Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Fecal Calprotectin

Description/Background

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

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic inflammatory condition typically associated with the symptoms diarrhea, defecation urgency, and sometimes rectal bleeding and abdominal pain. There are two main forms of the disorder, Crohn's disease (CD) and ulcerative colitis (UC), which overlap in clinical and pathologic characteristics but have distinct features. CD can involve the entire gastrointestinal (GI) tract and is characterized by transmural inflammation. UC 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 (e.g., abdominal pain, bloody diarrhea, perianal fistulae), systemic (e.g., weight loss, fatigue, growth failure in children), or extraintestinal (e.g., characteristic rashes, uveitis, arthritis) in nature. Patients may present with or develop a range of severity levels, including life-threatening illness. Treatments include oral and rectal salicylates, glucocorticoids, immunomodulators (e.g., methotrexate), and multiple biologic therapies (e.g., infliximab), depending on disease severity, which are recommended by the American Gastroenterological Association and other organizations.[1]

Diagnosis

Making a diagnosis of 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 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).

There is, thus, a need for simple, accurate, noninvasive tests to detect intestinal inflammation and to differentiate it from functional intestinal disturbances. 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 one protein that could possibly be used as a marker of inflammation. It is a calcium- and zinc-binding protein that accounts for approximately 30-60% of the neutrophils' 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, a potential advantage of fecal 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 distant 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 use to distinguish between inflammatory bowel disease and non-inflammatory disease.

Fecal calprotectin testing has been used to differentiate between organic (e.g., 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 the appropriate use of the marker is in its use to distinguish between inflammatory bowel disease and non-inflammatory bowel disease. In practice, the test might be suitable for selecting patients with IBD symptoms for endoscopy, i.e. 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 potentially be used to change treatment, such as adjusting medication levels.

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

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, CalPrest®NG (Eurospital SpA) were cleared for marketing by the FDA through the 510(k) process.[1-2] 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 (Bühlmann Laboratories) received FDA clearance in 2018 for the quantitative measurement of fecal calprotectin in human stool.[3] In 2018, LIAISON® Calprotectin test (DiaSorin Inc.) also received FDA clearance and was determined to be substantially equivalent to the predicate PhiCal™ device.[4]

In 2019, ALPCO received 510(k) clearance from the FDA for its new fecal Calprotectin Chemiluminescence ELISA test.[5] 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.[6] 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; Quantum Blue Calprotectin, Bühlmann Laboratories). Rapid tests have not been approved by the FDA for use in the U.S.

Medical Policy Statement

The clinical utility of fecal calprotectin testing has been established for **adult and pediatric** individuals. It can be a useful option when criteria have been met.

Inclusionary and Exclusionary Guidelines

Inclusions

Pediatric Individuals
- As an adjunctive non-invasive test to confirm diagnosis of inflammatory bowel disease (IBD).
- For confirming a recurrence/relapse of IBD.
- To determine if endoscopy may be needed.

Adult Individuals
- To differentiate between inflammatory bowel disease and non-inflammatory bowel disease (including irritable bowel syndrome).
- For monitoring of gastrointestinal conditions such as inflammatory bowel disease.
- To assess response to therapy and relapse for inflammatory bowel disease.

Exclusions

- The use of fecal calprotectin testing in any other clinical situation.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

83993

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

SUSPECTED INFLAMMATORY BOWEL DISEASE

Clinical Context and Test Purpose

In individuals who have suspected IBD, the purpose of fecal calprotectin testing is to inform the decision whether to proceed to endoscopy with biopsy in order to confirm a diagnosis of IBD, either ulcerative colitis or Crohn's disease.

Both Irritable bowel syndrome (IBS) and IBD can share common presenting symptoms such as diarrhea and abdominal pain. IBS is generally managed by antidiarrheal agents, diet, and lifestyle changes. IBD has a more serious prognosis. For example, Crohn's disease can result in bowel obstruction or fistulas requiring surgical intervention. Ulcerative colitis has similar complications but is more localized.

