Cigna Medical Coverage Policy

Subject **Serological Testing for Inflammatory Bowel Disease**

Effective Date **8/15/2014**
Next Review Date **8/15/2015**
Coverage Policy Number **0121**

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Coverage Policy

Cigna does not cover testing for serological markers for the diagnosis or management of inflammatory bowel disease because it is considered experimental, investigational or unproven. Tests/test panels include, but are not limited to the following:

- anti-neutrophilic cytoplasmic antibody (ANCA), perinuclear anti-neutrophilic cytoplasmic antibody (pANCA)
- anti-saccharomyces cerevisiae antibody (ASCA)
- anti-outer membrane porin C (anti-OmpC) antibody
- anti-CBir1 flagellin (anti-CBir1) antibody
- anti-I2
- antilaminaribioside carbohydrate IgG (ALCA)
- antichitobioside carbohydrate IgA (ACCA)
- anti-synthetic mannoside antibodies (AΣMA or AMCA).
- Pseudomonas-associated sequence I-2 (Anti-I2
- Prometheus® IBD sgi Diagnostic™
- Prometheus® Crohn's Prognostic

Cigna does not cover testing for the measurement of antibodies to infliximab or adalimumab, performed individually or as part of a test panel (e.g., Prometheus® Anser™ IFX, Prometheus® Anser™ ADA), because it is considered experimental, investigational or unproven.

General Background

Diagnosis of IBD and Prediction of Disease-Related Complications

Perinuclear anti-neutrophilic cytoplasmic antibody (pANCA) and anti-saccharomyces cerevisiae antibody (ASCA) are serological markers that have been proposed as tools to assist in diagnosing inflammatory bowel disease, in differentiating ulcerative colitis from Crohn's disease in patients with indeterminate colitis, and in determining therapy and monitoring response to treatment. ANCA has been used in the diagnosis and classification of various vasculitis-associated and autoimmune disorders, and has been associated with renal manifestations of small vessel vasculitis with rapidly progressing glomerulonephritis. pANCA is an antibody directed against the cytoplasmic components of neutrophils with a perinuclear staining pattern. Serum pANCA has been reported to be present in up to 70% of patients with ulcerative colitis, and in only 10–40% of patients with Crohn's disease. Elevated levels of serum pANCA in ulcerative colitis patients are believed to be caused by pANCA production in the colonic mucosa.

ASCA is an antibody that reacts to a component of yeast commonly found in food. ASCA has been detected in the serum of a majority of Crohn's disease patients, but fewer ulcerative colitis patients. The origin of ASCA is not clear, nor is it known why this antibody occurs in only a subset of patients with Crohn's disease. ASCA has been detected in approximately 50–60% of Crohn's disease patients, and in only 10% or less of ulcerative colitis patients.

Several additional antibodies have been described as serological markers for IBD, including anti-outer membrane porin C (anti-OmpC) and Anti-CBir1 flagellin (anti-CBir1). These antibodies are directed against luminal bacterial components seen in IBD. Anti-OmpC, directed against the outer membrane porin C of Escherichia coli, is reportedly seen more often in patients with a mixed family history of Crohn's disease (CD) and ulcerative colitis (UC) as opposed to those with a family history of only UC. Anti-CBir1 is an antibody to flagellin from Clostridium species and is reported to be found in approximately 6% of UC patients and 50% of patients with CD, and may be associated with more complicated disease. Pseudomonas-associated sequence I-2 (Anti-I2 is a bacterial DNA fragment, and has been identified in lamina propria mononuclear cells of active CD patients. Anticarbohydrate antibodies have also been used in inflammatory bowel disease management, including antilaminaribioside carbohydrate IgG (ALCA), antichitobioside carbohydrate IgA (ACCA), and anti-synthetic mannoside antibodies (AΣMA or AMCA). ALCA, ACCA, and AMCA are similar to ASCA in that they are antibodies to sugars on the surface of microorganisms. ALCA and ACCA are reported to be associated with CD, and are found in 17-28% of CD patients AΣMA is an antibody against synthetic oligomannose epitopes, and is found to be positive in 24% of patients with CD who were negative for ASCA, and had a lower sensitivity but higher specificity compared to ASCA. (Feldman, 2010, Bossuyt, 2006; Iskandar, 2012).

