Inflammatory Bowel Disease: Measurement of Antibodies to Immunosuppressive Therapies

MEDICAL POLICY NUMBER: 237

Effective Date: 6/1/2023

Last Review Date: 3/2023

Next Annual Review: 8/2023

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, Providence Plan Partners, and Ayin Health Solutions 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 (e.g., Prometheus® Anser®-IFX, -ADA, UST, or -VDZ), 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 2022.

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]

Nonrandomized Studies

Three studies evaluated the efficacy of measuring antibody levels to infliximab, adalimumab, and/or vedolizumab to monitor treatment in patients with inflammatory bowel disease.[6-8] 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.[9] 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."

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".[10] 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.

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. One clinical practice guideline gives a conditional recommendation (very low-quality evidence) on reactive therapeutic drug monitoring to guide treatment changes. However, the American College of Gastroenterology (ACG) does not recommend the use of antibody testing for IBD, and state that the low sensitivity of testing limit the usefulness of it as a diagnostic tool.

BILLING GUIDELINES AND CODING

CODES*		
CPT	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.

REFERENCES

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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.