In an individual whose symptoms have not responded to conservative management, endoscopy with biopsy would be required to confirm a diagnosis of IBD and inform treatment choice, which may include biologic disease-modifying agents. However, in a significant proportion of individuals undergoing endoscopy with biopsy, IBD is not present. If fecal calprotectin testing can predict which individuals are unlikely to have IBD, fewer individuals would be subjected to endoscopy with biopsy.

Review of Evidence

Shi et al (2022) published an umbrella review that summarized the sensitivity and specificity of fecal calprotectin (and 16 other noninvasive tests for IBD, including ESR, CRP, and fecal lactoferrin) from published systematic reviews and meta-analyses, including the Petryszyn et al (2019)[7], and Waugh et al (2013)[8], studies discussed below.[9] Diagnostic performance and test validity were classified into 3 clinical scenarios: diagnosis, activity assessment, and prediction of recurrence. A total of 106 assessments were included from 43 studies. For diagnosis, in distinguishing IBD from non-IBD, fecal calprotectin had a pooled sensitivity of 0.99 (95% confidence interval [CI], 0.92 to 1.00), the highest among all tests, and specificity of 0.65 (95% CI, 0.54 to 0.74). The performance of fecal calprotectin in patients with Crohn's disease (sensitivity, 0.95; specificity, 0.84) was generally better than in patients with ulcerative colitis (sensitivity and specificity, 0.78). In distinguishing IBD from IBS, fecal calprotectin was again the most sensitive test. With a cutoff of 50 µg/g, fecal calprotectin had a sensitivity of 0.97 (95% CI, 0.91 to 0.99) and specificity of 0.76 (95% CI, 0.66 to 0.84).

Petryszyn et al (2019) conducted a meta-analysis that evaluated the efficacy of fecal calprotectin as a diagnostic marker of IBD in patients with symptoms suspicious for the disease. [7] The analysis included 19 studies (15 prospective and 4 retrospective; published through December 2018) with 5032 patients. Patients were over 16 years of age and had gastrointestinal symptoms, chronic diarrhea, or any other reason that may raise IBD suspicion. In the majority of included studies the diagnostic fecal calprotectin cutoff value was 50 µg/g (n=14). An IBD diagnosis was confirmed in 620 (12.3%) patients, with prevalence ranging from 2.7% to 68.1%. The calculated pooled sensitivity was 0.882 (95% confidence interval [CI], 0.827 to 0.921), while the pooled specificity was 0.799 (95% CI, 0.693 to 0.875). There was a higher sensitivity of fecal calprotectin among studies with an IBD prevalence ≤ 30% as compared to among studies with a prevalence > 30% (0.902 [95% CI, 0.856 to 0.935] versus 0.825 [95% CI, 0.661 to 0.920]; p=0.041). Regarding risk of bias, the overall methodological quality of included studies was deemed to be "good"; however, 11 studies included some patients that were not representative of those who would receive the fecal calprotectin test in clinical practice and selection bias may have existed in 5 studies. The authors concluded that out of 100 hypothetical cases with an IBD prevalence of 12.3%, 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%.

Waugh et al (2013) published a systematic review as part of the U.K. Health Technology Assessment program. [8] Investigators included 28 studies using fecal calprotectin tests to evaluate inflammation of the lower intestine in newly presenting patients. Studies using fecal calprotectin tests to monitor disease progression or response to treatment were excluded. Endoscopy with histology was the preferred reference standard, although some studies included used imaging or clinical follow-up. Studies were pooled when there was a minimum of 4 using the same calprotectin cutoff. A pooled analysis of 5 studies using fecal calprotectin detected by enzyme-linked immunosorvent assay to differentiate between IBD and IBS in adults at a cutoff of 50 µg/g was performed (see Table 1). One study was rated as low risk of bias and 3 studies had at least 3 domains with high or unclear risk of bias. The pooled studies had a combined sensitivity of 93% and a combined specificity of 94% to predict the presence of inflammatory disease on biopsy (1 study evaluated the absence of inflammatory disease). See Table 2 clinical validity results and Tables 3 and 4 for individual study characteristics and results, with Table 4 presented in the order of increasing prevalence of IBD. Out of 100 cases with a prevalence of 20%,[10] 76 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 68%,[11] 35 invasive tests would be avoided with 5 cases missed.

