Fecal Calprotectin Testing

Policy Number: 2.04.69   **Last Review:** 9/2014
Origination: 3/2008   **Next Review:** 9/2015

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

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

Background

Inflammatory bowel disease (IBD) is a chronic inflammatory condition typically associated with the symptoms diarrhea, defecation urgency, and sometimes rectal bleeding and abdominal pain.

There are two main forms of the disorder, Crohn's disease (CD) and ulcerative colitis (UC). Noninvasive diagnosis of inflammatory intestinal disease is difficult because the clinical manifestation of intestinal disorders and colon cancer are relatively non-specific. For example, a patient presenting with diarrhea or abdominal pain has a wide range of diagnostic possibilities. Endoscopy with histology is the gold standard method for diagnosing bowel inflammation. Limitations of this approach are that it is invasive, with an associated risk of adverse events, and not well-tolerated by some patients.

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

Fecal calprotectin is one protein that could possibly be used as a marker of inflammation.

It is a calcium- and zinc-binding protein that accounts for 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, a potential advantage of fecal calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to 1 week–leaving enough time for patients to collect samples at home and send them to a distant laboratory for testing. In contrast, lactoferrin, another potential fecal marker of intestinal inflammation, is stable at room temperature for only about 2 days.

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

Fecal calprotectin testing has been used to differentiate between organic and functional intestinal disease. Some authors consider fecal calprotectin to be a marker of neutrophilic intestinal inflammation rather than a marker of organic disease and believe the appropriate use of the marker is in its use to distinguish between inflammatory bowel disease and non-inflammatory bowel disease. In practice, the test might be suitable for selecting patients with IBD symptoms for endoscopy, i.e. deciding which patients do not require endoscopy. Fecal calprotectin testing has also been proposed to evaluate the response to IBD treatment and for predicting relapse. If found to be sufficiently accurate, results of calprotectin testing could potentially be used to change treatment, such as adjusting medication levels.

There is a commercially available enzyme-linked immunosorbent assay (ELISA) test measuring fecal calprotectin levels, the PhiCal™ (Genova Diagnostics). Recent literature from Europe has also discussed a rapid test for fecal calprotectin that could be used in the home; rapid tests have not been FDA-approved for use in the United States.

Regulatory Status
In March 2006, the PhiCal™ (Genova Diagnostics) quantitative ELISA 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 to aid in the diagnosis of inflammatory bowel disease (IBD) and to differentiate IBD from irritable bowel syndrome (IBS); it is intended to be used in conjunction with other diagnostic testing and clinical considerations.

Rationale

Literature Review

The policy was created with a literature search using MEDLINE through February 2011 and updated regularly with a literature review. The most recent literature review was performed through February 28, 2014. The key literature is summarized next.

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

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 performance is evaluated by the ability of a test to accurately diagnose a clinical condition in comparison 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 who are 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.

Technical performance

The FDA substantial equivalence determination decision summary for the PhiCal test includes data on technical performance.(1) 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 and 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 indicate that the assay is reproducible within acceptable limits along the reportable range.

Diagnostic performance

Diagnosis of IBD

Several systematic reviews evaluating the accuracy of fecal calprotectin testing for diagnosing IBD have been published. In 2013, Waugh et al in the U.K. published a meta-analysis as part of the national Health Technology Assessment program.(2) The investigators searched for studies using fecal calprotectin tests to evaluate inflammation of the lower intestine in newly presenting patients compared with a reference standard, preferably histology. Both studies on laboratory-based or point-of-care were included and those using fecal calprotectin tests to monitor disease progression or response to treatment were excluded. The authors assessed 83 full-text articles for eligibility and 28 were deemed eligible and were included in the quantitative synthesis. Studies were pooled when there were a minimum of 4 using the same calprotectin cutoff. A pooled analysis of 5 studies using fecal calprotectin to differentiate between IBD and irritable bowel syndrome (IBS) in adults at a cutoff of 50 µg/g had a combined sensitivity of 0.93 (95% confidence interval [CI], 0.83 to 0.97) and a combined specificity of 0.94 (95% CI, 0.73 to 0.99). A pooled analysis of 6 studies using fecal calprotectin to differentiate between IBD and non-IBD in adults and children had a combined sensitivity of 0.99 (95% CI, 0.95 to 1.00) and a combined specificity of 0.74 (95% CI, 0.59 to 0.86). The authors concluded that calprotectin testing is a reliable method for differentiating between inflammatory and noninflammatory disease of the bowel. They noted that most studies have been done in specialty settings. A limitation of the evidence, noted in the review, is that the optimal cutoff for calprotectin tests is not known; most studies used the cutoff of 50 µg/g and did not evaluate other potential cutoffs. Accordingly, the authors recommend using the 50 µg/g cutoff and reevaluating this cutoff as additional evidence accumulates.

