

## FEP 2.04.84 Measurement of Serum Antibodies to Infliximab and Adalimumab

**Effective Date:** April 15, 2018

**Related Policies:** None

### Measurement of Serum Antibodies to Infliximab and Adalimumab

#### Description

Infliximab (Remicade) is an intravenous tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) 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 TNF- $\alpha$  inhibitor that is approved by the Food and Drug Administration for treatment of Crohn disease and ulcerative colitis in adults only and juvenile idiopathic arthritis. Following 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.

#### 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 (San Diego, CA), 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<sup>TM</sup>IFX (for infliximab) and Anser<sup>TM</sup>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.

#### 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

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

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### RATIONALE

#### Summary of Evidence

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (eg, Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for anti-TNF- $\alpha$  inhibitor ATI or to adalimumab, the evidence includes multiple systematic reviews, a randomized controlled trial, and observational studies. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. ATI or antibodies to adalimumab 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 et al

Clinical guidelines from the American College of Gastroenterology,<sup>33,34</sup> the American College of Rheumatology,<sup>35</sup> and the European League Against Rheumatism<sup>36</sup> have not included recommendations for testing for antidrug antibodies in patients treated with tumor necrosis factor (TNF) inhibitors. An important question included in the European League research recommendations was whether “measurement of serum drug and/or drug antibody levels [is] useful in clinical practice?”

##### National Institute for Health and Care Excellence

In 2016, the National Institute for Health and Care Excellence issued guidance on therapeutic monitoring of TNF- $\alpha$  inhibitors in the treatment of patients with Crohn disease.<sup>37</sup> The Institute recommended that laboratories monitoring TNF- $\alpha$  inhibitors in patients with Crohn disease who have lost response to the treatment, should work with clinicians to collect data through either a prospective study, a local audit, or a 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.

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### POLICY HISTORY

Date	Action	Description
December 2013	New Policy	
December 2014	Update Policy	Policy updated with literature review. References 4-5, 15-18, 22, and 25-30 added. No changes to policy statements.
March 2017	Update Policy	Policy updated with literature review through November 3, 2016; references 4 and 33 added. Policy statements unchanged.
March 2018	Update Policy	Policy updated with literature review through September 11, 2017; references 14 and 21-23 added. Policy statements unchanged.

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