DRAFT

BlueCross BlueShield of Alabama

Name of Policy:

Measurement of Serum Antibodies to Infliximab, Adalimumab, and Vedolizumab

Policy #: 510
Category: Laboratory

Latest Review Date: July 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Proprietary Information of Blue Cross and Blue Shield of Alabama
An Independent Licensee of the Blue Cross and Blue Shield Association

Description of Procedure or Service:

Infliximab (Remicade) is an intravenous tumor necrosis factor α (TNF-α) blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira) is a subcutaneous TNF alpha inhibitor that is FDA-approved for treatment of the above indications (Crohn's disease and ulcerative colitis in adults only) and juvenile idiopathic arthritis. Following primary response to infliximab and adalimumab, some patients become secondary nonresponders. The development of antidrug antibodies (ADA) is considered to be a cause of this secondary nonresponse.

Infliximab and Adalimumab in Autoimmune Disease

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor alpha α (TNF-α) monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF-alpha. Therapy with monoclonal antibodies has revolutionized therapy in patients with inflammatory diseases such as inflammatory bowel disease (IBD; e.g., Crohn disease, ulcerative colitis), rheumatoid arthritis and psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for induction and maintenance of clinical remission. However, not all patients respond, and a high proportion of patients lose response over time. An estimated one-third of patients do not respond to induction therapy (primary nonresponse), and among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remains a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to ADA. ADA are also associated with acute infusion reactions (infliximab), injection site reactions (adalimumab) and delayed hypersensitivity reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies like infliximab.

Detection of Antidrug Antibodies

The detection and quantitative measurement of antidrug antibodies is difficult, owing to drug interference and identifying when antibodies likely have a neutralizing effect. First-generation assays, (i.e., enzyme-linked immunoabsorbent assays [ELISA]) can only measure antidrug antibodies in the absence of detectable drug levels due to interference of the drug with the assay. Other techniques available for measuring antibodies include the radioimmunoassay (RIA) method, and more recently, the homogenous mobility shift assay (HMSA) using high-performance liquid chromatography. Disadvantages of the RIA method are associated with the complexity of the test and prolonged incubation time, and safety concerns related to the handling of radioactive material. The HMSA measures antidrug antibodies when infliximab is present in the serum. Studies evaluating the validation of results among different assays are lacking, making inter-study comparisons difficult. One retrospective study (2012) in 63 patients demonstrated comparable diagnostic accuracy between two different ELISA methods in patients with inflammatory bowel disease (i.e., double antigen ELISA and antihuman lambda chain-based ELISA). This study did not include an objective, clinical and endoscopic scoring system for validation of results.

Treatment Options for Secondary Nonresponse to Anti-TNF Therapy

A diminished or suboptimal response to infliximab or adalimumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different anti-

TNF agent (in patients who continue to have loss of response after receiving the increased dose), or switching to a non-anti-TNF agent.

Policy:

Measurement of antibodies to infliximab in a patient receiving treatment with infliximab, either alone or as a combination test which includes the measurement of serum infliximab levels **does not meet** Blue Cross and Blue Shield of Alabama medical criteria for coverage and is considered **investigational**.

Measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab, either alone or as a combination test which includes the measurement of serum adalimumab levels **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Measurement of antibodies to vedolizumab in a patient receiving treatment with vedolizumab, either alone or as a combination test which includes the measurement of serum vedolizumab levels **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature update was performed through June 1, 2018.

Validation of the clinical use of any genetic test focuses on three main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

Antibodies to Infliximab and Adalimumab

We assessed the literature to identify studies on the analytic validity, clinical validity, and clinical utility of measuring serum antidrug antibodies (ADA). Most studies evaluating antibodies to infliximab (ATI) or to adalimumab (ATA) have reported serum drug together with

ADA levels and correlate levels to disease response. Serum drug levels and disease response will not be addressed in this policy, which focuses instead on the data reported on ADA.

Most evidence concerning testing for ADA is derived from the data available for patients with inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). Less literature exists on other diseases comprising spondyloarthropathies (SpA; e.g., ankylosing spondylitis, psoriatic arthritis, IBD-related arthritis, reactive arthritis, juvenile idiopathic arthritis) and psoriasis.

Analytic Validity

Measurement of Antibodies to Infliximab

Wang et al (2012) developed and validated a non-radio-labeled homogeneous mobility shift assay (HMSA) to measure ATI and infliximab levels in serum samples. Full method validation was performed on both the ATI-HMSA and infliximab-HMSA, and the clinical sample test results were compared with those obtained from a bridging ELISA method to evaluate the difference in performance between the two assays. Intra- and inter-assay precision rates (as indicated by the coefficient of variation [CV]) for the ATI- and infliximab-HMSA were <4% and <15%, respectively, and <6% and <15%, respectively, considered to be robust. Hernandez-Breijo described the use of the HMSA protocol in measuring ATI in 50 infliximab-treated Crohn disease patients, using similar methods as Wang et al.

Sera from 100 healthy subjects (blood bank donors) were tested to determine the cut points of the assay, defined to have an upper negative limit of approximately 97.5%. Using receiver operating characteristic analysis, a cut point of 1.19 μg/mL was calculated for ATI yielding a sensitivity of 95% (95% CI: 89 to 98) with a false positive rate of 3%. For serum infliximab levels, a cut point of 0.98 μg/mL was calculated; the false positive rate with this cut point was 5%. One hundred serum samples that previously had tested positive with ELISA were reanalyzed by the new method. There was a high correlation between the two methods for ATI levels ($p<0.001$). The new method identified five false-positive samples from the bridging ELISA method, thought to be due to a higher rate of nonspecific binding in the ELISA method.

