Name of Policy:
Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease

Policy #: 285       Latest Review Date: October 2015
Category: Medical
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Inflammatory bowel disease (IBD) 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 ulcerative colitis and Crohn’s disease cannot be made with certainty. Two serum antibodies, anti-neutrophilic cytoplasmic antibodies (ANCA) and anti- *Saccharomyces cerevisiae* (ASCA) have been associated with IBD; however, they have low sensitivities and are not completely specific to the disease. A number of subtypes of these markers have also been identified based on the specific antigen that is targeted. Testing for ANCA is currently available in most clinical laboratories. ASCA is a more recent assay that is becoming more widely available, but the reliability of testing for ASCA among different labs may be more variable as compared to ANCA.

These 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 versus 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.

PROMETHEUS IBD sgi Diagnostic™ is a 4th-generation IBD diagnostic test and the first test to combine serologic, genetic, and inflammation markers using the proprietary Smart Diagnostic Algorithm which is suggested to add diagnostic clarity. The test is proposed to aid healthcare providers in differentiating IBD vs non-IBD and CD vs UC in one comprehensive blood test. PROMETHEUS IBD sgi Diagnostic includes nine serological markers, including Anti-Fla-X, Anti-A4-Fla2, anti-CBir1, anti-OmpC, and DNAse-sensitive pANCA. It is thought that genetic susceptibility influences immune responses and this assay includes evaluation of ATG16L1, STAT3, NKX2-3, and ECM1. Inflammatory markers include VEGF, ICAM, VCAM, CRP, SAA. While most other labs only offer assay values, according to PROMETHEUS Therapeutics & Diagnostics, they provide additional clarity in diagnosing IBD, UC, and CD.

According to Prometheus Labs’ website, PROMETHEUS® Crohn’s Prognostic test is the first and only test that combines proprietary serologic and genetic (serogenetic) markers in a logistic regression model to provide individualized probabilities for developing disease complications after diagnosis in patients with Crohn’s disease. This test may allow physicians to stratify their CD patients according to their risks of developing complications over time and personalize the disease treatment plan for the patients.

The Prometheus® NOD2/CARD15 is a genetic profile designed to detect three primary mutations associated with the down-regulation of the body’s immune response to chronic inflammation in Crohn’s disease. Detection of one or more of these mutations suggests likelihood for an earlier age of onset, small bowel strictureing and an elevated association with fibrostenosing disease associated with Crohn’s disease. The utility of this profile is to help physicians establish a prognosis which may guide therapeutic decisions for Crohn’s patients.
Policy:

Determination of anti-neutrophil cytoplasmic antibody (ANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in the workup and monitoring of patients with inflammatory bowel disease.

The use of serologic markers* do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for all indications, including but not limited to:
- The diagnosis and monitoring of patients with inflammatory bowel disease; and/or
- Distinguishing ulcerative colitis from Crohn's disease

*Serologic markers include, but are not limited to:
- anti-neutrophil cytoplasmic antibodies (ANCA)
- anti-Saccharomyces cerevisiae (ASCA)
- antibodies of outer membrane porin C of the bacteria Eschericia coli (anti-OmpC)
- Pseudomonas fluorescens-associated sequence I2 (anti-I2)
- flagellin CBir1 (anti-cBir1)
- antichitobioside antibodies (ACCA IgA)
- antilaminaribioside antibodies (ALCA IgG)
- antimannobioside antibodies (AMCA IgG))

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

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

1. The use of both tests as a first screen in patients with clinical signs and symptoms suggestive of inflammatory bowel disease (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.

2. ANCA as a confirmatory test for ulcerative colitis, and ANCA as a confirmatory test for
Crohn’s disease.
   • 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 could be
   foregone.

