | 1211.9 µg/g (122-1800) |

CDEIS: Crohn's disease endoscopic index of severity; SES-CD: Simple endoscopic score for Crohn's disease.

FC and ileocolonic or colonic disease ($P < 0.001$)[49]. However, in isolated ileal CD, FC did not correlate with endoscopic SES-CD scores ($P = 0.161$) but did correlate with histology ($P < 0.001$). In a slightly larger study of 115 ileocolonoscopies, endoscopic findings exhibited excellent correlation with FC in ileocolonic disease ($r = 0.879$; $P < 0.001$) but only moderate correlation in ileal disease ($r = 0.437$; $P = 0.016$)[74]. Sipponen *et al*[75] found low sensitivity (59%) and moderate specificity (71%) when using FC to predict inflammatory small bowel lesions on subsequent capsule endoscopy.

In a more recent study of 44 patients with CD, 9 patients with isolated ileal disease had significantly lower FC levels when compared to patients with ileocolonic disease ($297 \pm 81$ µg/g *vs* $1523 \pm 97$ µg/g, $P < 0.0001$)[76]. However, even though the levels of FC were significantly lower in isolated ileal disease, the FC levels were still elevated. Despite lower FC levels in patients with isolated ileal disease, there was still good overall correlation with SES-CD endoscopic scores ($r = 0.76$, $P < 0.0001$). Separate analysis of SES-CD correlation with FC levels in isolated ileal disease was not reported.

Schoepfer *et al*[77] described good correlation between FC levels and SES-CD for isolated ileal disease ($r = 0.649$, $P < 0.001$), but again, correlation between FC levels and SES-CD for ileocolonic disease was better ($r = 0.795$, $P < 0.001$).

In a study of children with CD, levels of FC were similar between isolated ileal disease and ileocolonic disease. In 60 newly diagnosed children with untreated CD, the median level of FC did not differ between children with isolated small bowel disease (47 patients) (2198 µg/g) and children with colonic involvement (2400 µg/g)[78].

## PREDICTION OF RELAPSE USING FC

Despite continuous treatment, the majority of IBD patients will relapse. Evaluating which asymptomatic patients have smoldering subclinical inflammation is key to preventing further intestinal damage. Anticipating and altering treatment proactively helps prevent long-term complications. Approximately 35% of CD patients develop at least one fistula during the course of disease, and fistulas recur in one-third of patients[79]. Twenty-five percent of CD patients will have at least one small bowel stricture[80].

FC has been shown to correlate with histologic inflammation and to successfully predict relapses[81]. In a single-center, prospective study, 92 Crohn's patients in clinical remission (CDAI < 150) were observed for 12 mo. Ten patients (11%) relapsed by the end of one year. Median levels of FC were higher for relapsers than nonrelapsers (414 µg/g *vs* 96 µg/g, respectively; $P < 0.005$)[82]. In this study, Naismith *et al*[82] calculated that a FC greater than 240 µg/g was associated with a 12 times increased risk of relapse (Table 5). A meta-analysis of 6 studies with a total of 672 IBD patients (318 UC and 354 CD) reported a composite sensitivity of 78% (95%CI: 72-83%) and specificity of 73% (95%CI: 68%-77%) for predicting relapse using FC[83]. However, this meta-analysis did not report an optimal cutoff value for predicting relapse nor did the authors include CD patients with isolated ileal disease. Several studies have calculated optimal FC cutoffs to predict presence of endoscopic disease (Table 6).

Elevated FC levels have been reported to be present up to three months prior to clinical presentation of a UC flare[84,85]. De Vos *et al*[84] used FC levels to prospectively follow 87 patients with UC on maintenance infliximab therapy. FC levels were collected every 4 wk. Of these patients, 30 (34.4%) sustained deep remission (partial Mayo score < 3 and endoscopic Mayo score of 0 at one year) while 13 (14.9%) relapsed (Mayo score ≥ 2 or need for change in treatment) during one year follow-up. Those patients in deep remission maintained very low FC levels (< 40

**Table 5  Calprotectin cutoffs for predicting clinical relapse**

| Ref. | Disease | FC value | Relative risk | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| García-Sánchez *et al*[107] | UC | > 120 μg/g | 6 | 80 | 60 |
| | CD | > 200 μg/g | 4 | | |
| Tibble *et al*[108] | UC/CD | > 50 μg/g | 13 | 90 | 83 |
| Kallel *et al*[109] | CD | > 340 μg/g | 18 | 80 | 90.7 |
| Naismith *et al*[82] | CD | ≥ 240 μg/g | 12.18 | 80 | 74.4 |
| Costa *et al*[110] | UC | > 150 μg/g | 14 | 89 | 92 |
| | CD | > 150 μg/g | 2 | 87 | 43 |
| D'Inca *et al*[103] | UC/CD | > 130 mg/kg | - | 68 | 67 |

FC: Fecal calprotectin.

**Table 6  Calculated fecal calprotectin cutoffs based on endoscopic score**

| Ref. | Disease | Endoscopic tool | Score | FC cutoff | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|---|
| Guidi *et al*[111] | UC/CD | CDEIS | < 3 (mucosal healing) | 121 μg/g[a] | 79 | 57 | - | - |
| D'Haens *et al*[64] | CD | CDEIS | < 3 (inactive) | 250 μg/g | 94.1 | 62.2 | 48.5 | 96.6 |
| | UC | Mayo | 1-3 (any inflammation) | 250 μg/g | 71 | 100 | 100 | 47.1 |
| Sipponen *et al*[88] | CD | CDEIS | ≥ 3 (active) | 200 μg/g | 87 | 100 | 100 | 70 |
| af Björkesten *et al*[25] | CD | SES-CD | 0 (inactive) | 94 μg/g | 82 | 78 | - | - |
| Lobatón *et al*[48] | UC | Mayo | 0-1 (inactive-mild)[1] | 250 μg/g[1,b] | 73.5 | 89.7 | 86.2 | 79.5 |
| | | | 0-1 (inactive-mild)[2] | 280 μg/g[2,b] | 75.4 | 89.1 | 86 | 80.3 |
| Takashima *et al*[67] | UC | Mayo | 0 (inactive) | 250 μg/g | 82 | 62 | 61 | 83 |

[1]FC-ELISA; [2]FC-POCT; [a]*P* = 0.038; [b]*P* < 0.001 *vs* control. CDEIS: Crohn's disease endoscopic index of severity; SES-CD: Simple endoscopic score for Crohn's disease; FC: Fecal calprotectin.

mg/kg) with each sample analysis. Patients who flared exhibited elevated FC levels (> 300 mg/kg) beginning 3 mo prior to relapse. Interestingly, two consecutive FC levels greater than 300 mg/kg could predict relapse with a sensitivity of 61.5% and specificity of 100%.

