Fecal Calprotectin Testing

Policy Number: 2.04.69  Last Review: 9/2017
Origination: 3/2008  Next Review: 9/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for fecal measurement of calprotectin. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Fecal calprotectin testing is considered investigational in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease.

Description of Procedure or Service

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Summary

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.

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 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. The evidence is insufficient to determine the effects of the technology on health outcomes.
Background

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic condition that encompasses 2 main forms: Crohn disease and ulcerative colitis, which 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 1 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 extraintestinal (eg, characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity levels, including life-threatening illness. Treatments include oral and rectal salicylates, glucocorticoids, immunomodulators (eg, methotrexate), and multiple biologic therapies (eg, infliximab), depending on disease severity, which are recommended by the American Gastroenterological Association and other organizations. Making a diagnosis of IBD is associated with well-defined management changes.

Diagnostic Methods

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 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 extradigestive 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 1 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...
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, 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 (eg, 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 (ie, 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.

**Regulatory Status**

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 U.S. Food and Drug Administration (FDA) through the 510(k) process. This test is indicated as an aid in the diagnosis of irritable bowel disease (IBD) and to differentiate IBD from irritable bowel syndrome, when used with other diagnostic testing and clinical considerations.

In January 2014, CalPrest® (Eurospital SpA, Trieste, Italy) was 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. The only differences are the name of the test on the labels, the number of calibrators in the kit and the dynamic range of the assay.” CalPrest®NG (Eurospital SpA) was cleared for marketing in November 2016.

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 (eg, Calprosmart, Calpro AS, Norway; Quantum Blue Calprotectin®, Bühmann Laboratories, Switzerland). Rapid tests have not been approved by the Food and Drug Administration for use in the United States.
Rationale

Literature Review
The evidence review was originally created in April 2011 has been updated regularly with a literature search of the MEDLINE database. The most recent literature review was performed through March 6, 2017. The key literature is summarized in the following section.

Assessment of a diagnostic technology typically focuses on 3 parameters: (1) technical performance; (2) diagnostic accuracy (sensitivity, specificity, and positive and negative predictive value) in appropriate populations of patients; and (3) clinical utility (a demonstration that the diagnostic information can be used to improve patient outcomes).

Technical performance of a device is typically assessed with 2 types of studies: those that compare test measurements with a criterion standard and those that compare results taken with the same device on different occasions (test-retest).

Diagnostic accuracy is evaluated by the ability of a test to accurately diagnose a clinical condition compared with the criterion standard. The sensitivity of a test is the ability to detect a disease when the condition is present (true positive), while specificity indicates the ability to detect patients who are suspected of disease but who do not have the condition (true negative). Evaluation of diagnostic performance, therefore, requires independent assessment by the 2 methods in a population of patients suspected of disease but who do not all have the disease.

Evidence related to improvement of clinical outcomes with use of this testing assesses the data linking use of a test to changes in health outcomes (clinical utility). While, in some cases, tests can be evaluated adequately using technical and diagnostic performance, when a test identifies a new or different group of patients with a disease, randomized trials are needed to demonstrate impact of the test on the net health outcome.

Inflammatory Bowel Disease

Technical Performance
The U.S. Food and Drug Administration’s (FDA) substantial equivalence determination decision summary for the PhiCal test includes data on technical performance. For example, data on test reproducibility were obtained with 2 samples representing the low and high ends of the reportable range of the test. Each sample was extracted 24 times and all extracts were tested. The coefficients of variation (CV) were 12.6% for the low-end sample and 12.1% for the high-end sample. In an analysis of interassay precision, 10 samples (5 positive, 5 negative) were each extracted 5 times from individual pools of stool. Each extract was assayed in 5 replicates on 5 separate runs on different days. The CV range was 5.8% to 20.1%. The findings indicated that the assay is reproducible within acceptable limits along the reportable range.
Diagnosis of inflammatory bowel disease

Clinical Context and Test Purpose
The purpose of testing for fecal calprotectin in patients who have suspected irritable bowel disease (IBD) is to inform a decision whether to pursue additional testing (ie, endoscopy) to differentiate IBD from irritable bowel syndrome (IBS). In these cases, 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 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 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. Most patients would be expected to be evaluated by a gastroenterologist, although an initial workup may be completed by a primary care provider.