Since the 1999 TEC Assessment, numerous publications have evaluated the diagnostic accuracy
of these tests for the previous two indications, with results generally indicating performance
characteristics in a similar range. The largest of these studies evaluating ANCA reported
sensitivities of 50% and 30% and specificities of 95% and 99%, respectively. The largest studies
evaluating ASCA reported sensitivities of 60% and 52% and specificities of 91% and 96%,
respectively. These studies employed normal healthy subjects as the control population, so that
the reported specificity may not reflect the specificity in actual clinical practice.

3. The use of both tests to distinguish between Crohn’s disease and ulcerative colitis 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 specificity, although still
   relatively high, would still result in a significant number of patient misclassifications.
   In addition, in the studies the patients had either established ulcerative colitis or
   Crohn’s disease, and this is not the population of clinical interest.

Since the 1999 TEC Assessment, several publications have addressed this issue. Similar to
previous research, these studies all used populations of patients with established UC and CD,
with one exception. Joossens et al identified 97 patients with indeterminate colitis (IC) who were
followed up prospectively. A definitive diagnosis of UC was made in 11 patients; seven of 11
were ANCA positive and ASCA negative. A diagnosis of CD was made in ten patients; eight of
ten were ANCA negative and ASCA positive. Approximately half of the patients with IC did not
have positivity for either serum marker.

Several articles attempted to correlate titers of ANCA and/or ASCA with disease activity, but did
not generally find such a correlation. Mow and colleagues investigated whether serologic
antibodies were associated with disease complications. In this case series of 303 patients with
Crohn’s disease, certain antibodies were associated with fibrostenosis or perforating disease.
However, 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 these 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.
No studies reviewed 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. As concluded in the 1999 TEC Assessment, it does not appear that the use of these tests is likely to alter the diagnostic workup, the final diagnosis made, or the treatment provided for patients with suspected IBD. Therefore, based on this review, the policy statement remains unchanged.

A 2014 observational study done by Sura et al included 117 individuals at a single center with a diagnosis of indeterminate colitis (IC). These endoscopically and histologically diagnosed patients underwent testing for p-ANCA, ASCA and anti-OmpC and were followed for one year. The aim of the study was to investigate how well serology testing can predict a definitive diagnosis in this group of people. According to the study, 50% of the participants were diagnosed with UC, 42% diagnosed with CD and 9% were still considered IC. The authors stated that “The sensitivity/specificity of an initial positive p-ANCA for a subsequent diagnosis of UC was 78%/44%. For ASCA and anti-OmpC, the results were 18%/84% and 27%/75%, respectively, for a subsequent diagnosis of CD. A positive pANCA test was associated with a likelihood ratio (LR) of 1.4 (95% CI: 1.1–1.8) for a subsequent diagnosis of UC at one year. Neither positive ASCA (LR 1.1; 95% CI: 0.5–2.5) nor anti-OmpC (LR 1.1; 95% CI: 0.6–2.0) was associated with a subsequent diagnosis CD in patients with IC.” In conclusion, the authors stated that the overall ability of these assays being able to predict subsequent disease profile is modest at best.

In 2013, Mokhtarifar et al conducted a case control study of 97 individuals with IBD. Included were 72 participants with UC, 25 with CD, and 40 healthy individuals. The participants in the study had a colonoscopy, histopathological analysis, and a barium transit study to obtain a diagnosis of UC, CD, or negative. The individuals diagnosed with UC or CD were considered the case group, and those that had a normal colonoscopy and pathology were considered the control group. Upon the start of the study, all participants had blood taken and then later analyzed for ASCA and p-ANCA by two pathologists who were unaware of the patients’ diagnoses. According to the authors, four out of 25 (16%) people diagnosed with CD had positive ASCA results compared with one out of 72 (1%) that were diagnosed with UC. For the diagnosis of CD, ASCA had 97% specificity and a sensitivity of 16%. For UC, ASCA had a sensitivity of 1% and a specificity of 90%. For atypical p-ANCA for diagnosing UC, the test had 44% sensitivity and a 86% specificity. The sensitivity of atypical p-ANCA for CD was 16% and specificity of 66%. The authors also stated that there was no significant relationship between the atypical p-ANCA results and the site of GI involvement. They concluded stating that ASCA and atypical p-ANCA markers are not useful for IBD screening; however, p-ANCA may be helpful in differentiating UC from CD.