In 2010, van Rheenen et al published a meta-analysis on studies conducted in adults and/or children.(3) The authors only included studies that met 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 histological 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 of 670 (32%) of adults and 226 of 371 (61%) of the children. Eleven studies used the PhiCal test; 7 of the 11 (64%) 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 was 93% (95% CI, 85% to 97%) and 96% (95% CI, 79% to 99%), respectively. For children and teenagers, the corresponding numbers were a sensitivity of 92% (95% CI, 84% to 96%)

and specificity of 76% (95% CI, 62% to 86%). Specificity was significantly lower in children and teenagers than in adults (p=0.048). The 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 investigators calculated that, in a hypothetical population of 100 adults with suspected IBD (and 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 of 100 (33%) 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 (and 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, the authors did not recommend use of the test to screen asymptomatic patients or use of the test in a primary care setting. It is also worth noting that, when 95% CIs 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. The authors commented that, due to the relatively small number of studies meeting their eligibility criteria, they were not able to examine different test cutoffs. Seven of 13 (54%) used the manufacturer's recommended cutoff of 50 µg/g, but the remaining studies used cutoffs ranging from 24 µg/g to 100 µg/g. The authors also stated that, despite their 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 Van Roon et al in 2007.(4) The authors included studies that evaluated fecal calprotectin with histological diagnosis of Crohn disease (CD), ulcerative colitis (UC), or/and colorectal cancer. An addition to eligibility criteria was that studies include a control group either of healthy individuals or individuals with IBS. The authors identified 30 studies with a total of 5983 participants (3393 of whom were healthy controls). Nine studies (n=1297) provided data on the ability of fecal calprotectin to distinguish between IBD versus 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) using the 50 µg/g cutoff calculated a sensitivity of 71% (95% CI, 67% to 75%) and specificity of 80% (95% CI, 77% to 83%). When findings from the 3 studies with children (n=201) were pooled, the sensitivity was 83% (95% CI, 73% to 90%) and specificity was 85% (95% CI, 77% to 91%). Four studies (n=328) 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%). The authors noted that there may have been spectrum bias in the studies included in the review. 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 affect the sensitivity and specificity of the test.

Several systematic reviews were limited to studies in the pediatric population. In 2013, Henderson et al focused on studies of pediatric patients undergoing an initial investigation for suspected IBD.(5) The authors 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 studies clearly reported that they used an acceptable reference standard (ie, upper and lower endoscopy in all patients). Findings from the 6 studies were pooled. The pooled sensitivity and specificity of fecal calprotectin in identifying patients with IBD were 97.8% (95% CI, 94.7% to 99.6%) and 68.2% (50.2% to 86.3%), respectively. A 2012 meta-analysis by

Kostasis et al identified a total of 37 studies conducted with children.(6) Three studies were excluded because they did not report sufficient information about fecal calprotectin levels, which left 34 studies in the review. Studies were included in the review regardless of sample size or methodologic characteristics. Study findings were not pooled due to heterogeneity. The sensitivity of studies using fecal calprotectin to identify children with IBD ranged from 12.5% to 100% and specificity ranged from 58.3% to 100%. When the analysis was limited to patients with newly diagnosed and untreated IBD (ie, similar to the population included in the Henderson et al meta-analysis), the sensitivity of fecal calprotectin ranged from 73.5% to 100% and the specificity ranged from 65.9% to 100%. Representative diagnostic test studies using the fecal calprotectin test are described next:

A 2012 study from Switzerland by Manz et al included 575 consecutive adult patients with abdominal discomfort from a single center who were referred for endoscopy.(7) A fecal sample was collected within 24 hours of undergoing colonoscopy or sigmoidoscopy. Fecal calprotectin was measured using a commercially available ELISA test by staff blinded to the endoscopic findings. The gastroenterologists who conducted endoscopies were blinded to fecal calprotectin test results. A total of 538 of 575 (94%) patients were included in the analysis; 37 patients were excluded because they did not complete the study protocol. Endoscopies yielded clinically significant findings in 212 of 538 (39%) of patients. Median calprotectin levels were higher in patients with clinically significant findings (97 µg/g) than in patients with normal endoscopic findings (10 µg/g; p<0.001). Using a cutoff of 50 µg/g, the fecal calprotectin test had a sensitivity of 73% and specificity of 93% for identifying clinically significant disease. Receiver operator curve (ROC) analysis yielded an area under the curve (AUC) of 0.88 (95% CI, 0.85 to 0.90).

