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Health Insurance for New Yorkers

Reimbursement Policy

Subject:	Fecal Calprotectin Testing in Adults		
Policy Number:	PO-RE-054v3		
Effective Date:	02/01/2024	**Last Approval Date:**	11/20/2023

I. Policy Description

Calprotectin is a small calcium-binding protein found in high concentration in the cytosol of neutrophils (Fagerhol et al., 1980) and to a lesser extent monocytes and macrophages (Hsu et al., 2009). Active intestinal inflammation and disturbance of the mucosa results in entrance of neutrophils (containing calprotectin) into the lumen and subsequent excretion in feces. Detection of fecal calprotectin is used to distinguish inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) and other causes of abdominal discomfort, bloating, and diarrhea (Walsham & Sherwood, 2016).

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1. For individuals 18 years of age or older, fecal calprotectin testing for the differential diagnosis between non-inflammatory gastrointestinal disease (e.g., IBS) and inflammatory gastrointestinal disease (e.g., IBD) **MEETS COVERAGE CRITERIA**.
2. For individuals 18 years of age or older, fecal calprotectin testing either to assess for response to therapy or for relapse or to monitor gastrointestinal conditions such as inflammatory bowel disease (IBD) **MEETS COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

3. For individuals 18 years of age or older, fecal calprotectin testing for all other situations not discussed above **DOES NOT MEET COVERAGE CRITERIA**.

Scientific Background

Inflammatory bowel disease (IBD) includes several chronic, immune-mediated inflammatory gastrointestinal disorders, the most common being Crohn's disease and ulcerative colitis (Boirivant & Cossu, 2012). In contrast, irritable bowel syndrome (IBS), another gastrointestinal disorder, is a non-inflammatory condition. These disorders often share similar symptoms including abdominal discomfort, pain, bloating, and diarrhea (Burri & Beglinger, 2014). An estimated two thirds of Americans have experienced these IBS and/or IBD symptoms (Almario et al., 2018). Differentiating gastrointestinal tract symptoms due to IBS from those due to residual inflammation from IBD is challenging (Gibson, 2022; Halpin & Ford, 2012). However, the detection of fecal calprotectin can be used to effectively distinguish between these conditions (Walsham & Sherwood, 2016).

Calprotectin is a small calcium- and zinc-binding protein. This protein is primarily detected in monocytes and macrophages. During active intestinal inflammation, neutrophils migrate to the mucosa, damaging the mucosal structure. This causes leakage of these neutrophils and therefore calprotectin into the lumen and eventually the feces. Calprotectin is homogenously distributed in feces, is stable up to seven days at room temperature, and correlates well with the "gold standard" of the indium-labeled leukocyte test (Walsham & Sherwood, 2016).

Fecal calprotectin is now accepted as one of the most useful tools to assist with the clinical management of IBD, although the optimal cut-off laboratory value for both differentiating IBD from IBS and managing IBD may vary depending on clinical settings (Khaki-Khatibi et al., 2020; Maaser et al., 2019; Mumolo et al., 2018). A value of 50 µg/g is quoted by most manufacturers of calprotectin kits (Tibble et al., 2002). In a young patient, a cutoff of 150 µg/g is recommended. As fecal calprotectin is increased in gastroenteritis associated with viral or bacterial infection, a value between 50 µg/g and 150 µg/g should always be repeated two to three weeks later (Walsham & Sherwood, 2016).

Fecal calprotectin is typically measured with polyclonal or monoclonal antibodies that detect various features on the protein structure; these tests may be quantitative or qualitive. Manufacturers of this type of test include Calpro and Bühlmann (Walsham & Sherwood, 2016).

