Measurement of Antibodies to Immunosuppressive Therapies for Inflammatory Bowel Disease

MEDICAL POLICY NUMBER: 237

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as "Company" and collectively as "Companies").

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

I. The measurement of antibody serum levels to infliximab, adalimumab, ustekinumab or vedolizumab, performed individually or as part of a panel, which includes the measurement of serum biologic levels (e.g., Prometheus Anser-IFX, -ADA, UST, or -VDZ, Prometheus PredictrPK), is considered **not medically necessary**.

Link to Evidence Summary

POLICY CROSS REFERENCES

- Inflammatory Bowel Disease: Serologic Testing and Therapeutic Monitoring, MP218

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Inflammatory Bowel Disease

According to Hayes, "(i)nflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal (GI) tract that can be painful, debilitating, and, sometimes, life-threatening. IBD consists

of two major forms—ulcerative colitis (UC) and Crohn's disease (CD)."[1] UC involves inflammation of the large intestine (colon and rectum), which causes ulcers. CD causes inflammation and subsequent selling and irritation to any part of the GI tract from the mouth to the anus. This swelling disrupts normal GI function, which causes diarrhea, abdominal discomfort, bleeding, pus formation, fever, and anemia. Severe cases can lead to weight loss, nutritional deficiencies, and growth failure (in children). Furthermore, both diseases have also been associated with an increased risk for colorectal cancer. "Since there is no cure for UC or CD, treatment is aimed at reducing symptoms or repairing intestinal complications."[1]

Antibodies to Infliximab, Adalimumab, Ustekinumab and Vedolizumab

Infliximab, adalimumab, ustekinumab, and vedolizumab are monoclonal antibodies indicated for patients with moderately to severely active UC or CD and inadequate response to conventional therapies. According to Hayes, patients who initially respond to these therapies often lose response over time.[2] This is of clinical concern as these drugs are often a last resort treatment. It has been purported that patients treated with these agents may develop antibodies to the drugs which neutralize the anti-inflammatory action of the agent. According to Hayes, "the presence of detectable serum antibodies does not necessarily imply interference with clinical efficacy." [2] Furthermore, there are no standardized methods for evaluating concentrations of antibodies in the serum. "Loss of response to infliximab is typically managed with dose escalation, shorter intervals between infusions, addition of immunosuppressants, switching to another anti-TNF-α agent, or switching to a targeted agent of a different class."[2]

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of antibody levels to infliximab, adalimumab, and vedolizumab to monitor treatment in patients with inflammatory bowel disease. Below is a summary of the available evidence identified through July 2024.

Systematic Reviews

- In 2018, ECRI published an evaluation of the Anser UST assay for guiding treatment with ustekinumab for inflammatory bowel disease.[3] The authors identified a single conference abstract of a study with 59 participants, reporting that Anser UST identified positive therapy responses (as assessed with endoscopy) to ustekinumab therapy with moderate accuracy (72.2% sensitivity, 83.3% specificity, area under receiver operating curve 0.782) using a 4.5 µg/mL serum ustekinumab level threshold in patients with Crohn's disease. No other literature were identified.

- In 2018, ECRI conducted an evidence review evaluating the efficacy of Anser IFX Assay for guiding treatment with infliximab for the treatment of inflammatory bowel disease (IBD).[4] Investigators searched the literature through October 2018 and included 4 studies for review (1 systematic review; 2 retrospective diagnostic cohort studies; and 1 case series). Sample sizes across studies ranged from 22 to 482. While cohort studies and case series reported positive findings, the systematic review concluded that tests had a diagnostic inaccuracy rate of 20-30%.

Study limitations included the poor quality of the four studies assessed in the systematic review, and the retrospective designs and small sample sizes of the three individual studies. Moreover, no study compared clinical outcomes in patients receiving Anser IFX TDM, with alternative TDM methods, or with empirical therapy optimization. ECRI concluded that evidence was insufficient to establish efficacy, stating that studies provided only low-quality data on Anser IFX's clinical validity and clinical utility. Investigators called for large, multicenter cohort studies to validate the assay's clinical validity, and for additional controlled trials to compare outcomes of patients with IBD managed with and without Anser IFX monitoring to assess clinical utility.

