2.04.69  Fecal Calprotectin Testing

Original Policy Date: March 29, 2013  Effective Date: May 1, 2018
Section: 2.0 Medicine  Page: Page 1 of 15

Policy Statement

Fecal calprotectin testing is considered investigational in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease.

Policy Guidelines

The following CPT code is specific for this test:

- 83993: Calprotectin, fecal

Description

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 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, Trieste, Italy) 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 are manufactured by Eurospital SpA, 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.”

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, Norway; Quantum Blue Calprotectin®, Bühlmann Laboratories, Switzerland). Rapid tests have not been approved by the FDA for use in the United States.

Rationale

Background

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic condition that encompasses 2 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 (eg, abdominal pain, bloody diarrhea, perianal fistulae), systemic (eg, weight loss, fatigue, growth failure in children), or extra-intestinal (eg, characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity levels, including a life-threatening illness. Treatments include oral and rectal salicylates, glucocorticoids, immunomodulators (e.g., methotrexate), and multiple biologic therapies (e.g., infliximab), depending on disease severity, which are recommended by the American Gastroenterological Association1 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, 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 nonspecific and suggestive of other disorders, including infectious colitis, colon cancer, and functional bowel disorders, including irritable bowel syndrome.

Therefore, 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 antineutrophil cytoplasmic antibodies tend to have low sensitivity and specificity for intestinal inflammation because they are affected by inflammation outside of the GI tract. Fecal markers, in contrast, have the potential for being 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.

Fecal 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 fecal calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to 1 week, leaving enough time for patients to collect samples at home and send them to a laboratory for testing. In contrast, lactoferrin, also a potential fecal marker of intestinal inflammation, is stable at room temperature for about 2 days.

Among potential disadvantages of fecal calprotectin as a marker of inflammation are that fecal calprotectin levels increase after 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 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 be used to change treatment, such as adjusting medication levels.

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.

Diagnosis of Suspected Inflammatory Bowel Disease Clinical Context and Test Purpose
The purpose of testing for fecal calprotectin in patients who have suspected inflammatory bowel disease (IBD) is to inform a decision whether to pursue additional testing (i.e., endoscopy) to differentiate IBD from irritable bowel syndrome (IBS). In these cases, for patients 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 select patients who could be safely observed to determine if symptoms worsen, rather than obtaining endoscopy immediately. Such a test would have clinical utility.

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

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population of interest is individuals with mild IBD symptoms that overlap with IBS symptoms. This would include those treated in the outpatient, nonemergency 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 diagnostic decisions about IBD in patients in the relevant population (prior to or concurrent with fecal calprotectin): inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]), complete blood count (CBC), and plain film imaging.

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

A potential harmful outcome with use of fecal calprotectin is a delayed diagnosis of 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 3 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 response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a 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 fecal calprotectin for diagnosing IBD in patients with suspected IBD or IBS.

Systematic Reviews
Menees et al (2015) 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 IBS. Reviewers included prospective cohort studies that used the enzyme-linked immunosorbent assay test for fecal calprotectin (not the point-of-care test) and used Manning or Rome criteria for IBS diagnosis. Sixty-seven studies were reviewed, 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. Reviewers 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 a 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.

Waugh et al (2013) published a systematic review as part of the U.K. Health Technology Assessment program. 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 and 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 included in the quantitative synthesis. Studies were pooled when there was a minimum of four using the same calprotectin cutoff. A pooled analysis of 5 studies using fecal calprotectin to differentiate between IBD and IBS in adults at a cutoff of 50 μg/g had a combined sensitivity of 93% (95% confidence interval [CI], 83% to 97%) and a combined specificity of 94% (95% CI, 73% to 99%). A pooled analysis of 6 studies using fecal calprotectin to differentiate between IBD and non-IBD in adults and children had a combined sensitivity of 99% (95% CI, 95% to 100%) and a combined specificity of 74% (95% CI, 59% to 86%). Reviewers concluded that calprotectin testing is a reliable method for differentiating between inflammatory and noninflammatory disease of the bowel. They also noted that most studies had been conducted in specialty settings. A limitation of the evidence, noted in the review, was that the optimal cutoff for calprotectin tests is not known; most studies used 50 μg/g and did not evaluate other cutoffs. Accordingly, reviewers recommended 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.

**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 (RCTs).

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, and systematic reviews of these studies have been published. In general, these studies have indicated that the commercially available test has very high sensitivity for IBD. Studies varied in the cutoff of fecal calprotectin used to indicate the presence of disease but most used a 50 µg/g cutoff.