In 2010, Dotan stated that IBD are chronic intestinal disorders where, in genetically susceptible hosts, an intestinal microorganism triggers an over-reactive immune response. Antibodies against luminal antigens are specifically associated with CD. In addition to the previously described ANCA, ASCA, OmpC, I2 and CBir1 Flagellin, new anti-glycan antibodies were recently added to the armamentarium of serologic markers in IBD. The anti-glycan antibodies are directed against laminaribioside, chitobioside, mannobioside and mannan residues and are designated.
anti-laminaribioside carbohydrate antibodies (ALCA), anti-chitobioside carbohydrate antibodies (ACCA), anti-mannobioside carbohydrate antibodies (AMCA) and gASCA, respectively. Anti-laminarin IgA (Anti-L), and anti-chitin IgA (Anti-C) are new members of this family. Laminarin and chitobioside are capable of stimulating the innate immune system, thus the finding of antibodies against these glycans suggests a connection between the adaptive and innate arms of the immune response in CD patients. The contribution of serologic markers, specifically the anti-glycan antibodies, to IBD diagnosis may be in differentiating IBD from other gastrointestinal diseases, and between CD and UC, in better classifying undetermined colitis and for decision-making prior to proctocolectomy in UC patients. The anti-glycan antibodies are specifically important in ASCA-negative CD patients. Correlation between serologic markers and genetic variations may contribute to re-classifying IBD into new and more homogeneous subclasses.

In 2006, a meta-analysis of studies evaluating the diagnostic accuracy of ASCA and ANCA in inflammatory bowel disease was published. It included studies that compared ASCA or ANCA sensitivity and specificity to a “gold standard” (clinical, radiological, endoscopic and/or histologic diagnosis). Studies included patients who ultimately had a diagnosis of ulcerative colitis patients, 4019 patients with Crohn’s disease 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 2 studies were not reported). For the diagnosis of ulcerative colitis, the authors examined the sensitivity and specificity of ANCA in different combinations with ASCA, and for Crohn’s disease, they looked at ASCA in different combinations with ANCA. For ulcerative colitis, the most sensitive test combination was an ANCA-positive test without information regarding ASCA status; the pooled sensitivity was 55.4% and specificity was 88.5%. The most sensitive test for Crohn’s disease was ASCA IgG-positive or IgA-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 Crohn’s disease and ulcerative colitis. The most sensitive test for differentiating between the two conditions was the presence of 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 look stratify their findings by prospective versus retrospective studies, or by type of control group (i.e., healthy controls versus patients with conditions other than IBD).

Russell et al evaluated the association between ASCA status and disease phenotype. The study included a total of 301 patients (197 with Crohn’s disease, 76 with ulcerative colitis and 28 with indeterminate colitis). In multivariate analysis, they found a significant association between ASCA positivity and a higher likelihood of oral Crohn’s disease (adjusted odds ration [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.
Summary
A number of studies have examined the association between the serologic markers ASCA and ANCA and inflammatory bowel disease. 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. Because of the suboptimal sensitivity levels of these serological tests, routine use of this screening is not supported. These technologies are investigational for the diagnosis and monitoring of inflammatory bowel disease given the insufficient evidence to evaluate the impact on net health outcome.

Practice Guidelines and Position Statements
American Gastroenterological Association
No guideline or position statement was found on The American Gastroenterological Association website regarding the use of serum antibodies for the diagnosis of inflammatory bowel disease.

