**Medical Policy Reference Manual**
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# 11.01.029 Serum Antibody Marker Testing for Inflammatory Bowel Disease

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## Description

Blood serum tests have been proposed to provide a mechanism for diagnosing IBD rapidly and definitively. By testing blood samples for biomarkers, an objective diagnosis of IBD may be possible. The serum antibodies known as anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccaromyces cervesiae antibody (ASCA) are associated with the presence of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). Testing for the presence of these antibodies has been proposed as a diagnostic aid for the physician in a case of a patient presenting with symptoms suggestive of IBD. The rationale is that antibody testing could be used as a first step to conceivably rule out the need for more invasive studies such as endoscopic examination or imaging of the bowel. Other suggested uses for ANCA and ASCA testing include confirmatory testing for CD or UC, differentiation of UC and CD, and as a predictor of response to certain therapies.

Prometheus® Laboratories of San Diego, California markets a proprietary product dedicated to serum antibody testing for inflammatory bowel disease.

Cytolethal distending toxin B and vinculin IgG are biomarkers included in diagnostic blood tests for irritable bowel syndrome. Cytolethal distending toxin B (CdtB) is commonly produced by bacterial pathogens that cause gastroenteritis. It has an ability to disrupt tight junction proteins. The levels of circulating host antibodies to CdtB are correlated with levels of small intestine bacterial overgrowth, and these anti-CdtB antibodies cross-react with the enteric neuronal protein, vinculin, likely through molecular mimicry (where the similarities between foreign and self-peptides are sufficient to elicit cross-reactivity). ELISA testing for anti-CdtB and anti-vinculin can discriminate patients with irritable bowel syndrome with diarrhea (IBS-D) from those with inflammatory bowel disease (IBD). Blood tests for IBS are able to distinguish IBS from inflammatory bowel disease (IBD) and reduce the need for unnecessary testing to rule out more serious conditions.

The IBSDetex™ test is offered by Quest Diagnostics. The ibs-smart™ is offered by Gemelli Biotech. Both tests detect anti-CdtB and anti-vinculin antibodies for the purpose of distinguishing IBS from IBD.

## Policy

Testing for anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccaromyces cervesiae antibody (ASCA) is considered **not medically necessary** in the diagnosis and monitoring of patients with inflammatory bowel disease.

Testing for anti-Ctb and anti-viniculin antibody is considered **not medically necessary** in the diagnosis and monitoring of patients with inflammatory bowel disease.

## Policy Guidelines

Rationale:

1. The technology must have final approval from the appropriate U.S. government regulatory bodies:

Diagnostic tests are regulated by the FDA under CLIA. No specific FDA approval has been given, or is required, for ANCA or ASCA antibody testing, as measurement of the presence of these entities uses established laboratory methods. The first criterion is therefore met.

2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

In order for a laboratory test of this type to improve outcomes in the aforementioned manner, it must be both sensitive and specific. If the sensitivity is low, a negative result would not be clinically reliable enough for the physician to rule out the need for further diagnostic workup. On the other hand, if the specificity is low, a positive result may erroneously lead the physician to make the diagnosis of IBD. The patient would therefore be placed unnecessarily at risk for complications. Therefore, both sensitivity and specificity must be shown to be acceptably high in order to be considered as a first step diagnostic. There have been a number of controlled studies undertaken to determine the sensitivity and specificity of these markers. Characteristics of the control groups were highly variable, from normal healthy volunteers to those that had been diagnosed with GI diseases that were not IBD. In very few instances did the control consist of a patient population that had diarrheal illness that was not IBD. This may be interpreted as a source of bias in the studies that may skew the pooled data results. Nevertheless, there is sufficient data to yield a range of figures for sensitivity and specificity and positive predictive values, bearing in mind that actual specificities encountered in the practice setting may be lower than in the investigational setting.

