2.04.69	Fecal Calprotectin Testing		
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Section:	2.0 Medicine	**Page:**	Page 1 of 28

Policy Statement

I. Fecal calprotectin testing may be considered **medically necessary** for the evaluation of individuals when the differential diagnosis is inflammatory bowel disease or noninflammatory bowel disease (including irritable bowel syndrome) for whom endoscopy with biopsy is being considered.

II. Fecal calprotectin testing is considered **investigational** in the management of inflammatory bowel disease, including the management of active inflammatory bowel disease and surveillance for relapse of disease in remission.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

A fecal calprotectin level of less than 50 µg/g is suggestive of a low likelihood of inflammatory bowel disease.

Coding
The following CPT code is specific for this test:

- **83993**: Calprotectin, fecal

Description

Calprotectin is a calcium- and zinc-binding protein that is a potential marker of intestinal inflammation. Fecal calprotectin testing is proposed as a noninvasive means to diagnose inflammatory bowel disease (IBD). Other potential uses are to evaluate treatment response for patients with IBD and as a marker of relapse.

Related Policies

- Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In March 2006, the PhiCal® (Genova Diagnostics), an enzyme-linked immunosorbent assay test for measuring concentrations of fecal calprotectin in fecal stool, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. This test is indicated as an aid in the diagnosis of IBD and to differentiate IBD from IBS, when used with other diagnostic testing and clinical considerations.

The PhiCal®, as modified by Quest Diagnostics, is classified as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The modified PhiCal® is available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing.

In 2014, CalPrest® (Eurospital SpA) and, in 2016, CalPrest®NG (Eurospital SpA) were cleared for marketing by the FDA through the 510(k) process.[3,4,] According to the FDA summary, CalPrest® "is identical" to the PhiCal™ test in that they have the same manufacturer. Compared with CalPrest®, the "differences in CalPrest® NG include the name of the test on the labels, detection antibody, the use of a Horse-radish peroxidase/TMB conjugate/substrate system, the provided Stop solution, the concentration of calibrators and controls in the kit and the dynamic range of the assay."

The fCAL® ELISA Calprotectin Test (Bühlmann Laboratories) received FDA clearance in 2018 for the quantitative measurement of fecal calprotectin in human stool.[5,] In 2018, LIAISON® Calprotectin test (DiaSorin Inc.) also received FDA clearance and was determined to be substantially equivalent to the predicate PhiCal™ device.[6,]

In 2019, ALPCO received 510(k) clearance from the FDA for its new fecal Calprotectin Chemiluminescence ELISA test.[7,] This test exhibits a clinical specificity of 95.1% and provides the "lowest false positive rate of any currently cleared calprotectin test without sacrificing clinical sensitivity." In 2023, ALPCO received 510(k) clearance from the FDA for its Calprotectin Immunoturbidimetric Assay and it was determined to be substantially equivalent to the Calprotectin Chemiluminescence ELISA test and is indicated for in-vitro diagnostic use as an aid in the diagnosis of IBD[8,].

In 2022, DiaSorin Inc. submitted an application for modification of its LIAISON® Calprotectin test for the addition of the LIAISON® Q.S.E.T. Device Plus (the accessory used for stool sample collection and extraction) to the cleared assay.[9,] While the LIAISON® Calprotectin test is identical to its predicate cleared in 2018, the Q.S.E.T. Device Plus differs from its predicate Q.S.E.T. Device.
FDA product code: NXO.

Rapid fecal calprotectin tests that can be used in the home or physician's office are commercially available in Europe and Canada (e.g., Calprosmart, Calpro AS; Quantum Blue Calprotectin, Bühlmann Laboratories). Rapid tests have not been approved by the FDA for use in the U.S.

Rationale

Background

Inflammatory Bowel Disease

IBD is a chronic condition that encompasses two main forms: Crohn disease and ulcerative colitis. These conditions overlap in clinical and pathologic characteristics but have distinct features. Crohn disease can involve the entire gastrointestinal (GI) tract and is characterized by transmural

inflammation. Ulcerative colitis involves inflammation limited to the mucosal layer of the colon, almost always involving the rectum.

IBD is suggested by the presence of one or more of a variety of signs and symptoms that can be GI (e.g., abdominal pain, bloody diarrhea, perianal fistulae), systemic (e.g., weight loss, fatigue, growth failure in children), or extraintestinal (e.g., characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity of symptoms in the disease course, including a life-threatening illness.

Diagnosis

Diagnosing IBD is associated with well-defined management changes. A typical diagnostic approach to IBD includes stool testing for enteric pathogens, blood tests (complete blood count, inflammatory markers) to differentiate etiologies and evaluate disease severity, as well as small bowel imaging and endoscopy (upper GI, colonoscopy) with biopsies.

Fecal Calprotectin

In some cases, the clinical manifestations of IBD can be non-specific and suggestive of other disorders, including infectious colitis, colon cancer, and functional bowel disorders, including irritable bowel syndrome.

Thus, there is a need for simple, accurate, noninvasive tests to detect intestinal inflammation. Potential noninvasive markers of inflammation fall into several categories, including serologic and fecal. Serologic markers such as C-reactive protein and anti-neutrophil cytoplasmic antibodies tend to have low sensitivity and specificity for intestinal inflammation because they are affected by inflammation outside the GI tract. Fecal markers, in contrast, have the potential to be more specific to the diagnosis of GI tract disorders, because their levels are not elevated in extra-digestive processes. Fecal leukocyte testing has been used to evaluate whether there is intestinal mucosal inflammation. The level of fecal leukocytes can be determined by the microscopic examination of fecal specimens; however, leukocytes are unstable and must be evaluated promptly by skilled personnel. There is interest in identifying stable proteins in stool specimens, which may be representative of the presence of leukocytes, rather than evaluating leukocyte levels directly.

Calprotectin is a protein that could be used as a marker of inflammation. It is a calcium- and zinc-binding protein that accounts for approximately 60% of the neutrophil's cytoplasmic proteins. It is released from neutrophils during activation or apoptosis/necrosis and has a role in regulating inflammatory processes. In addition to potentially higher sensitivity and specificity than serologic markers, another advantage of calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to one week, leaving enough time for patients to collect samples at home and send them to a laboratory for testing. In contrast, lactoferrin, another potential fecal marker of intestinal inflammation, is stable at room temperature for about two days.

Among potential disadvantages of fecal calprotectin as a marker of inflammation are that fecal calprotectin levels increase after the use of nonsteroidal anti-inflammatory drugs, that levels may change with age, and that bleeding (e.g., nasal, menstrual) may cause an elevated fecal calprotectin level. Moreover, there is uncertainty about the optimal cutoff to distinguish between IBD and noninflammatory disease.

