FECAL CALPROTECTIN TESTING

Guideline Number: MMG044.H **Effective Date**: April 7, 2019

Instructions for Use

Table of Contents **Page**

Related Policies

None

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 guideline 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 the member specific benefit plan document 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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ICD-10 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

ICD-10 Diagnosis Code	Description
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
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

ICD-10 Diagnosis Code	Description
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
K51.914	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
K58.9	Irritable bowel syndrome without diarrhea
K59.1	Functional diarrhea
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 two 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 members 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 IDB including CD and UC. The use of FC has also been proposed as a predictive response to treatment in members 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 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 subscores 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 on the basis of 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).

A total of 80 individuals with IBD (40 with CD and 40 with UC) were included in a prospective cohort study by Ma, et al., assessing the specificity of noninvasive fecal immunochemical testing (FIT) and FC for the prediction of mucosal healing. In outpatients presenting for colonoscopy, stool samples were collected 48 hours prior to the procedure. Mucosal healing was defined by Simple Endoscopic Score for Crohn's disease (SES-CD = 0), Rutgeert's score (i0), and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS = 3). A multivariate logistic regression analysis revealed that FIT and FC have similar performance characteristics, with the combination of both low FIT and FC along with clinical remission being specific for mucosal healing (2017).

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 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.

In 2016, Kopylov and colleagues conducted a systematic review and diagnostic meta-analysis (3 prospective and 4 retrospective studies) of patients with suspected/established CD who underwent capsule endoscopy and FC testing (N = 463). The researchers concluded that FC has a significant diagnostic accuracy for the detection of small bowel CD and suggest that with FC levels < 50 µg/g, the likelihood of positive diagnosis of CD is very low.

Mao et al. (2012) performed a meta-analysis of the predictive capacity of FC in patients with IBD. The authors analyzed 6 prospective studies with a total of 672 IBD patients (318 patients with UC, 354 patients with CD). The pooled sensitivity and specificity of FC to predict relapse of IBD was 78% and 73%, respectively. The capacity of FC to predict relapse was comparable between UC and CD. The authors concluded that FC assessment is a simple and non-invasive test, but the diagnostic performance of this test was lower than expected. The authors noted that a limitation of the studies was that remission was based on subjective clinical activity indices. Additional prospective studies using endoscopy to confirm relapse are needed to clarify the role of FC.

van Rheenen et al. (2010) performed a meta-analysis on 13 studies to evaluate whether the use of FC reduces the number of unnecessary endoscopic procedures in patients with IBD. Six studies were done in adults (N = 670) and 7 studies in children and teenagers (N = 371). IBD was confirmed by endoscopy in 32% (N = 215) of the adults and 61% (N = 226) of the pediatric group. In adults, the pooled sensitivity and specificity of FC was 0.93 and 0.96 and in the studies of children and teens was 0.92 and 0.76, respectively. According to the authors, screening by measuring FC levels would result in a 67% reduction in the number of adults requiring endoscopy. Three of 33 adults who undergo endoscopy will not have IBD but may have a different condition for which endoscopy is inevitable. In the pediatric population, 65 instead of 100 would undergo endoscopy. Nine of them will not have IBD. The downside of such screening would be a delayed diagnosis in 6% of affected adults and in 8% of affected children because of false-negative test results. The authors concluded that testing for FC is a useful screening tool for identifying patients who are most likely to need endoscopy for suspected IBD. The researchers also point out methodological limitations of their meta-analysis. Two of the included studies in adults did not sample intestinal mucosa, which might have caused some patients to be misclassified as normal. In addition, none of the studies used a well-defined set of clinical findings or flow chart to identify patients with a high probability of IBD. The authors also noted that the pooled sensitivity and specificity found in their study should be interpreted with caution. The authors commented, "Despite a strict selection of studies based on proper patient recruitment and study design, heterogeneity was considerable."

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 diseases. 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 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.

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 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 studies meeting inclusion criteria and heterogeneity between selected studies. They 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.

Diamanti et al. (2010) assessed the diagnostic accuracy of the FC assay as a stool-screening biomarker for IBD. All patients suspected of IBD provided stool specimens for the calprotectin assay and subsequently underwent endoscopic procedures. Compared to histology, the cutoff of 100 µg/g reached a sensitivity and specificity of 100% and 68%, respectively. The cutoff value of 160 µg/g, however, produced the best joint estimate of sensitivity and specificity: 100% and 80%, respectively. Further study is needed to define the optimal FC cutoff value for evaluating IBD.

Meucci et al. (2010) evaluated the role of FC in 870 consecutive outpatients referred for colonoscopy. Mean levels of FC were significantly higher in patients with neoplastic and inflammatory disorders when compared with subjects with a normal colonoscopy or trivial endoscopic findings. Elevated FC levels (> 50mg/dl) were detected in 85% of patients with CRC and 81% of those with inflammatory conditions, but also in 37% of patients with normal or trivial endoscopic findings. In patients referred for chronic diarrhea, sensitivity and negative predictive value were 100% in detecting organic colonic disease. In patients referred for symptoms of "suspected functional origin," sensitivity and negative predictive value for CRC were also 100%. According to the investigators, in unselected outpatients referred for colonoscopy, a single measurement of FC is not sufficiently accurate to identify those with significant colorectal disease. However, a normal result can help rule out organic disease among patients with diarrhea and those with abdominal pain and/or constipation.

