Qualified Health Plans offered in North Carolina by CareSource North Carolina Co., d/b/a CareSource

Fecal Calprotectin Testing in Adults

Policy Number: AHS – G2061 – Fecal Calprotectin Testing in Adults	Prior Policy Name and Number, as applicable: AHS – G2061 – Fecal Calprotectin Testing
Effective Date: 01/01/2023	

I. Policy Description

Calprotectin is a small calcium-binding protein found in high concentration in the cytosol of neutrophils (Fagerhol, Dale, & Andersson, 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).

II. Related Policies

Policy Number	Policy Title
AHS-G2060	Fecal Analysis In The Diagnosis Of Intestinal Dysbiosis
AHS-G2121	Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease
AHS-G2155	General Inflammation Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website https://www.cms.gov/medicare-coverage-database/search.aspx or the manual website.

1) Fecal calprotectin testing **MEETS COVERAGE CRITERIA** when evaluating a differential diagnosis between non-inflammatory gastrointestinal disease (e.g. IBS) and inflammatory gastrointestinal disease (e.g. IBD).

2) Fecal calprotectin testing **MEETS COVERAGE CRITERIA** for monitoring of gastrointestinal conditions such as inflammatory bowel disease (IBD) and to assess response to therapy and relapse.

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 a patient's illness.

3) Fecal calprotectin testing **DOES NOT MEET COVERAGE CRITERIA** for any other conditions not mentioned above.

IV. Scientific Background

Inflammatory bowel disease (IBD) includes several chronic, immune-mediated inflammatory gastrointestinal disorders; the most common of these disorders are Crohn's disease and ulcerative colitis (Boirivant & Cossu, 2012). On the other hand, 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, 2021; 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 7 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 the majority of manufacturers of calprotectin kits (Tibble, Sigthorsson, Foster, Forgacs, & Bjarnason, 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 2-3 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 Validity and Utility

Fecal calprotectin is increasing in utilization for the evaluation of IBD (Higuchi & Bousvaros, 2020). Meta-analyses of fecal calprotectin by both von Roon et al. (2007) and van Rheenen, Van de Vijver, and Fidler (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; "For distinguishing between IBD and non-IBD in paediatric populations with ELISA tests, sensitivities ranged from 95% to 100% at cut-off of 50 µg/g and specificities of 44-93%" (Waugh et al., 2013). Others convey a slightly lower specificity in the pediatric population with a reported sensitivity of 97% and specificity of 70% (Degraeuwe et al., 2015).

Fecal calprotectin has also been studied as a marker to evaluate response to treatment. Turner et al. (2010) compared four fecal markers (M2-pyruvate kinase, calprotectin, lactoferrin, and S100A12) in their ability to predict steroid refractoriness in cases of severe pediatric ulcerative colitis. Stool samples from 101 children were studied, and the Pediatric UC (ulcerative colitis) Activity Index (PUCAI) was scored after three days of intravenous steroid therapy. The authors found that M2-pyruvate kinase was superior to the other three (calprotectin, lactoferrin, and S100A12) in predicting response to corticosteroid treatment and in construct validity, but it did not add to predictive ability of the PUCAI. The investigators concluded that "PUCAI, a simple clinical index, performed better than the faecal markers in predicting outcome following a course of intravenous corticosteroids in severe UC" (Turner et al., 2010).

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 1 year.

Molander et al. (2015) also 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).

Furthermore, 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).

Foster et al. (2019) also measured fecal calprotectin levels to predict relapse in pediatric Chron's disease patients. A cohort of 53 children participated in this study, and eight children experienced a clinical relapse; "Baseline fecal calprotectin levels were higher in patients that developed symptomatic relapse

[median (interquartile range), relapse 723 µg/g (283-1758) vs 244 µg/g (61-627), P = 0.02]" (Foster et al., 2019). The authors noted that fecal calprotectin levels > 250 µg/g were accurate predictors of a relapse occurring in the next three months; therefore, routine fecal calprotectin testing in children in clinical remission for Chron's disease may be useful to predict relapse.

