



MASSACHUSETTS

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Medical Policy

Measurement of Serum Antibodies to Selected Biologic Agents

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Policy Number: 917

BCBSA Reference Number: 2.04.84 (For Plan internal use only)

NCD/LCD: N/A

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Measurement of antidrug antibodies in a patient receiving treatment with a biologic-blocking agent*, either alone or as a combination test, which includes the measurement of serum TNF blocking agent levels, is considered INVESTIGATIONAL.

*Currently FDA approved biologic agents include infliximab, adalimumab, vedolizumab, and ustekinumab.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed inpatient.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed outpatient.

	Outpatient
Commercial Managed Care (HMO and POS)	This is not a covered service.
Commercial PPO and Indemnity	This is not a covered service.
Medicare HMO Blue SM	This is not a covered service.
Medicare PPO Blue SM	This is not a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
80145	Adalimumab
80230	Infliximab

Description

Infliximab, Adalimumab, Vedolizumab, and Ustekinumab in Autoimmune Diseases

Biologic agents (e.g. 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 in 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 is also associated with injection-site reactions and acute infusion reactions and delayed hypersensitivity reactions.

Detection of Antidrug Antibodies

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 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 Biologic Agents

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 biologic agent (in patients who continue to have a loss of response after receiving the increased dose), or switching to a non-biologic agent.

Summary

Biologic agents used to treat autoimmune diseases include infliximab, adalimumab, vedolizumab, and ustekinumab. 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 disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriatic arthritis in adults and those with juvenile idiopathic arthritis, hidradenitis suppurativa, and uveitis. Vedolizumab (Entyvio) is an intravenous integrin receptor antagonist that is FDA approved for treatment of ulcerative colitis and Crohn 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 disease, and ulcerative colitis in adults, and plaque psoriasis in children and adults. Following the primary response to these medications, some patients become secondary nonresponders. The development of antidrug antibodies is considered a cause of this secondary nonresponse.

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 serum antibodies to infliximab, adalimumab, vedolizumab, or ustekinumab, the evidence includes multiple systematic reviews, randomized controlled trials, and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. Antibodies to biologic agents 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 antidrug antibodies and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring antidrug antibodies 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 antidrug antibodies. A randomized controlled trial did not find a difference in relapse rates with therapeutic drug monitoring of infliximab using trough levels and antidrug antibodies compared to standard therapy without monitoring these levels. A small randomized controlled trial in patients with Crohn disease and other inflammatory diseases comparing antidrug antibody-informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the antidrug antibody-informed approach. Additionally, many assays, some having significant limitations, have been used in studies; antidrug antibody threshold values that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
1/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2021	Updated terminology throughout the policy to reflect the addition of the interleukin-2 and -23 antagonist ustekinumab. Policy statement otherwise unchanged.
1/2020	Annual policy review. Investigational policy statement reworded to include currently FDA-approved TNF blocking agents. Policy title changed to Measurement of Serum Antibodies to Selected Biologic Agents. Clarified coding information.
1/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2018	Annual policy review. New references added.
12/2016	Annual policy review. New references added.
1/2016	Annual policy review. New references added.
12/2014	Annual policy review. New references added.

3/2014	Annual policy review. New references added.
3/2013	New policy describing non-coverage. Effective 3/1/2013.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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