

2.04.69 Fecal Calprotectin Testing			
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Section:	2.0 Medicine	Page:	Page 1 of 32

Policy Statement

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

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

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 irritable bowel syndrome, 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. The modified PhiCal® is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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. 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.”

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 CalprotectinÖ, 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.

Suspected Inflammatory Bowel Disease

Clinical Context and Test Purpose

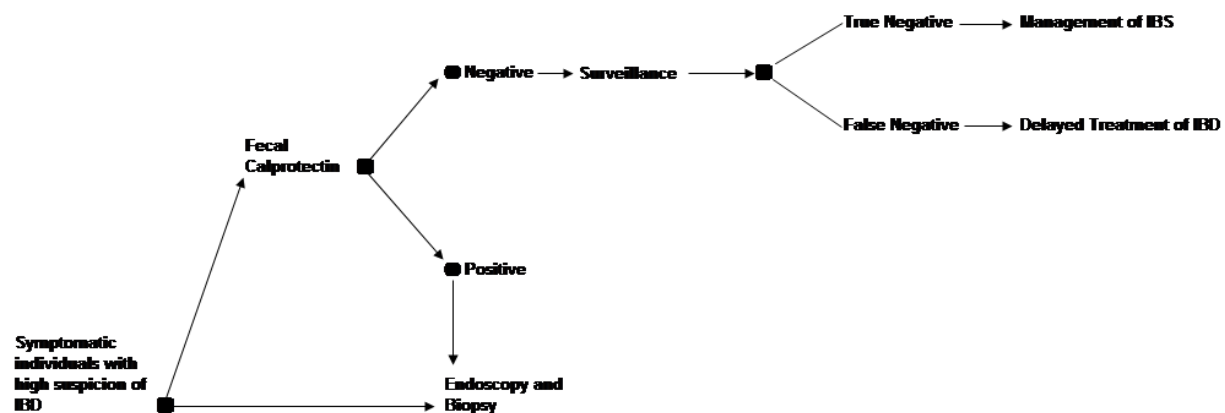
In patients who have suspected IBD, the purpose of fecal calprotectin testing is to inform the decision whether to proceed to endoscopy with biopsy in order to confirm a diagnosis of IBD, either ulcerative colitis or Crohn disease.

Irritable bowel syndrome (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 disease can result in a bowel obstruction or fistulas requiring surgical intervention. Ulcerative colitis has similar complications but is more localized.

In a patient 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 patients undergoing endoscopy with biopsy, IBD is not present. If fecal calprotectin testing can predict which patients are unlikely to have IBD, fewer patients would be subjected to endoscopy with biopsy (see Figure 1).

The question addressed in this evidence review is: Does fecal calprotectin testing predict the likelihood of bowel inflammation and thus inform the decision whether to proceed to endoscopy with biopsy?

Figure 1. Analytic Framework



IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are 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 (eg 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 Food and Drug Administration-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: the reference standard is endoscopy with biopsy. 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 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.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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.¹ 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 four using the same calprotectin cutoff.

A pooled analysis of 5 studies using fecal calprotectin detected by enzyme-linked immunosorbent assay to differentiate between IBD and IBS in adults at a cutoff of 50 µg/g was performed (see Table 1). One study was rated as low-risk of bias and three studies had at least three 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). See Table 2 clinical validity results and Tables 3 and 4 for 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%,² 76 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 68%,³ 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			Domains With >3 Studies at High-Risk of Bias
Study	Studies Included	Study Populations Included	Study Designs Included	Study Reference Standards Included	No Domains	1-2 Domains	>2 Domains	
Waugh et al (2013) ¹	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
	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) ¹ (pages 35, 38)	To detect IBD in adults with IBS or IBD (5 studies, n=596 patients)	93 (83 to 97)	94 (73 to 99)	24-100	73-100	10.9-69.0 (5.8 to 77.3)
Waugh et al (2013) ¹ (pages 48, 52)	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)	62-96	93-100	21.4-61.1 (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 (IBD vs IBS) 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) ⁴	New referrals with diarrhea ≥4 wk to rule out IBD	District General Hospital, England	Histology	4
Otten et al (2008) ²	Consecutive patients referred with lower abdominal symptoms to endoscopy unit. Excluded 25 patients with polyps or CRC.	Endoscopy unit, The Netherlands	Colonoscopy and biopsy	2
Li et al (2006) ⁵	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) ³	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) ⁶	GI symptoms for at least 6 mo, and endoscopy	Internal Medicine Department, Egypt	Colonoscopy into ileum with biopsies	3

Study	Study Population	Setting	Reference Standard	No. of Domains ^a at High or Unclear Risk of Bias
	necessary to exclude organic pathology. Excluded patients with CRC, diverticulitis, and polyps.			

