MEDICAL POLICY

Fecal Calprotectin Testing: Medical Policy (Effective 04/01/2014)

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FECAL CALPROTECTIN TESTING

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Related Policies: None

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, 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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COVERAGE RATIONALE

Fecal measurement of calprotectin is unproven and not medically necessary for the diagnosis and management of all conditions including but not limited to the following:

- Inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's disease
- Colorectal cancer

There is insufficient evidence that fecal calprotectin is effective as a biomarker for the diagnosis and management of intestinal disease. Before fecal calprotectin can be incorporated into routine clinical practice, studies in larger and diverse groups of patients will be needed to further clarify its role in clinical decision making and its effect on the outcome of treatment of the condition for which it is being used.
APPLICABLE CODES

The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit 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 claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

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<th>CPT® Code</th>
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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 and Crohn's disease are examples of IBD. Both diseases are characterized by an uncontrolled inflammatory response at the mucosal level resulting in tissue damage. Most cases of Crohn's disease and ulcerative colitis 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 stool in patients with IBD and other gastrointestinal conditions. Fecal calprotectin, used as a marker of intestinal inflammation, has been proposed to aid in the diagnosis and as a predictor of relapse in inflammatory bowel diseases (IBD) including Crohn’s disease and ulcerative colitis. The use of fecal calprotectin has also been proposed as a predictive response to treatment in patients with IBD rather than relying solely on clinical symptoms.

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

CLINICAL EVIDENCE

The clinical evidence was reviewed on January 17, 2014 with no additional information identified that would change the unproven and not medical necessary conclusion.

Inflammatory Bowel Disease (IBD)

Mao et al. (2012) performed a meta-analysis of the predictive capacity of fecal calprotectin (FC) in patients with inflammatory bowel disease (IBD). The authors analyzed 6 prospective studies with a total of 672 IBD patients (318 patients with ulcerative colitis (UC) and 354 patients with Crohn's disease (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 fecal calprotectin 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 to evaluate whether the use of fecal calprotectin reduces the number of unnecessary endoscopic procedures in patients with inflammatory bowel disease. A total of 13 studies up to October 2009 were included in the analysis. Six studies were done in adults (n=670) and seven studies in children and teenagers (n=371). Inflammatory bowel disease was confirmed by endoscopy in 32% (n=215) of the adults and 61% (n=226) of the children and teenagers. In adults, the pooled sensitivity and pooled specificity of calprotectin was 0.93 and 0.96 and in the studies of children and teenagers was 0.92 and 0.76. The lower specificity in the studies of children and teenagers was significantly different from that in adults. According to the authors, screening by measuring fecal calprotectin levels would result in a 67% reduction in the number of adults requiring endoscopy. Three of 33 adults who undergo endoscopy will not have inflammatory bowel disease but may have a different condition for which endoscopy is inevitable. In the population of children and teenagers, 65 instead of 100 would undergo endoscopy. Nine of them will not have inflammatory bowel disease. 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 fecal calprotectin is a useful screening tool for identifying patients who are most likely to need endoscopy for suspected inflammatory bowel disease. 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."

A quantitative meta-analysis to evaluate fecal calprotectin (FC) for inflammatory bowel disease (IBD) and colorectal cancer (CRC) in adults and children was performed on prospective studies, comparing FC levels against the histological diagnosis. Thirty studies of 5,983 patients were included. FC levels in patients with IBD were higher by 219.2 micrograms per gram (microg/g) compared with normal patients. Summary receiver-operating characteristic (sROC) curve analysis showed a sensitivity of 0.95 and specificity of 0.91. The diagnostic precision of FC for IBD was higher in children than adults with better accuracy at a cutoff level of 100 microg/g versus 50 microg/g. Sensitivity analysis and meta-regression analysis did not significantly alter the results. The investigators concluded that FC appears to offer a good diagnostic precision in distinguishing IBD from non-IBD diagnoses, with higher precision at a cutoff of 100 microg/g. Although the normal range has been defined for FC, an optimal cutoff point for distinguishing IDB from other diagnoses has not been defined (von Roon et al. 2007).

