Fecal measurement of calprotectin is unproven and not medically necessary for the diagnosis and management of all conditions including but not limited to the following:

- Inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD)
- Colorectal cancer (CRC)

There is insufficient evidence that fecal calprotectin (FC) is effective as a biomarker for the diagnosis and management of intestinal disease. Before FC can be incorporated into routine clinical practice, studies in larger and diverse groups of patients will be needed to further clarify its role in clinical decision making and its effect on the outcome of treatment of the condition for which it is being used.

The cause of IBD is unknown, possibly involving an autoimmune reaction of the body to its own intestinal tract. UC and CD are examples of IBD. Both diseases are characterized by an uncontrolled inflammatory response at the mucosal level resulting in tissue damage. Most cases of CD and UC can be diagnosed by history and physical examination supplemented by small bowel x-rays, computed tomography/magnetic resonance enterography, capsule endoscopy, enteroscopy or colonoscopy, and then possibly confirmed by biopsy. However, differentiation between these 2 diseases can be difficult because they have overlapping clinicopathologic features. Since the natural history of these diseases is not the same, accurate diagnosis is important for both prognostic and therapeutic reasons.

Calprotectin is a calcium binding protein that is excreted in stool in patients with IBD and other gastrointestinal (GI) conditions. FC, used as a marker of intestinal inflammation, has been proposed to aid in the diagnosis and as a predictor of relapse in IBD including CD and UC. The use of FC has also been proposed as a predictive response to treatment in patients with IBD rather than relying solely on clinical symptoms.
Although FC has been most frequently studied in IBD, several investigators have measured FC levels in other intestinal diseases such as CRC, diverticular disease, and colonic polyposis.

**CLINICAL EVIDENCE**

**Inflammatory Bowel Disease (IBD)**

Mao et al. (2012) performed a meta-analysis of the predictive capacity of FC in patients with IBD. The authors analyzed 6 prospective studies with a total of 672 IBD patients (318 patients with UC and 354 patients with CD). The pooled sensitivity and specificity of FC to predict relapse of IBD was 78% and 73%, respectively. The capacity of FC to predict relapse was comparable between UC and CD. The authors concluded that FC assessment is a simple and noninvasive test, but the diagnostic performance of this test was lower than expected. The authors noted that a limitation of the studies was that remission was based on subjective clinical activity indices. Additional prospective studies using endoscopy to confirm relapse are needed to clarify the role of FC.

van Rheenen et al. (2010) performed a meta-analysis to evaluate whether the use of FC reduces the number of unnecessary endoscopic procedures in patients with IBD. A total of 13 studies up to October 2009 were included in the analysis. Six studies were done in adults (n=670) and 7 studies in children and teenagers (n=371). IBD was confirmed by endoscopy in 32% (n=215) of the adults and 61% (n=226) of the children and teenagers. In adults, the pooled sensitivity and pooled specificity of FC was 0.93 and 0.96 and in the studies of children and teenagers was 0.92 and 0.76. The lower specificity in the studies of children and teenagers was significantly different from that in adults. According to the authors, screening by measuring FC levels would result in a 67% reduction in the number of adults requiring endoscopy. Three of 33 adults who undergo endoscopy will not have IBD but may have a different condition for which endoscopy is inevitable. In the population of children and teenagers, 65 instead of 100 would undergo endoscopy. Nine of them will not have IBD. The downside of such screening would be a delayed diagnosis in 6% of affected adults and in 8% of affected children because of false-negative test results. The authors concluded that testing for FC is a useful screening tool for identifying patients who are most likely to need endoscopy for suspected IBD. The researchers also point out methodological limitations of their meta-analysis. Two of the included studies in adults did not sample intestinal mucosa, which might have caused some patients to be misclassified as normal. In addition, none of the studies used a well-defined set of clinical findings or flow chart to identify patients with a high probability of IBD. The authors also noted that the pooled sensitivity and specificity found in their study should be interpreted with caution. The authors commented, "Despite a strict selection of studies based on proper patient recruitment and study design, heterogeneity was considerable."