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

Table 4. Results of Diagnostic Accuracy Studies (IBD vs IBS) 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) ⁴	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
Otten et al (2008) ²	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) ⁵	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) ³	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) ⁶	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; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; 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 immunosorbent assay to differentiate between IBD and non-IBD in children and adults were pooled (see 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 five studies had one to two 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 (see 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%,⁷ 47 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 51%,⁸ 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 (IBD vs Non-IBD) 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 et al (2008) ⁹	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) ⁷	Children ages 6-18 y referred for further investigation of high suspicion of IBD from pediatrician's global assessment, physical	Pediatric outpatient clinics at 6 general hospitals and 1 tertiary care hospital in the North Netherlands	68 patients had endoscopy; others had follow-up for at least 6 mo to confirm a diagnosis of IBS	1

Study	Study Population	Setting	Reference Standard	No. of Domains ^a at High or Unclear Risk of Bias
Henderson et al (2012) ¹⁰ .	examination, and blood results All children who had a fecal calprotectin measurement as part of initial diagnostic workup before endoscopy	Paediatric IBD Consortium 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) ⁸ .	Children ages 2-18 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) ¹¹ .	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) ¹² .	Children ages 6-17 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; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; OBD: organic bowel disease.

^a QUADAS ratings.

Table 6. Results of Diagnostic Accuracy Studies (IBD vs Non-IBD) 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) ⁹ .	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) ⁷ .	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) ¹⁰ .	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) ⁸ .	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) ¹¹ .	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) ¹² .	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; IBD: inflammatory bowel disease; 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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, 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 IBD

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 the inflammatory disease and can forgo a more invasive test (endoscopy with biopsy). Clinical input supported that the use of fecal calprotectin testing for individuals with suspected IBD provides a clinically meaningful improvement in net health outcomes by providing clinically valid and clinically useful information to guide clinical decision-making. 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. Further details from clinical input are included in the Clinical Input section later in the review and the Appendix.

Monitoring Active IBD**Clinical Context and Test Purpose**

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

The question addressed in this section is: Does the addition of fecal calprotectin testing to clinical assessment (based on standard scores and/or history and physical examination) and standard laboratory tests (e.g., complete blood count, ESR, CRP) in individuals with active IBD improve health outcomes?

The following PICO's were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with Crohn 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: the reference standard is a repeat endoscopy with biopsy. 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, a validated 8-item score used as a marker of Crohn disease remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe Crohn disease.¹³

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.

For the evaluation of the clinical utility of the fecal calprotectin test, studies must represent the intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Systematic reviews and meta-analyses have reviewed studies on fecal calprotectin testing to identify IBD patients with active disease.

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 disease to detect endoscopically confirmed active disease (see Table 7).¹⁴ Nineteen studies with 1069 ulcerative colitis patients and 1033 Crohn 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. (see 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 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	1-2 Domains	>2 Domains	Indicators with >6 Studies at High or Unclear Risk of Bias
Mosli et al (2015) ¹⁴	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) ¹⁴	To monitor disease activity in patients with CD or UC on maintenance therapy (N=2102)	88 (84 to 90)	73 (66 to 79)	52-91	67-95

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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.

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 disease with standard clinical management.¹⁵ The primary endpoint was mucosal healing with an absence of deep ulcers at 48 weeks after randomization (see 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 RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Colombel et al (2018) ¹⁵ .	U.S., E.U.	74	2011-2016	244 adults with moderate-to-severe active CD (CDEIS, >6; CDAI, 150-450) 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; FCP: fecal calprotectin; RCT: randomized controlled trial.

^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 vs baseline or CDAI score ≥200, or prednisone use in the previous week.

Table 10. Summary of Key RCT Results

Study	Mucosal Healing at	Adverse Events	Steroid-Free Remission at	Deep Remission
	48 Weeks		48 Weeks	
Colombel et al (2018) ¹⁵ ,	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	0.010		0.001	0.014

Values are n/n (%), n (%), or as otherwise indicated.

CI: confidence interval; RR: relative risk; RCT: randomized controlled trial.

The limitations tables (see Tables 11 and 12) display notable limitations identified in each study. The Colombel et al (2018) study does not specifically address the intervention of interest for this evidence review (fecal calprotectin) (see Table 11). The study evaluated tight control vs standard management. As noted in Table 12, additional study limitations were a lack of blinding to treatment assignment or outcomes assessment and a 25% loss to follow-up.

Table 11. Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Colombel et al (2018) ¹⁵ .		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 limitations 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
Colombel et al (2018) ¹⁵ .		1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician		1. 25% loss to follow-up (analysis was intention-to-treat)		

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

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

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 IBD

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 NPV of 86% and PPV of 76%. 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 disease. The contribution of fecal calprotectin to the tight control could not be determined from this study design.

Prediction of Relapse With IBD 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 were found to eliminate recurrences or reduce their severity.

The questions addressed in this evidence review section are: Does the addition of fecal calprotectin to clinical assessment (based on standard scores and/or history and physical examination) and standard laboratory tests (e.g., complete blood count, ESR, CRP) in individuals with diagnosed IBD improve relapse prediction? And does relapse prediction lead to improved outcomes in those with IBD?

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with Crohn 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: the reference standard is endoscopy with biopsy. The following tests are currently used to make

decisions about monitoring for IBD relapse in patients in the relevant population: patient's symptoms, inflammatory markers (ESR), 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 Crohn Disease Activity Index, a validated 8-item score used as a marker of Crohn disease remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe Crohn disease.¹³

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.

