BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Fecal Calprotectin Testing

Policy #: 472
Latest Review Date: December 2024
Category: Laboratory

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **fecal calprotectin testing** as a **covered benefit** for the evaluation of individuals when the differential diagnosis is inflammatory bowel disease or noninflammatory bowel disease (including irritable bowel syndrome) for whom endoscopy with biopsy is being considered.

Blue Advantage will treat **fecal calprotectin testing** as a **non-covered benefit** and as **investigational** in the **management of inflammatory bowel disease**, including the management of active inflammatory bowel disease and surveillance for relapse of disease in remission.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Calprotectin is a calcium- and zinc-binding protein that is a potential marker of intestinal inflammation. Fecal calprotectin testing is proposed as a noninvasive means to diagnose inflammatory bowel disease (IBD). Other potential uses are to evaluate treatment response for patients with IBD and as a marker of relapse.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic condition that encompasses 2 main forms: Crohn's disease and ulcerative colitis. These conditions overlap in clinical and pathologic characteristics but have distinct features. Crohn's disease can involve the entire gastrointestinal (GI) tract and is characterized by transmural inflammation. Ulcerative colitis involves inflammation limited to the mucosal layer of the colon, almost always involving the rectum.

IBD is suggested by the presence of 1 or more of a variety of signs and symptoms that can be GI (eg, abdominal pain, bloody diarrhea, perianal fistulae), systemic (eg, weight loss, fatigue, growth failure in children), or extraintestinal (eg, characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity of symptoms in the disease course, including life-threatening illness.

Diagnosis

Diagnosing IBD is associated with well-defined management changes. A typical diagnostic approach to IBD includes stool testing for enteric pathogens, blood tests (complete blood count,

inflammatory markers) to differentiate etiologies and evaluate disease severity, as well as small bowel imaging and endoscopy (upper GI, colonoscopy) with biopsies.

Fecal Calprotectin

In some cases, the clinical manifestations of IBD can be nonspecific and suggestive of other disorders, including infectious colitis, colon cancer, and functional bowel disorders, including irritable bowel syndrome (IBS).

Thus, there is a need for simple, accurate, noninvasive tests to detect intestinal inflammation. Potential noninvasive markers of inflammation fall into several categories including serological and fecal. Serologic markers such as C-reactive protein and anti-neutrophil cytoplasmic antibodies (ANCA) tend to have low sensitivity and specificity for intestinal inflammation because they are affected by inflammation outside of the gastrointestinal tract. Fecal markers, in contrast, have the potential for being more specific to the diagnosis of gastrointestinal tract disorders since their levels are not elevated in extra-digestive processes. Fecal leukocyte testing has been used to evaluate whether there is intestinal mucosal inflammation. The level of fecal leukocytes can be determined by the microscopic examination of fecal specimens; however, leukocytes are unstable and must be evaluated promptly by skilled personnel. There is interest in identifying stable proteins in stool specimens which may be representative of the presence of leukocytes rather than evaluating leukocyte levels directly.

Calprotectin is a protein that could be used as a marker of inflammation. It is a calcium- and zinc-binding protein that accounts for approximately 30% to 60% of the neutrophil's cytoplasmic proteins. It is released from neutrophils during activation or apoptosis/necrosis and has a role in regulating inflammatory processes. In addition to potentially higher sensitivity and specificity than serologic markers, another advantage of calprotectin as a marker is that it has been shown to be stable in feces at room temperature for up to 1 week, leaving enough time for patients to collect samples at home and send them to a laboratory for testing. A sample of a few grams of stool is sufficient enough for testing. A 50 mg/g fecal calprotectin concentration in a stool sample is usually recommended as the cutoff for the normal concentration for adults and children older than 4 years. Moderate increases in fecal calprotectin levels, up to 100 mg/g, have been described for individuals older than 65 years. The concentration of fecal calprotectin is physiologically higher for neonates, infants, and young children, and thus fecal calprotectin concentrations in this population should be interpreted with caution.

