Medical Coverage Policy

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Coverage Policy Number..... 0121

Inflammatory Bowel Disease - Testing for the Diagnosis and Management

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Related Coverage Resources

Immunomodulators
Pharmacogenetic Testing

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers

must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses testing for the diagnosis and management of inflammatory bowel disease (IBD).

Coverage Policy

Fecal calprotectin is considered medically necessary when EITHER of the following criteria is met:

- for the purpose of distinguishing irritable bowel syndrome (IBS) from inflammatory bowel disease (IBD) in individuals with chronic diarrhea
- for the management of inflammatory bowel disease

Fecal calprotectin for ANY other indication is not covered or reimbursable.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

The prevalence of IBD has been increasing globally with variations by geographic region. The amount of individuals affected by IBD across the globe increased from 3.7 million in 1990 to 6.8 million in 2017. Asia and the Middle East have a lower incidence and prevalence of Crohn disease and ulcerative colitis; however, in some newly industrialized countries in Africa, Asia, and South America, the incidence of IBD has been rising. In a large systematic review of population-based studies on the incidence of Crohn disease and ulcerative colitis, the following trends were noted: in Brazil, the annual percentage change (APC) increased for Crohn disease by 11.1 percent and for ulcerative colitis by 14.9 percent, and in Taiwan, the APC increased for Crohn disease by 4 percent and for ulcerative colitis by 4.8 percent. Ulcerative colitis and Crohn disease are more common in Jewish compared to non-Jewish populations. Hispanic and Black populations have a lower incidence of IBD compared to White populations (Peppercorn and Cheifetz, 2021).

There are significant differences in IBD phenotype and outcomes based on race and ethnicity. This difference is likely due to a multitude of factors that includes both social and biologic differences. Minority and lower socioeconomic status groups are more likely to use the emergency department,

be hospitalized, experience a complicated disease course and have IBD-related disability. Genes implicated in IBD risk differ in non-White compared with White patients with IBD. The data are increasing on the sex-based differences in IBD phenotype and outcomes, which may be related to differences in pathogenic pathways and progression. Females are more likely to experience consistent extraintestinal manifestations (EIMs). Additionally, girls are more likely to have EIMs and less likely to have growth impairment compared to boys, this could be related to lower insulin like growth factor-1 level in boys. CD and UC severity can vary from mild disease with few symptoms to complicated disease with strictures and fistulas. In a French population-based study, the cumulative probability of perianal CD varied between 11% and 19% at 1–10 years after diagnosis. In an Asian study of 983 patients with CD, stricturing or penetrating CD occurred in 41% and perianal disease in 25% of patients (Agrawal et al., 2021).

General Background

Inflammatory bowel disease (IBD) is a condition, not a specific disease, which is characterized by chronic or relapsing immune activation and inflammation within the GI tract. Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of IBD. CD is a chronic inflammatory disorder that can involve any part of the gastrointestinal tract from the mouth to the anus. UC is characterized by recurrent episodes of inflammation that is limited to the mucosal layer of the colon. The clinical characteristics of these disorders have substantial overlap. The symptoms of CD usually include diarrhea and abdominal pain which can be accompanied by weight loss. The symptoms of UC include bloody diarrhea with urgency. CD may manifest unique complications such as strictures and fistulas, which often necessitate surgery (Kaplan and Ng, 2021).

The diagnosis of IBD is established through a complete assessment of the clinical presentation with confirmatory evidence from radiologic, endoscopic, and, in most cases, pathologic findings. Endoscopic biopsies are helpful in the diagnosis of IBD and the differentiation of UC from CD through the recognition of microscopic changes suggestive of UC, CD, or both. Laboratory testing using stool and serological biomarkers are proposed to help predict ongoing intestinal inflammation, which could help decrease the repeated use of invasive and expensive testing in patients with non-specific symptoms. In the absence of biomarkers that are strongly predictive for disease activity, clinicians rely on endoscopy to monitor these patients. There are no available biomarkers with adequate sensitivity or specificity to directly diagnose IBD, rule out disease expression or that can distinguish hard to differentiate CD from UC. Fecal biomarkers are more specific for luminal inflammation than serologic biomarkers. Fecal calprotectin and lactoferrin concentrations often increase in the stool of patients with active IBD. They have been used to distinguish IBD from irritable bowel syndrome, which can have similar presentations and overlapping symptoms. Stool markers have been evaluated for use in the diagnosis and surveillance of disease activity in IBD, however none are clinically validated for replacement of endoscopy with biopsy (Winter and Weinstock, 2020).