Jellema et al. (2011) statistically analyzed and summarized the available evidence on diagnostic tests in patients with abdominal symptoms. Studies were selected if the design was a primary diagnostic study. Patients were adults attending with nonacute abdominal symptoms. Tests included clinical assessment, blood or fecal tests or abdominal ultrasonography. Diagnostic two-by-two tables and pooled estimates of sensitivity and specificity were calculated. A total of 24 studies were included. While the diagnostic performance of the individual symptoms was highly variable, the performance of symptom-based classification systems was both more consistent and better. Among fecal and blood tests, FC was studied most frequently and showed the best results (sensitivity 0.61-1.0, specificity 0.71-1.0). Statistical pooling for ultrasonography resulted in a sensitivity of 0.73 (0.65-0.80) and a specificity of 0.95 (0.91-0.97). The authors concluded that although FC and ultrasonography showed consistent and promising findings, none of the studies was performed in primary care. The authors stated that before FC can be used to guide clinical decisions in primary care, these markers need to be investigated by high-quality prospective studies in the primary care setting.

Kostakis et al. (2012) performed a systematic review that included 34 studies evaluating the use of FC testing in pediatric patients with IBD. The authors found that FC levels of patients with IBD are much higher than those of healthy controls or patients with functional disorders or other GI. The results varied greatly when taking all studies into consideration. According to the authors, in cases of newly diagnosed and/or active IBD, the results are more homogeneous, with high sensitivity and positive likelihood ratio, low negative likelihood ratio, but moderate specificity. The authors concluded that the FC test could be used for supporting diagnosis or confirming relapse of IBD in pediatric patients. According to the authors, a positive result could confirm the suspicion of either IBD diagnosis or IBD relapse, due to the high sensitivity of the test, but a negative result should not exclude these conditions, due to its moderate specificity. Further clinical trials with larger patient populations are needed to clarify the optimal role of FC testing for evaluating IBD in children.

A prospective multicenter study was conducted by Gisbert et al. (2009) to determine the role of FC and lactoferrin in the prediction of IBD relapses. A total of 163 patients with UC (n=74) and CD (n=89) who had been in clinical remission for 6 months were included in the study. At baseline, patients provided a single stool sample for FC and lactoferrin determination. Follow-up was 12 months in patients showing no relapse and until activity flare in relapsing patients. Twenty-six patients (16%) relapsed during follow-up. FC concentrations in patients who suffered a relapse were higher than in nonrelapsing patients. Relapse risk was higher in patients having high FC concentrations (30%...
versus 7.8%) or positive lactoferrin (25% versus 10%). FC (>150 microg/g) sensitivity and specificity to predict relapse were 69% and 69%, respectively. Corresponding values for lactoferrin were 62% and 65%, respectively. Better results were obtained when only colonic CD disease or only relapses during the first 3 months were considered (100% sensitivity). The investigators concluded that FC and lactoferrin determination may be useful in predicting impending clinical relapse–especially during the following 3 months—in both CD and UC patients. This study did not confirm the utility of such findings in improving care and outcome of patients.

Garcia-Sanchez et al. (2010) performed a prospective study of 135 patients diagnosed with IBD in clinical remission for at least 3 months. All patients were followed-up for one year. Sixty-six patients had CD and 69 had UC. Thirty-nine (30%) suffered from relapse. The FC concentration was higher among the patients with relapse than in those that remained in remission. Patients with CD and calprotectin greater than 200μg/g relapsed 4 times more often than those with lower marker concentrations. In UC, FC greater than 120μg/g was associated with a 6-fold increase in the probability of disease activity outbreak. The predictive value was similar in UC and CD with colon involvement and inflammatory pattern. In this group, FC greater than 120μg/g predicted relapse risk with a sensitivity of 80% and a specificity of 60%. Relapse predictive capacity was lower in patients with ileal disease. Larger studies are needed to demonstrate that FC testing has sufficient diagnostic accuracy to provide clinically relevant information when compared to other currently available diagnostic tests to allow for clinical decision-making.