Fecal calprotectin testing has been used to differentiate between organic (e.g., inflammation) and functional (no visible problem in the GI tract like irritable bowel syndrome) disease. Some consider fecal calprotectin to be a marker of neutrophilic intestinal inflammation rather than a marker of organic disease and believe it has utility to distinguish between IBD and non-IBD. In practice, the test might be suitable for selecting patients with IBD symptoms for endoscopy (i.e., deciding which patients do not require endoscopy). Fecal calprotectin testing has also been proposed to evaluate

the response to IBD treatment and for predicting relapse. If found to be sufficiently accurate, results of calprotectin testing could be used to change treatment, such as adjusting medication levels.

Treatment

Guidelines-based treatments include oral and rectal salicylates, glucocorticoids, immunomodulators (e.g., methotrexate), and multiple biologic therapies (e.g., infliximab), depending on disease severity.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Suspected Inflammatory Bowel Disease

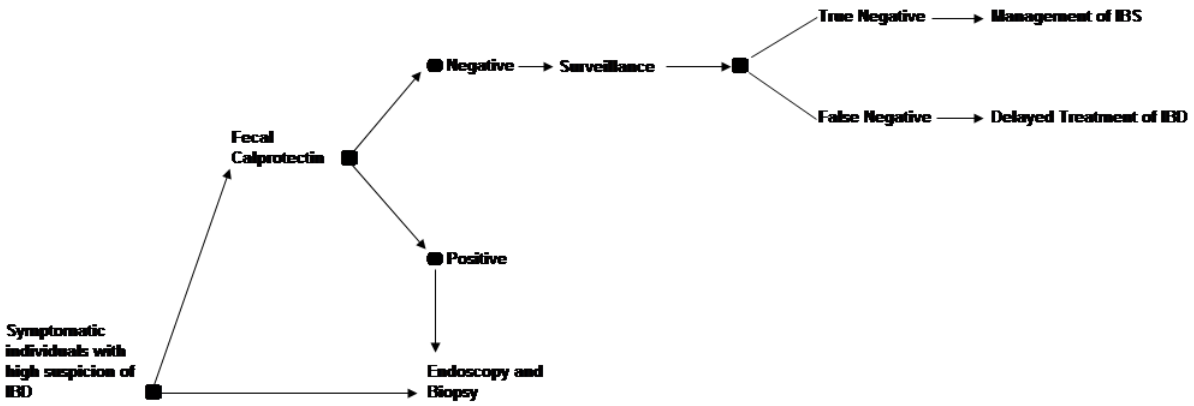
Clinical Context and Test Purpose

In individuals who have suspected inflammatory bowel disease (IBD), the purpose of fecal calprotectin testing is to inform the decision whether to proceed to endoscopy with biopsy in order to confirm a diagnosis of IBD, either ulcerative colitis or Crohn's disease.

Both IBS and IBD can share common presenting symptoms such as diarrhea and abdominal pain. IBS is generally managed by antidiarrheal agents, diet, and lifestyle changes. IBD has a more serious prognosis. For example, Crohn's disease can result in a bowel obstruction or fistulas requiring surgical intervention. Ulcerative colitis has similar complications but is more localized.

In an individual whose symptoms have not responded to conservative management, endoscopy with biopsy would be required to confirm a diagnosis of IBD and inform treatment choice, which may include biologic disease-modifying agents. However, in a significant proportion of individuals undergoing endoscopy with biopsy, IBD is not present. If fecal calprotectin testing can predict which individuals are unlikely to have IBD, fewer individuals would be subjected to endoscopy with biopsy (Figure 1).

Figure 1. Analytic Framework



IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who present with signs and symptoms of suspected IBD for whom endoscopy with biopsy is being considered. Alternative causes of abdominal pain and diarrhea would have been ruled out and there would be no other indication for endoscopy such as rectal bleeding or risk factors (e.g., age) for cancer.

Interventions
The test being considered is fecal calprotectin analysis, which detects the process of inflammation in the intestines. The labeling of the U.S. Food and Drug Administration (FDA) cleared PhiCal assay recommends the following interpretative guidelines: normal/healthy: less than 50 µg/g; indeterminate: 50 to 120 µg/g; abnormal: greater than 120 µg/g. Fecal calprotectin is also available as a laboratory-developed test and the upper threshold is being defined. Some laboratories use an upper threshold of 250 µg/g or higher to define a high probability of IBD.

Comparators
The following practice is currently being used to make decisions about diagnosing IBD: endoscopy with biopsy (reference standard). In clinical practice, other tests such as magnetic resonance imaging, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete hemogram are part of the evaluation for IBD.

Outcomes
The outcome of a fecal calprotectin test is used to inform the decision of whether to proceed to endoscopy with biopsy.

The beneficial outcome of correctly being classified as low-risk for IBD is avoiding an unnecessary invasive test. The harmful outcome of incorrect classification as low-risk for IBD is omission or deferral of a necessary biopsy, with a consequent delay of appropriate treatment.

For purposes of evaluating the clinical validity of fecal calprotectin testing to predict the results of endoscopy, the time frame is the availability of endoscopy results.

Study Selection Criteria
For the evaluation of the clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Included a suitable reference standard (endoscopy or clinical follow-up).

- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Shi et al (2022) published an umbrella review that summarized the sensitivity and specificity of fecal calprotectin (and 16 other noninvasive tests for IBD, including ESR, CRP, and fecal lactoferrin) from published systematic reviews and meta-analyses, including the Petryszyn et al (2019)[10,] and Waugh et al (2013)[11,] studies discussed below.[12,] Diagnostic performance and test validity were classified into 3 clinical scenarios: diagnosis, activity assessment, and prediction of recurrence. A total of 106 assessments were included from 43 studies. For diagnosis, in distinguishing IBD from non-IBD, fecal calprotectin had a pooled sensitivity of 0.99 (95% confidence interval [CI], 0.92 to 1.00), the highest among all tests, and specificity of 0.65 (95% CI, 0.54 to 0.74). The performance of fecal calprotectin in patients with Crohn's disease (sensitivity, 0.95; specificity, 0.84) was generally better than in patients with ulcerative colitis (sensitivity and specificity, 0.78). In distinguishing IBD from IBS, fecal calprotectin was again the most sensitive test. With a cutoff of 50 µg/g, fecal calprotectin had a sensitivity of 0.97 (95% CI, 0.91 to 0.99) and specificity of 0.76 (95% CI, 0.66 to 0.84).

