Fecal Calprotectin Testing

Policy Number: CS042.O
Effective Date: August 1, 2023

Instructions for Use

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Commercial Policy
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Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	None
Kentucky	Fecal Calprotectin Testing (for Kentucky Only)
Louisiana	Fecal Calprotectin Testing (for Louisiana Only)
New Jersey	Fecal Calprotectin Testing (for New Jersey Only)
Ohio	Fecal Calprotectin Testing (for Ohio Only)
Pennsylvania	Fecal Calprotectin Testing (for Pennsylvania Only)
Tennessee	Fecal Calprotectin Testing (for Tennessee Only)

Coverage Rationale

Fecal measurement of calprotectin is proven and medically necessary for establishing the diagnosis, or for management of, the following:

- Crohn's disease
- Ulcerative colitis

Due to insufficient evidence of efficacy, fecal measurement of calprotectin is unproven and not medically necessary for establishing the diagnosis, or for management of, any other condition.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may

require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
83993	Calprotectin, fecal

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Diagnosis Code	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

Diagnosis Code	Description
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
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
K51.50	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
K52.3	Indeterminate colitis
K58.0	Irritable bowel syndrome with diarrhea
K58.9	Irritable bowel syndrome without diarrhea
K59.1	Functional diarrhea
R19.5	Other fecal abnormalities
R19.7	Diarrhea, unspecified

Description of Services

The cause of inflammatory bowel disease (IBD) is unknown, possibly involving an autoimmune reaction of the body to its own intestinal tract. Ulcerative colitis (UC) and Crohn's disease (CD) are examples of IBD. Both diseases are characterized by an uncontrolled inflammatory response at the mucosal level resulting in tissue damage. Most cases of CD and UC can be diagnosed by history and physical examination supplemented by small bowel x-rays, computed tomography/magnetic resonance enterography, capsule endoscopy, enteroscopy or colonoscopy, and then possibly confirmed by biopsy. However, differentiation between these two diseases can be difficult because they have overlapping clinicopathologic features. Since the natural history of these diseases is not the same, accurate diagnosis is important for both prognostic and therapeutic reasons.

Calprotectin is a calcium binding protein that is excreted in the stool of individuals with IBD and other gastrointestinal (GI) conditions. Fecal calprotectin (FC), used as a marker of intestinal inflammation, has been proposed to aid in the diagnosis and as a predictor of relapse in IBD including CD and UC. The use of FC has also been proposed as a predictive response to treatment in individuals with IBD rather than relying solely on clinical symptoms.

Although FC has been most frequently studied in IBD, several investigators have measured FC levels in other intestinal diseases such as colorectal cancer (CRC), diverticular disease, and colonic polyposis.

Clinical Evidence

Inflammatory Bowel Disease (IBD)

In a 2022 systematic review and meta-analysis, of systematic reviews or meta-analyses, Shi et al. sought to evaluate the diagnostic performance and validity of reported non-invasive tests for IBD. A total of 46 articles were included in this review. Fecal calprotectin (FC) (0.99) and fecal lactoferrin (FL) (0.82) were the most sensitive for distinguishing IBD from non-IBD. Similarly, anti-neutrophil cytoplasmic antibodies (ANCA) (0.971) and FL (0.95) were the most specific for marker. To distinguish IBD from IBS, FC (cutoff 50 µg/g, 0.97; cutoff 100 µg/g, 0.92) and FL (0.94) were the most sensitive and specific markers. Anti-Saccharomyces cerevisiae antibodies (ASCA) (09.55), IgA, were the best test to distinguish Crohn's disease (CD) from ulcerative colitis (UC). Interferon-γ release assay (IGRA) was the best test to distinguish CD from intestinal tuberculosis (ITB). In assessing activity, ultrasound and magnetic resonance enterography were both sensitive and specific for disease activity, along with the high sensitivity of FC. Small intestine contrast ultrasonography (SICUS) had the highest sensitivity, and FC had the highest specificity for operative CD recurrence. The authors concluded that biomarkers played a role in diagnosis, while radiological examinations, especially MRE and US, were more prominent in assessing activity and predicting recurrence. Limitations of data and lack of reviews for specific populations would require further studies. (Systematic reviews by Jung 2021, Ye 2021, Petryszyn 2019, and Tham 2018 described below, are included in this systematic review.)

