



# Louisiana

## Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease

**Policy #** 00238

**Original Effective Date:** 06/17/2009

**Current Effective Date:** 06/20/2018

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers determination of anti-neutrophil cytoplasmic antibody (ANCA) and anti-saccharomyces cerevisiae antibody (ASCA) in the workup and monitoring of patients with inflammatory bowel disease (IBD) to be **investigational**.\*

### **Background/Overview**

Two serum antibodies, ANCA and ASCA have been associated with IBD. These antibodies may have potential use in the diagnosis of IBD, differentiating types of IBD, and predicting response to treatment.

Inflammatory bowel disease can be subdivided into ulcerative colitis (UC) and Crohn's disease (CD), both of which present with symptoms of diarrhea and abdominal pain. The definitive diagnosis can usually be established by a combination of radiographic, endoscopic and histologic criteria, although in 10%–15% the distinction between UC and CD cannot be made with certainty.

The serum antibodies have several potential uses. They can be used as diagnostic tests to improve the efficiency and accuracy of diagnosing IBD to decrease the extent of the diagnostic workup or to avoid invasive tests. As a diagnostic test, they might also be useful in differentiating between UC and CD in cases of indeterminate colitis. A second potential use is to classify subtypes of IBD by location of disease (i.e., proximal vs. distal bowel involvement) or by disease severity, thereby providing prognostic information. It has also been proposed that these markers may predict response to anti-tumor necrosis factor (TNF) therapy or identify susceptibility to IBD among family members of an affected individual.

The Prometheus<sup>®†</sup> IBD Serology 7 (Prometheus Inc., San Diego, CA) is a quantitative analysis of biomarkers for IBD prediction and differentiation. Prometheus IBD Serology 7 is only offered at Prometheus. This system uses a 2-step process to diagnose IBD and to differentiate between UC and CD. The first step is a panel of four markers intended to maximize the sensitivity and negative predictive value of the test. Patients who test positive on the initial screen are further analyzed by a set of proprietary markers and enzyme reagents to distinguish between true positive results and artifacts of fixation. In this way, the Prometheus system is intended to increase the specificity of the test compared to other laboratories. The company also markets a testing strategy for predicting response to anti-TNF therapy and to monitor therapy.

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### **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

Serum testing for ANCA and ASCA does not require FDA approval.

Centers for Medicare and Medicaid Services (CMS)

No Medicare national coverage determination available.

### **Rationale/Source**

This policy was originally based on a 1999 TEC Assessment that evaluated ANCA and ASCA in the following three clinical situations:

- The use of both tests as a first screen in patients with clinical signs and symptoms suggestive of IBD but who have not undergone confirmatory tests such as contrast radiographic studies of colonoscopy with biopsy.  
In this setting the sensitivity of the test, as averaged among studies, is 38% with an average specificity of 94%. The low sensitivity of the test indicates that a negative result will not be clinically helpful. A positive result indicates that IBD is likely, but it is difficult from the available data to reliably estimate the positive predictive value in a population presenting with signs and symptoms of IBD.
- ANCA as a confirmatory test for UC, and ASCA as a confirmatory test for CD.  
In this setting, the average specificity of ANCA and ASCA is 90% and 94%, respectively, but the TEC Assessment concluded that this specificity is not likely to be high enough to confirm the diagnosis such that additional testing would not be necessary.
- The use of both tests to distinguish between CD and UC in patients who have completed the standard workup, including pathologic evaluation of gastrointestinal biopsies.  
In this setting, the pooled sensitivity of the test is 84%. This sensitivity, although relatively high, would still result in a significant number of patient misclassifications. In addition, in the studies the patients had either established UC or CD, and this is not the population of clinical interest.

Following is a summary of the key updated literature:

In 2006, a meta-analysis of studies that evaluated the diagnostic accuracy of ASCA and ANCA in IBD was published. It included studies that compared ASCA or ANCA sensitivity and specificity to a “gold standard” (clinical, radiologic, endoscopic and/or histologic diagnosis). Studies included patients who ultimately had a diagnosis of UC and/or CD. A total of 60 eligible studies were identified; there were 3841 UC patients, 4019 patients with CD, and 3748 controls. Fifteen studies had a control group of healthy controls, 14 had a control group of individuals with non-IBD conditions, 14 had both types of control groups, and 15 studies had no control group (characteristics of two studies were not reported). For the diagnosis of UC, the authors examined the sensitivity and specificity of ANCA in different combinations with ASCA, and for CD, they looked at ASCA in different combinations with ANCA. For UC, the most sensitive test combination was an ANCA-positive test without information regarding ASCA status; the pooled sensitivity was 55.3% and specificity was 88.5%. The most sensitive test for CD was ASCA immunoglobulin (IgG)-positive or IgA-

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positive in sera that were ANCA-negative. The pooled sensitivity was 55% with a specificity of 93%. The tests were also examined for their ability to distinguish between CD and UC. The most sensitive test for differentiating between the two conditions was the presence of either ANCA or ASCA antibodies of any class. The combined sensitivity and specificity in this situation were 62.6% and 92.6%, respectively. The authors did a sensitivity analysis and found that including only high-quality studies ( $n = 18$ ) did not significantly change the findings. They did not stratify their findings by prospective versus retrospective studies or by type of control group (i.e., healthy controls vs. patients with conditions other than IBD).

