Policy Statement

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

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

Policy Guidelines

A fecal calprotectin level of less than 50 µg/g is suggestive of a low likelihood of inflammatory bowel disease.

Coding

The following CPT code is specific for this test:
- **83993**: Calprotectin, fecal

Description

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

Related Policies

- Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In March 2006, the PhiCal® (Genova Diagnostics), an enzyme-linked immunosorbent assay test for measuring concentrations of fecal calprotectin in fecal stool, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. This test is indicated as
Fecal Calprotectin Testing

Page 2 of 24

Reproduction without authorization from Blue Shield of California is prohibited

In 2014, CalPrest® (Eurospital SpA) and, in 2016, CalPrest® NG (Eurospital SpA) were cleared for marketing by the FDA through the 510(k) process. According to the FDA summary, CalPrest® “is identical” to the PhiCal® test in that they have the same manufacturer. Compared with CalPrest®, the “differences in CalPrest® NG include the name of the test on the labels, detection antibody, the use of a Horse-radish peroxidase/TMB conjugate/substrate system, the provided Stop solution, the concentration of calibrators and controls in the kit and the dynamic range of the assay.”

FDA product code: NXO.

Rapid fecal calprotectin tests that can be used in the home or physician’s office are commercially available in Europe and Canada (e.g., Calprosmart, Calpro AS; Quantum Blue Calprotectin, Bühlmann Laboratories). Rapid tests have not been approved by the FDA for use in the United States.

**Rationale**

**Background**

**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 (e.g., abdominal pain, bloody diarrhea, perianal fistulae), systemic (e.g., weight loss, fatigue, growth failure in children), or extraintestinal (e.g., characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity of symptoms in the disease course, including a life-threatening illness.

**Diagnosis**

Diagnosing IBD is associated with well-defined management changes. A typical diagnostic approach to IBD includes stool testing for enteric pathogens, blood tests (complete blood count, inflammatory markers) to differentiate etiologies and evaluate disease severity, as well as small bowel imaging and endoscopy (upper GI, colonoscopy) with biopsies.

**Fecal Calprotectin**

In some cases, the clinical manifestations of IBD can be non-specific and suggestive of other disorders, including infectious colitis, colon cancer, and functional bowel disorders, including irritable bowel syndrome.

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

Calprotectin is a protein that could be used as a marker of inflammation. It is a calcium- and zinc-binding protein that accounts for approximately 60% of the neutrophil's cytoplasmic proteins. It is released from neutrophils during activation or apoptosis/necrosis and has a role in regulating inflammatory processes. In addition to potentially higher sensitivity and specificity than serologic markers, another advantage of calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to 1 week, leaving enough time for patients to collect samples at home and send them to a laboratory for testing. In contrast, lactoferrin, another potential fecal marker of intestinal inflammation, is stable at room temperature for about 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 (e.g., inflammation) and functional (no visible problem in the GI tract like irritable bowel syndrome) disease. Some consider fecal calprotectin to be a marker of neutrophilic intestinal inflammation rather than a marker of organic disease and believe it has utility to distinguish between IBD and non-IBD. In practice, the test might be suitable for selecting patients with IBD symptoms for endoscopy (i.e., deciding which patients do not require endoscopy). Fecal calprotectin testing has also been proposed to evaluate the response to IBD treatment and for predicting relapse. If found to be sufficiently accurate, results of calprotectin testing could be used to change treatment, such as adjusting medication levels.

### Treatment

Guidelines-based treatments include oral and rectal salicylates, glucocorticoids, immunomodulators (e.g., methotrexate), and multiple biologic therapies (e.g., infliximab), depending on disease severity.

### Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.
2.04.69   Fecal Calprotectin Testing
Page 4 of 24

Suspected Inflammatory Bowel Disease
Clinical Context and Test Purpose
In patients who have suspected IBD, the purpose of fecal calprotectin testing is to inform the decision whether to proceed to endoscopy with biopsy in order to confirm a diagnosis of IBD, either ulcerative colitis or Crohn disease.

Irritable bowel syndrome (IBS) and IBD can share common presenting symptoms such as diarrhea and abdominal pain. IBS is generally managed by antidiarrheal agents, diet, and lifestyle changes. IBD has a more serious prognosis. For example, Crohn disease can result in bowel obstruction or fistulas requiring surgical intervention. Ulcerative colitis has similar complications but is more localized.

In a patient whose symptoms have not responded to conservative management, endoscopy with biopsy would be required to confirm a diagnosis of IBD and inform treatment choice, which may include biologic disease-modifying agents. However, in a significant proportion of patients undergoing endoscopy with biopsy, IBD is not present. If fecal calprotectin testing can predict which patients are unlikely to have IBD, fewer patients would be subjected to endoscopy with biopsy (see Figure 1).

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

Figure 1. Analytic Framework

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

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

Patients
The relevant population of interest are individuals who present with signs and symptoms of suspected IBD for whom endoscopy with biopsy is being considered. Alternative causes of abdominal pain and diarrhea would have been ruled out and there would be no other indication for endoscopy such as rectal bleeding or risk factors (e.g., age) for cancer.

