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CLINICAL UTILITY OF FECAL CALPROTECTIN IN INFLAMMATORY BOWEL DISEASE: FROM DIAGNOSIS TO TREATMENT MONITORING

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Abstract

Inflammatory bowel diseases (IBD), mainly Crohn's disease (CD) and ulcerative colitis (UC), require repeated assessment of mucosal inflammation, for which ileocolonoscopy remains the reference standard despite being invasive and costly. Fecal calprotectin (FC), an S100A8/S100A9 complex released by neutrophils, has become the most widely used non-invasive marker of intestinal inflammation. This narrative review, based on a structured search of PubMed/MEDLINE, Scopus, the Cochrane Library and Google Scholar, critically integrates the analytical and clinical evidence on FC, including guidelines and meta-analyses published between 2023 and 2026. In adults, FC distinguishes IBD from irritable bowel syndrome with a pooled sensitivity of about 86% and specificity of about 92%; its main value lies in its very high negative predictive value at the usual cut-off of 50 µg/g. In established IBD, a value < 150 µg/g (up to 250 µg/g depending on the assay) is used as a treat-to-target goal and to rule out active inflammation in patients in symptomatic remission, whereas values of 150–300 µg/g or rising consecutive values predict relapse with moderate accuracy (sensitivity and specificity of about 72–78%). After ileocolonic resection for CD, a value < 50 µg/g helps to avoid unnecessary endoscopy in low-risk patients. However, FC is not specific to IBD, performs less well in isolated small-bowel CD than in UC or colonic CD, and is strongly influenced by preanalytical conditions, drugs and the lack of inter-assay standardization. Results must therefore be interpreted according to the clinical context, the assay used and serial measurements in the same patient. Future priorities include international standardization, validated home-based tests, context-specific thresholds and combined strategies with intestinal ultrasound.

Keywords: Fecal calprotectin; Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Biomarker; Treat-to-target; Assay standardization

INTRODUCTION

Calprotectin, also called leukocyte protein L1 or the S100A8/S100A9 complex, is a major protein of polymorphonuclear neutrophils belonging to the S100 protein family [1]. Released by myelomonocytic cells, particularly in the gastrointestinal tract, it regulates inflammatory processes and has antimicrobial and antiproliferative properties [2]. It can be measured quantitatively in stool, where its concentrations are markedly increased in inflammatory and infectious diseases, especially IBD [3] and bacterial gastroenteritis [4]. Fecal calprotectin (FC) has therefore been proposed as a non-invasive surrogate marker of the degree of intestinal inflammation [5].

Over the last three years, the place of FC in IBD care has been substantially redefined. The American Gastroenterological Association (AGA) published dedicated biomarker guidelines for UC and CD in 2023 [6,7], and the European Crohn's and Colitis Organisation (ECCO) and the British Society of Gastroenterology (BSG) updated their recommendations on diagnosis and monitoring in 2025 [8,9]. In parallel, new meta-analyses have refined the diagnostic and prognostic performance of FC [10,11–12], and new assay platforms and rapid tests have entered routine practice [13,14].

Many reviews of FC are written either from a purely clinical perspective or from a purely laboratory perspective. The originality of the present review is to link these two viewpoints from the standpoint of the clinical laboratory. Its added value is fourfold: (i) it compares the available measurement techniques and their inter-assay variability; (ii) it details the preanalytical factors (sample collection, storage, stool consistency and drugs) that may affect accuracy; (iii) it separates the cut-off values used for diagnosis, monitoring, remission assessment, relapse prediction and postoperative surveillance, which are frequently confused in practice; and (iv) it critically discusses discrepancies between studies, false-positive and false-negative results, and differences between CD and UC, in the light of the

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most recent international guidelines. These points are summarized in three tables intended for use by clinicians and biologists.

LITERATURE SEARCH STRATEGY

This work is a narrative review based on a structured literature search. PubMed/MEDLINE, Scopus, the Cochrane Library and Google Scholar were searched for articles published from January 1990 to October 2026. The following keywords and Medical Subject Headings were combined with the Boolean operators AND/OR: “fecal calprotectin” OR “faecal calprotectin” OR “S100A8/S100A9”; AND “inflammatory bowel disease” OR “Crohn’s disease” OR “ulcerative colitis”; AND “diagnosis”, “disease activity”, “mucosal healing”, “relapse”, “postoperative recurrence”, “assay”, “preanalytical”, “stability” or “standardization”. The websites of ECCO, AGA, BSG and the International Organization for the Study of IBD (IOIBD) were also searched for guidelines, and the reference lists of the selected articles were hand-searched.