Molander *et al*[85] monitored patients in endoscopic remission after infliximab cessation. Over one year of follow up after infliximab cessation, 15 UC patients (31%) and 34 CD patients (69%) relapsed. The patients who relapsed were found to have consistently elevated FC levels for a median of 94 d prior to relapse. There was a significant increase in FC levels at 2, 4, and 6 mo before endoscopic relapse (*P* = 0.0014, 0.0056, 0.0029, respectively). This suggests that the trend, rather than an isolated measurement, may be more valuable in predicting relapses.

Lasson *et al*[86] conducted a prospective, randomized, controlled study focused on altering therapy based on FC levels. They collected monthly FC levels in 91 UC patients with mild to moderate UC. If the FC value was higher than 300 μg/g on two consecutive measurements within one week, the dose of 5-aminosalicylates (5-ASAs) was escalated to try to prevent relapse. Of the patients with FC greater than 300 μg/g, the patients who had dose escalation of 5-ASAs had significantly reduced relapse rates as compared to patients in the control group (*P* < 0.05). In 18 of 28 patients (64.3%) in the dose escalation arm, their FC values dropped to less than 200 μg/g.

Calprotectin has been used to predict response to anti-TNF treatment during short-term follow-up periods.

Several studies reported a significant correlation between decreases in FC and short-term endoscopic remission[50,87,88]. In one Dutch study of 53 patients with UC, patients in endoscopic remission at week 10 after infliximab induction had a steep decrease in week 2 FC levels as compared to pretreatment levels. At week 10, there was an excellent AUC for endoscopic remission and FC (AUC 0.91; 95%CI: 0.81-1.0)[87].

FC has also been used to predict long-term response to anti-TNFs. Molander *et al*[89] defined a cutoff of FC greater than 139 μg/g after completion of induction therapy to predict a risk of clinically active disease after 1 year for patients with IBD treated with either infliximab (*n* = 42) or adalimumab (*n* = 18). In pediatric IBD patients, long-term response (1.1 years median follow-up) after infliximab induction therapy was retrospectively linked to FC response between weeks 2 and 6[90]. Children who stopped therapy within the first year due to inadequate effect had higher median FC levels during induction than patients who responded (633 μg/g *vs* 219 μg/g, *P* < 0.025).

In children, the utility of FC varies greatly based on report. Sipponen *et al*[91] followed 72 children with IBD. The median age was 13. Twenty-five (35%) children clinically relapsed within the subsequent year with poor predictive value of FC for relapse (39.6% for FC > 100 μg/g; 42.9% for FC > 1000 μg/g). However, a systematic review of 34 pediatric studies determined that FC can be a marker of active inflammation with high sensitivity (range 94.4%-100%) and moderate specificity (71.9%-100%)[92]. As with adult studies, the

**Table 7 Predicting postoperative recurrence with fecal calprotectin**

| Ref. | Type of recurrence | Follow-up time | FC value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|------|-------------------|----------------|----------|-----------------|-----------------|---------|---------|
| Lasson *et al*[98] | Endoscopic | 1 yr | 100 μg/g | 85 | 35 | 50 | 75 |
| | | | 200 μg/g | 54 | 53 | 47 | 60 |
| | | | 250 μg/g | 46 | 53 | 43 | 56 |
| Wright *et al*[96] | Endoscopic | 6 mo | 135 μg/g | 91 | 62 | 55 | 93 |
| | | 18 mo | 127 μg/g | 88 | 67 | 58 | 91 |
| Orlando *et al*[94] | Endoscopic | 1 yr | 200 mg/L | 63 | 75 | | |
| Yamamoto *et al*[51] | Endoscopic | 1 yr | 140 μg/g | 70 | 70 | 70 | 70 |
| | Clinical | | 170 μg/g | 83 | 93 | 83 | 93 |
| Lobatón *et al*[74] | Endoscopic | Not specified | 203 μg/g[1] | 75 | 72 | - | - |
| | | | 283 μg/g[2] | 67 | 72 | | |
| Boschetti *et al*[44] | Endoscopic | Within 18 mo | 100 μg/g | 95 | 54 | 93 | 77 |

[1]FC-ELISA test; [2]FC Q-POCT (quantitative-point-of-care test). FC: Fecal calprotectin.

cutoff range for detecting active IBD was large (50-275 μg/g).

## PREDICTING POSTOPERATIVE RECURRENCE USING FC

Multiple studies have looked at FC for monitoring for postoperative recurrence of disease in CD with mixed results[44,52,74,93-97]. FC levels correlate with clinical indices such as the HBI[52] but not with the CDAI[51]. Several studies have reported that FC correlates with disease relapse both clinically[52] and endoscopically[44,51,74,96,97]. Papamichael *et al*[97] followed a group of 59 CD patients after ileocecal resection. Persistently elevated FC levels (> 60 μg/g) were found in 100% (15/59) of patients who had postoperative endoscopic recurrence (Rutgeerts score ⩾ i2) after ileocecal resection whereas CRP elevations (> 0.5mg/dL) were present in only half of the patients (*P* = 0.017).

Various cutoffs have been suggested to predict postoperative recurrence of disease (Table 7). Boschetti *et al*[44] reported a cutoff of 100 μg/g (sensitivity 95%, specificity 54%) to correlate with endoscopic recurrence (Rutgeerts score ⩾ i2) in 86 asymptomatic CD patients after ileocolonic resection. When evaluating correlation with Rutgeerts scores, FC performed better (*r* = 0.65, *P* < 0.001) than hsCRP (*r* = 0.34, *P* = 0.0016). This study excluded patients with perianal disease. Stool samples were collected one week prior to endoscopic evaluation.

Yamamoto *et al*[93] collected stool samples from 20 asymptomatic postoperative CD patients at the beginning of the study then followed them for 1 year. The mean duration from surgery to endoscopic evaluation was 7.2 mo. A calculated FC cutoff of 140 μg/g predicted endoscopic recurrence whereas a cutoff of 170 μg/g predicted future clinical recurrence.

On the other hand, several studies reported that calprotectin was not consistent in predicting recurrence after surgery. Scarpa *et al*[95] retrospectively studied 63 CD patient FC levels for a median of 40.5 mo after surgery. There was no significant difference in FC levels between patients who remained in clinical or endoscopic remission and patients who had a recurrence of disease. The authors cited the limited correlation of the CDAI with inflammation and the lag in time between stool sample collection and endoscopy as possible explanations for lack of significance. However, there was a significant difference in FC levels between patients who required further ileocolonic resection and patients who did not need more surgery (*P* = 0.04), but this result is limited by small sample size (5 patients required further surgery). Lasson *et al*[98] reported a nonsignificant trend towards lower FC levels in patients in remission and higher FC levels in patients with endoscopic recurrence at one year postoperatively (*P* = 0.25). The small sample size of 30 patients and follow-up time were limitations to the study; one patient from the remission group ended up having a flare 6 mo after the study ended.