FC and tumor M2-pyruvate kinase (M2-PK) were measured in 94 controls and 105 gastroenterology outpatients with a possible diagnosis of organic bowel disease. The diagnosis was made by clinical, endoscopic, and radiological criteria. Organic bowel disease was diagnosed in 14 patients (13%). Sensitivity, specificity, and positive and negative likelihood ratios for diagnosis of organic bowel disease were 93%, 92%, 11.6, and 0.07 for FC and 67%, 88% 5.6, and 0.18 for tumor M2-PK, respectively. FC in combination with tumor M2-PK had a sensitivity of 64%, specificity of 98%, and likelihood ratios of 32 and 0.03. An elevated FC or tumor M2-PK decreased specificity to 87%, but increased sensitivity to 100%. Further research is needed to determine whether FC testing improves clinical decision making and health outcomes in patients with bowel disease (Jeffery et al., 2009).

Diamanti et al. (2010) assessed the diagnostic accuracy of the FC assay as a stool-screening biomarker for IBD. All patients suspected of IBD provided stool specimens for the FC assay and subsequently underwent endoscopic procedures. Compared to histology, the cutoff of 100 μg/g reached a sensitivity and specificity of 100% and 68%, respectively. The cutoff value of 160 μg/g, however, produced the best joint estimate of sensitivity and specificity: 100% and 80%, respectively. Further study is needed to define the optimal FC cutoff value for evaluating IBD.

Turner et al. (2010) conducted a prospective multicentre cohort study to evaluate 4 fecal markers (calprotectin; lactoferrin, M2-pyruvate kinase (M2-PK), and S100A12). Stool samples from 101 children with severe UC were obtained at the third day of intravenous steroid therapy. Repeated samples at discharge were obtained from 24 children. Median values (IQR) were very high at baseline for all 4 markers. M2-PK was numerically superior to the other 3 markers and CRP in predicting response to corticosteroid treatment. However, it did not add to the predictive ability of the Pediatric UC Activity Index (PUCAI). M2-PK also had the highest construct validity but with a modest mean correlation with all constructs. None of the markers was responsive to change. According to the investigators, the PUCAI, a simple clinical index, performed better than the fecal markers in predicting outcome following a course of intravenous corticosteroids in severe UC.

Meucci et al. (2010) evaluated the role of FC in 870 consecutive outpatients referred for colonoscopy. Mean levels of FC were significantly higher in patients with neoplastic and inflammatory disorders when compared with subjects with a normal colonoscopy or trivial endoscopic findings. Elevated FC levels (>50mg/dl) were detected in 85% of patients with CRC, and 81% of those with inflammatory conditions but also in 37% of patients with normal or trivial endoscopic findings. In patients referred for chronic diarrhea, sensitivity and negative predictive value were 100% in detecting organic colonic disease. In patients referred for symptoms of "suspected functional origin" sensitivity and negative predictive value for CRC were also 100%. According to the investigators, in unselected outpatients referred for colonoscopy, a single measurement of FC is not sufficiently accurate to identify those with significant colorectal disease. However, a normal result can help rule out organic disease among patients with diarrhea and those with abdominal pain and/or constipation.

Koulaouzidis et al. (2011) investigated the value of FC as a selection tool for further investigation of the small bowel with small bowel capsule endoscopy (SBCE), in a cohort of patients who had negative bi-directional endoscopies, but with continuing clinical suspicion of CD. The authors retrospectively correlated the findings of SBCE with FC levels in patients referred with clinical suspicion of CD and negative bi-directional endoscopies. Seventy adult patients were included in the study. Twenty-three patients had normal FC (≤ 50 μg/g) and in all those the SBCE was normal. Forty-four patients had FC >50 μg/g; in this group, 9 patients had FC between 51 and 100 μg/g and all had a normal SBCE. Thirty-five patients had FC levels >100 μg/g; of those, 15 (42.85%) had SBCE findings compatible with CD and mean FC levels 326 μg/g. A definitive clinical diagnosis of CD, based on subsequent follow-up, was made in 10/35 (28.5%) of patients. These 10 patients were within the subgroup of 15 patients with positive SBCE findings and had median FC
levels 368 μg/g. The authors concluded that measurement of FC levels prior to referral for SBCE is a useful tool to select patients with possible small bowel CD. The authors stated that a FC >100 μg/g is good predictor of positive SBCE findings, while FC >200 μg/g was associated with higher SBCE yield (65%) and confirmed CD in 50% of cases. According to the authors, FC assessment should be carried out prior to their referral for SBCE in all patients with clinical suspicion of CD and negative bi-directional endoscopies. Where FC is <100 μg/g (NPV 1.0), SBCE is not indicated. These findings require confirmation in a larger study.

