MEDICAL POLICY

Medical Policy Title	**Testing for the Use of Biologic Therapeutics for the Treatment of Inflammatory Disorders**
Policy Number	**2.02.47**
Current Effective Date	**November 19, 2026**
Next Review Date	**November 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service.
(Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Measurement of serum and/or antibody levels for biologic therapies (e.g., Infliximab, Adalimumab, Vedolizumab, Ustekinumab) pre- or post-treatment in patients with inflammatory disorders, are considered **investigational**, and include but are not limited to **ANY** of the following tests:

   A. Procise ADL;

   B. Procise IFX;

   C. PredictrPK IFX;

   D. ADALX (Adalimumab Quantitative with Reflex to Antibody, Serum) test;

   E. Anser ADA test;

   F. Anser IFX test;

   G. Anser UST test;

   H. Anser VDZ test.

II. Testing used to predict the likelihood of response or non-response to biologic therapies (e.g., PrismRA), either alone or as a combination test are considered **investigational**.

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

Pharmacy Policies

Pharmacy-22 (regarding Adalimumab)

Pharmacy-44 (regarding Infliximab)

Pharmacy-73 (regarding Vedolizumab)

Pharmacy-59 (regarding Ustekinumab)

POLICY GUIDELINE(S)

Not Applicable

DESCRIPTION

Biological therapeutics are defined by the World Health Organization (WHO) as a class of medicines that are grown and then purified from large scale cell cultures of bacteria or yeast, plant, or animal cells. They are used in vaccines, growth factors, immune modulators, or monoclonal antibodies.

- Examples of biological therapeutics are infliximab (Remicade) (IFX), adalimumab (Humira)(ADA), vedolizumab (Entyvio) (VDZ), and ustekinumab (Stelara) (UST), etanercept (Enbrel), certolizumab (Cimzia).
- Infliximab, adalimumab, etanercept, certolizumab are anti-tumor necrosis factor-α (anti-TNF-α) therapies. These therapies are effective when there is insufficient control of disease with conventional treatment in patients with inflammatory disorders, such bowel disease (IBD), ulcerative colitis, Crohn's disease, rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis.

Up to 30% of patients may not initially respond to anti-TNF-α therapy, and among those who do, up to 60% may lose responsiveness over time. This diminished or absent response is thought to be linked to the development of antibodies against anti-TNF agents, particularly Infliximab. These antibodies, known as Anti-Infliximab Antibodies (ATI) or human antichimeric antibodies (HACAs), can form as early as after the first dose and persist for years, potentially reducing drug concentration and efficacy due to accelerated clearance. Their presence is also associated with adverse reactions, including acute infusion and delayed hypersensitivity responses. To manage nonresponse, clinicians may adjust the dose or interval, switch to another anti-TNF drug, or opt for a different class of medication. Because loss of response can lead to relapse, reduced quality of life, and increased healthcare costs, monitoring serum drug and antibody levels has been suggested as part of anti-TNF therapy regimens.

Detection of drug and antidrug antibodies is commonly performed using ELISA, radioimmunoassay (RIA), and homogenous mobility shift assay (HMSA), each with its own limitations. ELISA is restricted to measuring antidrug antibodies only when drug levels are undetectable, while RIA involves complex procedures, extended incubation times, and safety concerns due to radioactive materials. HMSA offers the advantage of detecting antibodies even in the presence of the drug in serum. However, technical inconsistencies across these methods hinder reliable interstudy comparisons, and standardized threshold values for Infliximab or adalimumab antibodies have yet to be established for each assay type.

Prometheus Laboratories Inc. offers non-radiolabeled, fluid-phase homogenous mobility shift assay (HMSA) tests called Anser IFX for infliximab, Anser ADA for adalimumab, Anser VDZ for vedolizumab, and Anser UST for ustekinumab. The four tests are not enzyme-linked immunosorbent assay (ELISA)-based; however, each can measure anti-drug antibodies in the presence of detectable drug levels,

improving on a major limitation of the ELISA method. The tests measure serum drug concentrations and anti-drug antibodies.

The PrismRA (Scipher Medicine laboratory) test predicts the likelihood of non-response to TNFi therapies. The test analyzes 23 biological features, including RNA expression data, demographic variables, and disease-associated clinical metrics, which are discriminatory between the molecular signatures of those who respond or do not respond adequately to TNFi therapies.