In general chronic diarrhea is defined as three or more loose or watery stools daily lasting for four or more weeks (Bonis and Lamont, 2022). Common causes include irritable bowel syndrome (IBS), inflammatory bowel disease, malabsorption syndromes (such as lactose intolerance and celiac disease), and chronic infections (particularly in patients who are immunocompromised). When the diarrhea is thought to be caused by inflammation, calprotectin testing is recommended. If there is a positive FC test, an ileocolonoscopy and biopsy to confirm the diagnosis of IBD is indicated. If fecal calprotectin is normal, a diagnosis of IBD is unlikely (Bonis and Lamont, 2022).

U.S. Food and Drug Administration (FDA)
PhiCal™ Fecal Calprotectin Immunoassay (Genova Diagnostics, Inc., Ashville, NC) received 510 (k) device approval in 2006. The immunoassay is a lab test that measures the amount of fecal

calprotectin in a patient's stool sample. The PhiCal test is indicated for use as an in vitro diagnostic to aid in the diagnosis of inflammatory bowel diseases (IBD) (Crohn's disease and ulcerative colitis), and to differentiate IBD from irritable bowel syndrome (IBS) when used in conjunction with other diagnostic testing and the total clinical picture.

BUHLMANN fCAL® ELISA (BUHLMANN Laboratories AG, Lexington, Kentucky) received 510 (k) approval 2018. It is an in vitro diagnostic assay that is intended for the quantitative measurement of fecal calprotectin in human stool. The test aids in the diagnosis of inflammatory bowel disease (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC) and aids in the differentiation of IBD from irritable bowel syndrome (IBS) in conjunction with other laboratory and clinical findings.

Literature Review - Fecal calprotectin: Chen et al. (2021) conducted a prospective study that evaluated the clinical significance of fecal calprotectin (FC) in the assessment of ulcerative colitis (UC) clinical activity and mucosal healing (MH). Patients (n=143) referred for a colonoscopy with a previously confirmed diagnosis of UC included in the study. Patients were diagnosed on the basis of clinical, endoscopic, and histologic criteria. A second cohort of 108 healthy volunteers served as controls. After providing stool samples, patients underwent total colonoscopy. FC was measured by an enzyme-linked immunosorbent assay (ELISA). Clinical activity was based on the Mayo score. Endoscopic findings was scored by the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). The median of FC levels was 211 μg/g in UC and 87.5 μg/g in the control group. According to Mayo scores, 49 (34.27%) UC patients were in remission, 46 (32.17%) UC patients had mild, 41 (28.67%) UC patients had moderate, and 7 (4.90%) UC patients had severe disease activity. Overall, mucosal healing, defined as UCEIS score 0 or 1, was observed in 48 ulcerative colitis patients (33.57%). The measured FC concentrations were 38 μg/g, 220.5 μg/g, 1,138 μg/g, and 2,481 μg/g, respectively with each stage (remission, mild, moderate and severe) classified by Mayo scores. There was a significant difference in FC levels between patients with mild disease and moderate disease ($p<0.05$) as well as between moderate disease and severe disease ($p<0.05$). Fecal calprotectin correlated significantly with both Mayo and UCEIS scores ($p<0.01$). With a cut-off value of 164μg/g for fecal calprotectin concentration, sensitivity was 85.42%, specificity was 73.68%, positive predictive value (PPV) was 62.12%, and negative predictive value (NPV) was 9.10% in predicting clinical active disease. Similarly, the power of FC to predict mucosal healing (MH) was modest. With a cut-off value of 154.5μg/g, the AUC was 0.839, sensitivity was 72.34%, and specificity was 85.71%. Author noted limitations included: small patient population, using FC as a predictive tool for MH requires analysis from patients in clinical remission and FC levels are variable. An additional limitation was that the study occurred in China and the results may not be applicable to other races or ethnic groups. The study concluded that FC is a clinically relevant biomarker for both clinically active disease and MH in patients with UC. However, the appropriate cut-off value needs to be determined.

