Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MPA G2105 - Immunopharmacologic Monitoring of Therapeutic Serum Antibodies

Section: Medical Policy

Subject: Immunopharmacologic Monitoring of Therapeutic Serum Antibodies

Applicable line of business:

Commercial	**x**	**Medicaid**	**x**
Medicare	**x**	**ACA**	**x**
CHIP	**x**		

I. Policy: Immunopharmacologic Monitoring of Therapeutic Serum Antibodies

II. Purpose/Objective: To provide a policy of coverage regarding Immunopharmacologic Monitoring of Therapeutic Serum Antibodies

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

Commercial

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicare

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

CHIP

Geisinger Health Plan Kids (GHP Kids) is a Children's Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicaid

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

V. Additional Definitions
Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and

the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient

Medicaid Business Segment
Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.
- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age.

Policy Description

To manage loss of response due to the development of anti-drug antibodies, immunopharmacologic monitoring of circulating drug and anti-drug antibody levels has been proposed. The presence of anti-drug antibodies may promote adverse effects and diminish drug efficacy (Bendtzen, 2024; Tighe & McNamara, 2017).

Targeted inhibitors of tumor necrosis factor-alpha (TNF) are widely used in the treatment of several inflammatory conditions, including rheumatoid arthritis (RA), spondyloarthritis, inflammatory bowel disease, and psoriasis. Some of these targeted inhibitors include, but are not limited to, infliximab, adalimumab, etanercept, and golimumab (Bendtzen, 2024).

Related Policies

Policy Number	Policy Title
AHS-G2098	Immune Cell Function Assay
AHS-G2155	General Inflammation Testing

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in "Applicable State and Federal Regulations" section of this policy document.

1) Drug and/or antibody concentration testing for anti-tumor necrosis factor (anti-TNF) therapies in patients with inflammatory bowel disease, spondylarthritis, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, and psoriasis **MEETS COVERAGE CRITERIA** in the following situations:
   a) At the end of induction for all anti-TNFs.
   b) At least once during maintenance therapy.

c) At the end of induction in primary non-responders.
d) For individuals with confirmed secondary loss of response.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

2) For individuals with conditions other than IBD (e.g., spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and psoriasis), drug and/or antibody concentration testing for anti-TNF therapies **DOES NOT MEET COVERAGE CRITERIA**.

3) For all other situations not addressed above, measurement of the serum drug levels **and/or** measurement of the antibodies to the drugs **DOES NOT MEET COVERAGE CRITERIA** for any of the following drugs (alone or as a combination test):

a) adalimumab
b) certolizumab
c) etanercept
d) golimumab
e) rituximab
f) ustekinumab
g) vedolizumab

Table of Terminology

Term	Definition
AAA	Antibodies against adalimumab
AACC	American Association for Clinical Chemistry
ACG	American College of Gastroenterology
ADA	Adalimumab
ADAbs	Anti-drug antibody status
AGA	American Gastroenterological Association
anti-TNF	Anti-tumor necrosis factor
ATA	Antibodies-to-adalimumab
ATI	Antibodies-to-infliximab
ATI-HMSA	Homogeneous mobility shift assay
bDMARDs	Biologic disease-modifying antirheumatic drugs
CD	Crohn's Disease
CER	Certolizumab
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
DBS	Dried blood spots
ELISA	Enzyme- linked immunosorbent assay
FDA	Food and Drug Administration
GOL	Golimumab
HMSA	Homogeneous mobility shift assay
IBD	Inflammatory bowel disease
IFX	Infliximab
LabCorp	Laboratory Corporation of America Holdings

LDTs	Laboratory developed tests
LFA	Lateral flow-based assay
NICE	National Institute for Health and Clinical Excellence
non-TDM	Non-therapeutic drug monitoring
OH	Ohio
pTDM	Proactive therapeutic drug monitoring
QI	Quality improvement
RA	Rheumatoid arthritis
RR	Risk ratio
TC	Trough concentration
TDM	Therapeutic drug monitoring
TNF	Tumor necrosis factor
UC	Ulcerative colitis
UST	Ustekinumab
VED	Vedolizumab

Scientific Background

Tumor necrosis factor (TNF) inhibitors competitively inhibit the binding of TNF to its receptors, reducing inflammation and halting disease progression (Lis et al., 2014). They are used for treatment of inflammatory conditions, including rheumatoid arthritis (RA), psoriatic arthritis, juvenile arthritis, inflammatory bowel disease (Crohn's and ulcerative colitis), and ankylosing spondylitis (Bendtzen, 2024; Lis et al., 2014). Five primary biologic TNF inhibitors are used for inflammatory diseases; infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept. However, these inhibitors may lead to the formation of auto-drug antibodies, potentially hindering treatment and causing other adverse effects such as allergic reactions (Bendtzen, 2024).