Petryszyn et al (2019) conducted a meta-analysis that evaluated the efficacy of fecal calprotectin as a diagnostic marker of IBD in patients with symptoms suspicious for the disease.[10,] The analysis included 19 studies (15 prospective and 4 retrospective; published through December 2018) with 5032 patients. Patients were over 16 years of age and had gastrointestinal symptoms, chronic diarrhea, or any other reason that may raise IBD suspicion. In the majority of included studies, the diagnostic fecal calprotectin cutoff value was 50 µg/g (n=14). An IBD diagnosis was confirmed in 620 (12.3%) patients, with prevalence ranging from 2.7% to 68.1%. The calculated pooled sensitivity was 0.882 (95% CI , 0.827 to 0.921), while the pooled specificity was 0.799 (95% CI, 0.693 to 0.875). There was a higher sensitivity of fecal calprotectin among studies with an IBD prevalence ≤30% as compared to among studies with a prevalence >30% (0.902 [95% CI, 0.856 to 0.935] versus 0.825 [95% CI, 0.661 to 0.920]; p=.041). Regarding risk of bias, the overall methodological quality of included studies was deemed to be "good"; however, 11 studies included some patients that were not representative of those who would receive the fecal calprotectin test in clinical practice, and selection bias may have existed in 5 studies. The authors concluded that out of 100 hypothetical cases with an IBD prevalence of 12.3%, 18 non-disease patients would have a colonoscopy performed and 1 patient with IBD would not be referred for a colonoscopy. Additionally, it was determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%.

Waugh et al (2013) published a systematic review as part of the U.K. Health Technology Assessment program. Investigators included 28 studies using fecal calprotectin tests to evaluate inflammation of the lower intestine in newly presenting patients.[11,] Studies using fecal calprotectin tests to monitor disease progression or response to treatment were excluded. Endoscopy with histology was the preferred reference standard, although some studies included used imaging or clinical follow-up. Studies were pooled when there was a minimum of 4 using the same calprotectin cutoff. A pooled analysis of 5 studies using fecal calprotectin detected by enzyme-linked immunosorvent assay to differentiate between IBD and IBS in adults at a cutoff of 50 µg/g was performed (Table 1). One study was rated as low-risk of bias and 3 studies had at least 3 domains with high or unclear risk of bias. The pooled studies had a combined sensitivity of 93% and a combined specificity of 94% to predict the presence of inflammatory disease on biopsy (1 study evaluated the absence of inflammatory disease). Table 2 summarizes clinical validity results and Tables 3 and 4 present individual study characteristics and results, with Table 4 presented in the order of increasing prevalence of IBD. Out of

100 cases with a prevalence of 20%,[13] 76 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 68%,[14] 35 invasive tests would be avoided with 5 cases missed.

Table 1. Characteristics of Studies at a Threshold of 50 µg/g

					11-Item QUADAS Quality Assessment			
					No. of Studies Rated as High or Unclear Risk of Bias			
Study	Studies Included	Study Populations Included	Study Designs Included	Study Reference Standards Included	No Domains	1-2 Domains	>2 Domains	Domains With >3 Studies at High-Risk of Bias
Waugh et al (2013)[11]	5 studies	Adults newly presenting with IBD or IBS referred by general practitioners	Diagnostic accuracy of FC to detect inflammation of the lower intestine	Most used endoscopy with biopsy	1	1	3	Blinding of reference standard
Waugh et al (2013)[11]	6 studies	Adults and children newly referred with IBD or non-IBD	Diagnostic accuracy of FC to detect inflammation of the lower intestine	• Most used endoscopy with biopsy • Some studies in children used clinical follow-up	0	5	1	Blinding of reference standard

FC: fecal calprotectin; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.

Table 2. Clinical Validity Study Results at a Threshold of 50 µg/g

Study	Scenario (N)	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV Range, %	NPV Range, %	Disease Prevalence Range (95% CI), %
Waugh et al (2013)[11]	To detect IBD in adults with IBS or IBD (5 studies, n=596 patients)	93 (83 to 97)	94 (73 to 99)	24 to 100	73 to 100	10.9 to 69.0 (5.8 to 77.3)
Waugh et al (2013)[11]	To detect IBD in children and adults with IBD or non-IBD (6 studies, n=516 patients)	99 (95 to 100)	74 (59 to 86)	62 to 96	93 to 100	21.4 to 61.1 (13.2 to 72.5)

CI: confidence interval; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; NPV: negative predictive value; PPV: positive predictive value.

Table 3. Characteristics of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Irritable Bowel Syndrome) in Adults with a Cutoff of 50 µg/g

Study	Study Population	Setting	Reference Standard	No. of Domains[a] at High or Unclear Risk of Bias
Basumani et al (2012)[15]	New referrals with diarrhea ≥4 wk to rule out IBD	District General Hospital, England	Histology	4
Ostlund et al (2008)[13]	Consecutive patients were referred with lower abdominal symptoms to the endoscopy unit.	Endoscopy unit, The Netherlands	Colonoscopy and biopsy	2

Study	Study Population	Setting	Reference Standard	No. of Domains[a] at High or Unclear Risk of Bias
	Excluded 25 patients with polyps or CRC.			
Li et al (2006)[16,]	Outpatients and inpatients with IBS or IBD, healthy controls; patients followed up after polyp removal with no recurrence. Excluded 60 patients with CRC.	Hospital, Peking	Colonoscopy with biopsy in IBD group	6
Schoepfer et al (2008)[14,]	Outpatients and inpatients with IBS or IBD. Excluded patients with CRC.	Gastroenterology Department, University Hospital, Switzerland	Colonoscopy including terminal ileum and biopsies	0
El-Badry et al (2010)[17,]	GI symptoms for at least 6 mo, and endoscopy necessary to exclude organic pathology. Excluded patients with CRC, diverticulitis, and polyps.	Internal Medicine Department, Egypt	Colonoscopy into ileum with biopsies	3

CRC: colorectal cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.
[a] QUADAS ratings.

Table 4. Results of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Irritable Bowel Syndrome) in Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence

Study	N	Prevalence (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
Basumani et al (2012)[15,]	110	10.91 (5.77 to 18.28)	1.00 (0.74 to 1.00)	0.60 (0.50 to 0.70)	0.24 (0.13 to 0.37)	1.00 (0.94 to 1.00)	2.51 (1.97 to 3.21)	0
Ostlund et al (2008)[13,]	114	20.18 (13.24 to 28.72)	0.96 (0.78 to 1.00)	0.87 (0.78 to 0.93)	0.65 (0.47 to 0.81)	0.99 (0.93 to 1.00)	7.25 (4.25 to 12.38)	0.05 (0.01 to 0.34)
Li et al (2006)[16,]	120	50.00 (40.74 to 59.26)	0.93 (0.84 to 0.98)	0.95 (0.86 to 0.99)	0.95 (0.86 to 0.99)	0.93 (0.84 to 0.98)	18.67 (6.18 to 56.63)	0.07 (0.03 to 0.18)
Schoepfer et al (2008)[14,]	94	68.09 (57.67 to 77.33)	0.83 (0.71 to 0.91)	1.00 (0.88 to 1.00)	1.00 (0.93 to 1.00)	0.73 (0.57 to 0.86)	NR	0.17 (0.10 to 0.29)
El-Badry et al (2010)[17,]	29	68.97 (49.17 to 84.72)	0.85 (0.62 to 0.97)	1.00 (0.66 to 1.00)	1.00 (0.81 to 1.00)	0.75 (0.43 to 0.95)	NR	0.15 (0.05 to 0.43)

CI: confidence interval; NLR: negative likelihood ratio; NPV: negative predictive value; NR: not reported; PLR: positive likelihood ratio; PPV: positive predictive value.