For the evaluation of the clinical utility of the fecal calprotectin test, studies must represent the intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Systematic Reviews

Heida et al (2017) conducted a systematic review to determine the accuracy of fecal calprotectin monitoring in asymptomatic patients (see Table 13).¹⁶ Six studies met the review inclusion criteria and evaluated fecal calprotectin levels every one to three months. One-third of patients had a relapse during the study period, although the definitions of relapse varied across studies. Five of the six studies used an upward trend of fecal calprotectin between two 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 (see Table 14). Calprotectin

levels began to rise two to three 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

					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
Heida et al (2017) ¹⁶ ,	6	552 patients with UC in remission	Prospective studies that assessed FC every 1-3 mo	· 5 studies used endoscopy · 1 study used clinical activity score	0	3	3

Adapted by Heida et al (2017).¹⁶

FC: fecal calprotectin; UC: ulcerative colitis.

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

Study	Scenario	Sensitivity Range, %	Specificity Range, %
Heida et al (2017) ¹⁶ ,	Prediction of relapse (552 patients) of whom 33.3% relapsed during observation	53-83	67-94

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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 (see Table 15).¹⁷ The fecal calprotectin monitoring group was included in the systematic review by Heida et al (2017) described above.¹⁶ 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 (see 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 (see Tables 17 and 18).

Table 15. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Lasson et al (2015) ¹⁷ ,	Sweden	5	2009-2012	• 91 adults with UC on maintenance therapy with oral 5-ASA medication	Escalation to maximally tolerable dose based on FC ≥300 µg/g and	Usual care based on symptoms

Study	Countries	Sites	Dates	Participants	Interventions
				Patients were in remission but at high-risk of relapse	lowered when FC <200 µg/g

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

Table 16. Summary of Key RCT Results

Study	Rate of Relapse at 1 Year
Lasson et al (2015) ¹⁷ , Fecal calprotectin monitoring, n/N (%)	18/51 (35.3)
Usual care, n/N (%)	20/40 (50)
p	0.23

RCT: randomized controlled trial.

Tables 17 and 18 display notable limitations identified in each study.

Table 17. Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Lasson et al (2015) ¹⁷ ,		3. Treatment of a flare-up based on patient complaint and not predetermined in study protocol			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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) ¹⁷ ,		1. Not blinded			2. 9 patients not providing at least 9 samples were excluded from 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 limitations assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., 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 IBD in Remission

A 2017 systematic review of 6 prospective studies that monitored fecal calprotectin 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.

Summary of Evidence

For individuals who have a suspicion of IBD when endoscopy with biopsy is being considered who receive fecal calprotectin testing to select patients who can forgo endoscopy, the evidence includes prospective and retrospective diagnostic accuracy studies and systematic reviews. Relevant outcomes are test validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. Twenty-eight studies in a systematic review evaluated the diagnostic accuracy of fecal calprotectin in patients suspected of having IBD for whom noninflammatory bowel disease, such as irritable bowel syndrome, remains a consideration. Studies varied in the fecal calprotectin protein level cutoff used to indicate the presence of disease but most used a cutoff of 50 µg/g, which is the recommended lower bound. Studies have indicated that, at this threshold, the test has a sensitivity of 93% to 99% for IBD and a negative predictive value of 73% to 100% for intestinal inflammation. Out of 100 cases of suspected IBD, approximately 49 invasive tests would be avoided with 1 case missed. Therefore, fecal calprotectin can be used to inform a decision of whether to proceed with endoscopy. Clinical input supported that the use of fecal calprotectin testing for individuals with suspected IBD provides a clinically meaningful improvement in net health outcomes by providing clinically valid and clinically useful information to guide clinical decision-making. 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 inflammatory bowel disease 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have active IBD who receive fecal calprotectin testing to monitor disease activity, the evidence includes prospective and retrospective diagnostic studies, systematic reviews, and a randomized controlled trial (RCT). Relevant outcomes are test validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. RCTs are needed to determine whether guiding treatment based on fecal calprotectin levels can improve disease management. A 2017 RCT included fecal calprotectin as one of several indicators of inflammation to test the effect of tight control of IBD on health outcomes. The independent contribution of fecal calprotectin could not be determined from this study design. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have IBD in remission who receive fecal calprotectin testing to predict relapse, the evidence includes prospective and retrospective diagnostic studies, systematic reviews, and an RCT. Relevant outcomes are test validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. One RCT found no significant difference in the rate of relapse in patients whose medication was modified based on fecal calprotectin or standard clinical indicators, however, this RCT had design and conduct limitations that affected the interpretation of its results. Further study in high-quality RCTs is needed to determine whether adding fecal calprotectin to standard clinical practice improves the management of IBD patients in remission. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input

Objective

In 2018, clinical input was sought to help determine whether the use of fecal calprotectin testing for individuals with suspected inflammatory bowel disease 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.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Academy of Pediatrics (AAP)
- Anonymous, MD, Gastroenterology/Inflammatory Bowel Disease, identified by the American Society for Gastrointestinal Endoscopy (ASGE)
- Sunanda V. Kane, MD, MSPH, FACG, Gastroenterology, Mayo Clinic, identified by American College of Gastroenterology (ACG).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by Blue Cross Blue Shield Association (BCBSA) nor any Blue Plan.