Tumor necrosis factor inhibitors are a subset of biologic disease-modifying antirheumatic drugs (bDMARDs), which "improve symptoms and reduce structural damage of joints, the gastrointestinal tract, and other affected organs." However, patients oftentimes do not respond to treatment, with upwards of 50% of patients attaining "secondary failure," or inadequate disease control. Important contributors to the secondary failure include anti-drug antibodies and low drug concentrations, which may then contribute to antidrug antibody formation. Generally, the approach to prescribing bDMARDs, such as infliximab, is to adjust or switch "only when there is clinical evidence that remission or low disease activity is not achieved or maintained, which may occur months after treatment initiation." Sometimes, drugs like methotrexate may be prescribed along with the bDMARDs to prevent antidrug antibody development. Guidelines recommending therapeutic drug monitoring (TDM) also vary by inflammatory disease – for example, it is recommended for inflammatory bowel disease (IBD) but not rheumatoid arthritis (RA). To prevent the drawbacks of using bDMARDs from accumulating further, proactive TDM is best supported, but it does not come without barriers like additional personnel needed for constant monitoring, and a dearth of understanding of how other bDMARDs are affected similarly or differently (Wallace & Sparks, 2021).

Most TNF inhibitors are given to individuals in a step wise manner, utilizing an induction period, whereby medication is given more frequently at the beginning of treatment, with frequency of drug delivery often decreasing following the initial induction period. The standard induction period for infliximab is intravenous drug delivery at zero, two, and six weeks, with maintenance therapy occurring every eight weeks. In contrast, adalimumab is given subcutaneously at week zero, week two, and week four, then every other week thereafter as maintenance therapy. Certolizumab induction is subcutaneous delivery at week zero, week two, and week four, then every four weeks for maintenance therapy. Individuals receiving treatment should receive therapeutic drug monitoring to ensure proper response to the dose of the medication and to the medication itself. The drug trough level (the lowest level of the drug in the individuals system) should be assessed no more than 24 hours prior to the next scheduled dose of the drug (Lichtenstein, 2024).

Additional biologics are approved for the treatment of IBD (ustekinumab and vedolizumab) and are often recommended as alternatives to TNF inhibitors. However, similar to the therapeutic drug monitoring required for TNF inhibitors, therapeutic drug monitoring is also essential in individuals receiving these biologics. Ustekinumab is given as a one-time intravenous infusion dose for individuals with moderate to severe Crohn disease (CD) or ulcerative colitis (UC); for individuals who respond to the initial dose, maintenance therapy by subcutaneous delivery should occur every eight weeks (Lexidrug™, 2024a). For individuals with CD or UC, vedolizumab is given by intravenous delivery at week zero, week two, and week six, then every eight weeks thereafter when maintenance is performed through intravenous delivery. After the first two intravenous infusions, subcutaneous delivery every two weeks is a viable option during the maintenance period (Lexidrug™, 2024b).

Proprietary Testing

To optimize dosing of TNF inhibitors, therapeutic drug monitoring (TDM) of both these drugs as well as anti-drug antibodies has been proposed. This dual monitoring is thought to help clinicians manage drug regimens for these patients, such as adjusting the dose or changing the drug entirely. Identifying the presence and concentration of these drugs and auto-drug antibodies may help avoid nonresponse to treatment. Most assays for the assessment of serum antibodies will also report the drug concentration (Lichtenstein, 2024). For example, HalioDx Inc. offers OptimAbs, which a set of assays for eight biologic agents (adalimumab, certolizumab pegol, golimumab, infliximab, infliximab-dyyb, infliximab-abda, ustekinumab, and vedolizumab). These assays are intended to allow providers to monitor, manage response, and optimize dose (Theradiag, 2018). Prometheus Anser also offers a series of assays for assessment of these anti-drug antibodies, with assessments for four biologics (adalimumab, infliximab, ustekinumab, and vedolizumab). They also measure the levels of antibodies against the drug in question (Prometheus Laboratories, 2024). LabCorp offers eight assays for 10 biologics (adalimumab, certolizumab, etanercept, golimumab, infliximab, infliximab- dyyb, infliximab-abda, rituximab, ustekinumab, and vedolizumab) encompassed in one portfolio called “DoseASSURE” (LabCorp, 2024).

