Fecal Calprotectin Testing AHS – G2061

Description of Procedure or Service

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).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for fecal calprotectin testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Fecal Calprotectin Testing is covered

Reimbursement is allowed for fecal calprotectin testing when evaluating a differential diagnosis between non-inflammatory gastrointestinal disease (e.g. IBS) and inflammatory gastrointestinal disease (e.g. IBD).

When Fecal Calprotectin Testing is not covered

Reimbursement is not allowed for fecal calprotectin testing for the management of gastrointestinal conditions, including the management of inflammatory bowel disease.

Policy Guidelines

Background
Abdominal discomfort including pain, bloating and diarrhea is common. It often arises from functional gastrointestinal disorders but may indicate inflammatory bowel disease (IBD) (Burri & Beglinger, 2014). Differentiating gastrointestinal tract symptoms due to irritable bowel syndrome
(IBS) from those due to residual inflammation from IBD is challenging (Halpin & Ford, 2012; MacDermott, 2017).

Active intestinal inflammation results in the migration of polymorphonuclear neutrophils to the intestinal mucosa. Disturbance of the mucosal architecture as a result of the inflammatory process results in leakage of neutrophils into the lumen and subsequent excretion in feces (Roseth, Aadland, Jahnsen, & Raknerud, 1997). Calprotectin is a small calcium-binding protein which contributes ~60% of the protein content of the cytosol in neutrophils (Fagerhol et al., 1980). The concentration of calprotectin in feces has been shown to correlate well with the “gold standard” Indium-labeled leukocyte test and to the severity of the intestinal inflammation (Roseth, Schmidt, & Fagerhol, 1999). Calprotectin appears to be distributed homogeneously in feces and is stable for up to 7 days at room temperature (Roseth, Fagerhol, Aadland, & Schjonsby, 1992).

Clinical Validity and Utility

Fecal calprotectin is increasingly being utilized as a screening test for IBD and as an index of disease activity (Carroccio et al., 2003; Costa et al., 2003; Dolwani, Metzner, Wassell, Yong, & Hawthorne, 2004; Eder, Stawczyk-Edery, Krela-Kazmierczak, & Linke, 2008; Langhorst et al., 2008; Langhorst et al., 2009; Schoepfer et al., 2013; Schroder, Naumann, Shastri, Povse, & Stein, 2007; Wassell, Dolwani, Metzner, Losty, & Hawthorne, 2004). Meta-analyses of fecal calprotectin by both von Roon et al. (von Roon et al., 2007) and van Rheenen et al. (van Rheenen, Van de Vijver, & 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: “For distinguishing between IBD and IBS in adults, these gave pooled sensitivity of 93% and specificity of 94% at FC cut-off level of 50 µg/g. Sensitivities at that cut-off ranged from 83% to 100%, and specificities from 60% to 100%. For distinguishing between IBD and non-IBD in pediatric populations with ELISA tests, sensitivities ranged from 95% to 100% at cut-off of 50 µg/g and specificities of 44-93%. Few studies used point-of-care testing but that seemed as reliable as ELISA, though perhaps less specific. The evidence did not provide any grounds for preferring one test over others on clinical effectiveness grounds. FC testing in primary care could reduce the need for referral and colonoscopies.” The specificity is slightly lower in pediatric reported a sensitivity of 97% at a specificity of 70% (Degraeuwe et al., 2015).

The optimal cutoff for differentiating IBS from IBD can vary. The 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).

The cost-effectiveness of the use of fecal calprotectin in the diagnosis of IBD has been investigated (Yang, Clark, & Park, 2014). The National Institute for Health and Clinical Excellence has concluded that the use of fecal calprotectin by primary care physicians prior to referral to a gastroenterology service was financially beneficial (NICE, 2013).

Fecal calprotectin has also been studied as a marker to evaluate response to treatment. Turner et al compared “four faecal markers for their ability to predict steroid refractoriness in severe pediatric ulcerative colitis (UC)” including calprotectin, M2-pyruvate kinase (M2-PK), and S100A12 and found that “The four markers were greatly elevated in severe pediatric UC. Only M2-PK had good construct and predictive validity, and none was responsive to change. The PUCAI, a simple clinical index, performed better than the fecal markers in predicting outcome following a course of intravenous corticosteroids in severe UC.” Molander et al (2012) evaluated “whether a normal FC after induction therapy with TNFα antagonist predicts the outcome of IBD patients during maintenance therapy” and found “After induction therapy with TNFα antagonists, a cutoff concentration of 139 µg/g for FC had a sensitivity of 72% and a specificity of 80% to predict a risk of clinically active disease after 1 year.” Molander et al (Molander et al., 2015) also studied “whether elevated fecal calprotectin (FC) concentrations after stopping TNFα-blocking therapy can
predict clinical or endoscopic relapse. In addition, we evaluated the impact of histological remission on the relapse risk and found “FC seems to increase and remain elevated before clinical or endoscopic relapse, suggesting that it can be used as a surrogate marker for predicting and identifying patients requiring close follow-up in clinical practice.”

Furthermore, fecal calprotectin has also been evaluated as a predictor of relapse. Mao et al (2012) performed “a meta-analysis of the predictive capacity of FC in IBD relapse” and found that “pooled sensitivity and specificity of FC to predict relapse of quiescent IBD was 78% (95% confidence interval [CI]: 72-83) and 73% (95% CI: 68-77), respectively. The area under the summary receiver-operating characteristic (sROC) curve was 0.83 and the diagnostic odds ratio was 10.31 (95% CI: 5.05-21.06). The capacity of FC to predict relapse was comparable between UC and CD.”