Jellema et al. (2011) statistically analyzed and summarized the available evidence on diagnostic tests in patients with abdominal symptoms. Studies were selected if the design was a primary diagnostic study. Patients were adults attending with nonacute abdominal symptoms. Tests included clinical assessment, blood or fecal tests or abdominal ultrasonography. Diagnostic two-by-two tables and pooled estimates of sensitivity and specificity were calculated. A total of 24 studies were included. While the diagnostic performance of the individual symptoms was highly variable, the performance of symptom-based classification systems was both more consistent and better. Among fecal and blood tests, calprotectin was studied most frequently and showed the best results (sensitivity 0.61-1.0, specificity 0.71-1.0). Statistical pooling for ultrasonography resulted in a sensitivity of 0.73 (0.65-0.80) and a specificity of 0.95 (0.91-0.97). The authors concluded that although calprotectin and ultrasonography showed consistent and promising findings, none of the studies was performed in primary care. The authors stated that before calprotectin can be used to guide clinical decisions in primary care, these markers need to be investigated by high-quality prospective studies in the primary care setting.
Kostakis et al. (2012) performed a systematic review that included 34 studies evaluating the use of fecal calprotectin testing in pediatric patients with inflammatory bowel disease. The authors found that fecal calprotectin levels of patients with inflammatory bowel disease are much higher than those of healthy controls or patients with functional disorders or other gastrointestinal diseases. The results varied greatly when taking all studies into consideration. According to the authors, in cases of newly diagnosed and/or active inflammatory bowel disease, the results are more homogeneous, with high sensitivity and positive likelihood ratio, low negative likelihood ratio, but moderate specificity. The authors concluded that the fecal calprotectin test could be used for supporting diagnosis or confirming relapse of inflammatory bowel disease in pediatric patients. According to the authors, a positive result could confirm the suspicion of either inflammatory bowel disease diagnosis or inflammatory bowel disease 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 fecal calprotectin testing for evaluating IBD in children.

A prospective multicenter study was conducted by Gisbert et al. (2009) to determine the role of fecal calprotectin and lactoferrin in the prediction of inflammatory bowel disease relapses. A total of 163 patients with ulcerative colitis (UC) (n=74) and Crohn's disease (CD) (n=89) who had been in clinical remission for 6 months were included in the study. At baseline, patients provided a single stool sample for calprotectin and lactoferrin determination. Follow-up was 12 months in patients showing no relapse and until activity flare in relapsing patients. Twenty-six patients (16%) relapsed during follow-up. Calprotectin concentrations in patients who suffered a relapse were higher than in nonrelapsing patients. Relapse risk was higher in patients having high calprotectin concentrations (30% versus 7.8%) or positive lactoferrin (25% versus 10%). Fecal calprotectin (>150 microg/g) sensitivity and specificity to predict relapse were 69% and 69%, respectively. Corresponding values for lactoferrin were 62% and 65%, respectively. Better results were obtained when only colonic CD disease or only relapses during the first 3 months were considered (100% sensitivity). The investigators concluded that fecal calprotectin and lactoferrin determination may be useful in predicting impending clinical relapse—especially during the following 3 months—in both CD and UC patients. This study did not confirm the utility of such findings in improving care and outcome of patients.

Garcia-Sanchez et al. (2010) performed a prospective study of 135 patients diagnosed with IBD in clinical remission for at least 3 months. All patients were followed-up for one year. Sixty-six patients had Crohn's disease (CD) and 69 had ulcerative colitis (UC). Thirty-nine (30%) suffered from relapse. The fecal calprotectin concentration was higher among the patients with relapse than in those that remained in remission. Patients with CD and calprotectin greater than 200µg/g relapsed 4 times more often than those with lower marker concentrations. In UC, calprotectin greater than 120µg/g was associated with a 6-fold increase in the probability of disease activity outbreak. The predictive value was similar in UC and CD with colon involvement and inflammatory pattern. In this group, calprotectin greater than 120µg/g predicted relapse risk with a sensitivity of 80% and a specificity of 60%. Relapse predictive capacity was lower in patients with ileal disease. Larger studies are needed to demonstrate that fecal calprotectin testing has sufficient diagnostic accuracy to provide clinically relevant information when compared to other currently available diagnostic tests to allow for clinical decision-making.