SUPPORTIVE LITERATURE

Bronsky et al (2025) conducted a prospective single-center observational study that evaluated the usefulness of therapeutic drug monitoring (TDM) for ustekinumab (USTE) and vedolizumab (VEDO) in pediatric inflammatory bowel disease (pIBD) patients. this study involved 87 children with Crohn's disease, ulcerative colitis, or unclassified IBD, analyzing 641 drug observations. The primary goal was to assess the relationship between serum trough levels (TLs) and disease activity, measured by fecal calprotectin (F-CPT). The study found that USTE trough levels were not significantly associated with disease activity, as measured by F-CPT, suggesting limited value of TDM for USTE in pediatric IBD. In contrast, VEDO trough levels showed a negative association with F-CPT levels, indicating a potential role for TDM in guiding VEDO therapy. However, the ability of VEDO trough levels to predict remission (F-CPT < 250 µg/g) was poor, with an optimal threshold of 15.1 µg/mL yielding high sensitivity (0.82) but low specificity (0.32), and an area under the curve (AUC) of only 0.56. Other factors such as treatment phase, drug intensification, undetectable TLs, and IBD type were not significantly linked to disease activity. Mild anti-drug antibodies were found in a few cases (5 USTE, 16 VEDO) but had no clinical impact. Overall, TDM may be helpful for VEDO but not for USTE, and clinically useful dosing thresholds remain difficult to establish.

Brun et al (2024) reported the results of the exploratory analysis of the NOR-DRUM randomized controlled trial that evaluated the impact of antidrug antibodies and proactive therapeutic drug monitoring (TDM) in 615 adults with immune-mediated inflammatory diseases receiving infliximab. Antidrug antibodies were detected in 24% of patients and were associated with significantly poorer outcomes. Patients with antibodies were less likely to achieve remission at 30 weeks (35% vs. 54%) and had higher rates of disease worsening, infusion reactions, and infliximab discontinuation compared with patients without antibodies. These negative effects were strongest among patients with high antibody concentrations. Regardless of antibody status, proactive TDM was associated with a lower risk of disease worsening and infusion reactions, although it was also linked to a higher rate of infliximab discontinuation, likely reflecting earlier treatment adjustments. Overall, the findings suggest that the timely detection of antidrug antibodies through proactive TDM can improve treatment decisions, reduce adverse outcomes, and optimize both the effectiveness and safety of infliximab therapy.

Nguyen et al (2022) conducted a systematic review and metanalysis of RCTs comparing TDM with conventional management in patients with IBD. Proactive TDM has been proposed to improve outcomes in patients with IBD being treated with TNFα antagonists. The study identified RCTs in patients with IBD treated with TNFα antagonists comparing proactive TDM through routine

assessments of trough concentration, regardless of trough concentrations, with conventional management where dose adjustments were driven by clinical assessments. In the nine RCTs that were used for the metanalysis, it was found that there was no significant difference in the failing to maintain clinical remission in patients who underwent proactive TDM. The proactive TDM arm was more likely to undergo dose escalation, however there was no difference found in the risk of developing antidrug antibodies or other serious adverse events. In conclusion it was found that in patients with IBD treated with TNFα antagonists, regardless of disease activity, routine TDM to target biologic concentration to specific thresholds did not show clinical benefit. The RCTs focused on adults and optimization of TNFα antagonist during the maintenance phase, further studies would be needed to assess induction phase of drug use, or if individuals with more severe phenotype may benefit from routine proactive TDM.

Syversen et al (2021) conducted a randomized, parallel-group, open-label clinical trial for 411 adults with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, or psoriasis initiating infliximab therapy. The researchers aimed to assess whether TDM during initiation of infliximab therapy improves the efficiency of treatment compared to the standard without TDM. Participants were randomized 1:1 (198 in the TDM group and 200 in the standard therapy group) Clinical readmission at 30 weeks was achieved in 50.5% for TDM and 53% in the standard groups. Adverse events were reported in 68% in TDM and 70% in standard groups. The finding reported do not support routine use of TDM during infliximab induction for improving disease remission rates. It was suggested that further studies should be completed to determine if TDM is associated with fewer infusion reactions. Limitations included lack of double blinding, open label, and discrepancies amongst assays for infliximab and antidrug antibodies, and individual patient responses to treatment.