Most studies were conducted in a specialty setting. There is relatively little data on the use of calprotectin in the general population and potential for spectrum effect. One 2017 retrospective review found that fecal calprotectin testing in primary care had low sensitivity and specificity and poor positive predictive value for diagnosing IBD. 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 Inflammatory Bowel Disease Clinical Context and Test Purpose**
For patients who are have been diagnosed with IBD, testing for fecal calprotectin could allow providers to monitor disease activity and guide therapeutic decision making.

The question addressed in this 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 health outcomes?

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

**Patients**
The relevant population of interest is individuals with Crohn disease (CD) or ulcerative colitis (UC) undergoing treatment.

**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 the relevant patient populations (prior to or concurrent with fecal calprotectin): inflammatory markers (CRP, ESR) and CBC.
Outcomes
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 CD remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe CD.6

Outcomes of interest are an improvement in symptoms and 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 systematic review by Mosli et al (2015) evaluated the diagnostic accuracy of fecal calprotectin in adults and children with previously diagnosed UC or CD who had active disease confirmed by endoscopy.7 Nineteen 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 area under the curve for fecal calprotectin was 0.89 (95% CI, 0.86 to 0.91).

Lin et al (2014) published a meta-analysis limited to studies of adults diagnosed with IBD.8 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. Reviewers selected the cutoff value from each study that had the highest diagnostic accuracy and used this estimate for the pooled analyses. The pooled sensitivity of fecal calprotectin for identifying active disease vs 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 274 μg/g in individual studies. At the manufacturer’s recommended cutoff of 50 μg/g, pooled sensitivity was 92%, and pooled specificity was 60%. At a cutoff of 100 μg/g, pooled sensitivity was 84%, and pooled specificity was 66%. The specific assay used might have contributed to variability in thresholds.9

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.

Two open-label RCTs have examined the use of fecal calprotectin testing for managing patients with IBD.

Colombe 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 end point 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 non-responder imputation. The trial met the primary end point, 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 2 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 1 year, there was no significant difference in relapse rates between the 2 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 Randomized Controlled Trial Characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Active</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombel et al</td>
<td>U.S., E.U.</td>
<td>74</td>
<td>2011-2016</td>
<td>Adults (n=244) with active CD and naïve to immunomodulators and biologics</td>
<td>Tight control including FC ≥250 μg/g and CRP &gt;5 mg/L</td>
<td>Clinical management</td>
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<td>(2018)</td>
<td></td>
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<tr>
<td>Lasson et al</td>
<td></td>
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<td></td>
<td>Adults (n=91) with UC on maintenance therapy with oral 5-ASA medication who had at least 1 flare-up during the previous year</td>
<td>Dose escalation to maximally tolerable dose based on FC ≥300 μg/g</td>
<td>Usual care</td>
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<tr>
<td>(2015)</td>
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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 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 2. Summary of Key Randomized Controlled Trial Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate of Relapse at 1 Year (Mayo Score of ≤2)</th>
<th>Mucosal Healing at 48 Weeks</th>
<th>Adverse Events</th>
<th>Steroid-Free Remission at 48 Weeks</th>
<th>Deep Remission</th>
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<tr>
<td>Colombel et al (2018)</td>
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<tr>
<td>Tight control</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
</tr>
<tr>
<td>Clinical monitoring</td>
<td>56/122 (46)</td>
<td>105 (86)</td>
<td>73 (59.8)</td>
<td>45 (36.9)</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>16.1 (3.9 to 28.3)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>p</td>
<td>0.010</td>
<td></td>
<td>0.001</td>
<td>0.014</td>
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</table>


| 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.

Section Summary: Monitoring Disease Activity in Patients with Diagnosed Inflammatory Bowel Disease

Studies using fecal calprotectin testing 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 activity 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. The contribution of fecal calprotectin to the tight control cannot be determined from this study design. Given the variability in cutoff values in diagnostic accuracy studies and the different results in the 2 RCTs (which also used different inclusion criteria, different cutoff values, and different biomarkers), further study is needed to establish the markers and cutoffs that are effective for treatment guidance in IBD. The ability to conduct tight monitoring outside of the investigational (i.e., research study) setting also needs to be confirmed.

Relapse Prediction in Patients with Diagnosed Inflammatory Bowel Disease

Clinical Context and Test Purpose
Calprotectin has been used to predict relapse in asymptomatic 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 is individuals with CD 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) and CBC.