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 test performance characteristics of the calprotectin test. Indirectly, we are interested in comparing symptom burden, quality of life, disease, and disease classification.

The primary potential harmful outcome with use of fecal calprotectin is delayed diagnosis of IBD due to initial misclassification as IBS.

Timing
The relevant time period for the impact of testing is years or decades.
Diagnostic Accuracy
A large body of research has assessed fecal calprotectin for diagnosing IBD in patients with suspected IBD or IBS.

Systematic Reviews
Most recently, 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 IBS.\(^3\) 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.

In 2013, Waugh et al in the U.K. published a meta-analysis as part of the national Health Technology Assessment program.\(^4\) 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 4 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, is 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.

In 2010, van Rheenen et al published a meta-analysis on studies conducted in adults and/or children.\(^5\) Reviewers only included studies meeting the following methodologic criteria: used prospective study design, included patients with suspected bowel disease, obtained stool samples before endoscopy, and evaluated all patients endoscopically with histologic verification of segmental biopsies.
Thirteen studies met eligibility criteria; 6 were conducted in adults and 7 in children and adolescents. IBD was confirmed by the reference test in 215 (32%) of 670 adults and in 226 (61%) of 371 children. Eleven studies used the PhiCal test; 7 (64%) of the 11 used a cutoff of 50 μg/g for a positive calprotectin test, and the remainder used cutoffs ranging from 24 to 100 μg/g. In the adult studies, the pooled sensitivity and specificity of the fecal calprotectin test for distinguishing between IBD and non-IBD were 93% (95% CI, 85% to 97%) and 96% (95% CI, 79% to 99%), respectively. For children and teenagers, the corresponding sensitivity and specificity rates were 92% (95% CI, 84% to 96%) and 76% (95% CI, 62% to 86%). Specificity was significantly lower in children and teenagers than in adults (p=0.048). Use of the fecal calprotectin test significantly changed the posttest probability of IBD in both age groups. In adults, an abnormal calprotectin test increased the probability of IBD from a pretest probability of 32% to a posttest probability of 91% (95% CI, 77% to 97%). Similarly, a normal calprotectin test reduced the probability from 32% to 3% (95% CI, 1% to 11%). In children and teenagers, an abnormal calprotectin test increased the probability of IBD from 61% to 86% (95% CI, 78% to 92%) and a normal calprotectin test reduced the probability from 61% to 15% (95% CI, 7% to 28%).

The reviewers calculated that, in a hypothetical population of 100 adults with suspected IBD (at a prevalence of 32%), fecal calprotectin testing would result in 30 true positives, 65 true negatives, 3 false positives, and 2 false negatives. If only patients with a positive test received endoscopy, 33 (33%) of 100 would receive endoscopy including 3 patients without disease. Two patients with disease would be missed. In a hypothetical population of 100 children with suspected IBD (at a prevalence of 61%), there would be 56 true positives, 30 true negatives, 9 false positives, and 5 false negatives. Nine of 100 without disease would get endoscopy and 5 patients with disease would be missed. In a lower prevalence population, the positive predictive value of fecal calprotectin testing would be lower; accordingly, reviewers did not recommend use of the test to screen asymptomatic patients or in a primary care setting. It is also worth noting that, when 95% confidence intervals were taken into account, the data were consistent with a posttest probability of having IBD with a negative fecal calprotectin test as high as 11% in adults and 28% in children. Reviewers commented that, due to the relatively small number of studies meeting their eligibility criteria, they were unable to examine different test cutoffs. Seven (54%) of 13 used the manufacturer’s recommended cutoff of 50 μg/g, but the remaining studies used cutoffs ranging from 24 to 100 μg/g. Reviewers also stated that, despite efforts to include patients most likely to be potential candidates for the test, none of the studies used a clear diagnostic algorithm to select patients at highest risk of IBD.