Articles written in English or French were eligible. Priority was given to international guidelines and consensus statements, systematic reviews and meta-analyses, prospective diagnostic-accuracy and cohort studies, and seminal studies that established the biological and clinical basis of FC measurement. Method-comparison and preanalytical studies were included for the analytical section. Case reports, conference abstracts without full text, animal studies and studies that did not report FC concentrations or diagnostic performance were excluded. Titles and abstracts were screened for relevance, and the full texts of potentially relevant articles were then assessed.

STRUCTURE AND BIOLOGICAL FUNCTIONS OF CALPROTECTIN

Calprotectin was initially described as a 36-kDa complex made up of a light chain (S100A8, 93 amino acids) and heavy chains (S100A9, 113 amino acids) linked non-covalently. It mainly occurs as S100A8/S100A9 heterodimers, which can associate into heterotetramers in the presence of calcium. The genes encoding both chains are located on chromosome 1q21 [1]. Each monomer can bind two Ca^{2+} ions with different affinities, a binding that is essential for the biological functions of the protein. These binding sites are not specific and can also bind other cations (Zn^{2+}, Mn^{2+}, Fe^{2+}, Ni^{2+}); by depriving micro-organisms of these essential nutrients, calprotectin exerts antimicrobial activity [15].

Calprotectin accounts for about 5% of total neutrophil proteins and 30–60% of the soluble proteins of their cytosol. It is expressed to a lesser extent by monocytes, dendritic cells, activated macrophages, keratinocytes and some mucosal epithelial cells. Intracellularly, the S100A8/S100A9 complex has immunomodulatory functions and contributes to the inflammatory response through microtubule rearrangement and modulation of cell adhesion. Once released, calprotectin is found in plasma, urine, saliva, intestinal secretions and stool. It then sustains inflammation through its chemotactic activity, inhibits the growth of bacteria and fungi [16] and promotes neutrophil recruitment to the inflammatory site [17].

Its luminal concentration is therefore directly proportional to neutrophil migration into the intestinal mucosa and lumen. In the late 1990s, Røseth et al. showed a close correlation between FC concentration and the fecal excretion of indium-111-labelled leukocytes, then the reference technique for demonstrating intestinal mucosal inflammation [18]. Unlike conventional inflammatory markers (white blood cell count, serum C-reactive protein [CRP]), which are non-specific and may be raised by extra-intestinal inflammation, FC directly reflects intestinal inflammation. It is used to assess disease activity and treatment response [19], as well as the risk of relapse during follow-up or after surgery.

ANALYTICAL ASPECTS OF FECAL CALPROTECTIN MEASUREMENT

1) Preanalytical phase (sample collection, storage, stool consistency and drugs)

Sample collection.

Calcium binding makes calprotectin resistant to proteolysis in the intestinal lumen. However, several studies have shown intra-individual variability in FC concentration depending on the time of collection, probably related to intestinal transit time; collection of the first stool of the morning is therefore preferred [20]. These variations, however, rarely change the therapeutic decision [21]. When the sample is collected at home, it must not be contaminated by urine or toilet water, and the same collection procedure should be used for repeated measurements in a given patient [21].

Storage conditions

Although early studies reported stability for 7 days at room temperature, more recent data limit this period to 2–3 days, and stability differs according to the assay and to whether the sample is stored as native stool or in extraction buffer [20]. Samples can be kept for up to one week at 2–8 °C [20]. Beyond that, they must be frozen at −20 °C, which allows storage for up to one year; one freeze–thaw cycle does not alter the result [22]. Prolonged transport at room temperature or high ambient temperature, which is common when samples are mailed or brought from rural areas, may therefore lead to falsely low values. Each laboratory must define the maximum delay between collection and analysis for its own assay.