Among potential disadvantages of fecal calprotectin as a marker of inflammation are that fecal calprotectin levels increase after the use of some medications (ie, nonsteroidal anti-inflammatory drugs; proton pump inhibitors), and that levels may change with other factors such as age, low fiber intake, and lack of exercise; other clinical situations associated with mucosal inflammation may also cause elevated fecal calprotectin levels such as gastrointestinal bleeding. Moreover, there is uncertainty about the optimal cutoff to distinguish between IBD and noninflammatory disease.

Fecal calprotectin testing has been used to differentiate between organic (eg, inflammation) and functional (no visible problem in the GI tract like IBS) disease. Some consider fecal calprotectin to be a marker of neutrophilic intestinal inflammation rather than a marker of organic disease and believe it has utility to distinguish between IBD and non-IBD. In practice, the test might be suitable for selecting patients with IBD symptoms for endoscopy (ie, deciding which patients do not require endoscopy). Fecal calprotectin testing has also been proposed to evaluate the response to IBD treatment and for predicting relapse. If found to be sufficiently accurate, the results of calprotectin testing could be used to change treatment, such as adjusting medication levels.

Treatment

Guideline-based treatments of IBD include oral and rectal salicylates, glucocorticoids, immunomodulators (eg, methotrexate), and multiple biologic therapies (eg, infliximab), depending on disease severity.

KEY POINTS:

The most recent literature review was performed through October 24, 2024.

Summary of Evidence

For individuals who have a suspicion of inflammatory bowel disease (IBD) when endoscopy with biopsy is being considered, who receive fecal calprotectin testing to select patients who can forgo endoscopy, the evidence includes prospective and retrospective diagnostic accuracy studies and systematic reviews. Relevant outcomes are test validity, symptoms, change in disease status, quality of life (QOL), hospitalizations, and medication use. Twenty-eight studies in a systematic review evaluated the diagnostic accuracy of fecal calprotectin in patients suspected of having IBD for whom noninflammatory bowel disease, such as irritable bowel syndrome (IBS) remains a consideration. Studies varied in the fecal calprotectin protein level cutoff used to indicate the presence of disease, but most used a cutoff of 50 µg/g, which is the recommended lower bound. Studies have indicated that, at this threshold, the test has a sensitivity of 93% to 99% for IBD and a negative predictive value of 73% to 100% for intestinal inflammation. Out of 100 cases of suspected IBD, approximately 49 invasive tests would be avoided with 1 case missed. In another meta-analysis involving 19 studies where the majority of studies again used the cutoff of 50 µg/g, investigators determined that out of 100 hypothetical patients, 18 non-disease patients would have a colonoscopy performed and 1 patient with IBD would not be referred for a colonoscopy. Additionally, it was determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%. Therefore, fecal calprotectin can be used to inform a decision of whether to proceed with endoscopy. Moreover, a recent review found that fecal calprotectin is the most sensitive noninvasive test in distinguishing IBD from non-IBD with a sensitivity of 99%. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have active IBD who receive fecal calprotectin testing to monitor disease activity, the evidence includes systematic reviews and 2 randomized controlled trials (RCTs). Relevant outcomes are test validity, symptoms, change in disease status, QOL, hospitalizations, and medication use. A systematic review determined that a fecal calprotectin level of 50 µg/g was the optimum threshold for triaging patients for endoscopy when they have symptoms of active disease, and another found high sensitivity in assessing IBD activity. More RCTs are needed to determine whether guiding treatment based on fecal calprotectin levels can improve disease management. A 2017 RCT included fecal calprotectin as 1 of several indicators of inflammation to test the effect of tight control of IBD on health outcomes. The independent contribution of fecal calprotectin could not be determined from this study design. In another RCT, self-monitoring with a home-based fecal calprotectin test among patients with established IBD demonstrated an increase in the proportion of patients seeking medical treatment; compliance to home-based testing in this study was low (29%). The use of a home-based fecal calprotectin test that is not available in the US limits the applicability of this study. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have IBD in remission who receive fecal calprotectin testing to predict relapse, the evidence includes systematic reviews and an RCT. Relevant outcomes are test validity, symptoms, change in disease status, QOL, hospitalizations, and medication use. A systematic review of studies that monitored fecal calprotectin in patients in remission demonstrated that fecal calprotectin levels began to rise 2 to 3 months before clinical relapse; an ideal fecal calprotectin cutoff for monitoring purposes was not identified. A meta-analysis of 24 prospective studies that monitored fecal calprotectin in patients in remission described an optimal cut-off value for fecal calprotectin of 152 µg/g and a pooled sensitivity and specificity of fecal calprotectin of 72% and 74%, respectively. Another review found that fecal calprotectin had a sensitivity of 78% and specificity of 73% in predicting recurrence, although magnetic resonance enterography (MRE) and ultrasound performed better. One RCT found no significant difference in the rate of relapse in patients whose medication was modified based on fecal calprotectin or standard clinical indicators, however, this RCT had design and conduct limitations that affected the interpretation of its results. Additional high-quality RCTs are needed to determine whether adding fecal calprotectin to standard clinical practice improves the management of IBD patients in remission. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Gastroenterological Association