Koulaouzidis et al. (2011) performed a retrospective study investigating the value of FC as a selection tool for further investigation of the small bowel with small bowel capsule endoscopy (SBCE) in a cohort of patients (N = 70) who had negative bi-directional endoscopies, but with continuing clinical suspicion of CD. Twenty-three patients had normal FC (≤ 50 µg/g) and in all those the SBCE was normal. Forty-four patients had FC > 50 µg/g; in this group, 9 patients had FC between 51-100 µg/g and all had a normal SBCE. Thirty-five patients had FC levels >100 µg/g; of those, 15 (42.85%) had SBCE findings compatible with CD and mean FC levels of 326 µg/g. A definitive clinical diagnosis of CD, based on subsequent follow-up, was made in 10 of 35 patients (28.5%). These 10 patients were within the subgroup of 15 patients with positive SBCE findings and had a median FC level of 368 µg/g. The authors concluded that measurement of FC levels prior to referral for SBCE is a useful tool to select patients with possible small bowel CD. The authors stated that a FC > 100 µg/g is good predictor of positive SBCE findings, while FC > 200 µg/g was associated with higher SBCE yield (65%) and confirmed CD in 50% of cases. According to the authors, FC assessment should be carried out prior to referral for SBCE in all patients with clinical suspicion of CD and negative bi-directional endoscopies. Where FC is <100 µg/g (NPV 1.0), SBCE is not indicated. These findings require confirmation in a larger study.

Koulaozidis and colleagues also conducted an international, multicenter retrospective study investigating the correlation between Lewis score and FC in 333 patients undergoing SBCE for suspected or known IBD. They also aimed to develop a model for predicting CE results (Lewis score) based on FC levels. 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. Lewis score appeared to show low correlation with FC and other serology markers indicating inflammation (2016).

Sipponen et al. (2012) studied the role of FC and fecal S100A12 in predicting inflammatory lesions of the small bowel in 84 patients (77 for suspicion of CD and 7 CD patients for evaluation of disease extent) undergoing wireless capsule endoscopy (WCE). Patients provided a stool sample for measurement of biomarkers, and underwent an esophagogastroduodenoscopy and ileocolonoscopy before WCE. WCE was abnormal in 35 of 84 patients (42%): 14 patients with CD, 8 with NSAID enteropathies, 8 with angioectasias, 4 with polyps or tumors, and 1 with ischemic stricture. FC was significantly higher in CD patients compared with those with normal WCE or other abnormalities, whereas fecal S100A12 did not differ between the groups. In detecting inflammatory small bowel lesions, sensitivity,

specificity, positive and negative predictive value for FC (cutoff 50 µg/g) were 59%, 71%, 42%, and 83%. The authors concluded that in predicting small bowel inflammatory changes, fecal biomarkers calprotectin and S100A12 have moderate specificity, but low sensitivity. Neither FC nor S100A12 can be used for screening or excluding small bowel CD.

Additional clinical trials indicate that patients with IDB have abnormal or elevated FC levels compared with control subjects (Henderson et al. 2012, Komraus et al. 2012, Schoepfer et al. 2010, Schoepfer et al. 2009, Erbayrak et al. 2009, Tursi et al. 2011, Aomatsu et al. 2011, Sipponen et al. 2010, Kallel et al. 2009). More recent studies and meta-analyses state that FC is a useful tool in evaluating UC and CD in certain circumstances, including IBD in children (Holtman et al. 2017, Holtman et al. 2016, Bressler et al. 2015, Wright et al. 2015, Kennedy, et al. 2015, Mosli et al. 2015, Menees et al. 2015, Lin et al. 2014, Qiu et al. 2015, Sandborn et al. 2015.). However, these studies did not confirm the utility of FC testing for altering therapeutic decisions, minimizing disease complications, or reducing the need for more invasive testing.

A Hayes report examined FC testing for prediction of endoscopic and clinically defined disease activity in patients with CD. Evidence from the published, peer-reviewed literature (which included 15 prospective cohort studies and 1 retrospective cross-sectional study with a range of 78-221 participants) was considered to be low quality. The authors determined 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). Additional studies are needed to define uniform cutoffs for FC testing to predict and monitor CD activity. There is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management for pediatric patients (2018a).

In monitoring for recurrence of CD in the postoperative patient, Hayes reviewed evidence (8 prospective cohort studies, 2 retrospective cross-sectional studies, and 1 subgroup analysis of a RCT, N = 20-135) which was also considered low quality. The authors 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 (2018b).

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 CD patients. 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.

Walsham and Sherwood (2016) performed a review focusing on the use of FC measurements in the diagnosis and monitoring of patients with IBD. Five meta-analyses and over 30 various studies taking place over 10+ years included over 15,000 adult and pediatric participants. The authors concluded that FC has adequate sensitivity and specificity to identify and differentiate IBD from functional disease permitting effective management of colonoscopy resources, it can be successfully used to monitor and initiate prompt therapy relating to clinical relapse of IBD, and FC measurements are determined to be beneficial when assessing and treating other intestinal diseases. The analysis did not translate research data into clinical guidelines that would affect physician practice patterns or patient management.