Sasidharan et al. (2022) conducted a multicenter, retrospective cohort study including patients with UC who were hospitalized for severe exacerbation of colitis. The primary outcome was the need for in-hospital medical or surgical rescue therapy. The study included 147 patients with UC. One-third (33%) required rescue therapy after failure to respond to intravenous steroids; and 13% underwent colectomy. Patients requiring rescue therapy had significantly higher FC (mean 1,748 mcg/g vs. 1,353 mcg/g, p = .02) compared with those who did not. An admission FC > 800 mcg/g independently predicted the need for inpatient medical rescue therapy (odds ratio, 2.61; 95% CI, 1.12-6.12) and surgery within 3 months (odds ratio, 2.88; 95% CI, 1.01-8.17). However, the area under the curve (AUC) for this cutoff point was only 0.61. The researchers concluded that, FC levels may serve as a useful noninvasive predictor of disease severity and surgical risk in individuals with UC presenting with acute severe colitis. Larger prospective studies to validate the use of calprotectin as a predictor of longer-term outcome merits further investigation.

In Lee et al. (2022), the results of a multicenter, retrospective cross-sectional study were reported. The study included 131 pediatric patients with CD who had experienced at least a 6-month clinical remission with anti-tumor necrosis factor (TNF) agents and simultaneously underwent ileocolonoscopy and FC tests during follow-up. The study was pursued to investigate if FC could serve as a surrogate marker in assessing mucosal healing (MH) in this population. MH was defined as the absence of any ulcer on ileocolonoscopy. Among the 131 patients, MH was discovered in 87 patients (66.7%). In patients with MH versus those without MH, the FC level was significantly lower (median 49.0 mg/kg vs. 599.0 mg/kg; p < 0.001). The researchers assert, a FC cutoff level of < 140 mg/kg can identify MH with a sensitivity of 78.2% and specificity of 88.6%. In this treat-to-target era,

FC can be used for this target population in treatment guidance regarding ileocolonoscopy. Confirmation of this cutoff point in an independent cohort is necessary.

In a 2021 systematic review and meta-analysis, Xiang et al. sought to evaluate the diagnostic accuracy of FC in predicting MH of patients with IBD. The authors systematically searched the databases for studies from inception to April 2020, that evaluated MH in IBD. A random-effects model was used to capture the diagnostic odds ratio, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio. The review included 16 studies embodying 1,682 patients with ulcerative colitis (UC) and 4 studies embodying 221 patients with CD. Based on the meta-analysis, the researchers concluded that an FC cutoff range 60-75 μg/g appears to have the best overall accuracy for predicting MH in UC patients. (Publication by Ma 2017 which was previously cited in this policy, is included in this systematic review.)

In a Hayes (2021a) Health Technology Assessment assessing the monitoring of disease activity and treatment of UC in adults, Hayes indicates that FC testing appears to distinguish UC in remission from mild UC in patients with no or few clinical symptoms. Regarding treatment, none of the studies included in the report evaluated whether FC test results would eliminate the need for colonoscopy in treatment decision making, nor if FC test results improve health outcomes. In Hayes (2022a) Health Technology Annual Review, 7 abstracts were retrieved, including 1 controlled comparison study, 1 comparison study, 1 post-hoc analysis, 2 cohort studies, 1 observational study, and 1 cross-sectional study. Based on the impact of the newly published studies, there was no change to the current recommendation.

The use of FC for predicting clinical relapse or treatment in adults with UC, Hayes (2021b) Health Technology Assessment suggests that in patients who have UC in remission, FC testing may offer some benefit for prediction of clinical relapse. None of the studies evaluated the effect of FC testing on long-term health outcomes of patients with UC. The report indicates that additional studies are also needed to determine whether FC testing has sufficient accuracy to improve the management of patients who have UC. In Hayes (2022b) Health Technology Annual Review, 3 new abstracts were retrieved, which included3 prospective cohort studies. Based on the impact of the newly published studies, there was no change to the current recommendation.

