BlueCross BlueShield of Alabama

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

Policy #: 285
Category: Medicine

Latest Review Date: June 2012
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. 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.

The new PROMETHEUS IBD sgi Diagnostic is the 4th-generation IBD diagnostic test and the first and only test to combine serologic, genetic, and inflammation markers in the proprietary Smart Diagnostic Algorithm for added diagnostic clarity. This test aids healthcare providers in differentiating IBD vs non-IBD and CD vs UC in one comprehensive blood test. This assay includes 9 serological markers including the proprietary Anti-Fla-X, Anti-A4-Fla2, anti-CBir1, anti-OmpC, and DNAse-sensitive pANCA that helps identify patients with IBD and utilizes Smart Diagnostic Algorithm Technology to improve the predictive accuracy. 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, PROMETHEUS IBD sgi Diagnostic provides added clarity in diagnosing IBD, UC, and CD.

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.

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 members' 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 3 following clinical situations.

- 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.

- 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 2 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.

- 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; 7 of 11 were ANCA positive and ASCA negative. A diagnosis of CD was made in 10 patients; 8 of 10 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 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.

In March 2001, the American College of Gastroenterology issued Practice Guidelines for Management of Crohn's Disease in Adults. The guidelines state for diagnosis of Crohn's disease that serological studies such as antibodies against Saccharomyces cerevisiae are evolving to support the diagnosis of Crohn's disease but may not be sufficiently sensitive or specific to be practical as screening tools.

July 2008 Update
A literature search did not identify any studies that would alter the coverage statement of this policy.

June 2010 Update
The most recent literature search was performed for a period through April 2010. The following is a summary of the key updated literature.

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 of93%. 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 with 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, of 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

A number of studies have examined by the association between the serologic markers ASCA and ANCA, and inflammatory bowel disease. Systematic reviews have found relatively low sensitivity and moderately high specificity.

June 2012 Update
Dotan (2010) 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. Their significance in diagnosing populations at risk, such as unaffected relatives of IBD patients and CD patients prior to diagnosis, is under current investigation.

Technology Assessment, Guidelines and Position Statements

The Institute for Clinical Systems Improvement (ICSI): In 2002, they released a technology assessment, "Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease (IBD); pANCA for Ulcerative Colitis (UC) and ASCA for Crohn's Disease (CD)." The following is a summary of the key findings…"With regard to serum antibodies for diagnosing inflammatory bowel disease (IBD) the ICSI Technology Assessment Committee finds:

1. The clinical utility of serological testing is not yet established for the diagnosis of inflammatory bowel disease in patients presenting with symptoms suggestive of IBD (Conclusion Grade III)
2. The clinical utility of serological testing is not yet established for differentiating between UC and CD in patients with inflammatory bowel disease (Conclusion Grade II)
3. Although serum testing is a safe procedure, risks are associated with false negative and false positive test results. Consequences due to false negative and false positive test results have not been evaluated.
4. There are well-established radiologic, histologic, and endoscopic techniques for diagnosing IBD and differentiating CD and UC.
5. There appears to be a high inter-laboratory variability of sensitivities and specificities."

American Gastroenterological Association has no guideline or position statement on the use of serum antibodies for the diagnosis of inflammatory bowel disease was found on their public website.

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 tools.

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.

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

Approved by Governing Bodies:

FDA approved

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: FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.
Pre-certification requirements: Not applicable

Current 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), indirect immunofluorescence (88347) or immunoassay, analyte, quantitative; not otherwise specified (83520) to bill for this test.

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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

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