MEDICAL POLICY – 2.04.516

Measurement of Serum Antibodies to Selected Biologic Agents

BCBSA Ref. Policy: 2.04.84
Effective Date: Feb. 1, 2020
Last Revised: Jan. 9, 2020
Replaces: 2.04.84

RELATED MEDICAL POLICIES:
None

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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), Entyvio® (vedolizumab), and Stelara® (ustekinumab). 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>
<tr>
<td><strong>Stelara® (ustekinumab)</strong></td>
<td>In a patient receiving treatment with ustekinumab, measurement of antibodies to ustekinumab, either alone or as a combination test, which includes the measurement of serum ustekinumab, is considered investigational.</td>
</tr>
</tbody>
</table>

## Coding

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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>80145</td>
<td>Adalimumab (Humira®) (new code effective 1/1/20)</td>
</tr>
<tr>
<td>80230</td>
<td>Infliximab (Remicade®) (new code effective 1/1/20)</td>
</tr>
<tr>
<td>80280</td>
<td>Vedolizumab (Entyvio®) (new code effective 1/1/20)</td>
</tr>
<tr>
<td>80299</td>
<td>Quantitation of therapeutic drug, not elsewhere specified</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted Chemistry Procedure</td>
</tr>
</tbody>
</table>
Related Information

N/A

Evidence Review

Description

Infliximab (Remicade) is an intravenous tumor necrosis factor α blocking agent approved by the U.S. Food and Drug Administration (FDA) 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 α inhibitor that is FDA approved for the treatment of Crohn’s disease and ulcerative colitis in adults and those with juvenile idiopathic arthritis. Vedolizumab (Entyvio) is an intravenous integrin receptor antagonist that is FDA approved for treatment of ulcerative colitis and Crohn’s Disease in adults. Ustekinumab (Stelara) is an intravenous and subcutaneous human interleukin-12 and -23 antagonist that is FDA approved for the treatment of psoriatic psoriasis, Crohn’s disease, and ulcerative colitis in adults, and plaque psoriasis in adolescents and adults. Following the primary response to these medications, some patients become secondary nonresponders. The development of antidrug antibodies (ADA) is considered a cause of this secondary nonresponse.

Background

Infliximab and Adalimumab, Vedolizumab, and Ustekinumab in Autoimmune Diseases

Tumor necrosis factor (TNF) inhibitors (eg, infliximab, adalimumab, vedolizumab, or ustekinumab) are used to treat multiple inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis; inflammatory bowel disease (eg, Crohn disease,
ulcerative colitis), ankylosing spondylitis, and plaque psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for the 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).\(^1\) ADA are also associated with injection-site reactions (adalimumab) and acute infusion reactions and delayed hypersensitivity reactions (infliximab).

**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 the 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 by Kopylov et al (2012), which evaluated 63 patients, demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with inflammatory bowel disease (ie, double-antigen ELISA and antihuman lambda chain-based ELISA.)\(^2\) 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, vedolizumab or ustekinumab 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 a 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 inhibitor antibodies to infliximab, adalimumab, vedolizumab, or ustekinumab, 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 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.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in November 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

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.

The guidelines did not address therapeutic drug monitoring in patients treated with vedolizumab or ustekinumab.

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence (NICE; 2016) issued guidance on therapeutic monitoring of tumor necrosis factor α inhibitors in the treatment of patients with Crohn disease. The Institute recommended that laboratories monitoring tumor necrosis factor α 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.”

**Medicare National Coverage**

There is no national coverage determination.

**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), Anser™ADA (for adalimumab),
Anser™VDZ for vedolizumab, and Anser™UST (for ustekinumab). These tests measure both serum drug concentrations and ADA. They are not based on an ELISA test, and can measure ADA in the presence of detectable drug levels, improving on a major limitation of the ELISA method.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/01/19</td>
<td>New policy, approved January 4, 2019. This policy replaces policy 2.04.84. Policy created with literature review through September 2018. Measurement of antibodies to infliximab, adalimumab, vedolizumab, and ustekinumab is considered investigational.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Interim Review, approved March 12, 2019. Reference 36 added. Added criteria to policy statement for ustekinumab test, Anser™ UST as investigational. Title changed from “Measurement of Serum Antibodies to Infliximab, Adalimumab, and Vedolizumab” to “Measurement of Serum Antibodies to Infliximab, Adalimumab, Vedolizumab, and Ustekinumab”. History section updated.</td>
</tr>
<tr>
<td>10/04/19</td>
<td>Coding update, added CPT code 80299.</td>
</tr>
<tr>
<td>01/01/20</td>
<td>Coding update, added CPT codes 80145, 80230, and 80280 (new codes effective 1/1/20).</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 local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-537-7697 (TDD)

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are 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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This Notice has Important Information. This notice may have important information on your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

アムハリ (Amharic):
አማርኛ (Amharic):

Arabic (Arabic):

العربية (Arabic):

Beekisinsi kun odeffannoo barbaachisaa qaba.

Oromo (Cushite):

Kreyöl (Creole):

Deutsche (German):

Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou tran kék aksyon avan sêten dat limit pou ka kere kouve'it asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou paile a, san ou pa gen pou pèye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Italian (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.

Chiama 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Hmoob (Hmong):

Deutsche (German):

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Iloko (Ilocano):

Illok (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalini nga adda ket naglaon iti napateg nga impormasion maiapengee iti aplikasyon wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelta iti daytoy a pakdaar. Mabalini nga adda rumbeng nga aramidey vo nga addang sakkay dagiti partikular a naituding nga aldaw tapno mapagtalaineyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulung ti bukodyo a pagassao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).
Este aviso contém informações importantes. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Favor, leia cuidadosamente as informações fornecidas.

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