Recognizing FC as a widely used marker of gut inflammation strongly associated with the severity of endoscopic lesions in CD, Boschetti et al. (2015) analyzed the relationships between levels of FC and high-sensitivity CRP and the presence and severity of postoperative endoscopic recurrence in asymptomatic CD patients. Eighty six patients were included in this prospective multicenter observational cohort. FC concentrations differed significantly in patients with endoscopic recurrence when compared with those in endoscopic remission. The best cutoff point for FC to distinguish between endoscopic remission and recurrence was 100 µg/g. Its sensitivity, specificity, positive and negative predictive values as well as overall accuracy were 95%, 54%, 69%, 93%, and 77%, respectively. The authors concluded that measurement of FC concentrations is a promising and useful tool for monitoring asymptomatic CD patients after ileocolonic resection. Taking into account the high negative predictive value of FC, a threshold below 100 µg/g could avoid systematic ileocolonoscopies in 30% of individuals from this patient group. A small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population.

The 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).

Colorectal Cancer (CRC)

Khoshbaten et al. (2014) utilized a case-control study to evaluate the diagnostic value of FC as a screening biomarker for GI malignancies. Calprotectin in feces seems to be a more sensitive marker for GI cancers than fecal occult blood, but its specificity may be too low for screening average risk populations. The case control study included 100 patients with GI malignancies (50 patients with CRC and 50 patients with gastric cancer) and 50 controls were recruited in 2 hospitals during a 24-month period. One to two weeks after the last endoscopy/ colonoscopy, fecal specimens were collected by the patients and examined by the enzyme-linked immunosorbent assay (ELISA) method for quantitative measurement of calprotectin content. The results were compared between the 3 groups. In gastric cancer, CRC and the control group with differences being significant and remaining after adjustment for age, median FC levels were 74, 19.3, and 19.3, respectively. The optimal cut-off point for FC was ≥ 75.8 µg/g for distinguishing CRC from normal cases (sensitivity and specificity of 80% and 84%, respectively). FC value was ≥ 41.9 µg/g for distinguishing gastric cancer from normal cases (sensitivity and specificity of 62%). The author's results revealed that FC might be a useful and non-invasive biomarker for distinguishing CRC from non-malignant GI conditions. However, due to low sensitivity and specificity, this biomarker may not help physicians distinguishing gastric cancer cases from healthy subjects.

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 noncancer 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

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), 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.

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. 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.

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.

Multiple types of fecal biomarkers were discussed by Siddiqui et al. (2017) in a review evaluating the current status of FC and FL in both clinical practice and in research of GI diseases. The authors stated that while FC and FL are well documented in the management of IBD, studies are still needed to understand their role in other GI pathologies.

Professional Societies

American College of Gastroenterology (ACG)

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)

In their clinical care pathway for treating relapse of CD and UC, the AGA recommends the use of objective measures of disease activity (FC and CRP) as part of the overall assessment of treatment response.

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).

World Gastroenterology Organization (WGO)

The WGO's 2015 global guideline for IBScites 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)

PhiCalTM 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 21, 2019)

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GUIDELINE HISTORY/REVISION INFORMATION

Date	Action/Description
04/07/2019	• Revised coverage rationale: ○ Simplified content ○ Added language to indicate fecal measurement of calprotectin is proven and medically necessary for establishing the diagnosis or for management of Crohn’s disease and ulcerative colitis

Date	Action/Description
	○ Replaced language indicating "fecal measurement of calprotectin is unproven and not medically necessary for the diagnosis *and* management of *all* conditions *including but not limited to [those listed in the policy]*" with "fecal measurement of calprotectin is unproven and not medically necessary for *establishing* the diagnosis *or for* management of *any other* condition *[not listed as proven and medically necessary]*" • Added list of applicable ICD-10 diagnosis codes: K50.00, K50.011, K50.012, K50.013, K50.014, K50.018, K50.019, K50.10, K50.111, K50.112, K50.113, K50.114, K50.118, K50.119, K50.80, K50.811, K50.812, K50.813, K50.814, K50.818, K50.819, K50.90, K50.911, K50.912, K50.913, K50.914, K50.918, K50.919, K51.00, K51.011, K51.012, K51.013, K51.014, K51.018, K51.019, K51.20, K51.211, K51.212, K51.213, K51.214, K51.218, K51.219, K51.30, K51.311, K51.312, K51.313, K51.314, K51.318, K51.319, K51.50, K51.511, K51.512, K51.513, K51.514, K51.518, K51.519, K51.80, K51.811, K51.812, K51.813, K51.814, K51.818, K51.819, K51.90, K51.911, K51.912, K51.914, K51.918, K51.919, K58.0, K58.9, K59.1, and R19.7 • Updated supporting information to reflect the most current description of services, clinical evidence, and references • Archived previous policy version MMG044.G

INSTRUCTIONS FOR USE

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines 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.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.