In 2014, Steenholdt et al published a post hoc comparison of different ATI assays. Blood samples were collected from 66 (96%) of 69 patients enrolled in a randomized controlled trial (RCT) that assessed algorithmic treatment for Crohn's disease (CD) relapse during infliximab therapy. Samples were analyzed by binding three assays (RIA, ELISA, and HMSA) and by a reporter gene assay, a functional cell-based technique. ATI were detected in 18 patients (27%) by radioimmunoassay, six patients (9%) by ELISA, and 22 patients (33%) by HMSA. The reporter gene assay detected anti-infliximab activity, most likely due to ATI, in seven patients (11%). As observed by the authors, findings suggested that ATI detected by RIA and HMSA are not necessarily functionally active or neutralizing. Five patients (8%) were ATI-positive and 43 patients (65%) were ATI-negative by all four assays. Correlations were statistically significant ($p<0.001$) for all pairwise comparisons (*r* range 0.77-0.96). However, statistical agreement between assays could not be estimated accurately (e.g., using the intraclass correlation coefficient) because different assays reported values on different arbitrary scales. Regardless of assay used, most patients (74%-88%) had therapeutic serum infliximab levels and undetectable ATI, suggesting nonpharmacologic reasons for relapse or for symptoms mimicking relapse.

Measurement of ATA
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, intra- and interassay precision, linearity of dilution, substance interference) was performed for both the ATA- and adalimumab-HMSA. Because the elimination half-life of adalimumab (10-20 days) overlaps the dosing interval (every two weeks), ATA-positive sera to provide calibration standards were difficult to collect (i.e., the drug-free interval for antibody formation is short.) 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. Over 29 experimental runs, intra-assay precision and accuracy for the adalimumab-HMSA (as indicated by the CV) were less than 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, CVs for intra-assay precision and accuracy were less than 3% and 13%, respectively; CVs for interassay precision and accuracy were less than 9% and less than 18%, respectively. ELISA could not be used as a standard comparator due to competition from circulating drug.

Following evaluation of the analytic validity of the non-radiolabeled HMSA assay, investigators tested sera from 100 healthy subjects (obtained from blood bank donors) to determine the cut points of the assay, defined as the threshold above which samples were deemed to be positive with an upper limit of approximately 99%. The calculated cut point for serum adalimumab levels was 0.68 μg/mL, which yielded a false-positive rate of 3%. For ATA, the calculated cut point was 0.55 U/mL, which yielded a false-positive rate of 1%. Analysis of 100 serum samples from patients who were losing response to adalimumab showed that 44% were above the cut point for ATA, and 26% were below the cut point for serum adalimumab level. In samples below the adalimumab cut point (0.68 μg/mL), 68% were ATA positive; in samples with adalimumab levels greater than 20 μg/mL, 18% were ATA-positive.

Section Summary: Analytic Validity
Analytic validity of ATI testing by homogeneous mobility shift assay has been demonstrated using ELISA as a standard comparator. Test performance characteristics were considered robust. However, a subsequent comparative study identified substantial variability across ATI assay methods using a functional cell-based assay as standard. The pharmacokinetic properties of adalimumab (long half-life relative to dosing interval) prevented use of ELISA as a standard comparator in tests of analytic validity of ATA. Test performance characteristics were determined by comparison to a standard curve generated by serial dilutions of pooled rabbit antisera. Lack of comparison to an alternative method of antibody detection raises uncertainty about the analytic validity of the ATA test. The commercial Prometheus® HMSA assays do not suffer from many of the technical performance limitations of older assays; however, the HMSA assays do not distinguish between neutralizing and non-neutralizing antibodies.

Clinical Validity
There is a substantial body of evidence (numerous systematic reviews and meta-analyses) examining associations between ADA and nonresponse as well as injection- or infusion-site reactions. Accordingly, our review of the evidence on clinical validity focuses on the most current systematic reviews (see Tables 1 through 3) and studies published subsequent to the

search dates of those reviews, as well as relevant studies not included in identified reviews (e.g., those focusing on adverse reactions and ADA).

Systematic Reviews
Six reviews published from 2012 through 2017 were identified. The number of included studies ranged from 11 to 68, varying by review objectives and conditions of interest. Although not detailed here, there was considerable overlap in selected studies across reviews.

Lee et al in 2012 conducted a meta-analysis of patients with inflammatory bowel disease (IBD) receiving infliximab to estimate the prevalence of ATI, effect of ATI on the prevalence of infusion reactions, and the effect of ATI on disease remission rates. Databases were searched through October 2011, and 18 studies involving 3,326 patients were selected. Studies included nine randomized controlled trials (RCTs), five prospective cohort studies, and four retrospective cohort studies. The prevalence of ATI was 45.8% when episodic infusions of infliximab were given and 12.4% when maintenance infliximab was given (Table 1). Patients with ATI were less likely to be in clinical remission (Table 2), but this was not statistically significant (RR=0.90; 95% CI, 0.79 to 1.02; p=0.10). The rates of infusion reactions were significantly higher in patients with ATI (relative risk [RR]: 2.07; 95% confidence interval [CI]: 1.61–2.67; see Table 3). Immunosuppressants resulted in a 50% reduction in the risk of developing ATI (p<0.001). Reviewers concluded that patients with IBD who test positive for ATIs are at an increased risk of infusion reactions, but have rates of remission similar to patients who test negative for ATIs.