Combined serological testing has been proposed as a screening method for patients who present with signs and symptoms of inflammatory bowel disease, and as a method to differentiate CD from UC. The Prometheus® IBD Serology 7 was commercially available through Prometheus (San Diego, CA) as a diagnostic panel consisting of ASCA IgA, ASCA IgG, anti-CBir1, ANCA, anti-OmpC, pANCA, and DNAse-senstitive pANCA. The updated test panel, Prometheus® IBD sgi Diagnostic™, combines serologic, genetic and inflammation markers in a proprietary Smart Diagnostic Algorithm, and is intended to assist in differentiating IBD vs. non-IBD and CD vs. UC in one comprehensive test (Prometheus website). The clinical utility of this testing has not been established, however. Patients with negative results would still need to undergo the standard diagnostic testing for inflammatory bowel disease. Patients with a positive result would still need to undergo additional testing to distinguish Crohn's disease from ulcerative colitis and to determine the extent of disease. .

Combined serological testing has also been proposed as a method of determining the risk for disease-related complications in patients with CD. Prometheus Crohn's Prognostic, combines proprietary serogenetic markers and serologic markers, including AntiI2 and many of the assays included in the IBD sgi Diagnostic panel. The test employs a logistic regression model to provide probabilities for developing disease complications in patients diagnosed with Crohn's disease.

There is insufficient evidence in the published medical literature to determine the role of serological testing, whether performed as individual assays or in test panels) in the diagnosis and management of inflammatory bowel disease. There is insufficient evidence to demonstrate that the use of these tests results in improved health outcomes.

Literature Review: Diagnosis of IBD and Prediction of Disease-Related Complications

Anand et al. (2008) conducted a retrospective study to evaluate the diagnostic accuracy of pANCA and ASCA as single agents, and in combination, for the diagnosis of Crohn's disease and ulcerative colitis, including cases of indeterminate colitis. Sera from 98 patients were evaluated, including 77 with Crohn's disease, 16 with ulcerative colitis, and 5 with indeterminate colitis. Medical records were reviewed to obtain diagnosis, demographics, symptoms, and medications. The presence of ASCA and pANCA were detected using ELISA, and the results were compared with clinical data obtained from the medical records. A positive pANCA test alone provided a sensitivity of 50% and a specificity of 82% for ulcerative colitis. A positive ASCA test alone provided a sensitivity of 40% and a specificity of 100% for Crohn's disease. A combination of pANCA-positive and ASCA-negative results showed a sensitivity of 50% for the diagnosis of ulcerative colitis, and a combination of ASCA-positive and pANCA-negative results provided a sensitivity and specificity of 32% and 100%, respectively for the diagnosis of Crohn's disease. Eighty percent of indeterminate colitis patients showed serology results consistent with ulcerative colitis. The authors concluded that this combination of serological markers provides generally high specificity, but the low sensitivity, especially in terms of Crohn's disease, precludes the possibility that they can replace currently available tools used for inflammatory bowel disease diagnosis and management. The authors also stated that these markers may prove beneficial in the management of indeterminate colitis.

A retrospective study by Sabery and Bass (2007) evaluated the use of serologic markers as a screening tool compared with elevated erythrocyte sedimentation rate and anemia in patients referred to a gastroenterology clinic for suspected inflammatory bowel disease. Patients were divided into four categories: ulcerative colitis, Crohn's disease, indeterminate colitis, and noninflammatory bowel disease. Patients were categorized based on clinical evaluation by board-certified pediatric gastroenterologists. A total of 227 patients had inflammatory bowel disease serology (IBD First Step and Confirmatory System, Prometheus Laboratories) performed between September 2002 and September 2004. A total of 40 children (19%) were found to have inflammatory bowel disease. Overall, serological testing for inflammatory bowel disease had 60% sensitivity and 92% specificity. A positive laboratory test for anemia or an elevated erythrocyte sedimentation rate had 83% sensitivity, and a combination of anemia and elevated erythrocyte sedimentation rate had 96% specificity. The positive predictive value of serologic testing was 60% compared to 79% in patients with anemia and elevated erythrocyte sedimentation rate. The positive predictive value of serological testing in the subgroup of patients without rectal bleeding (n=139) was only 35% compared to 60% using routine tests. Nearly a third of positive serologic tests were in patients with no demonstrable inflammatory bowel disease. The authors concluded that the measurement of the combination of elevated erythrocyte sedimentation rate and hemoglobin has a higher positive predictive value and is more sensitive and more specific than commercial serologic testing.

