Medical Coverage Policy | Fecal Calprotectin Testing

EFFECTIVE DATE: 01|01|2024
POLICY LAST REVIEWED: 01|22|2025

OVERVIEW

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.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

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

Fecal calprotectin testing is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products in the management of inflammatory bowel disease, including the management of active inflammatory bowel disease and surveillance for relapse of disease in remission as the evidence is insufficient to determine the effects of the technology on health outcomes.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L**. §27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

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

BACKGROUND

Inflammatory Bowel Disease

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

IBD is suggested by the presence of 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 of symptoms in the disease course, including 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 (IBS).

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 the 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 (eg, inflammation) and functional (no visible problem in the GI tract like IBS) 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 (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.

Treatment
Guideline-based treatments of IBD include oral and rectal salicylates, glucocorticoids, immunomodulators (eg, methotrexate), and multiple biologic therapies (eg, infliximab), depending on disease severity.

For individuals who have a suspicion of inflammatory bowel disease (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 (QOL), 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 IBS, 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. In another meta-analysis involving 19 studies where the majority of studies again used the cutoff of 50 μg/g, investigators determined that out of 100 hypothetical patients, 18 non-disease patients would have a colonoscopy performed and 1 patient with IBD would not be referred for a colonoscopy. Additionally, it was determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%. Therefore, fecal calprotectin can be used to inform a decision of whether to proceed with endoscopy. Moreover, a recent review found that fecal calprotectin is the most sensitive noninvasive test in distinguishing IBD from non-IBD with a sensitivity of 99%. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have active IBD who receive fecal calprotectin testing to monitor disease activity, the evidence includes reviews and 2 randomized controlled trials (RCTs). Relevant outcomes are test validity, symptoms, change in disease status, QOL, hospitalizations, and medication use. A systematic review determined that a fecal calprotectin level of 50 μg/g was the optimum threshold for triaging patients for endoscopy when they have symptoms of active disease. RCTs are needed to determine whether guiding treatment based on fecal calprotectin levels can improve disease management. A 2017 RCT included fecal calprotectin as 1 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. In another RCT, self-monitoring with a home-based fecal calprotectin test among patients with established IBD demonstrated an increase in the proportion of patients seeking medical treatment; compliance to home-based testing in this study was low (29%). The use of a home-based fecal calprotectin test that is not available in the US limits the applicability of this study. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have IBD in remission who receive fecal calprotectin testing to predict relapse, the evidence includes systematic reviews and an RCT. Relevant outcomes are test validity, symptoms, change in disease status, QOL, hospitalizations, and medication use. A systematic review of studies that monitored fecal calprotectin in patients in remission demonstrated that fecal calprotectin levels began to rise 2 to 3 months before clinical relapse; an ideal fecal calprotectin cutoff for monitoring purposes was not identified. A meta-analysis of 24 prospective studies that monitored fecal calprotectin in patients in remission described an optimal cut-off value for fecal calprotectin of 152 μg/g and a pooled sensitivity and specificity of fecal

calprotectin of 72% and 74%, respectively. Another review found that fecal calprotectin had a sensitivity of 78% and specificity of 73% in predicting recurrence, although magnetic resonance enterography (MRE) and ultrasound performed better. 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. Additional high-quality RCTs are 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 that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s) is considered medically necessary when filed with the ICD-10 Diagnosis Codes* listed below:

83993 Calprotectin, fecal

***ICD-10 Diagnosis Codes that may support medical necessity:**

K52.3
K52.89
K52.9
K58.0 - K58.9
R19.4
R19.5
R19.7
R19.8

RELATED POLICIES

Biomarker Testing Mandate
Genetic Testing Services

PUBLISHED

Provider Update, March 2025
Provider Update, March 2024
Provider Update, March/November 2023
Provider Update, May 2022
Provider Update, April 2021