Clinical Utility and Validity

Fecal calprotectin is increasing in utilization for the evaluation of IBD (Higuchi & Bousvaros, 2022). Meta-analyses of fecal calprotectin by both von Roon et al. (2007) and van Rheenen et al. (2010) found an overall sensitivity and specificity for IBD of >90%. Waugh et al. (2013) also completed a meta-analysis as part of the national Health Technology Assessment program which found a pooled sensitivity of 93% and specificity of 94% when distinguishing between IBS and IBD in adults with a fecal calprotectin cut-off of 50 µg/g.

Molander et al. (2012) evaluated fecal calprotectin levels after induction therapy with TNFα antagonists to determine whether this treatment can help to predict the outcome of IBD patients during maintenance therapy. Sixty patients with IBD were treated with TNFα antagonists and had their fecal calprotectin measured. Fecal calprotectin was found to be normalized (≤100 µg/g) in 31 patients and elevated in 29 patients. After 12 months, 26 of the 31 patients with normal fecal calprotectin levels were in clinical remission whereas only 11 of the 29 with elevated fecal calprotectin were in remission. A cutoff concentration of 139 µg/g was found to have a sensitivity of 72% *and* specificity of 80% to predict a risk of clinically active disease after one year (Molander et al., 2012).

Molander et al. (2015) studied whether fecal calprotectin can predict relapse after stopping TNFα-blocking therapy in IBD patients in remission. Forty-nine patients were examined, of which 15 relapsed (34 in remission). Relapsing patients showed an elevated fecal calprotectin for a median of 94 days before relapsing. Normal fecal calprotectin levels were “highly predictive” of clinical and endoscopic remission. The authors suggested that fecal calprotectin may be used as “a surrogate marker for predicting and identifying patients requiring close follow-up in clinical practice” (Molander et al., 2015).

Mao et al. (2012) performed a meta-analysis of the predictive capacity of fecal calprotectin in IBD relapse. A total of 672 patients (318 with ulcerative colitis, 354 with Crohn’s Disease) from six studies were examined. The authors found the pooled sensitivity and specificity of fecal calprotectin to predict relapse of quiescent IBD to be 78 and 73%, respectively. The area under the summary receiver-operating characteristic (sROC) curve was 0.83, and the diagnostic odds ratio was 10.31. The authors concluded that “as a simple and noninvasive marker, FC [fecal calprotectin] is useful to predict relapse in quiescent IBD patients” (Mao et al., 2012).

Rosenfeld et al. (2016) published a study to evaluate the perspective of gastroenterologists regarding the impact of fecal calprotectin on the management of patients with IBD. A total of 279 completed surveys were collected. Ninety surveys indicated fecal calprotectin testing was used to differentiate IBD from IBS, 85 indicated that fecal calprotectin was used to differentiate IBS symptoms from IBD in IBD patients, and 104 indicated fecal calprotectin was used as a marker for objective inflammation. Fecal calprotectin levels also resulted in a management change in 143 surveys, including 118 fewer colonoscopies. Overall, 272 surveys stated they would order fecal calprotectin again (Rosenfeld et al., 2016).

Abej et al. (2016) investigated the association between fecal calprotectin and other measures of clinical activity for patients with IBD. A total of 240 patients with IBD contributed 183 fecal samples, and a fecal calprotectin measurement above ≥250 µg was considered a positive result. Fecal calprotectin was associated with “colonoscopy findings of active IBD, low albumin, anemia, and elevated CRP.” The authors concluded that fecal calprotectin “is a useful marker of disease activity and a valuable tool in managing persons with IBD in clinical practice” (Abej et al., 2016).

Tham et al. (2018) showed that fecal calprotectin is an accurate surrogate marker of postoperative endoscopic recurrence of Crohn’s disease. They evaluated the diagnostic sensitivity, specificity, and diagnostic odds ratio (DOR), and constructed summary receiver operating characteristic (SROC) curves in a meta-analysis of 54 studies; Nine studies were eligible for analysis. Diagnostic accuracy was calculated for fecal calprotectin values of 50, 100, 150 and 200 µg/g. A significant threshold effect was observed for all fecal calprotectin values. The optimal diagnostic accuracy was obtained for a fecal calprotectin value of 150 µg/g, with a pooled sensitivity of 70% [95% confidence interval (CI) 59-81%], specificity 69% (95% CI 61-77%), and DOR 5.92 (95% CI 2.61-12.17); the area under the SROC curve was 0.73 (Tham et al., 2018).