In a clinical assessment, ECRI (2021a) concluded that the evidence for the FC for monitoring inflammatory bowel disease was inconclusive due to lack of data addressing clinical utility. The evidence suggests that FC testing is fair to good when identifying the likelihood of endoscopy relapse in individuals with CD or UC. When detecting histologic remission in individuals with UC, the assessment found that FC testing accuracy is fair. For managing therapy, the published evidence on FC testing is insufficient and additional prospective studies are needed to validate clinical utility.

An ECRI (2021b) clinical assessment for aiding diagnosis of inflammatory bowel disease concluded the evidence was inconclusive related to lack of data regarding clinical utility. The evidence identified by ECRI showed that FC has fair to good accuracy for determining IBD and good to high accuracy for individualizing IBD from IBS but there is a lack of prospective controlled studies addressing risks associated with false-negative results and whether these risks are low enough to rule out IBD without use of colonoscopy in clinical practice.

In State et al. (2021), a systematic review of studies was conducted to report the performance of biomarkers in diagnosing MH in patients with IBD. A total of 1,301 articles were gathered in the search. After applying exclusion criteria, 23 articles were used in the data extraction and analysis (14 prospective, 2 multicentric, 5 retrospective and 2 cross-sectional studies). The biomarkers reviewed included fecal markers, circulatory markers, and combined markers (serum and/or fecal markers). For assessing MH, FC was the most explored fecal marker. In ulcerative colitis, the FC cutoff levels in detecting MH ranged between 58 mcg/g and 490 mcg/g, the sensitivity was 89.7%-100% and the specificity was 62%-93.3%. For Crohn’s disease, the FC cutoff levels ranged from 71 mcg/g to 918 mcg/g (sensitivity 50%-95.9% and specificity 52.3%-100%). The authors note that FC has an established role in current clinical practice, however, none of the other biomarkers tested showed sufficient accuracy to replace endoscopy. The review concluded that biomarkers of MH should not replace endoscopic evaluations due to accuracy limitations. The authors recommend additional investigation into the use of biomarker panels with greater ability to predict MH than the use of a single biomarker.

In a multicenter, international, open-label, phase III randomized controlled trial (RCT) known as the CALM study, Colombel and colleagues compared endoscopic and clinical outcomes in patients with moderate to severe CD who were managed with a tight control algorithm, using clinical symptoms and biomarkers [such as FC and C-reactive protein (CRP)], versus patients managed with a clinical management algorithm. Adult patients (n = 244) with active endoscopic disease [Crohn's disease

Endoscopic Index of Severity (CDEIS) > 6; sum of CDEIS sub scores of > 6 in one or more segments with ulcers], 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 were randomized into 2 groups. In both groups, treatment was escalated in a stepwise manner, from no treatment to adalimumab induction followed by adalimumab every other week, then weekly, and lastly to both weekly adalimumab and daily azathioprine. The primary endpoint was mucosal healing (CDEIS < 4) with absence of deep ulcers 48 weeks after randomization. The researchers concluded that timely escalation with an anti-tumor necrosis factor therapy based on clinical symptoms combined with biomarkers in patients with early CD 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 (2018).

In a retrospective cohort study, El-Matary et al. examined the impact of FC measurements on decision making and clinical care of children with IBD. FC, clinical activity indices, and blood markers were measured in 115 fecal samples from 77 children (median age 14 years) with established diagnoses of IBD. Follow up occurred 3-6 months later. The study reflected that FC positively correlated with clinical activity indices and erythrocyte sedimentation, and negatively correlated with hemoglobin. Sixty four out of 74 (86%) positive FC measurements (≥ 250 μg/g of stools) resulted in treatment escalation with subsequent significant clinical improvement while in the FC negative group, 34 out of 41 (83%) measurements resulted in no change in treatment and were associated with remission on follow-up. Based on high FC, the majority of children had treatment escalation that resulted in clinical improvement. The authors concluded that FC measurements were useful and reliable in decision making and clinical care of children with IBD (2017).