Table 1. Characteristics of Studies at a Threshold of 50 µg/g

		11-Item QUADAS Quality Assessment No. of Studies Rated as High or Unclear Risk of Bias						
Study	**Studies Included**	**Study Populations Included**	**Study Designs Included**	**Study Reference Standards Included**	**No Domains**	**1-2 Domains**	**>2 Domains**	**Domains with >3 Studies at High Risk of Bias**
Waugh et al (2013)[8]	5	Adults newly presenting with IBD or IBS referred	Diagnostic accuracy of FC to detect inflammation	Most used endoscopy with biopsy	1	1	3	Blinding of reference standard

	by general practitioners	of the lower intestine					
6	Adults and children newly referred with IBD or non-IBD	Diagnostic accuracy of FC to detect inflammation of the lower intestine	Most used endoscopy with biopsy Some studies in children used clinical follow-up	0	5	1	Blinding of reference standard

FC: fecal calprotectin; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.

Table 2. Clinical Validity Study Results at a Threshold of 50 µg/g

Study	Scenario (N)	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV Range, %	NPV Range, %	Disease Prevalence Range (95% CI), %
Waugh et al (2013)[8]	To detect IBD in adults with IBS or IBD (5 studies, N=596)	93 (83 to 97)	94 (73 to 99)	24-100	73-100	10.9-69.0 (5.8 to 77.3)
Waugh et al (2013)[8]	To detect IBD in children and adults with IBD or non-IBD (6 studies, N=516)	99 (95-100)	74 (59-86)	62-96	93-100	21.4-61.1 (13.2 to 72.5)

CI: confidence interval; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; NPV: negative predictive value; PPV: positive predictive value.

Table 3. Characteristics of Diagnostic Accuracy Studies (IBD vs. IBS) in Adults with a Cutoff of 50 µg/g

Study	Study Population	Setting	Reference Standard	No. of Domains[a] at High or Unclear Risk of Bias
Basumani et al (2012)[12]	New referrals with diarrhea ≥4 wk to rule out IBD	District General Hospital, England	Histology	4
Ostlund et al (2008)[10]	Consecutive patients referred with lower abdominal symptoms to endoscopy unit. Excluded 25 patients with polyps or CRC.	Endoscopy unit, the Netherlands	Colonoscopy and biopsy	2
Li et al (2006)[13]	Outpatients and inpatients with IBS or IBD, healthy controls; patients followed up after polyp removal with no recurrence. Excluded 60 patients with CRC	Hospital, Peking	Colonoscopy with biopsy in IBD group	6

Schoepfer et al (2008)[11]	Outpatients and inpatients with IBS or IBD. Excluded patients with CRC.	Gastroenterology Department, University Hospital, Switzerland	Colonoscopy including terminal ileum and biopsies	0
El-Badry et al (2010)[14]	GI symptoms for at least 6 mo, and endoscopy necessary to exclude organic pathology. Excluded patients with CRC, diverticulitis, and polyps.	Internal Medicine Department, Egypt	Colonoscopy into ileum with biopsies	3

CRC: colorectal cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome.
[a] QUADAS ratings.