Steenholdt et al (2014) published a post hoc comparison of different ATI assays. Blood samples were collected from 66 of 69 patients enrolled in an RCT (discussed next) that assessed algorithmic treatment for CD relapse during infliximab therapy. Samples were analyzed by three binding assays: RIA, ELISA, and HMSA; and by a reporter gene assay, a functional cell-based technique. ATI were detected in 18 patients (27%) by radioimmunoassay, six patients (9%) by ELISA, and 22 patients (33%) by HMSA. The reporter gene assay reported anti-infliximab activity, most likely due to ATI, in seven patients (11%). As observed by the authors, this suggests that ATI detected by RIA and HMSA are not necessarily functionally active. Five patients (8%) were ATI-positive, and 43 patients (65%) were ATI-negative by all four assays. Correlations were statistically significant in all pairwise comparisons. However, statistical agreement between assays could not be estimated accurately (e.g., using the intraclass correlation coefficient) because different assays reported values on different arbitrary scales. Regardless of assay used, most patients (74%-88%) had therapeutic serum infliximab levels and undetectable ATI, suggesting nonpharmacologic reasons for relapse or for symptoms mimicking relapse.

Wang et al (2013) developed and validated a non-radiolabeled HMSA to measure antibodies-to-adalimumab (ATA) and adalimumab levels in serum samples. Analytic validation of performance characteristics (calibration standards, assay limits, intra- and inter-assay precision, linearity of dilution, substance interference) was performed for both the ATA- and adalimumab HMSA. Because the elimination half-life of adalimumab (10-20 days) overlaps the dosing interval (every two weeks),

ATA-positive sera to provide calibration standards were difficult to collect from human patients. (The drug-free interval for antibody formation is small.) Therefore, anti-sera from rabbits immunized with adalimumab were pooled to form calibration standards. Serial dilutions of these ATA calibration standards then generated a standard curve against which test samples were compared. Over the course of 29 experimental runs, intra-assay precision and accuracy for the adalimumab-HMSA (as indicated by the CV) was <20% and <3%, respectively; inter-assay (run-to-run, analyst-to-analyst, and instrument-to-instrument) precision and accuracy were less than 12% and less than 22%, respectively. For the ATA HMSA, CVs for intra-assay precision and accuracy were less than 3% and less than 13%, respectively; CVs for inter-assay precision and accuracy were less than 9% and less than 18%, respectively. ELISA could not be used as a standard comparator, due to competition from the circulating drug. Analysis of 100 serum samples from patients who were losing response to adalimumab showed that 44% were above the cut point for ATA (0.55 U/mL), and 26% were below the cut point for serum adalimumab level. In samples below the adalimumab cut point (0.68 µg/mL), 68% were ATA-positive; in samples with adalimumab levels greater than 20 µg/mL, 18% were ATA-positive.

Lee et al (2012) conducted a meta-analysis of patients with IBD receiving infliximab to determine the prevalence of ATI, the effect of ATI on the prevalence of infusion reactions, and the effect of ATI on disease remission rates. Databases were searched through October 2011, and 18 studies involving 326 patients were included. The studies included nine randomized, controlled trials (RCTs), five cohort studies, and four retrospective cohort studies. The prevalence of ATI was 45.8% when episodic infusions of infliximab were given and 12.4% when maintenance infliximab was given. The rates of infusion reactions were significantly higher in patients with ATI (relative risk [RR], 2.07; 95% confidence interval [CI], 1.61 to 2.67). Immunosuppressants resulted in a 50% reduction in the risk of developing ATI ($p<0.001$). Patients with ATI were less likely to be in clinical remission, but this was not statistically significant (RR=0.90; 95% CI, 0.79 to 1.02; $p=0.10$). The meta-analysis concluded that patients who test positive for ATI are at an increased risk of infusion reactions but have similar rates of remission compared with patients who test negative for ATI.

The clinical utility of vedolizumab trough levels (VTLs) in IBD is not well-defined. The data to support the routine use of therapeutic drug-monitoring during maintenance therapy are lacking. Further studies to determine the role of therapeutic drug-monitoring of vedolizumab are needed.