Interventions
The test being considered is fecal calprotectin analysis, which detects the process of inflammation in the intestines. The labeling of the Food and Drug Administration cleared PhiCal assay recommends the following interpretative guidelines: normal/healthy: less than 50 µg/g; indeterminate; 50 to 120 µg/g; abnormal: greater than 120 µg/g. Fecal calprotectin is also available as a laboratory-developed test and the upper threshold is being defined. Some laboratories use an upper threshold of 250 µg/g or higher to define a high probability of IBD.
Comparators
The following practice is currently being used to make decisions about diagnosing IBD: the reference standard is endoscopy with biopsy. In clinical practice, other tests such as magnetic resonance imaging, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete hemogram are part of the evaluation for IBD.

Outcomes
The outcome of a fecal calprotectin test is to inform the decision of whether to proceed to endoscopy with biopsy.

The beneficial outcome of correctly being classified as low-risk for IBD is avoiding an unnecessary invasive test. The harmful outcome of incorrect classification as low-risk for IBD is omission or deferral of a necessary biopsy, with a consequent delay of appropriate treatment.

Timing
For purposes of evaluating the clinical validity of fecal calprotectin testing to predict the results of endoscopy, the time frame is the availability of endoscopy results.

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.

Study Selection Criteria
For the evaluation of clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard (endoscopy or clinical follow-up)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

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

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Waugh et al (2013) published a systematic review as part of the U.K. Health Technology Assessment program. Investigators included 28 studies using fecal calprotectin tests to evaluate inflammation of the lower intestine in newly presenting patients. Studies using fecal calprotectin tests to monitor disease progression or response to treatment were excluded. Endoscopy with histology was the preferred reference standard, although some studies included used imaging or clinical follow-up. Studies were pooled when there was a minimum of 4 using the same calprotectin cutoff.

A pooled analysis of 5 studies using fecal calprotectin detected by enzyme-linked immunosorvent assay to differentiate between IBD and IBS in adults at a cutoff of 50 µg/g was performed (see Table 1). One study was rated as low risk of bias and 3 studies had at least 3 domains with high or unclear risk of bias. The pooled studies had a combined sensitivity of 93% and a combined specificity of 94% to predict the presence of inflammatory disease on biopsy (1 study evaluated the absence of inflammatory disease). See Table 2 clinical validity results and Tables 3 and 4 for individual study characteristics and results, with Table 4 presented in the order
of increasing prevalence of IBD. Out of 100 cases with a prevalence of 20%, NA invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 68%, NA invasive tests would be avoided with 5 cases missed.

**Table 1. Characteristics of Studies at a Threshold of 50 µg/g**

<table>
<thead>
<tr>
<th>Study</th>
<th>Studies Included</th>
<th>Study Populations Included</th>
<th>Study Designs Included</th>
<th>Study Reference Standards Included</th>
<th>No Domains</th>
<th>1-2 Domains</th>
<th>&gt;2 Domains</th>
<th>Domains with &gt;3 Studies at High Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waugh et al (2013)²</td>
<td>5 studies</td>
<td>Adults newly presenting with IBD or IBS referred by general practitioners</td>
<td>Diagnostic accuracy of FC to detect inflammation of the lower intestine</td>
<td>Most used endoscopy with biopsy</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>Blinding of reference standard</td>
</tr>
<tr>
<td>Waugh et al (2013)³</td>
<td>6 studies</td>
<td>Adults and children newly referred with IBD or non-IBD</td>
<td>Diagnostic accuracy of FC to detect inflammation of the lower intestine</td>
<td>Most used endoscopy with biopsy Some studies in children used clinical follow-up</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>Blinding of reference standard</td>
</tr>
</tbody>
</table>

FC: fecal calprotectin; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.

**Table 2. Clinical Validity Study Results at a Threshold of 50 µg/g**

<table>
<thead>
<tr>
<th>Study</th>
<th>Scenario (N)</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
<th>PPV Range, %</th>
<th>NPV Range, %</th>
<th>Disease Prevalence Range (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waugh et al (2013)²</td>
<td>To detect IBD in adults with IBS or IBD (5 studies, n=596 patients)</td>
<td>93 (83 to 97)</td>
<td>94 (73 to 99)</td>
<td>24-100</td>
<td>73-100</td>
<td>10.9-69.0 (5.8 to 77.3)</td>
</tr>
<tr>
<td>Waugh et al (2013)³</td>
<td>To detect IBD in children and adults with IBD or non-IBD (6 studies, n=516 patients)</td>
<td>99 (95 to 100)</td>
<td>74 (59 to 86)</td>
<td>62-96</td>
<td>93-100</td>
<td>21.4-61.1 (13.2 to 72.5)</td>
</tr>
</tbody>
</table>

CI: confidence interval; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; NPV: negative predictive value; PPV: positive predictive value.
### Table 3. Characteristics of Diagnostic Accuracy Studies (IBD vs IBS) in Adults with a Cutoff of 50 µg/g