Engström et al. (2019) conducted a cross-sectional study with longitudinal follow-up that assessed how fecal calprotectin (FC) and serum C-reactive protein (CRP) can be implemented in the clinical routine for monitoring sustained treatment response and the need of therapy adjustments or surgery over 48 weeks. The study included adults (n=123) aged 18–75 years of age that were diagnosed with CD (n=76) or UC (n=47) at least one year prior to study with a maximum dosage of mesalazine up to 4.8 grams per day. Patients received infliximab (IFX) induction therapy according to the standard protocol at weeks 0, two and six at a dose of 5 mg/kg followed by maintenance therapy every eight weeks. All patients underwent ileocolonoscopic examination prior to IFX administration. Fecal calprotectin, CRP and clinical assessments (Harvey–Bradshaw index (HBi) for CD and the partial Mayo Clinic score (pMCS) for UC) were evaluated at baseline and at 12 weeks. Responders were monitored 48 weeks for an 'incident' (dosage increase, shortened dosage interval, surgery). Clinical response was defined as a decrease of ≥ 3 points of either HBi or pMCS, and clinical remission as < 5 and ≤ 1 in HBi and pMCS, respectively. Following infliximab, FC and CRP significantly declined ($p<0.0001$) along with HBi for CD and pMCS for UC.

Optimal FC ROC cutoff was 221 mg/g (sensitivity 66%, specificity 67%, AUC 0.71) and CRP ROC cutoff 2.1mg/L (sensitivity 54%, specificity 60%, AUC 0.58). In CD, FC > 221 mg/g ($p<0.0001$), but not CRP > 2.1 mg/L predicted an incident (an increase of infliximab dosage, shortening of infliximab dosage interval, or surgery). However, combined FC and CRP also predicted an 'incident' ($p<0.042$). In UC, both FC > 221 mg/g ($p<0.0005$) and CRP > 2.1mg/L ($p=0.0334$) predicted 'incident', as did combined biomarkers ($p<0.005$). Limitations to the study include the small patient population, short term follow-up and that the study occurred in Sweden and the results may not be applicable to other races or ethnic groups. The authors concluded that a treatment 'incident' in CD while receiving infliximab treatment (dose adjustment, surgery) was predicted by high FC but not CRP values, whereas high values in FC and CRP in UC were predictive of a treatment incidence.

Brand et al. (2019) investigated whether published non-invasive models (including fecal calprotectin) (based on symptoms and biomarkers) to evaluate Crohn's disease (CD) activity have sufficient accuracy to replace ileocolonoscopy. The study found two of the 7 models (but not the FC or C-reactive protein [CRP] values) identified patients without endoscopic activity with a negative predictive value (NPV) of 90% or more, leading to correct prediction of endoscopic healing in 3.2% to 11.3% of all patients which lead to correct predicted endoscopic healing in a small proportion of patients. The authors concluded that Ileocolonoscopy must therefore be used to evaluate CD mucosal disease activity and healing.

Yamamoto et al. (2018) conducted a prospective study that compared the clinical relevance of endoscopic scoring to fecal biomarkers for predicting relapse after clinical remission and mucosal healing (MH). Adults (n=164) aged 20–75 years were included in the study if the following criteria were met: confirmed diagnosis of UC; clinical remission achieved (normal stool frequency and no rectal bleeding) with medical treatment; mucosal healing (MH) achieved (Mayo endoscopic subscore [MES] 0 or 1) at endoscopy that was performed when they went into clinical remission; and scheduled to receive mesalamine maintenance therapy after achieving clinical remission and MH. At study entry, fecal samples were collected and measured for calprotectin, lactoferrin and hemoglobin. Following the fecal samples, patients received mesalamine maintenance therapy, and followed in the clinic every two or three months up to 12 months. When a patient developed symptoms suggestive of a flare-up, an endoscopic examination was done. Endoscopic score was measured according to the MES. Forty-six patients (28%) relapsed. The relapse rate was not significantly different in patients with MES 1 or MES 0 ($p=0.16$). The median fecal calprotectin, lactoferrin, and hemoglobin were significantly higher in patients with relapse than those in remission (calprotectin, 182 vs. 94 µg/g; lactoferrin, 185.5 vs. 111 µg/g; hemoglobin, 168 vs. 104 ng/mL; all $p<0.0001$). A cutoff value of 115 µg/g calprotectin had 83% sensitivity and 81% specificity to predict relapse. There was a significant relationship between the MES and the fecal biomarkers. The median calprotectin, lactoferrin, and hemoglobin levels were significantly higher in patients with MES 1 than those with MES 0 (calprotectin, 112 vs. 96 µg/g, $p=0.01$; lactoferrin, 130 vs. 113 µg/g, $p=0.02$; hemoglobin, 128 vs. 112.5 ng/mL, $p=0.04$). There was a significant relationship between the occurrence of relapse and the levels of fecal biomarkers. The median calprotectin, lactoferrin, and hemoglobin levels were significantly higher in patients (n=46) with relapse than those (n=118) in remission (calprotectin, 182 vs. 94 µg/g, $p<0.0001$; lactoferrin, 185.5 vs. 111 µg/g, $p<0.0001$; hemoglobin, 168 vs. 104 ng/mL, $p<0.0001$). The cumulative relapse-free rate was significantly higher in patients with low fecal calprotectin (< 115 µg/g) compared with those with higher level (≥ 115 µg/g, $p<0.0001$). Likewise, the cumulative relapse-free rate was significantly higher in patients with low fecal lactoferrin (< 145 µg/g) compared with those with higher level (≥ 145 µg/g, $p<0.0001$). Endoscopic examination was not performed for all patients during the follow-up; however the levels of fecal biomarkers were not elevated in symptomatic patients without endoscopic activity. Author noted limitations included: (1) the different induction treatments used before entry and the change in therapy after remission induction, could have limited the accuracy of our findings; (2) histological evaluation was not done