Table 4. Results of Diagnostic Accuracy Studies (IBD vs. IBS) in Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence

Study	N	Prevalence (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
Basumani et al (2012)[12]	110	10.91 (5.77 to 18.28)	1.00 (0.74 to 1.00)	0.60 (0.50 to 0.70)	0.24 (0.13 to 0.37)	1.00 (0.94 to 1.00)	2.51 (1.97 to 3.21)	0
Ostlund et al (2008)[10]	114	20.18 (13.24 to 28.72)	0.96 (0.78 to 1.00)	0.87 (0.78 to 0.93)	0.65 (0.47 to 0.81)	0.99 (0.93 to 1.00)	7.25 (4.25 to 12.38)	0.05 (0.01 to 0.34)
Li et al (2006)[13]	120	50.00 (40.74 to 59.26)	0.93 (0.84 to 0.98)	0.95 (0.86 to 0.99)	0.95 (0.86 to 0.99)	0.93 (0.84 to 0.98)	18.67 (6.18 to 56.63)	0.07 (0.03 to 0.18)
Schoepfer et al (2008)[11]	94	68.09 (57.67 to 77.33)	0.83 (0.71 to 0.91)	1.00 (0.88 to 1.00)	1.00 (0.88 to 1.00)	0.73 (0.57 to 0.86)	NR	0.17 (0.10 to 0.29)
El-Badry et al (2010)[14]	29	68.97 (49.17 to 84.72)	0.85 (0.62 to 0.97)	1.00 (0.66 to 1.00)	1.00 (0.81 to 1.00)	0.75 (0.43 to 0.95)	NR	0.15 (0.05 to 0.43)

CI: confidence interval; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; NLR: negative likelihood ratio; NPV: negative predictive value; NR: not reported; PLR: positive likelihood ratio; PPV: positive predictive value.

Six studies using fecal calprotectin with an enzyme-linked immunosorvent assay to differentiate between IBD and non-IBD in children and adults were pooled (see Table 5). Five of the studies included only children, most of whom had been referred to pediatric gastroenterologists. The children had undergone fecal calprotectin testing prior to endoscopy with biopsy or were followed clinically. No studies were at low risk of bias and 5 studies had 1 to 2 domains with high or unclear risk of bias, as evaluated on the QUADAS quality assessment. The highest risk of bias was for blinding of the reference standard. The combined sensitivity was 99%, with a lower combined specificity (74%) to detect the absence of inflammatory disease on biopsy (see Table 6). Modeling indicated that use of fecal calprotectin in children would result in fewer children undergoing an unnecessary invasive test (i.e., endoscopy with biopsy). Out of 100 cases, at a prevalence of 36%,[15] 47 invasive tests would be avoided with 1 case of IBD missed. At a prevalence of 51%,[16] 36 invasive tests would be avoided with 1 case of IBS missed. Individual study characteristics (Table 5) and results, (Table 6) presented in the order of increasing prevalence of IBD.

Table 5. Characteristics of Diagnostic Accuracy Studies (IBD vs Non-IBD) in Children and Adults with a Cutoff of 50 µg/g

Study	Study Population	Setting	Reference Standard	No. of Domains[a] at High or Unclear Risk of Bias
Damms and Bischoff et al (2008)[17]	Patients ages >18 y referred for colonoscopy for GI disorders or CRC screening	Gastroenterology departments at 3 hospitals and 3 outpatient clinics in Germany	Colonoscopy: for CRC screening medical check-up	2
Van de Vijver et al (2012)[15]	Children ages 6-18 y referred for further investigation of high suspicion of IBD from pediatrician's global assessment, physical examination, and blood results	Pediatric outpatient clinics at 6 general hospitals and 1 tertiary care hospital in the North Netherlands Paediatric IBD Consortium	68 patients had endoscopy; others had follow-up for at least 6 mo to confirm a diagnosis of IBS	1
Henderson et al (2012)[18]	All children who had a fecal calprotectin measurement as part of initial diagnostic workup before endoscopy	Pediatric gastroenterology department at a children's hospital in UK	IBD patients: standard clinical, histologic, and radiologic findings Non-IBD (control) patients: upper and lower endoscopy	2
Sidler et al (2008)[16]	Children ages 2-18 y referred for further investigation of GI symptoms (chronic diarrhea, bloody stools, abdominal pain) suggestive of an OBD	Pediatric gastroenterology outpatient clinic at children's hospital in Australia	Upper GI endoscopy and complete ileocolonoscopy with biopsy	1
Tomas et al (2007)[19]	Patients referred for further investigation of GI symptoms (intense abdominal pain, chronic diarrhea, weight loss, rectal bleeding)	Pediatric gastroenterology unit of university hospital in Spain	Clinical criteria, laboratory, image and endoscopic test results	6
Fagerberg et al (2005)[20]	Children ages 6-17 y with GI symptoms and blood tests suggestive of inflammation who were scheduled for colonoscopy to rule out IBD	Pediatric gastroenterology departments at hospitals in Sweden	Complete ileocolonoscopy with biopsy	1