Six studies using fecal calprotectin with an enzyme-linked immunosorvent assay to differentiate between IBD and non-IBD in children and adults were pooled (Table 5). Five of the studies included only children, most of whom had been referred to pediatric gastroenterologists. The children had undergone fecal calprotectin testing prior to endoscopy with biopsy or were followed clinically. No studies were at low-risk of bias and 5 studies had 1 to 2 domains with high or unclear risk of bias, as evaluated on the QUADAS quality assessment. The highest risk of bias was for blinding of the reference standard. The combined sensitivity was 99%, with a lower combined specificity (74%) to detect the absence of inflammatory disease on biopsy (Table 6). Modeling indicated that the use of fecal calprotectin in children would result in fewer children undergoing an unnecessary invasive test (i.e., endoscopy with biopsy). Out of 100 cases, at a prevalence of 36%,[18,] 47 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 51%,[19,] 36 invasive tests would be avoided with 1 case of IBS missed. Individual study characteristics (Table 5) and results (Table 6) presented in the order of the increasing prevalence of IBD.

Table 5. Characteristics of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Non-Inflammatory Bowel Disease) in Children and Adults with a Cutoff of 50 µg/g

Study	Study Population	Setting	Reference Standard	No. of Domains[a] at High or Unclear Risk of Bias
Damms and Bischoff al (2008)[20,]	Patients ages >18 y referred for colonoscopy for GI disorders or CRC screening	Gastroenterology departments at 3 hospitals and 3 outpatient clinics in Germany	Colonoscopy: for CRC screening medical check-up	2
Van de Vijver et al (2012)[18,]	Children ages 6 to 18 y referred for further investigation of high suspicion of IBD from pediatrician's global assessment, physical examination, and blood results	Pediatric outpatient clinics at 6 general hospitals and 1 tertiary care hospital in the North Netherlands Paediatric IBD Consortium	68 patients had endoscopy; others had follow-up for at least 6 mo to confirm a diagnosis of IBS	1
Henderson et al (2012)[21,]	All children who had a FC measurement as part of initial diagnostic workup before endoscopy	Pediatric gastroenterology department at a children's hospital in U.K.	• IBD patients: standard clinical, histologic, and radiologic findings • Non-IBD (control) patients: upper and lower endoscopy	2
Sidler et al (2008)[19,]	Children ages 2 to 18 y referred for further investigation of GI symptoms (chronic diarrhea, bloody stools, abdominal pain) suggestive of an OBD	Pediatric gastroenterology outpatient clinic at children's hospital in Australia	Upper GI endoscopy and complete ileocolonoscopy with biopsy	1
Tomas et al (2007)[22,]	Patients referred for further investigation of GI symptoms (intense abdominal pain, chronic diarrhea, weight loss, rectal bleeding)	Pediatric gastroenterology unit of university hospital in Spain	Clinical criteria, laboratory, image, and endoscopic test results	6
Fagerberg et al (2005)[23,]	Children ages 6 to 17 y with GI symptoms and blood tests suggestive of inflammation who were scheduled for colonoscopy to rule out IBD	Pediatric gastroenterology departments at hospitals in Sweden	Complete ileocolonoscopy with biopsy	1

CRC: colorectal cancer; FC: fecal calprotectin; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; OBD; organic bowel disease.
[a] QUADAS ratings.

Table 6. Results of Diagnostic Accuracy Studies (Inflammatory Bowel Disease versus Non-Inflammatory Bowel Disease) in Children and Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence

Study	N	Prevalence (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
Damms et al (2008)[20],	84	21.43 (13.22 to 31.74)	1.00 (0.81 to 1.00)	0.79 (0.67 to 0.88)	0.79 (0.60 to 0.88)	1.00 (0.93 to 1.00)	4.71 (2.96 to 7.50)	0
Van de Vijver et al (2012)[18],	117	35.9 (27.24 to 45.29)	1.00 (0.92 to 1.00)	0.73 (0.62 to 0.83)	0.68 (0.55 to 0.79)	1.00 (0.94 to 1.00)	3.8 (2.6 to 5.5)	0
Henderson et al (2012)[21],	190	47.89 (40.61 to 55.25)	0.98 (0.92 to 1.00)	0.44 (0.34 to 0.55)	0.62 (0.53 to 0.70)	0.96 (0.85 to 0.99)	1.8 (0.15 to 2.1)	0.05 (0.01 to 0.20)
Sidler et al (2008)[19],	61	50.82 (37.70 to 63.86)	1.00 (0.89 to 1.00)	0.67 (0.47 to 0.83)	0.76 (0.60 to 0.88)	1.00 (0.83 to 1.00)	3.00 (1.81 to 4.98)	0
Tomas et al (2007)[22],	28	53.57 (33.87 to 72.49)	1.00 (0.78 to 1.00)	0.92 (0.64 to 1.00)	0.94 (0.70 to 1.00)	1.00 (0.74 to 1.00)	13.00 (1.98 to 85.46)	0
Fagerberg et al (2005)[23],	36	61.11 (43.46 to 76.86)	0.95 (0.77 to 1.00)	0.93 (0.66 to 1.00)	0.96 (0.77 to 1.00)	0.93 (0.66 to 1.00)	13.36 (2.02 to 88.54)	0.05 (0.01 to 0.33)

CI: confidence interval; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value.

Clinically Useful

A test is clinically useful if the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified that assessed the use of fecal calprotectin testing to diagnose suspected IBD.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Indirect evidence supports the clinical usefulness of fecal calprotectin in patients with suspected IBD for whom endoscopy is being considered. The evidence on clinical validity (sensitivity, specificity, negative predictive value [NPV]) permits inference on clinical usefulness as a result of avoidance of endoscopy with biopsy in patients who are unlikely to have an inflammatory disease.

Section Summary: Suspected Inflammatory Bowel Disease

A systematic review and meta-analysis of 28 studies pooled 11 studies that used a 50 µg/g threshold to evaluate intestinal inflammation. Five studies (n=596 patients) showed an NPV in the range of 73% to 100% in adults with IBS or IBD. The pooling of 6 studies in adults and children (n=1100) with IBD or non-IBD showed an NPV of 93% to 100%. Together, these results would suggest that fecal calprotectin testing at a threshold of 50 µg/g can identify patients who are unlikely to have IBD and can forgo a more invasive test (endoscopy with biopsy). In another meta-analysis involving 19 studies, investigators determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%. A recent umbrella review found that fecal calprotectin is the most sensitive noninvasive test in distinguishing IBD from non-IBD (sensitivity,

0.99), and IBD from IBS (sensitivity, 0.97 [cutoff 50 µg/g]. Although the sensitivity and specificity of fecal calprotectin were generally balanced, sensitivity was slightly better than specificity.