Outcomes
Outcomes may be assessed in clinical practice and the research setting with standardized measures, such as the Crohn Disease Activity Index.

Outcomes of interest are an improvement in symptoms and 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 1 to 3 months. Five studies used an upward trend of fecal calprotectin between 2 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 prospective study by Yamamoto et al (2014) in Japan evaluated 80 UC patients who had been in remission for at least 3 months and were taking mesalamine as maintenance therapy. Fecal calprotectin levels were measured at the beginning of the study. At 12-month follow-up, 21 (26%) patients had relapsed. The mean calprotectin level was 172.7 μg/g in patients who relapsed and 135.5 μg/g in patients who remained in remission (p=0.02). Based on calprotectin levels in study patients, the authors selected 170 μg/g as a calprotectin cutoff to evaluate diagnostic accuracy. Using this cutoff, fecal calprotectin had a sensitivity of 76% and a specificity of 76% for predicting relapse.
Lasson et al (2013) in Sweden published findings of a prospective study of newly diagnosed UC patients. After an initial workup, patients were monitored over 3 years, with planned follow-up after 3 months and yearly after that. Relapse was defined as an increase in symptoms of sufficient severity to justify changing treatment. A total of 101 patients were eligible to participate. Twenty-eight patients were subsequently excluded due to a missing stool sample at 3 months, three did not meet diagnostic criteria for UC, and one was lost to follow-up. Thus, 69 (68%) patients were included in the 1-year analysis. During the first year, 24 (35%) patients did not experience a UC relapse. These patients had a significantly lower median fecal calprotectin levels at 3 months (102 μg/g) than patients with relapsing UC (263 μg/g). Sixty-seven patients were included in the 2- and 3-year analyses. The 3-month fecal calprotectin levels were significantly higher in patients with relapsing disease at 2 years than those with mild disease. There was no significant relation between fecal calprotectin levels and relapsing disease at 3 years. The authors found that the 3-month fecal calprotectin concentration of 169 μg/g yielded the greatest sensitivity and specificity in predicting relapse at 1 year (64.4% and 70.8% respectively). The optimal cutoff of fecal calprotectin for predicting relapsing disease at 2 years was 262 μg/g (sensitivity, 51.1%; specificity, 81.8%).

A study by Gisbert et al (2009) in Spain included 163 patients (89 with CD, 74 with UC) who had been in remission for at least 6 months. One sample of fecal calprotectin was obtained at baseline, and patients were followed for 12 months. Mean baseline fecal calprotectin level was 153 μg/g (range, 6-1217 μg/g); levels were not reported separately for UC and CD patients. During follow-up, 13 (18%) of 74 UC patients and 13 (15%) of 89 CD patients experienced a relapse severe enough to warrant a change in treatment. Mean calprotectin levels were significantly higher in patients who relapsed compared with those who did not. In CD patients, mean levels were 266 μg/g in relapsing patients and 145 μg/g in nonrelapsing patients (p=0.002). Corresponding values for UC patients were 213 μg/g and 126 μg/g, respectively (p=0.03). A cutoff of 150 μg/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 53 patients on infliximab using a cutoff of 160 μg/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 lower when fecal calprotectin testing is used to assess patients with suspected IBD and in studies that compare health outcomes in patients managed with and without the use of fecal calprotectin testing.

Section Summary: Relapse Prediction in Patients with Diagnosed Inflammatory Bowel Disease
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. The diagnostic accuracy for fecal calprotectin used to predict relapse in patients with UC is uncertain, as are the patient management changes associated with specific calprotectin levels.
Summary of Evidence
For individuals who have suspected 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 50 μg/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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have diagnosed IBD who receive fecal calprotectin testing for disease activity assessment or relapse prediction, the evidence includes prospective and retrospective diagnostic studies, meta-analyses, and a 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

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 2 responses. Input was mixed on whether fecal calprotectin testing is considered investigational for the diagnosis of intestinal conditions and whether 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 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
National Institute for Health and Care Excellence
In 2013 (one of the recommendations was updated in 2017), the National Institute for Health and Care Excellence published guidance on fecal calprotectin testing for inflammatory diseases of the bowel.17 The guidance made the following recommendations:

“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 ...”

- cancer is not suspected, having considered the risk factors (for example, age)....
“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....”

**American Gastroenterological Association Institute**
In 2014, the American Gastroenterological Association 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.

**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 January 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

**References**


### Documentation for Clinical Review

- No records required

### 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.

**IE**

The following services may be considered investigational.

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<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
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### Policy History

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

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 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.