In a more recent prospective, randomized control trial in Australia and New Zealand, CD patients who underwent intestinal resection were followed up to 18 mo postoperatively. The median FC level decreased from 1347 μg/g prior to surgery to 166 μg/g at 6 mo postoperatively. Patients with endoscopic disease recurrence had higher median FC levels than patients who maintained remission (275 μg/g *vs* 72 μg/g, respectively; *P* < 0.001)[96]. Of note, CRP levels and clinical CDAI scores did not correlate with CD recurrence or severity of disease. A cutoff FC level of greater than 100 μg/g indicated endoscopic recurrence with a sensitivity of 89%, specificity of 58%, and negative predictive value of 91%. The high NPV of 91% suggests that endoscopy may be able to be avoided or deferred in patients with FC measurements less than 100 μg/g.

Overall, FC is a useful biomarker that is more specific for intestinal inflammation than CRP. FC correlates better with ileocolonic disease than with isolated ileal disease. FC is useful in predicting clinical and endoscopic relapse while in clinical remission, as well as monitoring response to medical therapy. Evidence suggests that monitoring for postoperative

recurrence is more reliable with FC than CRP.

## NEW APPLICATIONS: FECAL IMMUNOCHEMICAL TEST

Fecal immunochemical test (FIT) is an alternative modality being considered for use in IBD, much less utilized than FC or CRP. Quantitative FIT testing measures stool hemoglobin concentrations using an antibody specific for human hemoglobin[99]. FIT has mainly been publicized as a method for screening for colonic neoplasia[100]. As shown in a capsule endoscopy study, positive FIT tests can be explained by isolated small bowel lesions without colonic pathology[101].

Specifically relating to IBD, FIT has been used to predict mucosal healing in patients with UC with a 92% sensitivity and 71% specificity[99]. In a recent prospective trial from Japan, FIT was compared with FC to evaluate for mucosal healing in 92 patients with UC[67]. Of the 105 colonoscopies done, 77 (73%) were in patients in clinical remission. However, only 42% of colonoscopies demonstrated complete mucosal healing (Mayo score 0). Both the FIT and FC levels significantly correlated with the Mayo score. There was also significant correlation between the FIT values and FC levels (Spearman's correlation coefficient 0.64, $P < 0.0001$). The sensitivity and specificity of FIT for predicting mucosal healing was 95% and 62%, respectively, for a fecal hemoglobin concentration less than 100 ng/mL. Comparatively, for a FC cutoff less than 250 $\mu$g/g, there was lower sensitivity at 82% and equivalent specificity at 62% for predicting mucosal healing.

FIT is currently less expensive than FC. There may be a future role for FIT in disease monitoring in IBD, but more trials are needed.

## CONCLUSION

Our goals of treating IBD patients have evolved over the past few years to include mucosal healing in addition to clinical remission. Ideally, by monitoring disease activity via noninvasive blood or stool markers, we may be able to identify patients with subclinical disease activity and thereby optimize treatment prior to a clinical flare.

Furthermore, the practice of medicine is changing in the face of healthcare spending reforms. Cost cannot be overlooked. In the future, procedures such as colonoscopy may not always be cost-effective or time-efficient. Consistently reliable, noninvasive assays to evaluate subclinical disease activity will be valuable for determining which endoscopic evaluations may be deferred.

CRP and FC have emerged as two of the most commonly used biomarkers to evaluate for subclinical disease activity in IBD. There are pros and cons to keep in mind when ordering each biomarker.

CRP is low-cost, easy to obtain with simple blood-work, and quick to deliver data. CRP has been reported to have modest correlation with endoscopic and clinical findings, generally better with CD than UC. The major downsides to CRP are its lack of specificity for intestinal inflammation and moderate false negative rate. Genetic variations in CRP likely contribute to its overall lower sensitivity[23].

CRP does not reliably predict postoperative recurrence in CD. Just as postulated in active UC with normal CRP, early inflammation in postoperative recurrence may not be detectable using CRP due to lack of transmural inflammation. Existing data suggests that FC is a more sensitive measure of recurrent intestinal inflammation in postoperative CD patients.

FC is more expensive but is a more specific marker of intestinal inflammation. FC tends to correlate better with endoscopic findings in IBD than CRP, except in cases of isolated small bowel CD where FC levels are lower. CRP still plays a role in evaluation of isolated small bowel disease.

When considering the utility of FC in predicting endoscopic relapse in IBD and postoperative recurrence in CD, a noteworthy limiting factor for real-world use is the wide variation in defined cutoffs for inactive *vs* active disease (Tables 4-6). Generally, very high levels of FC indicate active disease, and FC levels less than 50 $\mu$g/g indicate inactive disease. However, many clinicians may find themselves questioning the significance of moderately elevated or upper limit of normal FC values.

The type of assay used (ELISA *vs* FC-QPOCT) may contribute to the wide range of cutoffs reported. Moreover, variations in calprotectin extraction methods can result in different FC quantitations from the same stool sample. During a quality assurance study, Whitehead *et al*[102] reported an average of 7.8% to 28.1% under-recovery of FC with different ELISA assays.

Heterogeneity in study design also may be a factor affecting FC cutoff levels. The definition of endoscopically inactive disease varies among studies. Also, time points for stool collection vary widely among studies. For example, one study may collect a stool sample on the day prior to colonoscopy[74] whereas another study may collect stool at an unspecified time point prior to clinical flare[103]. In the postoperative studies, there is variation in clinical status (remission *vs* symptomatic), disease phenotypes included, timing of postoperative endoscopic evaluation, as well as length of study follow up.

Perhaps a "one size fits all" approach does not pertain to calprotectin cutoffs in IBD. Optimal cutoffs may differ by disease (UC, CD), distribution of inflammation, age of patient, brand of assay used. For example, given that FC levels have been shown to be lower in isolated ileal disease, lower cutoff values may be needed for ileal CD without colitis. Also, in adults, the increase in FC with age may also need to be taken into account. Future investigations are needed to

further define these cutoffs.

In our practice, we use both CRP and FC to monitor patients in clinical remission. FC is preferred but not always sent due to cost and lack of coverage by certain insurance carriers. If FC is less than 50 μg/g, we do not routinely further evaluate the patient, whereas if the FC is greater than 250 μg/g, we rule out infection with stool studies and then consider an endoscopic evaluation. If the FC level is between 50 and 250 μg/g, we like to complete a colonoscopy at that time to correlate levels with endoscopic appearance. Still, in most cases, since levels vary from person to person, we find it most helpful to make treatment decisions based on a combination of FC, CRP, and endoscopic findings.

In the postoperative setting, we do not use CRP because of the lack of efficacy. We send FC levels at month 3. If elevated, we evaluate with colonoscopy. If normal, a colonoscopy is performed between 6 and 12 mo after resection.

