BlueCross BlueShield of Alabama

Name of Policy:
Fecal Calprotectin Testing

Policy #: 472
Category: Laboratory

Latest Review Date: March 2018
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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 that patient's illness, injury or disease.*

Description of Procedure or Service:

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

Inflammatory Bowel Disease

IBD is a chronic condition that encompasses two main forms: Crohn's disease (CD) and ulcerative colitis (UC), which overlap in clinical and pathological characteristics but have distinct features. Crohn disease can involve the entire gastrointestinal 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 gastrointestinal (e.g., abdominal pain, bloody diarrhea, perianal fistulae), systemic (e.g., weight loss, fatigue, growth failure in children), and extraintestinal (e.g., characteristic rashes, uveitis, arthritis). Patients may present with or develop a range of severity levels, including life-threatening illness. Treatments include oral and rectal salicylates, glucocorticoids, immunomodulators (e.g., methotrexate), and multiple biologic therapies (e.g., infliximab), depending on the disease severity, which are recommended by the American Gastroenterological Association and other organizations.

Diagnostic Methods

Making a diagnosis of 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 evaluate disease severity, potentially small bowel imaging, and endoscopy (upper gastrointestinal [GI] and colonoscopy) with biopsies.

Fecal Calprotectin

In some cases, the clinical manifestations of IBD can be nonspecific and suggestive of other disorders, including infectious colitis, colon cancer, and functional bowel disorders, including irritable bowel syndrome (IBS).

Therefore, there is a need for simple, accurate, noninvasive tests to detect intestinal inflammation. Potential noninvasive markers of inflammation fall into several categories including serological and fecal. Serologic markers such as C-reactive protein and anti-neutrophil cytoplasmic antibodies (ANCA) tend to have low sensitivity and specificity for intestinal inflammation because they are affected by inflammation outside of the gastrointestinal tract. Fecal markers, in contrast, have the potential for being more specific to the diagnosis of gastrointestinal tract disorders since 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.

Fecal calprotectin is one protein that could possibly be used as a marker of inflammation. It is a calcium- and zinc-binding protein that accounts for about 60% of the neutrophils' 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, a potential advantage of fecal 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 distant laboratory for testing. In contrast, lactoferrin, another potential fecal marker of intestinal inflammation, is stable at room temperature for only about two days.

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

Fecal calprotectin testing has been used to differentiate between organic and functional intestinal disease. Some consider fecal calprotectin to be a marker of neutrophilic intestinal inflammation rather than a marker of organic disease and believe its appropriate use is 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 potentially be used to change treatment, such as adjusting medication levels.

Policy:

For patients age 18 and under, fecal calprotectin testing meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in the diagnosis and management of inflammatory bowel disease.

For patients age 19 and older, fecal calprotectin testing does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was performed through January 8, 2018. The key literature is summarized in the following section.

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.

Diagnosis of Suspected Inflammatory Bowel Disease

Clinical Context and Test Purpose

The purpose of testing for fecal calprotectin in patients who have suspected IBD is to inform a decision whether to pursue additional testing (i.e., endoscopy) to differentiate IBD from IBS. In these cases, patients with presenting on the milder end of the disease spectrum, with symptoms that could be consistent with either IBD or IBS, a test that could reliably rule in or out IBD or to select patients who could be safely observed to determine if symptoms worsen, rather than obtaining endoscopy immediately, would have clinical utility.

The question addressed in this evidence review is: does the addition of fecal calprotectin to typical laboratory diagnostic testing in individuals with suspected IBD vs IBS improve the diagnosis of IBD?

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

Patients

The relevant population(s) of interest is individuals with mild IBD symptoms which overlap with IBS. This would include those who are being treated in the outpatient, non-emergency department setting. In addition to patients evaluated by specialists, patients evaluated in the nonspecialist setting are of interest.

Interventions

The intervention of interest is fecal calprotectin testing.