The cost-effectiveness of the use of fecal calprotectin in the diagnosis of IBD has been investigated (Yang et al., 2014). The authors compared cost-effectiveness of measuring fecal calprotectin before endoscopy compared to direct endoscopic evaluation alone. Fecal calprotectin screening was found to save $417 per adult patient, but delayed 2.2/32 adult diagnoses (of IBD. The authors noted that if endoscopic biopsy remained the diagnostic standard, direct endoscopic evaluation would cost an additional $18955 in adults to avoid one false-negative result from fecal calprotectin screening (Yang et al., 2014).

In a cross-sectional study, Campbell et al. (2021)assessed the clinical performance of the LIAISON Calprotectin Assay in differentiating inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) against the Genova Diagnostics PhiCal test. A total of 240 patients were included in the study in which 102 patients had IBD, 67 had IBS, and 71 had other GI disorders. Median fecal calprotectin levels were higher in IBD patients (522 µg/g) compared to IBS patients (34.5 µg/g). The LIAISON assay showed good correlation with the PhiCal test, holding a positive percent agreement of 97.8% and a negative percent agreement of 94.4%. Overall, the LIAISON Calprotectin Assay is efficient with a time to the first result of 35 minutes and "is a sensitive marker for distinguishing IBD from IBS with a cutoff of ~100 µg/g" (Campbell et al., 2021).

Johnson et al. (2022) compared fecal calprotectin and pancreatic elastase assays, aiming to understand the differences between the tests and manufacturers. Data from proficiency tests performed in Germany between 2015 and 2020 was included in the study. Fecal calprotectin assays had a “high degree of variability” between tests from the eight manufactures included. Pancreatic elastase assays were “harmonized” without significant variability between tests from the five manufacturers included. The authors concluded that “both calprotectin and pancreatic elastase assays could be improved by standardization efforts” (Johnson et al., 2022).

Guidelines and Recommendations

National Institute for Health and Care Excellence (NICE)

The NICE published guidance on fecal calprotectin testing which included the following recommendations:

- “Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if cancer is not suspected and appropriate quality assurance processes and locally agreed care pathways are in place for the testing” (NICE, 2017).

American Gastrointestinal Association (AGA)

The AGA published a practice update on functional gastrointestinal symptoms in patients with IBD. The following best practice advice recommendations on fecal calprotectin were given regarding the diagnosis and management of functional gastrointestinal symptoms in patients IBD:

- “Best practice advice 1: A stepwise approach to rule-out ongoing inflammatory activity should be followed in IBD patients with persistent GI symptoms (measurement of fecal calprotectin, endoscopy with biopsy, cross-sectional imaging).
- Best practice advice 2: In those patients with indeterminate fecal calprotectin levels and mild symptoms, clinicians may consider serial calprotectin monitoring to facilitate anticipatory management” (Colombel et al., 2019).

In 2023, the AGA published guidelines on the role of biomarkers for management of ulcerative colitis (Singh et al., 2023). For patients with ulcerative colitis in symptomatic remission, the AGA recommends that:

- "In patients with UC in symptomatic remission, the AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone."
- "In patients with UC in symptomatic remission, the AGA suggests using fecal calprotectin <150 µg/g, normal fecal lactoferrin, or normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease activity."
- "In patients with UC in symptomatic remission, the AGA suggests using fecal calprotectin <150 µg/g, normal fecal lactoferrin, or normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease activity."