In 2018, the American Gastroenterological Association (AGA) published a guideline on functional gastrointestinal symptoms in patients with IBD. AGA recommends a stepwise approach to rule-out ongoing inflammatory activity in IBD patients that includes fecal calprotectin, endoscopy with biopsy, and imaging. AGA recommends that in those patients with indeterminate fecal calprotectin levels and mild symptoms, calprotectin monitoring at three to six month intervals may allow anticipatory management of impending flares. However, "the optimal cutoff for biomarkers remains a source of debate" and overtreatment for symptoms that are due

to functional pathophysiology rather than inflammation can increase adverse effects with no symptomatic benefit.

A 2019 guideline from the AGA on laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome (IBS) in adults gave a conditional recommendation based on low quality evidence to use either fecal calprotectin or fecal lactoferrin to screen for IBD. A threshold value of 50 µg/g for fecal calprotectin was recommended to optimize sensitivity for IBD.

A 2021 clinical practice update from the AGA on the management of IBD in older adults states that: "Fecal calprotectin or lactoferrin may help prioritize patients with a low probability of IBD for endoscopic evaluation. Individuals presenting with hematochezia or chronic diarrhea with intermediate to high suspicion for underlying IBD, microscopic colitis, or colorectal neoplasia should undergo colonoscopy."

Two 2023 guidelines from the AGA were published on the role of biomarkers for the management of ulcerative colitis (UC) and Crohn's disease (CD). The recommendations regarding fecal calprotectin testing from both guidelines are summarized in Table 1.

Table 1. AGA Clinical Practice Guideline Recommendations on Role of Biomarkers for the Management of UC and CD

Recommendation	Strength of Recommendation	Certainty of Evidence
Ulcerative colitis		
In patients with UC in symptomatic remission, the AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone	Conditional	Moderate
In patients with UC in symptomatic remission, the AGA suggests using fecal calprotectin <150 µg, normal fecal lactoferrin, or normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease activity	Conditional	Low (for fecal calprotectin)

In patients with UC in symptomatic remission but elevated stool or serum markers of inflammation (fecal calprotectin >150 µg, elevated fecal lactoferrin, elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Very low
In patients with UC with moderate to severe symptoms suggestive of flare, the AGA suggests using fecal calprotectin >150 µg, elevated fecal lactoferrin, or elevated CRP to rule inactive inflammation and inform treatment adjustment and avoid routine endoscopic assessment solely for establishing presence of active disease	Conditional	Low (for fecal calprotectin)
In patients with UC with mild symptoms, with elevated stool or serum markers of inflammation (fecal calprotectin>150 µg, elevated fecal lactoferrin, or elevated CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.	Conditional	Very low
In patients with UC with mild symptoms, with normal stool or serum markers of inflammation (fecal calprotectin <150mg/g, normal fecal lactoferrin, or normal CRP), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment.	Conditional	Very low
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.	No recommendation	Knowledge gap
Crohn's disease		
In patients with CD in symptomatic remission, the AGA suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone	Conditional	Low