An earlier meta-analysis of studies on the diagnostic accuracy of fecal calprotectin testing in children and adults was published by von Roon et al in 2007. They selected studies that evaluated fecal calprotectin with histologic diagnosis of Crohn disease (CD), ulcerative colitis (UC), and/or colorectal cancer. An additional eligibility criterion was that studies have a control group of healthy people or people with IBS. Reviewers identified 30 studies (total N=5983 participants, 3393 of whom were healthy controls). Nine studies (n=1297 patients) provided data on
the ability of fecal calprotectin to distinguish between IBD and no IBD using a cutoff of 50 μg/g to indicate a positive test. The pooled sensitivity was 89% (95% CI, 86% to 91%) and the pooled specificity was 81% (95% CI, 78% to 84%). Stratifying by age group, a pooled analysis of 6 studies conducted in adults (n=1030 patients) using the 50 μg/g cutoff calculated a sensitivity of 71% (95% CI, 67% to 75%) and a specificity of 80% (95% CI, 77% to 83%). When findings from the 3 studies with children (n=201 children) were pooled, the sensitivity was 83% (95% CI, 73% to 90%) and the specificity was 85% (95% CI, 77% to 91%). Four studies (n=328 patients) provided data on differentiating between IBD and no IBD in adults and/or children using a calprotectin cutoff of 100 μg/g. The pooled sensitivity was 98% (95% CI, 93% to 99%) and the pooled specificity was 91% (95% CI, 86% to 95%). Reviewers noted that there might have been spectrum bias in the studies selected. That is, studies using fecal calprotectin to differentiate between IBD and non-IBD had differing proportions of patients with mild versus severe disease, and this could have affected the sensitivity and specificity of the test.

**Pediatric Studies**

Several systematic reviews focused on studies the pediatric populations. In 2014, Henderson et al assessed studies of pediatric patients undergoing an initial investigation for suspected IBD. Reviewers identified 8 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 50 μg/g and the other 2 used a cutoff of 100 μg/g. In their quality assessment, only 3 studies were judged to have a representative spectrum of patients and only 3 clearly reported using an acceptable reference standard (ie, upper and lower endoscopy in all patients). Findings from the 6 studies were pooled. 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 systematic review by Kostasis et al identified 37 studies conducted with children. Three studies were excluded because they did not report sufficient information on fecal calprotectin levels, leaving 34 studies for 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 the specificity ranged from 58.3% to 100%. When the analysis was limited to patients with newly diagnosed and untreated IBD (ie, similar to the population included in the Henderson meta-analysis), the sensitivity of fecal calprotectin ranged from 73.5% to 100% and the specificity ranged from 65.9% to 100%.

**Individual Diagnostic Test Studies**

Since publication of the systematic reviews (described above), additional diagnostic accuracy studies have been published. In 2015, Kennedy et al in the U.K. retrospectively evaluated the diagnostic accuracy of fecal calprotectin for diagnosing IBD by examining medical records at 2 teaching hospitals in Scotland. The study included patients ages 16 to 60 years who were presenting for the first time with gastrointestinal (GI) symptoms and had undergone fecal calprotectin testing prior to diagnosis. Medical records were reviewed to identify diagnostic
information using measures such as Lennard-Jones criteria for diagnosing IBD and Rome III criteria to classify IBS patients. If no diagnosis was recorded in the medical record, 2 gastroenterologists blinded to the fecal calprotectin test results reviewed clinical notes. Patients with an organic diagnosis or who had a full colonoscopy (n=467) were censored at the time of medical record review. A total of 895 patients were included in the final analysis. Of these, 566 (63.2%) were diagnosed with a functional disorder, 91 (10.2%) were diagnosed with IBD, and the remaining patients had other GI conditions or did not have a final diagnosis. Fecal calprotectin levels were significantly higher in patients diagnosed with IBD (median, 1251 μg/g) than those with a functional diagnosis (median, 20 μg/g) or other GI condition (median, 50 μg/g). According to receiver operator characteristic (ROC) analysis, the area under the curve (AUC) was 0.97 for distinguishing between IBD and functional disease. Using the manufacturer’s recommended cutoff of 50 μg/g, the sensitivity and specificity of fecal calprotectin for identifying IBD versus functional disorder were 97% (95% CI, 90% to 99%) and 74% (95% CI, 70% to 77%), respectively. At a cutoff of 70 μg/g, sensitivity remained at 97% (95% CI, 90% to 99%) and the specificity increased to 80% (95% CI, 76% to 83%).

