Fecal Calprotectin Testing (for Louisiana Only)

Policy Number: CS042LA.~~J~~K
Effective Date: ~~March 1, 2023~~TBD

➲ Instructions for Use

Table of Contents **Page**

Application

This Medical Policy only applies to the state of Louisiana.

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

CPT® is a registered trademark of the American Medical Association

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

Diagnosis Code	Description
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 2 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~~DB~~ 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 1748 mcg/g vs 1353 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 ~~Crohn's disease (CD)~~**CD** who had experienced at least a 6-month clinical remission with anti-tumor necrosis factor (TNF) agents and simultaneously underwent ileocolonoscopy and ~~fecal calprotectin (~~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 ileocolonscopy. 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. ~~(Author~~**(Publication by** Ma 2017 which was previously cited in this policy, is included in this systematic review.)

~~Jung et al. (2021) conducted a systematic review and an updated meta-analysis to evaluate the relationship between small bowel inflammation and FC in patients with suspected/established CD. Fourteen studies were included in the analysis: 8 prospective and 6 retrospective studies. There was a comparison of FC level cutoffs of 50 µg/g, 100 µg/g, and 200 µg/g in each study. The overall review revealed a strong connection between FC levels and active inflammation in the small bowel as detected by small bowel capsule endoscopy. The authors concluded that the FC can be utilized as a screening tool for detecting small bowel CD and a cutoff of 100 µg/g had the highest diagnostic accuracy for detecting small bowel inflammation. (Authors Kopylov 2016, Sipponen 2012, and Koulaouzidis 2011 which were previously cited in this policy, are included in this systematic review.)~~

In a ~~report~~**Hayes (2021a) Health Technology Assessment,** assessing the monitoring of disease activity and treatment of UC in adults, Hayes ~~(2021a)~~ 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 ~~an additional report on the~~**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.**

~~A Hayes report (2017a; updated 2021) examined FC testing for prediction of endoscopic and clinically defined disease activity in patients with CD. The report indicates that the available evidence suggests that FC testing is safe for adults and may have promise for monitoring disease activity due to the moderate to high diagnostic sensitivity. However, no direct evidence was available regarding the clinical utility (i.e., change in patient management or improved clinical outcomes). In addition, another Hayes report (2017b; updated 2021) reviewed evidence monitoring for recurrence of CD in the postoperative patient. This report concluded that FC testing has generally high negative predictive value and moderate sensitivity but low-to-moderate specificity for predicting recurrence in adult patients with CD who have previously undergone ileocolic resection. The overall diagnostic accuracy of FC testing varied widely across studies, from low to moderately high, and none of the studies directly assessed measures of clinical utility. In the pediatric population, the evidence was insufficient to determine whether FC monitoring had an impact on health outcomes or patient management.~~

In a clinical assessment, ECRI (2021a) concluded that the evidence for the ~~fecal calprotectin~~**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 1301 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 2021 meta-analysis, Ye et al. sought to determine the validity of FC for evaluating histological activity of UC, based on updated definitions. In the histological activity evaluation, UC adult participants were included when sufficient data could be extracted to calculate the accuracy of FC. From 5 studies, 1039 patients were included in the primary outcome analysis of histological response. The secondary outcome was histological remission which included 591 patients from 4 studies. The pooled sensitivity, specificity, and the area under the curve were 0.69 [95% confidence interval (CI): 0.52-0.82], 0.77 (95% CI: 0.63-0.87), and 0.80 (95% CI: 0.76-0.83), respectively, for the evaluation of histological response. Likewise, the estimates were 0.76 (95% CI: 0.71-0.81), 0.71 (95% CI: 0.62-0.78), and 0.79 (95% CI: 0.75-0.82) for histological remission. In the histological response assessment, the cut-off values of FC ranged from 50 to 172µg/g, and in studies with FC cut-off values > 100µg/g (0.77 versus 0.65) sensitivity was higher. The authors concluded that FC is a valid diagnostic tool in gauging histological activity in patients with UC. A cut-off value of 100-200µg/g is more effective in identifying patients in histological response and limiting patients' exposure to additional testing such as endoscopies and biopsies.~~

