BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 2.04.84 Measurement of Serum Antibodies to Selected Biologic Agents

### Effective Policy Date: April 1, 2023

### Original Policy Date: December 2013

### Related Policies:

5.50.002- Infliximab
5.50.012- Entyvio (vedolizumab)
5.70.029- Humira (adalimumab)
5.90.004- Stelara (ustekinumab)

## Measurement of Serum Antibodies to Selected Biologic Agents

### Description

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.

## 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, adalimumab, vedolizumab, or ustekinumab 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 antidrug antibodies in an individual receiving treatment with a biologic agent, either alone or as a combination test, which includes the measurement of serum tumor necrosis factor (TNF) blocking agent levels, is considered **investigational**.

# POLICY GUIDELINES

Selected U.S. Food and Drug Administration approved biologic agents include infliximab, adalimumab, vedolizumab, and ustekinumab.

# BENEFIT APPLICATION

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

None.

# 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 4 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). The 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.

# 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 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 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.

# SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### American College of Gastroenterology

In 2019, the American College of Gastroenterology published a guideline on ulcerative colitis (UC).[30,] The guideline stated: "In patients with moderately to severely active UC who are responders to anti-TNF [tumor necrosis factor] therapy and now losing response, we suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response (conditional recommendation, very low quality of evidence)."

In 2018, the American College of Gastroenterology published a guideline on Crohn disease (CD).[31,] Although acknowledging that a detailed review of therapeutic drug monitoring was beyond the scope of the guideline, it stated: "If active CD is documented, then assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered."

### American Gastroenterology Association Institute

In 2017, the American Gastroenterology Association Institute published guidelines on therapeutic drug monitoring in inflammatory bowel disease (IBD).[32,] The guidelines note that:

"In the presence of sufficient trough concentrations, results of antibody testing should not guide treatment decisions. If the trough concentration is low (below the suggested threshold, in patients with active IBD) and no anti-drug antibodies are present, then the index drug should be optimized using any of the following techniques: shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. If there is no detectable drug (zero trough concentration) and high-titer anti-drug antibodies are present, then the patient should consider switching to a different drug within the class or to a different drug class. If there is no detectable drug and low-titer antibodies are present, then one can consider trying to optimize the index drug by shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. Typically, optimizing the drug will be attempted before changing to a different drug within the class or switching to a new drug class, although some might opt to change to a different drug within the class or switch to a new drug class. It should be noted that 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

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 CD.[33,] The Institute recommended that laboratories monitoring TNF-α inhibitors in patients with CD 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."

In 2019, the National Institute for Health and Care Excellence issued guidance on therapeutic monitoring of TNF-α inhibitors in the treatment of patients with rheumatoid arthritis.[34,] The Institute stated: "Enzyme-linked immunosorbent assay (ELISA) tests for therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors (drug serum levels and antidrug antibodies) show promise but there is currently insufficient evidence to recommend their routine adoption in rheumatoid arthritis." It also recommended that "laboratories currently using ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis should do so as part of research and further data collection."

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

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

# REFERENCES


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## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| December 2013 | New policy | |
| December 2014 | Replace policy | Policy updated with literature review. References 4-5, 15-18, 22, and 25-30 added. No changed to policy statements. |
| March 2017 | Replace policy | Policy updated with literature review through November 3, 2016; references 4 and 33 added. Policy statements unchanged. |
| March 2018 | Replace policy | Policy updated with literature review through September 11, 2017; references 14 and 21-23 added. Policy statements unchanged. |
| March 2019 | Replace policy | Policy updated with literature review through September 6, 2018; reference 29 added. Policy statements unchanged. |
| March 2020 | Replace policy | Policy updated with literature review through November 12, 2019; no references added. Investigational policy statement reworded to include newer TNF blocking agents; statement added in Policy Guideline section listing currently FDA-approved TNF blocking agents. Policy title changed to "Measurement of Serum Antibodies to Selected Biologic Agents". |
| March 2021 | Replace policy | Policy updated with literature review through October 13, 2020; no references added. Updated terminology throughout the policy to reflect the addition of the interleukin-2 and -23 antagonist ustekinumab. Policy statement otherwise unchanged. |
| March 2022 | Replace policy | Policy updated with literature review through October 5, 2021; references added. Policy statement unchanged. |
| March 2023 | Replace policy | Policy updated with literature review through September 12, 2022; no references added. Minor editorial refinements to policy statements; intent unchanged. |