Clinical Utility and Validity

Wang et al. (2012) developed and validated a non-radiolabeled homogeneous mobility shift assay (HMSA) to measure the levels of both infliximab and the antibodies-to-infliximab (ATI) ratio in serum samples. The assay was validated for both items and the sample was compared to the traditional enzyme-linked immunosorbent assay (ELISA). Intra- and interassay precision rates for the ATI-HMSA were less than 4% and less than 15%, respectively, and less than 6% and less than 15%, respectively, for the infliximab-HMSA. The lower limit of quantitation of the ATI-HMSA was found to be 0.012 μg/mL in serum and the HMSA correlated well with the ELISA for ATI levels.

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, et al.) 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) and thus the drug-free interval for antibody formation is small, ATA-positive sera samples for calibration standards were difficult to collect from human patients. Instead, antisera 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. With over 29 experimental runs, intra-assay precision and accuracy for the adalimumab-HMSA was <20% and <3%, respectively; interassay (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, variance for intra-assay precision and accuracy were less than 3% and less than 13%, respectively; variance for interassay precision and accuracy were less than 9% and less than 18%, respectively (Wang et al., 2013). ELISA could not be used as a standard comparator due to competition from circulating drug.

Van Stappen et al. (2016) validated a rapid, lateral flow-based assay (LFA) for quantitative determination of infliximab and to assess thresholds associated with mucosal healing in patients with ulcerative colitis. They found that the LFA agreed well with the traditional ELISA for quantification of infliximab with correlation coefficients of 0.95 during induction. A trough concentration (TC) of ≥2.1 μg/ml was associated with mucosal healing. They concluded that "with a time-to-result of 20 min, individual sample analysis and user-friendliness, the LFA outplays ELISA as a rapid, accurate tool to monitor infliximab concentrations" (Van Stappen et al., 2016).

Steenholdt et al. (2014) investigated "the cost-effectiveness of interventions defined by an algorithm designed to identify specific reasons for therapeutic failure." A total of 69 patients with secondary infliximab (IFX) failure were randomized either to IFX dose intensification (n = 36) or interventions based on serum IFX and IFX antibody levels (n = 33). The researchers found that "Costs for intention-to-treat patients were substantially lower (34%) for those treated in accordance with the algorithm than by infliximab (IFX) dose intensification: €6038 vs €9178. However, disease control, as judged by response rates, was similar: 58% and 53%, respectively" (Steenholdt et al., 2014). They concluded that "treatment of secondary IFX failure using an algorithm based on combined IFX and IFX antibody measurements significantly reduces average treatment costs per patient compared with routine IFX dose escalation and without any apparent negative effect on clinical efficacy" (Steenholdt et al., 2014).

Roblin et al. (2014) conducted a prospective study of 82 patients with inflammatory bowel disease (IBD) having a disease flare while being on adalimumab (ADA) 40 mg every two weeks. All patients were primary responders to ADA therapy and were anti-TNF I. ADA trough levels and antibodies against ADA (AAA) were measured. All patients were optimized with ADA 40 mg weekly. Four months later, in the absence of clinical remission, patients were treated with infliximab. The researchers concluded, "The presence of low ADA trough levels without AAA is strongly predictive of clinical response in 67% of cases after ADA optimization. Conversely, low ADA levels with detectable AAA are associated with ADA failure, and switching to IFX should be considered. ADA trough levels >4.9 μg/ml are associated with failure of two anti-TNF agents (ADA and IFX) in 90% of cases and switching to another drug class should be considered" (Roblin et al., 2014).

Mitchell et al. (2016) studied if IFX TDM allows for objective decision making in patients with IBD and loss of response. A total of 71 patients with IBD that had IFX TDM were examined, and their serum concentration of anti-drug antibodies were measured. Patients were grouped by TDM results and changes in management were examined due to groupings: group one, low IFX/high ADA; group two, low IFX/low ADA; group three, therapeutic IFX. Of the 71 patients, 37% underwent an "appropriate" change in therapy based on group. The authors concluded that "a trend towards increased remission rates was associated with appropriate changes in management following TDM results. Many patients with therapeutic IFX concentrations did not undergo an appropriate change in management, potentially reflecting a lack of available out-of-class options at the time of TDM or due to uncertainty of the meaning of the reported therapeutic range" (Mitchell et al., 2016).

Barlow et al. (2016) evaluated the clinical utility of antibodies in relation to C-reactive protein concentrations. A total of 108 patients contributed 201 samples, and total anti-infliximab antibodies were measured in 164 samples. The authors found that median trough infliximab was 3.7 μg / mL, and 23% of the samples were ≤1 μg / mL. They also noted that "Serum C-reactive protein was found to be significantly higher where infliximab was ≤1 compared to >1 μg/mL," but no "strict" correlation was seen (Barlow et al., 2016). Approximately 85% of samples with positive anti-infliximab antibodies had infliximab ≤1 μg / mL and the authors concluded that "our findings support measurement of anti-infliximab antibodies only in the context of low infliximab concentrations <1 μg/mL. A higher therapeutic cut-off may be relevant in patients with negative antibodies. Further work is indicated to investigate the clinical significance of positive antibodies with therapeutic infliximab concentrations" (Barlow et al., 2016).