Stool consistency

Liquid stools are not a contraindication to measurement, especially as they are frequent in IBD flares. However, results are expressed per gram of wet stool, and the accuracy of extraction devices depends on stool consistency: errors have been reported with watery, mucous or, conversely, very hard stools, because these devices may under-sample the material retained in their grooves [23]. In such cases, weighing a known amount of stool (the reference extraction method) is preferable, and the stool consistency should be noted on the request form so that the result can be interpreted with caution.

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Medications

Non-steroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin, can induce enteropathy and increase FC, and proton pump inhibitors (PPIs) are also associated with higher values. Whenever possible, these drugs should be stopped about two weeks before measurement, or their use should at least be recorded so that a moderate increase is not wrongly attributed to IBD activity [21]. Conversely, ongoing IBD treatment (5-aminosalicylates, corticosteroids, immunomodulators, biologics or small molecules) lowers FC as mucosal inflammation resolves; this is the basis of its use for monitoring. The main preanalytical and biological factors and the corresponding practical recommendations are summarized in Table 1.

Table 1. Preanalytical and biological factors affecting fecal calprotectin results, and practical recommendations

Factor	Effect on the result	Practical recommendation
Time of collection	Intra-individual variability, probably related to transit time [20,21]	Collect the first stool of the morning; use the same procedure for serial samples
Contamination	Dilution by urine or toilet water	Use a dedicated collection container; give written instructions to patients
Storage at room temperature	Degradation after 2–3 days; assay- and buffer-dependent stability → falsely low values [20]	Deliver within 48–72 h; otherwise refrigerate (2–8 °C, ≤ 7 days) or freeze (−20 °C, ≤ 1 year) [20,22]
Freeze–thaw	One cycle does not affect the result [22]	Avoid repeated cycles
Stool consistency (watery, mucous or hard stools)	Inaccurate sampling with extraction devices; results expressed per gram of wet stool [23]	Prefer weighed extraction; record stool consistency on the request form
NSAIDs (including low-dose aspirin), PPIs	Increase in FC (false-positive results) [21]	Stop ~2 weeks before testing when possible, or record use
IBD treatment	Decrease in FC with mucosal healing	Interpret in relation to treatment start/changes; use for monitoring
Age	Physiologically high in infants and young children; moderate increase after 65 years [24,25]	Use age-adapted, method-specific reference values
Concomitant intestinal disease	Infections, neoplasia, diverticular disease, microscopic colitis, bleeding → increase [24]	Exclude infection (including *C. difficile*) before treatment escalation

FC, fecal calprotectin; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors.

2) Analytical phase (Extraction and measurement techniques)

A few grams of stool are enough for measurement. Whatever the technique, the first step is the preparation of a fecal extract. The reference method consists of weighing a known amount of stool and diluting it in an extraction buffer. As this protocol is lengthy, most manufacturers provide extraction devices, which save time but carry the risk of sampling errors described above [23].

All available techniques are immunoassays using polyclonal or monoclonal antibodies directed against different epitopes of the S100A8/S100A9 complex (dimers, tetramers or higher-order complexes). The main techniques are compared in Table 2. Enzyme-linked immunosorbent assays (ELISA) were the first quantitative methods and were used in most of the seminal clinical studies; they are reliable but slow and require batch analysis. They are being replaced by automated methods particle-enhanced turbidimetric immunoassays (PETIA), chemiluminescence immunoassays (CLIA) and fluoroenzyme immunoassays (FEIA) which allow random access, a short turnaround time and good precision. Lateral-flow immunochromatographic tests, read visually, with a dedicated reader or with a smartphone camera for home testing, provide results within minutes and are suited to point-of-care use and to settings with limited laboratory access [13].