CRC: colorectal cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; OBD; organic bowel disease.
[a] QUADAS ratings.

Table 6. Results of Diagnostic Accuracy Studies (IBD vs. Non-IBD) in Children and Adults with a Cutoff of 50 µg/g Stratified by Increasing Prevalence

Study	N	Prevalence (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI	PLR (95% CI)	NLR (95% CI)
Damms et al (2008)[17]	84	21.43 (13.22 to 31.74)	1.00 (0.81 to 1.00)	0.79 (0.67 to 0.88)	0.79 (0.60 to 0.88)	1.00 (0.93 to 1.00)	4.71 (2.96 to 7.50)	0
Van de Vijver et al (2012)[15]	117	35.9 (27.24 to 45.29)	1.00 (0.92 to 1.00)	0.73 (0.62 to 0.83)	0.68 (0.55 to 0.79)	1.00 (0.94 to 1.00)	3.8 (2.6 to 5.5)	0
Henderson et al (2012)[18]	190	47.89 (40.61 to 55.25)	0.98 (0.92 to 1.00)	0.44 (0.34 to 0.55)	0.62 (0.53 to 0.70)	0.96 (0.85 to 0.99)	1.8 (0.15 to 2.1)	0.05 (0.01 to 0.20)
Sidler et al (2008)[16]	61	50.82 (37.70 to 63.86)	1.00 (0.89 to 1.00)	0.67 (0.47 to 0.83)	0.76 (0.60 to 0.88)	1.00 (0.83 to 1.00)	3.00 (1.81 to 4.98)	0
Tomas et al (2007)[19]	28	53.57 (33.87 to 72.49)	1.00 (0.78 to 1.00)	0.92 (0.64 to 1.00)	0.94 (0.70 to 1.00)	1.00 (0.74 to 1.00)	13.00 (1.98 to 85.46)	0
Fagerberg et al (2005)[20]	36	61.11 (43.46 to 76.86)	0.95 (0.77 to 1.00)	0.93 (0.66 to 1.00)	0.96 (0.77 to 1.00)	0.93 (0.66 to 1.00)	13.36 (2.02 to 88.54)	0.05 (0.01 to 0.33)

CI: confidence interval; IBD: inflammatory bowel disease; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value.

Section Summary: Suspected IBD

A systematic review and meta-analysis of 28 studies pooled 11 studies that used a 50 µg/g threshold to evaluate intestinal inflammation. Five studies (n=596 patients) showed an NPV in the range of 73% to 100% in adults with IBS or IBD. Pooling of 6 studies in adults and children (N=1100) with IBD or non-IBD showed an NPV of 93% to 100%. Together, these results would suggest that fecal calprotectin testing at a threshold of 50 µg/g can identify patients who are unlikely to have inflammatory disease and can forgo a more invasive test (endoscopy with biopsy). In another meta-analysis involving 19 studies, investigators determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%. A recent umbrella review found that fecal calprotectin is the most sensitive noninvasive test in distinguishing IBD from non-IBD (sensitivity, 0.99), and IBD from IBS (sensitivity, 0.97 [cutoff 50 µg/g]. Although the sensitivity and specificity of fecal calprotectin were generally balanced, sensitivity was slightly better than specificity.

MONITORING IBD

Clinical Context and Test Purpose

For individuals who have been diagnosed with IBD, fecal calprotectin testing may allow clinicians to monitor disease activity and guide therapeutic decision making.