in our patients who achieved clinical and endoscopic remission; (3) the measurement of fecal biomarkers was only performed at baseline, consecutive monitoring was not done in predicting future relapse. An additional limitation is that the study occurred in Japan and the results may not be applicable to other races or ethnic groups. The authors concluded that additional large scale studies are needed to confirm the results of this study. Additionally, future studies should investigate whether or not early medical intervention is beneficial for the prevention of relapse in patients with elevated fecal biomarkers. The study concluded that fecal calprotectin, lactoferrin, and fecal hemoglobin (although to a lesser degree) appeared to be objective biomarkers for predicting patient relapse after achieving clinical remission and MH.

Columbel et al. (2017) conducted a multicenter, open label, phase 3 randomized controlled trial (CALM) that evaluated the safety and efficacy of two treatment algorithms, tight control and clinical management, in patients with moderate to severe Crohn's disease. The study included adults aged 18–75 years with active endoscopic Crohn's disease, a Crohn's Disease Activity Index (CDAI) of 150–450 depending on dose of prednisone at baseline, and no previous use of immunomodulators or biologics. Patients (n=244) were randomly assigned 1:1 to tight control (n=122) or clinical management (n=122), stratified by smoking status, weight (< 70 kg or ≥ 70 kg), and disease duration (≤ 2 years or > 2 years) after eight weeks of prednisone induction therapy, or earlier if they had active disease. The primary endpoint assessed mucosal healing which was defined as a Crohn's Disease Endoscopic Index of Severity (CDEIS) score of less than four and no deep ulcers 48 weeks after randomization. In both groups, Adalimumab treatment was escalated in a stepwise manner at 12, 24, and 36 weeks if patients met the treatment failure criteria, including laboratory assessments of serum concentrations of CRP and stool concentrations of FC at 11, 23, and 35 weeks. Treatment failure criteria was different between groups. Failure criteria in the tight control group included fecal calprotectin ≥ 250 µg/g, C-reactive protein ≥ 5mg/L, CDAI ≥ 150, or prednisone use in the previous week. Failure in the clinical management group included a CDAI ≥ 200 or a CDAI decrease of < 100 points compared with baseline or prednisone use in the previous week. De-escalation was possible for patients receiving weekly adalimumab and azathioprine or weekly adalimumab alone if failure criteria were not met. Ileocolonoscopies to assess CDEIS were done at study sites during screening and at 48 weeks after randomization or early termination. Twenty-nine (24%) patients in the clinical management group and 32 (26%) patients in the tight control group discontinued the study. At week 48, the primary endpoint was met in significantly more patients in the tight control group than the clinical management group (46% vs 30%, respectively; p=0.010). Treatment emergent adverse events occurred in 86% of patients in the tight control group and 82% of patients in the clinical management group; no treatment-related deaths occurred. The most common adverse events were nausea, nasopharyngitis, and headache in the tight control group, and worsening Crohn's disease, arthralgia, and nasopharyngitis in the clinical management group. Author noted limitations included: the open-label design, and short term follow-up (48 weeks). The authors concluded that timely escalation with an anti-tumor necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone. Future studies should assess the effects of such a strategy on long-term outcomes such as bowel damage, surgeries, hospital admissions, and disability. No health disparities were identified by the investigators.