In patients with CD in symptomatic remission with recent confirmation of endoscopic remission (without any change in clinical status, on stable therapy), the AGA suggests using fecal calprotectin <150 µ/g and/or CRP <5 mg/L to rule out active inflammation, and avoid routine endoscopic assessment of disease activity	Conditional	Low to moderate
In patients with CD in symptomatic remission without recent confirmation of endoscopic remission, the AGA suggests endoscopic evaluation to rule out active inflammation, rather than relying solely on fecal calprotectin or CRP	Conditional	Low to moderate
In patients with CD in symptomatic remission, with elevated biomarkers of inflammation (fecal calprotectin >150 µ/g, CRP >5 mg/L), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Low
In patients with symptomatically active CD, the AGA suggests a biomarker-based assessment and treatment adjustment strategy, rather than relying on symptoms alone	Conditional	Moderate
In patients with CD with mild symptoms and elevated biomarkers of inflammation (fecal calprotectin >150 µ/g, CRP >5 mg/L), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Very low
In patients with CD with mild symptoms and normal biomarkers of inflammation (fecal calprotectin <150 µ/g, CRP <5 mg/L), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Very low
In patients with CD with moderate to severe symptoms, the AGA suggests using fecal calprotectin >150 µ/g or CRP >5 mg/L, to rule in active inflammation and inform treatment adjustment and avoid routine endoscopic assessment of disease activity	Conditional	Low to moderate

In patients with CD with moderate to severe symptoms with normal biomarkers of inflammation (fecal calprotectin <150 µ/g, CRP <5 mg/L), the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment	Conditional	Low
In asymptomatic patients with CD after surgically induced remission within the past 12 months, who are at low risk of postoperative recurrence or who have 1 or more risk factors for recurrence but are on postoperative pharmacologic prophylaxis, the AGA suggests using fecal calprotectin <50 µ/g to avoid routine endoscopic assessment of disease activity	Conditional	Moderate
In asymptomatic patients with CD after surgically induced remission within the past 12 months, who are at high baseline risk of recurrence and are not receiving postoperative pharmacologic prophylaxis, the AGA suggests endoscopic evaluation rather than relying solely on biomarkers, for assessing endoscopic recurrence	Conditional	Low to moderate
In patients with CD, 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.	No recommendation	Knowledge gap

AGA: American Gastroenterological Association; CD: Crohn's disease; CRP: C-reactive protein; UC: ulcerative colitis

American College of Gastroenterology

In 2018, the American College of Gastroenterology (ACG) published a guideline on the management of Crohn's disease in adults.35, The College gave a strong recommendation based on a moderate level of evidence that fecal calprotectin is a helpful test that should be considered to differentiate the presence of IBD from irritable bowel syndrome (IBS). A summary statement without a recommendation indicated that fecal calprotectin measurements may have an adjunctive role in monitoring disease activity. A 2021 ACG guideline on the management of IBS likewise suggests evaluating fecal calprotectin (or fecal lactoferrin) and C reactive protein (CRP) in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out IBD (Strong recommendation; moderate quality of evidence for fecal calprotectin).

International Organization for the Study of Inflammatory Bowel Disease

In 2021, the Selecting Therapeutic Targets in IBD (STRIDE) group, which was initiated by the International Organization for the Study of IBD (IOIBD), updated its recommendations for treating to target in Crohn's disease and UC. In this update, the reduction of fecal calprotectin to an acceptable range has been added as a formal intermediate treatment target. Per STRIDE-II: "Normalization of CRP (to values under the upper limit of normal) and fecal calprotectin (to 100–250 mg/g) is an intermediate treatment target in UC and CD. Consider changing treatment if this target has not been achieved." The strength of this recommendation is 8.2 out of 10 ("10" denotes complete agreement and "1" complete disagreement); 80% of votes scored between 7 to 10 using this scale. The Group also notes that the cutoff value of fecal calprotectin is dependent on the desired outcome; lower thresholds (eg, <100 mg/g) have been proposed for deep healing (both endoscopic and transmural healing) or histological healing, and higher values (eg, <250 mg/g) for less stringent outcomes (eg, Mayo Endoscopic Subscore of 0 or 1 in UC).