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.

Abej, El-Matary, Singh, and Bernstein (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).

El-Matary, Abej, Deora, Singh, and Bernstein (2017) studied 115 fecal samples from 77 children with IBD. The authors found that fecal calprotectin positively correlated with other clinical activity indices and erythrocyte sedimentation rate. Fecal calprotectin was also found to negatively correlate with hemoglobin. Sixty-four of the 74 total positive fecal calprotectin measurements led to a "treatment escalation with subsequent significant clinical improvement while… 34 out of 41 (83%) measurements resulted in no change in treatment and were associated with remission on follow-up" (El-Matary et al., 2017).

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, Clark, & Park, 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 and $300 per pediatric patient, but delayed 2.2/32 adult diagnoses (of IBD) and 4.8/61 child diagnoses. The authors noted that if endoscopic biopsy remained the diagnostic standard, direct endoscopic evaluation would cost an additional $18955 in adults and $6250 in children to avoid one false-negative result from fecal calprotectin screening (Yang et al., 2014).

The National Institute for Health and Care Excellence (NICE) also provided an economic analysis of fecal calprotectin use from the External Assessment Group. The analysis compared three different

courses; "testing interpreted using a threshold of 50 micrograms/g followed by colonoscopy; testing interpreted using a threshold of 100 micrograms/g followed by colonoscopy; and direct referral for colonoscopy as separate diagnostic strategies in children with lower gastrointestinal symptoms of abdominal pain or discomfort, bloating or change in bowel habit, for at least 6 weeks, who had been referred for specialist investigation" (NICE, 2017a). The goal of this analysis was to identify subgroups with IBD and, of those with IBD, who would need further diagnostic testing such as a colonoscopy. Overall, 100% of the direct referral group received a colonoscopy, 61.5% of the group with the 50-microgram threshold received a colonoscopy, and 54.4% of the group with the 100-microgram threshold received a colonoscopy (NICE, 2017a). The 50-microgram threshold resulted in a savings of £205 per patient, and the 100-microgram threshold resulted in a savings of £240 per patient.

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. 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, Zierold, Rode, Blocki, & Vaughn, 2021).

V. Guidelines and Recommendations

National Institute for Health and Care Excellence (NICE) (NICE, 2017b)

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 (2017b)."

- "Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment (2017b)."

American Gastrointestinal Association (AGA) (Colombel, Shin, & Gibson, 2019)

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)."

American College of Gastroenterology (ACG) (Lichtenstein et al., 2018; Rubin, Ananthakrishnan, Siegel, Sauer, & Long, 2019)

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).

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 in regard to 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) (Gomollón et al., 2016; Magro et al., 2017)

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, and "might be useful deciding which patient should undergo an endoscopic investigation, especially in the paediatric setting." 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) (Maaser et al., 2019)

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 Requires bowel preparation and general

				anesthesia in children
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

European Society for Paediatric Gastroenterology and Nutrition Gastroenterology Committee (ESPGHAN) (Koninckx et al., 2021)

ESPGHAN published guidelines on the use of fecal calprotectin testing in pediatric disorders. The following recommendations were made:

Patient Screening

- "Due to high interindividual variability especially at young ages, any decision for clinical intervention should be based not only on FC levels but also additionally on the global clinical context.
- In preterm and infants younger than 1 year of age, FC may be elevated without any known cause for inflammation and until a normal range for this age group is firmly established, FC levels should be interpreted with particular caution.
- In children older than 4 years of age cut off values of 50 mg/g, as in adults, can be used, although healthy children may have FC levels up to 100 µg/g or even higher" (Koninckx et al., 2021).

Effect of drugs on FC levels

- "The ESPGHAN expert group recommends to exert caution when interpreting mildly elevated FC levels whilst a patient is on nonsteroidal anti-inflammatory drugs, ASA, and/or PPIs" (Koninckx et al., 2021).