Heida et al. (2017) performed a systematic review that included 193 studies evaluating the usefulness of repeated FC measurements to predict IBD relapses in asymptomatic patients. It was identified that individuals with FC levels above the study's cutoff level had a 53%-83% probability of developing disease relapse within the next 2-3 months. Patients with repeated normal FC values had a 67%-94% probability to remain in remission in the same timeframe. The ideal FC cutoff for monitoring could not be identified because of the limited number of studies meeting inclusion criteria as well as heterogeneity between selected studies. The authors concluded that 2 consecutively elevated FC values are highly associated with disease relapse, indicating a consideration to proactively optimize IBD therapy plans. More prospective data are necessary to assess whether FC monitoring improves health outcomes.

Two prospective studies on a total of 127 adults and 300 children evaluated the utility of FC testing for differentiating IBD from irritable bowel syndrome (IBS) and other gastrointestinal (GI) disorders. Authors concluded that FC levels were significantly higher in IBD patients versus those with other functional conditions, including IBS (Lozoya Angulo et al., 2017; Pieczarkowski et al., 2016).

Rosenfeld et al. (2016) conducted a multicenter prospective cohort study known as FOCUS, with the goal of evaluating the perspectives of gastroenterologists regarding the impact of FC on management of adults with IBD. Physicians completed an online "pre-survey" as well as a "post-survey" following receipt of the test results. Clinical outcomes for a subset of patients with follow-up data available beyond the completion of the "post survey" were collected and analyzed as well. Of 373 test kits distributed, 290 were returned, resulting in 279 fully completed surveys. One hundred and ninety patients were known to have IBD: 147 (77%) with CD, 43 (21%) UC, and 5 (2%) were IBD unclassified. Indications for FC testing included: differentiation of a new diagnosis of IBD from IBS (n = 90), differentiation of symptoms of IBS from IBD in patients with known IBD (n = 85), and as an objective measure of inflammation (n = 104). Overall, physicians found the test "sufficiently useful" 97.5% of the time and said they would order it again in similar situations. Results of the study concluded that the FC test effected a change in patient management 51.3% of the time and resulted in a significant reduction in the number of colonoscopies performed.

Koulaouzidis and colleagues conducted an international, multicenter retrospective study investigating the correlation between Lewis score and FC in 333 patients undergoing small-bowel capsule endoscopy (SBCE) for suspected or known IBD. All patients had SBCE, and FC done within 3 months. The researchers concluded that FC does not appear to be a reliable biomarker for significant small bowel inflammation, although FC level ≥ 76 μg/g may be associated with appreciable visual inflammation on SBCE in patients with negative prior diagnostic workup. The Lewis score appeared to show low correlation with FC and other serology markers indicating inflammation (2016).

Colorectal Cancer (CRC)

There is limited quality evidence in the peer-reviewed literature demonstrating the benefit of FC for CRC detection and staging.

Ross et al. (2022) conducted a systematic review and meta-analysis to evaluate the relationship between elevations of FC and colorectal neoplasia, to ascertain whether there may be any value in its routine assessment as part of the diagnostic process. A total of 35 studies are included in this review. The findings identified CRC patients are more likely than controls to have an elevated FC [OR 5.19, 95% CI 3.12–8.62, $p < 0.001$ with a heterogeneity ($I^2 = 27\%$)]. No tumor characteristics significantly correlated with FC. CRC staging showed signs that it may potentially correlate with FC. The authors concluded, FC high sensitivity in CRC suggests a potential role in the investigation and initial evaluation of CRC . The low specificity of FC prevents it from being used to diagnose or screen for CRC. Further studies are required due to the paucity and heterogeneity of this study. (Author Manz 2012 which was previously cited in this policy, is included in this systematic review.)