REFERENCES

1. Kapel N, Ouni H, Benahmed NA, et al. Fecal Calprotectin for the Diagnosis and Management of Inflammatory Bowel Diseases. Clin Transl Gastroenterol. Sep 01 2023; 14(9): e00617. PMID 37440723
2. Mendall MA, Chan D, Patel R, et al. Faecal calprotectin: factors affecting levels and its potential role as a surrogate marker for risk of development of Crohn's Disease. BMC Gastroenterol. Oct 07 2016; 16(1): 126. PMID 277173103.
3. Food and Drug Administration (FDA). 510(k) Summary: CALPREST. 2014; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K130945. Accessed October 22, 2024.
4. Food and Drug Administration (FDA). 510(k) Summary: Calprest NG. 2016; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K160447. Accessed October 21, 2024.
5. Food and Drug Administration (FDA). 510(k) Summary: BUHLMANN fCAL ELISA. 2018; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K181012. Accessed October 23, 2024.
6. Food and Drug Administration (FDA). 510(k) Summary: LIAISON Calprotectin, LIAISON Calprotectin Control Set, LIAISON Calprotectin Calibration Verifiers, LIAISON Q.S.E.T. Buffer, LIAISON Q.S.E.T. Device. 2018;

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K182698. Accessed October 20, 2024.
7. ALPCO. Now Available: 510(k) Cleared Fecal Calprotectin ELISA. ALPCO website. https://www.alpco.com/?gclid=Cj0KCQjwqP2pBhDMARIsAJQ0CzoPkOw05UVfjSzQ3X4xCuhZqNJcTH5YQF3zpNadEjes-wsn3sE8ki4aArWDEALw_wcB. Accessed October 24, 2024.
8. Food and Drug Administration (FDA). 510(k) Summary: ALPCO Calprotectin Immunoturbidimetric Assay. 2023; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K220763. Accessed October 24. 2024.
9. Food and Drug Administration (FDA). 510(k) Summary: LIAISON Calprotectin, LIAISON Q.S.E.T. Device Plus. 2022; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K213858. Accessed October 19, 2024.
10. Petryszyn P, Staniak A, Wolosianska A, et al. Faecal calprotectin as a diagnostic marker of inflammatory bowel disease inpatients with gastrointestinal symptoms: meta-analysis. Eur J Gastroenterol Hepatol. Nov 2019; 31(11): 1306-1312. PMID31464777
11. 11.Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess. Nov 2013; 17(55): xv-xix, 1-211. PMID 24286461
12. Shi JT, Zhang Y, She Y, et al. Diagnostic Utility of Non-invasive Tests for Inflammatory Bowel Disease: An Umbrella Review. Front Med (Lausanne). 2022; 9: 920732. PMID 35911403
13. Östlund I, Werner M, Karling P. Self-monitoring with home based fecal calprotectin is associated with increased medical treatment. A randomized controlled trial on patients with inflammatory bowel disease. Scand J Gastroenterol. Jan 2021;56(1): 38-45. PMID 33284639
14. Schoepfer AM, Trummler M, Seeholzer P, et al. Discriminating IBD from IBS: comparison of the test performance of fecal markers, blood leukocytes, CRP, and IBD antibodies. Inflamm Bowel Dis. Jan 2008; 14(1): 32-9. PMID 17924558
15. Basumani P, Bardhan K, Eyre R, et al. Faecal calprotectin: Rotherham experience (unpublished slide presentation). BSGAway; 2012 June 28.
16. Li XG, Lu YM, Gu F, et al. [Fecal calprotectin in differential diagnosis of irritable bowel syndrome]. Beijing Da Xue Xue BaoYi Xue Ban. Jun 18 2006; 38(3): 310-3. PMID 16778979
17. El-Badry A, Sedrak H, Rashed L. Faecal calprotectin in differentiating between functional and organic bowel diseases.Arab J Gastroenterol. May 23 2010;11(2):70-73.
18. Van de Vijver E, Schreuder AB, Cnossen WR, et al. Safely ruling out inflammatory bowel disease in children and teenagers without referral for endoscopy. Arch Dis Child. Dec 2012; 97(12): 1014-8. PMID 23019289
19. Sidler MA, Leach ST, Day AS. Fecal S100A12 and fecal calprotectin as noninvasive markers for inflammatory bowel disease in children. Inflamm Bowel Dis. Mar 2008; 14(3): 359-66. PMID 18050298
20. Damms A, Bischoff SC. Validation and clinical significance of a new calprotectin rapid test for the diagnosis of gastrointestinal diseases. Int J Colorectal Dis. Oct 2008; 23(10): 985-92. PMID 18629518
21. Henderson P, Casey A, Lawrence SJ, et al. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease. Am J Gastroenterol. Jun 2012; 107(6): 941-9. PMID 2237060422.
22. Bonnín Tomàs A, Vila Vidal M, Rosell Camps A. [Fecal calprotectin as a biomarker to distinguish between organic and functional gastrointestinal disease]. Rev Esp Enferm Dig. Dec 2007; 99(12): 689-93. PMID 18290691
23. Fagerberg UL, Lööf L, Myrdal U, et al. Colorectal inflammation is well predicted by fecal calprotectin in children with gastrointestinal symptoms. J Pediatr Gastroenterol Nutr. Apr 2005; 40(4): 450-5. PMID 15795593
24. Jørgensen LG, Fredholm L, Hyltoft Petersen P, et al. How accurate are clinical activity indices for scoring of disease activity in inflammatory bowel disease (IBD)?. Clin Chem Lab Med. 2005; 43(4): 403-11. PMID 15899657
25. 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 Meta-Analysis. Am JGastroenterol. Jun 2015; 110(6): 802-19; quiz 820. PMID 25964225

26. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. Dec 23 2017; 390(10114): 2779-2789. PMID 29096949
27. Shi JT, Chen N, Xu J, et al. Diagnostic Accuracy of Fecal Calprotectin for Predicting Relapse in Inflammatory BowelDisease: A Meta-Analysis. J Clin Med. Feb 02 2023; 12(3). PMID 36769850
28. Heida A, Park KT, van Rheenen PF. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide. Inflamm Bowel Dis. Jun 2017; 23(6): 894-902.PMID 28511198
29. Lasson A, Öhman L, Stotzer PO, et al. Pharmacological intervention based on fecal calprotectin levels in patients with ulcerative colitis at high risk of a relapse: A prospective, randomized, controlled study. United European Gastroenterol J.Feb 2015; 3(1): 72-9. PMID 25653861
30. Colombel JF, Shin A, Gibson PR. AGA Clinical Practice Update on Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: Expert Review. Clin Gastroenterol Hepatol. Feb 2019; 17(3): 380-390.e1. PMID 30099108
31. Smalley W, Falck-Ytter C, Carrasco-Labra A, et al. Spotlight: Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D). Gastroenterology. Sep 2019; 157(3): 858. PMID 31377275
32. Ananthakrishnan AN, Nguyen GC, Bernstein CN. AGA Clinical Practice Update on Management of Inflammatory BowelDisease in Elderly Patients: Expert Review. Gastroenterology. Jan 2021; 160(1): 445-451. PMID 33011177
33. Singh S, Ananthakrishnan AN, Nguyen NH, et al. AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis. Gastroenterology. Mar 2023; 164(3): 344-372. PMID 36822736
34. Ananthakrishnan AN, Adler J, Chachu KA, et al. AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Crohn's Disease. Gastroenterology. Dec 2023; 165(6): 1367-1399. PMID 3798135
35. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am JGastroenterol. Apr 2018; 113(4): 481-517. PMID 29610508
36. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am JGastroenterol. Jan 01 2021; 116(1): 17-44. PMID 33315591
37. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory BowelDisease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. Apr 2021; 160(5): 1570-1583. PMID 33359090
38. National Institute Health Care Excellence (NICE). Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. NICE website. October 2, 2013. Accessed October 24, 2024.