Review of Evidence

Abej, El-Matary, Singh, and Bernstein (2016) investigated the association between fecal calprotectin and other measures of clinical activity for patients with IBD.[21] 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"

Rosenfeld et al. (2016) performed a multicenter, prospective cohort study to evaluate the perspective of gastroenterologists regarding the impact of fecal calprotectin on the management of patients with IBD.[22] 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. The authors concluded the fecal calprotectin test effected a change in management 51.3% of the time and receipt of the result was associated with a reduction in the number of colonoscopies performed.

By performing a systematic review and meta-analysis, Tham et al. (2018) showed that fecal calprotectin is an accurate surrogate marker of postoperative endoscopic recurrence of Crohn's disease.[23] 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 µg/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 µg/g, with a pooled sensitivity of 70% [95% confidence interval (CI) 59-81%], specificity 69% (95% CI 61-77%), and DOR 5.92 (95% CI 2.61-12.17); the area under the SROC curve was 0.73. The authors concluded that fecal calprotectin is an accurate surrogate marker of postoperative endoscopic recurrence in CD patients. The FC cut-off 150 µg/g appears to have the best overall accuracy. Serial FC evaluations may eliminate or defer the need for colonoscopic evaluation in up to 70% of postoperative CD patients.

Section Summary: Monitoring IBD
Studies have demonstrated that the clinical use of fecal calprotectin in monitoring IBD plays a significant role. Fecal calprotectin has been shown to be a useful marker of disease activity and aids in the management of individuals with IBD. It has been demonstrated that use of this biomarker results not only in a change in management in individuals with IBD but also leads to a significant reduction in colonoscopies. Lastly, fecal calprotectin has been shown to be an accurate surrogate marker of postoperative recurrence in Crohn's disease and helps guide management decisions in these individuals.

RESPONSE TO THERAPY AND RELAPSE FOR IBD

Clinical Context and Test Purpose
For patients who have been diagnosed with IBD, fecal calprotectin has been used to assess response to therapy and relapse.

Review of Evidence
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.[24] Sixty patients with IBD were treated with TNFα antagonists and had their fecal calprotectin measured. Fecal calprotectin was found to be normalized (≤100μg/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 1 year. The authors concluded that a normal fecal calprotectin after induction therapy with TNFα antagonists predicts sustained clinical remission in the majority of patients on scheduled therapy with active luminal disease.

Molander et al. (2015) also studied whether fecal calprotectin can predict relapse after stopping TNFα-blocking therapy in IBD patients in remission.[25] 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”.

Mao et al. (2012) performed a meta-analysis of the predictive capacity of fecal calprotectin in IBD relapse.[26] 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”.

Foster et al. (2019) also measured fecal calprotectin levels to predict relapse in pediatric Chron’s disease patients.[27] A cohort of 53 children participated in this study, and eight children experienced a clinical relapse; “Baseline fecal calprotectin levels were higher in patients that developed symptomatic relapse [median (interquartile range), relapse 723 μg/g (283-1758) vs 244 μg/g (61-627), P = 0.02]” (Foster et al., 2019). The authors noted that fecal calprotectin levels > 250 μg/g were accurate predictors of a relapse occurring in the next three months; therefore, routine fecal calprotectin testing in children in clinical remission for Chron’s disease may be useful to predict relapse.

Section Summary: Response to therapy and relapse for IBD
Several studies have demonstrated that fecal calprotectin can be a useful marker in assessing response to treatment and assessing for relapse in patients diagnosed with IBD. Fecal calprotectin, evaluated after induction therapy with TNFα antagonists, has been shown to predict sustained clinical remission in patients with active luminal disease on scheduled therapy. The evaluation of fecal calprotectin may be used as a marker for predicting and identifying patients requiring close follow-up in clinical practice. A meta-analysis of the predictive capacity of fecal calprotectin in IBD relapse found that 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. This demonstrates that fecal calprotectin is a useful marker that can be used to predict relapse in IBD patients with inactive disease.