- In 2018, ECRI conducted an evidence review evaluating the efficacy of Anser VDZ Assay for guiding treatment with vedolizumab for the treatment of inflammatory bowel disease (IBD). Searching the literature through September 2018, investigators identified no studies that reported data on outcomes directly relevant to Anser VDZ's diagnostic accuracy (e.g. sensitivity, specificity) or clinical impact (e.g. remission rates, treatment changes) in patients receiving therapeutic drug monitoring with Anser VDZ.[5]

- In 2015 (updated 2017; archived 2019), Hayes conducted an evidence review evaluating the use of anti-infliximab antibody levels to monitor infliximab treatment in patients with inflammatory bowel disease (IBD).[2] The evidence review identified 13 clinical studies, including 1 randomized controlled trial (RCT), 1 sub-study of an RCT, 5 prospective cohort studies, 4 retrospective cohort studies, and 2 retrospective cross-sectional studies. The sample sizes ranged from 69 to 573 patients and follow-up times varied from 12 weeks to 48 months. Of the selected studies, 11 were determined to be of poor quality and 2 were very poor quality. The outcome of interest was the concentration, titers, or presence of antibodies measured using enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or homogeneous mobility shit assay (HMSA).

  Overall, there was insufficient evidence to support a conclusion as to whether or not the assessment of antibodies is needed to guide treatment of patients with inflammatory bowel disease. Of the 13 selected studies, only 1 RCT (poor-quality) was designed to determine whether or not knowledge of antibodies to these drugs was helpful in guiding patient management. This RCT found no significant differences between antibody testing and dose intensification for IBD management. The included studies had significant differences in design, patient populations, dosing schedules, endpoints, duration of follow-up, and analytical techniques.

  Due to the limited and conflicting body of evidence, Hayes gave a D2 rating (insufficient evidence) for the use of anti-infliximab antibody (ATI) levels to monitor infliximab treatment in patients with inflammatory bowel disease (IBD). Hayes concluded, "additional evidence is needed to determine whether the presence (or absence) of antibodies can be used to guide and optimize therapy in an individual patient. Ideally, a larger RCT with a longer duration of follow-up would be needed to evaluate clinical outcomes in patients with IBD who are managed using antibodies to guide treatment decisions."[2]

- In 2023, Hayes published a health technology assessment on the use of anti-infliximab antibody (ATI) levels to monitor Infliximab treatment in patients with Crohn Disease.[6] The report included 3 randomized controlled trials (RCTs), 3 prospective cohort studies,

4 retrospective cohort studies, 1 prospective trial with historical controls, and 1 retrospective registry analysis that evaluated ATI testing for patients with CD. Hayes found a very low-quality body of evidence evaluated ATI testing clinical validity (diagnosis or prognosis of response to IFX therapy) or clinical utility (capacity to guide management of IFX therapy and improve health outcomes). The overall very low-quality rating for the body of evidence reflects individual study limitations and inconsistency in study findings. The 6 studies evaluating clinical validity of ATI testing are split between assessment of diagnostic versus prognostic accuracy, definitions of CD response or remission were not consistent across studies, and none of the studies involved statistical analysis to determine whether ATI testing is more accurate than competing methods of detecting or predicting response to IFX treatment. The 6 studies that evaluated clinical utility of ATI testing used divergent protocols for responding to differing ATI levels, varying comparator strategies for management of treatment, and dissimilar definitions of CD response or remission. Further, use of ATI tests was subject to interference from serum IFX in some of the studies. Overall quality was determined based on the balance of benefits and harms and was assessed taking into consideration the quality of individual studies; the precision, directness, and consistency of data; and the applicability of data to general practice.

Hayes gave ATI for CD a D2 rating, concluding that "A very low-quality body of evidence evaluating ATI testing has not provided enough evidence to conclude that this technique has sufficient diagnostic or prognostic accuracy or capacity to improve management or health outcomes of patients undergoing IFX treatment for CD. Additional well-designed studies are needed to determine whether ATI testing increases accuracy for diagnosing or predicting response to IFX therapy and whether this testing can improve management of IFX therapy as well as health outcomes in patients with CD."[6]

Randomized Trials

A 2021 study by Syversen and colleagues reported results of a randomized, parallel-group, open-label trial of 411 adults with RA, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Chron's disease, or psoriasis who received either proactive therapeutic drug monitoring of infliximab therapy based on serum infliximab level and ADA testing, or standard therapy without serum infliximab level or ADA testing.[7] Serum trough infliximab levels and ADA levels were measured at each infusion in the therapeutic drug monitoring group. The infliximab dose or interval could be adjusted based on the therapeutic range during induction and during treatment. If ADA level was greater than 50 mcg/L at any point, therapy with infliximab was switched to a different agent. No significant difference between the therapeutic drug monitoring group and standard therapy group in clinical remission at week 30 was found (50.5% versus 53% of patients, respectively; p=0.78). During infliximab treatment, 36 (18%) patients in the therapeutic drug monitoring group and 34 (17%) in the standard therapy group developed ADAs ≥15 mcg/L. Antidrug antibodies ≥50 mcg/L (the threshold for discontinuation) occurred in 20 (10%) of patients in the therapeutic drug monitoring group and 30 (15%) in the standard therapy group. The remission rate in patients who developed ADAs was 56% in the therapeutic drug monitoring group and 35% in the standard therapy groups. The trial was limited by the small sample size of subjects who developed ADAs.