Dubinsky et al. (2006) conducted a prospective case series to examine the association of immune responses to microbial antigens with disease behavior and to determine the influence of immune reactivity on disease progression in pediatric CD patients. Serological testing for expression of ASCA, anti-outer membrane protein C (anti-OmpC), anti-12, and anti-CBir1 flagellin was performed in a blinded fashion by ELISA. Associations between immune responses and clinical phenotypes were evaluated. A total of 58 patients developed internal penetrating and/or stricturing (IP/S) disease after a median follow-up of 18 months. Anti-OmpC ($p<0.0006$) and anti-12 ($p<0.003$) were associated with IP/S disease. The frequency of IP/S disease increased with increasing numbers of immune responses (p trend=0.002). The chance of developing IP/S disease was highest in patients who were positive for all four immune responses. The presence and/or magnitude of ASCA and CBir1 did not significantly influence disease behavior, however. The authors concluded that immune responses to an increasing number of microbial antigens are associated with complicating IP/S disease in pediatric CD patients, and serum immune responses predict a more rapid progression from uncomplicated to complicated disease. The authors stated that further studies in large independent cohorts will be important to validate the clinical applicability of these findings.

Reese at al. (2006) conducted a meta-analysis to assess the diagnostic precision of ASCA and pANCA in inflammatory bowel disease. Sensitivity, specificity and likelihood ratios (LR) were calculated for different test combinations for Crohn's disease, ulcerative colitis and for inflammatory bowel disease compared with controls. A total of 66 studies/4019 patients were included. The ASCA+ with pANCA– test offered the best sensitivity for Crohn's disease (54.6%) with 92.8% specificity and an area under the ROC (receiver operating characteristic) curve (AUC) of 0.85 (LR + = 6.5; LR – = 0.5). Sensitivity and specificity of pANCA + tests for UC were 55.3% and 88.5%, respectively (AUC of 0.82; LR + = 4.5, LR – = 0.5). Sensitivity and specificity were improved to 70.3% and 93.4%, respectively, in a pediatric subgroup when combined with an ASCA test. The authors concluded that ASCA and pANCA testing are specific but not sensitive for CD and UC. The authors stated

ASCA and pANCA testing may be useful for differentiating UC from CD in the pediatric population, but this needs to be the subject of further research.

A prospective multicenter study conducted by Joosens et al. (2002) evaluated the value of ASCA and pANCA to increase diagnostic accuracy in categorizing indeterminate colitis. A total of 97 patients with indeterminate colitis from three centers were analyzed for pANCA and ASCA and followed up prospectively. A definitive diagnosis was reached using conventional techniques for 31 of 97 patients. The authors reported that a positive ASCA and negative pANCA predicted Crohn's disease in 80% of patients with indeterminate colitis, and a negative ASCA and positive pANCA predicted ulcerative colitis in 63.3% of patients with indeterminate colitis. A total of 48.5% of patients did not show antibodies against ASCA or pANCA, and most remained diagnosed with indeterminate colitis. Because only 31 patients had a confirmed diagnosis and only 21 of these patients were included in an evaluation of specificity and sensitivity, it is difficult to draw conclusions regarding the accuracy of serological testing in this study.

Dubinsky (2001) conducted a prospective study of pediatric patients to determine if accuracy of diagnosing IBD vs. functional childhood disorders was improved by the use of modified assays for pANCA and ASCA, with enzyme-linked immunosorbent assay test (ELISA) cut-off values maximized to increase sensitivity. ASCA, ANCA and pANCA profiles were obtained from 128 children undergoing diagnostic evaluation for IBD. Investigators were blinded to clinical diagnoses. Sensitivity of the modified assays for diagnosing IBD was 81% compared to 69% for the traditional tests, but specificity in terms of diagnosing IBD was lower, at 72% vs. 95%. The authors concluded that the incorporation of sequential noninvasive testing into a diagnostic strategy may avoid unnecessary and costly evaluations and facilitate clinical decision-making when the diagnosis of IBD in children is uncertain. The study was limited by small numbers in each group and a lack of distinction between UC and CD.

Measurement of Serum Levels and Antibodies to Infliximab and Adalimumab

Tumor necrosis factor (TNF) antagonist therapy (e.g., infliximab, adailmumab) may be used to treat inflammatory bowel disease. TNF blockers bind to the TNF-alpha, and block its interaction with the cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.

