

MEDICAL POLICY		Inflammatory Bowel Disease: Measurement of Antibodies to Immunosuppressive Therapies	
Effective Date: 10/1/2020		Section: LAB	Policy No: 403
 <div style="text-align: right;">10/1/2020</div>		Medical Policy Committee Approved Date: 12/17; 12/18; 5/19; 4/19; 08/2020	
		<div style="display: flex; justify-content: space-between;"> Medical Officer Date </div>	

See Policy CPT CODE section below for any prior authorization requirements

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”).

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid 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.

POLICY CRITERIA

I. The measurement of serum levels and antibodies to infliximab, adalimumab, ustekinumab or vedolizumab, performed individually or as part of a panel (i.e., Prometheus® Anser®-IFX, -ADA, UST, or -VDZ), is considered **investigational and is not covered**.

Link to [Policy Summary](#)

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CPT CODES

All Lines of Business	
Not Covered	
80145	Adalimumab
80230	Infliximab
80280	Vedolizumab
Unlisted Codes	
All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be denied as Not Covered .	
80299	Quantitation of therapeutic drug, not elsewhere specified
84999	Unlisted chemistry procedure

DESCRIPTION

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 swelling 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

REVIEW OF EVIDENCE

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 June 2020.

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 shift 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 2017 (archived 2019), Hayes conducted a systematic review evaluating the efficacy of Anser ADA for monitoring adalimumab treatment of inflammatory bowel disease.⁶ Investigators searched the literature through December 2017 and ultimately included 6 abstracts for review (1 prospective comparative study; 3 prospective uncontrolled studies; 1 validation study; and 1 technical review. Sample sizes ranged from 23 to 5509. Hayes concluded that published evidence was insufficient to assess the safety and/or impact on health outcomes or patient management for the use of Anser ADA for monitoring adalimumab treatment in patients with IBD.

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.⁷⁻⁹ 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.¹⁰ Investigators noted that “the reporting of anti-drug antibodies is variable between commercial assays, and [that] there is no standardized reporting of these values.”

CENTERS FOR MEDICARE & MEDICAID

As of July 2020, no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses the measurement serum drug levels or measurement of antibodies to immunosuppressive therapies for inflammatory bowel disease.

POLICY SUMMARY

There is insufficient evidence to conclude measurement of serum levels and antibodies 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 guidelines conditionally recommends reactive therapeutic drug monitoring, despite acknowledging the low-quality of evidence supporting efficacy and the variability of reporting between commercial assays.

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 Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

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.

REGULATORY STATUS

Mental Health Parity Statement

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.

MEDICAL POLICY CROSS REFERENCES

- Inflammatory Bowel Disease: Serologic Testing and Therapeutic Monitoring
- Celiac Disease: Serologic Testing

REFERENCES

1. Hayes Inc. *Serological Assays for the Diagnosis and Management of Inflammatory Bowel Disease: Ulcerative Colitis*. 2013 (updated 2017; archived 2018).
2. Hayes Inc. *Use of Anti-Infliximab Antibody Levels to Monitor Infliximab Treatment in Patients with Inflammatory Bowel Disease (IBD)*. 2015 (updated 2017; archived 2019).
3. ECRI Institute, Anser UST Assay (Prometheus Laboratories, Inc.) for Guiding Treatment with Ustekinumab for Inflammatory Bowel Disease. 2018.
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4. ECRI Institute, Anser IFX Assay (Prometheus Laboratories, Inc.) for Guiding Treatment with Infliximab for Inflammatory Bowel Disease. 2018.
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5. ECRI Institute, Anser VDZ Assay (Prometheus Laboratories, Inc.) for Guiding Treatment with Vedolizumab for Inflammatory Bowel Disease. 2018.
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7. Juncadella A, Papamichael K, Vaughn BP, Cheifetz AS. Maintenance adalimumab concentrations are associated with biochemical, endoscopic, and histologic remission in inflammatory bowel disease. *Digestive diseases and sciences*. 2018;63(11):3067-3073.
8. Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. Therapeutic Drug Monitoring to Guide Infliximab Dose Adjustment is Associated with Better Endoscopic Outcomes than Clinical Decision Making Alone in Active Inflammatory Bowel Disease. *Inflammatory bowel diseases*. 2017;23(7):1202-1209.
9. Koga A, Matsui T, Takatsu N, et al. Trough level of infliximab is useful for assessing mucosal healing in Crohn's disease: a prospective cohort study. *Intestinal research*. 2018;16(2):223.
10. Feuerstein J, Nguyen G, Kupfer S, Falck-Ytter Y, Singh S. American gastroenterological association institute clinical guidelines committee. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in inflammatory bowel disease. *Gastroenterology*. 2017;153(3):827-834.