Clinical Input Responses

Additional Comments

- “Our opinion is that the use of FCP testing for individuals with suspected IBD provides a clinically meaningful improvement in healthcare by adding important and actionable information to the clinical decision-making involved in referring for endoscopy with biopsy (if FCP is elevated) or in deciding that endoscopy with biopsy is not warranted (if FCP is within normal limits)... The use of FCP 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.” (AAP)
- “FCP testing for individuals with suspected IBD would provide a clinically meaningful improvement in net health outcome if a positive test would be used to identify patients who are most likely to need endoscopy for suspected inflammatory bowel disease and if a negative test would be used to safely exclude inflammatory bowel disease and avoid endoscopic evaluation. FCP has been shown to have high sensitivity and specificity for differentiating between IBD and functional gastrointestinal disorders.” (Anonymous, identified by ASGE)
- “Fecal calprotectin (FCP) is a highly reliable and very sensitive test for inflammation in patients with colonic inflammation and has also demonstrated a high negative predictive value for patients with Crohn’s disease who have had surgery. In both situations, appropriate use of this test is associated with decreased utilization of colonoscopy.” (Dr. Kane, identified by ACG)
- “Overall, there is strong evidence to believe that FCP has true negative results with acceptably low trade-offs in missed diagnoses of IBD in those who have false-negative FCP results.” (AAP)
- “As a specialist, I use the FCP to help guide my decision making on performing endoscopy, so I am not sure of a clinical scenario in which I ordered a negative FCP result and still followed it by endoscopy with biopsy. However, there have been instances where a primary care provider has sent FCP as part of an initial workup for diarrhea. The FCP is negative, but upon evaluation at GI clinic, we learn that patient has a family h/o CD, elevated CRP, and labs concerning for possible malabsorption (low vitamin D, low

albumin) where we are concerned about ileal CD or celiac disease and endoscopy with biopsy is still pursued. As has been reported in the literature, some studies suggest that FCP appears to better reflect disease activity in UC rather than CD and that FCP results are less reliable in patients with pure ileal CD, although data/ studies are mixed. Another area of uncertainty is an intermediate test result, which may lead to either repeat testing with FCP to establish a trend or an endoscopy with biopsy for follow-up.” (Anonymous, identified by ASGE)

- “The AAP wishes to be clear in its opinion that no test is perfect and it is unlikely that any one test will ever perfectly discriminate between children who have IBD and those who do not. Nevertheless, the AAP believes that the evidence is overwhelmingly strong that FCP used in appropriate clinical scenarios, and in combination with a medical history and other test results, can be used to identify patients with IBD with high levels of sensitivity, especially when compared with other more traditional markers of inflammation.” (AAP)

See Appendices 1 and 2 for details.

Supplemental Information

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

In response to requests from Blue Cross Blue Shield Association, clinical input on fecal calprotectin testing 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 in 2018.

Clinical input obtained in 2018 supports that the following indication provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice.

- Use of fecal calprotectin testing for individuals with suspected inflammatory bowel disease when endoscopy with biopsy is being considered.

2014 Input

In response to requests from Blue Cross Blue Shield Association, input was received through 4 physician specialty societies and 4 academic medical centers in 2014. One specialty society submitted two 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

American Gastroenterological Association

The American Gastroenterological Association (AGA) published a 2018 guideline on functional gastrointestinal symptoms in patients with inflammatory bowel disease (IBD).¹⁸ 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 three to six 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 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 mg/g for fecal calprotectin was recommended to optimize sensitivity for IBD.¹⁹

American College of Gastroenterology

The American College of Gastroenterology (2018) published guidelines on the management of Crohn disease in adults.²⁰ 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 inflammatory bowel disease from irritable bowel syndrome. A summary statement without a recommendation indicated that fecal calprotectin measurements may have an adjunctive role in monitoring disease activity.

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.²¹ 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

A search of ClinicalTrials.gov in September 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

Appendix

Appendix 1. Clinical Input respondents

Appendix Table 1. Respondent Profile

Specialty Society					
No.	Name of Organization			Clinical Specialty	
1	American Academy of Pediatrics			Pediatrics, Pediatric Gastroenterology, Hepatology and Nutrition	
Physician					
No.	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
Identified by American Society for Gastrointestinal Endoscopy					
2	Anonymous	MD		Gastroenterology/Inflammatory Bowel Disease	Gastroenterology
Identified by American College of Gastroenterology					
3	Sunanda V. Kane	MD, MSPH	Mayo Clinic	Gastroenterology	Gastroenterology; Internal Medicine

Appendix Table 2. Respondent Conflict of Interest Disclosure

No.	1. Research support related to the topic where clinical input is being sought		2. Positions, paid or unpaid, related to the topic where clinical input is being sought		3. Reportable, more than \$1000, health care-related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4. Reportable, more than \$350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	Yes/No	Explanation	Yes/No	Explanation	Yes/No	Explanation	Yes/No	Explanation
1	No		No		No		No	
2	No		No		No		No	
3	No		No		No		No	

Individual physician respondents answered at an individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response

Appendix 2. Clinical Input Responses

CI-Objective

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

The following PICO applies to this indication.

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected inflammatory bowel	Interventions of interest are: • Fecal calprotectin testing	Comparators of interest are: • Endoscopy with biopsy	Relevant outcomes include: • Test accuracy • Test validity

Populations	Interventions	Comparators	Outcomes
disease when endoscopy with biopsy is being considered			• Symptoms • Change in disease status • Quality of life • Hospitalizations • Medication use

Clinical input is sought to help determine whether the use of FCP testing for individuals with suspected 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.