National Institute for Health and Care Excellence

NICE (2013; recommendation 1.1 was updated in 2017), published guidance on fecal calprotectin testing for inflammatory diseases of the bowel. The guidance made the following recommendations:

1.1 "Faecal 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:

1. cancer is not suspected, having considered the risk factors (for example, age)....

1.2 Faecal 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…."

U.S. Preventive Services Task Force Recommendations

Not Applicable.

KEY WORDS:

Fecal calprotectin testing, PhiCal™, CalPrest®, fCAL®

APPROVED BY GOVERNING BODIES:

In March 2006, the PhiCal™ (Genova Diagnostics), an enzyme-linked immunosorbent assay test for measuring concentrations of fecal calprotectin in fecal stool was cleared for marketing by the

Food and Drug Administration (FDA) through the 510(k) process. This test is indicated to aid in the diagnosis of irritable bowel disease and to differentiate IBD from irritable bowel syndrome (IBS) when used with other diagnostic testing and clinical considerations.

The PhiCal®, as modified by Quest Diagnostics, is classified as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The modified PhiCal® is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

In 2014, CalPrest® (Eurospital SpA) and, in 2016, CalPrest®NG (Eurospital SpA) were cleared for marketing by FDA through the 510(k) process. According to the FDA summary, CalPrest® "is identical" to the PhiCal™ test "in that they are manufactured by Eurospital S.p.A. Trieste, Italy. Compared with CalPrest®, the "differences in CalPrest® NG include the name of the test on the labels, detection antibody, the use of a Horse-radish peroxidase / TMB conjugate/substrate system, the provided Stop solution, the concentration of calibrators and controls in the kit and the dynamic range of the assay."

The fCAL® ELISA Calprotectin Test (Bühlmann Laboratories) received FDA clearance in 2018 for the quantitative measurement of fecal calprotectin in human stool. In 2018, LIAISON® Calprotectin test (DiaSorin Inc.) also received FDA clearance and was determined to be substantially equivalent to the predicate PhiCal™ device.

In 2019, ALPCO received 510(k) clearance from the FDA for its new fecal Calprotectin Chemiluminescence ELISA test. This test exhibits a clinical specificity of 95.1% and provides the "lowest false positive rate of any currently cleared calprotectin test without sacrificing clinical sensitivity." In 2023, ALPCO received 510(k) clearance from the FDA for its Calprotectin Immunoturbidimetric Assay and it was determined to be substantially equivalent to the Calprotectin Chemiluminescence ELISA test and is indicated for in-vitro diagnostic use as an aid in the diagnosis of IBD.

In 2022, DiaSorin Inc. submitted an application for modification of its LIAISON® Calprotectin test for the addition of the LIAISON® Q.S.E.T. Device Plus (the accessory used for stool sample collection and extraction) to the cleared assay. While the LIAISON® Calprotectin test is identical to its predicate cleared in 2018, the Q.S.E.T. Device Plus differs from its predicate Q.S.E.T. Device.

FDA product code: NXO.

Rapid fecal calprotectin tests that can be used in the home or physician's office are commercially available in Europe and Canada (e.g., Calprosmart, Calpro AS, Norway; Quantum Blue

Calprotectin®, Bühlmann Laboratories, Switzerland). Rapid tests have not been approved by the FDA for use in the U.S.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

83993	Calprotectin, fecal

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POLICY HISTORY:

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Medical Policy Group, October 2012
Medical Policy Group, April 2013

Medical Policy Group, June 2014
Medical Policy Group, April 2015
Medical Policy Group, July 2015
Medical Policy Group, May 2017
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Medical Policy Group, January 2019
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Medical Policy Group, December 2020
Medical Policy Group, December 2021
Medical Policy Group, December 2022
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Medical Policy Group, January 2024
UM Committee, January 2024: Annual review of policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, December 2024
UM Committee January 2025: Annual review of policy approved by UM Committee for use for Blue Advantage business.