Monitoring Active Inflammatory Bowel Disease

Clinical Context and Test Purpose

For individuals who have been diagnosed with IBD, fecal calprotectin testing could allow clinicians to monitor disease activity and guide therapeutic decision-making.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with Crohn's disease or ulcerative colitis.

Interventions

The test being considered is fecal calprotectin analysis.

Comparators

The following practice is currently being used to make decisions about monitoring IBD: a repeat endoscopy with biopsy (reference standard). In clinical practice, other tests such as ESR, CRP, and complete hemogram are part of the evaluation for monitoring disease activity in IBD.

Outcomes

The beneficial outcome of a true test result, if correctly classified as low disease activity, is the avoidance of endoscopy and unnecessary medications.

If correctly classified as high activity, the administration of appropriate treatment is another beneficial outcome.

Outcomes may be assessed in clinical practice and in the research setting with standardized measures, such as the Crohn Disease Activity Index (CDAI), a validated 8-item score used as a marker of Crohn's disease remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe Crohn's disease.[24,]

The relevant time period for the impact of testing is weeks to months.

Study Selection Criteria

For the evaluation of the clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Included a suitable reference standard (endoscopy).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

The umbrella review by Shi et al (2022), discussed previously in the section on suspected IBD, also reported the diagnostic performance of fecal calprotectin in assessing disease activity.[12,] The review, which included the study by Mosli et al (2015)[25,] summarized below, found that fecal calprotectin with a cutoff of 50 µg/g had the highest sensitivity (0.92; 95% CI, 0.90 to 0.94) among the noninvasive

tests evaluated in assessing IBD activity. However, ultrasound and magnetic resonance enterography (MRE) performed better, with comparable sensitivity and higher specificity.

A systematic review by Mosli et al (2015) evaluated the sensitivity and specificity of fecal calprotectin in adults and some children with previously diagnosed ulcerative colitis or Crohn's disease to detect endoscopically confirmed active disease (Table 7).[25,] Nineteen studies with 1069 ulcerative colitis patients and 1033 Crohn's disease patients met eligibility criteria. Individual studies used a variety of cutoffs for fecal calprotectin, ranging from 6 to 280 µg/g. Pooled sensitivity and specificity estimates for fecal calprotectin were 88% and 73%, respectively. (Table 8). The optimal threshold was determined to be 50 µg/g. At a threshold of 50 µg/g, the NPV for inflammation at a prevalence of 0.50 was 86%, and the positive predictive value (PPV) was 76%. This information might be used to triage patients for endoscopy when they have symptoms of active disease.

Table 7. Characteristics of Clinical Validity Reviews Assessing Monitoring of Active Disease

					11-Item QUADAS Quality Assessment			
					No. of Studies Rated as High or Unclear Risk of Bias			
Study	**Studies Included**	**Study Populations Included**	**Study Designs Included**	**Study Reference Standards Included**	**No Domains**	**1 to 2 Domains**	**>2 Domains**	**Indicators with >6 Studies at High or Unclear Risk of Bias**
Mosli et al (2015)[25],	19	1069 UC and 1033 CD patients (mostly adults) with symptomatic disease	Prospective cohorts or case-controls for evaluating disease activity	Endoscopy	2	9	8	• Inappropriate exclusions· Blinding of index test • Interval between tests • Exclusions in the analysis

CD: Crohn diseases; UC: ulcerative colitis.

Table 8. Results of Clinical Validity Reviews Assessing Detection of Endoscopically Confirmed Active Disease

Study	Scenario	Sensitivity (95% CI), %	Specificity (95% CI), %	Range PPV, %	Range NPV, %
Mosli et al (2015)[25],	To monitor disease activity in patients with CD or UC on maintenance therapy (N=2102)	88 (84 to 90)	73 (66 to 79)	52 to 91	67 to 95

CI: confidence interval; CD: Crohn disease; NPV: negative predictive value; PPV: positive predictive value; UC: ulcerative colitis

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

For monitoring disease activity in patients with active IBD, inferences cannot be made from clinical validity studies to clinical usefulness. How fecal calprotectin would be used to make decisions about endoscopy or intensification of therapy is not described in the Mosli et al (2015) review. Intervention studies will provide direct evidence of fecal calprotectin for monitoring disease activity in patients with active IBD.

Östlund et al (2021) reported on a 12-month RCT comparing self-monitoring of IBD using an at-home fecal calprotectin test (IBDoc® [not available in the US]) along with a digital application for answering symptom questionnaires plus standard of care versus standard of care alone in 153 patients with established IBD selected from the Swedish Inflammatory Bowel Disease Register (SWIBREG).[13,] Data were collected retrospectively from medical records. A primary outcome was not identified but the objective of the study was to evaluate home testing acceptance and adherence. The reported low compliance in the intervention group (~29%) and use of a test that is not available in the US limit the applicability of results from this study. Female gender was the only factor significantly associated with increased adherence to the test.

Colombel et al (2018) reported on an open-label multicenter RCT, the Efficacy and Safety Study to Evaluate Two Treatment Algorithms in Subjects With Moderate to Severe Crohn's Disease (CALM) that compared the effect of tight control of Crohn's disease with standard clinical management.[26,] The primary endpoint was mucosal healing with an absence of deep ulcers at 48 weeks after randomization (Tables 9 and 10). This trial did not test whether using fecal calprotectin, as decision criteria for treatment changes, improved the capability to achieve tight control. Although a post hoc analysis found that, in the tight management arm, fecal calprotectin levels frequently influenced the decision to escalate treatment, the contribution of fecal calprotectin to the tight control cannot be determined from this study design.

Table 9. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Östlund et al (2021)[13,]	Sweden	NR	NR	158 patients with established IBD from the Swedish Inflammatory Bowel Disease Register (SWIBREG)	Home-based fecal calprotectin test along with a digital application for answering symptom questionnaires plus standard of care	Standard of care alone
Colombel et al (2018)[26,]	U.S., E.U.	74	2011 to 2016	244 adults with moderate-to-severe active CD (CDEIS, >6; CDAI, 150 to 450) and naive to immunomodulators and biologics	Tight control[a] including FC ≥250 µg/g and CRP >5 mg/L	Clinical management[b]

CD: Crohn disease; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index of Severity; CRP: C-reactive protein; FC: fecal calprotectin; IBD: inflammatory bowel disease; NR: not reported.
[a] Tight control was determined by FC level ≥250 µg/g, CRP level ≥5 mg/L, CDAI score ≥150, or prednisone use in the previous week.
[b] Clinical management was based on a CDAI score decrease of <100 points versus baseline or CDAI score ≥200, or prednisone use in the previous week.