ESPGHAN also released recommendations on fecal calprotectin testing in various disease states:

Disease State	**Recommendations**
Inflammatory Bowel Disease	• "The ESPGHAN expert group recommends to perform a diagnostic endoscopy where IBD is strongly suspected and not to wait for FC results prior if these cannot be obtained in a timely

	fashion, to avoid any delay in confirming the diagnosis. • The ESPGHAN expert group recommends NOT use FC as a prognostic marker in acute severe colitis. • The ESPGHAN expert group suggests to include FC measurement in the laboratory investigations of IBD patients at least every 6 months during follow-up, even in remission, unless clinical picture suggests a relapse, where earlier investigation may be indicated. • The ESPGHAN expert group suggests consider endoscopic evaluation in IBD patients in clinical remission with a FC >300 μg/g as this cut off level accurately predicts mucosal inflammation.
Crohn's Disease	• The ESPGHAN expert group recommends to measure FC repeatedly after intestinal resection as it is superior to CRP to detect early asymptomatic relapse requiring endoscopic evaluation.
Post-colectomy Patients	• The ESPGHAN expert group recommends to use FC levels after colectomy to screen for pouchitis and inflammation at the anastomosis.
Infant Colic	• The ESPGHAN expert group recommends to NOT use FC in babies with infantile colic.
Functional Abdominal Pain	• The ESPGHAN expert group recommends to use FC as a tool to differentiate functional abdominal pain disorders from organic diseases.
Functional Constipation	• The ESPGHAN expert group recommends to NOT measure FC in children with constipation as it cannot differentiate between functional and the majority of organic causes (eg, Hirschsprung disease).

Food Allergy	• The ESPGHAN expert group recommends to NOT use FC either as diagnostic tool or as prognostic marker of cow's milk protein allery (CMPA) in children.
Celiac Disease	• The ESPGHAN expert group recommends to NOT use FC as a marker for the diagnosis or monitoring of CD.
Cystic Fibrosis	• The ESPGHAN expert group recommends to be cautious when interpreting individual FC values as a marker of enteropathy in CF.
Infectious Gastroenteritis	• The ESPGHAN expert group recommends to NOT use FC in acute gastroenteritis to distinguish bacterial from viral gastroenteritis in children.
Acute Appendicitis	• The ESPGHAN expert group recommends to NOT use FC, either alone or in combination with other inflammatory biomarkers, in screening children with abdominal pain for the presence of AA.
Helicobacter *pylori*	• The ESPGHAN expert group recommends to NOT use FC measurement for screening or follow up of *H pylori* infection or *H pylori*-related diseases.
Obesity	• The ESPGHAN expert group recommends to NOT use FC as a routine measurement in obese children if no other clinical condition relevant to FC measurement is suspected.
Severe acute malnutrition (SAM)	• The ESPGHAN expert group recommends to not use FC for establishing therapeutic efficacy in SAM.
Necrotising Enterocolitis (NEC)	• The ESPGHAN expert group recommends to consider using serial FC measurements as a noninvasive screening tool to alert to the risk of developing NEC.

Intestinal Polyps Short Bowel Syndrome	• The ESPGHAN expert group suggests to NOT use FC as a screening tool in children with a suspicion of intestinal polyps. • The ESPGHAN expert group suggests to NOT use FC routinely in SBS children.
Small intestinal bacterial overgrowth (SIBO)	• The ESPGHAN expert group suggests to NOT use FC measurement for the diagnosis of SIBO in previously healthy children.
Autism	• The ESPGHAN expert group recommends to NOT use FC measurement in children with autism unless they have symptoms suggestive of conditions relevant to FC levels.
Henoch-Schönlein purpura	• The ESPGHAN expert group suggests to consider using FC measurement to identify gastrointestinal involvement in children with Henoch-Schönlein purpura in the absence of overt bleeding" (Koninckx et al., 2021).