~~Petryszyn et al. (2019) conducted a meta-analysis aimed to assess the efficacy of fecal calprotectin as a diagnostic marker of IBD. The authors systematically evaluated the value of fecal calprotectin as a marker of IBD in 5032 patients with gastrointestinal symptoms, chronic diarrhea or suspected IBD coming from 19 different studies. The pooled sensitivity was 0.882 (95% CI, 0.827-0.921) and the pooled specificity was 0.799 (95% CI, 0.693-0.875). The meta-analysis was done according to the Diagnostics Assessment Programme manual by NICE and for each study fecal calprotectin concentration must have been measured using the enzyme-linked immunosorbent assay (ELISA) method. The conclusion was fecal calprotectin testing is a useful screening test in patients with suspected IBD.~~

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~~**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).

~~Tham and colleagues (2018) conducted a systematic review and meta-analysis on FC and its utility in detecting postoperative endoscopic recurrence in CD. Nine studies (n = 588 patients) were analyzed, evaluating the accuracy of common FC cut-offs for detection of endoscopic recurrence. The results of the meta-analysis confirm the strong correlation between FC levels and postoperative endoscopic recurrence in patients with CD. Despite some limitations, most of which are inherent to all diagnostic meta-analyses, the researchers found that the data demonstrates that FC is an accurate surrogate marker of postoperative endoscopic recurrence in patients with CD. The FC cut-off of 150 µg/g appeared to have the best overall accuracy for this indication. They concluded that serial calprotectin evaluations may eliminate or defer the need for colonoscopic evaluation for postoperative recurrence surveillance in up to 70% of patients. (Author Boschetti 2015 which was previously cited in this policy, is included in this systematic review.)~~

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. ~~The authors found~~**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 ~~and~~ **as well as** heterogeneity between selected studies. ~~They~~**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~~**N** = 90), differentiation of symptoms of IBS from IBD in patients with known IBD (~~n~~**N** = 85), and as an objective measure of inflammation (~~n~~**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 ~~fecal calprotectin (FC) in~~**FCin** 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).

~~Kostakis et al. (2012) performed a systematic review that included 34 studies evaluating the use of FC testing in pediatric patients with IBD. The authors found that FC levels with IBD are much higher than those of healthy controls or patients with functional disorders or other GI. The results varied greatly when taking all studies into consideration. According to the authors, in cases of newly diagnosed and/or active IBD, the results are more homogeneous, with high sensitivity and positive likelihood ratio, low negative likelihood ratio, but moderate specificity. The authors concluded that the FC test could be used for supporting diagnosis or confirming relapse of IBD in pediatric patients. According to the authors, a positive result could confirm the suspicion of either IBD diagnosis or IBD relapse, due to the high sensitivity of the test, but a negative result should not exclude these conditions, due to its moderate specificity. Further clinical trials with larger patient populations are needed to clarify the optimal role of FC testing for evaluating IBD in children.~~

Colorectal Cancer (CRD)

There is limited quality evidence in the peer-reviewed literature demonstrating the benefit of ~~fecal calprotectin~~**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 = 97~~**N = 297**) with colorectal neoplasia had non-significantly higher FC levels by 132.2 ~~µg~~**microg**/g compared with ~~noncancer~~**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 ~~fecal calprotectin~~**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.

~~In an observational study, Manz et al. (2012) evaluated the diagnostic value of FC in 575 patients with abdominal discomfort who were referred for endoscopy. Calprotectin was measured in stool samples collected within 24 hours before the investigation using ELISA. The presence of a clinically significant finding in the GI tract was the primary endpoint of the study. Final diagnoses were adjudicated, blind to FC values. Median calprotectin levels were higher in patients with significant findings than in patients without significant findings. Using 50 µg/g as cut off yielded a sensitivity of 73% and a specificity of 93% with good positive and negative likelihood ratios (10.8 and 0.29, respectively). FC was useful as a diagnostic parameter both for findings in the upper intestinal tract and for the colon with higher diagnostic precision for the latter. In patients > 50 years, the diagnostic precision remained unchanged. The authors concluded that in patients with abdominal discomfort, FC is a useful non-invasive marker to identify clinically significant findings of the GI tract, irrespective of age. According to the authors, further prospective studies directly comparing recommended guidelines of appropriateness for endoscopy with FC measurements are warranted to establish the value of a biomarker-guided assessment of patients with abdominal discomfort.~~