Laharie et al. (2011) evaluated the association between FC concentration and CD clinical relapse in patients achieving remission with infliximab (IFX). Sixty-five patients were included in the study. Median FC level at week 14 was similar in patients with and without CD clinical relapse (200 and 150μg/g respectively). When considering two suggested FC cut-offs to predict CD relapse, sensitivities and specificities were 61% and 48% for 130μg/g, respectively, and 43% and 57% for 250μg/g. Neither FC nor CRP at baseline and at week 14 could predict relapse even when CD location subgroup analysis was considered. The authors concluded that in patients responding to an infliximab induction regimen, FC measurement at week 14 cannot predict CD clinical relapse at 1 year.

Sipponen et al. (2012) studied the role of FC and fecal S100A12 in predicting inflammatory lesions of small bowel in 84 patients (77 for suspicion of CD and 7 CD patients for evaluation of disease extent) undergoing wireless capsule endoscopy (WCE). Patients provided a stool sample for measurements of biomarkers. Patients underwent an esophagogastroduodenoscopy and ileocolonoscopy before WCE. WCE was abnormal in 35 (42%) of 84 patients: 14 patients with CD, 8 with NSAID enteropathies, 8 with angioectasias, 4 with polyps or tumors, and 1 with ischemic stricture. FC was significantly higher in CD patients compared with those with normal WCE or other abnormalities, whereas fecal S100A12 did not differ between the groups. In detecting inflammatory small bowel lesions, sensitivity, specificity, positive predictive value, and negative predictive value for FC (cutoff 50 μg/g) were 59%, 71%, 42%, and 83%. The authors concluded that in predicting small bowel inflammatory changes, fecal biomarkers calprotectin and S100A12 have moderate specificity, but low sensitivity. Neither FC nor S100A12 can be used for screening or excluding small bowel CD.

Additional clinical trials indicate that patients with IDB have abnormal or elevated FC levels compared with control subjects (Henderson et al. 2012, Komraus et al. 2012, Schoepfer et al. 2010, Schoepfer et al. 2009, Erbayrak et al. 2009, Tursi et al. 2011, Amatsu et al. 2011, Sipponen et al. 2010, Kallel et al. 2009). More recent studies and meta-analyses state that FC is a useful tool in evaluating UC and CD in certain circumstances including IBD in children (Holtman et al. 2017, Holtman et al. 2016. Bressler et al. 2015, Wright et al. 2015, Kennedy, et al. 2015, Mosli et al. 2015, Menees et al. 2015, Lin et al. 2014, Qiu et al. 2015, Sandborn et al. 2015.) However, these studies did not confirm the utility of FC testing for altering therapeutic decisions, minimizing disease complications, or reducing the need for more invasive testing.

A Hayes report examined FC testing for prediction of endoscopic and clinically defined disease activity in patients with CD. Evidence from the published, peer-reviewed literature (which included 15 prospective cohort studies and 1 retrospective cross-sectional study with a range of 78-221 participants) was considered to be low quality. The authors concluded that the available evidence suggests that FC testing is safe for adults and may have promise for monitoring disease activity due to the moderate-to-high diagnostic sensitivity. However, no direct evidence was available regarding the clinical utility (i.e., change in patient management or improved clinical outcomes). Additional studies are needed to define uniform cutoffs for FC testing to predict and monitor CD activity. There is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management for pediatric patients (2017a).

In monitoring for recurrence of CD in the postoperative patient, Hayes reviewed evidence (8 prospective cohort studies, 2 retrospective cross-sectional studies, and 1 subgroup analysis of a RCT, n = 20-135) which was also considered low quality. The authors concluded that FC testing has generally high negative predictive value and moderate sensitivity but low-to-moderate specificity for predicting recurrence in adult patients with CD who have previously undergone ileocolic resection. The overall diagnostic accuracy of FC testing varied widely across studies, from low to moderately high, and none of the studies directly assessed measures of clinical utility. In the pediatric population, the evidence was insufficient to determine whether FC monitoring had an impact on health outcomes or patient management (2017b).