The main analytical problem is inter-assay variability. In the absence of an international reference material and of standardized calibrators, the results of different assays are not interchangeable. Comparisons of several ELISA kits and of six different assays have shown marked differences in absolute values, particularly in the intermediate and high concentration ranges, with consequences for clinical classification [23,26]. More recent comparisons confirm this: a rapid immunochromatographic test showed a sensitivity of 97.8% and a specificity of 80.6% compared with a CLIA, with a correlation coefficient of 0.82 [13]; and a 2026 comparison of a PETIA and a CLIA showed a proportional bias, with substantially lower values by the PETIA above 800 µg/g, but an overall clinical agreement of 87.5% ($\kappa = 0.69$) [14]. Within-run and between-run precision of modern automated assays is good

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(coefficients of variation below 5–7%) [14], indicating that the variability results mainly from differences in calibration, antibody specificity and extraction rather than from imprecision. In practice, the same assay should be used for the follow-up of a given patient; the assay and its cut-offs should be stated on the report; and any change of method in the laboratory should be preceded by a method-comparison study and communicated to clinicians [21].

Table 2. Comparison of the main fecal calprotectin measurement techniques

Technique	Principle / format	Advantages	Limitations
ELISA	Sandwich immunoassay on microplate; manual or semi-automated	Historical reference used in most seminal studies; wide measuring range; low reagent cost	Long turnaround; batch analysis; operator-dependent; marked between-kit variability [23]
PETIA (immunoturbidimetry)	Latex particles coated with antibodies; agglutination measured on clinical-chemistry or dedicated analysers	Fully automated; random access; short turnaround; good precision (CV < 5%) [14]	Narrower measuring range; proportional bias at high concentrations versus other methods [14]
CLIA	Chemiluminescent immunoassay on automated platforms	Automated; random access; wide measuring range; good precision (inter-assay CV ~6%) [14]	Dedicated analyser; higher cost; values not interchangeable with other methods [26]
FEIA	Fluoroenzyme immunoassay on automated immunology platforms	Automated; good reproducibility; integration into existing workflow	Platform-dependent calibration; inter-method differences [26]
Rapid lateral-flow tests (point-of-care)	Immunochromatography with visual, reader-based or smartphone-camera reading	Results within minutes; minimal equipment; suitable for low-resource settings and home monitoring	Semi-quantitative or limited range; lower precision; specificity ~81% versus CLIA in one comparison [13]; dependent on correct patient handling

CLIA, chemiluminescence immunoassay; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; FEIA, fluoroenzyme immunoassay; PETIA, particle-enhanced turbidimetric immunoassay. Because of the lack of an international reference material, results obtained with different techniques are not interchangeable; the same assay should be used for the follow-up of a given patient [21,26].

3) Reference values and physiological variation

Most manufacturers use an upper reference limit of 50 µg/g of stool in adults and in children over 4 years of age, without distinction by sex [21,22]. A moderate increase, of the order of 100 µg/g, has been described in subjects over 65 years of age [24]. In newborns, infants and young children, FC concentrations are physiologically high; results must therefore be interpreted with caution in paediatrics, and each laboratory should establish its own reference values for its method [25]. Finally, FC can be raised in many conditions associated with intestinal mucosal inflammation: gastrointestinal infections, colonic polyps and diverticular disease, colorectal cancer, gastrointestinal bleeding, microscopic colitis, pouchitis and rheumatic diseases [24]. The result must therefore always be interpreted in the patient's clinical context.

CLINICAL APPLICATIONS AND DECISION THRESHOLDS

The cut-off values used in clinical practice differ according to the question asked (Table 3). The value of 50 µg/g is a diagnostic threshold designed to rule out intestinal inflammation in symptomatic patients; it should not be confused with the threshold of 150 µg/g (up to 250 µg/g) used as a remission target in patients with established IBD, nor with the higher or kinetic thresholds used to predict relapse.

1) Diagnosis (Differentiating IBD from irritable bowel syndrome)

Using first-generation assays, Tibble et al. showed that an elevated FC concentration in symptomatic patients identified organic intestinal disease, whatever its cause, with a positive predictive value of 76% and a negative predictive value of 89%, much better than serum inflammatory markers [3]. An early meta-analysis reported a sensitivity of 80–98% and a specificity of 68–96% in adults [27]. A more recent meta-analysis of 17 studies (1956 patients), limited to the distinction between IBD and irritable bowel syndrome (IBS) defined by the Rome criteria, reported a pooled sensitivity of 85.8% and a specificity of 91.7%. At an IBD prevalence of 1%, the negative predictive value was 99.8%, whereas the positive predictive value was only 9%. Sensitivity was higher with a cut-off ≤ 50 µg/g than with higher cut-offs (87% *vs* 79%) and higher in Western than in Eastern countries (88% *vs* 73%) [10]. FC also performs much

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better than anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) [28].

