



BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy:

Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease

Policy #: 285
Category: Medicine

Latest Review Date: December 2020
Policy Grade: A

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - *Furnished in a setting appropriate to the patient's medical needs and condition;*
 - *Ordered and furnished by qualified personnel;*
 - *One that meets, but does not exceed, the patient's medical need; and*
 - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **the use of serologic markers*** as a **non-covered benefit** and as **investigational** for all indications, including but not limited to:

- antibodies of outer membrane porin C of the bacteria Escherichia coli (anti-OmpC)
- anti-chitobioside antibodies (ACCA IgA)
- anti-laminaribioside antibodies (ALCA IgG)
- anti-mannobioside antibodies (AMCA IgG)
- anti-neutrophil cytoplasmic antibodies (ANCA)
- anti-Saccharomyces cerevisiae (ASCA)
- flagellin CBir1 (anti-cBir1)
- Pseudomonas fluorescens-associated sequence 12 (anti-12)

Blue Advantage 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 Advantage administers benefits based on the members' contract and 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.

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.

The Prometheus© 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.

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.

KEY POINTS:

This policy is based on an evidence review that was recently performed on December 31, 2020.

Summary of Evidence

At present, no single marker with qualities that are satisfactory for the diagnosis and treatment of IBD has been identified, although panels of some antibodies are being evaluated with keen interest. The discovery of novel IBD-specific and sensitive markers is anticipated. Such markers could minimize the use of endoscopic and radiologic examinations and could enable clinicians to implement individualized treatment plans designed to improve the long-term prognosis of patients with IBD.

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. Although the specificity of these tests are relatively high (82-100%), the sensitivity is low (32 -50%), which indicates that a negative result will not be clinically helpful. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

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 tools.

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

Not applicable.

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, IBSchek, Biomarker, Serological antibody, antibodies of outer membrane porin C of the bacteria Escherichia 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

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.

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:

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)
0164U	Gastroenterology (irritable bowel syndrome [IBS]), immunoassay for anti-CdtB and anti-vinculin antibodies, utilizing plasma, algorithm for elevated or not elevated qualitative results
0176U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (i.e., ELISA) (Effective 07/01/2020) (For IBSchek)

According to information on the Prometheus Laboratories Inc. website, the Prometheus® IBD sgi Diagnostic™ test is billed using 83520 (x8), 82397 (x3), 86140 (x1), 88346, 88350, 81479 (x4).

According to information on Prometheus Laboratories Inc. website, the Prometheus® Crohn's Prognostic test is billed using 83520 (x5), 88346, 88350, and 81401.

PREVIOUS CODING:**CPT codes:**

0085U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (i.e. ELISA) (Deleted 12/31/2020) (For IBSchek)
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POLICY HISTORY:

Adopted for Blue Advantage, July 2006

Available for comment August 22-October 5, 2006

Medical Policy Group, July 2008

Medical Policy Group, July 2010

Medical Policy Group, June 2012

Medical Policy Group, October 2015

Medical Policy Group, December 2015

Medical Policy Group, October 2019

Medical Policy Group, February 2020: Removed codes 81401 and 81479 from policy.

Medical Policy Group, March 2020: Quarterly coding update. Added new CPT code 0164U to Current Coding.

Medical Policy Group, August 2020: Quarterly coding update: Added CPT code 0176U to Current Coding for IBSchek.

Medical Policy Group, October 2020: 2021 Annual Coding Update. Code 0085U was already listed in Previous Coding Section. Added deleted effective date of 12/31/2020.

Medical Policy Group, December 2020

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.