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 ~~fecal~~ 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 ~~March 18, 2022~~ **February 28, 2023**)

References

Akpinar E, Vargas J, Kato T, et al. Fecal calprotectin level measurements in small bowel allograft monitoring: a pilot study. Transplantation. 2008 May 15;85(9):1281-6.

American Gastroenterological Association (AGA). **AGA** ~~IBD~~ Care Pathway**s**. **https://ibd.care/provider/aga-care-pathways/aga-care-pathways-introduction. Accessed April 20, 2023.** ~~https://www.ibd.care/care-navigator/aga-care-pathways. Accessed March 18, 2022.~~

Baldassarre ME, Fanelli M, Lasorella ML, et al. Fecal calprotectin (FC) in newborns: is it a predictive marker of gastrointestinal and/or allergic disease? Immunopharmacol Immunotoxicol. 2011 Mar;33(1):220-3.

Berman D, Parker SM, Siegel J, et al. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. Cancer Immun. 2010 Nov 24;10:11.

Boschetti G, Laidet M, Moussata D, et al. Levels of fecal calprotectin are associated with the severity of postoperative endoscopic recurrence in asymptomatic patients with Crohn's disease. Am J Gastroenterol. 2015 Jun;110(6):865-72.

Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicenter, randomized, controlled phase 3 trial. Lancet. 2018 Dec 23;390(10114):2779-2789.

ECRI Institute. Clinical Evidence Assessment. Fecal calprotectin for monitoring inflammatory bowel disease. May 2021a.

ECRI Institute. Clinical Evidence Assessment. Fecal calprotectin for aiding diagnosis of inflammatory bowel disease. April 2021b.

El-Matary W, Abej E, Deora V, et al. Impact of fecal calprotectin measurement on decision-making in children with inflammatory bowel disease. Front Pediatr. 2017 Jan;5:7.

Ertekin V, Selimoğlu MA, Turgut A, et al. Fecal calprotectin concentration in celiac disease. J Clin Gastroenterol. 2010 Sep;44(8):544-6.

Falloon K, Cohen BL, Ottichilo R, et al. Biomarkers for the evaluation of pouch inflammation: a systematic review. Crohns Colitis 360. 2022 Nov 24;4(4):otac043.

Hayes Inc. Health Technology Annual Review. Fecal calprotectin assay for monitoring disease activity and treatment management of ulcerative colitis in adults. Lansdale, PA: Hayes, Inc.; August 2022a.

Hayes Inc. Health Technology Annual Review. Fecal calprotectin for predicting clinical relapse or treatment response in adult patients with ulcerative colitis. Lansdale, PA: Hayes, Inc.; September 2022b.

Hayes Inc. **Health** ~~Medical~~ Technology **Assessment** ~~Directory~~. Fecal calprotectin assay for monitoring disease activity and treatment management of ulcerative colitis in adults. Lansdale, PA: Hayes, Inc.; August 17, 2021a.

Hayes Inc. **Health** ~~Medical~~ Technology **Assessment** ~~Directory~~. Fecal calprotectin for predicting clinical relapse or treatment response in adult patients with ulcerative colitis. Lansdale, PA: Hayes, Inc.; August 17, 2021b.

Hayes Inc. Medical Technology Directory. Fecal calprotectin assay for monitoring disease activity in Crohn disease. Lansdale, PA: Hayes, Inc.; July 7, 2017a. Updated May 2021. **Archived August 2022.**

Hayes Inc. Medical Technology Directory. Fecal calprotectin assay for monitoring postoperative recurrence of Crohn disease. Lansdale, PA: Hayes, Inc.; June 30, 2017b. Updated May–, 2021. **Archived July 2022.**

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. 2017;23(6):894-902.