Responses

1. We are seeking your opinion on whether using FCP testing for the above indication provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:
 - a. Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
 - b. Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
 - c. Considerations for use in the pediatric population; and \
 - d. Supporting evidence from the authoritative scientific literature (please include PMID).

No.	Response
1	Our opinion is that the use of FCP testing for individuals with suspected IBD provides a clinically meaningful improvement in healthcare by adding important and actionable information to the clinical decision-making involved in referring for endoscopy with biopsy (if FCP is elevated) or in deciding that endoscopy with biopsy is not warranted (if FCP is within normal limits). In brief, ALL EVIDENCE SUGGESTS that FCP adds the most diagnostic value to symptoms compared with blood markers. Adding fecal calprotectin to the diagnostic workup of pediatric patients with symptoms suggestive of IBD considerably decreases the number of patients in the group in whom challenges in clinical decision making are most prevalent. There is no relevant inclusion/exclusion criteria, as IBD can affect children and adults of all ages, all ethnicities and with all co-morbidities, and should be considered in the appropriate clinical scenarios. The use of FCP 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. There is much supporting evidence from the authoritative literature. We call your attention particularly to the following: • Holtman GA, Lisman-van Leeuwen Y, Day AS, et al. Use of Laboratory Markers in Addition to Symptoms for Diagnosis of Inflammatory Bowel Disease in Children: A Meta-analysis of Individual Patient Data. <i>JAMA Pediatr.</i> Oct 2017;171(10): 984-991. PMID 28806445 "Of 16 eligible studies, authors of 8 studies (n = 1120 patients) provided their data sets. All blood markers and fecal calprotectin individually significantly improved the discrimination between pediatric patients with and those without IBD, when added to evaluation of symptoms. The best marker-fecal calprotectin-improved the area under the curve of symptoms by 0.26 (95% CI, 0.21-0.31). The second best marker-

No.	Response
	erythrocyte sedimentation rate-improved the area under the curve of symptoms by 0.16 (95% CI, 0.11-0.21). When fecal calprotectin was added to the model, the proportion of patients without IBD correctly classified as low risk of IBD increased from 33% to 91%. The proportion of patients with IBD incorrectly classified as low risk of IBD decreased from 16% to 9%. The proportion of the total number of patients assigned to the intermediate-risk category decreased from 55% to 6%."
2	a.FCP testing for individuals with suspected IBD would provide a clinically meaningful improvement in net health outcome if a positive test would be used to identify patients who are most likely to need endoscopy for suspected inflammatory bowel disease and if a negative test would be used to safely exclude inflammatory bowel disease and avoid endoscopic evaluation. FCP has been shown to have high sensitivity and specificity for differentiating between IBD and functional gastrointestinal disorders. The ACG (PMID: 29610508) endorses the use of FCP as "a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (strong recommendation, moderate level of evidence". NICE endorses the use of FCP as a decision diagnostic for inflammatory bowel disease and irritable bowel syndrome and use of this test is consistent with generally accepted medical practice. A recent expert opinion (Reenars C, Bossuyt P, Hindrycks P et al: Expert opinion for use of faecal calprotectin in diagnosis and monitoring of inflammatory bowel disease in daily clinical practice. <i>United European Gastroenterology Journal</i>. 2018 accessible at: https://doi.org/10.1177/2050640618784046) that utilized an electronic Delphi process and reports concordance rate within the expert panel provides further support for the use of FCP in clinical practice, stating: • "FC > 250 mg/g identifies patients who are most likely to have intestinal inflammation and justifies further endoscopic examination. (91%) • FC between 100 and 250 mg/g could require a second measurement within three months. (97%) • FC < 100 mg/g has a very high negative predictive value for IBD, justifying its use as a screening test to reduce the number of endoscopies and thereby the costs of health care management. This strategy delays the diagnosis in only a small proportion of patients. (97%)" b.The BSG guidelines state, "It should not be used in patients with acute diarrhea, bloody diarrhea, or in older patients where the need to rule out polyps or cancer mandates colonoscopy anyway." These are reasonable exclusion criteria. c.I defer to pediatric GI specialist d. See references below: - o Banerjee A, Srinivas M, Eyre R, et al. Faecal calprotectin for differentiating between irritable bowel syndrome and inflammatory bowel disease: a useful screen in daily gastroenterology practice. <i>Frontline Gastroenterol</i>. Jan 2015;6(1):20-26. PMID 28839790 - o Menees SB, Powell C, Kurlander J, et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. <i>Am J Gastroenterol</i>. Mar 2015;110(3):444-54. PMID 25732419 - o Kennedy NA, Clark A, Walkden A, et al. Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16-50 years. <i>J Crohns Colitis</i>. Jan 2015;9(1):4109. PMID 25135754 - o van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. <i>BMJ</i>. July 2010;15;341. PMID 20634346 - o Yang Z, Clark N, Park KT. Effectiveness and cost-effectiveness of measuring fecal calprotectin in diagnosis of inflammatory bowel disease in adults and children. <i>Clin Gastroenterol Hepatol</i>. Feb 2014;12(2):253-62. PMID 23883663 - o Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. <i>Health Technol Assess</i>. Nov 2013;17(55):xv-xix. 1-211. PMID 24286461 - o Lin JF, Chen JM, Zuo JH, et al. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. <i>Inflamm Bowel Dis</i>. Aug 2014;20(8):1407-15. PMID 24983982 - o Dhaliwal A, Zeino Z, Tomkins C, et al. Utility of faecal calprotectin in inflammatory bowel disease (IBD): what cut-offs should we apply? <i>Frontline Gastroenterol</i>. Jan 2015;6(1):14-19. PMID 25580205 - o Chang MH, Chou JW, Chen SM, et al. Faecal calprotectin as a novel biomarker for differentiating between inflammatory bowel disease and irritable bowel syndrome. <i>Mol Med Rep</i>. Jul 2014;10(1):522-6. PMID 24788223