Nonrandomized Studies

- A 2020 observational study by Fernandes and colleagues investigated the effects of proactive infliximab drug monitoring versus conventional management in IBD.[8] There were 56 participants in the proactive therapeutic drug monitoring (TDM) group, which was prospectively assigned, while the conventional management group was a retrospective cohort of 149 participants. Both trough levels and antidrug antibodies were measured in the pTDM group. The pTDM group had higher rates of treatment escalation and also required less surgery than the control group. The authors concluded that proactive TDM is associated with fewer surgeries and higher rates of mucosal healing compared to conventional non TDM-based management. This study had a number of limitations, including a lack of randomization and blinding, small sample size, and the use of retrospective data as the comparison group, leading to high risk of bias.

- A 2019 retrospective observational study by Kamperidis and colleagues was published on the impact of therapeutic drug level monitoring (TDM) on outcomes of 291 patients with Crohn's disease treated with Infliximab (IFX).[9] Primary outcomes were clinicians' response to each TDM result and the rate of IFX discontinuation due to secondary loss of response or serious adverse event. Secondary outcomes included the intestinal surgery rate after IFX initiation and remission six months after TDM. Two hundred thirty-eight (81.8%) patients were tested for TDM at least once during their follow-up with 672 TDM results. 95/238 patients (39.9%) had undetectable levels and 76 (31.9%) had positive antibodies to infliximab (ATI) at least once. IFX was discontinued in 109 patients (37.5%). TDMs results were not followed by altered patient management in 526/672 (78.3%) of the observations. Treatment was discontinued in 40 (75.5%) patients never tested for TDM compared with 69 (29.0%) of those tested ($p<0.01$). Fewer TDM tested patients (29; 12.2%) required intestinal surgery post IFX initiation compared with those not TDM tested (15; 28.3%). In this retrospective study, data collected on clinical outcomes relied on record keeping and physician response was taken as the measure of clinical remission. These methods may be subject to interpretation bias.

A number of other observational studies evaluated the efficacy of measuring antibody levels (alone or in combination with drug levels) to infliximab, adalimumab, and/or vedolizumab to monitor treatment in patients with inflammatory bowel disease.[10-13] Studies reported mixed findings. In addition to the studies' non-randomized design, results were limited by studies' small sample sizes and lack of long-term follow-up.

CLINICAL PRACTICE GUIDELINES

American Gastroenterological Association (AGA)

In 2017, the AGA published guidelines on therapeutic drug monitoring in inflammatory bowel disease.[14] Investigators noted that "the reporting of anti-drug antibodies is variable between commercial assays, and [that] there is no standardized reporting of these values." The AGA guideline also states "Currently, there are many commercial assays available to test trough concentrations and antibodies. In general, measurement of trough concentrations, but not of anti-drug antibodies, is relatively comparable with acceptable specificity, accuracy, and reproducibility between assays."

American College of Gastroenterology (ACG)

The 2019 ACG evidence-based clinical practice guideline for ulcerative colitis states "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".[15] The guideline also states "there is insufficient evidence supporting a benefit for proactive therapeutic drug monitoring in all unselected patients with UC in remission". The guideline does not specifically discuss thiopurine metabolites.

The 2018 ACG evidence-based clinical practice guideline for Crohn's Disease in adults states "A detailed critical examination of the role of therapeutic drug monitoring was beyond the scope of this guideline. If active CD is documented, then assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered."[16]

EVIDENCE SUMMARY

There is insufficient evidence to conclude measurement of antibody serum levels to infliximab, adalimumab, ustekinumab and vedolizumab is efficacious for management of patients with inflammatory bowel disease (IBD). Further studies of good methodological quality are required to determine if this testing aids in treatment decisions and improves patient outcomes. While some clinical practice guideline gives a conditional recommendation (very low-quality evidence) on reactive therapeutic drug monitoring to guide treatment changes, they are not supported by clinical utility evidence. Therefore measurement of antibody serum levels for IBD is considered not medically necessary.

BILLING GUIDELINES AND CODING

CODES*		
CPT	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)
	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)
	80145	Adalimumab
	80230	Infliximab
	80280	Vedolizumab
	84999	Unlisted chemistry procedure

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.

- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
6/2023	Changed denial from investigational to not medically necessary.
10/2023	Annual update. Clarification of combination testing was added to criterion.
8/2024	Annual update. No changes to criteria.
10/2024	Q3 2024 code set update.