Most studies have included populations of patients with established UC and CD. An exception is Joossens et al. which identified 97 patients with indeterminate colitis followed up prospectively. A definitive diagnosis of UC was made in 11 patients; 7 of 11 were ANCA positive and ASCA negative. A diagnosis of was made in 10 patients; 8 of 10 were ANCA negative and ASCA positive. Approximately half of the patients with indeterminate colitis did not have positivity for either serum marker.

Several articles attempted to correlate titers of ANCA and/or ASCA with disease activity. Mow and colleagues investigated whether serologic antibodies were associated with disease complications. In this case series of 303 patients with CD, certain antibodies were associated with fibrostenosis or perforating disease. In a study conducted in Scotland, Russell and colleagues evaluated the association between ASCA status and disease phenotype. The study included a total of 301 patients (197 with CD, 76 with UC, and 28 with indeterminate colitis). In multivariate analysis, they found a significant association between ASCA positivity and a higher likelihood of oral CD (adjusted odds ratio [OR] = 22.2, 95% confidence interval [CI] = 3.4-142.9) and the presence of hypoalbuminemia (adjusted OR = 4.78, 95% CI = 1.40-16.4). Confidence intervals were wide, indicating a high degree of uncertainty. In both the Mow and Russell studies, it is unclear how this information would be used in the management of the patient.

Other studies evaluated the presence of serum markers in unaffected relatives of patients with IBD, reporting positive results in approximately 25–50% of family members. However, these studies did not report on the incidence of IBD in relatives with positive antibodies. Two additional antibodies have been also been studied, Escherichia coli outer membrane porin C (anti-OmpC) and I2 antibody. However, the same limitations in the published literature apply to these antibodies.

A study by Schoepfer and colleagues studied the results of various testing in 64 patients to compare the accuracy of fecal markers (i.e., PhiCal Test, IBD-SCAN), C-reactive protein, blood leukocytes, and antibody panels (ASCA and pANCA) for discriminating IBD from irritable bowel syndrome and to define a "best test." The authors concluded PhiCal Test and IBD-SCAN are highly accurate for discriminating IBD from irritable bowel syndrome. Additional diagnostic accuracy is only marginal when the PhiCal Test and IBD-SCAN are combined with ASCA and pANCA. ASCA and pANCA have a high specificity for IBD; however, they should not be primarily measured for discriminating IBD from irritable bowel syndrome, as their additional value to fecal leukocyte markers in this issue is only marginal.

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A review article published in 2007 discussed the expansion of the panel of serologic markers for IBD. An increasing amount of data are available on newly discovered antibodies (i.e., Anti-OmpC, Anti-12, Anti-CBir1, and antiglycan antibodies) directed against various microbial antigens. However, ASCA and P-ANCA remain the most widely investigated. The authors noted that the role of the assessment of various antibodies in the current IBD diagnostic algorithm is often questionable due to limited sensitivity. They concluded that further prospective clinical studies are needed to establish the clinical role of serologic tests in IBD.

### Summary

A number of studies have examined the association between the serologic markers ASCA and ANCA and IBD. Systematic reviews have found relatively low sensitivity and moderately high specificity. Moreover, the clinical utility of these assays has not been demonstrated. No studies demonstrated the use of these markers in lieu of a standard workup for IBD. A number of authors claim that these markers can be used to avoid invasive testing, but no studies demonstrated an actual decrease in the number of invasive tests through use of serum markers. These technologies are investigational for the diagnosis and monitoring of IBD given the insufficient evidence to evaluate the impact on net health outcome.

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### Policy History

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06/04/2009 Medical Director review

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06/17/2009	Medical Policy Committee approval.
06/03/2010	Medical Policy Committee approval.
06/16/2010	Medical Policy Implementation Committee approval. No change to coverage.
06/02/2011	Medical Policy Committee approval.
06/15/2011	Medical Policy Implementation Committee approval. No change to coverage.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2018	Coding update
Next Scheduled Review Date:	06/2019

### **Coding**

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	83516, 83518, 83519, 83520, 88346, 88350
HCPCS	No codes
ICD-10 Diagnosis	K50.00 K50.011-K50.019 K50.10 K50.111-K50.119 K50.80 K50.811-K50.819 K50.90 K50.911-K50.919 K51.00 K51.011-K51.019 K51.20 K51.211-K51.219 K51.30 K51.311-K51.319 K51.40 K51.411-K51.419 K51.50 K51.511-K51.519 K51.80 K51.811-K51.819 K51.90 K51.911-K51.919 Z87.19

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

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