Moore et al. (2016) performed a systematic review and meta-analysis of studies that reported serum infliximab levels according to IBD outcomes. Twenty-two studies were examined, encompassing 3483 patients. Twelve studies reported IFX levels in a manner "suitable" for estimating the effect. The researchers found that "During

maintenance therapy, patients in clinical remission had significantly higher mean trough IFX levels than patients not in remission: 3.1 μg/ml versus 0.9 μg/ml. The standardized mean difference in serum IFX levels between groups was 0.6 μg/ml. Patients with an IFX level > 2 μg/ml were more likely to be in clinical remission (risk ratio [RR]: 2.9), or achieve endoscopic remission [RR 3] than patients with levels < 2 μg/ml." The study concluded, "There is a significant difference between serum infliximab levels in patients with IBD in remission, compared with those who relapse. A trough threshold during maintenance > 2 μg/ml is associated with a greater probability of clinical remission and mucosal healing" (Moore et al., 2016).

Wang et al. (2018) submitted an abstract to the 2018 Therapeutic Drug Management and Toxicology Division Abstract Competition on July 30, 2018, conducted by the American Association for Clinical Chemistry (AACC). This abstract focused on InformTx's assays for TDM and the authors reviewed TDM results for six biologics: adalimumab (ADA), certolizumab (CER), golimumab (Syversen et al.), infliximab (IFX), ustekinumab, and vedolizumab (VED). A total of 18837 sera samples were analyzed with InformTx's assays and patients' responses were predicted based on drug and anti-drug antibody status (ADAbs). The need for drug optimization was assessed by comparing patient drug levels to recommended therapeutic drug levels and laboratory defined higher ADAbs. The authors found that "64.1%, 30.2%, 83.9%, 60.4%, 25.2%, and 69.1% of the patients treated with ADA, CER, GOL, INF, UST, and VED, respectively, had drug level equal to or greater than the recommended therapeutic level and undetectable ADAbs." Approximately 4.5%-33% patients had a drug concentration above the recommended therapeutic level. In contrast, patients (31.0% in ADA, 57.0% in CER, 12.1% in GOL, 32.5% in INF, 74.4% in UST, and 30.6% in VED) had undetectable or suboptimal levels of drugs and undetectable or lower levels of ADAbs (Wang et al., 2018).

Fernandes et al. (2019) examined whether TDM can improve clinical outcomes in Crohn's disease (CD) and ulcerative colitis (UC) patients. A total of 205 patients were included in the study, and 56 patients were placed in a "proactive" regimen. This proactive regimen involved measuring infliximab (IFX) trough levels and antidrug antibodies before the fourth infusion and subsequently every two infusions. The regimen aimed to establish an IFX trough level of 3-7 ug/mL for CD patients and 5-10 ug/mL for UC patients. The control group was made of patients treated with IFX but without TDM. The authors found that treatment escalation was more common in the proactive TDM (pTDM) group (76.8% vs 25.5%), mucosal healing was more common (73.2% vs 38.9%), and surgery was less common (8.9% vs 20.8%). Proactive TDM also decreased the odds of any unfavorable outcome by an odds ratio of 0.358. The authors concluded that "Proactive TDM is associated with fewer surgeries and higher rates of mucosal healing than conventional non-TDM-based management" (Fernandes et al., 2019).

Negoescu et al. (2019) performed a cost-effectiveness analysis of proactive verses reactive TDM in a simulated population of individuals with CD on IFX. The proactive strategy measured IFX concentration and antibody status every six months, or at the time of a flare, then dosed IFX appropriately. The reactive strategy measured both IFX concentration and antibodies at the time of a flare. The authors found that the proactive strategy led to fewer flares, finding an "incremental cost-effectiveness ratio of $146,494 per quality-adjusted life year." More patients stayed on IFX in the proactive strategy (63.4% vs 58.8% at year five). The authors concluded that "assuming 40% of the average wholesale acquisition cost of biologic therapies, proactive TDM for IFX is marginally cost-effective compared with a reactive TDM strategy. As the cost of infliximab decreases, a proactive monitoring strategy is more cost-effective" (Negoescu et al., 2019).