Otten et al in the Netherlands published a study in 2008 evaluating the ability of fecal calprotectin and lactoferrin to discriminate between IBD and IBS.(8) The study included 144 adult patients who were referred for colonoscopy or sigmoidoscopy due to lower gastrointestinal (GI) abdominal complaints. A fecal sample was obtained before endoscopy. Endoscopy data were not available for 5 patients; 114 of the remaining 139 (82%) were diagnosed with either IBD (n=23) or IBS (n=91) and were included in the analysis. At a cutoff of 50 mg/kg, the PhiCal ELISA calprotectin test had a sensitivity of 95.7% (95% CI, 76.0% to 99.8%) and a specificity of 86.8% (95% CI, 77.7% to 92.7%) for distinguishing between IBD and IBS in the 114 patients. In contrast, an ELISA test measuring lactoferrin (cutoff, 7.25 mg/mL) had a sensitivity of 78.3% (95% CI, 55.8% to 91.7%) and specificity of 90.1% (95% CI, 81.6% to 95.1%).

In 2007, Schroder et al in Germany published a study with 76 adults who had a history of chronic diarrhea lasting at least 4 weeks with no overt GI bleeding.(9) Patients underwent a complete workup, including having a stool sample assayed for fecal neutrophil-derived proteins and undergoing colonoscopy. Gastroenterologists who performed colonoscopies were unaware of the results of stool testing. Mean fecal calprotectin levels were 143 µg/g in the patients diagnosed by endoscopy with CD (n=25), 137 µg/g in the patients diagnosed with UC (n=20), and 6 in the patients diagnosed with IBD (n=31). Levels of calprotectin were significantly elevated in patients with either form of IBD compared with the IBS group (all p<0.001). At a cutoff of 15 µg/g, the sensitivity of calprotectin for differentiating between IBD and IBS was 93% with a specificity of 100%. Using ROC analysis, the maximal sum of sensitivity and specificity of fecal calprotectin for differentiating between IBD and IBS was at a cutoff of 24 µg/g; this resulted in an AUC of 0.99 (95% CI, 0.94 to 1.00).

In 2008, Sidler et al published a study conducted in Australia that included 61 children aged 2 to 18 years referred for endoscopy for GI tract symptoms suggestive of organic disease.(10) Children with an established diagnosis of an organic GI tract disease were excluded. Stool samples were collected before endoscopy. Thirty-one children (51%) were diagnosed with IBD, and 30 were diagnosed with a non-IBD condition. At a cutoff of 50 mg/kg, fecal calprotectin had a sensitivity of 100% and a specificity of 67% for differentiating between IBD and non-IBD conditions. At a cutoff of 200 mg/kg, fecal calprotectin had a sensitivity of 90% and a specificity of 97%.

Ashorn et al in Finland published a study in 2009 that included 73 children and adolescents who underwent endoscopy because of clinical suspicion of IBD.(11) IBD was diagnosed in 60 patients

(82%), and 13 patients had a non-IBD disease. Data on calprotectin level was available for 55 patients (92%). Using a cutoff of 100 µg/g, the sensitivity of the calprotectin test was 89% (95% CI, 82% to 100%) and the specificity was 90% (95% CI, 90% to 91%) for distinguishing IBD from non-IBD conditions.

Section summary

A number of well-conducted studies have been published that evaluate the accuracy of fecal calprotectin levels for diagnosing IBD. Additionally, several systematic reviews of these studies have been published. In general, the studies indicate that the commercially available test is reasonably accurate for use in patients with clinical suspicion of disease. Studies varied in the cutoff of fecal calprotectin that was used to indicate the presence of disease. As reported in systematic reviews, the greatest amount of evidence exists for the cutoff of 50 µg/g; however, an optimal cutoff for diagnosing IBD is not yet clear from the available studies. Moreover, most studies have been conducted in specialty care; there is less evidence on the diagnostic accuracy of fecal calprotectin tests in the primary care setting.