These data support the use of FC in the initial work-up of symptomatic patients to select those who need endoscopy, which reduces the number of normal endoscopies and therefore the cost of care [3]. The 2025 European and British guidelines endorse this use [8,9]. Its main strength is therefore to rule out IBD (low value) rather than to confirm it (high value), because an elevated result has many other causes. This strategy may nevertheless delay the diagnosis in a small proportion of patients with paucisymptomatic IBD, particularly isolated ileal CD, whose FC remains below 50 µg/g.

For intermediate values, between 50 and 150 µg/g (or 250 µg/g depending on the assay), urgent endoscopy is not necessary in the absence of alarm features, and it seems reasonable to repeat the test after 4–6 weeks before referring the patient for endoscopy, which remains the only examination that can confirm the diagnosis. Conversely, patients with organic disease rarely have values below this range. In children, sensitivity is comparable but specificity is lower: a meta-analysis of eight studies including 715 children with suspected IBD reported a sensitivity of 98% and a specificity of 68%, probably because infectious enteropathies are more frequent in this population [29].

2) Assessment of disease activity, treatment response and remission

Endoscopy with histology remains the reference method to assess the extent and severity of lesions using dedicated scores, particularly since mucosal healing has become a therapeutic target that changes the natural history of the disease, reduces the need for surgery and improves prognosis and quality of life [30]. However, endoscopy is invasive and costly, which limits its use for regular monitoring. FC is an objective and reliable surrogate in this setting.

Many studies have confirmed the early work of Røseth et al., showing that FC correlates not only with clinical activity but also with endoscopic and histological scores, and better than CRP, platelets or leukocytes [5]. In CD, Schoepfer et al. showed that FC discriminated inactive disease from mild endoscopic activity (104 ± 138 *vs* 231 ± 244 µg/g; $p < 0.001$), mild from moderate activity (231 ± 244 *vs* 395 ± 256 µg/g; $p = 0.008$) and moderate from severe activity (395 ± 256 *vs* 718 ± 320 µg/g; $p < 0.001$), and correlated better with the Simple Endoscopic Score for CD (SES-CD) than CRP, blood leukocytes and the Crohn's Disease Activity Index (CDAI) [31]. In UC, median (interquartile range) FC concentrations were 16 µg/g (10–30) and 35 µg/g (25–48) for endoscopic grades 0 and 1, usually associated with mucosal healing, 102 µg/g (44–159) for grade 2, 235 µg/g (176–319) for grade 3 and 611 µg/g (406–868) for grade 4 [32]. A meta-analysis of 19 studies reported a sensitivity of 0.88 and a specificity of 0.73 for the detection of endoscopic activity [33], and thresholds up to 150–250 µg/g have been used to define remission with mucosal healing, with a sensitivity above 80% [34].

The STRIDE-II recommendations of the IOIBD retain an FC < 150 µg/g as a treat-to-target goal associated with remission, this threshold being extendable to 250 µg/g to take account of assay diversity. Normalization of FC together with resolution of symptoms is now an intermediate therapeutic target, whatever the treatment [35]. The clinical relevance of this strategy was demonstrated by the CALM trial, in which treatment escalation driven by biomarkers (FC ≥ 250 µg/g, CRP ≥ 5 mg/L) in addition to symptoms led to better endoscopic outcomes in early CD than symptom-driven management [36].

The 2023 AGA guidelines translated these data into practical rules [6,7]. In patients in symptomatic remission, they recommend combining biomarkers and symptoms rather than relying on symptoms alone, and suggest that an FC < 150 µg/g can be used to rule out active inflammation and avoid routine endoscopy. In UC patients with moderate-to-severe symptoms, an FC > 150 µg/g can be used to rule in active inflammation and adjust treatment. In contrast, in patients with mild symptoms, or in CD patients in symptomatic remission with an elevated FC, endoscopic assessment is preferred over empirical treatment adjustment, because the predictive values of FC are insufficient in these situations [6,7]. ECCO also recommends FC in UC to distinguish a flare from coexisting functional bowel symptoms in symptomatic patients, these two conditions overlapping in about 30% of cases [37]. The 2025 BSG guidelines recommend FC for the monitoring of CD of known location when a baseline value is available [9], which underlines the value of an individual reference value measured when the disease is active.