Papamichael, Juncadella, et al. (2019) studied the therapeutic drug monitoring of adalimumab in populations with IBD. This multicenter retrospective cohort study included data from 382 patients with IBD (including 311 patients with CD). Participants received either standard of care or at least one proactive TDM. "Multiple Cox regression analyses showed that at least one proactive TDM was independently associated with a reduced risk for treatment failure" (Papamichael, Juncadella, et al., 2019). This study shows that proactive TDM of adalimumab may help to decrease rates of treatment failure for IBD patients.

In February 2016, Guido et al. (2020) developed quality improvement (QI) methods to improve post-induction TDM in pediatric IBD patients initiating anti-TNF therapy at the Nationwide Children's Hospital in Columbus,

OH. They implemented interventions to improve TDM using the Institute for Healthcare Improvement Plan-Do-Study-Act cycle approach. Their QI approaches improved post-induction anti-TNF TDM from a baseline off 43% in 2015 to greater than 80% by the end of 2017. Specifically, infliximab post-induction TDM and adalimumab post-induction TDM improved from a baseline of 59% to 89% and 14% to 79%, respectively. Most importantly, they note that "subtherapeutic post-induction infliximab levels were common, indicating a strong need for anti-TNF TDM and an opportunity for dose optimization."

Syversen et al. (2021) studied the therapeutic drug monitoring of infliximab in populations with immune-mediated inflammatory disease. Proactive therapeutic drug monitoring (TDM) as an alternative to standard therapies was proposed to treat patients safely and effectively during biologic drug therapies, specifically, in this study, patient populations who were prescribed Infliximab. A randomized, parallel-group and open-label clinical trial was established with a total of 458 adults with the diagnosis of rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, or psoriasis. All patients participating in Infliximab maintenance therapy were from a selection of Norwegian hospitals. Routine monitoring of serum drug levels and antidrug antibodies was performed on a randomized 1:1 basis (i.e. some patients received standard therapy, while others received scheduled monitoring of serum drug levels and anti-TNF antibodies). The primary outcome of sustained disease control without disease worsening was evident in 167 patients, which comprised 73.6% of the therapeutic drug monitoring cohort. A total of 127 patients in the standard therapy group (55.9%) showed sustained disease control outcomes. This comprised an "estimated adjusted difference" of 17.6% between the two groups. In conclusion, the authors stated that they found "proactive TDM was more effective than treatment without TDM in sustaining disease control without disease worsening. Further research is needed to compare proactive TDM with reactive TDM, to assess the effects on long-term disease complications, and to evaluate the cost-effectiveness of this approach."

Cox et al. (2021) conducted a retrospective review of rheumatology patients who had antidrug antibody levels tested between October 2015 and April 2019 in order to assess the reasons for and outcomes in patients on adalimumab or infliximab. From the 237 patients included on the analysis, most patients were tested due to "clinical evidence of a flare in disease" and "patient reported worsening of symptoms." A total of 38% changed biologics and 2% had dosing schedules changed, which is consistent with the 30-40% failure rate of response to first-line biologics. It was also found that "those with strongly positive antibodies were more likely to switch biologics than those with normal antibodies (84% vs 28%, p =0.01)," and that "patients with clinically active disease but normal antibodies and drug levels were more likely to switch biologics than patients with no evidence of active disease but positive antibodies (p=0.03)." This demonstrates the benefit of antidrug antibody level monitoring on informing treatment among specific patient populations (Cox et al., 2021).

Pan et al. (2022) utilized drug concentrations of infliximab, adalimumab, and ustekinumab in patients with postoperative Crohn's disease to investigate the impact on clinical outcomes. From 130 patients, the researchers found that in patients treated with infliximab with ≥3µg/mL and in patients treated with adalimumab ≥7.5µg/mL, "higher rates of deep remission existed," and similar differences were found for both clinical and objective remission. However, for ustekinumab, "clinical and objective remission were similar between patients regardless of drug concentration." These conclusions demonstrated that "established anti-tumor necrosis factor concentrations" could inform the rationale behind clinical improvement for certain patients that suffer from diseases that lack prior data to support the positive use of bDMARDs (Pan et al., 2022).

Guidelines and Recommendations

National Institute for Health and Clinical Excellence (NICE)

The 2016 Guidelines for therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease stated that "enzyme-linked immunosorbent assay (ELISA) kits show promise for therapeutic monitoring of TNF-alpha inhibitors in people with Crohn's disease but there is insufficient evidence to recommend their routine adoption" (NICE, 2016).

The NICE also states that use of ELISA tests should be a part of research and/or data collection and that more research is needed to determine the clinical effectiveness of ELISA tests for therapeutic monitoring of TNF-alpha inhibitors for rheumatoid arthritis. “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. The ELISA tests covered by this guidance are Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and tests used by Sanquin Diagnostic Services” (NICE, 2019).