For ANCA and ASCA, the specificity range is from 71-100%; pooled data overall determines a 66% likelihood that a positive result is a true positive. Sensitivity is considerably lower, with a 22-63% range. Therefore, patients with a negative result would still likely require further workup to either confirm or rule out IBD as a diagnosis in a patient presenting initially with symptoms.

ANCA has been proposed as a confirmatory test for UC, and in this scenario the specificity of the test is slightly higher, but still insufficient to be considered a valid confirmatory test. As a test to distinguish between patients with UC versus CD, sensitivity is somewhat improved, while specificity is somewhat reduced (84% average). This would likely result in a considerable number of patients being misclassified.

It has been demonstrated that CdtB antibodies react with proteins outside of the gut. Additionally, anti-bacterial cytotoxins and anti-vinculin antibodies were significantly higher in Diarrhea-IBS individuals compared to individuals with celiac disease, IBD and healthy subjects. The relevance of this information for net health outcomes is unclear.

3. The technology must improve the net health outcome:

This technology would improve net health outcomes if it reduces the need for further diagnostic testing or improves diagnostic accuracy. The sensitivity of the test as shown in the clinical studies is too low to be relied upon, so that accepting the results of a negative test places the physician in the position of failing to make the appropriate diagnosis. Conversely, the specificity of the test while acceptable to some is overall insufficient to add to its diagnostic accuracy. Therefore, it cannot be concluded that the technology improves net health outcomes.

4. The technology must be as effective as any established alternatives:

In a patient with signs and symptoms of IBD, the physician typically will perform a history and physical exam, selected laboratory tests and imaging studies and possibly endoscopy. The evidence to date does not support the use of serum antibody testing as an alternative to these accepted diagnostic methods.

5. The improvement must be attainable outside the investigational settings:

Improvement in outcomes has not been demonstrated in the investigational settings. There are authors that have supported their use in disease research, and one other has used the ASCA marker to identify subtypes of Crohn's disease, although no mention is made as to how one subtype would be treated any differently. Still another has identified ways to perhaps improve the sensitivity of the tests. In the medical community, however, there is little scientifically-based support for routine use of ANCA and ASCA antibody testing.

Based on the above observations, there is evidence that serological testing may have some application in categorizing patients with symptoms of inflammatory bowel disease as having ulcerative colitis versus Crohn's disease, as the ANCA marker is more specific to UC, while the ASCA marker is identified with Crohn's disease. The body of evidence lacks studies as to how the results of the test would influence patient management decisions. As a screening tool, there is insufficient evidence that serological antibody testing is effective as a "first step" in diagnosing inflammatory bowel disease, as the test currently is not sensitive enough to safely base treatment decisions on a negative value. As a confirmatory test, serologic antibody testing lacks specificity thresholds sufficient to place full trust in a positive value in the context of results of other diagnostic testing and history and physical examination results.

Serological measurement of ANCA and ASCA antibodies for the diagnosis of inflammatory bowel disease does not meet criteria for coverage. Serological measurement of anti-Ctb and anti-viniculin antibodies for the diagnosis of inflammatory bowel disease does not meet criteria for coverage.

Update 2006:

A review of the peer-reviewed literature from June 2004 to June 2006 did not demonstrate any clinical advantage with the use of the above markers. It does not appear that the use of ANCA and ASCA antibodies is likely to alter the diagnostic work-up, the final diagnosis, or the treatment provided for patients with suspected IBD.

Update 2008:

A review of the peer-reviewed literature was performed from June 2006 through June 2008. Findings in the literature do not change the indications for ANCA or ASCA antibody testing in the current policy. Therefore, the policy remains unchanged.