Comparators

The following tests are currently used to make decisions about the diagnosis of IBD in patients in the relevant population (prior to or concurrent with fecal calprotectin): inflammatory markers (c-reactive protein [CRP], erythrocyte sedimentation rate ESR]); CBC; and plain film imaging.

Outcomes
The outcomes of interest are the sensitivity, specificity, and other test performance characteristics of the calprotectin test. Indirectly, we are interested in comparing symptom burden, quality of life, disease, disease classification.

A potential harmful outcome with the use of fecal calprotectin is delayed diagnosis of true IBD due to initial misclassification as IBS. A false positive test may lead to unnecessary testing or treatment.

Timing
The relevant time period for the impact of testing is years to obtain a correct diagnosis.

Setting
This test is expected to be used in the outpatient, nonemergency department setting. Most patients would likely be evaluated by a gastroenterologist, although an initial workup could be completed by a primary care provider.

Simplifying Test Terms
There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting response to therapy.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires 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).

A large body of research has assessed of fecal calprotectin for diagnosing IBD in patients with suspected IBD versus IBS.

Systematic Reviews
In 2015, Menees et al published a systematic review of studies evaluating the ability of fecal calprotectin and other markers to identify patients with IBD and to distinguish between IBD and irritable bowel syndrome (IBS). Reviewers included prospective cohort studies that used the enzyme-linked immunosorbent assay (ELISA) test for fecal calprotectin (not the point-of-care test) and used Manning or Rome criteria for IBS diagnosis. Sixty-seven studies were reviewed in detail and 12 met the inclusion criteria. Eight studies on fecal calprotectin had data suitable for analysis. Studies included a total of 1062 participants, 565 with IBD, 259 with IBS, and 239 healthy controls. The authors found that the likelihood of IBD increased as the level of fecal calprotectin increased, with a maximal predictive value of 78.7% at 1000 μg/g. A patient with a fecal calprotectin level below 40 μg/g had 1% chance or less of having IBD. However, no fecal calprotectin level could accurately exclude the possibility of IBS. The predictive value of fecal calprotectin for IBS was 11.6% at 20 μg/g and 7.6% at 1000 μg/g.

In 2013, Waugh et al in the U.K. published a systematic review as part of the national Health Technology Assessment program. The investigators searched for studies using fecal calprotectin tests to evaluate inflammation of the lower intestine in newly presenting patients compared with a reference standard, preferably histology. Studies on both laboratory-based or point-of-care tests were included. Studies using fecal calprotectin tests to monitor disease progression or response to treatment were excluded. Reviewers assessed 83 full-text articles for eligibility and 28 were deemed eligible and were included in the quantitative synthesis. Studies were pooled when there were a minimum of four using the same calprotectin cutoff. A pooled analysis of five studies using fecal calprotectin to differentiate between IBD and irritable bowel syndrome (IBS) in adults at a cutoff of 50 μg/g had a combined sensitivity of 0.93 (95% confidence interval [CI], 0.83 to 0.97) and a combined specificity of 0.94 (95% CI, 0.73 to 0.99). A pooled analysis of six studies using fecal calprotectin to differentiate between IBD and non-IBD in adults and children had a combined sensitivity of 0.99 (95% CI, 0.95 to 1.00) and a combined specificity of 0.74 (95% CI, 0.59 to 0.86). Reviewers concluded that calprotectin testing is a reliable method for differentiating between inflammatory and noninflammatory disease of the bowel. They noted that most studies have been done in specialty settings. A limitation of the evidence, noted in the review, is that the optimal cutoff for calprotectin tests is not known; most studies used the cutoff of 50 μg/g and did not evaluate other potential cutoffs. Accordingly, the authors recommend using the 50 μg/g cutoff and reevaluating this cutoff as additional evidence accumulates.