Table 10. Summary of Key Randomized Controlled Trial Results

Study		
Östlund et al (2021)[13,]	**Patients who received increased medical treatment during the study, n (%)**	**Patients who received decreased medical treatment during the study, n (%)**
IBD-Home group	28/84 (33)	13/84 (16)
Control	11/74 (15)	10/74 (14
p-value	.007	.727
IBD-Home group (compliers)	14/24 (58)	5/24 (21)
IBD-Home group (non-compliers)	14/60 (23)	8/60 (13)

Study				
p-value	.002	.201		
Colombel et al (2018)[26,]	Mucosal Healing at 48 Weeks	Adverse Events	Steroid-Free Remission at 48 Weeks	Deep Remission
	244	244	244	244
Tight control	56/122 (46)	105 (86)	73 (59.8)	45 (36.9)
Clinical monitoring	37/122 (30)	100 (82)	48 (39.3)	28 (23.0)
RR (95% CI)	16.1 (3.9 to 28.3)			
p	.010		.001	.014

Values are n/n (%), n (%), or as otherwise indicated.
CI: confidence interval; IBD-Home: inflammatory bowel disease monitoring using an at-home fecal calprotectin test; RR: relative risk.

Tables 11 and 12 display notable limitations identified in each study.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Östlund et al (2021)[13,]	4. Study population was patients with established IBD (median of 8 years since diagnosis), which may have impacted uptake of home testing	4. Test used (Bühlmann HBFCT IBDoc®) is not available in the US	1. Not clearly defined	1, 4. Primary outcome not defined; medical interventions not defined	
Colombel et al (2018)[26,]		4. In addition to FCP, CRP, prednisone use, and different thresholds of CDAI were used in the tight control arm			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; FCP: fecal calprotectin.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Östlund et al (2021) [13,]	4. Randomized by the day in the month patients were born	1,2. Blinding not described			1. Poor adherence (29% in the intervention group)	
Colombel et al (2018)[26,]		1. Not blinded to treatment assignment 2. Not blinded outcome assessment		1. 25% loss to follow-up (analysis		

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
		3. Outcome assessed by treating physician		was intention-to-treat)		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Because the clinical utility of fecal calprotectin testing has not been established for monitoring active IBD, a chain of evidence cannot be constructed.

Section Summary: Monitoring Active Inflammatory Bowel Disease

Studies to manage IBD have not used consistent cutoff values. A systematic review determined that 50 µg/g was the optimum threshold; at a prevalence of 0.50, fecal calprotectin had an NPV of 86% and PPV of 76%. A recent umbrella review found that fecal calprotectin with a threshold of 50 µg/g had the highest sensitivity (0.92; 95% CI, 0.90 to 0.94) among the noninvasive tests evaluated in assessing IBD activity. However, ultrasound and MRE perform better, with comparable sensitivity and higher specificity. One RCT using fecal calprotectin testing along with other measures to monitor disease activity in patients with IBD on maintenance therapy was identified. The investigators reported that tight control using both clinical status and biologic markers (fecal calprotectin level, ≥250 µg/g; CRP level, ≥5 mg/L) resulted in greater mucosal healing in patients with Crohn's disease. The contribution of fecal calprotectin to the tight control could not be determined from this study design. In another RCT, self-monitoring with a home-based fecal calprotectin test among patients with established IBD demonstrated an increase in the proportion of patients seeking medical treatment; compliance to home-based testing in this study was low (29%). The use of a home-based fecal calprotectin test that is not available in the US limits the applicability of this study.

Prediction of Relapse With Inflammatory Bowel Disease in Remission

Clinical Context and Test Purpose

Calprotectin has been used to predict relapse in individuals with IBD who are in remission. A marker to predict relapse could improve the net health outcome if preemptive treatment was found to eliminate recurrences or reduce their severity.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with Crohn's disease or ulcerative colitis who are in remission.

Interventions

The test being considered is fecal calprotectin analysis.

Comparators
The following practice is currently being used to make decisions about monitoring IBD: endoscopy with biopsy (reference standard). The following tests are currently used to make decisions about monitoring for IBD relapse in individuals in the relevant population: symptoms, inflammatory markers (ESR, CRP), and complete blood count.

Outcomes
The beneficial outcome of a true test result, if correctly classified as low disease activity, is the avoidance of unnecessary medications.

If correctly classified as high activity, the administration of appropriate treatment is another beneficial outcome.

In making a decision to increase medications, fecal calprotectin testing as an adjunct to clinical assessment is being used as a test to support a "rule in" decision, so PPV is the key measure of clinical validity.

Outcomes of interest are an improvement in symptoms and disease activity scores. Outcomes may be assessed in clinical practice and in the research setting with standardized measures, such as the CDAI, a validated 8-item score used as a marker of Crohn's disease remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe Crohn's disease.[24,]

The relevant time period for the impact of testing is weeks to months.

Study Selection Criteria
For the evaluation of the clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology.
- Included a suitable reference standard (endoscopy).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Systematic Reviews
Shi et al (2023) conducted a meta-analysis to evaluate the diagnostic accuracy of fecal calprotectin for predicting relapse in IBD. [27,]A total of 24 prospective studies (N=2260) were included in the analysis. Methodological assessment of studies was based on the second Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist. The pooled sensitivity and specificity of fecal calprotectin for IBD was 0.720 (0.528 to 0.856) and 0.740 (0.618 to 0.834), respectively. An optimal fecal calprotectin cut-off value for predicting IBD relapse of 152 µg/g was identified. Characteristics and results are shown in Tables 13 and 14.

The umbrella review by Shi et al (2022), discussed in the previous sections, also reported the diagnostic performace of fecal calprotectin in predicting recurrence.[12,] The review included studies assessed by Heida et al (2017)[28,] summarized below. Fecal calprotectin was the only test used for IBD, with a sensitivity of 0.78 (95% CI, 0.72 to 0.83) and specificity of 0.73 (95% CI, 0.68 to 0.77). The sensitivity and specificity of fecal calprotectin for Crohn's disease were 0.75 (95% CI, 0.64 to 0.84) and 0.71 (95% CI, 0.64 to 0.76), respectively. For ulcerative colitis, sensitivity and specificity were 0.75 (95%

CI, 0.70 to 0.79) and 0.77 (95% CI, 0.74 to 0.80), respectively. Radiological examinations (particularly MRE and ultrasound), however, were more prominent in predicting recurrence.