Rosenfeld et al (2016) published a study to “evaluate the perspective of gastroenterologists regarding the impact of fecal calprotectin (FC) on the management of patients with inflammatory bowel disease (IBD).” They found that “Indications for FC testing included: 90 (32.2%) to differentiate a new diagnosis of IBD from Irritable Bowel Syndrome (IBS), 85 (30.5%) to distinguish symptoms of IBS from IBD in those known to have IBD and 104 (37.2%) as an objective measure of inflammation. FC levels resulted in a change in management 51.3% of the time which included a significant reduction in the number of colonoscopies (118) performed (P < 0.001). Overall, 97.5% (272/279) of the time, the physicians found the test sufficiently useful that they would order it again in similar situations. Follow-up data was available for 172 patients with further support for the clinical utility of FC provided. The FC test effected a change in management 51.3% of the time and receipt of the result was associated with a reduction in the number of colonoscopies performed.”

Abej et al (2016) also found that “FCAL is a useful marker of disease activity and a valuable tool in managing persons with IBD in clinical practice”

El-Mataray (2017) et al studied “the impact of FC measurements on decision-making and clinical care of children with IBD” and found “FC positively correlated with clinical activity indices ($r = 0.481$, $P < 0.05$) and erythrocyte sedimentation rate ($r = 0.40$, $P < 0.05$) and negatively correlated with hemoglobin ($r = -0.40$, $P < 0.05$). Sixty four out of 74 (86%) positive FC measurements ($\geq 250$ μg/g of stools) resulted in treatment escalation with subsequent significant clinical improvement while in the FC negative group, 34 out of 41 (83%) measurements resulted in no change in treatment and were associated with remission on follow-up. Based on high FCI, the majority of children had treatment escalation that resulted in clinical improvement. FC measurements were useful and reliable in decision-making and clinical care of children with IBD.”

However in the most recent expert review Ministro and Martins (2017) stated that that although fecal markers are relevant in IBD patient follow-up, “In the decision making process, FM have only an establish role as markers of inflammation, and therefore FM aren’t currently replacing other standard methods for IBD activity monitoring, such as cross sectional imaging technics in CD or endoscopy in UC.”

Macdermott (2017) stated that “Elevated levels of fecal calprotectin and fecal lactoferrin have been demonstrated to be very helpful in discriminating IBD from IBS. Studies have reported a sensitivity and specificity of calprotectin ranging from 64 to 100 and 80 percent, respectively.” Wanke (2017) note that fecal calprotectin levels are increased in intestinal inflammation and may be useful for distinguishing inflammatory from noninflammatory causes of chronic diarrhea. The authors concluded that “fecal calprotectin can be considered as an adjunctive test in diagnostic evaluation of patients with chronic diarrhea.”

Higuchi and Bousvaros (2017) stated that “fecal calprotectin levels are elevated in inflammatory intestinal diseases, and may be useful for distinguishing inflammatory gastrointestinal disease including IBD from noninflammatory causes of chronic diarrhea (such as functional abdominal pain).” In settings with a high prevalence of IBD, elevated fecal calprotectin can be used to identify
patients with a high likelihood of having IBD. On the other hand, in settings with a low prevalence of IBD, fecal calprotectin is more useful to rule out IBD. The authors also stated that “this test can be useful in monitoring response to treatment, but because of limited sensitivity and specificity it should be used in conjunction with other laboratory tests and symptoms to arrive at clinical decisions. The potential benefits of this test also must be weighed against the cost, and against the fact that it will not provide a definitive IBD diagnosis.”

Tham et al (2018) showed that FC is an accurate surrogate marker of postoperative endoscopic recurrence of Crohn’s disease. They evaluated the diagnostic sensitivity, specificity, diagnostic odds ratio (DOR) and constructed summary receiver operating characteristic (SROC) curves in a meta-analysis of 54 studies; 9 studies were eligible for analysis. Diagnostic accuracy was calculated for FC values of 50, 100, 150 and 200 µg/g. A significant threshold effect was observed for all FC values. The optimal diagnostic accuracy was obtained for FC 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.

Jang et al (2018) used FC to assess feeding intolerance in preterm infants. They found that the FC levels in AAF-fed infants with FI showed significantly lower than those in the BM- or PF-fed infants with FI. The mitigation of gut inflammation through the decrease of FC levels in AAF-fed infants with FI could be presumed.

Applicable Federal Regulations

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.

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.

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.

Guidelines and Recommendations

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence

NICE (2013) published guidance on fecal calprotectin testing which stated:

“Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or IBS in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if cancer is not suspected. 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”.

American College of Gastroenterology
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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. 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 μg/g indicate endoscopic recurrence with a sensitivity in the range of 89%. In patients with an infliximab-induced remission, fecal calprotectin of >160 μg/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 CDAI (Crohn’s Disease Activity Index) is a tool that can be used to give numerical value in assessing CD; however, fecal calprotectin is not a criterion of the index. Within the supplemental information of the guidelines, the author’s 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.”

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

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 83993

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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Specialty Matched Consultant Advisory Panel review 11/2019

Policy Implementation/Update Information

1/1/2019  BCBSNC will provide coverage for fecal calprotectin testing when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

10/29/19  Wording in the “Policy”, “When Covered”, and/or “Not Covered” section(s) changed from “Medically Necessary” to “Reimbursement is allowed” or “Investigational” to “Reimbursement is not allowed” when necessary. (gm)
Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.