3) Prediction of relapse

The natural history of IBD is marked by alternating flares and remissions. A reliable predictor of relapse would allow early treatment adjustment while avoiding overtreatment of low-risk patients. An early study reported a 14-fold increase in the relative risk of relapse at one year in UC patients with FC > 150 µg/g [38]. Other authors proposed higher thresholds: Kallel et al. reported a cut-off of 340 µg/g associated with an 18-fold increase in the risk of relapse in colonic CD [39]. A meta-analysis of six prospective studies (318 UC and 354 CD patients) reported a pooled sensitivity of 78% (95% CI: 72–83%) and a specificity of 73% (95% CI: 68–77%) for thresholds of 120–340 µg/g [40]. A more recent meta-analysis of 24 prospective studies identified an optimal cut-off of 152 µg/g, with a pooled sensitivity of 72% and a specificity of 74% [11].

The kinetics of FC are more informative than a single value. In a prospective study of UC patients in remission under infliximab with monthly FC measurements, patients who remained in clinical remission had normal FC (< 50 µg/g) throughout the study [41]; similar results have been reported with other treatments [42]. In contrast, patients who relapsed had elevated values (median: 300 µg/g) as early as 2–3 months before clinical relapse. A threshold of 300 µg/g predicted relapse with a sensitivity of 58.3% and a specificity of 93.3%; when two consecutive measurements one month apart exceeded 300 µg/g, specificity reached 100% (sensitivity 61.5%) [41]. Less frequent monitoring (every six months, or even yearly in asymptomatic patients) can therefore be proposed in patients whose FC remains consistently below 50 µg/g. Theede et al. also showed that FC predicted UC relapse several months in advance and reflected histological healing [43].

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4) Postoperative recurrence of Crohn's disease

Despite therapeutic advances, surgery is still frequently required, with cumulative risks at 1, 5 and 10 years after diagnosis estimated at 16.3%, 33.3% and 46.6% for CD and 4.9%, 11.6% and 15.6% for UC, respectively [44]. Whereas colectomy cures UC (apart from pouchitis), postoperative recurrence is frequent in CD. Ileocolonoscopy remains the reference examination for its detection. Several studies have evaluated FC for detecting postoperative recurrence of CD in adults and children [45]. A meta-analysis of nine studies identified a cut-off > 150 µg/g as offering the best overall accuracy, with a sensitivity of about 70% [46]. A more recent meta-analysis of 17 biomarker studies (1080 patients) found that, at a threshold of 50 µg/g, FC had a sensitivity of 76% and a specificity of 66%, compared with 45% and 83% for CRP; cross-sectional imaging, particularly intestinal ultrasound, was more sensitive [12]. Accordingly, the AGA suggests using an FC < 50 µg/g 6–12 months after surgery to rule out endoscopic recurrence in patients at low risk, whereas endoscopy remains necessary in high-risk patients or when FC is elevated [7]. FC therefore has a role in postoperative surveillance, mainly as a rule-out test combined with imaging.

5) Support for treatment de-escalation

Biologics, with or without immunomodulators, are widely used to induce and maintain remission, but their prolonged use raises concerns about cost and the risk of opportunistic infections and lymphoma. The STORI study evaluated the risk of relapse in 115 CD patients in stable remission on infliximab (anti-tumor necrosis factor α [TNF-α]) plus an immunomodulator. After infliximab withdrawal, 52 patients relapsed during a median follow-up of 28 months, and an FC ≥ 300 µg/g at inclusion was one of the independent risk factors for relapse [47]. Together with clinical follow-up, FC therefore helps to identify patients at low risk of relapse in whom de-escalation can be considered, and to monitor them after treatment withdrawal.