Pediatric Studies
A number of systematic reviews have focused on studies in pediatric populations. Holtman et al (2017) reviewed the use of laboratory markers in addition to symptoms for the diagnosis of IBD in children. They included individual patient data from 8 studies (n=1120 patients), finding that all blood markers and fecal calprotectin individually significantly improved the discrimination of

pediatric patients with and without IBD. Fecal calprotectin was the best marker and improved the area under the curve of symptoms by 0.26 (95% CI, 0.21 to 0.31). When calprotectin was added to their model, the proportion of patients without IBD correctly classified as low risk of IBD increased from 33% to 91%. The authors concluded that a fecal calprotectin value less than 50 µg/g would make the diagnosis of IBD unlikely.

Several systematic reviews were limited to studies in the pediatric population. In 2014, Henderson et al focused on studies of pediatric patients undergoing an initial investigation for suspected IBD. Reviewers identified eight studies that reported fecal calprotectin levels before endoscopic investigation of IBD in patients younger than 18 years. Six studies used a fecal calprotectin cutoff of 50µg/g and the other two used a cutoff of 100 µg/g. In their quality assessment, only three studies were judged to have a representative spectrum of patients and only three studies clearly reported that they used an acceptable reference standard (i.e., upper and lower endoscopy in all patients). Findings from the six studies were pooled. The pooled sensitivity and specificity of fecal calprotectin in identifying patients with IBD were 97.8% (95% CI, 94.7% to 99.6%) and 68.2% (50.2% to 86.3%), respectively. A 2012 meta-analysis by Kostasis et al identified a total of 37 studies conducted with children. Three studies were excluded because they did not report sufficient information about fecal calprotectin levels, which left 34 studies in the review. Studies were selected regardless of sample size or methodologic characteristics. Study findings were not pooled due to heterogeneity. The sensitivity of studies using fecal calprotectin to identify children with IBD ranged from 12.5% to 100% and specificity ranged from 58.3% to 100%. When the analysis was limited to patients with newly diagnosed and untreated IBD (i.e., similar to the population included in the Henderson et al meta-analysis), the sensitivity of fecal calprotectin ranged from 73.5% to 100% and the specificity ranged from 65.9% to 100%.

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 randomized controlled trials. No clinical trials evaluating the use of calprotectin for diagnosis of IBD were identified.

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.

Section Summary: Diagnosis in Patients with Suspected Inflammatory Bowel Disease

A number of well-conducted studies have evaluated the accuracy of fecal calprotectin levels for diagnosing IBD. Additionally, several systematic reviews of these studies have been published. In general, the studies indicate that the commercially available test has very high sensitivity for IBD. Studies in the pediatric population have shown that fecal calprotectin was the best marker

and improved the area under the curve of symptoms by 26%. Studies varied in the cutoff of fecal calprotectin that was used to indicate the presence of disease, but most use a cutoff of 50μg/g.

Most studies were conducted in a specialty setting. However, there is relatively little data on the use of calprotectin in the general population and potential for spectrum effect; given the possibility of more widespread use in practice, additional clinical validity data in the target population would be indicated.

Monitoring Disease Activity in Patients with Diagnosed IBD

Clinical Context and Test Purpose

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

The question addressed in this evidence review section is: does the addition of fecal calprotectin to clinical assessment (based on standard scores and/or history and physical) and standard laboratory tests (e.g., CBC, ESR, CRP) in individuals with diagnosed IBD improve outcomes?

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

Patients

The relevant population of interest is individuals with Crohn disease or UC undergoing therapy.

Interventions

The intervention of interest is fecal calprotectin testing.

Comparators

The following tests are currently used to make decisions about the diagnosis of IBD in patients in the relevant population (prior to or concurrent with fecal calprotectin): inflammatory markers (c-reactive protein [CRP], erythrocyte sedimentation rate ESR]); CBC.

Outcomes

Outcomes may be assessed in clinical practice and in research with standardized measures, such as the Crohn disease activity index (CDAI), a validated 8-item score which is used as a marker of Crohn disease remission, with values <150 considered consistent with remission and values >450 considered a marker of severe Crohn disease.

Outcomes of interest are improvement in symptoms or in disease activity scores.