Due to the nature of clinical research, most clinical studies focus on short-term patient responses to treatments. Less is known about long-term results of chronic biologic and immunomodulators therapies. The ultimate goal of therapy in IBD patients is to minimize the long-term sequelae of chronic inflammation while avoiding exposing the patient to unnecessary risks such as infection and neoplasia[104]. In 2009, the STORI trial evaluated stopping infliximab in patients on combination therapy who had been in steroid-free clinical remission for at least 6 mo[105]. Other studies have evaluated stopping immunomodulators while patients are maintained solely on infliximab[106]. The optimal duration of these drug holidays is unknown. With future trials underway evaluating the safety and logistics of withdrawing therapy, the role of monitoring clinically silent disease will be key in differentiating those patients who will remain quiescent and those who should re-escalate therapy.

## REFERENCES

1 **Lichtenstein GR**, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. *Am J Gastroenterol* 2009; **104**: 465-483; quiz 464, 484 [PMID: 19174807 DOI: 10.1038/ajg.2008.168]

2 **Sandborn WJ**, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009; **137**: 1250-1260; quiz 1520 [PMID: 19596014 DOI: 10.1053/j.gastro.2009.06.061]

3 **Cellier C**, Sahmoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, Florent C, Bouvry M, Mary JY, Modigliani R. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. *Gut* 1994; **35**: 231-235 [PMID: 7508411]

4 **Papi C**, Fascì-Spurio F, Rogai F, Settesoldi A, Margagnoni G, Annese V. Mucosal healing in inflammatory bowel disease: treatment efficacy and predictive factors. *Dig Liver Dis* 2013; **45**: 978-985 [PMID: 24018244 DOI: 10.1016/j.dld.2013.07.006]

5 **Lichtenstein GR**, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology* 2005; **128**: 862-869 [PMID: 15825070]

6 **Frøslie KF**, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: 17681162 DOI: 10.1053/j.gastro.2007.05.051]

7 **Schnitzler F**, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1295-1301 [PMID: 19340881 DOI: 10.1002/ibd.20927]

8 **Sands BE**. Biomarkers of Inflammation in Inflammatory Bowel Disease. *Gastroenterology* 2015; **149**: 1275-1285.e2 [PMID: 26166315 DOI: 10.1053/j.gastro.2015.07.003]

9 **Wu F**, Guo NJ, Tian H, Marohn M, Gearhart S, Bayless TM, Brant SR, Kwon JH. Peripheral blood microRNAs distinguish active ulcerative colitis and Crohn's disease. *Inflamm Bowel Dis* 2011; **17**: 241-250 [PMID: 20812331 DOI: 10.1002/ibd.21450]

10 **Poulsen NA**, Andersen V, Møller JC, Møller HS, Jessen F, Purup S, Larsen LB. Comparative analysis of inflamed and non-inflamed colon biopsies reveals strong proteomic inflammation profile in patients with ulcerative colitis. *BMC Gastroenterol* 2012; **12**: 76 [PMID: 22726388 DOI: 10.1186/1471-230X-12-76]

11 **Tillett WS**, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. *J Exp Med* 1930; **52**: 561-571 [PMID: 19869788]

12 **Vermeire S**, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? *Gut* 2006; **55**: 426-431 [PMID: 16474109 DOI: 10.1136/gut.2005.069476]

13 **Fengming Y**, Jianbing W. Biomarkers of inflammatory bowel disease. *Dis Markers* 2014; **2014**: 710915 [PMID: 24963213 DOI: 10.1155/2014/710915]

14 **Ridker PM**, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; **342**: 836-843 [PMID: 10733371 DOI: 10.1056/NEJM200003233421202]

15 **Bataille R**, Boccadoro M, Klein B, Durie B, Pileri A. C-reactive protein and beta-2 microglobulin produce a simple and powerful myeloma staging system. *Blood* 1992; **80**: 733-737 [PMID: 1638024]

16 **Solem CA**, Loftus EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11**: 707-712 [PMID: 16043984]

17 **Fagan EA**, Dyck RF, Maton PN, Hodgson HJ, Chadwick VS, Petrie A, Pepys MB. Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis. *Eur J Clin Invest* 1982; **12**: 351-359 [PMID: 6814926]

18 **Vermeire S**, Van Assche G, Rutgeerts P. The role of C-reactive protein as an inflammatory marker in gastrointestinal diseases. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 580-586 [PMID: 16327837 DOI: 10.1038/ncpgasthep0359]

19 **Saverymuttu SH**, Hodgson HJ, Chadwick VS, Pepys MB. Differing acute phase responses in Crohn's disease and ulcerative colitis. *Gut* 1986; **27**: 809-813 [PMID: 3732890]

20 **Talstad I**, Gjone E. The disease activity of ulcerative colitis and Crohn's disease. *Scand J Gastroenterol* 1976; **11**: 403-408 [PMID: 935802]

21 **Karoui S**, Ouerdiane S, Serghini M, Jomni T, Kallel L, Fekih M, Boubaker J, Filali A. Correlation between levels of C-reactive protein and clinical activity in Crohn's disease. *Dig Liver Dis* 2007; **39**: 1006-1010 [PMID: 17889628 DOI: 10.1016/j.dld.2007.06.015]

22 **Tilakaratne S**, Lemberg DA, Leach ST, Day AS. C-reactive protein and disease activity in children with Crohn's disease. *Dig Dis Sci* 2010; **55**: 131-136 [PMID: 19830556 DOI: 10.1007/s10620-009-1017-8]

23 **Jones J**, Loftus EV, Panaccione R, Chen LS, Peterson S,

McConnell J, Baudhuin L, Hanson K, Feagan BG, Harmsen SW, Zinsmeister AR, Helou E, Sandborn WJ. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2008; **6**: 1218-1224 [PMID: 18799360 DOI: 10.1016/j.cgh.2008.06.010]

24    **Kiss LS**, Szamosi T, Molnar T, Miheller P, Lakatos L, Vincze A, Palatka K, Barta Z, Gasztonyi B, Salamon A, Horvath G, Tóth GT, Farkas K, Banai J, Tulassay Z, Nagy F, Szenes M, Veres G, Lovasz BD, Vegh Z, Golovics PA, Szathmari M, Papp M, Lakatos PL. Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 911-922 [PMID: 21883326 DOI: 10.1111/j.1365-2036.2011.04827.x]

25    **af Björkesten CG**, Nieminen U, Turunen U, Arkkila P, Sipponen T, Färkkilä M. Surrogate markers and clinical indices, alone or combined, as indicators for endoscopic remission in anti-TNF-treated luminal Crohn's disease. *Scand J Gastroenterol* 2012; **47**: 528-537 [PMID: 22356594 DOI: 10.3109/00365521.2012.660542]

26    **Hanauer SB**, Sandborn W; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol* 2001; **96**: 635-643 [PMID: 11280528 DOI: 10.1111/j.1572-0241.2001.3671_c.x]

27    **Henriksen M**, Jahnsen J, Lygren I, Stray N, Sauar J, Vatn MH, Moum B. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. *Gut* 2008; **57**: 1518-1523 [PMID: 18566104 DOI: 10.1136/gut.2007.146357]

