Introduction

Antibodies are a specific type of protein. They are made by the body’s immune system. Antibodies help fight germs and other substances inside the body that the immune system sees as harmful. The immune system custom-creates each type of antibody to fight what it sees as invading and destructive things. However, the body can also make antibodies to fight drugs that are intended to treat specific diseases. Blood tests have been developed that try to look at whether a person’s body has developed antibodies to the drugs Remicade® (infliximab), Humira® (adalimumab), and Entyvio® (vedolizumab). These blood tests are investigational (unproven). Medical studies so far have not shown that changes in treatment based on the results of these blood tests have improved health results. More and larger studies are needed to show if and how well these types of blood tests work.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remicade® (infliximab)</strong></td>
<td>In a patient receiving treatment with infliximab, measurement of antibodies to infliximab, either alone or as a combination test, which includes the measurement of serum infliximab levels, is considered investigational.</td>
</tr>
<tr>
<td><strong>Humira® (adalimumab)</strong></td>
<td>In a patient receiving treatment with adalimumab, measurement of antibodies to adalimumab, either alone or as a combination test, which includes the measurement of serum adalimumab levels, is considered investigational.</td>
</tr>
<tr>
<td><strong>Entyvio® (vedolizumab)</strong></td>
<td>In a patient receiving treatment with vedolizumab, measurement of antibodies to vedolizumab, either alone or as a combination test, which includes the measurement of serum vedolizumab levels, is considered investigational.</td>
</tr>
</tbody>
</table>

## Coding

According to materials from Prometheus Laboratories on Anser™IFX, Anser™ADA, and Anser™VDZ, these tests will be reported using 1 unit of the following CPT code:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Unlisted Chemistry Procedure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>84999</td>
<td>Unlisted Chemistry Procedure</td>
</tr>
</tbody>
</table>

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## Related Information

N/A
Evidence Review

Description

Infliximab (Remicade) is an intravenous tumor necrosis factor α (TNF-α) blocking agent approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis, Crohn disease, pediatric Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, ulcerative colitis, and pediatric ulcerative colitis. Adalimumab (Humira) is a subcutaneous TNF-α inhibitor that is approved by the Food and Drug Administration for treatment of Crohn disease, pediatric Crohn disease, ulcerative colitis, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, hidradenitis suppurativa, and uveitis. Following a 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.

Background

*Infliximab and Adalimumab in Autoimmune Diseases*

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor α (TNF-α) monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF-α. Therapy with monoclonal antibodies has revolutionized therapy for patients with inflammatory diseases such as inflammatory bowel disease (IBD; eg, Crohn disease, ulcerative colitis), rheumatoid arthritis, and psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. It is estimated that 1 out of 3 patients do not respond to induction therapy (primary nonresponse); further, among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to antidrug antibodies (ADA). ADA are also associated with injection-site reactions (adalimumab) and acute infusion reactions and delayed hypersensitivity reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies like infliximab.
Vedolizumab (Entyvio) is an intravenous tumor necrosis factor blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult ulcerative colitis (UC) and adult Crohn’s disease (CD). Vedolizumab is generally given for those patients who have had an inadequate response with, lost response to, or were intolerant to tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. This drug is used for achieving clinical response or remission, or achieving corticosteroid-free remission.

Serum concentrations of vedolizumab (VDZ) may vary among equally dosed patients which can affect patient outcomes. Some patients may develop immunogenicity (non-response) to VDZ by producing antibodies to vedolizumab and the presence of persistent anti-vedolizumab antibody has been observed to reduce serum concentrations of vedolizumab. Incorporating therapeutic drug monitoring into clinical practice has been proposed to allow clinicians to optimize treatment by maintaining effective drug concentrations over time and affecting a patient’s loss of response.