Heida et al (2017) conducted a systematic review to determine the accuracy of fecal calprotectin monitoring in asymptomatic patients (Table 13).[28,] Six studies met the review inclusion criteria and evaluated fecal calprotectin levels every 1 to 3 months. Methodological assessment of studies was based on the second Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist. One-third of patients had a relapse during the study period, although the definitions of relapse varied across studies. Five of the 6 studies used an upward trend of fecal calprotectin between 2 measurements as the threshold. Asymptomatic patients with IBD who had fecal calprotectin levels above the study's cutoff had a 53% to 83% probability of developing disease relapse within the next 2 to 3 months, while patients with normal fecal calprotectin levels had a 67% to 94% probability of remaining in remission in the next 2 to 3 months (Table 14). Calprotectin levels began to rise 2 to 3 months before clinical relapse. The investigators could not identify the best fecal calprotectin cutoff for monitoring purposes.

Table 13. Characteristics of Clinical Validity Reviews Assessing Prediction of Relapse

Study	Studies Included	Study Populations Included	Study Designs Included	Study Reference Standards Included
Shi et al (2023)[27,]	24	2260 patients with IBD in remission	Prospective studies that assessed FC	5 studies used endoscopy 19 studies used clinical symptoms or therapy change
Heida et al (2017)[28,]	6	552 patients with UC in remission	Prospective studies that assessed FC every 1 to 3 mo	5 studies used endoscopy 1 study used clinical activity score

Adapted by Heida et al (2017).[28,]
FC: fecal calprotectin; UC: ulcerative colitis.

Table 14. Results of Clinical Validity Reviews Assessing Prediction of Relapse

Study	Scenario	Sensitivity Range, %	Specificity Range, %
Shi et al (2023) [27,]	Prediction of relapse (2260 patients) of whom 31.6% relapsed during observation	52.8 to 85.6	61.8 to 83.4
Heida et al (2017)[28,]	Prediction of relapse (552 patients) of whom 33.3% relapsed during observation	53 to 83	67 to 94

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

A prospective, nonblinded, controlled trial by Lasson et al (2015) randomized patients with ulcerative colitis in remission at high risk of relapse in a 3:2 ratio to medication dosing decisions based on fecal calprotectin levels or to usual care (Table 15).[29,] The fecal calprotectin monitoring group was included in the systematic review by Heida et al (2017) described above.[28,] Both groups submitted fecal samples at baseline and on a monthly basis. In the intervention group, a fecal calprotectin cutoff of 300 µg/g was used for escalating the 5-aminosalicylic acid dose to the maximally tolerable dose. The high dose was continued for 3 months and then reduced when fecal calprotectin levels fell below 200 µg/g. The primary outcome was the number of patients to relapse by 18 months. At 1 year, there was no significant difference in relapse rates between the 2 groups (Table 16). For 10 of the 18 patients in the intervention group who had a relapse, fecal calprotectin levels did not rise above the 300 µg/g

cutoff for medication dosage escalation. In the subgroup of patients who had levels of 300 µg/g or more, there was a significantly lower rate of relapse in the intervention group (28.6%) than in the control group (57.1%). Trial limitations included lack of blinding, exclusion of patients without intention-to-treat analysis, and insufficient power (Tables 17 and 18).

Table 15. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Lasson et al (2015)[29,]	Sweden	5	2009 to 2012	• 91 adults with UC on maintenance therapy with oral 5-ASA medication • Patients were in remission but at high risk of relapse	Escalation to a maximally tolerable dose based on FC ≥300 µg/g and lowered when FC <200 µg/g	Usual care based on symptoms

5-ASA: 5-aminosalicylic acid; FC: fecal calprotectin; RCT: randomized controlled trial; UC: ulcerative colitis.

Table 16. Summary of Key Randomized Controlled Trial Results

Study	Rate of Relapse at 1 Year
Lasson et al (2015)[29,]	
Fecal calprotectin monitoring, n/N (%)	18/51 (35.3)
Usual care, n/N (%)	20/40 (50)
p	.23

RCT: randomized controlled trial.
Tables 17 and 18 display notable limitations identified in the study.

Table 17. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Lasson et al (2015)[29,]			3. Treatment of a flare-up based on patient complaint and not predetermined in the study protocol		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 18. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Lasson et al (2015)[29,]		1. Not blinded			2. 9 patients not providing at least 9 samples were excluded from the experimental group 3. Not intention-to-treat 3. Target sample size not achieved	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Section Summary: Prediction of Relapse With Inflammatory Bowel Disease in Remission

A recent umbrella review found that fecal calprotectin had a sensitivity of 0.78 and specificity of 0.73 in predicting recurrence, although radiological examinations (MRE and ultrasound) performed better. A 2023 meta-analysis of 24 prospective studies that monitored fecal calprotectin in patients in remission described an optimal cut-off value for fecal calprotectin of 152 µg/g and a pooled sensitivity and specificity of fecal calprotectin of 0.720 and 0.740, respectively. A 2017 systematic review of 6 prospective studies in patients in remission found no consistency in the thresholds used to determine treatment. One RCT evaluated the relapse rates in patients with ulcerative colitis whose medication doses were managed with fecal calprotectin test results (≥300 µg/g) and, in its primary analysis, found no significant difference in relapse rates. Trial limitations were in the domains of blinding, power, follow-up, and analysis. In addition, this trial did not enroll the planned number of patients and might have been underpowered. There is a need for high-quality RCTs to determine whether monitoring fecal calprotectin in patients who are in remission can reduce relapse rates and improve the quality of life (QOL) for patients with IBD.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2018 Input

Clinical input was sought to help determine whether the use of fecal calprotectin testing for individuals with suspected inflammatory bowel disease (IBD) when endoscopy with biopsy is being considered would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies including physicians affiliated with academic medical centers.

For individuals who have suspected IBD (when endoscopy with biopsy is being considered) who receive fecal calprotectin testing, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice. Specifically, fecal calprotectin testing can inform the decision by using a positive fecal calprotectin result to refer for endoscopy with biopsy, or to use negative fecal calprotectin results to exclude IBD and avoid endoscopy with biopsy, with acceptably low tradeoffs in missed diagnoses of IBD in those who have false-negative fecal calprotectin results. Input further highlighted that the use of fecal calprotectin is particularly important in pediatric populations, where children may not be able to fully participate as medical historians and may have non-specific and/or atypical symptoms.

2014 Input

In response to requests, input was received through 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. One specialty society submitted 2 responses. Input was mixed on whether fecal calprotectin testing is considered investigational for the diagnosis of intestinal conditions and whether the results of diagnostic testing are being used to change patient management. Clinicians who disagreed with the investigational designation tended to argue that a medically necessary use of the test for diagnosis would be to differentiate inflammatory from noninflammatory conditions. There was near consensus that fecal calprotectin testing is considered investigational in the management of intestinal conditions. Most reviewers did not think that, when the test is used for the management of intestinal disorders, results change patient management. There was near consensus that the manufacturer's recommended cutoff of 50 µg/g should be used to indicate a positive fecal calprotectin test.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Gastroenterological Association

In 2018, the American Gastroenterological Association (AGA) published a guideline on functional gastrointestinal symptoms in patients with IBD.[30,] The AGA recommends a stepwise approach to rule-out ongoing inflammatory activity in IBD patients that includes fecal calprotectin, endoscopy with biopsy, and imaging. The AGA recommends that in those patients with indeterminate fecal calprotectin levels and mild symptoms, calprotectin monitoring at 3 to 6 month intervals may allow anticipatory management of impending flares. However, "the optimal cutoff for biomarkers remains a source of debate" and overtreatment for symptoms that are due to functional pathophysiology rather than inflammation can increase adverse effects with no symptomatic benefit.

