FECAL CALPROTECTIN TESTING

Policy Number: DIAGNOSTIC 052.10 T2
Effective Date: March 1, 2017

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INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

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

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

NON-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 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 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 may apply.

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<th>CPT Code</th>
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<td>83993</td>
<td>Calprotectin, fecal</td>
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*CPT® is a registered trademark of the American Medical Association*

**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 readily by history and physical examination, by barium enema x-ray or colonoscopy, and 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**

**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 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 to evaluate whether the use of fecal calprotectin (FC) reduces the number of unnecessary endoscopic procedures in patients with inflammatory bowel disease (IBD). 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). IBD 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 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 population of children and teenagers, 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.
Fecal Calprotectin with bowel disease. Research is needed to determine whether or tumor M2 and tumor M2 and 0.07 for cancer. 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, respectively. Calprotectin in combination with tumor M2-PK had a sensitivity of 64%, specificity of 98%, and likelihood ratios of 32 and 0.03. Elevated calprotectin or tumor M2-PK decreased specificity to 87%, but increased sensitivity to 100% (Jeffery et al., 2009). Further research is needed to determine whether FC testing improves clinical decision making and health outcomes in patients with bowel disease.

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 (FC) testing in pediatric patients with inflammatory bowel disease (IBD). The authors found that FC levels of patients with IBD 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 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.

A prospective multicenter study was conducted by Gisbert et al. (2009) to determine the role of fecal calprotectin (FC) and lactoferrin in the prediction of inflammatory bowel disease (IBD) 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%). FC (>150 µg/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 FC 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 (FC) concentration was higher among the patients with relapse than in those that remained in remission. Patients with CD and calprotectin greater than 200 µg/g relapsed 4 times more often than those with lower marker concentrations. In UC, calprotectin greater than 120 µg/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 120 µg/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 FC 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 (FC) 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. Elevated calprotectin or tumor M2-PK decreased specificity to 87%, but increased sensitivity to 100% (Jeffery et al., 2009). Further research is needed to determine whether FC 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 (FC) 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 FC 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 on 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 (FC) 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 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) 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, 9 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 (FC) concentration and Crohn’s disease (CD) clinical relapse in patients achieving remission with infliximab (IFX). Sixty-five patients were included in the study. Median FC level at week 14 was similar in patients with and without CD clinical relapse (200 and 150μg/g respectively). When considering two suggested FC 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 FC 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, FC measurement at week14 cannot predict CD clinical relapse at 1year.

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 (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 predictive value, 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 fecal calprotectin (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 (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 Medical Technology report determined that with regard to Crohn’s Disease, the results of the best available studies suggest that fecal calprotectin (FC) testing is reasonably safe and may be feasible but the available studies do not provide sufficient information to support clinical use of FC testing (2016).

Walsham and Sherwood (2016) performed a review focusing on the use of fecal calprotectin (FC) measurements in the diagnosis and monitoring of patients with inflammatory bowel disease (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 fecal calprotectin (FC) as a widely used as marker of gut inflammation strongly associated with the severity of endoscopic lesions in Crohn's disease (CD), Boschetti et al. (2015) analyzed the relationships between levels of FC and high-sensitivity C-reactive protein (hsCRP) and the presence and severity of postoperative endoscopic recurrence in asymptomatic CD patients. 86 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 (NPVs), 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 NPV 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.

**Colorectal Cancer**

Khoshbaten et al. (2014) utilized a case-control study to evaluate the diagnostic value of fecal calprotectin (FC) as a screening biomarker for GI malignancies. Calprotectin in feces seems to be a more sensitive marker for gastrointestinal (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 colorectal cancer (CRC) and 50 patients with gastric cancer) and 50 controls were recruited in Tabriz Imam Reza and Sina 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 ELISA method for quantitative measurement of calprotectin content. The results were compared between the three groups. The mean FC level was 109.1 ± 105.3 (2.3-454.3, median: 74), 241.1 ± 205.2 (3.4-610.0, median: 19.3) and 45.9 ± 55.1 μg/g (1.3-257.1, median: 19.3) in gastric cancer, CRC and control group, respectively, the differences being significant (p<0.001) and remaining after adjustment for age. The optimal cut-off point for FC was ≥ 75.8 μg/g for distinguishing colorectal cancer from normal cases (sensitivity and specificity of 80% and 84%, respectively). This value was ≥ 41.9 μg/g for distinguishing gastric cancer from normal cases (sensitivity and specificity of 62%). The authors 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 colorectal cancer (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

Fecal calprotectin (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 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 fecal calprotectin (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 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). 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 gastrointestinal 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 gastrointestinal immune-related adverse events. A total of 115 patients with unresectable 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 2015 global guideline for irritable bowel syndrome (IBS), lists fecal inflammation marker (e.g., calprotectin) in the IBS Diagnostic Cascade Level 1 Category:

- 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)


REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2017T0434K]


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**POLICY HISTORY/REVISION INFORMATION**

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| 03/01/2017 | ○ Reformatted and reorganized policy; transferred content to new template  
          | ○ Updated benefit considerations; added instruction to check the member specific  
          | ○ benefit plan document and any federal or state mandates, if applicable, before  
          | ○ using this policy  
          | ○ Updated supporting information to reflect the most current clinical evidence and  
          | ○ references; no change to non-coverage rationale or list of applicable codes  
          | ○ Archived previous policy version DIAGNOSTIC 052.9 T2 |