Data from earlier studies by Manz et al (2012), Otten et al (2008), and Sidler et al (2008), which evaluated fecal calprotectin as a diagnostic test in samples of 575, 144, and 61 patients, respectively, have been since included in the Waugh technology assessment.

Section Summary: Diagnostic Accuracy for Diagnosis of 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, 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. 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.

Clinical Utility

Direct Evidence
Direct evidence of clinical utility is provided by studies comparing health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials (RCTs). No clinical trials evaluating the use of calprotectin for diagnosis of IBD were identified.
**Chain of Evidence**
Indirect evidence for clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

**Response to Treatment and Disease activity assessment**

**Clinical Context and Test Purpose**
Testing for fecal calprotectin in patients with diagnosed IBD may have several purposes. For patients who are undergoing treatment, it could allow providers to determine the adequacy of their disease control to make decisions about their medication dose or therapy selection; for those off therapy, it could allow for the assessment of the disease activity to make determinations about starting treatment.

The questions addressed in this section are: Does the addition of fecal calprotectin to clinical assessment (based on standard scores and/or history and physical) and typical laboratory tests (eg, CBC, ESR, CRP) in individuals with diagnosed IBD who are undergoing treatment improve outcomes? And does the addition of fecal calprotectin to clinical assessment (based on standard scores and/or history and physical) and typical laboratory tests (eg, CBC, ESR, CRP) in individuals with diagnosed IBD who are considering treatment improve outcomes?

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

**Patients**
The relevant population of interest is individuals with CD or UC undergoing or considering 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 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 (CDAI), 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.13

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

**Timing**
The relevant time period for the impact of testing is weeks to months.
**Diagnostic Accuracy**

Two recent 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.\(^{14}\) 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 AUC for fecal calprotectin was 89% (95% CI, 86% to 91%). In 2014, Lin et al (2014) published a meta-analysis limited to studies of adults diagnosed with IBD.\(^{15}\) 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. 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 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%.

Several studies have evaluated the accuracy of calprotectin and other fecal markers for predicting treatment outcomes in patients with bowel disease. For example, a 2010 prospective multicenter study by Turner et al examined the ability of 4 fecal markers to predict steroid refractoriness in 101 children with severe UC.\(^{16}\) The markers were fecal calprotectin, lactoferrin, M2-pyruvate kinase (M2-PK), and S100A12. Stool samples were obtained from children when they were admitted to the hospital for intravenous steroid treatment. Twenty-six (26%) patients failed steroid treatment within a median of 10 days. Levels of all fecal markers were elevated at baseline. The mean value of fecal calprotectin at sampling for patients who later responded to treatment was 3307 μg/g and for those who failed treatment it was 7516 μg/g; this difference was statistically significant (p=0.039). The ability of the fecal markers to predict treatment response was assessed using ROC analysis. An ROC curve of greater than 0.7 was considered fair, 0.8, good, and greater than 0.9, excellent at discriminating between steroid responders and nonresponders. ROC values for the markers were 0.64 for calprotectin, 0.51 for lactoferrin, 0.75 for M2-PK, and 0.39 for S100A12; only M2-PK was considered to be at least a “fair” marker. In addition, the Pediatric Ulcerative Colitis Activity Index, a clinical scoring system, had an AUC of 0.81.