Table 3. Clinical applications of fecal calprotectin: decision thresholds and diagnostic performance

Clinical setting	Threshold (µg/g)	Performance / interpretation	Sources
Diagnosis: IBD vs IBS (adults)	50	Se 85.8%, Sp 91.7%; NPV 99.8% and PPV 9% at 1% prevalence; earlier meta-analysis: Se 80–98%, Sp 68–96%	[10,27]
Diagnosis: suspected paediatric IBD	50	Se 98%, Sp 68% (lower specificity due to infections)	[29]
Intermediate ("grey") zone	50–150 (up to 250)	No urgent endoscopy without alarm features; repeat test after 4–6 weeks	[21,35]
Detection of endoscopic activity	50–250 (assay-dependent)	Se 0.88, Sp 0.73 (19 studies); good correlation with SES-CD and UC endoscopic grade	[31–33]
Remission / treat-to-target goal	< 150 (up to 250)	Intermediate target associated with mucosal healing; Se > 80% for remission	[34,35]
Symptomatic remission: rule out active inflammation	< 150	Can avoid routine endoscopy (UC; CD with recent endoscopic remission)	[6,7]
Moderate-to-severe UC symptoms: rule in activity	> 150	Supports treatment adjustment without systematic endoscopy	[6]
Biomarker-driven treatment escalation (early CD)	≥ 250 (with CRP ≥ 5 mg/L)	Tight control improved endoscopic outcomes versus symptom-driven care	[36]
Relapse prediction (patients in remission)	120–340 (optimal ~150)	Se 78%, Sp 73% (120–340); Se 72%, Sp 74% (152); two consecutive values > 300: Se 61.5%, Sp 100%	[11,40,41]
Postoperative recurrence of CD	< 50 (rule out); > 150 (rule in)	At 50: Se 76%, Sp 66%; at > 150: Se ~70%; FC < 50 at 6–12 months avoids endoscopy in low-risk patients	[7,12,46]
Treatment de-escalation (anti-TNF withdrawal)	≥ 300	Independent risk factor for relapse after infliximab withdrawal	[47]
Isolated small-bowel CD	Lower (77 proximal; 123 distal)	Lower sensitivity; FC gradient from proximal small bowel to colon	[7,48]

CD, Crohn's disease; CRP, C-reactive protein; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; SES-CD, Simple Endoscopic Score for Crohn's disease; Sp, specificity; TNF, tumor necrosis factor; UC, ulcerative colitis. Thresholds are assay-dependent and must be adapted to the method used by each laboratory.

DISCUSSION

1) Comparison of findings and sources of discrepancy between studies

FC reflects neutrophilic mucosal inflammation and has a high negative predictive value the performance estimates vary widely between studies. In the diagnostic setting, specificity ranges from 68% to 96% [27], and sensitivity is lower in Eastern than in Western studies [10]. For relapse prediction, proposed cut-offs range from 120 to 340 µg/g [11,39,40], and for postoperative recurrence from 50 to more than 150 µg/g

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[12,46]. These discrepancies have several explanations: (i) different assays and extraction methods, whose results are not interchangeable [14,23,26]; (ii) different reference standards (ileocolonoscopy with various endoscopic scores, histology, capsule endoscopy or cross-sectional imaging) and definitions of remission or relapse; (iii) different populations (primary *vs* referral care, adults *vs* children, CD *vs* UC, disease location and phenotype), which change the pretest probability and therefore the predictive values; (iv) cut-offs derived *a posteriori* from ROC curves in small single-centre studies, which tend to overestimate performance; and (v) heterogeneous intervals between FC measurement and the reference examination. Consequently, a published cut-off cannot be transferred directly to another assay or population, and the predictive values reported in referral centres overestimate the positive predictive value expected in primary care.

2) False-positive and false-negative results

False-positive results

Elevated FC without active IBD are mainly due to other causes of intestinal neutrophilic inflammation (infectious gastroenteritis, NSAID-induced enteropathy, PPI use, colorectal cancer and polyps, diverticular disease, microscopic colitis, gastrointestinal bleeding and pouchitis) [4,21,24]. Age is also a factor: values are physiologically high in infants and young children and moderately raised in older adults [24,25]. In a patient with known IBD, a moderate elevation may thus reflect an intercurrent infection or drug intake rather than a flare; stool cultures (including *Clostridioides difficile* testing) and a drug history should be obtained before treatment escalation. The low positive predictive value in low-prevalence populations (9% at a prevalence of 1%) [10] explains why a high FC alone does not justify an IBD diagnosis.