No.	Response
	o Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Guideline: Management of Crohn's Disease in Adults. <i>Am J Gastroenterol.</i> Apr 2018;113(4):481-517. PMID 29610508 o https://www.nice.org.uk/guidance/dg11/chapter/1-Recommendations o https://www.bsg.org.uk/resource/bsg-guidance-on-the-use-of-faecal-calprotectin-testing-in-ibd.html o https://doi.org/10.1177/2050640618784046
3	Fecal calprotectin (FCP) is a highly reliable and very sensitive test for inflammation in patients with colonic inflammation and has also demonstrated a high negative predictive value for patients with Crohn's disease who have had surgery. In both situations, appropriate use of this test is associated with decreased utilization of colonoscopy. Most recently, the test has demonstrated utility in a "treat to target" strategy in Crohn's disease that will transform our management, and definitely improve outcomes. In the CALM study, using a combination of CRP and FCP as targets for therapeutic adjustments resulted in a statistically greater successful mucosal healing and steroid-free remission. There are now two recent studies that specifically address the utility of fecal calprotectin to predict mucosal healing. A retrospective study in 68 patients with ulcerative colitis who had fecal calprotectin levels collected within 6 weeks of colonoscopy were reviewed. Fecal calprotectin significantly correlated with mucosal healing and histological activity with a sensitivity of 86% and a specificity of 87%. In a prospective study of 80 Canadian IBD patients undergoing scheduled colonoscopy had fecal calprotectin levels obtained 48 hours prior to their procedure. Fecal calprotectin alone had a positive predictive value for mucosal healing of 77% and in combination with clinical symptoms increased it to 84%. Fecal calprotectin is cost-effective care. From a resource utilization standpoint, FCP is far less expensive than endoscopic evaluations (as well as cross-sectional radiologic imaging) and far more preferable from a patient tolerability point of view. Any rationale that calprotectin is sensitive for any inflammation, and therefore not helpful, is precisely why it is helpful for discerning active disease in patients with known IBD versus patients in a non-inflammatory state with similar symptoms (IBS, bile salt diarrhea, functional diarrhea). The goal is to be able to prevent a patient from an invasive test like endoscopy, which also significantly saves costs. A recent study demonstrated that the complication rate for colonoscopy is higher in IBD patients also suggests that anything we can do to reduce the need for a colonoscopy will improve care. Since we now treat to the goal of mucosal healing, for which there is sufficient evidence of improved outcomes, having a noninvasive test to assess for any disease activity promotes quality of care and reduces programmatic costs. • Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. <i>Lancet.</i> Dec 2018;390(10114):2779-2789. PMID 29096949 • Boschetti G, Laidet M, Moussata D, et al. Levels of fecal calprotectin are associated with the severity of postoperative endoscopic recurrence in asymptomatic patients with Crohn's disease. <i>Am J Gastroenterol.</i> Jun 2015;110(6):865-872. PMID 25781366 • Patel A, Panchal H, Dubinsky M. Fecal Calprotectin Levels Predict Histologic Healing in Ulcerative Colitis. <i>Inflamm Bowel Dis.</i> Sep 2017;23(9):1600-1604. PMID 28590341 • Ma C, Lumb R, Walker EV, et al. Noninvasive Fecal Immunochemical Testing and Fecal Calprotectin Predict Mucosal Healing in Inflammatory Bowel Disease: A Prospective Cohort Study. <i>Inflamm Bowel Dis.</i> Sep 2017;23(9):1643-1649. PMID 28644184 • Ferreira J, Akbari M, Gashin L, et al. Prevalence and lifetime risk of endoscopy-related complications among patients with inflammatory bowel disease. <i>Clin Gastroenterol Hepatol.</i> Oct 2013;11(10):1288-93. PMID: 23669305 • Laharie D, Mesli S, El Hajbi F, et al. Prediction of Crohn's disease relapse with faecal calprotectin in infliximab responders: a prospective study. <i>Aliment Pharmacol Ther.</i> Aug 2011;34(4):462-469. PMID: 21671970 • Turner D, Leach ST, Mack D, et al. Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis: a prospective multicentre comparison of predicting outcomes and monitoring response. <i>Gut.</i> Sep 2010;59(9):1207-1212. PMID: 20801771

2. An important health outcome is avoiding negative endoscopy with biopsy, and for there to be a meaningful clinical benefit FCP must yield true negative results with an acceptably low trade-off in a missed diagnosis of IBD in those who have false-negative FCP results. Considering the clinical scenario described in your response to question 1, address these points:
 - a. What would be the negative predictive value of FCP testing required to achieve a clinically meaningful reduction in the frequency of negative endoscopy and biopsy?
 - b. Under what circumstances might negative FCP results still require endoscopy with biopsy?
 - c. Supporting evidence from the authoritative scientific literature (please include PMID).

