FEP Medical Policy Manual

FEP 2.04.69 Fecal Calprotectin Testing

Effective Policy Date: April 1, 2022

Original Policy Date: December 2012

Related Policies:

2.04.26 - Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Fecal Calprotectin Testing

Description

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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.

OBJECTIVE

The objective of this evidence review is to determine whether fecal calprotectin testing improves the net health outcome in individuals with or suspected of having inflammatory bowel disease.

POLICY STATEMENT

Fecal calprotectin testing may be considered **medically necessary** for the evaluation of patients when the differential diagnosis is inflammatory bowel disease or noninflammatory bowel disease (including irritable bowel syndrome) for whom endoscopy with biopsy is being considered.

Fecal calprotectin testing is considered **investigational** in the management of inflammatory bowel disease, including the management of active inflammatory bowel disease and surveillance for relapse of disease in remission.

POLICY GUIDELINES

A fecal calprotectin level of less than 50 g/g is suggestive of a low likelihood of inflammatory bowel disease.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

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 U.S. Food and Drug Administration (FDA) through the 510(k) process. This test is indicated as an aid in the diagnosis of IBD and to differentiate IBD from 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 (CLIA). The modified PhiCal is available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing.

In 2014, CalPrest (Eurospital SpA) and, in 2016, CalPrestNG (Eurospital SpA) were cleared for marketing by the FDA through the 510(k) process. According to the FDA summary, CalPrest "is identical" to the PhiCal™ test in that they have the same manufacturer. 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 (Bhlmann Laboratories) received FDA clearance in 2018 for the quantitative measurement of fecal calprotectin in human stool. In 2019, ALPCO received 510(k) clearance from the FDA for its new fecal Calprotectin Chemiluminescence ELISA test.[1,] 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."

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 (eg, Calprosmart, Calpro AS; Quantum Blue Calprotectin, Bhlmann Laboratories). Rapid tests have not been approved by the FDA for use in the U.S.

RATIONALE

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, 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 more recent 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. 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 a systematic review 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. 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 a systematic review 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. 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Gastroenterological Association

In 2018, the American Gastroenterological Association (AGA) published a guideline on functional gastrointestinal symptoms in patients with IBD.[21.] The AGA recommends a stepwise approach to rule-out ongoing inflammatory activity in IBD patients that includes fecal calprotectin, endoscopy with biopsy, and imaging. The AGA recommends that in those patients with indeterminate fecal calprotectin levels and mild symptoms, calprotectin monitoring at 3 to 6 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.[22,]

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."[23,]

American College of Gastroenterology

In 2018, the American College of Gastroenterology (ACG) published a guideline on the management of Crohn disease in adults.[24,] 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 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).[25,]

International Organization for the Study of IBD (IOIBD)

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 disease and ulcerative colitis.[26,] 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

The National Institute for Health and Care Excellence (2013; recommendation 1.1 was updated in 2017), published guidance on fecal calprotectin testing for inflammatory diseases of the bowel.[27,] 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.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2012	New policy	Fecal calprotectin testing is considered not medically necessary in the diagnosis and management of intestinal conditions, including the diagnosis and management of inflammatory bowel disease.
June 2013	Replace policy	Policy updated with new literature. No changes to policy statement. References updated.
June 2014	Replace policy	Policy updated with literature review. No change in policy statement. References 2, 5, 16 and 19 added; others renumbered or removed.
September 2015	Replace policy	Policy updated with literature review; references 2, 8, 15-16, and 21 added. No change in policy statement.
March 2017	Replace policy	Policy reviewed with no policy statement changes.
June 2018	Replace policy	Policy updated with literature review through January 8, 2018; references 4, 9- 10, 12, and 18-19 added; references 17-18 updated; some references removed. Policy statement unchanged except "not medically necessary" corrected to "investigational" due to FDA 510(k) status.
September 2019	Replace policy	Policy updated with literature review through September 7, 2018; reference 15 added. Policy statement revised; fecal calprotectin testing is considered medically for the evaluation of patients when the differential diagnosis is inflammatory bowel disease or irritable bowel syndrome for whom endoscopy with biopsy is being considered.
March 2020	Replace policy	Policy updated with literature review through November 12, 2019; references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 27, 2020; references added. Policy statements unchanged.
March 2022	Replace policy	Policy updated with literature review through October 29, 2021; references added. Policy statements unchanged.