28    **Mosli MH**, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, Sandborn WJ, Feagan BG. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2015; **110**: 802-819; quiz 820 [PMID: 25964225 DOI: 10.1038/ajg.2015.120]

29    **Boirivant M**, Leoni M, Tariciotti D, Fais S, Squarcia O, Pallone F. The clinical significance of serum C reactive protein levels in Crohn's disease. Results of a prospective longitudinal study. *J Clin Gastroenterol* 1988; **10**: 401-405 [PMID: 3418087]

30    **Koelewijn CL**, Schwartz MP, Samsom M, Oldenburg B. C-reactive protein levels during a relapse of Crohn's disease are associated with the clinical course of the disease. *World J Gastroenterol* 2008; **14**: 85-89 [PMID: 18176967]

31    **Bitton A**, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, Cohen A, Vermeire S, Dufresne L, Franchimont D, Wild GE. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut* 2008; **57**: 1386-1392 [PMID: 18390994 DOI: 10.1136/gut.2007.134817]

32    **Consigny Y**, Modigliani R, Colombel JF, Dupas JL, Lémann M, Mary JY. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. *Inflamm Bowel Dis* 2006; **12**: 551-557 [PMID: 16804391 DOI: 10.1097/01.ibd.0000225334.60990.5b]

33    **Travis SP**, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG, Jewell DP. Predicting outcome in severe ulcerative colitis. *Gut* 1996; **38**: 905-910 [PMID: 8984031]

34    **Gelbmann CM**. Prediction of treatment refractoriness in ulcerative colitis and Crohn's disease--do we have reliable markers? *Inflamm Bowel Dis* 2000; **6**: 123-131 [PMID: 10833072]

35    **Vargas EJ**, Ramos Rivers CM, Regueiro M, Baidoo L, Barrie A, Schwartz M, Swoger JM, Coates M, Dunn MA, Dudekula A, Binion DG. 557 Silent Crohn's Disease: Elevated C Reactive Protein in Asymptomatic Patients and Risk of Subsequent Hospitalization. *Gastroenterology* 2013; **144**: S-102 [DOI: 10.1016/S0016-5085(13)60377-7]

36    **Reinisch W**, Wang Y, Oddens BJ, Link R. C-reactive protein, an indicator for maintained response or remission to infliximab in patients with Crohn's disease: a post-hoc analysis from ACCENT I. *Aliment Pharmacol Ther* 2012; **35**: 568-576 [PMID: 22251435 DOI: 10.1111/j.1365-2036.2011.04987.x]

37    **Jürgens M**, Mahachie John JM, Cleynen I, Schnitzler F, Fidder H, van Moerkercke W, Ballet V, Noman M, Hoffman I, van Assche G, Rutgeerts PJ, van Steen K, Vermeire S. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2011; **9**: 421-427.e1 [PMID: 21334460 DOI: 10.1016/j.cgh.2011.02.008]

38    **Karmiris K**, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, Claes K, Coopman T, Van Schuerbeek N, Van Assche G, Vermeire S, Rutgeerts P. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology* 2009; **137**: 1628-1640 [PMID: 19664627 DOI: 10.1053/j.gastro.2009.07.062]

39    **Hibi T**, Sakuraba A, Watanabe M, Motoya S, Ito H, Sato N, Yoshinari T, Motegi K, Kinouchi Y, Takazoe M, Suzuki Y, Matsumoto T, Kawakami K, Matsumoto T, Hirata I, Tanaka S, Ashida T, Matsui T. C-reactive protein is an indicator of serum infliximab level in predicting loss of response in patients with Crohn's disease. *J Gastroenterol* 2014; **49**: 254-262 [PMID: 23604570 DOI: 10.1007/s00535-013-0807-0]

40    **Schoepfer AM**, Lewis JD. Serial fecal calprotectin measurements to detect endoscopic recurrence in postoperative Crohn's disease: is colonoscopic surveillance no longer needed? *Gastroenterology* 2015; **148**: 889-892 [PMID: 25805423 DOI: 10.1053/j.gastro.2015.03.022]

41    **Peyrin-Biroulet L**, Reinisch W, Colombel JF, Mantzaris GJ, Kornbluth A, Diamond R, Rutgeerts P, Tang LK, Cornillie FJ, Sandborn WJ. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut* 2014; **63**: 88-95 [PMID: 23974954 DOI: 10.1136/gutjnl-2013-304984]

42    **Regueiro M**, Kip KE, Schraut W, Baidoo L, Sepulveda AR, Pesci M, El-Hachem S, Harrison J, Binion D. Crohn's disease activity index does not correlate with endoscopic recurrence one year after ileocolonic resection. *Inflamm Bowel Dis* 2011; **17**: 118-126 [PMID: 20848538 DOI: 10.1002/ibd.21355]

43    **Sorrentino D**, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. *Clin Gastroenterol Hepatol* 2010; **8**: 591-599.e1; quiz e78-e79 [PMID: 20139033 DOI: 10.1016/j.cgh.2010.01.016]

44    **Boschetti G**, Laidet M, Moussata D, Stefanescu C, Roblin X, Phelip G, Cotte E, Passot G, Francois Y, Drai J, Del Tedesco E, Bouhnik Y, Flourie B, Nancey S. Levels of Fecal Calprotectin Are Associated With the Severity of Postoperative Endoscopic Recurrence in Asymptomatic Patients With Crohn's Disease. *Am J Gastroenterol* 2015; **110**: 865-872 [PMID: 25781366 DOI: 10.1038/ajg.2015.30]

45    **Smith LA**, Gaya DR. Utility of faecal calprotectin analysis in adult inflammatory bowel disease. *World J Gastroenterol* 2012; **18**: 6782-6789 [PMID: 23239916 DOI: 10.3748/wjg.v18.i46.6782]

46    **Fagerhol MK**, Dale I, Andersson T. A radioimmunoassay for a granulocyte protein as a marker in studies on the turnover of such cells. *Bull Eur Physiopathol Respir* 1980; **16** Suppl: 273-282 [PMID: 7225633]

47    **Røseth AG**, Fagerhol MK, Aadland E, Schjønsby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. *Scand J Gastroenterol* 1992; **27**: 793-798 [PMID: 1411288]

48    **Lobatón T**, Rodríguez-Moranta F, Lopez A, Sánchez E, Rodríguez-Alonso L, Guardiola J. A new rapid quantitative test for fecal calprotectin predicts endoscopic activity in ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 1034-1042 [PMID: 23470502 DOI: 10.1097/MIB.0b013e3182802b6e]

49    **Sipponen T**, Kärkkäinen P, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. *Aliment Pharmacol Ther* 2008; **28**: 1221-1229 [PMID: 18752630 DOI: 10.1111/j.1365-2036.2008.03835.x]

50    **Sipponen T**, Björkesten CG, Färkkilä M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. *Scand J Gastroenterol* 2010; **45**: 325-331 [PMID: 20034360 DOI:

10.3109/00365520903483650]