No.	Response
1	Overall, there is strong evidence to believe that FCP has true negative results with acceptably low trade offs in missed diagnoses of IBD in those who have false-negative FCP results. In particular, evidence suggests that FCP can predict the onset of inflammatory bowel disease with high accuracy and precision. In one study, FCP screening in adults saved \$417/patient but delayed diagnosis for 2.2/32 patients with IBD among 100 screened patients. In children, FCP screening saved \$300/patient but delayed diagnosis for 4.8/61 patients with IBD among 100 screened patients. If endoscopic biopsy analysis is considered standard for diagnosis, modeling suggests that direct endoscopic evaluation would cost an additional \$18,955 in adults and \$6250 in children to avoid 1 false-negative result from FC screening. • Yang Z, Clark N, Park KT. Effectiveness and Cost-effectiveness of Measuring Fecal Calprotectin in Diagnosis of Inflammatory Bowel Disease. <i>Clinical Gastroenterology and Hepatology</i>. Feb 2014;12(2):253 - 262.e2. PMID 23883663 To ask about the negative predictive value of FCP testing required to achieve a clinically meaningful reduction in the frequency of negative endoscopy and biopsy is a false premise, as it misses the fact that FCP results reflect pre-test likelihood of having the disease. Sensitivity analyses suggest that the cost-effectiveness of FC screening varies with the sensitivity of the test and the pre-test probability of IBD in adults and children. Pre-test probabilities for IBD of $\leq 75\%$ in adults and $\leq 65\%$ in children make FC screening cost-effective, but it can be cost-ineffective if the probabilities were $\geq 85\%$ and $\geq 78\%$ in adults and children, respectively. Compared with the FC cutoff level of 100 $\mu\text{g/g}$, the cutoff level of 50 $\mu\text{g/g}$ cost an additional \$55 and \$43 for adults and children, respectively, but it yielded 2.4 and 6.1 additional accurate diagnoses of IBD per 100 screened adults and children, respectively. What this means is that screening adults and children to measure fecal levels of calprotectin is effective and cost-effective in identifying those with IBD on a per-case basis when the pre-test probability is $\leq 75\%$ for adults and $\leq 65\%$ for children. Negative FCP results might still require endoscopy with biopsy or imaging in non-inflammatory predominant Crohn's such as stricturing small bowel disease with no colonic involvement. Children with this disease present with growth failure, but no diarrhea or other colonic inflammatory symptoms or findings. If it is a chronic disease, there may not even be active inflammation; serum markers may all be negative and FCP may be negative as well. Generally speaking, these children may have other signs of chronic disease, including anemia, but even blood counts may be unreliable in positively predicting that endoscopy with biopsy will find granulomatous disease.
2	a. A meta-analysis (PMID: 20634346) that included six studies in adults and seven in children and teenagers, which included studies where data were collected prospectively in a consecutive series of patients with suspected inflammatory bowel disease where patients first underwent FCP testing and then endoscopy, found that in adults the pooled sensitivity of FCP testing was 0.93 (95% confidence interval 0.85 to 0.97) and the pooled specificity was 0.96 (0.79 to 0.99). Per this analysis, in a hypothetical population of 100 adults with suspected inflammatory bowel disease (and an overall mean prevalence of 32%) 3 patients without the disease would go on to have endoscopy and 2 patients with the disease would be missed, reducing the number of adults requiring endoscopy by 67%. These are acceptable values. A limitation of this analysis is that cut-off level is not clear, since results are described as normal or not normal. A systematic review and economic evaluation (PMID 24286461) used an FCP cut-off level of 50 $\mu\text{g/g}$ and reported a pooled sensitivity of 93% and specificity of 94% for distinguishing between IBD and IBS. A retrospective cohort study (PMID 25135754) found that using a threshold of $\geq 50 \mu\text{g/g}$ for IBD vs. functional disease yielded a sensitivity of 0.97, specificity of 0.74, positive predictive value of 0.37 and negative predictive value of 0.99. These are favorable test characteristics. In any clinical scenario, the NPV of FCP will depend on the cut-off values that are used to