For patients with symptomatically active ulcerative colitis, the AGA recommends that:

- "In patients with symptomatically active UC, the AGA suggests an evaluation strategy that combines biomarkers and symptoms, rather than symptoms alone, to inform treatment adjustments."
- "In patients with symptomatically active UC, the AGA suggests an evaluation strategy that combines biomarkers and symptoms, rather than symptoms alone, to inform treatment adjustments."
- "In patients with UC with mild symptoms, with elevated stool or serum markers of inflammation (fecal calprotectin >150 µg/g, elevated fecal lactoferrin, or elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment."
- "In patients with UC with mild symptoms, with normal stool or serum markers of inflammation (fecal calprotectin <150 µg/g, normal fecal lactoferrin, normal CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment."

For treat-to-target strategies for ulcerative colitis, the AGA recommends that:

- "In patients with UC, the AGA makes no recommendation in favor of, or against, a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy to improve long-term outcomes" (Singh et al., 2023).

American College of Gastroenterology (ACG)

The ACG Clinical Guideline (Lichtenstein et al., 2018) for the Management of Crohn's disease in adults recommends:

"Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence)."

"In patients who have symptoms of active Crohn's disease, stool testing should be performed to include fecal pathogens, *Clostridium difficile* testing, and may include studies that identify gut inflammation such as a fecal calprotectin."

"Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity. Fecal markers may have a role in noninvasively monitoring disease activity in CD [Crohn's disease]. Studies have shown that both fecal lactoferrin and fecal calprotectin are sensitive markers of disease activity and correlate with a number of the endoscopic activity indices such as the colonic SES-CD. There have been several studies that suggest that levels of fecal calprotectin can be used to monitor patients for postoperative recurrence after ileocolic resection for Crohn's disease. Levels of >100 µ g/g indicate endoscopic recurrence with a sensitivity in the range of 89%. In patients with an infliximab-induced remission, fecal calprotectin of >160 µ g/g has a sensitivity of 91.7% and a

specificity of 82.9% to predict relapse… The presence of biomarkers of disease activity can be assessed (such as CRP, fecal calprotectin) but should not exclusively serve as end point for treatment as normalization of the biomarker can occur despite having active mucosal inflammation/ulceration… Although not specific for CD activity, determination of serum CRP and/or fecal calprotectin is suggested as a useful laboratory correlate with disease activity assessed by the CDAI" (Lichtenstein et al., 2018).

The Crohn's Disease Activity Index (CDAI) is a tool that can provide a numerical value in assessing Crohn's disease; however, fecal calprotectin is not a criterion of the index. Within the supplemental information of the guidelines, the authors state, "This is a weighted subjective tool that includes scores for liquid bowel movements per day, general wellbeing, abdominal pain and extra-intestinal manifestations. This index does require 7 days of measurements making it difficult to use in the clinic setting. Due to the subjective nature of some of the measurements it is not an optimal tool for measuring disease activity and is generally not used in routine clinical practice"(Lichtenstein et al., 2018).

The guidelines do not address the frequency of fecal calprotectin testing for adjunctive monitoring.

The ACG also published guidelines for clinical management of ulcerative colitis in adults in 2019. In it, they note that "Fecal calprotectin (FC) can be used in patients with UC as a noninvasive marker of disease activity and to assess response to therapy and relapse" (Rubin et al., 2019). The ACG also recommends:

- "Stool testing to rule out *Clostridioides difficile (C. diff)* in patients suspected of having UC (strong recommendation, very low quality of evidence)."
- Recommends against "serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence)."
- Recommends against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence)" (Rubin et al., 2019).

In 2021, the ACG published guidelines on the management of irritable bowel syndrome. They recommend that that fecal calprotectin, either fecal calprotectin 1 or fecal lactoferrin 2 and C-reactive protein 1, be checked in patients with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease. ACG includes that two fecal-derived markers of intestinal inflammation, fecal lactoferrin (FL) and fecal calprotectin (fCal), are both diagnostically useful and could be superior to serologic tests such as CRP or ESR regarding discriminating IBD from IBS. "In summary, fCal and FL are safe, noninvasive, generally available, and can identify IBD with good accuracy" (Lacy et al., 2021).