False-negative results

Normal or low FC despite active disease are mainly observed in isolated small-bowel CD, particularly proximal disease; in stricturing or penetrating disease with limited mucosal ulceration; in mild or very limited disease; and with preanalytical errors, such as prolonged storage at room temperature or inadequate sampling of watery stools with extraction devices [20,23,48]. In these situations, a low FC should not override discordant clinical, endoscopic or imaging findings.

3) Differences between Crohn's disease and ulcerative colitis

FC performs better in UC and colonic CD than in isolated ileal CD. In UC, inflammation is continuous and in direct contact with the stool, and FC correlates closely with the endoscopic grade [32]. In CD, inflammation is segmental and transmural, so FC reflects mucosal ulceration better than deep or fibrotic disease. The evidence on small-bowel CD is conflicting, Jensen et al. reported equivalent sensitivity in small-bowel and colonic CD [49], whereas the 2023 AGA evidence review reported a sensitivity of 43–100% for small-bowel inflammation [7], and a 2025 capsule-endoscopy study of 214 patients showed a gradient of FC concentrations, from proximal to distal small bowel and to the colon, for a similar degree of inflammation (median 63, 190 and 542 µg/g, respectively), with optimal cut-offs of only 77 and 123 µg/g for proximal and distal small-bowel inflammation [48]. These differences may be explained by different reference standards, inflammation severity and disease extent. Similarly, FC has been reported to be a stronger predictor of relapse in UC than in CD [38]. In practice, lower thresholds and the patient's own baseline value should be used in small-bowel CD, and FC should be combined with intestinal ultrasound or magnetic resonance enterography [8,9].

4) Limitations of the evidence and clinical implications

The evidence base has several limitations. Most studies are single-centre, use different assays and cut-offs, and were performed in referral centres. Data from Africa and the Middle East, including Morocco, are scarce, although the epidemiology of IBD and the prevalence of infectious enteritis a major cause of false-positive results may differ from those of Western populations [10]. Few studies have evaluated home-based tests or the cost-effectiveness of FC-based strategies in low- and middle-income countries. Finally, FC is a marker of inflammation, not of IBD: it cannot distinguish CD from UC, does not assess disease extent or complications, and does not replace endoscopy for diagnosis, dysplasia surveillance or the evaluation of strictures.

From a practical standpoint, we suggest the following: (i) use FC mainly as a rule-out test in symptomatic patients, with repeat testing for intermediate values; (ii) interpret each result in the light of the clinical context, drugs and preanalytical conditions; (iii) follow patients with the same assay and establish a baseline value at the time of active disease; (iv) favour trends over single values, using two consecutive elevated results before considering relapse; and (v) confirm discordant results by endoscopy or cross-sectional imaging. Close communication between clinicians and biologists, together with reports stating the assay and context-specific cut-offs, is essential.

CONCLUSION

Fecal calprotectin is the best-documented non-invasive biomarker of intestinal inflammation in IBD. Its main strength is its very high negative predictive value (a value below 50 µg/g makes IBD unlikely in symptomatic patients and helps to avoid unnecessary endoscopy). In patients with established IBD, a value below 150 µg/g (250 µg/g depending on the assay) is a recognized treat-to-target goal and can be used to rule out active inflammation in symptomatic remission, whereas rising or persistently elevated values predict relapse and, after surgery, a value below 50 µg/g helps to avoid endoscopy in low-risk CD patients.

However, FC has important limitations. It is not specific to IBD, has a low positive predictive value in low-prevalence populations, is less reliable in isolated small-bowel CD than in UC or colonic CD, and is affected by sample collection, storage, stool consistency and drugs. In the absence of standardization, results from different assays are not interchangeable, so the same assay must be used for follow-up, and published cut-offs must be adapted to the assay and clinical

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context. FC complements, but does not replace, endoscopy and imaging.

Future priorities include the development of an international reference material and harmonization of assays, validation of home-based and point-of-care tests, prospective validation of context-specific and assay-specific thresholds (particularly in African and Moroccan populations), and evaluation of combined strategies associating FC with intestinal ultrasound and other biomarkers within treat-to-target algorithms.

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