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Setting</th>
<th>Reference Standard</th>
<th>No. of Domains(^a) at High or Unclear Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basumani et al (2012)(^4)</td>
<td>New referrals with diarrhea &gt;=4 wk to rule out IBD</td>
<td>District General Hospital, England</td>
<td>Histology</td>
<td>4</td>
</tr>
<tr>
<td>Otten et al (2008)(^2)</td>
<td>Consecutive patients referred with lower abdominal symptoms to endoscopy unit. Excluded 25 patients with polyps or CRC.</td>
<td>Endoscopy unit, The Netherlands</td>
<td>Colonoscopy and biopsy</td>
<td>2</td>
</tr>
<tr>
<td>Li et al (2006)(^5)</td>
<td>Outpatients and inpatients with IBS or IBD, healthy controls; patients followed up after polyp removal with no recurrence. Excluded 60 patients with CRC</td>
<td>Hospital, Peking</td>
<td>Colonoscopy with biopsy in IBD group</td>
<td>6</td>
</tr>
<tr>
<td>Schoepfer et al (2008)(^3)</td>
<td>Outpatients and inpatients with IBS or IBD. Excluded patients with CRC.</td>
<td>Gastroenterology Department, University Hospital, Switzerland</td>
<td>Colonoscopy including terminal ileum and biopsies</td>
<td>0</td>
</tr>
<tr>
<td>El-Badry et al (2010)(^6)</td>
<td>GI symptoms for at least 6 mo, and endoscopy necessary to exclude organic pathology. Excluded patients with CRC, diverticulitis, and polyps.</td>
<td>Internal Medicine Department, Egypt</td>
<td>Colonoscopy into ileum with biopsies</td>
<td>3</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.

\(^a\) QUADAS ratings.

### Table 4. Results of Diagnostic Accuracy Studies (IBD vs IBS) in Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prevalence (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PLR (95% CI)</th>
<th>NLR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basumani et al (2012)(^4)</td>
<td>110</td>
<td>10.91 (5.77 to 18.28)</td>
<td>1.00 (0.74 to 1.00)</td>
<td>0.60 (0.50 to 0.70)</td>
<td>0.24 (0.13 to 0.37)</td>
<td>1.00 (0.94 to 1.00)</td>
<td>2.51 (1.97 to 3.21)</td>
<td>0</td>
</tr>
<tr>
<td>Otten et al (2008)(^2)</td>
<td>114</td>
<td>20.18 (13.24 to 28.72)</td>
<td>0.96 (0.78 to 1.00)</td>
<td>0.87 (0.78 to 0.93)</td>
<td>0.65 (0.47 to 0.81)</td>
<td>0.99 (0.93 to 1.00)</td>
<td>7.25 (4.25 to 12.38)</td>
<td>0.05 (0.01 to 0.34)</td>
</tr>
<tr>
<td>Li et al (2006)(^5)</td>
<td>120</td>
<td>50.00 (40.74 to 59.26)</td>
<td>0.93 (0.84 to 0.98)</td>
<td>0.95 (0.86 to 0.99)</td>
<td>0.95 (0.86 to 0.99)</td>
<td>0.93 (0.84 to 0.98)</td>
<td>18.67 (6.18 to 56.63)</td>
<td>0.07 (0.03 to 0.18)</td>
</tr>
<tr>
<td>Schoepfer et al (2008)(^3)</td>
<td>94</td>
<td>68.09 (57.67 to 77.33)</td>
<td>0.83 (0.71 to 0.91)</td>
<td>1.00 (0.88 to 1.00)</td>
<td>1.00 (0.93 to 1.00)</td>
<td>0.73 (0.57 to 0.86)</td>
<td>NR</td>
<td>0.17 (0.10 to 0.29)</td>
</tr>
</tbody>
</table>
Six studies using fecal calprotectin with an enzyme-linked immunosorbent assay to differentiate between IBD and non-IBD in children and adults were pooled (see Table 1). Five of the studies included only children, most of whom had been referred to pediatric gastroenterologists. The children had undergone fecal calprotectin testing prior to endoscopy with biopsy or were followed clinically. No studies were at low risk of bias and 5 studies had 1 to 2 domains with high or unclear risk of bias, as evaluated on the QUADAS quality assessment. The highest risk of bias was for blinding of the reference standard. The combined sensitivity was 99% with a lower combined specificity (74%) to detect the absence of inflammatory disease on biopsy (see Table 2). Modeling indicated that use of fecal calprotectin in children would result in fewer children undergoing an unnecessary invasive test (i.e., endoscopy with biopsy). Out of 100 cases, at a prevalence of 36%\(^7\), NA invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 51%\(^8\), NA invasive tests would be avoided with 1 case of IBS missed. Individual study characteristics (Table 5) and results, (Table 6) presented in the order of increasing prevalence of IBD.

### Table 5. Characteristics of Diagnostic Accuracy Studies (IBD vs Non-IBD) in Children and Adults with a Cutoff of 50 µg/g

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Setting</th>
<th>Reference Standard</th>
<th>No. of Domains(^a) at High or Unclear Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damms and Bischoff et al (2008)(^9)</td>
<td>Patients ages &gt;18 y referred for colonoscopy for GI disorders or CRC screening</td>
<td>Gastroenterology departments at 3 hospitals and 3 outpatient clinics in Germany</td>
<td>Colonoscopy: for CRC screening medical check-up</td>
<td>2</td>
</tr>
<tr>
<td>Van de Vijver et al (2012)(^7)</td>
<td>Children ages 6-18 y referred for further investigation of high suspicion of IBD from pediatrician's global assessment, physical examination, and blood results</td>
<td>Pediatric outpatient clinics at 6 general hospitals and 1 tertiary care hospital in the North Netherlands Paediatric IBD Consortium</td>
<td>68 patients had endoscopy; others had follow-up for at least 6 mo to confirm a diagnosis of IBD</td>
<td>1</td>
</tr>
<tr>
<td>Henderson et al (2012)(^10)</td>
<td>All children who had a fecal calprotectin measurement as part of initial diagnostic workup before endoscopy</td>
<td>Pediatric gastroenterology department at a children's hospital in UK</td>
<td>IBD patients: standard clinical, histologic, and radiologic findings Non-IBD (control) patients upper and lower endoscopy</td>
<td>2</td>
</tr>
<tr>
<td>Sidler et al (2008)(^8)</td>
<td>Children ages 2-18 y referred for further investigation of GI symptoms (chronic diarrhea, bloody stools, abdominal pain) suggestive of an OBD</td>
<td>Pediatric gastroenterology outpatient clinic at children's hospital in Australia</td>
<td>Upper GI endoscopy and complete ileocolonoscopy with biopsy</td>
<td>1</td>
</tr>
</tbody>
</table>
Study | Study Population | Setting | Reference Standard | No. of Domains\(^a\) at High or Unclear Risk of Bias
---|---|---|---|---
Tomas et al (2007)\(^{11}\) | Patients referred for further investigation of GI symptoms (intense abdominal pain, chronic diarrhea, weight loss, rectal bleeding) | Pediatric gastroenterology unit of university hospital in Spain | Clinical criteria, laboratory, image and endoscopic test results | 6
Fagerberg et al (2005)\(^{12}\) | Children ages 6-17 y with GI symptoms and blood tests suggestive of inflammation who were scheduled for colonoscopy to rule out IBD | Pediatric gastroenterology departments at hospitals in Sweden | Complete ileocolonoscopy with biopsy | 1