Nanda et al (2013) conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of ATI in patients with IBD. Several databases were searched to February 2012 (one was searched to August 2012). Eleven studies involving 707 patients were selected. Six studies (two RCTs, one prospective cohort study, three retrospective cohort studies) were included. In at least one quality domain (study eligibility criteria, measurement of exposure and outcome, control for confounders, completeness of follow-up), all included studies had high risk of bias. The prevalence of detectable ATI in the included studies ranged from 22.4% to 46% (see Table 1). The outcome of interest was loss of response to infliximab, defined as "relapse of clinical symptoms in patients who were in clinical remission from, or had responded to, infliximab." Measures of loss of response varied across studies and included clinician assessment, standardized scales (Crohn's Disease Activity Index [CDAI], Harvey-Bradshaw Index, Simple Clinical Colitis Activity Index), and requirement for surgery or presence of nonhealing fistula. Patients with ATIs had a three-fold greater risk of loss of response than those without ATIs (RR=3.2; 95% CI, 2.0 to 5.0; shown in Table 1 as the RR of clinical response in treated vs untreated patients to allow comparison with other meta-analyses). This result was influenced primarily by 532 patients with CD (RR=3.2; 95% CI, 1.9 to 5.5); pooled results for 86 patients with ulcerative colitis (UC) were not statistically significant (pooled RR=2.2; 95% CI, 0.5 to 9.0). (Eighty-nine patients with unspecified IBD also were included in the meta-analysis.) In addition to potential bias in included studies and heterogeneity in outcome assessment, the meta-analysis is limited by variability in the method of ATI detection (double-antigen ELISA, antihuman lambda chain-based ELISA, fluid-phase RIA).

Garces et al in 2013 performed a meta-analysis of studies of infliximab and adalimumab used to treat RA, IBD, SpA, and psoriasis. Databases were searched to August 2012, and reviewers selected 12 prospective cohort studies involving 860 patients (540 with rheumatoid arthritis, 132

with spondyloarthritis, 130 with IBD, and 58 with psoriasis). The outcome of interest was response, assessed by using standard assessment scales for rheumatologic diseases (e.g., European League Against Rheumatism [EULAR] criteria for rheumatoid arthritis; Assessment in Ankylosing Spondylitis 20% response criteria or Ankylosing Spondylitis Disease Activity Score for spondyloarthritis; Psoriasis Area and Severity Index for psoriasis) and clinician assessment for IBD. Overall, detectable ADA were associated with a 68% reduction in drug response (pooled risk ratio [RR] 0.32 [95% CI: 0.22–0.48]). Significant heterogeneity was introduced by varying use of immunosuppressant therapy (e.g., methotrexate) across studies. To assess anti-drug antibodies, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

A systematic review and meta-analysis by Thomas et al (2015) included 68 studies (total N=14,651 patients). Patients had RA (n=8766), SpA (n=1534), or IBD (n=4351). Immunogenicity was examined for infliximab (39 comparisons), adalimumab (15), etanercept (5), golimumab (14), and certolizumab (8). Reviewers identified studies published through December 2013 and included 38 RCTs and 30 observational studies (study quality rated as good [n=32], moderate [n=26], poor [n=10]). The pooled prevalence of ADA varied by disease and drug (see Table 1, highest with infliximab: 25.3%). Duration of exposure (reported in 60 studies) was examined for its potential effect on the development of ADA, and most studies employed ELISA assays. The presence of ADA was associated with lower odds of response across most drugs and diseases (see Table 2). An exception was in studies of IBD (similar to that reported by Lee et al). Use of immunosuppressive agents substantially decreased the risk of ADA (odds ratio [OR], 0.26; 95% CI, 0.21 to 0.32). Finally, infusion reactions and injection-site reactions were more common (see Table 3) when ADA were detectable (OR=3.25; 95% CI, 2.35 to 4.51). Evaluation of potential publication bias or overall assessment (e.g., GRADE or similar) for the body of evidence was not reported. Additionally, no measures of heterogeneity were reported.

The systematic review by Meroni et al (2015) searched PubMed through March 2013 and included 57 studies of infliximab (n=34), adalimumab (n=18), and etanercept (n=5). Studies primarily included patients with IBD and RA, but also SpA and psoriasis. Most had prospective cohort designs (n=42) and a formal assessment of study quality (bias) was not reported. Reviewers noted considerable variability in the time from drug administration to ADA and drug bioavailability testing across studies. Various antibody testing assay methods were used and included solid-phases RIA, traditional ELISA, fluid-phase RIA, and bridging ELISA; cutoffs for positive test results were also inconsistently reported. The ranges of patients with detectable ADA varied substantially (see Table 1) but were consistent with other reviews. Qualitatively, the presence of ATI was associated with lower levels of infliximab and lower risk of disease control or remission. The presence of ATI also increased the risk of infusion reactions. When ascertained, the time to development of ATI varied from as little as 16 weeks to over a year. The time to ATA positivity varied (e.g., 50% of patients with detectable ATA at 28 weeks to a median time of 1 year). Finally, for both infliximab and adalimumab, immunosuppression was associated with less ADA positivity. Reviewers concluded that "…the lack of homogeneity in study design and methodologies used … limited the opportunity to establish the time-course and clinical consequences of anti-drug antibody development...." Although qualitative, reviewers included many studies, and provided a detailed review of each not reported by the other meta-analyses.

