



**EFFECTIVE DATE:** 10|01|2015  
**POLICY LAST UPDATED:** 12|18|2018

## OVERVIEW

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.

## MEDICAL CRITERIA

Not applicable.

## PRIOR AUTHORIZATION

Not applicable.

## POLICY STATEMENT

### BlueCHiP for Medicare

Fecal calprotectin testing is considered not covered in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease as the evidence is insufficient to determine the effects of the technology on health outcomes.

### Commercial Products

Fecal calprotectin testing is considered not medically necessary in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease as the evidence is insufficient to determine the effects of the technology on health outcomes.

## COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

## BACKGROUND

Inflammatory bowel disease (IBD) is a chronic condition that encompasses 2 main forms: Crohn disease and ulcerative colitis, which overlap in clinical and pathologic characteristics but have distinct features. Crohn disease can involve the entire gastrointestinal (GI) tract and is characterized by transmural inflammation. Ulcerative colitis involves inflammation limited to the mucosal layer of the colon, almost always involving the rectum.

IBD is suggested by the presence of 1 or more of a variety of signs and symptoms that can be GI (eg, abdominal pain, bloody diarrhea, perianal fistulae), systemic (eg, weight loss, fatigue, growth failure in children), or extraintestinal (eg, characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity levels, including life-threatening illness. Treatments include oral and rectal salicylates, glucocorticoids, immunomodulators (eg, methotrexate), and multiple biologic therapies (eg, infliximab), depending on disease severity, which are recommended by the American Gastroenterological Association and other organizations. Making a diagnosis of IBD is associated with well-defined management changes.

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

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

Therefore, there is need for simple, accurate, noninvasive tests to detect intestinal inflammation. Potential noninvasive markers of inflammation fall into several categories, including serologic and fecal. Serologic markers such as C-reactive protein and antineutrophil cytoplasmic antibodies tend to have low sensitivity and specificity for intestinal inflammation because they are affected by inflammation outside of the GI tract. Fecal markers, in contrast, have the potential for being more specific to the diagnosis of GI tract disorders, because their levels are not elevated in 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 1 protein that could be used as a marker of inflammation. It is a calcium- and zinc binding protein that accounts for approximately 60% of the neutrophils' cytoplasmic proteins. It is released from neutrophils during activation or apoptosis/necrosis and has a role in regulating inflammatory processes. In addition to potentially higher sensitivity and specificity than serologic markers, another advantage of fecal calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to 1 week, leaving enough time for patients to collect samples at home and send them to a laboratory for testing. In contrast, lactoferrin, also a potential fecal marker of intestinal inflammation, is stable at room temperature for about 2 days.

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

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

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

Studies using fecal calprotectin to predict response to treatment have variable findings and have not used consistent cutoff values. These factors make the diagnostic accuracy of fecal calprotectin in evaluating the response to treatment or disease active in IBD uncertain.

For individuals who have suspected inflammatory bowel disease (IBD) who receive fecal calprotectin testing, the evidence includes prospective and retrospective diagnostic accuracy studies and systematic reviews. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, quality of life, hospitalizations, and medication use. There is a large body of evidence evaluating the diagnostic accuracy of

fecal calprotectin in patients considered to have IBD, and for whom irritable bowel syndrome is a consideration. In general, these studies have indicated that the commercially available test has very high sensitivity for IBD. Studies have varied in the cutoff of fecal calprotectin used to indicate the presence of disease, but most have used a cutoff of 50 µg/g. However, there is relatively little data on the use of calprotectin in the general population and potential for spectrum effect; given the possibility of more widespread use in practice, additional clinical validity data in the target population would be indicated. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

### **CODING**

The following CPT code is not covered for BlueCHIP for Medicare and not medically necessary for Commercial Products:

**83993** Calprotectin, fecal

### **RELATED POLICIES**

Not applicable

### **PUBLISHED**

Provider Update, February 2019

Provider Update, June 2017

Provider Update, January 2017

Provider Update, August 2015

### **REFERENCES**

1. FDA. PhiCal 510(k) Substantial Equivalence Determine Decision Summary. Available online at: [http://www.accessdata.fda.gov/cdrh\\_docs/reviews/K050007.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/K050007.pdf). Last accessed March, 2014.
2. Waugh N, Cummins E, Royle P et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-IBDs: systematic review and economic evaluation. *Health Technol Assess* 2013; 17(55):xv-xix, 1-211.
3. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected IBD: diagnostic meta-analysis. *BMJ* 2010; 341:c3369.
4. von Roon A C., Karamountzos L., Purkayastha S. et al. Diagnostic precision of fecal calprotectin for IBD and colorectal malignancy. *Am J Gastroenterol* 2007; 102(4):803-13.
5. Henderson P, Anderson NH, Wilson DC. The Diagnostic Accuracy of Fecal Calprotectin During the Investigation of Suspected Pediatric IBD: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2013.
6. Kostakis ID, Cholidou KG, Vaiopoulos AG et al. Fecal Calprotectin in Pediatric IBD: A Systematic Review. *Dig Dis Sci* 2012.
7. Manz M, Burri E, Rothen C et al. Value of fecal calprotectin in the evaluation of patients with abdominal discomfort: an observational study. *BMC Gastroenterol* 2012; 12:5.

8. Otten CM, Kok L, Witteman BJ et al. Diagnostic performance of rapid tests for detection of fecal calprotectin and lactoferrin and their ability to discriminate inflammatory from irritable bowel syndrome. *Clin Chem Lab Med* 2008; 46(9):1275-80.
9. Schroder O, Naumann M, Shastri Y et al. Prospective evaluation of faecal neutrophil-derived proteins in identifying intestinal inflammation: combination of parameters does not improve diagnostic accuracy of calprotectin. *Aliment Pharmacol Ther* 2007; 26(7):1035-42.
10. Sidler MA, Leach ST, Day AS. Fecal S100A12 and fecal calprotectin as noninvasive markers for IBD in children. *Inflamm Bowel Dis* 2008; 14(3):359-66.
11. Ashorn S, Honkanen T, Kolho KL et al. Fecal calprotectin levels and serological responses to microbial antigens among children and adolescents with IBD. *Inflamm Bowel Dis* 2009; 15(2):199-205.
12. Turner D, Leach ST, Mack D et al. Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe UC: a prospective multicentre comparison of predicting outcomes and monitoring response. *Gut* 2010; 59(9):1207-12.
13. Molander P, af Bjorkestén CG, Mustonen H et al. Fecal calprotectin concentration predicts outcome in IBD after induction therapy with TNF $\alpha$  blocking agents. *Inflamm Bowel Dis* 2012; 18(11):2011-7.
14. Wagner M, Peterson CG, Ridefelt P et al. Fecal markers of inflammation used as surrogate markers for treatment outcome in relapsing IBD. *World J Gastroenterol* 2008; 14(36):5584-9; discussion 88.
15. Mao R, Xiao YL, Gao X et al. Fecal calprotectin in predicting relapse of IBDs: a meta-analysis of prospective studies. *Inflamm Bowel Dis* 2012; 18(10):1894-9.
16. Yamamoto T, Shiraki M, Bamba T et al. Fecal calprotectin and lactoferrin as predictors of relapse in patients with quiescent UC during maintenance therapy. *Int J Colorectal Dis* 2013.
17. Lason A, Simren M, Stotzer PO et al. Fecal Calprotectin Levels Predict the Clinical Course in Patients With New Onset of UC. *Inflamm Bowel Dis* 2013.
18. Gisbert JP, Bermejo F, Perez-Calle JL et al. Fecal calprotectin and lactoferrin for the prediction of IBD relapse. *Inflamm Bowel Dis* 2009; 15(8):1190-8
19. Ferreiro-Iglesias R, Barreiro-de Acosta M, Otero Santiago M, et al. Fecal Calprotectin as Predictor of Relapse in Patients With Inflammatory Bowel Disease Under Maintenance Infliximab Therapy. *J Clin Gastroenterol*. Feb 2016;50(2):147-151. PMID 25811118
20. National Institute for Health and Care Excellence (NICE). Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel [DG11]. 2013; <http://guidance.nice.org.uk/DG11>. Accessed November 29, 2016.
21. Mosli MH, Zou G, Garg SK, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and metaanalysis. *Am J Gastroenterol*. Jun 2015;110(6):802-819; quiz 820. PMID 25964225

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