SUMMARY OF EVIDENCE

For individuals who have a suspicion of 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, 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 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 a meaningful improvement in the net health outcome.

For individuals who have IBD, studies have demonstrated that the clinical use of fecal calprotectin in monitoring their disease plays a significant role. It has been shown to be a useful marker of disease activity and aids in the management of individuals with IBD. It has also been demonstrated that use of this biomarker results not only in a change in management in individuals with IBD but leads to a significant reduction in colonoscopies. Lastly, fecal calprotectin has been shown to be an accurate surrogate marker of postoperative recurrence in Crohn’s disease and helps guide management decisions in these individuals and may eliminate or defer the need for colonoscopic evaluation in Chron’s disease patients.

For pediatric individuals, several studies have found that calprotectin is significantly more likely to be raised than any commonly employed blood tests at IBD diagnosis. When used in combination with these bloods tests an abnormality was demonstrated in 1 or both tests in all patients at diagnosis in this study. Fecal calprotectin measurement may be an advance when used contemporaneously and in addition to a routine pane of blood tests in the diagnosis of pediatric IBD. The evidence is sufficient to determine the effects of the technology on health outcomes.

For assessing response to therapy and relapse in individuals who have IBD, several studies have demonstrated that fecal calprotectin can be a useful marker. It has been shown to predict sustained clinical remission in individuals with active luminal disease on scheduled therapy following induction therapy with TNFα antagonists. Fecal calprotectin may be used as a marker for predicting and identifying patients requiring close follow-up in clinical practice. A meta-analysis of the predictive capacity of fecal calprotectin in IBD relapse found that 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 above demonstrates that fecal calprotectin is a useful marker that can be used to predict relapse in IBD patients with inactive disease.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2018 Input

Clinical input was sought to help determine whether the use of fecal calprotectin testing for individuals with suspected inflammatory bowel disease (IBD) when endoscopy with biopsy is being considered would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 1 specialty society-level response and 2 physician-level responses identified through specialty societies including physicians affiliated with academic medical centers.

For individuals who have suspected IBD (when endoscopy with biopsy is being considered) who receive fecal calprotectin testing, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice. Specifically, fecal calprotectin testing can inform the decision by using a positive fecal calprotectin result to refer for endoscopy with biopsy, or to use negative fecal calprotectin results to exclude IBD and avoid endoscopy with biopsy, with acceptably low tradeoffs in missed diagnoses of IBD in those who have false-negative fecal calprotectin results. Input further highlighted that the use of fecal calprotectin is particularly important in pediatric populations, where children may not be able to fully participate as medical historians and may have non-specific and/or atypical symptoms.

2014 Input

In response to requests, input was received through 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. One specialty society submitted 2 responses. Input was mixed on whether fecal calprotectin testing is considered investigational for the diagnosis of intestinal conditions and whether results of diagnostic testing are being used to change patient management. Clinicians who disagreed with the investigational designation tended to argue that a medically necessary use of the test for

diagnosis would be to differentiate inflammatory from noninflammatory conditions. There was near consensus that fecal calprotectin testing is considered investigational in the management of intestinal conditions. Most reviewers did not think that, when the test is used for management of intestinal disorders, results change patient management. There was near consensus that the manufacturer's recommended cutoff of 50 µg/g should be used to indicate a positive fecal calprotectin test.

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.[28] 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 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.[29]

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." [30]

A 2023 guideline from the AGA on the role of biomarkers for the management of ulcerative colitis (UC) made the following recommendations regarding fecal calprotectin testing: [36]

Table 7. AGA Clinical Practice Guideline Recommendations on Role of Biomarkers for the Management of UC

Recommendation	Strength of Recommendation	Certainty of Evidence
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 mg/g, 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 mg/g, 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 >150mg/g, 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>150mg/g, 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

AGA: American Gastroenterological Association; UC: ulcerative colitis

American College of Gastroenterology

The American College of Gastroenterology (2018) published guidelines on the management of Crohn's disease in adults.[31] 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 inflammatory bowel disease from irritable bowel syndrome. 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). [32]

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's disease and ulcerative colitis (UC).[33] 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 (e.g., <100 mg/g) have been proposed for deep healing (both endoscopic and transmural healing) or histological healing, and higher values (e.g., <250 mg/g) for less stringent outcomes (e.g., Mayo Endoscopic Subscore of 0 or 1 in UC)."