\(^a\) Q U ADAS ratings.

Table 6. Results of Diagnostic Accuracy Studies (IBD vs Non-IBD) in Children and Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prevalence (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PLR (95% CI)</th>
<th>NLR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damms et al (2008)(^{9})</td>
<td>84</td>
<td>21.43 (13.22 to 31.74)</td>
<td>1.00 (0.81 to 1.00)</td>
<td>0.79 (0.67 to 0.88)</td>
<td>0.79 (0.60 to 0.88)</td>
<td>1.00 (0.93 to 1.00)</td>
<td>4.71 (2.96 to 7.50)</td>
<td>0</td>
</tr>
<tr>
<td>Van de Vijver et al (2012)(^{7})</td>
<td>117</td>
<td>35.9 (27.24 to 45.29)</td>
<td>1.00 (0.92 to 1.00)</td>
<td>0.73 (0.62 to 0.83)</td>
<td>0.68 (0.55 to 0.79)</td>
<td>1.00 (0.94 to 1.00)</td>
<td>3.8 (2.6 to 5.5)</td>
<td>0</td>
</tr>
<tr>
<td>Henderson et al (2012)(^{10})</td>
<td>190</td>
<td>47.89 (40.61 to 55.25)</td>
<td>0.98 (0.92 to 1.00)</td>
<td>0.44 (0.34 to 0.55)</td>
<td>0.62 (0.53 to 0.70)</td>
<td>0.96 (0.85 to 0.99)</td>
<td>1.8 (0.15 to 2.1)</td>
<td>0.05 (0.01 to 0.20)</td>
</tr>
<tr>
<td>Sidler et al (2008)(^{8})</td>
<td>61</td>
<td>50.82 (37.70 to 63.86)</td>
<td>1.00 (0.89 to 1.00)</td>
<td>0.67 (0.47 to 0.83)</td>
<td>0.76 (0.60 to 0.88)</td>
<td>1.00 (0.83 to 1.00)</td>
<td>3.00 (1.81 to 4.98)</td>
<td>0</td>
</tr>
<tr>
<td>Tomas et al (2007)(^{11})</td>
<td>28</td>
<td>53.57 (33.87 to 72.49)</td>
<td>1.00 (0.78 to 1.00)</td>
<td>0.92 (0.64 to 1.00)</td>
<td>0.94 (0.70 to 1.00)</td>
<td>1.00 (0.74 to 1.00)</td>
<td>13.00 (1.98 to 85.46)</td>
<td>0</td>
</tr>
<tr>
<td>Fagerberg et al (2005)(^{12})</td>
<td>36</td>
<td>61.11 (43.46 to 76.86)</td>
<td>0.95 (0.77 to 1.00)</td>
<td>0.93 (0.66 to 1.00)</td>
<td>0.96 (0.77 to 1.00)</td>
<td>0.93 (0.66 to 1.00)</td>
<td>13.36 (2.02 to 88.54)</td>
<td>0.05 (0.01 to 0.33)</td>
</tr>
</tbody>
</table>

CI: confidence interval; IBD: inflammatory bowel disease; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value.

Clinically Useful
A test is clinically useful if the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified that assessed the use of fecal calprotectin testing to diagnose suspected IBD.
Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Indirect evidence supports the clinical usefulness of fecal calprotectin in patients with suspected IBD for whom endoscopy is being considered. The evidence on clinical validity (sensitivity, specificity, NPV) permits inference on clinical usefulness as a result of avoidance of endoscopy with biopsy in patients who are unlikely to have an inflammatory disease.

Section Summary: Suspected IBD
A systematic review and meta-analysis of 28 studies pooled 11 studies that used a 50 µg/g threshold to evaluate intestinal inflammation. Five studies (n=596 patients) showed an NPV in the range of 73% to 100% in adults with IBS or IBD. Pooling of 6 studies in adults and children (N=1100) with IBD or non-IBD showed an NPV of 93% to 100%. Together, these results would suggest that fecal calprotectin testing at a threshold of 50 µg/g can identify patients who are unlikely to have the inflammatory disease and can forgo a more invasive test (endoscopy with biopsy). Clinical input supported that the use of fecal calprotectin testing for individuals with suspected IBD provides a clinically meaningful improvement in net health outcome by providing clinically valid and clinically useful information to guide the clinical decision-making. Specifically, fecal calprotectin testing can inform the decision by using a positive fecal calprotectin result to refer for endoscopy with biopsy or to use a negative fecal calprotectin results to exclude inflammatory bowel disease and avoid endoscopy with biopsy with acceptably low tradeoffs in missed diagnoses of IBD in those who have false negative fecal calprotectin results. Input further highlighted that the use of FCP is particularly important in pediatric populations, where children may not be able to fully participate as medical historians and may have non-specific and/or atypical symptoms. Further details from clinical input are included in the Clinical Input section later in the review and the Appendix.