Table 1: Estimated Prevalence of Antidrug Antibodies From Meta-Analysis

Author	Included Studies	Drugs			Disease			Prevalence of ADA	
		IFX	ADL	Other[a]	IBD	RA	SpA	Pooled (95% CI)	Range in Studies
Lee (2012)	18[b]	●			●			20.8% (19.2 to 22.5)	
Episodic	5	●			●			45.8% (41.7 to 50.0)	
Maintenance	10	●			●			12.4% (10.8 to 14.1)	
Nanda (2013)	11	●			●				22.4%-46%
Thomas (2015)	39[c]	●			●	●	●	25.3% (19.5 to 32.3)	
	15[c]		●		●	●	●	6.9% (3.4 to 13.5)	
	20	●	●		●			15.8% (9.6 to 24.7)	
	44	●	●	●		●		12.1% (8.1 to 17.6)	
	11	●	●	●			●	8.9% (3.8 to 19.2)	
Meroni (2015)	14	●				●			19%-47%
	14	●			●				15%-61%
	5	●					●		26%-50%
	12		●			●			5%-54%
	3		●		●				9%-46%
	3		●				●		18%-45%

ADA: antidrug antibodies; ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; RA: rheumatoid arthritis; SpA: spondyloarthropathy.
a Includes etanercept, golimumab, certolizumab.
b Includes 3 studies including both maintenance and episodic therapy.
c Number of comparisons in table; did not report studies for pooled prevalence.
d Also psoriasis.

Table 2. Results From Meta-Analysis of Antidrug Antibodies and Clinical Response

Author	Included Studies	Drugs			Disease			Clinical Response: ADA vs None		
		IFX	ADL	Other[a]	IBD	RA	SpA	RR (95% CI)	OR (95% CI)	I^2
Lee (2012)	18	●			●			0.90 (0.79 to 1.02)		37%
Nanda (2013)	11	●			●			0.33 (0.20 to 0.40)		70%
Garces (2013)	12	●	●		●	●	●[b]	0.32 (0.22 to 0.48)		46%
Thomas (2015)	4	●	●	●	●				1.16 (0.66 to 2.03)	NR
	13	●	●	●		●			0.27 (0.20 to 0.36)	NR
	4	●	●	●			●		0.18 (0.09 to 0.37)	NR
	9	●			●	●	●		0.42 (0.30 to 0.58)	NR

ADA: antidrug antibodies; ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; NR: not reported; OR: odds ratio; RA: rheumatoid arthritis; RR: relative risk; SpA: spondyloarthropathy.
[a] Includes etanercept, golimumab, certolizumab.
[b] Also psoriasis.

Table 3. Increased Risk of Adverse Reactions Associated With the Presence of Antidrug Antibodies

Author	Included Studies	Drugs			Disease			Adverse Reactions: ADA vs None	
		IFX	ADL	Others[a]	IBD	RA	SpA	OR (95% CI)	RR (95% CI)
Lee (2012)	18	●			●				2.07 (1.61 to 2.67)[a]
Thomas (2015)	NR	●	●	●	●	●	●	3.25 (2.35 to 4.51)	

ADA: antidrug antibodies; DL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; NR: not reported; OR: odds ratio; RA: rheumatoid arthritis; RR: relative risk; SpA: spondyloarthropathy.
a Infusion reaction.

A systematic review and meta-analysis by Pecoraro et al (2017) included 34 studies (total N=4273 patients), including RCTs (n=4), prospective observational (n=22), retrospective observational (n=6), and cross sectional (n=2). Studies evaluated RA (n=18), UC (n=2), CD (n=5), PsA (n=4), AS (n=5), Ps (n=4), spondyloarthritis (n=1). Most of patients (45%) received infliximab, 35% received adalimumab and 21% received etanercept. None received golimumab or certolizumab. Reviewers identified studies published through August 2016 and rated study quality as good (n=17), fair (n=16), and poor (n=1). The effect of antidrug antibodies (ADA) was evaluated in 19 studies, showing a significant ($p<0.05$) reduction of response (RR=0.43; 95% CI, 0.3 to 0.63 in ADA-positive patients relative to ADA-negative patients, with ADL therapy demonstrating a greater reduction (RR=0.40; 95% CI, 0.25 to 0.65; $p<0.001$) than IFX (RR=0.37; 95% CI, 0.2 to 0.7; $p<0.001$). Measures of heterogeneity were 84%, 57%, and 79%, respectively. Fourteen studies reported the effect of ADA on clinical response (see Table 4). Eleven studies found the risk of developing ADA to be significantly ($p=0.03$) lower in patients treated with concomitant MTX therapy relative to those without MTX (RR=0.65; 95% CI, 0.47 to 0.9). Studies comparing treatment response with nonresponse (n=15) found responders to have a significantly ($p<0.001$) lower risk of developing ADA relative to nonresponders (RR=0.31; 95% CI, 0.18 to 0.52). The presence of ADA was associated with a significant reduction of anti-TNF- α serum concentration (see Table 5). Of the 20 studies (n>2800) reporting data on adverse events, 31% (n=2 studies) developed infections, 18% (n=12 studies) developed injection site reactions, 8% (n=11 studies) discontinued treatment due to adverse effects, and 5% (n=1 study) developed serious adverse events (5%). Although ADA significantly reduced TNF- α response, the results should be viewed with caution due to reported study limitations, including small number of studies included and considerable heterogeneity.

Table 4. Effect of Antidrug Antibodies on Clinical Response

Outcome Measures	No. Studies	MD	95% Confidence Interval	*I*2, %	p
Disease Activity Score 28	9	0.93	0.41 to 1.44	84	.0004
BASDAI	2	-0.62	-1.51 to 0.27	0	0.17
ASDAS	2	0.96	-0.27 to 2.2	0	0.13
Psoriasis Area Severity Index	1	4.7	-1.15 to 9.25	NR	0.04

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; *I*2: heterogeneity measure; NR: not reported.