Timing

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

Setting

This test might be ordered in an outpatient setting by either a gastroenterologist or primary care provider.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires 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).

A number of meta-analyses have reviewed studies on fecal calprotectin testing to identify IBD patients with active disease.

A 2015 systematic review by Mosli et al evaluated the diagnostic accuracy of fecal calprotectin in adults and children with previously diagnosed UC or CD who had active disease confirmed by endoscopy. A total of 19 studies with 1069 UC patients and 1033 CD 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% (95% CI, 84% to 90%) and 73% (95% CI, 66% to 79%), respectively. The AUC for fecal calprotectin was 89% (95% CI, 86% to 91%).

In 2014, Lin et al published a meta-analysis limited to studies of adults diagnosed with IBD. The studies evaluated fecal calprotectin for monitoring IBD activity and use of an endoscopic scoring system as the reference standard. Ten studies with 744 UC patients and 727 CD patients met eligibility criteria. The authors selected the cutoff value from each study that had the highest diagnostic accuracy and used this estimate for the pooled analyses. Pooled sensitivity of fecal calprotectin for identifying active disease versus remission was 85% (95% CI, 82% to 87%). Pooled specificity was 81% (95% CI, 77% to 84%). Cutoff values for testing positive for fecal calprotectin ranged from 30 to 274μg/g in individual studies. At the manufacturer's recommended cutoff of 50μg/g, pooled sensitivity was 92% and pooled specificity was 60%. At a cutoff of 100μg/g, pooled sensitivity was 84% and pooled specificity was 66%. The specific assay used might have contributed to variability in thresholds.

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 randomized controlled trials.

Two open-label randomized controlled trials (RCTs) have examined the use of fecal calprotectin testing for managing patients with IBD.

Colombel et al (2018) reported on an industry-sponsored multicenter trial (CALM) that compared tight control of CD with standard clinical management. Tight control was based on biomarkers and clinical factors that included fecal calprotectin levels of 250 µg/g or higher and CRP of 5 mg/L or higher (see Table 1). Of note, inclusion was limited to patients with fecal calprotectin levels of 250 µg/g or greater and CRP of 5 mg/L or greater prior to randomization. The primary endpoint was mucosal healing with an absence of deep ulcers at 48 weeks after randomization (see Table 2). About 25% of patients discontinued the trial, primarily because of adverse events, but there was no significant difference in the percentage of dropouts in the 2 groups, and analysis was performed by intention-to-treat. Missing values were imputed using nonresponder imputation. The trial met the primary endpoint, with an improvement in mucosal healing in the tight control group. Three (2%) patients in the tight control group and 24 (20%) in the control group moved to rescue therapy. Steroid-free remission was also improved in the tight control group. The percentage of patients reporting adverse events was similar in the two groups, but the type of adverse events differed. In the tight control group, the most common adverse events were nausea, nasopharyngitis, and headache, while the clinical management group reported worsening CD, arthralgia, and nasopharyngitis.

A prospective nonblinded study, published by Lasson et al (2015) randomized patients with UC 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 1). 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. At one year, there was no significant difference in relapse rates between the two groups. For 10 of the 18 patients in the intervention group who had a relapse, fecal calprotectin level did not rise above the 300 µg/g cutoff for medication dosage escalation. In the subgroup of patients who did have 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%).

Table 1. Summary of Key RCT Characteristics

					Interventions	
Author	Countries	Sites	Dates	Participants	Active	Comparator
Colombel et al (2017)	U.S., E.U.	74	2011-2016	Adults (n=244) with active CD and naïve to immunomodulators and biologics	Tight control including FC≥5 mg/L	Clinical Management
Lasson et al (2015)				Adults (n=91) with UC on maintenance therapy with oral 5-ASA medication who had at least 1 flare up during the previous year	Dose escalation to maximally tolerable dose based on FC≥ 300µg/g	Usual care