A 2012 study by Molander et al in Finland included 60 patients with IBD (34 had CD, 26 had UC).\(^{17}\) The study evaluated whether a normal fecal calprotectin level after induction therapy predicted response to maintenance therapy 1 year later. Patients, all of whom had elevated fecal calprotectin levels at baseline (mean, 810 μg/g). After 8 weeks of treatment, 31 (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 1 year; the other 12 stopped due to lack of response. At the 1-year follow-up, 26 (84%) of the 31 patients with normal fecal calprotectin after induction were in clinical remission compared with 11 (38%) of 29 of those with an elevated fecal calprotectin level after induction ($p < 0.001$). Using ROC analysis, a fecal calprotectin level of 139 $\mu$g/g after induction therapy was selected as the best cutoff to predict risk of having clinically active disease at 1 year. This cutoff had a sensitivity of 72%, a specificity of 80%, and an AUC of 0.84.

A 2008 study by Wagner et al in Sweden included 40 patients with relapsed IBD. Two patients were excluded, leaving 27 with UC and 11 with CD. All patients were evaluated clinically before and after treatment (4 and 8 weeks), and patients with UC also underwent endoscopy. Treatment of relapse was individualized; most patients received topical and/or systemic 5-aminosalicylic acid (5-ASA). Samples were tested for fecal calprotectin levels (>50 $\mu$g/g was considered positive), as well as for fecal myeloperoxidase (MPO) and fecal eosinophil protein X (EPX). Mean fecal calprotectin levels in UC patients were 5600 $\mu$g/g at baseline, 1730 $\mu$g/g at 4 weeks, and 1820 $\mu$g/g at 8 weeks. Mean levels in CD patients were 5010 $\mu$g/g at baseline, 2440 $\mu$g/g at 4 weeks, and 1460 $\mu$g/g at 8 weeks. In UC patients, a complete response was defined as return of clinical and endoscopic scores to normal. Fourteen (52%) of 27 UC patients experienced a CR after 4 weeks and 21 (78%) of 27 after 8 weeks. There was a statistically significant decline in fecal calprotectin levels in complete responders ($p < 0.01$) with UC, but this trend was not observed in partial or nonresponders. In the CD group, 9 (81%) of 11 had a complete response after 4 weeks and 10 (91%) of 11 after 8 weeks. The change in fecal calprotectin levels in complete responders was not statistically significant. Normalized fecal calprotectin levels at the end of the study predicted a complete response in 100% of patients. However, elevated fecal calprotectin levels were inconclusive. These elevated levels were unlikely to indicate an imminent relapse. Patients with continued high levels of fecal calprotectin were followed retrospectively, and none was found to have had a relapse within 3 months of conclusion of the study. There was a strong correlation in fecal calprotectin values at all time periods and values of MPO and EPX.

**Section Summary: Diagnostic Accuracy of Response to Treatment and Disease Activity Assessment**

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.

**Clinical Utility**

**Direct Evidence**

No studies evaluating clinical utility of fecal calprotectin testing for diagnosis of IBD, the FDA-cleared indication, were identified. However, 1 RCT has examined use of fecal calprotectin testing for managing patients with UC at high risk of
relapse. This prospective nonblinded study, published by Lasson et al (2015), included adults with UC on maintenance therapy with oral 5-ASA medication who had at least 1 flare-up during the previous year. Patients were randomized in a 3:2 ratio to medication dosing decisions based on fecal calprotectin levels or to usual care (control). 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-ASA dose to the maximally tolerable dose. The high dose of 5-ASA was continued for 3 months and then reduced when the fecal calprotectin levels fell below 200 μg/g. The primary outcome was the rate of relapse at 18 months, with relapse defined as a Mayo Score for UC of 2 or less, with no single variable greater than 1. At 1 year, 18 (35.3%) of 51 patients in the intervention group and 20 (50%) of 40 in the control group had experienced at least 1 relapse. The difference between groups was not statistically significant (p=0.23). Trialists noted that 10 of the 18 patients in the intervention group had had a relapse but did not have a fecal calprotectin level above the cutoff for medication dosage escalation and, 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%).

Chain of Evidence
It is not possible to construct an indirect chain of evidence for clinical utility due to the lack of diagnostic accuracy.