Update 2010:

In July of 2006 Prometheus Laboratories made available an expanded panel of markers. Called IBD Serology 7, the panel is composed of five markers: ASCA IgA, ASCA IgG, anti-OmpC IgA, anti-CBir1, and IBD-specific pANCA. The results of the component tests are analyzed using a proprietary computer algorithm, which Prometheus maintains is able to predict the presence of IBD. Most of the available evidence published in the peer-reviewed literature is focused on testing of ANCA and ASCA antibodies. There is insufficient published evidence to permit conclusions on diagnostic capability or patient outcomes for the IBD Serology 7 panel. Furthermore, a review by Sabery and Bass (2007) evaluated an earlier generation serology test by Prometheus called IBD First Step and determined an overall 60% sensitivity and 92% specificity. A positive test for anemia and erythrocyte sedimentation rate (ESR) however showed an 83% sensitivity and 96% specificity. The authors concluded that a combination of ESR and hemoglobin has a higher positive predictive value for IBD and is more sensitive and specific than commercial serologic testing. Criteria 2-5 are not met for the IBD Serology 7 panel; therefore, the policy statement is unchanged.

Update 2012:

A review of the peer-reviewed literature was performed for June 2010 through September 2012. Findings in the literature do not change the indication for ANCA or ASCA antibody testing. Therefore, the policy remains unchanged.

Update 2014:

A review of the peer-reviewed literature was performed for October 2012 through September 2014. A Hayes Directory review (2013) assigned a C rating for serological assays using a combination of antibodies (including ASCA and ANCA) as an adjunct to conventional diagnostic techniques. According to the Hayes review although these assays may be beneficial in confirming a diagnosis of Crohn's disease, the quality of the evidence is low, there is uncertainty regarding the optimal combination of antibodies, and there is a lack of evidence demonstrating a positive impact on patient management or outcomes. A D1 rating was assigned for population screening of Crohn's disease in asymptomatic individuals due to the evidence of low sensitivity. A D2 rating was assigned for serological assays using a combination of antibodies to predict disease phenotype, disease progression, or response to treatment due to low-quality and/or limited evidence as well as lack of studies evaluating the impact on patient management or outcomes. Findings in the literature do not change the indication for ANCA or ASCA antibody testing. Therefore, the policy remains unchanged.

Update 2016:

A review of the peer-reviewed literature was performed for October 2014 through November 2016. A Hayes Directory review (2016) assigned a C rating for serological assays using a combination of antibodies (including ASCA and ANCA) as an adjunct to conventional diagnostic techniques. According to the Hayes review although these assays may be beneficial in confirming a diagnosis of Crohn's disease, the quality of the evidence is low, there is uncertainty regarding the optimal combination of antibodies, and there is a lack of evidence demonstrating a positive impact on patient management or outcomes. A D1 rating was assigned for population screening of Crohn's disease in asymptomatic individuals due to the evidence of low sensitivity. A D2 rating was assigned for serological assays using a combination of antibodies to predict disease phenotype, disease progression, or response to treatment due to low-quality and/or limited evidence as well as lack of studies evaluating the impact on patient management or outcomes. Findings in the literature do not change the indication for ANCA or ASCA antibody testing. Therefore, the policy remains unchanged.

Update 2019:

A review of the peer-reviewed literature was performed from December 2016 through January 2019. Findings in the recent literature do not change the conclusion on anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccaromyces cervesiae antibody (ASCA) testing in the diagnosis and monitoring of patients with inflammatory bowel disease. Therefore, the policy remains experimental / investigational.

Update 2021:

A review of the peer-reviewed literature was performed from the period of February 2019 through January 2021. Findings in the recent literature do not change the conclusions regarding anti-neutrophilic cytoplasmic antibody (ANCA) and anti-Saccaromyces cervesiae antibody (ASCA) testing in the diagnosis and monitoring of patients with inflammatory bowel disease. Therefore, the policy statements are not medically necessary.

## Cross References to Related Policies and Procedures

Wireless Capsule Endoscopy (Enteral Camera), Policy 7.01.076

Pharmacogenomic and Serologic Metabolite Markers for Inflammatory Bowel Disease Patients Treated with Azathioprine, Policy 11.01.031 (archived)

Serologic Metabolite Markers for Inflammatory Bowel Disease Patients Treated with Azathioprine, Policy 11.01.075

## References

**The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.**

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