American Gastroenterological Association

The AGA published guidelines on Therapeutic Drug Monitoring in Inflammatory Bowel Disease recommending:

“In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence” (Feuerstein et al., 2017).

In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring (Feuerstein et al., 2017).

A technical report released by the AGA in the same year noted that for patients with quiescent IBD being treated with anti-TNF agents, the benefit of routine proactive TDM was “uncertain” compared to no monitoring. However, they observe a potential benefit for reactive TDM (Vande Casteele et al., 2017).

American College of Rheumatology and National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis

These guidelines do not mention monitoring of TNF inhibitors for antidrug antibodies or TNF inhibitor levels (Singh et al., 2019).

American College of Gastroenterology (ACG)

The ACG released an update regarding management of Crohn’s Disease (CD), stating that “if active CD is documented, then assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered” (Lichtenstein et al., 2018).

The ACG published guidelines on management of ulcerative colitis. In it, they observe that “the patient with nonresponse or loss of response to therapy should be assessed with therapeutic drug monitoring to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy.” However, they remark that there is “insufficient evidence” to support a benefit for proactive TDM in “all unselected patients with UC in remission” (Rubin et al., 2019).

Consensus Statement on Therapeutic Drug Monitoring of Biologic Agents for Patients With IBD

A consensus statement on appropriate therapeutic drug monitoring for IBD patients has been published. This statement was published in the journal of Clinical Gastroenterology and Hepatology, which is published by Elsevier on behalf of the AGA. A total of 28 statements were provided to a 13-member panel, and 24 of these statements reached a consensus. All statements were rated on a scale of one to ten, and statements were accepted if 80% or more of the participants agreed with a score ≥ seven. All 28 statements are shown below. Overall, “For anti-tumor necrosis factor (anti-TNF) therapies, proactive TDM was found to be appropriate after induction and at least once during maintenance therapy, but this was not the case for the other biologics. Reactive TDM was appropriate for all agents both for primary non-response and secondary loss of response. The panelists also agreed on several statements regarding TDM and appropriate drug and anti-drug antibody concentration thresholds for biologics in specific clinical scenarios” (Papamichael, Cheifetz, et al., 2019).

"**Table 4:** Scenarios of Applying Therapeutic Drug Monitoring of Biological Therapy in Patients with Inflammatory Bowel Disease

Anti-TNFs

1. It is appropriate to order drug/antibody concentration testing in responders at the end of induction for all anti-TNFs. 92 (12/13)
2. It is appropriate to order drug/antibody concentration testing at least once during maintenance for patients on all anti-TNFs. 100 (13/13)
3. It is appropriate to order drug/antibody concentration testing of anti-TNFs at the end of induction in primary non-responders. 100 (13/13)
4. It is appropriate to order drug/antibody concentration testing for all anti-TNFs in patients with confirmed secondary loss of response. 100 (13/13)

Vedolizumab

5. It is appropriate to order drug/antibody concentration testing for vedolizumab in responders at the end of induction. 15 (2/13)a
6. It is appropriate to order drug/antibody concentration testing at least once during maintenance for patients on vedolizumab. 46 (6/13)a
7. It is appropriate to order drug/antibody concentration testing for vedolizumab in non-responders at the end of induction. 92 (12/13)
8. It is appropriate to order drug/antibody concentration testing for vedolizumab in patients with confirmed secondary loss of response. 83 (10/12)

Ustekinumab

9. It is appropriate to order drug/antibody concentration testing for ustekinumab in responders at the end of induction. 39 (5/13)a
10. It is appropriate to order drug/antibody concentration testing at least once during maintenance for patients on ustekinumab. 31 (4/13)a
11. It is appropriate to order drug/antibody concentration testing for ustekinumab in non-responders at the end of induction (at 8 weeks). 92 (12/13)
12. It is appropriate to order drug/antibody concentration testing for ustekinumab in patients with confirmed secondary loss of response. 83 (10/12)" (Papamichael, Cheifetz, et al., 2019)

Table 5: Biological Drug Concentrations and Anti-Drug Antibodies When Applying Therapeutic Drug Monitoring in Inflammatory Bowel Disease

General

13. There is no difference in indication for ordering drug/antibody concentrations or interpretation of results for biosimilars or the originator drug. 100 (13/13)
14. The threshold drug concentration may vary depending on disease phenotype and desired therapeutic outcome. 100 (13/13)
15. In the presence of adequate trough drug concentrations, anti-drug antibodies are unlikely to be clinically relevant. 100 (12/12)
16. Other than for anti-infliximab antibodies, there are not enough data to recommend a threshold for high anti-drug antibody titers for the biologic drugs. 100 (12/12)