5-ASA: 5-aminosalicylic acid; CD: Crohn disease; CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; FC: fecal calprotectin; UC: ulcerative colitis. a Tight control was10 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

Table 2. Summary of Key RCT Results

Study	Rate of Relapse at 1 Year (Mayo Score of ≤2)	Mucosal Healing at 48 Weeks	Adverse Events	Steroid Free Remission at 48 Weeks	Deep Remission
Colombel et al (2017)		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
Lasson et al (2015)					
FC monitoring	18/51 (35.3)				
Usual care	20/40 (50)				
P	0.23				

Values are n/n (%), n (%), or as otherwise indicated. CI: confidence interval; FC: fecal calprotectin; RR: relative risk

A 2012 study by Molander and colleagues in Finland included 60 patients with inflammatory bowel disease (34 had Crohn's disease and 26 had ulcerative colitis). The study evaluated whether a normal fecal calprotectin level after induction therapy predicted the response to maintenance therapy a year later. Patients, all of whom had an elevated fecal calprotectin level at baseline (mean=810ug/g) (52%) of patients had a normal fecal calprotectin value and 29 (48%) had an elevated fecal calprotectin. Forty-eight patients used maintenance therapy for approximately one year; the other 12 stopped due to lack of response. At the one year follow-up, 26 of the 31 (84%) patients with normal fecal calprotectin after induction were in clinical remission compared to 11 of 29 (38%) of those with an elevated fecal calprotectin level after induction; $p<0.0001$. Using ROC analysis, a fecal calprotectin level of 139ug/g after induction therapy was selected as the best cutoff to use to predict risk of having clinically active disease at one year. Using this cutoff, there was a sensitivity of 72%, a specificity of 80% and the area under the curve was 0.84.

Section Summary: Monitoring Disease Activity in Patients with Diagnosed IBD
Studies using fecal calprotectin to predict response to treatment have variable findings, and have not used consistent cutoff values. These factors make the diagnostic accuracy of fecal calprotectin in evaluating the response to treatment or disease active in IBD uncertain.

Two RCTs have provided direct evidence on the utility of treatment modification based on fecal calprotectin level in patients with IBD. One RCT evaluated the relapse rate in patients with UC whose medication doses were managed with and without fecal calprotectin test results (≥300 µg/g) and, in its primary analysis, found no significant difference in relapse rates. A second RCT found that tight control using both clinical and biologic markers (fecal calprotectin level ≥250 µg/g and CRP level ≥5 mg/L) resulted in greater mucosal healing in patients with CD.

Relapse Prediction in Patients with Diagnosed IBD

Clinical Context and Test Purpose

Calprotectin has been used to predict relapse for individuals with IBD. The clinical utility in this setting is uncertain. A marker to predict relapse could have clinical utility if preemptive treatment were found to eliminate recurrences or reduce 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) and standard laboratory tests (e.g., CBC, ESR, CRP) in individuals with diagnosed IBD improve relapse prediction? And does relapse prediction lead to improved outcomes in IBD?

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

Patients

The relevant population of interest are individuals with Crohn disease or UC.

Interventions

The intervention of interest is fecal calprotectin testing.

Comparators

The following tests are currently used to make decisions about the diagnosis of IBD in patients in the relevant population (prior to or concurrent with fecal calprotectin): inflammatory markers (ESR); CBC.

Outcomes

Outcomes may be assessed in clinical practice and in research with standardized measures, such as the CDAI.

Outcomes of interest are improvement in symptoms or in disease activity scores.

Timing

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

Setting

This test might be ordered in an outpatient setting by either a gastroenterologist or primary care provider.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires 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. Six studies met the review inclusion criteria and evaluated fecal calprotectin levels every one to three months. Five studies used an upward trend of fecal calprotectin between two measurements. 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. Calprotectin began to rise two to three months before clinical relapse. Reviewers commented that "we were not able to identify the best FC [fecal calprotectin] cutoff for monitoring purposes. Currently, there is no consensus among IBD experts about the range of FC associated with mucosal healing, indicating a need for prospective and randomized studies comparing monitoring strategies that vary in thresholds."