Fecal calprotectin and tumor M2-pyruvate kinase (M2-PK) were measured in 94 controls and 105 gastroenterology outpatients with a possible diagnosis of organic bowel disease. The diagnosis was made by clinical, endoscopic, and radiological criteria. Organic bowel disease was diagnosed in 14 patients (13%). Sensitivity, specificity, and positive and negative likelihood ratios for diagnosis of organic bowel disease were 93%, 92%, 11.6, and 0.07 for calprotectin and 67%, 88% 5.6, and 0.18 for tumor M2-PK, respectively. Calprotectin in combination with tumor M2-PK had a sensitivity of 64%, specificity of 98%, and likelihood ratios of 32 and 0.03. An elevated calprotectin or tumor M2-PK decreased specificity to 87%, but increased sensitivity to 100%
Further research is needed to determine whether fecal calprotectin testing improves clinical decision making and health outcomes in patients with bowel disease.

Diamanti et al. (2010) assessed the diagnostic accuracy of the fecal calprotectin assay as a stool-screening biomarker for inflammatory bowel disease (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 fecal calprotectin cutoff value for evaluating IBD.

Turner et al. (2010) conducted a prospective multicentre cohort study to evaluate four fecal markers (calprotectin; lactoferrin, M2-pyruvate kinase (M2-PK), and S100A12). Stool samples from 101 children with severe ulcerative colitis (UC) were obtained at the third day of intravenous steroid therapy. Repeated samples at discharge were obtained from 24 children. Median values (IQR) were very high at baseline for all four markers. M2-PK was numerically superior to the other three markers and CRP in predicting response to corticosteroid treatment. However, it did not add to the predictive ability of the Pediatric UC Activity Index (PUCAI). M2-PK also had the highest construct validity but with a modest mean correlation with all constructs. None of the markers was responsive to change. According to the investigators, the PUCAI, a simple clinical index, performed better than the fecal markers in predicting outcome following a course of intravenous corticosteroids in severe UC.

Meucci et al. (2010) evaluated the role of fecal calprotectin in 870 consecutive outpatients referred for colonoscopy. Mean levels of calprotectin were significantly higher in patients with neoplastic and inflammatory disorders when compared with subjects with a normal colonoscopy or trivial endoscopic findings. Elevated calprotectin levels (>50mg/dl) were detected in 85% of patients with colorectal cancer, 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 colorectal cancer were also 100%. According to the investigators, in unselected outpatients referred for colonoscopy, a single measurement of fecal calprotectin 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) investigated the value of fecal calprotectin (FC) as a selection tool for further investigation of the small bowel with small bowel capsule endoscopy (SBCE), in a cohort of patients who had negative bi-directional endoscopies, but with continuing clinical suspicion of Crohn’s disease (CD). The authors retrospectively correlated the findings of SBCE with FC levels in patients referred with clinical suspicion of CD and negative bi-directional endoscopies. Seventy adult patients were included in the study. 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, nine patients had FC between 51 and 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 326 μg/g. A definitive clinical diagnosis of CD, based on subsequent follow-up, was made in 10/35 (28.5%) of patients. These 10 patients were within the subgroup of 15 patients with positive SBCE findings and had median FC levels 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 their 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.

Laharie et al. (2011) evaluated the association between fecal calprotectin concentration and Crohn’s disease (CD) clinical relapse in patients achieving remission with infliximab (IFX). Sixty-five patients were included in the study. Median fecal calprotectin level at week 14 was similar in patients with and without CD clinical relapse (200 and 150μg/g respectively). When considering two suggested fecal calprotectin cut-offs to predict CD relapse, sensitivities and specificities were 61% and 48% for 130μg/g, respectively, and 43% and 57% for 250μg/g. Neither fecal calprotectin nor CRP at baseline and at week 14 could predict relapse even when CD location subgroup analysis was considered. The authors concluded that in patients responding to an infliximab induction regimen, fecal calprotectin measurement at w14 cannot predict Crohn's disease clinical relapse at 1 year.