51    **Yamamoto T**, Shiraki M, Bamba T, Umegae S, Matsumoto K. Faecal calprotectin and lactoferrin as markers for monitoring disease activity and predicting clinical recurrence in patients with Crohn's disease after ileocolonic resection: A prospective pilot study. *United European Gastroenterol J* 2013; **1**: 368-374 [PMID: 24917985 DOI: 10.1177/2050640613501818]

52    **Lamb CA**, Mohiuddin MK, Gicquel J, Neely D, Bergin FG, Hanson JM, Mansfield JC. Faecal calprotectin or lactoferrin can identify postoperative recurrence in Crohn's disease. *Br J Surg* 2009; **96**: 663-674 [PMID: 19384912 DOI: 10.1002/bjs.6593]

53    **Sipponen T**. Diagnostics and prognostics of inflammatory bowel disease with fecal neutrophil-derived biomarkers calprotectin and lactoferrin. *Dig Dis* 2013; **31**: 336-344 [PMID: 24246984 DOI: 10.1159/000354689]

54    **Limburg PJ**, Ahlquist DA, Sandborn WJ, Mahoney DW, Devens ME, Harrington JJ, Zinsmeister AR. Fecal calprotectin levels predict colorectal inflammation among patients with chronic diarrhea referred for colonoscopy. *Am J Gastroenterol* 2000; **95**: 2831-2837 [PMID: 11051356 DOI: 10.1111/j.1572-0241.2000.03194.x]

55    **Tibble JA**, Sigthorsson G, Foster R, Scott D, Fagerhol MK, Roseth A, Bjarnason I. High prevalence of NSAID enteropathy as shown by a simple faecal test. *Gut* 1999; **45**: 362-366 [PMID: 10446103]

56    **Naismith GD**, Smith LA, Barry SJ, Munro JI, Laird S, Rankin K, Morris AJ, Winter JW, Gaya DR. A prospective single-centre evaluation of the intra-individual variability of faecal calprotectin in quiescent Crohn's disease. *Aliment Pharmacol Ther* 2013; **37**: 613-621 [PMID: 23347334 DOI: 10.1111/apt.12221]

57    **Calafat M**, Cabré E, Mañosa M, Lobatón T, Marín L, Domènech E. High within-day variability of fecal calprotectin levels in patients with active ulcerative colitis: what is the best timing for stool sampling? *Inflamm Bowel Dis* 2015; **21**: 1072-1076 [PMID: 25793326 DOI: 10.1097/MIB.0000000000000349]

58    **Pavlidis P**, Chedgy FJ, Tibble JA. Diagnostic accuracy and clinical application of faecal calprotectin in adult patients presenting with gastrointestinal symptoms in primary care. *Scand J Gastroenterol* 2013; **48**: 1048-1054 [PMID: 23883068 DOI: 10.3109/00365521.2013.816771]

59    **Poullis A**, Foster R, Shetty A, Fagerhol MK, Mendall MA. Bowel inflammation as measured by fecal calprotectin: a link between lifestyle factors and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 279-284 [PMID: 14973103]

60    **Joshi S**, Lewis SJ, Creanor S, Ayling RM. Age-related faecal calprotectin, lactoferrin and tumour M2-PK concentrations in healthy volunteers. *Ann Clin Biochem* 2010; **47**: 259-263 [PMID: 19740914 DOI: 10.1258/acb.2009.009061]

61    **Li F**, Ma J, Geng S, Wang J, Liu J, Zhang J, Sheng X. Fecal calprotectin concentrations in healthy children aged 1-18 months. *PLoS One* 2015; **10**: e0119574 [PMID: 25742018 DOI: 10.1371/journal.pone.0119574]

62    **Sipponen T**, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008; **14**: 40-46 [PMID: 18022866 DOI: 10.1002/ibd.20312]

63    **Walkiewicz D**, Werlin SL, Fish D, Scanlon M, Hanaway P, Kugathasan S. Fecal calprotectin is useful in predicting disease relapse in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2008; **14**: 669-673 [PMID: 18240279 DOI: 10.1002/ibd.20376]

64    **D'Haens G**, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, Geens P, Iwens D, Aerden I, Van Assche G, Van Olmen G, Rutgeerts P. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 2218-2224 [PMID: 22344983 DOI: 10.1002/ibd.22917]

65    **Schoepfer AM**, Beglinger C, Straumann A, Safroneeva E, Romero Y, Armstrong D, Schmidt C, Trummler M, Pittet V, Vavricka SR. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. *Inflamm Bowel Dis* 2013; **19**: 332-341 [PMID: 23328771 DOI: 10.1097/

MIB.0b013e3182810066]

66    **Røseth AG**, Aadland E, Jahnsen J, Raknerud N. Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein. *Digestion* 1997; **58**: 176-180 [PMID: 9144308]

67    **Takashima S**, Kato J, Hiraoka S, Nakarai A, Takei D, Inokuchi T, Sugihara Y, Takahara M, Harada K, Okada H, Tanaka T, Yamamoto K. Evaluation of Mucosal Healing in Ulcerative Colitis by Fecal Calprotectin Vs. Fecal Immunochemical Test. *Am J Gastroenterol* 2015; **110**: 873-880 [PMID: 25823769 DOI: 10.1038/ajg.2015.66]

68    **Tibble J**, Teahon K, Thjodleifsson B, Roseth A, Sigthorsson G, Bridger S, Foster R, Sherwood R, Fagerhol M, Bjarnason I. A simple method for assessing intestinal inflammation in Crohn's disease. *Gut* 2000; **47**: 506-513 [PMID: 10986210]

69    **Costa F**, Mumolo MG, Bellini M, Romano MR, Ceccarelli L, Arpe P, Sterpi C, Marchi S, Maltinti G. Role of faecal calprotectin as non-invasive marker of intestinal inflammation. *Dig Liver Dis* 2003; **35**: 642-647 [PMID: 14563186]

70    **Røseth AG**, Aadland E, Grzyb K. Normalization of faecal calprotectin: a predictor of mucosal healing in patients with inflammatory bowel disease. *Scand J Gastroenterol* 2004; **39**: 1017-1020 [PMID: 15513345 DOI: 10.1080/00365520410007971]

71    **Falvey JD**, Hoskin T, Meijer B, Ashcroft A, Walmsley R, Day AS, Gearry RB. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. *Inflamm Bowel Dis* 2015; **21**: 824-831 [PMID: 25738372 DOI: 10.1097/MIB.0000000000000341]

72    **Bunn SK**, Bisset WM, Main MJ, Gray ES, Olson S, Golden BE. Fecal calprotectin: validation as a noninvasive measure of bowel inflammation in childhood inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2001; **33**: 14-22 [PMID: 11479402]

73    **Fagerberg UL**, Lööf L, Myrdal U, Hansson LO, Finkel Y. Colorectal inflammation is well predicted by fecal calprotectin in children with gastrointestinal symptoms. *J Pediatr Gastroenterol Nutr* 2005; **40**: 450-455 [PMID: 15795593]