European Crohn's and Colitis Organisation (ECCO)

The ECCO released a consensus on diagnosis and management of ulcerative colitis (UC). In it, they state that fecal calprotectin should be included on an initial investigation of UC. ECCO considers fecal calprotectin an "accurate" marker of colonic inflammation and "a useful non-invasive marker in the follow-up of UC patients" (Magro et al., 2017).

The ECCO also provided a statement on diagnosis and management of Crohn's Disease. ECCO notes that fecal calprotectin may be used in the initial laboratory investigation. Fecal calprotectin is also observed to be an emerging surrogate marker for mucosal healing but has not demonstrated a clear predictive value. Fecal calprotectin may also help in monitoring disease activity (Gomollón et al., 2016).

European Crohn's and Colitis Organisation (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR)

The ECCO-ESGAR published guidelines for the diagnostic assessment in IBD. When monitoring known IBD cases, the following guidelines were provided:

- "Response to treatment in active ulcerative colitis [UC] should be determined by a combination of clinical parameters, endoscopy, and laboratory markers such as C-reactive protein [CRP] and faecal calprotectin [EL1]
- In patients with UC who clinically respond to medical therapy, mucosal healing [MH] should be determined endoscopically or by faecal calprotectin [FC] approximately 3 to 6 months after treatment initiation [EL5]" (Maaser et al., 2019).

A relevant portion of "**Table 1.** Markers of disease activity for monitoring asymptomatic IBD patients" is shown below (Maaser et al., 2019):

	Validity [correlation with gold standard]	Responsiveness to changes in condition	Signal-to-noise ratio [ability to differentiate changes in condition from background variability]	Practicality
Endoscopy	Gold standard	Gold standard	Gold standard	Low
Faecal calprotectin	Good	Good Rises quickly in case of relapse; falls rapidly with successful treatment	Moderate Risk of false-positive results	High Possible reluctance of patients for repeated stool collection

II. Applicable Codes

Code	Description	Comment
83993	Assay for calprotectin fecal	

III. Definitions

Term	Meaning

N/A	N/A

IV. Related Policies

Policy Number	Policy Description
PO-RE-058	Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease
PO-RE-063	General Inflammation Testing

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Procedure codes appearing in Reimbursement Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Reference Materials

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VI. Revision History

Revision Date	Summary of Changes
09/06/2023	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity and consistency:

	All CC edited to include “for all individuals 18 years of age or older” language so that it’s clear that coverage in this policy is only relevant to adult individuals. Previously only clarified by “in Adults” within the title.

Disclaimer

Healthfirst’s claim edits follow national industry standards aligned with CMS standards that include, but are not limited to, the National Correct Coding Initiative (NCCI), the National and Local Coverage Determination (NCD/LCD) policies, appropriate modifier usage, global surgery and multiple procedure reduction rules, medically unlikely edits, duplicates, etc. In addition, Healthfirst’s coding edits incorporate industry-accepted AMA and CMS CPT, HCPCS and ICD-10 coding principles, National Uniform Billing Editor’s revenue coding guidelines, CPT Assistant guidelines, New York State-specific coding, billing, and payment policies, as well as national physician specialty academy guidelines (coding and clinical). Failure to follow proper coding, billing, and/or reimbursement policy guidelines could result in the denial and/or recoupment of the claim payment.

This policy is intended to serve as a resource for providers to use in understanding reimbursement guidelines for professional and institutional claims. This information is accurate and current as of the date of publication. It provides information from industry sources about proper coding practice. However, this document does not represent or guarantee that Healthfirst will cover and/or pay for services outlined. Reimbursement decisions are based on the terms of the applicable evidence of coverage, state and federal requirements or mandates, and the provider’s participation agreement. This includes the determination of any amounts that Healthfirst or the member owes the provider.