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

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

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

Patients
The relevant population of interest are individuals with Crohn disease or ulcerative colitis.

Interventions
The test being considered is fecal calprotectin analysis.

Comparators
The following practice is currently being used to make decisions about monitoring IBD: the reference standard is a repeat endoscopy with biopsy. In clinical practice, other tests such as ESR, CRP, and complete hemogram are part of the evaluation for monitoring disease activity in IBD.

Outcomes
The beneficial outcome of a true test result, if correctly classified as low disease activity, is avoidance of endoscopy and unnecessary medications.
If correctly classified as high activity, administration of appropriate treatment is another beneficial outcome.

Outcomes may be assessed in clinical practice and in the research setting with standardized measures, such as the Crohn Disease Activity Index, a validated 8-item score used as a marker of Crohn disease remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe Crohn disease.\(^\text{13}\).

**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 a gastroenterologist or a primary care provider.

**Study Selection Criteria**

For the evaluation of clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard (endoscopy)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

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

**Technically Reliable**

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

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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

A systematic review by Mosli et al (2015) evaluated the sensitivity and specificity of fecal calprotectin in adults and some children with previously diagnosed ulcerative colitis or Crohn disease to detect endoscopically confirmed active disease (see Table 7).\(^\text{14}\). Nineteen studies with 1069 ulcerative colitis patients and 1033 Crohn disease patients met eligibility criteria. Individual studies used a variety of cutoffs for fecal calprotectin, ranging from 6 to 280 µg/g. Pooled sensitivity and specificity estimates for fecal calprotectin were 88% and 73%, respectively (see Table 8). The optimal threshold was determined to be 50 µg/g. At a threshold of 50 µg/g, the NPV for inflammation at a prevalence of 0.50 was 86% and the PPV was 76%. This information might be used to triage patients for endoscopy when they have symptoms of active disease.
Table 7. Characteristics of Clinical Validity Reviews Assessing Monitoring of Active Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Studies Included</th>
<th>Study Populations Included</th>
<th>Study Designs Included</th>
<th>Study Reference Standards Included</th>
<th>No. Domains</th>
<th>1-2 Domains</th>
<th>&gt;2 Domains</th>
<th>Indicators with &gt;6 Studies at High or Unclear Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosli et al (2015)</td>
<td>19</td>
<td>1069 UC and 1033 CD patients (mostly adults) with symptomatic disease</td>
<td>Prospective cohorts or case-controls for evaluating disease activity</td>
<td>Endoscopy</td>
<td>2</td>
<td>9</td>
<td>8</td>
<td>Inappropriate exclusions Blinding of index test Interval between tests Exclusions in the analysis</td>
</tr>
</tbody>
</table>

CD: Crohn disease; UC: ulcerative colitis.

Table 8. Results of Clinical Validity Reviews Assessing Detection of Endoscopically Confirmed Active Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Scenario</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
<th>Range PPV, %</th>
<th>Range NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosli et al (2015)</td>
<td>To monitor disease activity in patients with CD or UC on maintenance therapy (N=2102)</td>
<td>88 (84 to 90)</td>
<td>73 (66 to 79)</td>
<td>52-91</td>
<td>67-95</td>
</tr>
</tbody>
</table>

CI: confidence interval; CD: Crohn disease; NPV: negative predictive value; PPV: positive predictive value; UC: ulcerative colitis

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

For monitoring disease activity in patients with active IBD, inferences cannot be made from clinical validity studies to clinical usefulness. How fecal calprotectin would be used to make decisions about endoscopy or intensification of therapy is not described in the Mosli et al (2015) review. Intervention studies will provide direct evidence of fecal calprotectin for monitoring disease activity in patients with active IBD.

Colombel et al (2018) reported on an open-label multicenter RCT (CALM) that compared the effect of tight control of Crohn disease with standard clinical management. The primary end point was mucosal healing with the absence of deep ulcers at 48 weeks after randomization (see Tables 9 and 10). This trial did not test whether using fecal calprotectin, as decision criteria for treatment changes, improved the capability to achieve tight control. Although a post hoc analysis found that, in the tight management arm, fecal calprotectin levels frequently...
influenced the decision to escalate treatment, the contribution of fecal calprotectin to the tight control cannot be determined from this study design.

Table 9. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombel et al (2018)</td>
<td>U.S., E.U.</td>
<td>74</td>
<td>2011-2016</td>
<td>244 adults with moderate-to-severe active CD (CDEIS &gt;6; CDAI, 150-450) and naive to immunomodulators and biologics</td>
<td>Tight control(^a) including FC &gt;=250 µg/g and CRP &gt;5 mg/L Clinical management(^b)</td>
</tr>
</tbody>
</table>

CD: Crohn disease; CDAI: Crohn’s Disease Activity Index; CDEIS: Crohn’s Disease Endoscopic Index of Severity; CRP: C-reactive protein; FCP: fecal calprotectin; RCT: randomized controlled trial.