74    **Lobatón T**, López-García A, Rodríguez-Moranta F, Ruiz A, Rodríguez L, Guardiola J. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn's disease. *J Crohns Colitis* 2013; **7**: e641-e651 [PMID: 23810085 DOI: 10.1016/j.crohns.2013.05.005]

75    **Sipponen T**, Haapamäki J, Savilahti E, Alfthan H, Hämäläinen E, Rautiainen H, Koskenpato J, Nuutinen H, Färkkilä M. Fecal calprotectin and S100A12 have low utility in prediction of small bowel Crohn's disease detected by wireless capsule endoscopy. *Scand J Gastroenterol* 2012; **47**: 778-784 [PMID: 22519419 DOI: 10.3109/00365521.2012.677953]

76    **Gecse KB**, Brandse JF, van Wilpe S, Löwenberg M, Ponsioen C, van den Brink G, D'Haens G. Impact of disease location on fecal calprotectin levels in Crohn's disease. *Scand J Gastroenterol* 2015; **50**: 841-847 [PMID: 25636819 DOI: 10.3109/00365521.2015.1008035]

77    **Schoepfer AM**, Beglinger C, Straumann A, Trummler M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; **105**: 162-169 [PMID: 19755969 DOI: 10.1038/ajg.2009.545]

78    **Shaoul R**, Sladek M, Turner D, Paeregaard A, Veres G, Wauters GV, Escher J, Dias JA, Lionetti P, Staino A, Kolho KL, de Ridder L, Nuti F, Cucchiara S, Sheva O, Levine A. Limitations of fecal calprotectin at diagnosis in untreated pediatric Crohn's disease. *Inflamm Bowel Dis* 2012; **18**: 1493-1497 [PMID: 22275268 DOI: 10.1002/ibd.21875]

79    **Gecse K**, Khanna R, Stoker J, Jenkins JT, Gabe S, Hahnloser D, D'Haens G. Fistulizing Crohn's disease: Diagnosis and management. *United European Gastroenterol J* 2013; **1**: 206-213 [PMID: 24917961 DOI: 10.1177/2050640613487194]

80    **Chang CW**, Wong JM, Tung CC, Shih IL, Wang HY, Wei SC. Intestinal stricture in Crohn's disease. *Intest Res* 2015; **13**: 19-26 [PMID: 25691840 DOI: 10.5217/ir.2015.13.1.19]

81   **Konikoff MR**, Denson LA. Role of fecal calprotectin as a biomarker of intestinal inflammation in inflammatory bowel disease. *Inflamm Bowel Dis* 2006; **12**: 524-534 [PMID: 16775498]

82   **Naismith GD**, Smith LA, Barry SJ, Munro JI, Laird S, Rankin K, Morris AJ, Winter JW, Gaya DR. A prospective evaluation of the predictive value of faecal calprotectin in quiescent Crohn's disease. *J Crohns Colitis* 2014; **8**: 1022-1029 [PMID: 24566170 DOI: 10.1016/j.crohns.2014.01.029]

83   **Mao R**, Xiao YL, Gao X, Chen BL, He Y, Yang L, Hu PJ, Chen MH. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. *Inflamm Bowel Dis* 2012; **18**: 1894-1899 [PMID: 22238138 DOI: 10.1002/ibd.22861]

84   **De Vos M**, Louis EJ, Jahnsen J, Vandervoort JG, Noman M, Dewit O, D'haens GR, Franchimont D, Baert FJ, Torp RA, Henriksen M, Potvin PM, Van Hootegem PP, Hindryckx PM, Moreels TG, Collard A, Karlsen LN, Kittang E, Lambrecht G, Grimstad T, Koch J, Lygren I, Coche JC, Mana F, Van Gossum A, Belaiche J, Cool MR, Fontaine F, Maisin JM, Muls V, Neuville B, Staessen DA, Van Assche GA, de Lange T, Solberg IC, Vander Cruyssen BJ, Vermeire SA. Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. *Inflamm Bowel Dis* 2013; **19**: 2111-2117 [PMID: 23883959 DOI: 10.1097/MIB.0b013e31829b2a37]

85   **Molander P**, Färkkilä M, Ristimäki A, Salminen K, Kemppainen H, Blomster T, Koskela R, Jussila A, Rautiainen H, Nissinen M, Haapamäki J, Arkkila P, Nieminen U, Kuisma J, Punkkinen J, Kolho KL, Mustonen H, Sipponen T. Does fecal calprotectin predict short-term relapse after stopping TNFα-blocking agents in inflammatory bowel disease patients in deep remission? *J Crohns Colitis* 2015; **9**: 33-40 [PMID: 25052347 DOI: 10.1016/j.crohns.2014.06.012]

86   **Lasson A**, Öhman L, Stotzer PO, Isaksson S, Überbacher O, Ung KA, Strid H. Pharmacological intervention based on fecal calprotectin levels in patients with ulcerative colitis at high risk of a relapse: A prospective, randomized, controlled study. *United European Gastroenterol J* 2015; **3**: 72-79 [PMID: 25653861 DOI: 10.1177/2050640614560785]

87   **De Vos M**, Dewit O, D'Haens G, Baert F, Fontaine F, Vermeire S, Franchimont D, Moreels T, Staessen D, Terriere L, Vander Cruyssen B, Louis E. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naïve patients with ulcerative colitis. *J Crohns Colitis* 2012; **6**: 557-562 [PMID: 22398050 DOI: 10.1016/j.crohns.2011.11.002]

88   **Sipponen T**, Savilahti E, Kärkkäinen P, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. *Inflamm Bowel Dis* 2008; **14**: 1392-1398 [PMID: 18484671 DOI: 10.1002/ibd.20490]

89   **Molander P**, af Bjorkesten C, Mustonen H, Haapamaki J, vauhkonen M, Kolho K, Farkkila M, sipponen T. Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFa blocking agents. *Inflamm bowel dis* 2012; **18**: 2011-2017 [PMID: 22223566 DOI: 10.1002/ibd.22863]

90   **Kolho KL**, Sipponen T. The long-term outcome of anti-tumor necrosis factor-α therapy related to fecal calprotectin values during induction therapy in pediatric inflammatory bowel disease. *Scand J Gastroenterol* 2014; **49**: 434-441 [PMID: 24597837 DOI: 10.3109/00365521.2014.886719]

91   **Sipponen T**, Kolho KL. Faecal calprotectin in children with clinically quiescent inflammatory bowel disease. *Scand J Gastroenterol* 2010; **45**: 872-877 [PMID: 20377469 DOI: 10.3109/00365521003782389]

92   **Kostakis ID**, Cholidou KG, Vaiopoulos AG, Vlachos IS, Perrea D, Vaos G. Fecal calprotectin in pediatric inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2013; **58**: 309-319 [PMID: 22899243 DOI: 10.1007/s10620-012-2347-5]

