KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Prometheus Lab Testing

- Anser ™ ADA for Adalimumab (Humira) Antibodies
- Anser TM IFX test for Infliximab (Remicade) Antibodies
- Anser VDZ (Vedolizumab)
- IBD SGI Diagnostic Test

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	MolDX: Prometheus IBD sgi Diagnostic Policy (L37313) This service is not covered per Noridian LCD.
Local Coverage Article	Billing and Coding: MolDX: Prometheus IBD sgi Diagnostic Policy (A57517)
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance specific to Anser antibody levels for infliximab or adalimumab, Kaiser Permanente has chosen to use their own Clinical Review Criteria, “Prometheus Testing,” for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Service	Criteria
Anser antibody levels for infliximab or adalimumab	Anser antibody levels for infliximab or adalimumab can be approved under **ALL of the following** conditions: 1. Ordered by a gastroenterologist 2. Is being ordered as a consideration of changing to alternate therapy in the setting of a concern for loss of response
Homogenous Mobility Shift Assay (HMSA) Anser VDZ (Vedolizumab) Prometheus IBD sgi Diagnostic Test	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage

Background

Many chronic inflammatory diseases are mediated by up-regulation of the pro-inflammatory cytokine tumor necrosis factor-alpha ((TNF)-α. Protein-based drugs that block TNF-α such as Infliximab (IFX), are effective in

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reducing the disease activity of these inflammatory disorders. IFX is a chimeric mouse-human monoclonal antibody approved by the FDA for the treatment of patients with Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and chronic severe plaque psoriasis. IFX is highly effective in inducing and maintaining remission in a large proportion of these patients. However, more than 30% of cases fail to respond to anti-TNF-α therapy, and 20-60% of those who initially respond, lose their clinical response over time despite maintenance treatment. This loss of response (LOR) usually requires escalation of the dose, shortening the interval between doses, change in the anti-TNF agent to regain the clinical remission, or switching to a non-anti-TNF therapy (Wang 2012, Nanda 2013, Wang 2013, FDA web page accessed August 26, 2013).

The reason for loss of response to IFX is still debatable, but the anti-drug antibody formation is believed to play an important role. IFX is a chimeric mouse/human IgG1 molecule and thus the antibodies are primarily directed against the murine fragment. Antibodies to IFX (ATI), also frequently called human antichimeric antibodies (HACAs), are reported to develop in up to approximately 60% of patients depending on the dosing schedule, administration of concurrent steroids or immunomodulators, and the method of measuring the antibodies in the blood. The antibodies can appear as soon as after the first IFX dose and can persist in the blood for up to 4.5 years even after discontinuation of the therapy. ATI may increase the drug clearance in treated patients and/or neutralize its effect. Researchers found that a lower serum IFX levels is associated with a significantly higher risk of loss of clinical response to the drug. This loss of clinical response and remission due to immunogenicity is a potential major limitation to IFX leading to clinical relapse, impaired quality of life, and increased cost of care. Anti-drug antibodies may also cause serum sickness and hypersensitivity reactions. Despite these observed associations, some researchers dispute the clinical relevance of anti-infliximab antibodies and question whether the presence of antibodies to TNF agents is directly correlated to the decreased efficacy. To date, there is insufficient knowledge about the factors influencing the formation of the antibodies, and on whether the immune reaction to IFX can be transient. It is assumed however, that once the antibody is initiated, it cannot be overcome (Afif 2010, Kopylov 2012, Vande Casteele 2013, Nanda 2013, Wang 2013).

It is suggested that accurate monitoring of the serum drug and anti-drug antibody levels should be an important part of therapy in patients receiving anti TNF-α drugs. However, there is no gold standard technique or test for the detection and quantitative measurement of anti-infliximab antibodies (ATI). Anti-drug antibodies and drug levels in the serum are assessed by the bridging ELISA method, or less commonly by the radioimmunoassay (RIA) method. Each of these two methods has its limitations; the main limitation of the bridge ELISA method is its inability to accurately detect the antibodies in the presence of the drug in the circulation due to cross interference between the drug and the assay. This lowers the sensitivity of the test in detecting antibodies in the presence of IFX. Thus, ELISA can accurately measure the anti-drug antibodies only when there is no drug in the circulation, which limits its clinical utility. RIA method is limited by its complexity, safety concerns of handling radioactive material, and prolonged time needed to reach equilibrium for proper management (Wang 2012).