Sipponen et al. (2012) studied the role of calprotectin and fecal S100A12 in predicting inflammatory lesions of 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 measurements of biomarkers. Patients underwent an esophagogastroduodenoscopy and ileocolonoscopy before WCE. WCE was abnormal in 35 (42%) of 84 patients: 14 patients with CD, 8 with NSAID enteropathies, 8 with angioectasias, 4 with polyps or tumors, and 1 with ischemic stricture. Fecal calprotectin 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 predictive value, and negative predictive value for fecal calprotectin (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 fecal calprotectin nor S100A12 can be used for screening or excluding small bowel CD.

Additional clinical trials indicate that patients with IDB have abnormal or elevated fecal calprotectin 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). However, these studies did not confirm the utility of fecal calprotectin testing for altering therapeutic decisions and reducing disease complications and more invasive testing. Larger studies are needed to clarify the role of fecal calprotectin in clinical practice and to define the optimal cutoff point for distinguishing IDB from other diagnoses.

**Colorectal Cancer**

A quantitative meta-analysis to evaluate the diagnostic precision of FC for inflammatory bowel disease (IBD) and colorectal cancer (CRC) in adults and children was performed on prospective studies, comparing FC levels against the histological diagnosis. Thirty studies of 5,983 patients were included. Patients with colorectal neoplasia had nonsignificantly 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. The diagnostic precision of FC for IBD was higher in children than adults with better accuracy at a cutoff level of 100 microg/g versus 50 microg/g. 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).

Damms and Bischoff (2008) assessed the potential of measuring fecal calprotectin as screening method for intestinal inflammation and colorectal malignancies in 140 patients and concluded that fecal calprotectin assays are effective in identifying active inflammatory bowel disease (IBD) and colorectal carcinoma (CRC) but lack analytical sensitivity in separating CRC from adenoma as well as adenoma from the control group.
Six markers, including immunologic fecal occult blood test (iFOBT), were evaluated in a collective of 551 samples (186 colorectal cancer (CRC), 113 advanced adenoma, and 252 control patients) to establish the diagnostic performance of each marker and marker combinations. The study included testing of the known stool markers hemoglobin (iFOBT), hemoglobin-haptoglobin, calprotectin, carcinoembryogenic antigen, and the novel fecal markers tissue inhibitor of metalloproteinase-1 (TIMP-1) and S100A12. The best diagnostic performance was found for S100A12 with an area under the curve of 0.95, followed by TIMP-1 (0.92), hemoglobin-haptoglobin (0.92), hemoglobin (0.91), calprotectin (0.90), and carcinoembryogenic antigen (0.66) (Karl et al, 2008).

In a prospective study, Shitrit et al. (2007) assessed the value of fecal calprotectin in predicting abnormal histologic findings in patients undergoing colonoscopy. Stool specimens supplied before colonoscopy by 72 consecutive patients were measured for calprotectin levels, and the findings correlated with the colonoscopy results and other fecal and blood parameters. Patients with abnormal histologic findings had significantly higher calprotectin levels than patients with normal colonoscopy. Patients with active inflammatory bowel disease had higher calprotectin levels than the rest of the study patients. On multivariate analysis, calprotectin was a significant predictor of abnormal colonic histology. A fecal calprotectin concentration of 150 microg/ml had a sensitivity of 75 percent, specificity of 84 percent, positive predictive value of 80 percent, and negative predictive value of 75 percent in predicting abnormal colonic histology.

Summerton et al. (2002) assessed the potential of measuring the calcium-binding protein calprotectin in faeces as a method of screening for alimentary inflammation and neoplasia. Eighteen patients with known inflammatory bowel disease (seven patients), gastric carcinoma (one patient), colorectal cancer (eight patients) and colorectal adenoma (two patients) had faeces analyzed. The investigators found that calprotectin levels are elevated in inflammation and cancer but are not helpful in differentiating between these disorders. Calprotectin was not elevated in colonic polyps or adenomata.