Hille A, Schmidt-Giese E, Hermann RM, et al. A prospective study of fecal calprotectin and lactoferrin in the monitoring of acute radiation proctitis in prostate cancer treatment. Scand J Gastroenterol. 2008 Jan;43(1):52-8.

Jung ES, Lee SP, Kae SH, et al. Diagnostic accuracy of fecal calprotectin for the detection of small bowel Crohn's disease through capsule endoscopy: An updated meta-analysis and systematic review. Gut Liver. 2021 Sep 15;15(5):732-741.

Khoshbaten M, Pishahang P, Nouri M, et al. Diagnostic value of fecal calprotectin as a screening biomarker for gastrointestinal malignancies. Asian Pac J Cancer Prev. 2014;15(4):1667-70.

Kopylov U, Yung DE, Engel T, et al. Fecal calprotectin for the prediction of small-bowel Crohn's disease by capsule endoscopy: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2016 Oct;28(10):1137-44.

~~Kostakis ID, Cholidou KG, Vaiopoulos AG, et al. Fecal calprotectin in pediatric inflammatory bowel disease: a systematic review. Dig Dis Sci. 2013 Feb;58(2):309-19.~~

Koulaouzidis A, Douglas S, Rogers MA, et al. Fecal calprotectin: a selection tool for small bowel capsule endoscopy in suspected IBD with prior negative bi-directional endoscopy. Scand J Gastroenterol. 2011 May;46(5):561-6.

Koulaouzidis A, Sipponen T, Nemeth A, et al. Association between fecal calprotectin levels and small-bowel inflammation score in capsule endoscopy: A multicenter retrospective study. Dig Dis Sci. 2016 Jul;61(7):2033-2040.

Lacy BE, Pimentel M, Brenner DM, et al. ACG clinical guideline: Management of irritable bowel syndrome. Am J Gastroenterol. 2021 Jan 1;116(1):17-44.

Lee YM, Choi S, Choe BH, et al. Association between fecal calprotectin and mucosal healing in pediatric patients with Crohn's disease who have achieved sustained clinical remission with anti-tumor necrosis factor agents. Gut Liver. 2022 Jan 15;16(1):62-70.

Licata A, Randazzo C, Cappello M, et al. Fecal calprotectin in clinical practice: a noninvasive screening tool for patients with chronic diarrhea. J Clin Gastroenterol. 2012 Jul;46(6):504-8.

Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: Management of Crohn's disease in Adults. Am J Gastroenterol. 2018 Apr;113(4):481-517.

Lozoya Angulo ME, de Las Heras Gómez I, Martinez Villanueva M, et al. Fecal calprotectin, a useful marker in discriminating between inflammatory bowel disease and functional gastrointestinal disorders. Gastroenterol Hepatol. 2017 Mar;40(3):125-131.

Ma C, Lumb R, Walker E, et al. Noninvasive fecal immunochemical testing and fecal calprotectin predict mucosal healing in inflammatory bowel disease: A prospective cohort study. Inflamm Bowel Dis. 2017 Sep;23(9):1643-1649.

Manz M, Burri E, Rothen C, et al. Value of fecal calprotectin in the evaluation of patients with abdominal discomfort: An observational study. BMC Gastroenterol. 2012 Jan 10;12:5.

Mercer DF, Vargas L, Sun Y, et al. Stool calprotectin monitoring after small intestine transplantation. Transplantation. 2011 May 27;91(10):1166-71.

Nasir Kansestani A, Zare ME, Tong Q, ~~Zhang J~~**et al**. Comparison of f**a**ecal protein biomarkers' diagnostic accuracy for colorectal advanced neoplasms: a systematic review and meta-analysis. Sci Rep. 2022 Feb 16;12(1):2623.

National Institute for Health and Care Excellence (NICE). Fecal calprotectin diagnostic tests for inflammatory diseases of the bowel. Diagnostics guidance [DG11] Published date: October 2013. Revision date: May 2017.