\(^a\) Tight control was determined by FC level >=250 µg/g, CRP level >=5 mg/L, CDAI score >=150, or prednisone use in the previous week.

\(^b\) Clinical management was based on a CDAI score decrease of <100 points vs baseline or CDAI score >=200, or prednisone use in the previous week.

Table 10. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Mucosal Healing at 48 Weeks</th>
<th>Adverse Events</th>
<th>Steroid-Free Remission at 48 Weeks</th>
<th>Deep Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombel et al (2018)</td>
<td>244</td>
<td>244</td>
<td>244</td>
<td>244</td>
</tr>
<tr>
<td>Tight control</td>
<td>56/122 (46)</td>
<td>105 (86)</td>
<td>73 (59.8)</td>
<td>45 (36.9)</td>
</tr>
<tr>
<td>Clinical monitoring</td>
<td>37/122 (30)</td>
<td>100 (82)</td>
<td>48 (39.3)</td>
<td>28 (23.0)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>16.1 (3.9 to 28.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p)</td>
<td>0.010</td>
<td>0.001</td>
<td>0.014</td>
<td></td>
</tr>
</tbody>
</table>

Values are n/n (%), n (%), or as otherwise indicated. CI: confidence interval; RR: relative risk; RCT: randomized controlled trial.

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

Table 11. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population(^a)</th>
<th>Intervention(^b)</th>
<th>Comparator(^c)</th>
<th>Outcomes(^d)</th>
<th>Follow-Up(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombel et al (2018)</td>
<td></td>
<td>4. In addition to FCP, CRP, prednisone use, and different thresholds of CDAI were used in the tight control arm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CDAD: Crohn's Disease Activity Index; CRP: C-reactive protein; FCP: fecal calprotectin.

\(^a\) Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

\(^b\) Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

\(^c\) Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
Table 12. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Selectiona</th>
<th>Blindingb</th>
<th>Delivery of Test</th>
<th>Selective Reportingd</th>
<th>Data Completenesse</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombel et al (2018)</td>
<td>Not blinded to treatment assignment</td>
<td>Not blinded to treatment assignment</td>
<td>Outcome assessed by treating physician</td>
<td>1. 25% loss to follow-up (analysis was intention-to-treat)</td>
<td>1. 25% loss to follow-up (analysis was intention-to-treat)</td>
<td>1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.</td>
</tr>
</tbody>
</table>

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

e Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical utility of fecal calprotectin testing has not been established for monitoring active IBD, a chain of evidence cannot be constructed.

Section Summary: Monitoring Active IBD

Studies to manage IBD have not used consistent cutoff values. A systematic review determined that 50 µg/g was the optimum threshold; at a prevalence of 0.50, fecal calprotectin had NPV of 86% and PPV of 76%. One RCT using fecal calprotectin testing along with other measures to monitor disease activity in patients with IBD on maintenance therapy was identified. The investigators reported that tight control using both clinical status and biologic markers (fecal calprotectin level, ≥250 µg/g; CRP level, ≥5 mg/L) resulted in greater mucosal healing in patients with Crohn disease. The contribution of fecal calprotectin to the tight control could not be determined from this study design.

Prediction of Relapse with IBD in Remission

Clinical Context and Test Purpose

Calprotectin has been used to predict relapse in individuals with IBD who are in remission. A marker to predict relapse could improve the net health outcome if preemptive treatment were found to eliminate recurrences or reduce their severity.

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

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

**Patients**
The relevant population of interest are individuals with Crohn disease or ulcerative colitis who are in remission.

**Interventions**
The test being considered is fecal calprotectin analysis.

**Comparators**
The following practice is currently being used to make decisions about monitoring IBD: the reference standard is endoscopy with biopsy. The following tests are currently used to make decisions about monitoring for IBD relapse in patients in the relevant population: patient’s symptoms, inflammatory markers (ESR), and complete blood count.

**Outcomes**
The beneficial outcome of a true test result, if correctly classified as low disease activity, is the avoidance of unnecessary medications. If correctly classified as high activity, administration of appropriate treatment is another beneficial outcome.

In making a decision to increase medications, fecal calprotectin testing as an adjunct to clinical assessment is being used as a test to support a “rule in” decision, so PPV is the key measure of clinical validity.

Outcomes of interest are an improvement in symptoms and disease activity scores. Outcomes may be assessed in clinical practice and in the research setting with standardized measures, such as the Crohn Disease Activity Index, a validated 8-item score used as a marker of Crohn disease remission, with values less than 150 considered consistent with remission and values greater than 450 considered a marker of severe Crohn disease.

