FEP 2.04.84 Measurement of Serum Antibodies to Infliximab and Adalimumab

**Measurement of Serum Antibodies to Infliximab and Adalimumab**

**Description**
Infliximab (Remicade) is an intravenous tumor necrosis factor a blocking agent approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira) is a subcutaneous tumor necrosis factor-alpha inhibitor that is approved by the Food and Drug Administration for the treatment of Crohn disease and ulcerative colitis in adults only and juvenile idiopathic arthritis. Following the primary response to infliximab and adalimumab, some patients become secondary nonresponders. The development of antidrug antibodies (ADA) is considered a cause of this secondary nonresponse.

**OBJECTIVE**
The objective of this evidence review is to evaluate and compare the net health outcome of 2 types of treatment: the first, when serum antibody testing for infliximab and/or adalimumab is used in patients being managed with those drugs; the second, when a patient receives standard of care to manage conditions (eg, rheumatoid arthritis, Crohn disease, ulcerative colitis) associated with the aforementioned drugs.

**POLICY STATEMENT**
Measurement of antibodies to infliximab in a patient receiving treatment with infliximab, either alone or as a combination test, which includes the measurement of serum infliximab levels, is considered investigational.

Measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab, either alone or as a combination test, which includes the measurement of serum adalimumab levels, is considered investigational.

**BENEFIT APPLICATION**
Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic
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panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus Laboratories, a College of American Pathologists accredited lab under the Clinical Laboratory Improvement Amendments, offers non-radio-labeled, fluid-phase homogenous mobility shift assay tests called Anser™IFX (for infliximab) and Anser™ADA (for adalimumab). Neither is based on an ELISA test, and each can measure ADA in the presence of detectable drug levels, improving on a major limitation of the ELISA method. Both tests measure serum drug concentrations and ADA.

RATIONALE

Summary of Evidence

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for anti-TNF-α inhibitor ATI or to ATA, the evidence includes multiple systematic reviews, a randomized controlled trial, and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. ATI or ATA develop in a substantial proportion of treated patients and are believed to neutralize or enhance clearance of the drugs. Considerable evidence has demonstrated an association between ADA and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring ADA hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring ADA. A small randomized controlled trial in patients with Crohn disease comparing ATI-informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the ATI-informed approach. Additionally, many assays—some having significant limitations—have been used in studies; ADA threshold values that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Gastroenterology Institute

The American College of Gastroenterology Institute (2017) published guidelines on therapeutic drug monitoring in inflammatory bowel disease. ≥ The guidelines note that:

"When anti-drug antibodies are detected, it is unclear what antibody level is clinically meaningful…. the reporting of anti-drug antibodies is variable between commercial assays, with some assays being very sensitive for detecting very-low-titer antibodies of limited clinical
significance. Uniform thresholds for clinically relevant antibody titers are lacking. At this time, it is unclear how antibodies affect drug efficacy when both active drug and antibodies are detected. In cases of low trough concentrations and low or high anti-drug antibodies, the evidence to clarify optimal management is lacking.”

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2016) issued guidance on therapeutic monitoring of tumor necrosis factor-alpha inhibitors in the treatment of patients with Crohn disease. The Institute recommended that laboratories monitoring tumor necrosis factor- alpha inhibitors in patients with Crohn disease who have lost response to the treatment should “work with clinicians to collect data through a prospective study, for local audit, or for submission to an existing registry.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


POLICY HISTORY

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<th>Date</th>
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<th>Description</th>
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<tbody>
<tr>
<td>December 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review through November 3, 2016; references 4 and 33 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>March 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature review through September 6, 2018; reference 29 added. Policy statements unchanged.</td>
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