Kronborg et al. (2000) measured the sensitivity and specificity of fecal calprotectin for the detection of adenomas in high risk individuals undergoing colonoscopy. A total of 814 patients planned for colonoscopy were included for the following indications: positive faecal occult blood test, 25; neoplasia surveillance, 605; newly detected polyp, 130; and family risk, 54. Adenoma patients had significantly higher calprotectin levels than normal subjects. There was no significant decrease in calprotectin levels after polypectomy. Levels in cancer patients were significantly higher than those in all other subgroups. With a cut off limit of 10 mg/l, the sensitivity for cancer was 74% and for adenoma 43%. Corresponding specificity values were 64% for no cancer and 67% for no neoplasia (cancer+adenoma). Specificity varied from 71% for one stool sample to 63% for four samples. The investigators concluded that the sensitivity and specificity of faecal calprotectin levels as a marker for colorectal adenoma and carcinoma justifies its use in high risk groups, but specificity is too low for screening of average risk persons.

Other Intestinal Conditions
Fecal calprotectin 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, Shastri et al. 2008), intestinal allograft monitoring (Akpinar et al. 2008, Sudan et al. 2007), colonic polyposis (Pezzilli et al. 2008), celiac disease (Ertekin et al. 2010), gastrointestinal disease in neonates (Selimoğlu et al. 2012, Baldassarre et al. 2011), and acute radiation proctitis monitoring (Hille et al. 2008, Larsen et al. 2004). Patients with these conditions may have elevated fecal calprotectin concentration compared with healthy control subjects; however, successful identification of these conditions by fecal calprotectin has been inconsistent and studied in small populations. Further studies in larger populations are needed to clarify the role of fecal calprotectin for these conditions.
In an observational study, Manz et al. (2012) evaluated the diagnostic value of fecal calprotectin 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 an enzyme-linked immunosorbent assay. The presence of a clinically significant finding in the gastrointestinal tract was the primary endpoint of the study. Final diagnoses were adjudicated blinded to calprotectin 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). Fecal calprotectin 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, fecal calprotectin is a useful non-invasive marker to identify clinically significant findings of the gastrointestinal tract, irrespective of age. According to the authors, further prospective studies directly comparing recommended guidelines of appropriateness for endoscopy with fecal calprotectin 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 gastrointestinal immune-related adverse events. A total of 115 patients with unrespectable stage III/IV melanoma were included in the study. Outcome measures included fecal calprotectin levels. Despite an observed association between colonic inflammation and grade 2 or higher diarrhea, no baseline biomarkers could reliably predict development of gastrointestinal 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 stool calprotectin monitoring was not strongly supported in this study.

Professional Societies
World Gastroenterology Organisation (WGO): The WGO’s global 2009 guideline for irritable bowel syndrome (IBS), lists fecal inflammation marker (e.g., calprotectin) in the IBS diagnostic cascade Level 1 category:
Diagnostic Cascade Level 1 for IBS:
- History, physical examination, exclusion of alarm symptoms, consideration of psychological factors
- Full blood count (FBC), erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), stool studies (white blood cells, ova, parasites, occult blood)
- Thyroid function, tissue transglutaminase (TTG) antibody
- Colonoscopy and biopsy
- Fecal inflammation marker (e.g., calprotectin)

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:

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)
Medicare does not have a National Coverage Determination (NCD) for the fecal measurement of calprotectin used for the diagnosis and management of inflammatory bowel disease (IBD),
ulcerative colitis, Crohn's disease and colorectal cancer. Local Coverage Determinations (LCDs) do not exist at this time. (Accessed January 17, 2014)

REFERENCES


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<td>04/01/2014</td>
<td>• Reorganized policy content</td>
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<td>• Updated coverage rationale; added language to indicate the unproven services are “not medically necessary”</td>
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<td>• Updated supporting information to reflect the most current clinical evidence, CMS information and references</td>
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