A novel Homogenous Mobility Shift Assay (HMSA) was recently developed and validated by group of researchers In San Diego (Wang and colleagues 2012) to quantitatively measure the induced ATI and IFX levels in serum samples of patients treated with infliximab. The Anser ™IFX test is not ELISA-based and is believed to be able to measure both the serum concentrations of infliximab and infliximab antibodies in the presence of serum infliximab. In the HMSA, serum samples are acidified during sample preparation to dissociate drug-anti-drug-antibody (IFX-ATI) complexes, thereby allowing the detection of ATI in the presence of IFX and overcoming the limitation of bridge ELISA (Casteele 2013).

Medical Technology Assessment Committee (MTAC)

Homogenous Mobility Shift Assay (HMSA)

10/21/2013: MTAC REVIEW

Evidence Conclusion: ***Analytic validity*** There is insufficient evidence to determine the analytic validity of the existing tests for measuring the antibodies to IFX. There is no gold standard technique for anti-infliximab antibodies (ATI) measurement and comparing the technical performance and accuracy of ATI assays in detecting ATI in the presence of IFX may be problematic. As indicated in the introduction the ELISA and RIA have their limitations, and there are no standards available for comparison. Several confounding factors can influence the measurement of these antibodies, and in turn the accuracy and reproducibility of the test. ***Clinical validity*** The results of studies that examined the association between ATI and clinical efficacy of IFX are inconsistent. While some studies showed that detectable levels of ATI using different ELISA methods or RIA were correlated with low concentrations or undetectable trough levels of IFX and higher rates of loss of response to IFX treatment, others showed no significant effect of ATI on loss of response. Two published meta-analyses (Lee et al, 2012 and Nanda et al, 2013) had conflicting results. Both had their limitations and pooled the results of randomized trials together with observational studies. In these studies, ATI was measured at one time point which may not capture

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its possible fluctuating, transient, or latent occurrence; different methods and assays, mainly ELISA, were used to measure ATI with no standardization; patients were on different IFX regimes (episodic or maintenance); and immunosuppressants were used among some, but not all patients. Lee et al' (2012), meta-analysis pooled the results of 18 studies to determine the prevalence of ATI, its effect on perfusion reactions and on disease remission rates among IBD patients treated with infliximab. The analysis included 9 RCTs, 5 cohort studies, and 4 retrospective studies with a total of 3,326 patients. The pooled results showed that patients who tested positive for ATI (using ELISA) were at increased risk of infusion reactions (RR= 2.07 [95% CI, 1.61-2.67]), but with no significant difference in the rates of remission compared to those who tested negative for ATI (RR=0.90, 95% CI 0.79-1.02). On the other hand, the pooled results of the more recent meta-analysis (Nanda et al, 2013) of 13 studies involving 1,378 patients with IBD showed that the presence of ATI was associated with lower IFX serum levels and significantly higher risk of loss of clinical response (LOR) to IFX with a pooled risk ratio for LOR = 3.2 (2.0-4.9). The ATI was measured by different methods including double antigen ELISA, antihuman chain ELISA, immunochromatography-based ELISA, fluid-phase RIA, and western blot. The results of the meta-analysis, however, have to be interpreted with caution due to the high risk of bias in the studies included, significant heterogeneity between studies, publication bias, and combining the results of randomized studies together with of observational studies. In addition, there were differences between studies in the method of assessing ATI, IFX dosing regimens, immunosuppressants use, and assessment of clinical response. The Anser IFX (HMSA) Wang and colleagues (2012) developed and validated a homogenous mobility shift assay (HMSA) to measure the serum levels of infliximab (IFX) and antibodies to IFX (ATI). They compared the performance of the newly developed IFX-HMSA to bridge ELISA and measured the ATI levels with the new test in 100 patients with ELISA positive ATI and found a high correlation between the two methods. HMSA identified five false-positive samples from the bridging ELISA method. Intra-and inter-assay precision rates for ATI were <4% and <15% respectively which, are considered high. The cutoff point of the assay was determined using sera of 100 healthy subjects who were naïve to IFX. The mean values of ATI in patient serum samples were significantly higher than those in the drug naïve health controls (mean $\pm$SD=9.57+11.43, vs. 0.73 $\pm$ 0.29, p<0.0001). The area under the curve (AUC) was 0.986, the sensitivity was 95% (95% CI, 88.72-98.36%) The authors concluded that the HMSA-IFX method showed a high assay sensitivity, precision and accuracy. However, validation was performed by using bridging ELISA methodology which can only accurately measure the anti-drug antibodies when there is no drug in the circulation.