National Institute for Health and Care Excellence

In 2013, the National Institute for Health and Care Excellence published guidance on fecal calprotectin testing for inflammatory disease of the bowel.[34] The guidance made the following recommendations (updated 2017):

"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 … cancer is not suspected."
"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…"

The World Gastroenterology Organization (WGO)

The WGO's global 2009 guideline (updated 2015) for both irritable bowel syndrome and inflammatory bowel disease lists fecal inflammation marker (e.g., calprotectin) as a recommended laboratory test to diagnose IBD.[35]

Ongoing and Unpublished Clinical Trials
A search of clinicaltrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National / Local:

There are no national or local coverage determinations on this topic. 83993 has a fee on the 2021 CMS fee schedule.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 7, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/08	3/6/08	5/1/08	Joint policy established
7/1/09	4/21/09	5/14/09	References added.
9/1/10	6/15/10	6/29/10	Routine review of non-established service. References added
12/1/12	9/27/12	9/27/12	Routine review of non-established service. Policy reformatted to mirror BCBSA medical policy. References added. No change in policy status.
3/1/14	12/10/13	1/6/14	Routine update. Updated policy to reflect coverage for pediatric patients only. References and rationale updated.
1/1/16	10/13/15	10/27/15	Routine maintenance. No changes in policy statement
1/1/17	10/11/16	10/11/16	Routine policy maintenance. No changes in policy statement.
1/1/18	10/19/17	10/19/17	Added information on IBD to background section, added summary to pediatric section, added input to supplemental information section, added references 3, 14, 21 and 28. No change in policy status.
1/1/19	10/16/18	10/16/18	Extensive reformatting of rationale, added references # 4, 9-10, 12, 18-19. No change in policy status.
1/1/20	11/26/19		MPS changed to “Pediatric Patients The clinical utility of fecal calprotectin testing has been established for pediatric patients. It can be a useful option when used as an adjunctive non-invasive test for confirming a diagnosis or recurrence of inflammatory bowel disease and in determining if an endoscopy may be needed. Adult Patients Fecal calprotectin testing has been established 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 experimental/investigational in the routine management of inflammatory bowel disease, including the management of active inflammatory bowel disease and surveillance for relapse of disease in remission. Fecal calprotectin testing is E/I in the management of inflammatory bowel disease, including the management of active inflammatory bowel disease and surveillance for relapse of disease in remission". Rationale section revised.
1/1/21	10/20/20		Routine maintenance, no change in policy status.
1/1/22	10/19/21		Routine maintenance, no change in policy status.
1/1/23	10/18/22		Routine maintenance, no change in policy status. (ky)
1/1/24	10/17/23		Routine maintenance, references updated. Updated MPS to: The clinical utility of fecal calprotectin testing has been established for adult and pediatric individuals. It can be a useful option when criteria have been met. Updated Inclusionary and Exclusionary Guidelines. Added coverage for monitoring of gastrointestinal conditions such as inflammatory bowel disease and to assess response to therapy and relapse for inflammatory bowel disease. Updated Monitoring IBD and Response to therapy and relapse for IBD sections under rationale section.

			Vendor: Avalon (ky) **Post JUMP** This JUMP policy has a variance to Avalon's policy as Avalon's policy G2061 6/1/22 – only covers Fecal Calprotectin Testing in Adults.
1/1/25	10/15/24		Routine maintenance, no change in policy status. Vendor: Avalon (ky)

Next Review Date: 4th Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: FECAL CALPROTECTIN

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.