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

**Setting**
This test may be ordered in an outpatient setting by a gastroenterologist or a primary care provider.

**Study Selection Criteria**
For the evaluation of clinical validity of the fecal calprotectin test, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard (endoscopy)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

For the evaluation of clinical utility of the fecal calprotectin test, studies must represent the intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy.
**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Systematic Reviews**
Heida et al (2017) conducted a systematic review to determine the accuracy of fecal calprotectin monitoring in asymptomatic patients (see Table 13). Six studies met the review inclusion criteria and evaluated fecal calprotectin levels every 1 to 3 months. One-third of patients had a relapse during the study period, although the definitions of relapse varied across studies. Five of the 6 studies used an upward trend of fecal calprotectin between 2 measurements as the threshold. Asymptomatic patients with IBD who had fecal calprotectin levels above the study’s cutoff had a 53% to 83% probability of developing disease relapse within the next 2 to 3 months, while patients with normal fecal calprotectin levels had a 67% to 94% probability of remaining in remission in the next 2 to 3 months (see Table 14). Calprotectin levels began to rise 2 to 3 months before clinical relapse. The investigators could not identify the best fecal calprotectin cutoff for monitoring purposes.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Studies</th>
<th>Study Populations</th>
<th>Study Designs</th>
<th>Study Reference Standards</th>
<th>No Domains</th>
<th>1-2 Domains</th>
<th>&gt;2 Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heida et al (2017)</td>
<td>6</td>
<td>552 patients with UC in remission</td>
<td>Prospective studies that assessed FC every 1-3 mo</td>
<td>5 studies used endoscopy study used clinical activity score</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>


**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.
A prospective nonblinded controlled trial by Lasson et al (2015) randomized patients with ulcerative colitis in remission at high-risk of relapse in a 3:2 ratio to medication dosing decisions based on fecal calprotectin levels or to usual care (see Table 15). The fecal calprotectin monitoring group was included in the systematic review by Heida et al (2017) described above. Both groups submitted fecal samples at baseline and on a monthly basis. In the intervention group, a fecal calprotectin cutoff of 300 µg/g was used for escalating the 5-aminosalicylic acid dose to the maximally tolerable dose. The high dose was continued for 3 months and then reduced when fecal calprotectin levels fell below 200 µg/g. The primary outcome was the number of patients to relapse by 18 months. At 1 year, there was no significant difference in relapse rates between the 2 groups (see Table 16). For 10 of the 18 patients in the intervention group who had a relapse, fecal calprotectin levels did not rise above the 300 µg/g cutoff for medication dosage escalation. In the subgroup of patients who had levels of 300 µg/g or more, there was a significantly lower rate of relapse in the intervention group (28.6%) than in the control group (57.1%). Trial limitations included lack of blinding, exclusion of patients without intention-to-treat analysis, and insufficient power (see Tables 17 and 18).

Table 15. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasson et al</td>
<td>Sweden</td>
<td>5</td>
<td>2009-2012</td>
<td>91 adults</td>
<td>Escalation to maximally tolerable dose based on FC &gt;=300 µg/g and lower when FC &lt;200 µg/g</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with UC</td>
<td>Usual care based on symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>on maintenance therapy with oral 5-ASA medication</td>
<td>Patients were in remission but at high risk of relapse</td>
</tr>
</tbody>
</table>

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

Table 16. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate of Relapse at 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasson et al (2015)</td>
<td>18/51 (35.3)</td>
</tr>
<tr>
<td>Fecal calprotectin monitoring, n/N (%)</td>
<td>18/51 (35.3)</td>
</tr>
<tr>
<td>Usual care, n/N (%)</td>
<td>20/40 (50)</td>
</tr>
<tr>
<td>p</td>
<td>0.23</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial.

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

Table 17. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Follow-Upe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasson et al (2015)</td>
<td></td>
<td></td>
<td>3. Treatment of a flare-up based on patient complaint and not predetermined in study protocol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
Table 18. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Blinding</th>
<th>Delivery of Test</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasson et al (2015)</td>
<td>1. Not described</td>
<td>1. Not blinded</td>
<td>2. 9 patients not providing at least 9 samples were excluded from experimental group</td>
<td>3. Not intention-to-treat</td>
<td>3. Target sample size not achieved</td>
<td></td>
</tr>
</tbody>
</table>

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

a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
b Blinding key: 1. Not blinded to results of reference or other comparator tests.
c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Section Summary: Prediction of Relapse with IBD in Remission

A 2017 systematic review of 6 prospective studies that monitored fecal calprotectin in patients in remission found no consistency in the thresholds used to determine treatment. One RCT evaluated the relapse rates in patients with ulcerative colitis whose medication doses were managed with fecal calprotectin test results (≥300 µg/g) and, in its primary analysis, found no significant difference in relapse rates. Trial limitations were in the domains of blinding, power, follow-up, and analysis. In addition, this trial did not enroll the planned number of patients and might have been underpowered. There is a need for high-quality RCTs to determine whether monitoring fecal calprotectin in patients who are in remission can reduce relapse rates and improve quality of life for patients with IBD.

Summary of Evidence

For individuals who have a suspicion of IBD when endoscopy with biopsy is being considered who receive fecal calprotectin testing to select patients who can forgo endoscopy, the evidence includes prospective and retrospective diagnostic accuracy studies and systematic reviews. Relevant outcomes are test validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. Twenty-eight studies in a systematic review evaluated the diagnostic accuracy of fecal calprotectin in patients suspected of having IBD for whom noninflammatory bowel disease, such as irritable bowel syndrome, remains a consideration. Studies varied in the fecal calprotectin protein level cutoff used to indicate the presence of disease but most used a cutoff of 50 µg/g, which is the recommended lower bound. Studies have indicated that, at this threshold, the test has a sensitivity of 93% to 99% for IBD and a negative predictive value of 73% to 100% for intestinal inflammation. Out of 100 cases of suspected IBD, approximately 49 invasive tests would be avoided with 1 case missed. Therefore,
Fecal calprotectin testing can be used to inform a decision of whether to proceed with endoscopy. Clinical input supported that the use of fecal calprotectin testing for individuals with suspected IBD provides a clinically meaningful improvement in net health outcome by providing clinically valid and clinically useful information to guide the clinical decision-making. Specifically, fecal calprotectin testing can inform the decision by using a positive fecal calprotectin result to refer for endoscopy with biopsy or to use a negative fecal calprotectin result to exclude inflammatory bowel disease and avoid endoscopy with biopsy with acceptably low tradeoffs in missed diagnoses of IBD in those who have false negative FCP results. Input further highlighted that the use of fecal calprotectin is particularly important in pediatric populations, where children may not be able to fully participate as medical historians and may have non-specific and/or atypical symptoms. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