Table 5. Evaluation of Anti-TNF- Concentration

Outcome Measures	No. Studies	MD, mg/L	95% Confidence Interval	*I*2, %	p
ADA+ vs ADA -	8	-7.07	-8.9 to -5.25	98	<0.001
Responders vs no responders	13	2.77	1.97 to 3.58	82	<0.001
Adalimumab therapy	6	5.07	3.77 to 6.36	62	<0.001
Infliximab	4	2.74	0.59 to 4.89	62	<0.001
Etanercept	3	0.85	0.41 to 1.13	82	<0.001
DAS28 change from baseline	8	-2.18	-2.91 to -1.44	97	<0.001

Adapted from Pecoraro et al (2017)
ADA: antidrug antibodies; DAS28: Disease Activity Score; *I*2: heterogeneity measure; MD: mean difference; TNF: tumor necrosis factor.

Cohort Studies

Three recent publications not included in a systematic review were identified. Results were consistent with conclusions of the systematic reviews.

Arstikyte et al (2015) prospectively evaluated the association of ADA with adverse events, clinical response, and drug levels in 143 symptomatic patients (62 with RA, 81 with SpA; mean age 45 years [SD=13]) treated with TNF blockers in Lithuania. All patients receiving adalimumab or infliximab were tested and one in three patients given etanercept (because it is more commonly used). A response in RA patients was defined was either good, moderate, or low using EULAR criteria; SpA disease activity considered inactive, moderate, high, or very high by established criteria with inactive and moderately active disease defined as response. At least three months after therapy initiation, a single serum sample was obtained prior to dosing between 2012 and 2013; disease activity and other patient characteristics (e.g., symptom duration, health status) were assessed concurrently. Serum adalimumab, infliximab, and etanercept levels were obtained; ADA was assayed using a bridging ELISA. Of 57 patients receiving infliximab, 14 (24.6%) had detectable antibodies with 13 of the 14 undetectable infliximab trough levels. Disease activity at baseline was unassociated with the development of ADA in either disease. In patients achieving response infliximab and adalimumab trough levels were higher, but not significantly (p=0.09 and p=0.14 respectively). However, Adalimumab concentrations were significantly higher in nonresponders (p<0.001). Antibodies to infliximab were associated with infusion reactions but with little certainty (OR=5.9; 95% CI, 1.0 to 33.3) as was stopping infliximab treatment or changing agent. Study strengths included its prospective design, standardized assessments, and responder definition. Limitations involved the small number of nonresponders and no indication whether any eligible participants declined enrollment.

Frederiksen et al (2014) conducted a single-center retrospective cohort study of IBD patients treated with infliximab (n=187) or adalimumab (n=57) in Denmark. ADA were assayed using fluid-phase RIA - 49% of infliximab-treated patients developed antibodies compared with 21% of those treated with adalimumab. Development of ATA was associated with secondary nonresponse: positive predictive value was 91% (95% CI, 59% to 100%), sensitivity was 50% (95% CI, 27% to 73%); negative predictive value was 74% (95% CI, 57% to 87%), and specificity was 97% (95% CI, 82% to 100%) (values varied by adalimumab trough levels). The authors also reported that patients switching from infliximab to adalimumab who had antibodies were more likely to develop ATA. These findings are consistent with other studies and evaluation of ADA using RIA (a strength of this study). Conclusions were limited by the retrospective design and sample size.

Jani et al (2015) measured ADA by RIA together with drug levels in 331 RA patients treated with adalimumab (n=160) and etanercept (n=171) between 2008 and 2013. Patients were participants in the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate conducted in 60 centers across the UK. Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28) score. A response was evaluated using EULAR response criteria or change in DAS28 score. Following 12 months of adalimumab therapy, ADA were detectable in 24.8% of patients (almost all were detectable by six months) and were associated with lower drug levels. Both routine (non-trough) drug levels and antibodies to adalimumab were associated with DAS28 at 12 months. In predicting EULAR nonresponse, the AUC for adalimumab concentration less than 5 mg/mL at three months was 0.66 (95% CI, 0.55 to 0.77) and for presence of ADA 0.68 (95% CI, 0.54 to 0.81). None of the etanercept patients developed detectable ADA. Although derived from a well-established observational study designed to examine predictors (genetic and other) of treatment response, ADA levels were not used to inform treatment decisions. These results corroborate other research findings.

While many studies have evaluated clinical validity using single ADA measurements, at least one study assessed their persistence over time. Vande Casteele et al (2013) analyzed infliximab trough and ATI levels using an HMSA assay with banked serum obtained from 90 IBD patients treated between 1999 and 2011. ATI levels had been previously assayed using an ELISA-based test. A total of 1232 samples were evaluated (mean 14 per patient). Treatment decisions were made solely on clinical evaluation and CRP levels. ATI were detected in 53 of 90 (59%) of patients but subsequently were nondetectable in 15 of the 53 (28%). Persistent ATIs were associated with discontinuation of infliximab (RR=5.1; 95% CI, 1.4 to 19.0), but the wide confidence interval reflects considerable uncertainty. Although transience of ATI in IBD has not been carefully scrutinized, if replicated, these results suggest interpreting a single ATI result cautiously.

Cludts et al (2017) conducted a single-center retrospective cohort analysis of patients with RA (n=18), PsA (n=9), or AS (n=12) in Italy. Serum samples were taken prior to ADL therapy and after 12 and 24 weeks of treatment. PsA and AS patients were grouped together (SpA) due to axial involvement in all PsA patients. Although ADL levels varied among patients (0 to 30 lg/mL), median levels were significantly lower at 12 and 24 weeks in ATA-positive samples, and antibody formation was associated with decreasing levels of circulating ADL. A reporter gene assay detected neutralizing antibodies against TNF antagonists in ATA-positive, therapeutic-

negative patients; however, neutralization could not be confirmed in all ATA-positive samples due to ADL interference. There was a negative correlation between ATA levels and ADL in all groups, with 43.6% and 41% of the ADL-treated patients developing antibodies at 12 and 24 weeks, respectively. These percentages increased to 48.7% and 46% after subjecting the samples to acid treatment. There was a negative correlation of ADL trough levels with Disease Activity Score 28 (DAS28) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) values ($p<0.001$). There were no significant differences between BASDAI in ATA-positive compared with ATA-negative patients at 12 or 24 weeks. The study is consistent with others suggesting that ADL levels can serve as an indicator of ATA; however, limitations include small sample size, retrospective research design, and that neutralization could not be confirmed in all ATA positive samples.