Prospective Trials

Representative trials are described next. A 2014 prospective study by Yamamoto et al in Japan studied 80 UC patients who had been in remission for at least three months and were taking mesalamine as maintenance therapy. Fecal calprotectin levels were measured at the beginning of the study. After 12 months of follow-up, 21 (26%) patients had relapsed. The mean calprotectin level was 172.7µg/g in patients who relapsed and 135.5µg/g in patients who remained in remission (p=0.02). Based on levels in the study's patients, the authors selected 170µg/g as a cutoff for calprotectin in their evaluation of diagnostic accuracy. Using this cutoff, fecal calprotectin had a sensitivity of 76% and a specificity of 76% for predicting relapse.

In 2013, Lasson et al in Sweden published findings of a prospective study with newly diagnosed UC patients. After an initial work-up, patients were monitored over three years, with planned follow-ups after three months and yearly thereafter. Fecal calprotectin was monitored at each visit. Relapse was defined as an increase in symptoms of sufficient severity to justify changing treatment. A total of 101 patients were eligible to participate in the study. Twenty-eight patients were subsequently excluded due to a missing stool sample at three months, three did not meet diagnostic criteria for UC and one was lost to follow-up. Thus, 69 patients (68%) were included in the one-year analysis. During the first year, 24 patients (35%) did not experience a relapse of UC. These patients had a significantly lower median level of fecal calprotectin at three months (102ug/g) compared to patients with relapsing UC (263ug/g). Sixty-seven patients were included in the two- and three-year analyses. The three-month fecal calprotectin levels were significantly higher in patients with relapsing disease at two years compared to those with mild disease. There was not a significant relationship between fecal calprotectin and relapsing disease at three years. The authors found that the three-month fecal calprotectin concentration of 169ug/g yielded the greatest sensitivity and specificity to predict relapse at one year (64.4% and 70.8%, respectively). The optimal cutoff of fecal calprotectin for predicting relapsing disease at two years was 262ug/g (sensitivity: 51.1%, specificity: 81.8%).

A 2009 study by Gisbert et al in Spain included 163 patients (89 CD, 74 UC) who had been in remission for at least six months. One sample of fecal calprotectin was obtained at baseline, and patients were followed for 12 months. The mean baseline level of fecal calprotectin was 153µg/g

(range, 6-1217 µg/g); levels were not reported for UC versus CD patients. During the follow-up period, 13 of 74 (18%) UC patients and 13 of 89 (15%) CD patients experienced a relapse severe enough to warrant a change in treatment. Mean levels of calprotectin were significantly higher in patients who relapsed compared with those who did not relapse. In CD patients, mean levels were 266 µg/g in relapsing patients and 145 µg/g in nonrelapsing patients (p=0.002). Corresponding values in UC patients were 213 µg/g and 126 µg/g, respectively (p=0.03). A cutoff of 150µg/g for fecal calprotectin was found to best predict relapses of IBD. At 150 µg/g, fecal calprotectin had 31% sensitivity and 91% specificity for predicting UC and 28% specificity and 93% specificity for predicting CD.

Ferreiro-Iglesias et al (2016) used fecal calprotectin to predict relapse for patients on infliximab (N=53), using a cutoff of 160µg/g.

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.

There is interest in studies that evaluate whether the endoscopy rate is decreased when fecal calprotectin testing is used to evaluate patients with suspected IBD and also in studies that compare health outcomes in patients managed with and without use of fecal calprotectin testing.

Section Summary: Relapse Prediction in Patients with Diagnosed IBD
Monitoring of fecal calprotectin could be predictive of relapse, but the cutoff values of fecal calprotectin have varied across studies. Also, studies have tended to base definitions of remission on subjective clinical remission indices, rather than on endoscopic findings.