Clinical utility- In a retrospective study, Afif and colleagues (2010) evaluated the clinical utility of measuring Human Anti-Chimeric Antibody (HACA) concentration in patients with IBD treated with infliximab. They used recorded data for 155 patients treated in one center (from 2003-2008) who had ATI and IFX concentrations measured. Testing for IFX and ATI levels was performed by ELISA at the discretion of the treating physician with no systematic strategy and was not done for all patients receiving IFX. 72% of the initial tests were ordered by a single physician, and the assay(s) used were not defined. Indications for testing were mainly due to loss of response (49%), partial response (22%) and autoimmune or delayed hypersensitivity reaction (10%). There was no control or comparison group and according to the authors, the study population represented only a subset of the total population receiving IFX at the clinic, and the clinical response was abstracted through review of patients' charts using predefined clinical criteria. The use of validated instruments as Crohn's disease Activity Index, Harvey-Bradshaw Index and endoscopic improvement could not be obtained retrospectively. 47% of the patients were on immunosuppressives, and 43 patients (29%) had the dose or frequency of IFX increased before testing. 35 patients had positive ATI based on which, the dose was increased in 6 patients, and 12 were put on a different anti-TNF. The overall results suggest that change to another anti-TNF in these ATI positive patients was associated with a significantly higher complete or partial response than those who received a dose escalation (92% vs. 17%). The authors concluded that measurement of ATI and IFX concentrations had an impact on management and was clinically useful. These results have to be interpreted with caution due to the study design and its imitations. In addition, there was no control group to determine whether any change in management in the absence of ATI measurement would have a similar or different clinical outcome. It also to be noted that 29% of the patients had the dose or frequency of IFX increased before testing. A more recent study (Vande Casteele and colleagues, 2013), used the new HMSA to retrospectively measure 1,232 consecutive frozen serum samples of 90 patients with IBD treated in one center from 1999-2011. The HMSA confirmed ATI in 59% of the patients, this was transient (disappeared by time) in 28% and was sustained in 72% of the patients. All treatment decisions to optimize and to stop therapy were based on clinical grounds and C-reactive protein level without knowledge of infliximab trough levels (TLI) or ATI status. The results of the analysis show that 68% of the patients with sustained ATI needed to discontinue IFX treatment vs. 13% with transient ATI (RR 5.1, 95% CI, 1.4-19.0). The overall results suggest, but do not provide good evidence that ATI may be transient, and that optimizing the IFX dose in patients with low-level ATI may be useful. It also indicates that sustained ATI increases the risk of loss of response to IFX. Based on these results, the authors recommended measuring IFX trough levels at week 14 and at time of loss of treatment response, and only measure ATI at consecutive time points when the trough levels of IFX are undetectable or low. These results have to be interpreted with caution due to the nature of the study and