Infliximab is an intravenously administered chimeric (i.e., combination of non-human and human genetic material) monoclonal antibody to tumor necrosis factor-alpha, and may be used in selected patients for the treatment of moderate to severe ulcerative colitis (UC) or Crohn's disease (CD). Some patients do not respond to initial therapy, and a percentage of patients who do respond to initial therapy become unresponsive over time. It has been suggested that this loss of response may be due to the production of antibodies to infliximab. Infusion reactions to infliximab may also occur, and are typically associated with antibodies to infliximab, also referred to as HACA (human antichimeric antibodies).

Antibodies to infliximab (ATI) are less likely to occur in patients treated with glucocorticoids or immune modulators. Delayed hypersensitivity reactions although unusual, may occur two to twelve days after an infusion, and high ATI appear after such reactions, but are not necessarily found before reinfusion. Long delays between infusions are considered to be a significant risk factor for delayed hypersensitivity. Delayed hypersensitivity is less common when a standard induction regime is used and an immune modulator is administered concurrently. Options for treatment of diminished response therefore include decreasing the interval between doses or increasing the dose, and if necessary, changing to a different anti-TNF agent

Adallimumab is a fully human monoclonal antibody, administered subcutaneously, and may be used in the treatment of moderate to severe CD. Antibodies to the drug may also occur with adalimumab; with formation of antihuman antibodies (HAHAs). There is no consensus on the clinical significance of the presence of antidrug antibodies, but with episodic therapy there is an association between lower infliximab serum levels when ATI formation is highest, and a decreased response rate to adailnumab in patients with HAHAs (Feldman: Sleisenger and Fordtran's Gastrointestinal and Liver Disease,.2010).

Prometheus® Anser™ IFX is a quantitative infliximab monitoring assay designed to measure infliximab (IFX) and antibodies to infliximab (ATI) levels. The test is intended to provide clarity on factors contributing to a patient's loss of response and to guide treatment decisions. A similar test, Prometheus® Anser™ ADA, measures serum adalimumab (ADA) and antibodies to adalimumab (AMA) levels.

There is insufficient evidence in the published medical literature to determine the role of measurement of antibodies to infliximab or adailnumab, whether performed separately or combined with testing of blood levels, in the management of inflammatory bowel disease. There is insufficient evidence to demonstrate that the use of these tests results in improved health outcomes compared to usual clinical management.

Literature Review : Measurement of Serum Levels and Antibodies to Infliximab and Adalimumab
Nanda et al. (2013) conducted a meta-analysis of studies that reported clinical outcomes and infliximab levels according to the antibodies to infliximab (ATI) status in patients treated for ulcerative colitis (UC) or Crohn's disease (CD) (13 studies, 1378 patients). Included studies consisted of controlled trials, observational studies, and cohort studies. The pooled risk ratio of loss of clinical response to infliximab in patients with IBD who had ATIs was 3.2 (95% confidence internal [CI: 2.0-4.9, p<0.0001) when compared to patients without ATIs. This effect estimate was primarily based on CD patients (n=494). In patients with UC (n=86) with ATIs, there was a non-significant risk ratio of loss of response of 2.2 (95% CI: 0.5-9.0, p=0.3). The authors noted limitations of the analysis, including heterogeneity among the studies in methods of ATI detection and clinical outcomes reported, a high risk of bias in at least one quality domain in each study, and the fact that a funnel plot suggested publication bias.

Paul et al. (2013) conducted a prospective case series to evaluate the relationship between infliximab (IFX) trough levels and antibodies to infliximab (ATI) and mucosal healing in 52 patients with IBD (34 with CD and 18 with UC). According to the authors, accumulating evidence indicates that mucosal healing may change the natural course of the disease by decreasing the need for surgery and reducing hospitalization. Consecutive patients receiving IFX (5 mg/kg) treatment who were developing secondary failure to IFX were included. IFX trough levels, antibodies to IFX concentrations, C-reactive protein levels, and fecal calprotectin were measured prior to IFX optimization and at week eight. On the day of the first IFX optimization, a proctrosigmoidoscopy was performed and was repeated at week eight in patients with UC. After IFX dose intensification, half of the CD and UC patients achieved mucosal healing. Increase in IFX trough levels (called "delta IFX" in micrograms per milliliter) was associated with mucosal healing in both groups (p=0.001). A delta IFX >0.5 ug/ml was associated with mucosal healing (sensitivity 0.88; specificity 0.77; p=0.0001, area under the receiver operating characteristic curve, 0.89). The only factor associated with mucosal healing after IFX optimization was a delta IFX >0.5 ug/ml (likelihood ratio=2.02, 95% confidence internal, 1.01-4.08, p=0.48) the authors stated that because of small sample size, these results need to be confirmed in studies including a higher number of patients.