VI. State and Federal Regulations, as applicable

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

In March 2006, the PhiCal™ (Genova Diagnostics) quantitative ELISA test for measuring concentrations of fecal calprotectin in fecal stool was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) processes. This test is indicated to aid in the diagnosis of inflammatory bowel disease (IBD) and to differentiate IBD from irritable bowel syndrome (IBS); it is intended to be used in conjunction with other diagnostic testing and clinical considerations (FDA, 2006). On December 26, 2018, a successor device called "LIAISON Calprotectin, LIAISON Calprotectin Control Set, LIAISON Calprotectin Calibration Verifiers, LIAISON Q.S.E.T. Buffer, LIAISON Q.S.E.T. Device" was approved.

The new description is as follows: "The DiaSorin LIAISON® Calprotectin assay is an in vitro diagnostic chemiluminescent immunoassay (CLIA) intended for the quantitative measurement, in human stool, of fecal calprotectin, a neutrophilic protein that is a marker of mucosal inflammation. The LIAISON® Calprotectin assay can be used as an aid in the diagnosis of inflammatory bowel diseases (IBD), specifically Crohn's disease and ulcerative colitis, and as an aid in differentiation of IBD from irritable bowel syndrome (IBS). Test results are to be used in conjunction with information obtained from the patients' clinical evaluation and other diagnostic procedures. The test has to be performed on the LIAISON® XL Analyzer" (FDA, 2018a).

In January 2014, CalPrest® (Eurospital SpA, Trieste, Italy) was cleared for marketing by FDA through the 510(k) processes. According to the FDA summary, CalPrest® "is identical" to the PhiCal™ test "in that they are manufactured by Eurospital S.p.A. Trieste, Italy. The only differences are the name of the test on the labels, the number of calibrators in the kit and the dynamic range of the assay." CalPrest®NG (Eurospital SpA) was cleared for marketing in November 2016 (FDA, 2016).

On October 16, 2018, the FDA approved the QUANTA Flash Calprotectin And Fecal Extraction Device. The device's intended use is as follows: "QUANTA Flash Calprotectin is a chemiluminescent immunoassay for the quantitative determination of fecal calprotectin in extracted human stool samples. Elevated levels of fecal calprotectin, in conjunction with clinical findings and other laboratory tests, can aid in the diagnosis of inflammatory bowel disease (IBD) (ulcerative colitis and Crohn's disease), and in the differentiation of IBD from irritable bowel syndrome (IBS)." This device has a predicate device, which was approved in 2017 (FDA, 2018a).

On December 26, 2018, the FDA approved the LIAISON Calprotectin Assay. The device's intended use is as follows: "The DiaSorin LIAISON® Calprotectin assay is an in vitro diagnostic chemiluminescent immunoassay (CLIA) intended for the quantitative measurement, in human stool, of fecal calprotectin, a neutrophilic protein that is a marker of mucosal inflammation. The LIAISON® Calprotectin assay can be used as an aid in the diagnosis of inflammatory bowel diseases (IBD), specifically Crohn's disease and ulcerative colitis, and as an aid in differentiation of IBD from irritable bowel syndrome (IBS). Test results are to be used in conjunction with information obtained from the patients' clinical evaluation and other diagnostic procedures" (FDA, 2018b).

On September 24, 2019, BUHLMANN Laboratories AG received FDA approval for the Buhlmann FCAL Turbo And CALEX Cap fecal calprotectin extraction device. This device is to be used in conjunction with the automated calprotectin test, BÜHLMANN fCAL® turbo. The BÜHLMANN fCAL® turbo is an in vitro diagnostic assay which quantitatively measures fecal calprotectin (FDA, 2019).

Rapid fecal calprotectin tests, such as CalproSmart™, are available internationally for use as point-of-care testing, but these have not been approved for use in the U.S. by the FDA.

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

Code Number	Code Description
83993	Assay for calprotectin fecal

VIII. Evidence-based Scientific References

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IX. Revision History

Revision Date	Summary of Changes
01/01/2023	Initial Effective Date