93   **Yamamoto T**. The clinical value of faecal calprotectin and lactoferrin measurement in postoperative Crohn's disease. *United European Gastroenterol J* 2015; **3**: 5-10 [PMID: 25653853 DOI: 10.1177/2050640614558106]

94   **Orlando A**, Modesto I, Castiglione F, Scala L, Scimeca D, Rispo A, Teresi S, Mocciaro F, Criscuoli V, Marrone C, Platania P, De Falco T, Maisano S, Nicoli N, Cottone M. The role of calprotectin in predicting endoscopic post-surgical recurrence in asymptomatic Crohn's disease: a comparison with ultrasound. *Eur Rev Med Pharmacol Sci* 2006; **10**: 17-22 [PMID: 16494106]

95   **Scarpa M**, D'Incà R, Basso D, Ruffolo C, Polese L, Bertin E, Luise A, Frego M, Plebani M, Sturniolo GC, D'Amico DF, Angriman I. Fecal lactoferrin and calprotectin after ileocolonic resection for Crohn's disease. *Dis Colon Rectum* 2007; **50**: 861-869 [PMID: 17473939 DOI: 10.1007/s10350-007-0225-6]

96   **Wright EK**, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, Leach S, Gorelik A, Liew D, Prideaux L, Lawrance IC, Andrews JM, Bampton PA, Jakobovits SL, Florin TH, Gibson PR, Debinski H, Macrae FA, Samuel D, Kronborg I, Radford-Smith G, Selby W, Johnston MJ, Woods R, Elliott PR, Bell SJ, Brown SJ, Connell WR, Day AS, Desmond PV, Gearry RB. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology* 2015; **148**: 938-947.e1 [PMID: 25620670 DOI: 10.1053/j.gastro.2015.01.026]

97   **Papamichael K**, Karatzas P, Mantzaris GJ. Faecal calprotectin but not C-reactive protein (CRP) or Crohn's Disease Activity Index (CDAI) may predict post-operative endoscopic recurrence of Crohn's disease. *J Crohns Colitis* 2013; **7**: e700-e701 [PMID: 23953238 DOI: 10.1016/j.crohns.2013.07.008]

98   **Lasson A**, Strid H, Ohman L, Isaksson S, Olsson M, Rydström B, Ung KA, Stotzer PO. Fecal calprotectin one year after ileocaecal resection for Crohn's disease--a comparison with findings at ileocolonoscopy. *J Crohns Colitis* 2014; **8**: 789-795 [PMID: 24418661 DOI: 10.1016/j.crohns.2013.12.015]

99   **Nakarai A**, Kato J, Hiraoka S, Kuriyama M, Akita M, Hirakawa T, Okada H, Yamamoto K. Evaluation of mucosal healing of ulcerative colitis by a quantitative fecal immunochemical test. *Am J Gastroenterol* 2013; **108**: 83-89 [PMID: 23007005 DOI: 10.1038/ajg.2012.315]

100  **Vilkin A**, Rozen P, Levi Z, Waked A, Maoz E, Birkenfeld S, Niv Y. Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *Am J Gastroenterol* 2005; **100**: 2519-2525 [PMID: 16279909 DOI: 10.1111/j.1572-0241.2005.00231.x]

101  **Levi Z**, Gal E, Vilkin A, Chonen Y, Belfer RG, Fraser G, Niv Y. Fecal immunochemical test and small bowel lesions detected on capsule endoscopy: results of a prospective study in patients with obscure occult gastrointestinal bleeding. *Eur J Gastroenterol Hepatol* 2011; **23**: 1024-1028 [PMID: 21975696 DOI: 10.1097/MEG.0b013e32834a3e00]

102  **Whitehead SJ**, French J, Brookes MJ, Ford C, Gama R. Between-assay variability of faecal calprotectin enzyme-linked immunosorbent assay kits. *Ann Clin Biochem* 2013; **50**: 53-61 [PMID: 23129721 DOI: 10.1258/acb.2012.011272]

103  **D'Inca R**, Dal Pont E, Di Leo V, Benazzato L, Martinato M, Lamboglia F, Oliva L, Sturniolo GC. Can calprotectin predict relapse risk in inflammatory bowel disease? *Am J Gastroenterol* 2008; **103**: 2007-2014 [DOI: 10.1111/j.1572-0241.2008.01870.x]

104  **Pariente B**, Laharie D. Review article: why, when and how to de-escalate therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014; **40**: 338-353 [PMID: 24957164 DOI: 10.1111/apt.12838]

105  **Louis E**, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Porcher R, Paintaud G, Piver E, Colombel JF, Lemann M. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012; **142**: 63-70.e5; quiz e31 [PMID: 21945953 DOI: 10.1053/j.gastro.2011.09.034]

106  **Van Assche G**, Magdelaine-Beuzelin C, D'Haens G, Baert F, Noman M, Vermeire S, Ternant D, Watier H, Paintaud G, Rutgeerts P. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology* 2008; **134**: 1861-1868 [PMID: 18440315 DOI: 10.1053/j.gastro.2008.03.004]

107  **García-Sánchez V**, Iglesias-Flores E, González R, Gisbert JP, Gallardo-Valverde JM, González-Galilea A, Naranjo-Rodríguez A, de Dios-Vega JF, Muntané J, Gómez-Camacho F. Does fecal calprotectin predict relapse in patients with Crohn's disease and ulcerative colitis? *J Crohns Colitis* 2010; **4**: 144-152 [PMID: 21122498 DOI: 10.1016/j.crohns.2009.09.008]

108  **Tibble JA**, Sigthorsson G, Bridger S, Fagerhol MK, Bjarnason I. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Gastroenterology* 2000; **119**: 15-22 [PMID: 10889150]

109  **Kallel L**, Ayadi I, Matri S, Fekih M, Mahmoud NB, Feki M, Karoui S, Zouari B, Boubaker J, Kaabachi N, Filali A. Fecal calprotectin is a predictive marker of relapse in Crohn's disease involving the colon: a prospective study. *Eur J Gastroenterol Hepatol* 2010; **22**: 340-345 [PMID: 19581809 DOI: 10.1097/MEG.0b013e32832bab49]

110  **Costa F**, Mumolo MG, Ceccarelli L, Bellini M, Romano MR, Sterpi C, Ricchiuti A, Marchi S, Bottai M. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. *Gut* 2005; **54**: 364-368 [PMID: 15710984 DOI: 10.1136/gut.2004.043406]

111  **Guidi L**, Marzo M, Andrisani G, Felice C, Pugliese D, Mocci G, Nardone O, De Vitis I, Papa A, Rapaccini G, Forni F, Armuzzi A. Faecal calprotectin assay after induction with anti-Tumour Necrosis Factor α agents in inflammatory bowel disease: Prediction of clinical response and mucosal healing at one year. *Dig Liver Dis* 2014; **46**: 974-979 [PMID: 25096964 DOI: 10.1016/j.dld.2014.07.013]