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its limitations. In conclusion there is insufficient evidence to determine analytic and clinical validity of HMSA in detecting ATI to IFX. There is also inconclusive evidence to determine that ATI measurement has a significant impact on management of patients treated with infliximab or significant effect on clinical outcomes.
Articles: The published literature on the validity and clinical utility of measuring the antibodies to infliximab (ATI) levels among patients treated with IFX agent is limited. The therapeutic effect of IFX and measuring of the drug and antibody levels were mainly studied for patients with inflammatory bowel disease (IBD). The search revealed one study on the development and validation of a HMSA test, two meta-analyses on the impact of anti-IFX among IBD patients, two observational retrospective studies on clinical utility of measuring the anti-chimeric antibody concentration (ACAC), as well two studies that compared different ELISA methods in their ability to detect ATI.The meta-analysis with more valid methodology, the validation study on the new Anser IFX (HMSA) test, and the larger observational study on the clinical utility of detecting ATI were selected for critical appraisal, Afif W, Loftus EV, Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2010; 105: 1133-1139. See Evidence Table. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol*. 2013; 108:962-971. See Evidence Table. Lee LY, Sanderson JD, Irving PM. Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. *Eur J Gastroenterol Hepatol*. 2012; 24:1078-1085. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am J Gastroenterol.* 2013; 108:40-47. See Evidence Table. Wang SL, Ohrmund L, Hauenstein S, et al. Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum. *J Immunol Methods*. 2012; 382:177-188.

The use of Homogenous Mobility Shift Assay (HMSA) (Anser TM IFX test) for Infliximaub Antibodies does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Prometheus IBD sgi Diagnostic

10/17/2017: MTAC REVIEW

Evidence Conclusion: Analytic validity: No studies were identified **Clinical validity:** One study (Lawrence et al., 2015) with low evidence was reviewed. Fifty patients with symptoms of IBD and glycogen storage disease (GSD) type Ib were enrolled consecutively. Of 50 patients who were screened using Prometheus IBD, 11 (22%) tested positive for IBD. Of 11 patients who tested positive, 5 were Crohn's Disease, 5 were ulcerative colitis, and one was non-IBD. However, the major limitations included the sample size, lack of reference test (no test had been performed to confirm the diagnosis of IBD), non-randomized design of the study. **Clinical utility:** No studies were identified.

Conclusion:

- No studies assessing analytic validity or clinical utility were identified
- Only one study with non-randomized design and small sample size assessed clinical validity
- There is insufficient evidence to support for or against the use of Prometheus IBD sgi Diagnostic test for patients who present with symptoms of IBD

Articles: The search yielded 18 articles, none of which were relevant except one study (Lawrence, Chengsupanimit, Brown, & Weinstein, 2015) with low evidence.

The use of Prometheus IBD sgi Diagnostic does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met (Anser antibody levels for infliximab or adalimumab):

CPT® or HCPC Codes	Description
84999	Unlisted chemistry procedure

Considered Not Medically Necessary when requested/submitted as a panel (IBD sgi Diagnostic Test):

CPT® or HCPC Codes	Description

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83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
82397	Chemiluminescent assay
86140	C-reactive protein;
88346	Immunofluorescence, per specimen; initial single antibody stain procedure
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
81479	Unlisted molecular pathology procedure

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Creation Date	Date Reviewed	Date Last Revised
12/03/2013	12/03/2013[MPC],1/07/2014[MPC], 11/04/2014[MPC], 09/01/2015[MPC], 07/05/2016[MPC], 05/02/2017[MPC], 03/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC], 02/01/2022[MPC], 02/07/2023[MPC], 10/01/2024[MPC]	02/02/2021

[MPC] Medical Policy Committee

Revision History	Description
05/02/2017	Adopted KPWA medical policy for Medicare members
06/06/2017	MPC approved medical necessity criteria for Anser Antibody testing
02/06/2018	Added MTAC review for Prometheus IBD sgi Diagnostic
02/02/2021	Added Medicare/Noridian LCD and LCA for IBD sgi Diagnostic Test

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