Clinical Input
Objective
In 2018, clinical input was sought by Blue Cross Blue Shield Association to help determine whether the use of fecal calprotectin testing for individuals with suspected inflammatory bowel disease when endoscopy with biopsy is being considered would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

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

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

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Blue Cross Blue Shield Association (BCBSA) Evidence Street® clinical input process provide
review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

Clinical Input Responses

Additional Comments

- "Our opinion is that the use of FCP testing for individuals with suspected IBD provides a clinically meaningful improvement in healthcare by adding important and actionable information to the clinical decision-making involved in referring for endoscopy with biopsy (if FCP is elevated) or in deciding that endoscopy with biopsy is not warranted (if FCP is within normal limits)... The use of FCP is particularly important in pediatric populations, where children may not be able to fully participate as medical historians and may have non-specific and/or atypical symptoms.” (AAP)

- "FCP testing for individuals with suspected IBD would provide a clinically meaningful improvement in net health outcome if a positive test would be used to identify patients who are most likely to need endoscopy for suspected inflammatory bowel disease and if a negative test would be used to safely exclude inflammatory bowel disease and avoid endoscopic evaluation. FCP has been shown to have high sensitivity and specificity for differentiating between IBD and functional gastrointestinal disorders.” (Anonymous, identified by ASGE)

- "Fecal calprotectin (FCP) is a highly reliable and very sensitive test for inflammation in patients with colonic inflammation and has also demonstrated a high negative predictive value for patients with Crohn’s disease who have had surgery. In both situations, appropriate use of this test is associated with decreased utilization of colonoscopy.” (Dr. Kane, identified by ACG)

- "Overall, there is strong evidence to believe that FCP has true negative results with acceptably low trade-offs in missed diagnoses of IBD in those who have false negative FCP results.” (AAP)

- "As a specialist, I use the FCP to help guide my decision making on performing endoscopy, so I am not sure of a clinical scenario in which I ordered a negative FCP result and still followed it by endoscopy with biopsy. However, there have been instances where a primary care provider has sent FCP as part of an initial work-up for diarrhea. The FCP is negative, but upon evaluation at G1 clinic we learn that patient has a family h/o CD, elevated CRP and labs concerning for possible malabsorption (low vitamin D, low albumin) where we are concerned about ileal CD or celiac disease and endoscopy with biopsy is still pursued. As has been reported in the literature, some studies suggest that FCP appears to better reflect disease activity in UC rather than CD and that FCP results are less reliable in patients with pure ileal CD, although data/ studies are mixed. Another area of uncertainty is an intermediate test result, which may lead to either repeat testing with FCP to establish a trend, or an endoscopy with biopsy for follow-up.” (Anonymous, identified by ASGE)

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

See Appendices 1 and 2 for details.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of an appropriate
reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2018 Input
In response to requests from Blue Cross Blue Shield Association, clinical input on fecal calprotectin testing was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies including physicians affiliated with academic medical centers in 2018.

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

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

2014 Input
In response to requests from Blue Cross Blue Shield Association, input was received through 4 physician specialty societies and 4 academic medical centers in 2014. One specialty society submitted 2 responses. Input was mixed on whether fecal calprotectin testing is considered investigational for the diagnosis of intestinal conditions and whether the results of diagnostic testing are being used to change patient management. Clinicians who disagreed with the investigational designation tended to argue that a medically necessary use of the test for diagnosis would be to differentiate inflammatory from non-inflammatory conditions. There was near consensus that fecal calprotectin testing is considered investigational in the management of intestinal conditions. Most reviewers did not think that, when the test is used for the management of intestinal disorders, results change patient management. There was near consensus that the manufacturer’s recommended cutoff of 50 µg/g should be used to indicate a positive fecal calprotectin test.

Practice Guidelines and Position Statements
American College of Gastroenterology
The American College of Gastroenterology (2018) published guidelines on the management of Crohn disease in adults.18 The College gave a strong recommendation based on a moderate level of evidence that fecal calprotectin is a helpful test that should be considered to differentiate the presence of inflammatory bowel disease from irritable bowel syndrome. A summary statement without a recommendation indicated that fecal calprotectin measurements may have an adjunctive role in monitoring disease activity.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (2013; recommendation 1.1 was updated in 2017), published guidance on fecal calprotectin testing for inflammatory diseases of the bowel.19 The guidance made the following recommendations:

1.1 Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
   • cancer is not suspected, having considered the risk factors (for example, age)....

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

U.S. Preventive Services Task Force Recommendations
Not applicable.
**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in September 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

---

**References**


### Documentation for Clinical Review

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

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

- Consultation and medical clearance report(s), when applicable

- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)

- Laboratory results

### Post Service

- Results/reports of tests performed

### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>83993</td>
<td>Calprotectin, fecal</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Reproduction without authorization from Blue Shield of California is prohibited
Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/29/2013</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/29/2014</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>05/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>05/01/2019</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

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 government 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.