No.	Response
	define a negative, positive and intermediate test. result. In addition, as recommended by the BSG, local laboratory quality assurance processes and care pathways should be established. b. As a specialist, I use the FCP to help guide my decision making on performing endoscopy, so I am not sure of a clinical scenario in which I ordered a negative FCP result and still followed it by endoscopy with biopsy. However, there have been instances where a primary care provider has sent FCP as part of an initial workup for diarrhea. The FCP is negative, but upon evaluation at GI clinic, we learn that patient has a family h/o CD, elevated CRP, and labs concerning for possible malabsorption (low vitamin D, low albumin) where we are concerned about ileal CD or celiac disease and endoscopy with biopsy is still pursued. As has been reported in the literature, some studies suggest that FCP appears to better reflect disease activity in UC rather than CD and that FCP results are less reliable in patients with pure ileal CD, although data/ studies are mixed. Another area of uncertainty is an intermediate test result, which may lead to either repeat testing with FCP to establish a trend or an endoscopy with biopsy for follow-up. c. See references below • van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. <i>BMJ</i>. July 2010;15;341. PMID 20634346 • Kennedy NA, Clark A, Walkden A, et al. Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16-50 years. <i>J Crohns Colitis</i>. Jan 2015;9(1):4109. PMID 25135754 • Smith LA, Gaya DR. Utility of faecal calprotectin analysis in adult inflammatory bowel disease. <i>World J Gastroenterol</i>. Dec 2012;18(46):6782-9. PMID 23239916 • Costa F, Mumolo MG, Ceccarelli L, et al. Calprotectin in a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. <i>Gut</i>. Mar 2005;54(3):364-8. PMID 15710984 • Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. <i>Am J Gastroenterol</i>. Jan 2010;105(1):162-9. PMID 19755969 • https://www.bsg.org.uk/resource/bsg-guidance-on-the-use-of-faecal-calprotectin-testing-in-ibd.html
3	The negative predictive value of any test is based on the background prevalence of the disease in question. Since FCP would be used to detect inflammation, the prevalence is high for various other GI conditions. Therefore a negative predicted value greater than 75% (which is currently the care) translates to a clinically meaningful reduction in unnecessary endoscopy. The patients who have other indications for endoscopy i.e. iron deficiency, overt bleeding, or unexplained weight loss may result in a negative FCP where endoscopy is still required. • ASGE Standards of Practice Committee, Fisher DA, Shergill AK, Early DS, et al. Role of endoscopy in the staging and management of colorectal cancer. <i>Gastrointest Endosc</i>. Jul 2013;78(1):8-12. PMID 23664162 • Hassan C, Di Giulio E, Marmo R, et al. Appropriateness of the indication for colonoscopy: systematic review and meta-analysis. <i>J Gastrointest Liver Dis</i>. Sep 2011;20(3):279-86. PMID: 21961096 • Davila RE, Rajan E, Adler DG, et al. Standards of Practice Committee. ASGE Guideline: the role of endoscopy in the patient with lower-GI bleeding. <i>Gastrointest Endosc</i>. Nov 2005;62(5):656-60. PMID 16246674
3.	Based on the evidence and your clinical experience for the clinical indication below:
a.	Respond Yes or No whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
b.	Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
1	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes			X
2	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes		X	
3	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes		X	

4. Based on the evidence and your clinical experience for the clinical indication below:
- Respond Yes or No whether this intervention is consistent with generally accepted medical practice; AND
 - Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes					X
2	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes				X	
3	Use of FCP testing for individuals with suspected IBD when endoscopy with biopsy is being considered	Yes					X

5. Additional narrative rationale or comments and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

No.	Additional Comments
1	- The AAP wishes to be clear in its opinion that no test is perfect and it is unlikely that any one test will ever perfectly discriminate between children who have IBD and those who do not. Nevertheless, the AAP believes that the evidence is overwhelmingly strong that FCP used in appropriate clinical scenarios, and in combination with a medical history and other test results, can be used to identify patients with IBD with high levels of sensitivity, especially when compared with other more traditional markers of inflammation. - The AAP also believes the evidence is strong that FCP is a reliable marker of mucosal improvement, especially if it is used in combination with other measures including serum markers (i.e. C-reactive protein) and clinical symptoms scores. In turn, the AAP believes the evidence that FCP is a useful test for disease monitoring of children with IBD, especially those with colonic sites of involvement. Treating to achieve mucosal healing will improve long-term health outcomes for children and thereby could decrease morbidity related costs. Implementation of a non-invasive marker such as calprotectin to assess for presence/absence of mucosal healing is particularly valuable in children, in whom we try to perform less invasive endoscopic procedures. - FCP is non-invasive and non-painful. It is easily obtained and does not require special equipment. Compared with colonoscopy, FCP is preferable as a test, which if negative may allow a physician to reassure a family that IBD is considerably less likely as a primary diagnosis. In those children with IBD, a decreasing FCP may allow reassurance that the disease is under better control. - Manceau H, Chicha-Cattoir V, Puy H, et al. Fecal calprotectin in inflammatory bowel diseases: update and perspectives. <i>Clin Chem Lab Med.</i> 2017;55(4):474-483. PMID 27658156 - D'Angelo F, Felley C, Frossard JL. Calprotectin in Daily Practice: Where Do We Stand in 2017? <i>Digestion.</i> 2017;95(4):293-301. PMID 28511188

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2	See PMID above
3	Please see above discussion

6. Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

No.	Yes/No	Citations of Missing Evidence
1	No	
2	Yes	See PMID above
3	No	

References

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
 - o Clinical findings (i.e., pertinent symptoms and duration)
 - o Comorbidities
 - o Activity and functional limitations
 - o Family history if applicable
 - o Reason for procedure/test/device, when applicable
 - o Past and present diagnostic testing and results
 - o Past treatment regimen(s) including antibiotic used and response(s)
 - o Prior conservative treatments, duration, and response
 - o 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

- 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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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.

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 (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.

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.