Summary of Evidence
For individuals who have suspected inflammatory bowel disease (IBD) who receive fecal calprotectin testing, the evidence includes prospective and retrospective diagnostic accuracy studies and systematic reviews. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. There is a large body of evidence evaluating the diagnostic accuracy of fecal calprotectin in patients considered to have IBD, and for whom irritable bowel syndrome is a consideration. In general, these studies have indicated that the commercially available test has very high sensitivity for IBD. Studies have varied in the cutoff of fecal calprotectin used to indicate the presence of disease, but most have used a cutoff of 50µg/g. However, there is relatively little data on the use of calprotectin in the general population and potential for spectrum effect; given the possibility of more widespread use in practice, additional clinical validity data in the target population would be indicated.

For individuals who have diagnosed IBD who receive fecal calprotectin testing for treatment assessment, or disease activity assessment, or relapse prediction, the evidence includes prospective and retrospective diagnostic studies, meta-analyses, and 1 randomized controlled trial. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. The diagnostic accuracy for fecal calprotectin for these indications is uncertain, as are the patient management changes associated with specific calprotectin levels.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence

In 2013, (with one of the recommendations being updated in 2017), the National Institute for Health and Care Excellence published guidance on fecal calprotectin testing for inflammatory diseases of the bowel. The guidance had the following recommendations:

- Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or IBS in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if cancer is not suspected.

- Fecal 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.

American Gastroenterological Association Institute

In 2014, the American Gastroenterological Association (AGA) Institute published guidelines on the identification, assessment, and initial medical treatment in Crohn disease. Fecal calprotectin is listed among other clinical lab tests to assess inflammatory status.

U.S. Preventive Services Task Force Recommendations

Not Applicable.

Key Words:

Fecal calprotectin testing, PhiCal™, CalPrest®

Approved by Governing Bodies:

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

The PhiCal®, as modified by Quest Diagnostics, is classified as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. 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, Trieste, Italy) and, in 2016, CalPrest®NG (Eurospital SpA) were cleared for marketing by FDA through the 510(k) process. According to the FDA summary, CalPrest® "is identical" to the PhiCal™ test "in that they are manufactured by Eurospital S.p.A. Trieste, Italy. 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."

There is a commercially available enzyme-linked immunosorbent assay test measuring fecal calprotectin levels, PhiCal. 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, Norway; Quantum Blue Calprotectin®, Bühlmann Laboratories, Switzerland). Rapid tests have not been approved by the Food and Drug Administration for use in the United States.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

83993	Calprotectin, fecal

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Policy History:

Medical Policy Panel, April 2011
Medical Policy Group, April 2011 **(2):** New policy
Medical Policy Administration Committee, May 2011
Medical Policy Group, May 2011 **(2):** Age clarification
Medical Policy Group June 2011
Medical Policy Administration Committee, June 2011
Available for comment June 8 – July 25, 2011
Medical Policy Group, April 2012 **(1):** 2012 Update to Key Points and References related to MPP update; no change to policy statement
Medical Policy Panel, April 2013
Medical Policy Group, April 2013 **(1):** 2013 Updates to Key Points and References; no change to policy statement
Medical Policy Panel, April 2014
Medical Policy Group, June 2014 **(1):** 2014 Update to Key Points and References; no change to policy statement
Medical Policy Group, April 2015 **(3)**: clarification statement "in the diagnosis and management of inflammatory bowel disease" added to coverage criteria for ages 18 and under; no change in intent of original policy statement
Medical Policy Panel, July 2015
Medical Policy Group, July 2015 **(3):** 2015 Updates to Key Points, Approved by Governing Bodies, Key Words, and References; no change to policy statement.
Medical Policy Panel, April 2017
Medical Policy Group, May 2017 **(3):** 2017 Updates to Description, Key Points, Governing Bodies & References; no change in Policy statement
Medical Policy Panel, March 2018

Medical Policy Group, March 2018 **(4):** Updates to Description, Key Points, Approved by Governing Bodies, and References. No change to policy statement.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.