Verdejo et al. (2018) conducted a prospective study of 86 patients at five centers with the aim to evaluate the predictive value of a rapid test of FC for the presence and severity of postoperative endoscopic recurrence in patients with Crohn's disease (CD), compared with C-reactive protein (CRP) and the clinical evaluation of disease activity. Blood and fecal samples were collected in consecutively recruited patients with CD who had undergone ileocolonic resection and required a colonoscopy to assess postoperative recurrence, as defined by the Rutgeerts score (RS). Overall, 49 (57%) had CD recurrence. FC concentrations trended to increase with RS severity; FC median (interquartile range) was significantly higher in patients with endoscopic recurrence than those in

endoscopic remission. The same occurred for C-reactive protein and the Harvey-Bradshaw index (HBI) [4 (2-7) vs. 1 (0-3.5)]. The three variables significantly correlated. The area under the curve to discriminate between patients in endoscopic remission and recurrence was 0.698 for FC, with 62 µg/g being the optimal cut-off point. This indicated FC would have 85.7% sensitivity and 45.9% specificity in detecting any recurrence, having positive predictive value and negative predictive value of 67.7 and 70.8%, respectively. Area under the curve for CRP and HBI were both 0.710. The combination of CRP and HBI provided a positive predictive value 95.7 and a diagnostic odds ratio of 30.8. The authors concluded that FC is not better than CRP combined with HBI to predict endoscopic postoperative recurrence of CD.

El-Matary et al. (2017) reported on a retrospective cohort study that examined the impact of fecal calprotectin (FCal) measurements on decision-making and clinical care of children with IBD. FCal, clinical activity indices, and blood markers were measured in 77 (115 fecal samples) children with diagnoses of IBD. Pearson correlation coefficient analysis was performed to examine association between FCal and other markers. Then decisions based on FCal measurements were prospectively documented and participants were evaluated three to six months later. FCal positively correlated with clinical activity indices ($r = 0.481$, $P < 0.05$) and erythrocyte sedimentation rate ($r = 0.40$, $P < 0.05$) and negatively correlated with hemoglobin ($r = -0.40$, $P < 0.05$). Sixty-four out of 74 (86%) positive FCal measurements (≥250 µg/g of stools) resulted in treatment escalation with subsequent significant clinical improvement while in the FCal negative group, 34 out of 41 (83%) measurements resulted in no change in treatment and were associated with remission on follow-up. The study was limited by lack of randomization, retrospective design, and small sample size in particular for those for those who had colonoscopy.

Abej et al. (2016) reported on a prospective cohort study performed to determine the relationship between fecal calprotectin (FCAL) and imaging studies and other biochemical inflammatory markers and the impact of FCAL measurements on decision-making in IBD patient management in usual clinical practice. The study included 240 persons with IBD. The correlation between FCAL values and other markers for disease activity such as serum albumin (alb), hemoglobin (Hg), and C-reactive protein (CRP) and diagnostic imaging or colonoscopy were examined. FCAL ≥ 250 mcg/g of stool was considered a positive result indicating active IBD. The results of 183 stool samples (76.3%) were returned. The return rate in the pediatric and adult cohorts was 91% (n=82) and 67.3% (n=101), respectively ($p<0.0001$). Positive FCAL was associated with colonoscopy findings of active IBD ($p<0.05$), low albumin ($p<0.05$), anemia ($p<0.01$), and elevated CRP ($p<0.01$). There was no significant difference for FCAL results by outcomes on small bowel evaluation among the 21 persons with small bowel CD. Most persons (87.5%) with normal FCAL and no change in therapy remained in remission during subsequent three months. Of 11 subjects with a positive FCAL who underwent imaging, only six had active disease on imaging; a positive FCAL was not significantly associated with radiologic evidence of active disease ($p=0.31$).this study was limited by lack of controls, and the small number who underwent imaging and endoscopy.

Bar-Gil Shitrit et al. (2016) reported on a study that prospectively assessed the value of fecal calprotectin and lactoferrin in 68 patients with Crohn's disease (CD) to predict capsule endoscopy (CE) findings. Stool samples for calprotectin and lactoferrin and blood samples were collected for relevant parameters. Correlation between fecal markers and CE findings was assessed and receiver operating characteristic (ROC) curves were built to determine the predictive values of fecal markers for the diagnosis of CD. Fecal calprotectin data was available for all the patients and lactoferrin data for 38. CE findings compatible with CD were found in 23 (33%) patients and 45 (67%) were negative for CD. The average age of the CD group was 34 compared to 46 in the non-CD group ($p=0.048$). Median calprotectin and lactoferrin in the CD group and control group were 169 mg/kg vs. 40 ($p=0.004$) and 6.6 mg/kg versus 1 ($p=0.051$), respectively. The area under the ROC curve was 0.767 for calprotectin and 0.70 for lactoferrin. A fecal calprotectin concentration of

95 mg/kg and fecal lactoferrin of 1.05 mg/kg had a sensitivity, specificity, positive predictive value and negative predictive value of 77 and 73%, 60 and 65%, 50 and 50%, and 84 and 84% in predicting CE findings compatible with CD. The study is limited by small number of participants and lack of controls.