Evaluating response to treatment

Several studies have evaluated the accuracy of calprotectin and other fecal markers for predicting treatment outcome 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.(12) 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 patients (26%) subsequently 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 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. A ROC of greater than 0.7 was considered fair, 0.8, good, and greater than 0.9, excellent at discriminating between steroid responders and nonresponders. The 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, a clinical scoring system known as the Pediatric Ulcerative Colitis Activity Index (PUCAI) 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).(13) The aim of the study was to evaluate whether a normal fecal calprotectin level after induction therapy predicted the response to maintenance therapy 1 year later. Patients, all of whom had an elevated fecal calprotectin level at baseline (mean, 810 µg/g), were initially treated with tumor necrosis factor alpha antagonists. 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 of the 31 (84%) patients with normal fecal calprotectin after induction were in clinical remission compared with 11 of 29 (38%) of those with an elevated fecal calprotectin level after induction (p<0.001). Using ROC analysis, a fecal calprotectin level of 139 µg/g after induction therapy was selected as the best cutoff to use to predict risk of having clinically active disease at 1 year. Using this cutoff, there was a sensitivity of 72%, a specificity of 80% and AUC was 0.84.

A 2008 study by Wagner et al in Sweden included 40 patients with IBD who had symptoms of relapse.(14) 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. Fecal samples were obtained at baseline and at 4 and 8 weeks after starting treatment for their recurrence. Samples were tested for fecal calprotectin levels (>50 µg/g was considered to be positive), as well as for fecal myeloperoxidase (MPO) and fecal eosinophil protein X

(EPX). Mean fecal calprotectin levels in UC patients were 5600 μg/g at baseline, 1730 μg/g at 4 weeks, and 1820 μg/g at 8 weeks. Mean levels in CD patients were 5010 μg/g at baseline, 2440 μg/g at 4 weeks, and 1460 μg/g at 8 weeks. In UC patients, a complete response (CR) was defined as return of clinical and endoscopic scores to normal. Fourteen of 27 (52%) of UC patients experienced a CR after 4 weeks, and 21 of 27 (78%) had a CR after 8 weeks. There was a statistically significant decline in fecal calprotectin levels in complete responders (p<0.01) with UC, and this was not observed in partial or nonresponders. In the CD group, 9 of 11 (81%) had a CR after 4 weeks and 10 of 11 (91%) 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 CR in 100% of patients. However, elevated fecal calprotectin levels were inconclusive. Elevated fecal calprotectin levels were found in 10 of 21 patients with UC and 6 of 9 patients with CD who responded to treatment by the end of the study. These elevated levels were not likely to indicate an imminent relapse. Patients with continued high levels of fecal calprotectin were followed retrospectively, and none were found to have had a relapse within 3 months of the 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

The available data on using fecal calprotectin testing to predict response to treatment are preliminary investigations. Potential cutoff values derived from study data would need to be verified using other samples of patients. Cutoffs varied among studies. In addition, a common limitation of the studies predicting response to treatment are that none of them provided data on how treatment decisions and/or health outcomes would differ with and without use of the test.

Predicting relapse

In 2012, Mao et al published a meta-analysis of studies evaluating fecal calprotectin in predicting relapse of IBD.(15) Their systematic review included prospective studies of adult patients that measured fecal calprotectin at relapse, included estimates of diagnostic accuracy (eg, sensitivity and specificity), and based their definition of relapse on clinical activity indices or endoscopic findings. The authors identified 11 studies; on closer examination, 4 of these were found to not meet their inclusion criteria. Thus, a total of 6 studies with 672 patients were included in the meta-analysis. Five of these 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 was 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. The authors concluded that the diagnostic test performance was not as high as expected but that advantages of fecal calprotectin assessment are that it is a simple and noninvasive test. They noted that a limitation of the studies was that remission was based on subjective clinical activity indices and that additional prospective studies using endoscopic relapse are needed.

Representative trials included in the Mao 2012 meta-analysis or published more recently are described next.