Nasir Kansestani et al. (2022) conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of fecal protein biomarkers, immunochemical fecal occult blood test (iFOBT), pyruvate kinase-M2 (PK-M2) and FC, for the detection of colorectal neoplasms. The investigators searched Web of Science, Scopus, and MEDLINE/PubMed until June 10, 2021, with no language restrictions. Related data were extracted by two investigators independently. A total of 49 studies were eligible and included in the analysis. The methodology utilized was the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The accuracy of iFOBT was significantly higher than that of PK-M2 and FC for CRC detection. The results indicate that FC has lower moderate accuracy for the diagnosis of CRC based on its likelihood ratio values. (Author Khoshbaten 2014 which was previously cited in this policy, is included in this systematic review.)

Ye et al. (2018) conducted a systematic review and meta-analysis for FC in diagnostic accuracy of CRC. Out of a 213-article search, 20 studies published between 1993 and 2017, were included in this review. Heterogeneity of studies was validated. The Fagan plot was applied to assess the clinical utility of the FC test for predicting CRC. After robust review and analysis, the authors concluded that the FC test cannot be recommended for CRC detection; however, they do propose the test be used as an auxiliary tool for clinicians as it may help predict CRC development. Limitations included variations of the FC assay across studies, the inability to determine the sensitivity and specificity of FC for CRC and variations of a definition for advanced adenoma across the studies; further investigation and additional studies are warranted.

A quantitative meta-analysis to evaluate the diagnostic precision of FC for CRC was performed on prospective studies, comparing FC levels against the histological diagnosis. Patients (n = 297) with colorectal neoplasia had non-significantly higher FC levels by 132.2 microg/g compared with non-cancer controls. Sensitivity and specificity of FC for the diagnosis of CRC were 0.36 and 0.71, respectively, with an AUC of 0.66. Sensitivity analysis and meta-regression analysis did not significantly alter the results. The investigators concluded that FC cannot be recommended as a screening test for CRC in the general population (von Roon et al., 2007).

Other Intestinal Conditions

There is insufficient quality evidence that FC is successful in identifying other intestinal conditions.

Falloon et al. (2022) conducted a systematic review to evaluate biomarkers for the evaluation and prediction of inflammation in patients with ileal pouch-anal anastomosis (IPAA) as tested against pouchoscopy as the gold standard. After applying inclusion criteria, 28 studies (5 case-control studies, and 23 observational cohort studies) were identified. Fecal biomarkers were assessed in 23 studies with FC being the most studied with sensitivities ranging from 57% to 92% and specificities from 19% to 92%, respectively. In examination of serum biomarkers associated with pouch inflammation, none demonstrated a high sensitivity or specificity. The longitudinal assessment of biomarkers studied, only three reported a predictive role of biomarkers in diagnosing endoscopic inflammation. The authors concluded biomarkers have potential to improve the management of pouchitis due to the ease of sampling in comparison to pouchoscopy. Unfortunately, no serum or stool biomarker can qualify as an ideal marker of pouch inflammation. Randomized control trials evaluating biomarkers reliability are warranted.

FC level measurement has been investigated in other intestinal conditions such as colonic diverticular disease (Tursi et al., 2009), acute or chronic diarrhea (Licata et al., 2012), intestinal allograft monitoring (Akpinar et al., 2008), celiac disease (Ertekin et al., 2010), gastrointestinal (GI) disease in neonates (Selimoğlu et al., 2012; Baldassarre et al., 2011), and acute radiation proctitis monitoring (Hille et al., 2008). Patients with these conditions may have elevated FC concentration compared with healthy control subjects; however, successful identification of these conditions by FC has been inconsistent and studied in small populations. Further studies in larger populations are needed to clarify the role of FC for these conditions.

Mercer et al. (2011) measured calprotectin levels in 732 stool samples collected and analyzed from 72 patients who had undergone total small intestine transplants, and correlated them with clinical indications, ostomy output, and pathologic

findings. The authors found that although frequent prospective sampling could perhaps demonstrate an advantage in early indication of rejection, routine FC monitoring was not strongly supported in this study.