A 2019 guideline from the AGA on laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome (IBS) in adults gave a conditional recommendation based on low quality evidence to use either fecal calprotectin or fecal lactoferrin to screen for IBD. A threshold value of 50 µg/g for fecal calprotectin was recommended to optimize sensitivity for IBD.[31,]
A 2021 clinical practice update from the AGA on the management of IBD in older adults states that: "Fecal calprotectin or lactoferrin may help prioritize patients with a low probability of IBD for endoscopic evaluation. Individuals presenting with hematochezia or chronic diarrhea with intermediate to high suspicion for underlying IBD, microscopic colitis, or colorectal neoplasia should undergo colonoscopy."[32,]

A 2023 guideline from the AGA on the role of biomarkers for the management of ulcerative colitis (UC) made the following recommendations regarding fecal calprotectin testing[33,]:

Table 19. AGA Clinical Practice Guideline Recommendations on Role of Biomarkers for the Management of UC

Recommendation	Strength of Recommendation	Certainty of Evidence
In patients with UC in symptomatic remission, the AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone	Conditional	Moderate
In patients with UC in symptomatic remission, the AGA suggests using fecal calprotectin <150 mg/g,	Conditional	Low (for fecal calprotectin)

Recommendation	Strength of Recommendation	Certainty of Evidence
normal fecal lactoferrin, or normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease activity		
In patients with UC in symptomatic remission but elevated stool or serum markers of inflammation (fecal calprotectin >150 mg/g, elevated fecal lactoferrin, elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Very low
In patients with UC with moderate to severe symptoms suggestive of flare, the AGA suggests using fecal calprotectin >150mg/g, elevated fecal lactoferrin, or elevated CRP to rule inactive inflammation and inform treatment adjustment and avoid routine endoscopic assessment solely for establishing presence of active disease	Conditional	Low (for fecal calprotectin)
In patients with UC with mild symptoms, with elevated stool or serum markers of inflammation (fecal calprotectin>150mg/g, elevated fecal lactoferrin, or elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.	Conditional	Very low
In patients with UC with mild symptoms, with normal stool or serum markers of inflammation (fecal calprotectin <150mg/g, normal fecal lactoferrin, or normal CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.	Conditional	Very low
In patients with UC, the AGA makes no recommendation in favor of, or against, a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy to improve long-term outcomes.	No recommendation	Knowledge gap

AGA: American Gastroenterological Association; UC: ulcerative colitis

American College of Gastroenterology

In 2018, the American College of Gastroenterology (ACG) published a guideline on the management of Crohn's disease in adults.[34,] The College gave a strong recommendation based on a moderate level of evidence that fecal calprotectin is a helpful test that should be considered to differentiate the presence of IBD from IBS. A summary statement without a recommendation indicated that fecal calprotectin measurements may have an adjunctive role in monitoring disease activity. A 2021 ACG guideline on the management of IBS likewise suggests evaluating fecal calprotectin (or fecal

lactoferrin) and C reactive protein (CRP) in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out IBD (Strong recommendation; moderate quality of evidence for fecal calprotectin).[35,]

International Organization for the Study of Inflammatory Bowel Disease

In 2021, the Selecting Therapeutic Targets in IBD (STRIDE) group, which was initiated by the International Organization for the Study of IBD (IOIBD), updated its recommendations for treating to target in Crohn's disease and UC.[36,] In this update, the reduction of fecal calprotectin to an acceptable range has been added as a formal intermediate treatment target. Per STRIDE-II: "Normalization of CRP (to values under the upper limit of normal) and fecal calprotectin (to 100–250 mg/g) is an intermediate treatment target in UC and CD. Consider changing treatment if this target has not been achieved." The strength of this recommendation is 8.2 out of 10 ("10" denotes complete agreement and "1" complete disagreement); 80% of votes scored between 7 to 10 using this scale. The Group also notes that the cutoff value of fecal calprotectin is dependent on the desired outcome; lower thresholds (e.g., <100 mg/g) have been proposed for deep healing (both endoscopic and transmural healing) or histological healing, and higher values (e.g., <250 mg/g) for less stringent outcomes (e.g., Mayo Endoscopic Subscore of 0 or 1 in UC).

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2013; recommendation 1.1 was updated in 2017), published guidance on fecal calprotectin testing for inflammatory diseases of the bowel.[37,] The guidance made the following recommendations:
1.1 "Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent-onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
1. cancer is not suspected, having considered the risk factors (for example, age)....
1.2 Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment...."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 19.

Table 20. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04646187	De-escalation of Anti-TNF Therapy in Adolescents and Young Adults With IBD With Tight Faecal Calprotectin and Trough Level Monitoring	148	Jun 2023
NCT03549988	Pro-active Fecal Calprotectin Monitoring to Improve Patient Outcomes in Ulcerative Colitis: A Prospective Randomized Controlled Trial	654	Dec 2023
NCT03038984	Are Rates of Colectomies, Resections, Mortalities, and Cancer Reduced by Home Monitoring of IBD Patients Tightly on Demand or Every 3 Months by Fecal Calprotectin and Disease Activity?	120	Aug 2026

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04973423	Study of the Added Value of a Transmural Evaluation in Patients with Crohn's Disease Under Biotherapy with Close Fecal Calprotectin Follow-Up	180	Aug 2027

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history if applicable
  - Reason for procedure/test/device, when applicable
  - Past and present diagnostic testing and results
  - Past treatment regimen(s) including antibiotic used and response(s)
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	83993	Calprotectin, fecal
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/29/2013	BCBSA Medical Policy adoption
08/29/2014	Policy revision without position change
02/01/2017	Policy revision without position change
06/01/2017	Policy revision without position change
05/01/2018	Policy revision without position change
05/01/2019	Policy revision with position change
03/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2024	Policy reactivated. Previously archived from 04/01/2020 to 02/29/2024.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Fecal Calprotectin Testing 2.04.69** **Policy Statement:** I. Fecal calprotectin testing may be considered **medically necessary** for the evaluation of individuals when the differential diagnosis is inflammatory bowel disease or noninflammatory bowel disease (including irritable bowel syndrome) for whom endoscopy with biopsy is being considered. II. Fecal calprotectin testing is considered **investigational** in the management of inflammatory bowel disease, including the management of active inflammatory bowel disease and surveillance for relapse of disease in remission.