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Corporate Medical Policy

Immunopharmacologic Monitoring of Therapeutic Serum Antibodies AHS - G2105

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Description of Procedure or Service

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

Targeted inhibitors of tumor necrosis factor-alpha (TNF), including, but not limited to, infliximab, adalimumab, etanercept, and golimumab, are widely used in the treatment of a number of inflammatory conditions, including rheumatoid arthritis (RA), spondyloarthritis, inflammatory bowel disease, and psoriasis (Bendtzen, 2019a).

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for immunopharmacologic monitoring of therapeutic serum antibodies and therapeutic drug levels when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When immunopharmacologic monitoring of therapeutic serum antibodies and therapeutic drug levels is covered

1. Reimbursement is allowed for drug and/or antibody concentration testing for anti-tumor necrosis factor (anti-TNF) therapies in patients with inflammatory bowel disease 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. In patients with confirmed secondary loss of response

2. Reimbursement is allowed for drug and/or antibody concentration testing for vedolizumab or ustekinumab therapies in patients with inflammatory bowel disease in the following situations:

    a. In non-responders at the end of induction
    b. In patients with confirmed secondary loss of response

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When immunopharmacologic monitoring of therapeutic serum antibodies and therapeutic drug levels is not covered

Reimbursement is not allowed for the measurement of the serum drug levels and/or measurement of the antibodies to the following drugs for any other reason, either alone or in a combination test, in an outpatient setting.

a. adalimumab
b. certolizumab
c. etanercept
d. golimumab
e. infliximab
f. infliximab-dyyb
g. infliximab-abda
h. rituximab
i. ustekinumab
j. vedolizumab

Policy Guidelines

Background

Tumor necrosis factor (TNF) inhibitors competitively inhibit the binding of TNF to its receptors to reduce inflammation and stop disease progression (Lis, Kuzawińska, & Bałkowiec-Iskra, 2014). They are used for treatment of inflammatory conditions, such as rheumatoid arthritis (RA), psoriatic arthritis, juvenile arthritis, inflammatory bowel disease (Crohn's and ulcerative colitis), and ankylosing spondylitis (Bendtzen, 2019b; 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, which may hinder treatment and cause other adverse effects, such as allergic reactions (Bendtzen, 2017).

Therapeutic drug monitoring (TDM) of both these drugs and anti-drug antibodies has been proposed to optimize dosing of TNF inhibitors. This monitoring is thought to help clinicians manage drug regimens for these patients, such as changing the dose or changing the drug entirely. Identifying the presence and concentration of both these drugs and auto-drug antibodies may help avoid nonresponse to treatment. Most assays for assessment of serum antibodies will also report the drug concentration (MacDermott, 2018). For example, InformTx offers assays for eight biologic agents (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, golimumab, infliximab-dyyb, and infliximab-abda), and is intended to allow providers to monitor, manage response, and optimize dose (InformTx, 2019). Prometheus Anser also offers a series of assays for assessment of these antibodies. Prometheus has assessments for four biologics (adalimumab, infliximab, ustekinumab, and vedolizumab), which also measure the levels of antibodies against the drug in question (Anser, 2019). LabCorp offers assays for 10 biologics encompassed in one portfolio called "DoseASSURE." These biologics include adalimumab, infliximab, infliximab-dyyb, infliximab-abda, etanercept, rituximab, golimumab, vedolizumab, ustekinumab, and certolizumab (LabCorp, 2019).

Clinical Validity and Utility

S. L. Wang et al. (2012) developed and validated a non-radiolabeled homogeneous mobility shift assay (HMSA) to measure the antibodies-to-infliximab (ATI) and infliximab levels in serum samples. The assay was validated for both items, and the sample was compared to the traditional ELISA. Intra- and interassay precision rates for the ATI- and infliximab-HMSA were less than 4% and less than 15%, respectively, and less than 6% and less than 15%, respectively. 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.

S. L. 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 2 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, 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 (S. L. 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 enzyme-linked immunosorbent assay (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, "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 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 with 82 patients with inflammatory bowel disease (IBD) having a disease flare while being on ADA 40 mg every 2 weeks. All patients were primary responders to ADA therapy and were anti-tumor necrosis factor (TNF) naive. 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 infliximab (IFX) therapeutic drug monitoring (TDM) allows for objective decision making in patients with inflammatory bowel disease (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: group 1, low IFX/high ADA; group 2, low IFX/low ADA; group 3, therapeutic IFX, and changes in management were examined due to groupings. Of the 71 patients, 37% underwent an "appropriate" change in therapy based on group. The authors concluded, "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, Mohammed, and Berg (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, "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, Corbett, and Moss (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 standardised 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)."