Professional Societies/Organizations

American College of Gastroenterology (ACG): The ACG clinical guideline on the management of Crohn's disease in adults included the following recommendation for the use of fecal calprotectin (Lichtenstein, et al., 2018):

- Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence).
- In patients who have symptoms of active Crohn's disease, stool testing should include fecal pathogens, Clostridium difficile testing and may include studies that identify gut inflammation such as a fecal calprotectin.(summary statement, no level of evidence)
- Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity.(summary statement, no level of evidence)

  Level of evidence:
  Moderate: (further research would be likely to have an impact on the confidence in the estimate of effect)

  Recommendation grading:
  Strength of a recommendation graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects.

Summary statements are descriptive and do not have associated evidence-based ratings.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD		No Local Coverage Determinations found	

Note: Please review the current Medicare Policy for the most up-to-date information

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Fecal Calprotectin

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
83993	Calprotectin, fecal

ICD-10-CM Diagnosis Codes	Description
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications
K51.00	Ulcerative (chronic) pancolitis without complications
K51.011	Ulcerative (chronic) pancolitis with rectal bleeding
K51.012	Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication
K51.019	Ulcerative (chronic) pancolitis with unspecified complications
K51.20	Ulcerative (chronic) proctitis without complications
K51.211	Ulcerative (chronic) proctitis with rectal bleeding
K51.212	Ulcerative (chronic) proctitis with intestinal obstruction
K51.213	Ulcerative (chronic) proctitis with fistula
K51.214	Ulcerative (chronic) proctitis with abscess

ICD-10-CM Diagnosis Codes	Description
K51.218	Ulcerative (chronic) proctitis with other complication
K51.219	Ulcerative (chronic) proctitis with unspecified complications
K51.30	Ulcerative (chronic) rectosigmoiditis without complications
K51.311	Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312	Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.314	Ulcerative (chronic) rectosigmoiditis with abscess
K51.318	Ulcerative (chronic) rectosigmoiditis with other complication
K51.319	Ulcerative (chronic) rectosigmoiditis with unspecified complications
K51.40	Inflammatory polyps of colon without complications
K51.411	Inflammatory polyps of colon with rectal bleeding
K51.412	Inflammatory polyps of colon with intestinal obstruction
K51.413	Inflammatory polyps of colon with fistula
K51.414	Inflammatory polyps of colon with abscess
K51.418	Inflammatory polyps of colon with other complication
K51.419	Inflammatory polyps of colon with unspecified complications
K51.50	Left sided colitis without complications
K51.511	Left sided colitis with rectal bleeding
K51.512	Left sided colitis with intestinal obstruction
K51.513	Left sided colitis with fistula
K51.514	Left sided colitis with abscess
K51.518	Left sided colitis with other complication
K51.519	Left sided colitis with unspecified complications
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication
K51.819	Other ulcerative colitis with unspecified complications
K51.90	Ulcerative colitis, unspecified, without complications
K51.911	Ulcerative colitis, unspecified with rectal bleeding
K51.912	Ulcerative colitis, unspecified with intestinal obstruction
K51.913	Ulcerative colitis, unspecified with fistula
K51.914	Ulcerative colitis, unspecified with abscess
K51.918	Ulcerative colitis, unspecified with other complication
K51.919	Ulcerative colitis, unspecified with unspecified complications
K58.0	Irritable bowel syndrome with diarrhea
K58.1	Irritable bowel syndrome with constipation
K58.2	Mixed irritable bowel syndrome
K58.8	Other irritable bowel syndrome
K58.9	Irritable bowel syndrome, unspecified
K59.31	Toxic megacolon

ICD-10-CM Diagnosis Codes	Description
R19.7	Diarrhea, unspecified

Not Covered or Reimbursable:

ICD-10-CM Diagnosis Codes	Description
	All other codes

References

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	Removed policy statements related to testing for serological and genetic markers for the diagnosis or management of IBD, and therapeutic drug monitoring for IBD.	4/15/2025
Focused Review	No policy statement changes.	11/01/2024
Annual Review	No policy statement changes.	3/15/2024