Using an observational, cross-sectional study design, Ara-Martin et al (2017) analyzed the impact of immunogenicity on response to anti-TNF therapy in 137 adults with moderate-to-severe plaque psoriasis at 35 centers in Spain between 2012 and 2014. All patients experienced secondary nonresponse to adalimumab (n=65), etanercept (n=47), and infliximab (n=19) ≥ 6 months of treatment. Serum ADA was identified in 48%, 0%, and 42% of patients of patients treated with adalimumab, etanercept, and infliximab, respectively. Loss of efficacy was assessed using the Psoriasis Area and Severity Index (PASI; >5), 75% improvement in PASI score from baseline (PASI75) and/or the Physician Global Assessment (PGA, >2). PGA values for ADA-positive vs. ADA-negative patients were significantly worse in the adalimumab group (3.7 vs. 3.2; p=0.02), but not in the infliximab group. There was a significant negative linear correlation between serum drug concentrations and ADA in both the adalimumab group (p=0.001) and among the three groups combined (p=0.001), and a significant (p=0.019) correlation between serum ADA titer and body surface area. Inconsistent with other studies, the use of concomitant anti-rheumatic drugs was not associated with anti-TNF immunogenicity in any of the groups. This study provides evidence of antibody development against adalimumab and infliximab (not against etanercept) in patients with psoriasis, with ADA formation accounting for half of the secondary nonresponse associated with these therapies. However, conclusions are limited due to the cross-sectional study design, use of ELISA to detect ADAs due to drug interference, the potential presence of neutralizing antibodies as confounding factors, and limited information about patients' health status prior to the study period.

A case-control, longitudinal study by Lombardi et al (2016) excludes possible confounding factors by analyzing ADL treatment for psoriasis in five distinct groups, including individuals who received: (n=20) biological therapies after switching from ADL; (n=30) ongoing ADL therapy; (n=30) novel ADL therapy; (n=15) biological therapies other than ADL; and (n=15) no treatment with immunosuppressants or biologicals, serving as a quasi-control. The clinical severity of psoriasis was scored using the PASI. At 12-month follow-up, ADA was highest (87%) in patients who received biological therapies after switching from ADL. The false-positive rate was 23% for ADL detection and 22% for anti-ADL antibodies in individuals who were never treated with ADL. There was no significant difference in median PASI score between the anti-ADL antibody-negative patients (1.1) and the anti-ADL antibody-positive patients (4.0). There was no association between PASI score or TNF-α concentration and the presence of anti-adalimumab antibodies in patients receiving ADL. Additionally, there were no significant differences in TNF-α and C reactive protein concentrations. Study limitations include the

observational design, small sample size, use of ELISA method to measure ADA, and high variability of results. The authors conclude that the assay has limited clinical utility.

Section Summary: Clinical Validity

A large body of evidence has evaluated the clinical validity of ADA testing. ADA has been associated with secondary nonresponse in RA, SpA, but possibly IBD. The presence of ADA has been consistently associated with an increased risk of infusion-site reaction related to infliximab and injection site reactions related to adalimumab. A concomitantly administered immunosuppressant agent may reduce the risk of developing ADA. Although ADA significantly reduced TNF- α response in a recent meta-analysis, considerable heterogeneity limits those findings. In addition, a recent observational study found no association between concomitant immunosuppressants and anti-TNF immunogenicity in patients with psoriasis; and a second cohort study found no association between PASI score or TNF- α concentration and the presence of anti-adalimumab antibodies in patients receiving ADL to treat psoriasis.

Clinical Utility

Several algorithms have been developed for management of patients with IBD or RA who have relapsed during TNF-inhibitor therapy. These algorithms are generally based on evidence that has indicated an association between ADA, reduced serum drug levels, and relapse. None of the algorithms has included evidence demonstrating improved health outcomes, such as reduced time to recovery from relapse (response).

Afif et al (2010) evaluated the clinical utility of measuring ATI (referred to as human antichimeric antibodies [HACA] in the study) and infliximab concentrations by retrospectively reviewing patient medical records. Record review from 2003 to 2008 identified 155 patients who had had ATI, had data on infliximab concentrations, and met the study inclusion criteria. A single physician ordered 72% of the initial tests. The authors retrospectively determined clinical response to infliximab. Forty-seven percent of patients were on concurrent immunosuppressive medication. The main indications for testing were loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune or delayed hypersensitivity reaction (10%). ATI were identified in 35 (23%) patients and therapeutic infliximab concentrations in 51 (33%) patients. Of 177 tests assessed, the results impacted treatment decisions in 73%. In ATI-positive patients, change to another anti-TNF agent was associated with a complete or partial response in 92% of patients, whereas dose escalation occurred in 17%.

The authors concluded that measurement of ATI and infliximab concentration had a clinically useful effect on patient management. The strategy of increasing infliximab dose in patients with ATI was ineffective whereas in patients with subtherapeutic infliximab concentrations this strategy was a good alternative to changing to another anti-TNF agent. Study limitations included the retrospective design and using ELISA testing for ATI. Because there was no control group, one cannot determine what changes in management would have been made absent ATI measurement. Because clinicians are likely to change management for patients who do not achieve or maintain a clinical response, it is important to understand how these management decisions differ when ATI are measured.