Infliximab

17. The current evidence suggests that the variability of infliximab concentrations between the different assays is unlikely to be clinically significant. 100 (13/13)a

18. There is insufficient evidence that inter-assay drug concentration results are comparable for biologic drugs other than for infliximab. 100 (13/13)
19. The minimal trough concentration for infliximab post-induction at week 14 should be greater than 3 μg/mL, and concentrations greater than 7 μg/mL are associated with an increased likelihood of mucosal healing. 100 (13/13)
20. During maintenance the minimal trough concentration for infliximab for patients in remission should be greater than 3 μg/mL. For patients with active disease, infliximab should generally not be abandoned unless drug concentrations are greater than 10 μg/mL. 92 (12/13)
21. In the absence of detectable infliximab, high titer anti-infliximab antibodies require a change of therapy. Low level antibodies can sometimes be overcome. For the ANSER assay, a high titer anti-infliximab antibody at trough is defined as 10 U/mL, for RIDAscreen the cutoff is 200 ng/mL, and for InformTx/Lisa Tracker the cutoff is 200 ng/mL. For other assays, there are insufficient data to define an adequate cutoff for a high titer anti-infliximab antibody. 100 (13/13)

Adalimumab

22. The minimum drug concentration at week 4 for adalimumab should at least be 5 μg/mL. Drug concentrations greater than 7 μg/ml are associated with an increased likelihood of mucosal healing. 83 (10/12)a
23. During maintenance the minimum trough concentration for adalimumab for patients in remission should be greater than 5 μg/mL. For patients with active disease, adalimumab should generally not be abandoned unless drug concentrations are greater than 10 μg/mL. 100 (12/12)

Certolizumab pegol

24. The minimum concentrations for certolizumab pegol at week 6 should be greater than 32 μg/mL. 100 (12/12)
25. During maintenance the minimum trough concentration for certolizumab pegol for patients in remission should be 15 μg/mL. 92 (11/12)

Golimumab

26. The minimum drug concentration at week 6 for golimumab should at least be 2.5 μg/mL. 92 (11/12)
27. During maintenance the minimum trough concentration for golimumab for patients in remission should be greater than 1 μg/mL. 92 (11/12)

Vedolizumab/ustekinumab

28. Although there are emerging data that may show an association between drug concentrations and outcomes, they are not sufficient to guide specific induction and maintenance drug concentrations for vedolizumab and ustekinumab other than confirming that there is detectable drug. 100 (12/12)" (Papamichael, Cheifetz, et al., 2019)

Consensus Statement Regarding the Clinical Utility of TDM for Biologics in Inflammatory Bowel Disease (IBD).

A comprehensive literature review was performed regarding "TDM of biologic therapies in IBD and 45 statements were subsequently formulated on the potential application of TDM in IBD. The statements, along with literature, were then presented to a panel of 10 gastroenterologists with expertise in IBD and TDM who anonymously rated them on a scale of 1 to 10 (1=strongly disagree and 10=strongly agree)" (Cheifetz et al., 2021).

Table 1.

Statements regarding reactive therapeutic drug monitoring of biologics

Statement	Vote agreement, %	Strength of recommendation
1. Reactive TDM should be performed in patients with confirmed primary non-response to anti-TNF therapy.	100	9.7
2. Reactive TDM should be performed in patients with confirmed secondary loss of response to anti-TNF therapy.	100	9.8
3. Reactive TDM has been proven more cost-effective than empiric anti-TNF therapy optimization.	100	8.6
4. When performing reactive TDM for secondary loss of response to infliximab, treatment discontinuation should not be considered until a drug concentration of at least 10-15µg/ml is achieved.	90	8.5
5. When performing reactive TDM for secondary loss of response to adalimumab, treatment discontinuation should not be considered until a drug concentration of at least 10-15µg/ml is achieved.	90	8.3
6. Reactive TDM should be performed in patients with confirmed primary non-response to vedolizumab prior to switching therapy.	100	8.3
7. Reactive TDM should be performed in patients with confirmed primary non-response to ustekinumab prior to switching therapy.	90	7.4
8. Reactive TDM should be performed in patients with confirmed secondary loss of response to vedolizumab.	100	8.9
9. Reactive TDM should be performed in patients with confirmed secondary loss of response to ustekinumab.	90	8.5

Table 2.

Statements regarding proactive therapeutic drug monitoring of biologics.

