MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Testing for the Use of Biologic Therapeutics for the Treatment of Inflammatory Disorders**
Policy Number	**2.02.47**
Category	**Technology Assessment**
Original Effective Date	**12/17/15**
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Product Disclaimer	• *Services are contract dependent; If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), 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 STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, measurement of antidrug antibodies (ADA) in patients receiving treatment for the treatment of inflammatory disorders with a biologic therapeutic (e.g. anti-tumor necrosis factor-α [anti-TNF-α] therapies), either alone or as a combination test considered **investigational**, including but not limited to **ANY** of the following biologic therapeutics:
   A. Infliximab;
   B. Adalimumab;
   C. Vedolizumab**;**
   D. Ustekinumab.

II. Based upon our criteria and lack of the peer-reviewed literature, 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**.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

POLICY GUIDELINES

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

II. 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.

III. 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.

IV. These tests were developed, and the labs determined their performance characteristics. None have been cleared or approved by the United States Food and Drug Administration (FDA).

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). Of those medications 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.

Options for those who do not respond include increasing the dose, interval, or changing to another anti-TNF drug or to a drug from a different class. Up to 30% of patients may not respond to anti-TNF-α therapy, and up to 60% of those who do respond to the therapy lose response over time. The reason for nonresponse or loss of response is unclear, but it may be due to formation of antibodies to anti-TNF agents. Antibodies to Infliximab, or Anti-Infliximab Antibodies (ATI), also referred to as human antichimeric antibodies (HACAs), are reported to develop in up to approximately 60% of patients depending on the dosing schedule, the administration of concurrent steroids or immunomodulators, and the method of measuring the antibodies in the blood. The antibodies can appear after the first Infliximab dose and can persist in the blood for up to 4.5 years after the drug is discontinued. The presence of antibodies has been associated with decreased concentration, possibly from an accelerated clearance of the drug that results in decreased efficacy. Antidrug antibodies have also been associated with acute infusion reactions and delayed hypersensitivity reactions. Loss of clinical response of anti-TNF-α is a potential major limitation of this therapy, leading to clinical relapse, impaired quality of life, and increased cost of care. Thus, accurate monitoring of serum drug and anti-drug antibody levels has been suggested as part of anti-TNF therapy regimens.

Detection of drug and antidrug antibodies can be accomplished by ELISA, radioimmunoassay (RIA), and homogenous mobility shift assay (HMSA); however, each method has disadvantages. ELISA can only measure antidrug antibodies in the absence of detectable drug levels. RIA is a complex test with prolong incubation time and safety concerns related to the handling of radioactive material. HMSA has the advantage of being able to measure anti-drug antibodies when the drug is present in the serum. Technical factors related to different assay methods are unresolved, making interstudy comparisons difficult, and Infliximab or adalimumab antibody threshold values for each assay have not been established.

RATIONALE

In the 2019 American College of Gastroenterology clinical guidelines for ulcerative colitis (UC) in adults they state: "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)".

Afif et al. (2010) evaluated the clinical utility of measuring ATI, (referred to as HACA in the study) and infliximab concentrations by retrospectively reviewing the medical records of patients with IBD who had had ATI and infliximab concentrations measured. The study sought to determine whether these results affected clinical management. Medical record review from 2003 to 2008 identified 155 patients who had had ATI and infliximab concentrations measured and who met the study's inclusion criteria. A single physician ordered 72% percent of the initial tests. Clinical response to

infliximab was retrospectively determined by the authors. 47% percent of patients were on concurrent immunosuppressive medication. The main indications for testing were loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune/delayed hypersensitivity reaction (10%). ATI were identified in 35 patients (23%) and therapeutic infliximab concentrations were identified in 51 patients (33%). Of 177 tests assessed, the results impacted treatment decisions in 73% of patients. In ATI-positive patients, change to another anti-TNF agent was associated with a complete or partial response in 92% of patients, whereas dose escalation had a response of 17%. The authors concluded that measurement of ATI and infliximab concentration impacted management and was clinically useful. Increasing the infliximab dose in patients with ATI was ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy was considered a suitable alternative to changing to another anti-TNF agent. Limitations to the study included its retrospective design and the use of the ELISA method to test for antibodies to infliximab. Because there was no control group in this study, it is not possible to determine what changes in management would have been made in the absence of ATI measurement. Clinicians are likely to make some changes in management for patients who do not achieve or maintain a clinical response, and it is important to understand how these management decisions differ when ATI are measured.