Section Summary: Clinical Utility
A single RCT has evaluated the relapse rate in patients with UC whose medication doses were managed with and without fecal calprotectin test results and, in its primary analysis, found no significant difference in relapse rates at 18 months. There is uncertainty about the diagnostic accuracy of fecal calprotectin treatment assessment or for disease activity assessment, so a strong chain evidence cannot be developed.

Predicting Relapse

Clinical Context and Test Purpose
Calprotectin has been used to predict relapse of individuals with IBD. The clinical utility in this setting is uncertain. Were a preventive therapy shown to be effective, a marker to predict relapse could have clinical utility.

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 typical laboratory tests (eg, 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 in the research setting with standardized measures, such as the CDAI.

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

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

Diagnostic Accuracy

Systematic Reviews
In 2012, Mao et al published a meta-analysis of studies evaluating fecal calprotectin in predicting relapse of IBD. The meta-analysis included prospective studies of adults that measured fecal calprotectin at relapse, estimates of diagnostic accuracy (eg, sensitivity, specificity), and, based their definition of relapse, clinical activity indices or endoscopic findings. Reviewers identified 6 studies (total N=672 patients) were included in the meta-analysis. Five included patients with both CD and UC and the sixth study included only patients with CD. In all studies, fecal calprotectin was measured when patients were in clinical remission and used to predict relapse 1 year later. The pooled sensitivity and specificity of fecal calprotectin to predict relapse of IBD was 78% (95% CI, 72% to 83%) and 73% (95% CI, 68% to 77%), respectively. The pooled area under the ROC curve was 0.83. Reviewers found that diagnostic test performance was not as high as expected, but that fecal calprotectin assessment was a simple and noninvasive test. They also noted that determination of remission was based on subjective (not objective) clinical activity indices.

Prospective Trials
Representative trials are described next. A 2014 prospective study by Yamamoto et al 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.
In 2013, Lasson et al 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 thereafter. 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 samples at 3 months, 3 did not meet diagnostic criteria for UC, and 1 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 a 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 2009 study by Gisbert et al 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.

**Section Summary: Diagnostic Accuracy for Predicting Relapse**

A 2012 meta-analysis of 6 prospective studies found a pooled sensitivity of 78% and a pooled specificity of 73% for the fecal calprotectin test in predicting relapse in IBD patients in remission. Cutoff values of fecal calprotectin varied across studies, and studies tended to base definitions of remission on subjective clinical remission indices, rather than endoscopic findings.
Clinical Utility
Clinical utility for all potential uses of the test is best evaluated by prospective controlled studies, ideally RCTs, assessing the impact of the test on patient management decisions and/or health outcomes. For example, 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 use of fecal calprotectin testing.

Section Summary: Predicting Relapse
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 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 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 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. 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, input was received through 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. One specialty society submitted 2 responses. Input was mixed on whether fecal calprotectin testing is considered investigational for the diagnosis of intestinal conditions and whether 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, the National Institute for Health and Care Excellence published guidance on fecal calprotectin testing for inflammatory diseases of the bowel. 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."

"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 2013, the American Gastroenterological Association Institute published guidelines on the use of thiopurines, methotrexate, and anti-tumor necrosis factor inhibitors for induction and maintenance of remission in Crohn disease. The guidelines do not mention the use of fecal calprotectin.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.
Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in March 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

References
5. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ. 2010;341:c3369. PMID 20634346


Billing Coding/Physician Documentation Information

83993 Calprotectin, fecal

ICD-10 Codes

K51-90 Ulcerative colitis, unspecified, without complications
K52.3 Indeterminate colitis
R19.8 Other specified symptoms and signs involving the digestive system and abdomen

Policy Implementation/Update Information

3/1/08 New policy; considered investigational.
9/1/08 No policy statement changes.
3/1/09 No policy statement changes.
9/1/09 No policy statement changes.
3/1/10 No policy statement changes.
9/1/10 No policy statement changes.
9/1/11 No policy statement changes.
9/1/12 No policy statement changes.
1/1/13 Policy title and number revised, previously was 2.04.502 Fecal Measurement of Calprotectin. Remains investigational.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.