Statement	Vote agreement, %	Strength of recommendation
10. Proactive TDM should be performed post induction for patients treated with anti-TNF therapy.	90	9
11. Proactive TDM should be performed at least once during maintenance therapy for patients treated with anti-TNF therapy.	90	8.8
12. Proactive TDM should be utilized after reactive TDM of anti-TNF therapy.	80	8.1
13. Proactive TDM is most important in more severely active patients and in patients who have higher drug clearance.	90	8.5
14. When infliximab de-escalation (dose reduction) is considered in patients in remission, proactive TDM both prior to and after de-escalation should be performed.	100	9.2

Statement	Vote agreement, %	Strength of recommendation
15. Proactive TDM for optimizing anti-TNF monotherapy is better than unoptimized anti-TNF monotherapy.	100	9
16. Proactive TDM for optimizing anti-TNF monotherapy in select patients is an alternative to combination anti-TNF therapy with an immunomodulator.	90	8.5
17. More data are needed to support the use of proactive TDM for biologics other than anti-TNF therapies.	100	9.2

Table 3.

General statements regarding therapeutic drug monitoring of biologics.

Statement	Vote agreement, %	Strength of recommendation
18. There is clinical utility for TDM to be performed in patients treated with anti-TNF therapy during induction.	80	8
19. Increased anti-TNF clearance is associated with anti-drug antibodies, male gender, low albumin, high baseline CRP and high BMI.	90	9.2
20. TDM (drug concentration and antibodies to infliximab) should be performed following a drug holiday in patients treated with infliximab prior to second dose after re-starting.	100	9
21. Patients should be followed over time with the same TDM assay, if possible, until commercial assays are accurately cross-validated and standardized.	80	8.1
22. There are no differences in performing and interpreting the results of TDM between biosimilars and originator biologic drugs.	100	9.4

Table 4.

Statements regarding immunogenicity of biologics.

Statement	Vote agreement, %	Strength of recommendation
23. Anti-drug antibodies are more clinically relevant when trough drug concentrations are undetectable.	90	9.1
24. Patients with secondary loss of response to anti-TNF therapy due to the development of high-titer anti-drug antibodies should not be dose-escalated, but instead should be switched to a different therapy (within-class or out of class).	100	9.4

Statement	Vote agreement, %	Strength of recommendation
25. When considering switching within drug class in case of secondary loss of response to a first anti-TNF drug due to the development of anti-drug antibodies, an immunomodulator should be added to a subsequent anti-TNF therapy.	90	8.5
26. All commercially available assays are appropriate to use for TDM, however, for antibody measurement, beyond the homogeneous mobility shift assay there are not sufficient data to support specific clinically relevant cut-offs to define high-titer antibodies.	100	8.3
27. Low-titer antibodies to infliximab can be defined as <10 U/ml for the homogeneous mobility shift assay.	90	8.1
28. Low titer anti-drug antibodies can be overcome by treatment optimization (dose escalation, dose interval shortening and/or addition of an immunomodulator).	100	8.4
29. The formation of antibodies to infliximab or adalimumab can be reduced by the use of immunomodulators.	100	9.1
30. HLA-DQA1*05 is associated increased risk of development of antibodies to infliximab and adalimumab.	100	9.3
31. Vedolizumab is associated with less immunogenicity than anti-TNFs.	100	9.2
32. Ustekinumab is associated with less immunogenicity than anti-TNFs.	100	9.9

Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
80145	Adalimumab
80230	Infliximab
80280	Vedolizumab
80299	Quantitation of therapeutic drug, not elsewhere specified

82397	Chemiluminescent assay
84999	Unlisted chemistry procedure
0514U	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 (µg/mL) Proprietary test: Procise ADL™ Lab/Manufacturer: ProciseDx Inc
0515U	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 (µg/mL) Proprietary test: Procise IFXT™ Lab/Manufacturer: ProciseDx Inc

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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Revision History

Effective Date	Summary
01/01/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: CC1 and 2 combined and edited for clarity on frequency of allowed TDM based on guideline recommendations and drug dosing information. CC1 now reads: "1) For individuals with inflammatory bowel disease (IBD), drug and/or antibody concentration testing once every two weeks for anti-tumor necrosis factor (anti-TNF) therapies, vedolizumab therapy, or ustekinumab therapy MEETS COVERAGE CRITERIA." Added CPT code 0514U, 0515U (effective date 10/1/2024)
12/01/2023	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review

	did not necessitate any modifications to coverage criteria. The following edits were made for clarity: All CC edited for clarity and consistency
06/01/2022	Initial Policy Implementation

EXCLUSIONS:
Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at https://www.geisinger.org/health-plan/providers/ghp-clinical-policies