In 2014, Steenholdt et al reported results of a noninferiority trial and cost-effectiveness analysis of 69 patients with CD who relapsed (CDAI ≥220 and/or ≥1 draining perianal fistula) during infliximab therapy. Patients were randomized to infliximab dose intensification (5 mg/kg every four weeks) or algorithmic treatment based on serum infliximab level and ATI: Patients with subtherapeutic infliximab level (<0.5 μg/mL) had infliximab dose increased if ATI were undetectable or were switched to adalimumab if ATI were detectable; patients with therapeutic infliximab level underwent repeat testing of infliximab and ATI levels if ATI were detectable or diagnostic reassessment if ATI were undetectable. Serum infliximab and ATI levels were measured in all patients using RIA in single-blind fashion (patients unaware but investigators aware of test results). Randomized groups were similar at baseline; overall, 55 (80%) of 69 patients had non-fistulizing disease. Most patients (70%) had therapeutic serum infliximab levels without detectable ATI; revised diagnoses in six (24%) of 25 such patients in the algorithm arm included bile acid malabsorption, strictures, and IBS. In both intention-to-treat and per-protocol analyses, similar proportions of patients in each randomized group achieved clinical response at week 12, defined as a minimum 70- point reduction from baseline CDAI for patients with non-fistulizing disease and a minimum 50% reduction in active fistulas for patients with fistulizing disease (intention-to-treat: 58% in the algorithm group vs 53% in the control group; p=0.810; per-protocol: 47% in the algorithm group vs 53% in the control group; p=0.781). Only the ITT analysis fell within the prespecified noninferiority margin of -25% for the difference between groups.

Conclusions on the noninferiority of an algorithmic approach compared with dose intensification from this trial are limited. The noninferiority margin was arguably large and was exceeded in the conservative per protocol analysis. Dropouts were frequent and differential between groups; 17 (51%) of 33 patients in the algorithm group and 28 (78%) of 36 patients in the control group completed the 12-week trial. A large proportion of patients (24%) in the algorithmic arm were potentially misdiagnosed (i.e., CD flare was subsequently determined not to be the cause of relapse); the comparable proportion in the control arm was not reported. In most patients (80% who had non-fistulizing disease), only a subjective measure of treatment response was used (minimum 70-point reduction from baseline CDAI).

Roblin et al in 2014 conducted a single-center, prospective observational study of 82 patients with IBD (n=45 CD, n=27 UC) with clinical relapse (CDAI >220 or Mayo Clinic >5) during treatment with adalimumab 40 mg every two weeks. For all patients, trough adalimumab levels and ADA were measured in a blinded fashion using ELISA, and adalimumab dose was optimized to 40 mg weekly. Those who did not achieve clinical remission (CDAI <150 or Mayo score <2) within four months underwent repeat trough adalimumab and anti-adalimumab antibody testing and were switched to infliximab. Clinical and endoscopic responses after adalimumab optimization and after infliximab therapy for six months were compared among three groups: (1) those with therapeutic adalimumab level (>4.9 μg/mL), (2) those with subtherapeutic adalimumab level and undetectable ATA; and (3) those with subtherapeutic adalimumab level and detectable ATA. After adalimumab optimization, more group 2 patients achieved clinical remission (16 [67%] of 24 patients) than group 1 (12 [29%] of 41 patients; p<0.01 vs group 2) and group 3 (2 [12%] of 17 patients; p<0.01 vs group 2) patients. Duration of remission was longest in group 2 (mean], 15 months) compared with group 1 (mean, 5 months) and group 3 (mean, 4 months; p<0.01 for both comparisons vs group 2). At one year, 13 (52%)

of 24 patients in group 2 maintained clinical remission compared with no patients in groups 1 or 3 ($p<0.01$ for both comparisons vs group 2). Results were similar when remission was defined using calprotectin levels (<250 μg/g stool) or endoscopic Mayo score (<2).

Fifty-two patients (n=30 CD, n=22 UC) who failed to achieve clinical remission after adalimumab optimization were switched to infliximab. More patients in Group 3 achieved clinical remission (12 [80%] of 15 patients) than in Group 1 (2 [7%] of 29 patients) or Group 2 (2 [25%] of 8 patients; $p<0.01$ for both comparisons vs Group 3). Duration of response after switching to infliximab was longest in Group 3 (mean, 14 months) compared with Group 1 (mean, 3 months) and Group 2 (mean , 5 months; $p<0.01$ for both comparison vs Group 3). At one year, 8 (55%) of 15 patients in Group 3 maintained clinical remission compared with no patients in Groups 1 or 2 ($p<0.01$ for both comparisons vs Group 3). Results were similar using objective measures of clinical remission (calprotectin level, endoscopic Mayo score).

These results suggested that patients with IBD who relapse on adalimumab and have subtherapeutic serum adalimumab levels may benefit from a higher adalimumab dose if ATA are undetectable or from a change to another TNF inhibitor if ATA are detectable. Relapsed patients who have therapeutic serum adalimumab levels may benefit from change to a different drug class. Strengths of the study include its use of subjective and objective measures of remission and blinded serum drug level and ATA monitoring. However, results were influenced by the small sample size, use of ELISA for antibody testing, and lack of ADA levels for decision making. Subsequent study comparing the management using the algorithm proposed with usual care is needed. Ideally, using more than 1 method of assaying antibodies would further assessment of analytic validity. Finally, the lead author of the study received lecture fees from the ADA test provider (Theradiag).