Petryszyn P, Staniak A, Wolosianska A, et al. Fecal calprotectin as a diagnostic marker of inflammatory bowel disease in patients with gastrointestinal symptoms: Meta-analysis. Eur J Gastroenterol Hepatol. 2019 Nov;31(11):1306-1312.

Pieczarkowski S, Kowalska-Duplaga K, Kwinta P, et al. Diagnostic value of fecal calprotectin (S100 A8/A9) test in children with chronic abdominal pain. Gastroenterol Res Pract. 2016;2016:8089217.

Quigley EM, Fried M, Gwee KA, et al. World gastroenterology Organization global guidelines irritable bowel syndrome: A global perspective update September 2015. J Clin Gastroenterol. 2016 Oct;50(9):704-13.

Rosenfeld G, Greenup A-J, Round A, et al. FOCUS: Future of fecal calprotectin utility study in inflammatory bowel disease. World J Gastroenterol. 2016 Sep 28;22(36):8211-8218.

Ross FA, Park JH, Mansouri D, et al. The role of faecal calprotectin in diagnosis and staging of colorectal neoplasia: a systematic review and meta-analysis. BMC Gastroenterol. 2022 Apr 9;22(1):176.

Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. Gastroenterology. 2014 Sep;147(3):702-5.

Sasidharan S, Sasson AN, Shannon KM, et al. Fecal calprotectin is a predictor of need for rescue therapy in hospitalized severe colitis. Inflamm Bowel Dis. 2022 Dec 1;28(12):1833-1837.

Selimoğlu MA, Temel I, Yıldırım Ç, et al. The role of fecal calprotectin and lactoferrin in the diagnosis of necrotizing enterocolitis. Pediatr Crit Care Med. 2012 Jul;13(4):452-4.

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 Jul 11;9:920732

Singh S, Ananthakrishnan AN, Nguyen NH, et al. Electronic address: clinicalpractice@gastro.org. AGA clinical practice guideline on the role of biomarkers for the management of ulcerative colitis. Gastroenterology. 2023 Mar;164(3):344-372.

Sipponen T, Haapamäki J, Savilahti E, et al. Fecal calprotectin and S100A12 have low utility in prediction of small bowel Crohn's disease detected by wireless capsule endoscopy. Scand J Gastroenterol. 2012 Jul;47(7):778-84.

Smalley W, Falck-Ytter C, Carrasco-Labra A, et al. AGA clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology. 2019 Sep;157(3):851-854.

State M, Negreanu L, Voiosu T, et al. Surrogate markers of mucosal healing in inflammatory bowel disease: A systematic review. World J Gastroenterol. 2021 Apr 28;27(16):1828-1840.

Tham YS, Yung DE, Fay S, et al. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis. Therap Adv Gastroenterol. 2018 Jul 8;11:1756284818785571.

Tursi A, Brandimarte G, Elisei W, et al. Fecal calprotectin in colonic diverticular disease: a case-control study. Int J Colorectal Dis. 2009 Jan;24(1):49-55.

von Roon AC, Karamountzos L, Purkayastha S, et al. Diagnostic precision of fecal calprotectin for inflammatory bowel disease and colorectal malignancy. Am J Gastroenterol. 2007 Apr;102(4):803-13.

Xiang BJ, Jiang M, Sun MJ, et al. Optimal range of fecal calprotectin for predicting mucosal healing in patients with inflammatory bowel disease: A systematic review and meta-analysis. Visc Med. 2021 Oct;37(5):338-348.

Ye X, Huai J, Ding J. Diagnostic accuracy of fecal calprotectin for screening patients with colorectal cancer: A meta-analysis. Turk J Gastroenterol. 2018 Jul;29(4):397-405.

Ye X, Wang Y, Wang HHX, et al. Can fecal calprotectin accurately identify histological activity of ulcerative colitis? A meta-analysis. Therap Adv Gastroenterol. 2021 Feb 27;14:1756284821994741.

Policy History/Revision Information

Date	Summary of Changes
TBD	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS042LA.J

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.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.