

Fecal Calprotectin Testing in Adults

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I. Policy Description

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

II. Related Policies

Policy Number	Policy Title
AHS-G2060	Fecal Analysis in the Diagnosis of Intestinal Dysbiosis and Fecal
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. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

This policy is specific to individuals 18 years of age or older. Criteria below do not apply to individuals less than 18 years of age.

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

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

- 3) Fecal calprotectin testing for all other situations not discussed above **DOES NOT MEET COVERAGE CRITERIA.**

IV. Table of Terminology

Term	Definition
ACG	American College of Gastroenterology
AGA	American Gastrointestinal Association
CD	Crohn's disease
CDAI	Crohn's disease activity index
<i>C. diff</i>	<i>Clostridioides difficile</i>
CI	Confidence interval
CRP	C-reactive protein
DOR	Diagnostic odds ratio
ECCO	European Crohn's and Colitis Organisation
ELISA	Enzyme linked immunosorbent assay
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESR	Erythrocyte sedimentation rate
FC	Fecal calprotectin
FCAL	Fecal calprotectin
FDA	Food and Drug Administration
FL	Fecal lactoferrin
GI	Gastrointestinal
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
NICE	National Institute for Health and Care Excellence
SAM	Severe acute malnutrition
SES-CD	Simple endoscopic score for Crohn disease
SROC	Summary receiver operating characteristic
TNF α	Tumor necrosis factor alpha
UC	Ulcerative colitis

V. Scientific Background

Inflammatory bowel disease (IBD) includes several chronic, immune-mediated inflammatory gastrointestinal disorders, the most common being Crohn's disease and ulcerative colitis (Boirivant & Cossu, 2012). In contrast, irritable bowel syndrome (IBS), another gastrointestinal disorder, is a non-inflammatory condition. These disorders often share similar symptoms including abdominal discomfort, pain, bloating, and diarrhea (Burri & Beglinger, 2014). An estimated two thirds of Americans have experienced these IBS and/or IBD symptoms (Almario et al., 2018). Differentiating gastrointestinal tract symptoms due to IBS from those due to residual

inflammation from IBD is challenging (Gibson, 2022; Halpin & Ford, 2012). However, the detection of fecal calprotectin can be used to effectively distinguish between these conditions (Walsham & Sherwood, 2016).

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

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

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

Clinical Utility and Validity

Fecal calprotectin is increasing in utilization for the evaluation of IBD (Higuchi & Bousvaros, 2024). Meta-analyses of fecal calprotectin by both von Roon et al. (2007) and van Rheenen et al. (2010) found an overall sensitivity and specificity for IBD of >90%. Waugh et al. (2013) also completed a meta-analysis as part of the national Health Technology Assessment program which found a pooled sensitivity of 93% and specificity of 94% when distinguishing between IBS and IBD in adults with a fecal calprotectin cut-off of 50 µg/g.

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

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

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

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

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

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

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

In a cross-sectional study, Campbell et al. (2021) assessed the clinical performance of the LIAISON Calprotectin Assay in differentiating inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) against the Genova Diagnostics PhiCal test. A total of 240 patients were included in the study in which 102 patients had IBD, 67 had IBS, and 71 had other GI disorders. Median fecal calprotectin levels were higher in IBD patients (522 $\mu\text{g}/\text{g}$) compared to IBS patients (34.5 $\mu\text{g}/\text{g}$). 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 $\sim 100 \mu\text{g/g}$ " (Campbell et al., 2021).

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

VI. Guidelines and Recommendations

National Institute for Health and Care Excellence (NICE)

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

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

American Gastrointestinal Association (AGA)

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

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

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

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

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

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

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

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

American College of Gastroenterology (ACG)

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

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

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

“Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity. Fecal markers may have a role in noninvasively monitoring disease activity in CD [Crohn’s disease]. Studies have shown that both fecal lactoferrin and fecal calprotectin are sensitive markers of disease activity and correlate with a number of the endoscopic activity indices such as the colonic SES-CD. There have been several studies that suggest that levels of fecal calprotectin can be used to monitor patients for postoperative recurrence after ileocolic resection for Crohn’s disease. Levels of >100 µ g/g indicate endoscopic recurrence with a sensitivity in the range of 89%. In patients with an infliximab-induced remission, fecal calprotectin of >160 µ g/g has a sensitivity of 91.7% and a specificity of 82.9% to predict relapse... The presence of biomarkers of disease activity can be assessed (such as CRP, fecal calprotectin) but should not exclusively serve as end point for treatment as normalization of the biomarker can occur despite having active mucosal inflammation/ulceration... Although not specific for CD activity, determination of serum CRP and/or fecal calprotectin is suggested as a useful laboratory correlate with disease activity assessed by the CDAI” (Lichtenstein et al., 2018).

The Crohn’s Disease Activity Index (CDAI) is a tool that can provide a numerical value in assessing Crohn’s disease; however, fecal calprotectin is not a criterion of the index. Within the supplemental information of the guidelines, the authors state, “This is a weighted

subjective tool that includes scores for liquid bowel movements per day, general wellbeing, abdominal pain and extra-intestinal manifestations. This index does require 7 days of measurements making it difficult to use in the clinic setting. Due to the subjective nature of some of the measurements it is not an optimal tool for measuring disease activity and is generally not used in routine clinical practice”(Lichtenstein et al., 2018).

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

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

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

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

European Crohn’s and Colitis Organisation (ECCO)

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

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

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

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

- “Response to treatment in active ulcerative colitis [UC] should be determined by a combination of clinical parameters, endoscopy, and laboratory markers such as C-reactive protein [CRP] and faecal calprotectin [EL1]

- In patients with UC who clinically respond to medical therapy, mucosal healing [MH] should be determined endoscopically or by faecal calprotectin [FC] approximately 3 to 6 months after treatment initiation [EL5]” (Maaser et al., 2019).

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

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

VII. Applicable State and Federal Regulations

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: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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 the 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, BÜHLMANN 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.

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
83993	Calprotectin, fecal

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

IX. Evidence-based Scientific References

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