



CIGNA MEDICAL COVERAGE POLICY

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Subject Serological Testing for Inflammatory Bowel Disease

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Etanercept (Enbrel®)
 Genotyping for Thiopurine Methyltransferase (TPMT) Deficiency in Individuals With Inflammatory Bowel Disease (IBD)
 Infliximab (Remicade®)
 Monitoring Thiopurine Metabolite Levels in Inflammatory Bowel Disease (IBD)

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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 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

General Background

Inflammatory bowel disease is a general term that encompasses two idiopathic diseases; Crohn's disease and ulcerative colitis. Ulcerative colitis is typically a mucosal inflammation of the large intestine with extension to the rectum, while Crohn's disease usually involves a patchy transmural inflammation that may affect any part of the intestinal tract. The diagnosis of ulcerative colitis and Crohn's disease is complicated by the fact that the symptoms and clinical presentation of these conditions frequently overlap. In approximately 10% of patients with

inflammatory bowel disease limited to the colon, it is not initially possible to distinguish ulcerative colitis from Crohn's disease. These patients are given a diagnosis of indeterminate colitis. Serological testing has been proposed as a method to reach a definitive diagnosis in such patients.

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 and 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 Crohn's disease, and may be associated with more complicated disease (Feldman, 2010, Bossuyt, 2006).

Combined serological testing for the presence of these antibodies (ANCA, pANCA, ASCA, anti-OmpC, and anti-CBir1) 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 Crohn's disease from ulcerative colitis. The Prometheus® IBD Serology 7 commercially available through Prometheus (San Diego, CA) is a diagnostic panel consisting of ASCA IgA, ASCA IgG, anti-CBir1, ANCA, anti-OmpC, pANCA, and DNase-sensitive pANCA. Individual test results are analyzed using a proprietary algorithm. Serological assays are also offered commercially through several other companies.

Literature Review

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 et 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.

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 to be recommended for use as a screening tool.

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.

Summary

Serological testing has been proposed as a screening test for patients who present with signs and symptoms of inflammatory bowel disease, and as a tool to differentiate ulcerative colitis from Crohn's disease in cases of indeterminate colitis. The presence of anti-neutrophilic cytoplasmic antibody (ANCA), perinuclear anti-neutrophilic cytoplasmic antibody (pANCA) and anti-saccharomyces cerevisiae antibody (ASCA) markers appear to be associated with inflammatory bowel disease (IBD). Several additional antibodies have also been described as serological markers for IBD, including anti-outer membrane porin C (anti-OmpC) and Anti-CBir1 flagellin (anti-CBir1). Serological testing is a promising technology, but further study of the test characteristics is needed to clarify its utility as a tool to diagnose and manage inflammatory bowel disease. 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. The clinical utility of these tests has not been established.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
83516 [†]	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method
83520 [†]	Immunoassay, analyte, quantitative; not otherwise specified
86021 [†]	Antibody identification; leukocyte antibodies
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

† **Note: Experimental/Investigational/Unproven and not covered when used to report testing for serological markers for the diagnosis or management of inflammatory bowel disease.**

ICD-9-CM Diagnosis Codes	Description
555.0 – 555.9	Regional enteritis
556.0 – 556.9	Ulcerative colitis
564.1	Irritable bowel syndrome

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	07/15/2008/	0121	Serological Testing for Inflammatory Bowel Disease (ANCA/pANCA/ASCA)

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