Lee et al. (2012) conducted a meta-analysis to determine the prevalence of ATIs in patients receiving infliximab, the effect of immunosuppressants on the prevalence of ATI, the effect of ATIs on the prevalence of infusion reactions and the effect of ATIs on the rates of remission (18 studies/3326 patients). The prevalence of ATIs was 45.8% when episodic infusion of infliximab was given and 12.4% when maintenance infliximab was given. Infusion reaction rates were significantly higher in patients with ATIs (relative risk: 2.07; 95% CI, 1.61-2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ATIs (p<0.00001). The presence or absence of ATIs did not affect the rates of clinical remission, however. The authors stated that further analysis is required to determine whether loss of response is dependent on the titer of ATIs.

A systematic review and meta-analysis was conducted by O'Meara et al. (2014) to provide a pooled estimate of the risk of infusion reactions according to patients' ATI status and to analyze the relationship of immunomodulators (e.g., methotrexate) to this risk. Eight studies (1351 patients) met the inclusion criteria; 7 of the 8 studies had a high risk of bias in at least one quality domain. The cumulative data indicated that in patients with ATIs compared to those without ATIs, there was a higher risk ratio (RR) of any acute infusion reaction (RR 2.4; 95% CI 1.5-3.8, p<0.001) and severe infusion reactions (RR 5.8, 95% CI 1.7-19), p=0.004). The authors noted that there was statistical heterogeneity among the studies that implies that the summary RR should be interpreted with caution. Patients who were prescribed immunomodulators during maintenance therapy had a reduction in the risk of ATI development (RR 0.6, 95% CI 0.4-0.9, p=0.02) and infusion reactions (RR 0.6, 95% CI 0.4-0.8, p<0.001).

Afif et al. (2010) conducted a retrospective review to evaluate the clinical utility of measuring HACA and infliximab concentrations in patients with IBD (n=155). Medical records were reviewed for patients for whom HACA and infliximab concentrations had been measured, to determine whether the result affected clinical management. Indications for testing included loss of response to infliximab (49%), partial response after

initiation of infliximab (22%) and possible autoimmune/delayed hypersensitivity reaction (10%). Antibodies to infliximab (ATI) were identified in 35 patients (23%), and therapeutic drug concentrations in 51 patients (33%). In HACA-positive patients, change to another anti-TNF agent resulted in a complete or partial response in 92% of patients, and dose escalation resulted in a response rate of 17%. The authors concluded that measurement of HACA and infliximab concentration impacts management and is clinically useful, and that a prospective randomized trial should be conducted to confirm these findings.

Cassinotti and Travis (2009) conducted a systematic review to evaluate the incidence of ATIs in CD and their impact on the efficacy and safety of infliximab. The authors stated that the observation that Infliximab use is associated over time with loss of response and infusion reactions has led to the presumption that this is due to immunogenicity, and that ATIs are the principal cause. The authors stated that the mechanisms for ATI development are poorly understood, and the incidence depends on multiple patient-specific and treatment-related analytical and clinical factors. The review demonstrated that the presence of ATIs is weakly and variably associated with clinical response or infusion reactions, but not with reactions relevant to clinical decision making. The authors stated that enormous variation in the methods of reporting ATIs and immunogenicity of infliximab make almost any interpretation possible from different studies, but few have clinical relevance. The authors concluded that there is no clear evidence that ATIs have an impact on efficacy or safety, nor a need to measure or prevent them in clinical practice.

Professional Societies/Organizations
The American College of Gastroenterology Practice Guidelines for Management of Crohn's disease in adults (Lichtenstein et al., 2009) state that serological studies evaluating antibodies against *Saccharomyces cerevisiae*, antineutrophil cytoplasmic antibodies, antibodies directed against CBir1, OmpC are evolving to provide adjunctive support for the diagnosis of Crohn's disease, but are not sufficiently sensitive or specific be recommended for use as a screening tools.

The American College of Gastroenterology Ulcerative Colitis Practice Guidelines in Adults, updated in 2010, states that pANCA have been identified in 60–70% of UC patients but are also found in up to 40% of patients with CD. These pANCA-positive CD patients typically have a clinical phenotype resembling left-sided UC patients, so ANCA detection alone is of little value in distinguishing between UC and CD. The low sensitivity of pANCA for the diagnosis of UC prevents it from serving as a useful diagnostic tool. These assays may be useful, however, in the occasional patient in whom no other clinical or pathologic features allow a differential diagnosis between UC and Crohn's colitis.