Y. Wang, Turner, Bedeir, Patel, and Gulizia (2018) submitted an abstract to the 2018 Therapeutic Drug Management and Toxicology Division Abstract Competition conducted by the American Association for Clinical Chemistry (AACC) on July 30, 2018. This abstract focused on InformTx's assays for TDM, and the authors reviewed TDM results for six biologics: adalimumab (ADA), certolizumab (CER), golimumab (GOL), infliximab (INF), ustekinumab (UST), and vedolizumab (VED). A total of 18837 sera samples were analyzed with InformTx's assays, and patient responses were predicted based on drug and anti-drug antibody status (ADAbs). The need for drug optimization were 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 (Y. 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 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 6 months, at the time of a flare, then dosed IFX appropriately. The reactive strategy measured 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 5). 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 or 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.

State and Federal Regulations, as applicable
A search for "tumor necrosis factor" on the FDA website on 07/27/2020, yielded zero results. Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements
National Institute for Health and Clinical Excellence (NICE) (NICE, 2016; Singh et al., 2019)
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 tumor necrosis factor (TNF)-alpha inhibitors in people with Crohn's disease but there is insufficient evidence to recommend their routine adoption" (NICE, 2016).

NICE also states that use of ELISA tests should be used as 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 (AGA) (Vande Casteele, Herfarth, Katz, Falck-Ytter, & Singh, 2017)
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, Nguyen, Kupfer, Falck-Ytter, & Singh, 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 (Singh et al., 2019)
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) (Lichtenstein et al., 2018; Rubin, Ananthakrishnan, Siegel, Sauer, & Long, 2019)
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 (Papamichael, Cheifetz, et al., 2019)

A consensus statement has been published on appropriate therapeutic drug monitoring for IBD patients. 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 1-10, and statements were accepted if 80% or more of the participants agreed with a score ≥7. 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 panellists also agreed on several statements regarding TDM and appropriate drug and anti-drug antibody (ADA) 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)

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)"

International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) (Capiau et al., 2019)

The IATDMCT have published guidelines to validate the use of dried blood spots (DBS) for the quantitative determination of small molecule drugs using chromatographic methods. This guideline is not focused on serum antibody testing methods, and do not mention monitoring of TNF inhibitors for antidrug antibodies or TNF inhibitor levels.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes:80145, 80230, 80280, 80299, 82397, 84999

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 2/2020

Policy Implementation/Update Information

1/1/19	New policy developed. Immunopharmacologic Monitoring of Infliximab, Adalimumab and other Therapeutic Serum Antibodies is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)
10/1/19	Policy statement revised to read: Reimbursement is not allowed for immunopharmacologic monitoring of Infliximab, Adalimumab and other therapeutic serum antibodies. Wording revised in the Not Covered section. "Investigational" changed to read "Reimbursement is not allowed…" Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)
12/10/19	Policy title changed from "Immunopharmacologic Monitoring of Infliximab, Adalimumab and other Therapeutic Serum Antibodies" to "Immunopharmacologic Monitoring of Therapeutic Serum Antibodies". Avalon Q3 CAB Update. Coding section updated to reflect new codes for 2020. When not covered section reworded for clarity to include both serum antibodies or serum drug levels either alone or in combination with listed drugs. (eel)
12/31/19	Entry date on previous update note corrected from 10/1/19 to 12/10/19. (eel)
3/10/20	Specialty Matched Consultant Advisory Panel review 2/19/2020. No change to policy statement. (eel)
5/26/20	Language under When not covered section updated from reimbursement to investigational for adalimumab, infliximab, infliximab-dyyb, infliximab-abda, and vedolizumab. Policy statement clarified as "Immunopharmacologic monitoring of Infliximab, Adalimumab and other therapeutic serum antibodies is not covered for any indication." 80299 added to Coding section. (eel)
6/9/20	Clarified language in change log entry dated 5/26/20. 80187 removed from Coding section. (eel)
11/10/20	Reviewed by Avalon 3rd Quarter 2020 CAB. Background, policy guidelines, and references updated. Related policies section added. Added items 1 and 2 under When Covered. Updated When Not Covered item 1: added reimbursement language and "for any other reason", removed "are investigational", consolidated list of drugs, and removed item 2. CPT codes 80235 and 80285 removed, CPT code 82397 added in the Billing/Coding section. Medical Director review 10/2020. (bb)
3/9/21	Added therapeutic drug levels to Policy statement for clarification. Specialty Matched Consultant Advisory Panel review 2/16/2021. No change to policy statement. (bb)