American College of Gastroenterology
The American College of Gastroenterology practice guidelines for management of CD in adults stated that serological studies evaluating ASCA, ANCA, anti-CBir1, anti-OmpC are evolving to provide adjunctive support for the diagnosis of CD; however, they are not sensitive or specific enough to be recommended for use as a screening tool.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
In 2012, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition stated that commercially available serologic assays fail to detect CD in at least 30% of children with this disorder and may wrongly suggest a diagnosis of IBD that is not supported by subsequent and definitive (endoscopic study) testing. They further stated that it may be most prudent for primary care providers to avoid ordering these tests and instead pursue referral and more conclusive specialty testing.

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn’s and Colitis Foundation of America's consensus conference report on differentiating UC from CD in children and young adults stated that the clinical value of serology in patients with indeterminate colitis (IC) remains a topic of research, and further investigation should ascertain, among other areas, the role of surrogate laboratory markers (e.g., genetics, microbiology, and serology) in distinguishing these entities. A proposed algorithm to aid clinicians in differentiating UC from CD does not include serological testing.

U.S. Preventive Services Task Force
Diagnostic testing for IBD is not considered a preventive service.

Key Words:
ANCA, Antibodies for the Diagnosis of Ulcerative Colitis and Crohn’s Disease, ASCA, Crohn’s Disease, (ANCA, ASCA), Prometheus System, Diagnosis of Inflammatory Bowel Disease,
Ulcerative Colitis, Prometheus Labs, anti-neutrophil cytoplasmic antibody, anti-Saccharomyces cerevisiae antibody, DNA testing for Crohn’s disease, inflammatory bowel disease, Prometheus, Prometheus Crohn’s prognostic test for DNA testing, Prometheus NOD2/CARD15, Prometheus IBD sgi diagnostic

**Approved by Governing Bodies:**
Prometheus is located in San Diego, CA and licensed in several states including New York and California. It has not been cleared or approved by the U.S. Food and Drug Administration. Prometheus Laboratories Inc. is a CAP accredited CLIA laboratory.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**

**CPT Codes:**
There is no specific CPT code for detection of ANCA or ASCA. Providers may be using the following nonspecific CPT codes:

- **81401** Molecular pathology procedure, Level 2 (e.g. SNPs, 1 methylated variant, or 1 somatic variant [typically using non-sequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat).
- **81479** Unlisted molecular pathology procedure
- **82397** Chemiluminescent assay
- **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.
- **86140** C-reactive protein
- **88346** Immunofluorescence, per specimen; initial single antibody stain procedure
- **88350** each additional single antibody stain procedure (List separately in addition to code for primary procedure) *(Effective 01/01/2016)*

According to information on the Prometheus Laboratories Inc. website, the Prometheus® IBD sgi Diagnostic™ test is billed using **83520** (x8), **82397** (x3), **86140** (x1), **88347** (x2), **88346**, **88350**, **81479** (x4).
According to information on Prometheus Laboratories Inc. website, the Prometheus® Crohn’s Prognostic test is billed using 83520 (x5), 88347 (2), 88346, 88350, and 81401.

**Previous Coding:**

CPT Codes:

There is no specific CPT code for detection of ANCA or ASCA. Providers may be using the nonspecific CPT codes describing immunoassay (83516), immunofluorescence (88346), additional antibody stain procedure (88350) or immunoassay, analyte, quantitative; not otherwise specified (83520) to bill for this test.

88347 Immunofluorescent study, each antibody; indirect method.  
*(Deleted effective 01/01/2016)*

**References:**


Policy History:
Medical Policy Group, July 2006 (2)
Medical Policy Administration Committee, August 2006
Available for comment August 15-September 28, 2006
Medical Policy Group, July 2008 (1)
Medical Policy Group, July 2010 (1)
Medical Policy Group, June 2012 (1) Update to Description, Key Points and References; no change in policy statement
Medical Policy Group, October 2015 (3): Updates to Description, Key Points, Key Words, Approved Governing Bodies, Coding and References. Policy statement clarified by adding additional serologic markers. No change in policy intent.
Medical Policy Group, November 2015: 2016 Annual Coding Update. Added CPT code 88346 and new CPT code 88350 to current coding section and moved CPT code 88347 from current coding to previous coding.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.