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America consensus conference report on differentiating UC from CD in children and young adults (Bousvaros, et al., 2007) states that the value of serology in a patient with IC remains a topic of study, and further research should examine, among other areas, the role of surrogate laboratory markers (genetics, serology, microbiology) in distinguishing these entities. A proposed algorithm to assist clinicians in differentiating UC from CD does not include serological testing.

Recommendations for testing for the measurement of antibodies to infliximab or adalimumab are not included in any of the above guidelines.

The American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti–TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease (Terdiman et al., 2013) does not discuss testing for antibodies to anti-TNF agents.

Use Outside the U.S.
The second European evidence-based consensus on the diagnosis and management of ulcerative colitis, part 1, definitions and diagnosis (Dignass et al, 2012) includes the following statement:

- No evidence-based recommendations can be made to implement the routine clinical use of molecular markers (genetic, serologic) for the classification of UC patients.

The authors noted that number of (auto) antibodies have been described in patients with UC, including with pANCA. Positive pANCA serology is found in approximately 50–60% of patients, but large variability exists due

to differences in methodology. Overall, pANCA has shown good accuracy to differentiate CD from UC, but sensitivity is not high enough to justify their use in diagnosis. These antibodies also lack accuracy in patients with colitis-yet to be classified, where diagnostic markers would be of greatest clinical value.

The second European evidence-based consensus on the diagnosis and management of Crohn's disease, definitions and diagnosis (Van Asschet al, 2010) does not include a recommendation regarding serologic testing. In a discussion of initial laboratory investigations, the authors state that currently available serologic testing may be used as an adjunct to diagnosis, but the accuracy of the available tests (ASCA, ANCA) is such that they are unlikely to be useful in routine diagnosis, and are ineffective at differentiating colonic Crohn's disease from ulcerative colitis. Other serologic markers, including anti-OmpC and CBir1 have not yet been shown to help in differentiating CD from UC. The authors also note that despite advances in Crohn's disease genetics, there are currently no genetic tests which are recommended routinely for diagnoses.

Summary
Serological testing, and test panels with various combinations of serologic, genetic, and inflammation markers have been proposed as diagnostic tools to differentiate inflammatory bowel disease (IBD) from non-IBD, differentiate ulcerative colitis from Crohn's disease in cases of indeterminate colitis, and predict the risk of disease-related complications in patients diagnosed with Crohn's disease. There is insufficient evidence in the published medical literature to determine the role of serological testing, whether performed as individual assays or in test panels) in the diagnosis and management of inflammatory bowel disease. There is insufficient evidence to demonstrate that the use of these tests results in improved health outcomes. The clinical utility of these tests has not been established.

Anti-tumor necrosis factor (TNF) (e.g., infliximab, adalimumab) may be used to treat inflammatory bowel disease. Testing for antibodies to infliximab and adalimumab has been proposed as a method to guide treatment decisions in patients with inflammatory bowel disease. There is a lack of consensus, however, regarding the clinical significance of the presence of antidrug antibodies. There is insufficient evidence in the published medical literature to determine the role of measurement of antibodies to infliximab or adailnumab, whether performed separately or combined with testing of blood levels, in the management of inflammatory bowel disease. Recommendations for such testing are not included in relevant professional society/organization guidelines. There is insufficient evidence to demonstrate that the use of these tests results in improved health outcomes compared to usual clinical management.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Experimental/Investigational/Unproven/Not Covered when used to report testing for serological markers for the diagnosis or management of inflammatory bowel disease:

CPT* Codes	Description
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) NOD2 (nucleotide-binding oligomerization domain containing 2) (eg, Crohn's disease, Blau syndrome), common variants (eg, SNP 8, SNP 12, SNP 13)
81479	Unlisted molecular pathology procedure
82397	Ceruloplasmin
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, quantitative, not otherwise specified
84999	Unlisted chemistry procedure
86021	Antibody identification; leukocyte antibodies

86140	C-reactive protein
86255	Fluorescent noninfectious agent antibody; screen, each antibody
86256	Fluorescent noninfectious agent antibody; titer, each antibody
86671	Antibody; fungus, not elsewhere specified
88347	Immunofluorescent study, each antibody; indirect method

Experimental/Investigational/Unproven/Not Covered when used to report testing for the measurement of antibodies to infliximab or adalimumab:

CPT* Codes	Description
84999	Unlisted chemistry procedure

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