Walsham and Sherwood (2016) performed a review focusing on the use of FC measurements in the diagnosis and monitoring of patients with IBD. Five meta-analyses and over 30 various studies taking place over 10+ years included over 15,000 adult and pediatric participants. The authors concluded that FC has adequate sensitivity and specificity to identify and differentiate IBD from functional disease permitting effective management of colonoscopy resources, it can be successfully used to monitor and initiate prompt therapy relating to clinical relapse of IBD, and FC measurements are determined to be beneficial when assessing and treating other intestinal diseases. The analysis did not translate research data into clinical guidelines that would affect physician practice patterns or patient management.
Recognizing FC as a widely used as marker of gut inflammation strongly associated with the severity of endoscopic lesions in CD, Boschetti et al. (2015) analyzed the relationships between levels of FC and high-sensitivity C-reactive protein (hsCRP) and the presence and severity of postoperative endoscopic recurrence in asymptomatic CD patients. 86 patients were included in this prospective multicenter observational cohort. FC concentrations differed significantly in patients with endoscopic recurrence when compared with those in endoscopic remission. The best cutoff point for FC to distinguish between endoscopic remission and recurrence was 100 μg/g. Its sensitivity, specificity, positive and negative predictive values (NPVs), as well as overall accuracy were 95%, 54%, 69%, 93%, and 77%, respectively. The authors concluded that measurement of FC concentrations is a promising and useful tool for monitoring asymptomatic CD patients after ileocolonic resection. Taking into account the high NPV of FC, a threshold below 100 μg/g could avoid systematic ileocolonoscopies in 30% of individuals from this patient group. A small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population.

**National Institute for Health and Care Excellence (NICE)**

NICE recommends FC testing as an option to support clinicians with the differential diagnosis of IBD or IBS in children, and in adults but only if cancer is not suspected (2017).

**Colorectal Cancer (CRC)**

Khoshbaten et al. (2014) utilized a case-control study to evaluate the diagnostic value of FC as a screening biomarker for GI malignancies. Calprotectin in feces seems to be a more sensitive marker for GI cancers than fecal occult blood, but its specificity may be too low for screening average risk populations. The case control study included 100 patients with GI malignancies (50 patients with CRC and 50 patients with gastric cancer) and 50 controls were recruited in Tabriz Imam Reza and Sina hospitals during a 24-month period. One to two weeks after the last endoscopy/colonoscopy, fecal specimens were collected by the patients and examined by ELISA method for quantitative measurement of calprotectin content. The results were compared between the 3 groups. The mean FC level was 109.1 ± 105.3 (2.3-454.3, median:74), 241.1 ± 205.2 (3.4-610.0, median:19.3) and 45.9 ± 55.1 μg/g (1.3-257.1, median:19.3) in gastric cancer, CRC and control group, respectively, the differences being significant (p<0.001) and remaining after adjustment for age. The optimal cut-off point for FC was ≥ 75.8 μg/g for distinguishing CRC from normal cases (sensitivity and specificity of 80% and 84%, respectively). This value was ≥ 41.9 μg/g for distinguishing gastric cancer from normal cases (sensitivity and specificity of 62%). The author’s results revealed that FC might be a useful and non-invasive biomarker for distinguishing CRC from non-malignant GI conditions. However, due to low sensitivity and specificity, this biomarker may not help physicians distinguishing gastric cancer cases from healthy subjects.

A quantitative meta-analysis to evaluate the diagnostic precision of FC for CRC was performed on prospective studies, comparing FC levels against the histological diagnosis. Patients (n=297) with colorectal neoplasia had nonsignificantly higher FC levels by 132.2 microg/g compared with noncancer controls. Sensitivity and specificity of FC for the diagnosis of CRC were 0.36 and 0.71, respectively, with an AUC of 0.66. Sensitivity analysis and meta-regression analysis did not significantly alter the results. The investigators concluded that FC cannot be recommended as a screening test for CRC in the general population (von Roon et al. 2007).