A 2013 prospective study by Yamamoto et al in Japan studied 80 UC patients who had been in remission for at least 3 months and were taking mesalamine as maintenance therapy.(16) Fecal calprotectin levels were measured at the beginning of the study. After 12 months of follow-up, 21 (26%) patients had relapsed. The mean calprotectin level was 172.7 μg/g in patients who relapsed and 135.5 μg/g in patients who remained in remission (p=0.02). Based on levels in the study's patients, the authors selected 170 μg/g as a cutoff for calprotectin in their evaluation of diagnostic accuracy. Using this cutoff, fecal calprotectin had a sensitivity of 76% and a specificity of 76% for predicting relapse. In 2013, Lasson et al in Sweden published findings of a prospective study with newly diagnosed UC patients.(17) After an initial workup, patients were monitored over 3 years, with planned follow-up after 3 months and yearly thereafter. Fecal calprotectin was monitored at each visit. Relapse was defined as an increase in symptoms of sufficient severity to justify changing treatment. A total of 101 patients were

eligible to participate in the study. Twenty-eight patients were subsequently excluded due to a missing stool sample at 3 months, 3 did not meet diagnostic criteria for UC and 1 was lost to follow-up. Thus, 69 patients (68%) were included in the 1-year analysis. During the first year, 24 patients (35%) did not experience a relapse of UC. These patients had a significantly lower median level of fecal calprotectin at 3 months (102 µg/g) compared with 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 compared with those with mild disease. There was not a significant relationship between fecal calprotectin 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 to predict 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 CD, 74 UC) who had been in remission for at least 6 months.(18) One sample of fecal calprotectin was obtained at baseline, and patients were followed for 12 months. The mean baseline level of fecal calprotectin was 153 µg/g (range, 6-1217 µg/g); levels were not reported for UC versus CD patients. During the follow-up period, 13 of 74 (18%) UC patients and 13 of 89 (15%) CD patients experienced a relapse severe enough to warrant a change in treatment. Mean levels of calprotectin were significantly higher in patients who relapsed compared with those who did not relapse. In CD patients, mean levels were 266 µg/g in relapsing patients and 145 µg/g in nonrelapsing patients (p=0.002). Corresponding values in UC patients were 213 µg/g and 126 µg/g, respectively (p=0.03). A cutoff of 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.

Section summary

A 2012 meta-analysis of 6 prospective studies found a pooled sensitivity of 78% and a pooled specificity of 73% of the fecal calprotectin test in predicting relapse in IBD patients in remission. Cutoff values of fecal calprotectin have varied in the studies, and studies tended to base their definitions of remission on subjective clinical remission indices, rather than endoscopic data. In addition, like the studies on predicting response to treatment, the impact of fecal calprotectin testing on health outcomes in UC and CD patients in remission has not been evaluated in controlled studies.

Clinical utility

Clinical utility for all potential uses of the test is best evaluated by prospective controlled studies, ideally RCTs, evaluating 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 decreased when fecal calprotectin testing is used to evaluate patients with suspected IBD and also in studies that compare health outcomes in patients managed with and without use of fecal calprotectin testing. No studies evaluating clinical utility of fecal calprotectin testing were identified.

Summary

Numerous studies have evaluated the ability of fecal calprotectin testing to distinguish between patients with inflammatory bowel disease (IBD) and non-IBD, the Food and Drug Administration–approved indication for the fecal calprotectin test. Generally, studies have shown that the fecal calprotectin test is reasonably accurate for this purpose when used in an appropriate patient population, ie, patients with clinical suspicion of IBD based on examination and history. Studies have also examined the association between fecal calprotectin levels and the response to treatment or risk of relapse in patients known to have IBD. However, studies have used various cutoffs to indicate an abnormally high fecal calprotectin level for diagnosing or monitoring patients. Although the greatest amount of evidence exists for the cutoff of 50 µg/g, the optimal cutoff remains unknown. Moreover most diagnostic accuracy studies have been conducted in the specialty care setting, and there is insufficient evidence of accuracy in primary

care where disease level is likely lower. Furthermore, no prospective trials were identified that evaluated the clinical utility of the test; namely, the ability of test findings to improve patient management and/or health outcomes for any of its potential applications. Thus, fecal calprotectin testing is considered investigational in the diagnosis and management of intestinal conditions.

Practice Guidelines and Position Statements

In 2013, the National Institute for Health and Care Excellence published guidance on fecal calprotectin testing for inflammatory diseases of the bowel.(19) The guidance had the following recommendations:

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

Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment.

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.

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Billing Coding/Physician Documentation Information

83993   Calprotectin, fecal

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.
9/1/13	No policy statement changes.
9/1/14	No policy statement changes.