**Detection of ADA**

The detection and quantitative measurement of ADA is difficult, owing to drug interference and identifying when antibodies likely have a neutralizing effect. First-generation assays, (ie, enzyme-linked immunosorbent assays [ELISA]) can measure only ADA in the absence of detectable drug levels due to interference of the drug with the assay. Other techniques available for measuring antibodies include the radioimmunoassay method, and more recently, the homogenous mobility shift assay using high-performance liquid chromatography. Disadvantages of the radioimmunoassay method are associated with the complexity of the test and prolonged incubation time, along with safety concerns related to the handling of radioactive material. The homogenous mobility shift assay measures ADA when infliximab is present in the serum. Studies evaluating the validation of results among different assays are lacking, making interstudy comparisons difficult. One retrospective study (2012) in 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with IBD (ie, double-antigen ELISA and antihuman lambda chain-based ELISA). This study did not include an objective clinical and endoscopic scoring system for validation of results.
Treatment Options for Secondary Nonresponse to Anti-TNF therapy

A diminished or suboptimal response to infliximab, adalimumab, or vedolizumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different anti-TNF agent (in patients who continue to have loss of response after receiving the increased dose), or switching to a non-anti-TNF agent.

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-α antibodies (eg, antibodies to infliximab [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 lead to changes in management, and thereby 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.

For individuals who have ulcerative colitis (UC) or Crohn’s disease (CD) receiving vedolizumab, there is an interest in monitoring this therapy not only for the purpose of identifying markers that will serve as end points for successful treatment, but also for timely cessation or switching of therapy in those unlikely to respond. However, based on the peer reviewed medical literature further randomized controlled trials are needed to investigate the efficacy of proposed preventative and management algorithms regarding antidrug antibodies (ADA) testing. Currently there are no society guidelines that include recommendations for ADA testing. More controlled data is needed to define the best cut-off to define abnormal values of the measured
monitor parameters, define optimal thresholds for the different interventions and the subpopulations as to who will benefit the most from this testing. The evidence is insufficient to determine the effects of the technology on net health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01638715</td>
<td>A Randomized, Multi-Center Biomarker Trial to Predict Therapeutic Responses of Patients With Rheumatoid Arthritis to a Specific Biologic Mode of Action</td>
<td>200</td>
<td>Dec 2017</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01895764</td>
<td>Effect of the Combination of Methotrexate and Adalimumab on Reduction of Immunization in Ankylosing Spondylitis (COMARIS)</td>
<td>110</td>
<td>Apr 2015 (completed)</td>
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<tr>
<td>NCT01971918</td>
<td>Comparative Analysis of Two Therapeutic Strategies in Patients With Spondyloarthritis Treated With Anti-TNF Biologics (STRADA)</td>
<td>104</td>
<td>Nov 2016 (terminated)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial

**Practice Guidelines and Position Statements**

*American College of Gastroenterology et al*

Clinical guidelines from the American College of Gastroenterology\(^{33,34}\) the American College of Rheumatology\(^{35}\) and the European League Against Rheumatism\(^{36}\) have not included recommendations for testing 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-α inhibitors in the treatment of patients with Crohn disease. The Institute recommended that laboratories monitoring TNF-α 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.

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.

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™IFX (for infliximab), Anser™ADA (for adalimumab), and Anser™ VDZ for vedolizumab. These tests are 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.

References


39. Raine, T. Vedolizumab for inflammatory bowel disease:: Changing the game, or more of the same? United European Gastroenterology 2014 Vol 2 (5) 333-344


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/09/12</td>
<td>New Policy. Measurement of antibodies to infliximab, either alone or as a combination test which includes the measurement of serum infliximab levels, is considered investigational.</td>
</tr>
<tr>
<td>11/11/13</td>
<td>Replace Policy. Policy reviewed with literature search through July 2013; references 2, 6-12 added. Title changed to add “...and Adalimumab.” “Measurement of antibodies to adalimumab in a patient receiving adalimumab, either alone or as a combination test which includes the measurement of serum adalimumab levels” added to the policy statement; considered investigational. Brand names added to policy for clarity.</td>
</tr>
<tr>
<td>12/08/15</td>
<td>Annual Review. Policy updated with literature review through September 30, 2015; references 1, 7-8, 12-18, and 30-32 added. Policy statements unchanged, although section titles added.</td>
</tr>
<tr>
<td>11/10/17</td>
<td>Policy moved to new format; no changes to policy statement.</td>
</tr>
<tr>
<td>02/01/18</td>
<td>Annual Review, approved January 16, 2018. Policy updated with literature review through September 2017; references 14, 21-23, and 38-42 added. Added criteria to policy statement for vedolizumab test Anser™ VDZ as investigational.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and
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  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
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  - Qualified interpreters
  - Information written in other languages

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U.S. Department of Health and Human Services
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Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
Office for Civil Rights Complaint Portal, available at
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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