Finckh et al. (2010) tested whether the presence of ATI and residual circulating infliximab levels prior to another infusion were associated with acquired infliximab resistance in RA. A multi-variate logistic regression was used to analyze the relationship between ATI, residual infliximab concentrations, and acquired infliximab resistance in a nested cohort within a Swiss RA registry. Sixty-four RA patients on longstanding infliximab therapy were included; 24 had an acquired therapeutic resistance to infliximab, and 40 had continuous good response to infliximab. The two groups had similar disease characteristics; however, patients with acquired infliximab resistance required significantly higher dosages of infliximab and shorter infusion intervals than long-term good responders. The presence of residual infliximab tended to be associated with a decreased risk of acquired therapeutic resistance (odds ratio [OR], 0.4; 95% CI, 0.1 to 1.5), while the presence of ATI tended to be associated with an increased risk of acquired therapeutic resistance (OR=1.8; 95% CI, 0.4 to 9.0). The presence of either high ATI levels or low residual infliximab concentrations was strongly associated with acquired therapeutic resistance to infliximab (OR=5.9; 95% CI, 1.3 to 26.6). However, just 42% of patients with acquired infliximab resistance had either low infliximab or high ATI levels. The authors concluded that their results suggested that the assessment of ATI and residual infliximab levels is of limited value for individual patients in routine clinical care.

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.

Garces et al. (2012) conducted a meta-analysis of studies of infliximab and adalimumab used to treat RA, ankylosing spondylitis, spondyloarthritis, psoriasis, Crohn's disease (CD), and ulcerative colitis (UC). Databases were searched to August 2012, and 12 prospective cohort studies involving 860 patients (540 with RA, 132 with spondyloarthritis, 130 with IBD, 58 with psoriasis) were included. The outcome of interest was drug response, assessed by using standard assessment scales for rheumatologic diseases (e.g., European League Against Rheumatism criteria for RA; Assessment in Ankylosing Spondylitis 20% response criteria, or ASDAS for spondyloarthritis; Psoriasis Area and Severity Index for psoriasis) and clinician assessment for IBD. Overall, detectable antidrug antibodies were associated with a 68% reduction in drug response (pooled RR=0.32; 95% CI, 0.22 to 0.48). Significant heterogeneity was introduced by varying use of immunosuppressant cotherapy (e.g., methotrexate) across studies. To assess antidrug antibodies, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

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.

In 2014, Steenholdt et al., 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 ($p<0.001$) in all pairwise comparisons (Pearson *r*, 0.77-0.96). 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.

Nguyen et al. (2022) conducted a systematic review and metanalysis of randomized control trials (RCTs) comparing Therapeutic Drug Monitoring (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 PCTs 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 PCTs 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.

ATI or ATA are present in a substantial number of patients treated with infliximab or adalimumab, respectively, and there may be a correlation between the level of these antibodies and clinical response. However, the clinical utility of measuring antidrug antibody concentrations has not been established, as it is unknown how patient management would change based on test results. Limited evidence describes changes in management after measurement of ATI but does not compare these management changes with those made in the absence of ATI measurement. Additionally, technical factors related to different assay methods are unresolved, and ATI or ATA threshold values that are informative for discriminating treatment response have not been definitively established.

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.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

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
0456U **(E/I)**	Autoimmune (rheumatoid arthritis), next-generation sequencing (NGS), gene expression testing of 19 genes, whole blood, with analysis of anti-cyclic citrullinated peptides (CCP) levels, combined with sex, patient global assessment, and body mass index (BMI), algorithm reported as a score that predicts nonresponse to tumor necrosis factor inhibitor (TNFi) therapy (PrismRA, Scipher Medicine) *(Effective 07/01/24)*
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) *(Effective 10/01/24)*
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) *(Effective 10/01/24)*

HCPCS Codes

Code	Description
J0135	Injection, adalimumab, 20 mg
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)
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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*Key Article

KEY WORDS

Antibodies to infliximab, antibodies to adalimumab, AnserIFX, AnserADA, Anser VDZ, Anser UST.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

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