**Other Intestinal Conditions**

FC level measurement has been investigated in other intestinal conditions such as colonic diverticular disease (Tursi et al. 2009), acute or chronic diarrhea (Licata et al. 2012), intestinal allograft monitoring (Akpinar et al. 2008), celiac disease (Ertekin et al. 2010), GI disease in neonates (Selimoğlu et al. 2012, Baldassarre et al. 2011), and acute radiation proctitis monitoring (Hille et al. 2008). Patients with these conditions may have elevated FC concentration compared with healthy control subjects; however, successful identification of these conditions by FC has been inconsistent and studied in small populations. Further studies in larger populations are needed to clarify the role of FC for these conditions.

In an observational study, Manz et al. (2012) evaluated the diagnostic value of FC in 575 patients with abdominal discomfort who were referred for endoscopy. Calprotectin was measured in stool samples collected within 24 hours before the investigation using an enzyme-linked immunosorbent assay. The presence of a clinically significant finding in the GI tract was the primary endpoint of the study. Final diagnoses were adjudicated blinded to FC values. Median calprotectin levels were higher in patients with significant findings than in patients without significant findings. Using 50 μg/g as cut off yielded a sensitivity of 73% and a specificity of 93% with good positive and negative likelihood ratios (10.8 and 0.29, respectively). FC was useful as a diagnostic parameter both for findings in the upper intestinal tract and for the colon with higher diagnostic precision for the latter. In patients > 50 years, the diagnostic precision remained unchanged. The authors concluded that in patients with abdominal discomfort, FC is a useful non-invasive marker to identify clinically significant findings of the GI tract, irrespective of age. According to the authors, further prospective studies directly comparing recommended guidelines of appropriateness for endoscopy with FC measurements are warranted to establish the value of a biomarker-guided assessment of patients with abdominal discomfort.
Berman et al. (2010) conducted a study to identify potential biomarkers that could help in the prediction and management of GI immune-related adverse events. A total of 115 patients with unresectable stage III/IV melanoma were included in the study. Outcome measures included fecal FC levels. Despite an observed association between colonic inflammation and grade 2 or higher diarrhea, no baseline biomarkers could reliably predict development of GI toxicity.

Mercer et al. (2011) measured calprotectin levels in 732 stool samples collected and analyzed from 72 patients who had undergone total small intestine transplants, and correlated them with clinical indications, ostomy output, and pathologic findings. The authors found that although frequent prospective sampling could perhaps demonstrate an advantage in early indication of rejection, routine FC monitoring was not strongly supported in this study.

Multiple types of fecal biomarkers were discussed by Siddiqui et al. (2017) in a review evaluating the current status of FC and FL in both clinical practice and in research of GI diseases. The authors stated that while FC and FL are well documented in the management of IBD, studies are still needed to understand their role in other GI pathologies.

**Professional Societies**

**American Gastroenterological Association (AGA)**
In a clinical care pathway for identification, assessment and initial medical treatment in CD, the AGA cites FC in a list of laboratory tests to assess inflammatory status. In a similar clinical care pathway for UC, FC is not included in the list of tests to make a diagnosis and assess inflammatory status. The AGA makes no statement regarding the utility of FC testing in the management of CD or UC (2015).

**World Gastroenterology Organization (WGO)**
The WGO's 2015 global guideline for IBS, cites fecal inflammation marker (e.g., calprotectin) in a list of "high resource level" diagnostics, indicating the importance of the marker for distinguishing IBS from IBD. In their global guideline for IBD, WGO cited FC it as a simple, reliable, and readily available test for measuring IBD activity (2015).

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

PhiCal™ Fecal Calprotectin Immunoassay was classified as Class II on April 26, 2006 (Product Code NXO). Additional information is available at:
- [http://www.accessdata.fda.gov/cdrh_docs/reviews/K050007.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/K050007.pdf)

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination (NCD) for the fecal measurement of calprotectin used for the diagnosis and management of inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease and colorectal cancer. Local Coverage Determinations (LCDs) do not exist at this time.
(Accessed December 1, 2017)

**REFERENCES**


American Gastroenterological Association (AGA). IBD Care Pathway. Website.


Menees SB, Powell C, Kurlander J1 et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 2015 Mar;110(3):444-54.


### POLICY HISTORY/REVISION INFORMATION

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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