PROFESSIONAL GUIDELINE(S)

American College of Gastroenterology 2025 Clinical Guidelines for Ulcerative Colitis (UC) in Adults, states:

- "In patients with moderately to severely active UC who are responders to anti-TNF 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)". (Rubin et al 2025)

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) regulates vaccines, blood and blood products, and biologics via the Center for Biologics Evaluation and Research (CBER) which ensures the safety, efficacy, and quality of these products. Refer to the FDA vaccines/blood/biologics website. Available from: https://www.fda.gov/vaccines-blood-biologics [accessed 2026 Oct 22]

The FDA maintains information for consumers and health professionals on vaccine, blood and biologics warnings and other safety information. Available from: Recalls (Biologics) | FDA [accessed 2026 Oct 22]

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 (CLIA).

Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. More information is available at: Clinical Laboratory Improvement Amendments (CLIA) | FDA [accessed 2026 Oct 22]

ProciseDx has been U.S. Food and Drug Administration cleared for therapeutic Drug Monitoring (TDM) for Infliximab and Adalimumab.

Anser tests by Prometheus Laboratories have not been cleared or approved by the US FDA.

Infliximab, adalimumab, vedolizumab, and ustekinumab are biologic therapeutics that have received approval by the U.S. Food and Drug Administration (FDA).

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
80145 (E/I)	Adalimumab (Therapeutic level testing)
80230 (E/I)	Infliximab (Therapeutic level testing)
80280 (E/I)	Vedolizumab (Therapeutic level testing)
84999	Unlisted chemistry procedure

Code	Description
0514U (E/I)	Gastroenterology (irritable bowel disease [IBD]), immunoassay for quantitative determination of adalimumab (ADL) levels in venous serum in patients undergoing adalimumab therapy, results reported as a numerical value as micrograms per milliliter (mcg/mL) (Procise ADL, ProciseDx Inc.)
0515U (E/I)	Gastroenterology (irritable bowel disease [IBD]), immunoassay for quantitative determination of infliximab (IFX) levels in venous serum in patients undergoing infliximab therapy, results reported as a numerical value as micrograms per milliliter (mcg/mL) (Procise IFX, ProciseDx Inc.)

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HCPCS Codes

Code	Description
J1745	Injection, infliximab, excludes biosimilar, 10 mg
J3357	Ustekinumab, for subcutaneous injection, 1 mg
J3358	Ustekinumab, for intravenous injection, 1 mg
J3380	Injection, vedolizumab, 1 mg

ICD10 Codes

Code	Description
K50.00-K50.919	Crohn's disease (code range)
K51.00-K51.919	Ulcerative (chronic) pancolitis (code range)
L40.50-L40.59	Arthropathic psoriasis (code range)
M05.40 – M05.479	Rheumatoid myopathy with rheumatoid arthritis (code range)
M06.4	Inflammatory polyarthropathy
M08.00-M08.09	Juvenile rheumatoid arthritis (code range)
M08.3	Juvenile rheumatoid polyarthritis (seronegative)

Code	Description
M08.40-M08.48	Pauciarticular juvenile rheumatoid arthritis (code range)
M12.00-M12.09	Chronic postrheumatic arthropathy [Jaccoud] (code range)
M45.0-M45.9	Ankylosing spondylitis of the spine (code range)

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for Measurement of Serum Antibodies to Infliximab and Adalimumab.

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a

specific service, medical policy criteria apply to the benefit.

- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
12/17/15, 12/15/16, 12/21/17, 12/20/18, 12/19/19, 12/17/20, 12/16/21, 12/22/22, 11/16/23, 11/21/24, 11/20/25, 11/19/26	
Date	**Summary of Changes**
11/19/26	• Annual review; intent to policy unchanged.
11/20/25	• Annual review; intent to policy unchanged. Code 0456U deleted. Added Procise ADL and IFX, PredictrPK IFX, ADALX (Adalimumab Quantitative with Reflex to Antibody, Serum), Anser ADA, IFX, UST, VDZ to the list of investigational tests.
01/01/25	• Summary of changes tracking implemented.
12/17/15	• Original effective date