Berman et al. (2010) conducted a study to identify potential biomarkers that could help in the prediction and management of GI immune-related adverse events from ipilimumab. A total of 115 patients with unresectable stage III/IV melanoma were included in the study. Outcome measures included FC levels. Despite an observed association between colonic inflammation and grade 2 or higher diarrhea, no baseline biomarkers could reliably predict development of GI toxicity.

Clinical Practice Guidelines

American College of Gastroenterology (ACG)

In their 2021 clinical guideline on the management of IBS, the ACG strongly recommends FC (or fecal lactoferrin) and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out IBD. (Lacy et al.).

In their 2018 clinical guideline on the management of CD in adults, the ACG strongly recommends FC as a helpful test that should be considered to help differentiate the presence of IBD from IBS. The guideline does not address the clinical utility of FC or its impact on overall patient care and health outcomes (Lichtenstein et al.).

American Gastroenterological Association (AGA)

The AGA 2023 Clinical Practice Guidelines on the role of biomarkers for the management of UC states the following:

- In UC patients in symptomatic remission, AGA suggests:
  - A monitoring strategy that combines biomarkers and symptoms rather than symptoms alone
  - Using FC < 150 mg/g, normal fecal lactoferrin, or normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease activity
  - Endoscopic assessment of the disease activity rather than empiric adjustment if in symptomatic remission but has elevated stool or serum markers of inflammation (fecal calprotectin > 150 mg/g, elevated fecal lactoferrin, elevated CRP) or in UC patients with mild symptoms with normal stool or serum markers of inflammation (fecal calprotectin < 150 mg/g, normal fecal lactoferrin, normal CRP)
- In patients with symptomatically active UC, AGA suggests:
  - An evaluation strategy that combines biomarkers and symptoms, rather than symptoms alone, to inform treatment adjustments
  - In patients with UC with moderate to severe symptoms suggestive of flare, using fecal calprotectin > 150 mg/g, elevated fecal lactoferrin, or elevated CRP to rule in active inflammation and inform treatment adjustment and avoid endoscopic assessment solely for establishing presence of active disease
  - In patients with UC with mild symptoms, with elevated stool or serum markers of inflammation (fecal calprotectin > 150 mg/g, elevated fecal lactoferrin, or elevated CRP), use endoscopic assessment of disease activity rather than empiric treatment adjustment
  - In patients with UC, the AGA makes no recommendation in favor of, or against, a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy to improve long-term outcomes
    (Singh et al., 2023)

The AGA's 2019 clinical practice guideline on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D) recommends the use of either fecal calprotectin or fecal lactoferrin to screen for IBD in patients presenting with chronic diarrhea. Conditional recommendation; low-quality evidence (Smalley et al.).

The AGA Identification, Assessment, and Initial Medical Treatment in Crohn's Disease: Clinical Decision Support Tool includes using FC in conjunction with other laboratory tests for assessing CD inflammation in patients, reducing the need for frequent colonoscopic confirmation (Sandborn, 2014).

National Institute for Health and Care Excellence (NICE)

NICE recommends FC testing as an option to support clinicians with the differential diagnosis of IBD or IBS in children, and in adults when cancer is not suspected (2017).

World Gastroenterology Organization (WGO)

The WGO's 2015 global guideline for IBS cites fecal inflammation marker (e.g., calprotectin) in a list of "high resource level" diagnostics, indicating the importance of the marker for distinguishing IBS from IBD. In their global guideline for IBD, WGO cited FC it as a simple, reliable, and readily available test for measuring IBD activity (Quigley et al.).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

PhiCal™ Fecal Calprotectin Immunoassay was classified as Class II on April 26, 2006 (Product Code NXO). Additional information is available at:

- http://www.accessdata.fda.gov/cdrh_docs/reviews/K050007.pdf
- http://www.accessdata.fda.gov/cdrh_docs/pdf5/K050007.pdf
  (Accessed February 28, 2023)

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Policy History/Revision Information

Date	Summary of Changes
08/01/2023	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS042.N

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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