Section Summary: Clinical Utility

Convincing evidence for the clinical utility of ADA testing currently is lacking. Uncontrolled retrospective studies in IBD have demonstrated the impact of ADA testing on treatment decisions but cannot demonstrate improved patient outcomes compared with a no-testing strategy. Additional limitations of these studies include lack of clinical follow-up after treatment decisions were made (in Afif) and lack of clinical assessments to guide treatment decisions (in Steenholdt). Additionally, determination of a clinically relevant threshold for ADA level is complicated by the use of various assay methods. A small, nonrandomized prospective study suggested that ADA levels may be informative in relapsed patients with IBD who have low serum adalimumab levels, but this finding requires confirmation in larger, randomized trials. Methodological flaws, including relapse misclassification limit conclusions from the RCT in patients with relapsed IBD. Direct or indirect evidence for clinical utility in patients with RA or SpA was not identified. Finally, although ADA are associated with increased risk of infliximab infusion and adalimumab injection site reactions, whether testing for ADA can reduce that risk is unclear. For example, Lichtenstein et al (2013) conducted a systematic review of infliximab-related infusion reactions and concluded “there is a paucity of systematic and controlled data on the risk, prevention, and management of infusion reactions to infliximab.” He added that “[m]ore randomized controlled trials are needed in order to investigate the efficacy of the proposed preventive and management algorithms.”

Summary of Evidence Regarding Measurement of Serum Antibodies to Infliximab (Remicade) and Adalimumab (Humira)
For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for anti-TNF-α inhibitor ATI or to adalimumab, the evidence includes multiple systematic reviews, a randomized controlled trial, and observational studies. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. ATI or antibodies to adalimumab develop in a substantial proportion of treated patients and are believed to neutralize or enhance clearance of the drugs. Considerable evidence has demonstrated an association between ADA and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring ADA hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring ADA. A small randomized controlled trial in patients with Crohn disease comparing ATI-informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the ATI-informed approach. Additionally, many assays—some having significant limitations—have been used in studies; ADA threshold values that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

Measurement of Serum Antibodies to Vedolizumab (Entyvio)
Vedolizumab (Entyvio) is an intravenous tumor necrosis factor blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of: moderately to severely active ulcerative colitis (UC); and moderately to severely active Crohn's disease (CD). Vedolizumab is generally given for those patients who have had an inadequate response with, lost response to, or were intolerant to tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. This drug is used for achieving clinical response or remission, or achieving corticosteroid-free remission.

Serum concentrations of vedolizumab (VDZ) may vary among equally dosed patients which can affect patient outcomes. Some patients may develop immunogenicity (non-response) to VDZ by producing antibodies to vedolizumab and the presence of persistent anti-vedolizumab antibody has been observed to reduce serum concentrations of vedolizumab. Incorporating therapeutic drug monitoring into clinical practice has been proposed to allow clinicians to optimize treatment by maintaining effective drug concentrations over time and affecting a patient's loss of response.

For individuals who have ulcerative colitis (UC) or Crohn's disease (CD) receiving vedolizumab, there is an interest in monitoring this therapy not only for the purpose of identifying markers that will serve as end points for successful treatment, but also for timely cessation or switching of therapy in those unlikely to respond. However, based on the peer reviewed medical literature further randomized controlled trials are needed to investigate the efficacy of proposed preventative and management algorithms regarding antidrug antibodies (ADA) testing. Currently there are no society guidelines that include recommendations for ADA testing. More controlled data is needed to define the best cut-off to define abnormal values of the

measured monitor parameters, define optimal thresholds for the different interventions and the subpopulations as to who will benefit the most from this testing. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American College of Gastroenterology et al

Clinical guidelines from the American College of Gastroenterology, the American College of Rheumatology, and EULAR have not included recommendations for testing for antidrug antibodies (ADA) in patients treated with tumor necrosis factor (TNF) inhibitors. An important question included in the EULAR research recommendations was whether "measurement of serum drug and/or drug antibody levels [is] useful in clinical practice?"

National Institute for Health and Care Excellence

In 2016, the National Institute for Health and Care Excellence (NICE) issued guidelines on therapeutic monitoring of TNF-α inhibitors in the treatment of patients with Crohn's disease. NICE recommends that laboratories monitoring TNF-α inhibitors in patients with Crohn disease who have lost response to the treatment, should work with clinicians to collect data through either a prospective study, a local audit, or a registry.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:

Serum infliximab, antichimeric antibodies, antibodies to infliximab, serum adalimumab, antibodies to adalimumab, serum vedolizumab, antibodies to vedolizumab, Anser IFX, Anser ADA, Anser VDZ, Humira, Remicade, Entyvio

Approved by Governing Bodies:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus® Laboratories(San Diego, CA), a College of American Pathologists–accredited lab under CLIA, offers non-radiolabeled, fluid-phase HMSA tests called Anser™ IFX (for infliximab), Anser™ ADA (for adalimumab), and Anser™ VDZ for vedolizumab. These tests are not based on an enzyme-linked immunosorbent assay, and each can measure antidrug antibodies in the presence of detectable drug levels, improving on a major limitation of the enzyme-linked immunosorbent assay method. Both tests measure serum drug concentrations and antidrug antibodies.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

84999 unlisted chemistry procedure

References:

1. Afif W, Loftus EV, Jr., 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(5):1133-9.
2. Ara-Martin M, Pinto PH, Pascual-Salcedo D. Impact of immunogenicity on response to anti-TNF therapy in moderate-to-severe plaque psoriasis: results of the PREDIR study. J Dermatolog Treat. Nov 2017; 28(7):606-612.
3. Arstikyte I, Kapleryte G, Butrimiene I, et al. Influence of Immunogenicity on the Efficacy of Long-Term Treatment with TNF alpha Blockers in Rheumatoid Arthritis and Spondyloarthritis Patients. Biomed Res Int. 2015; 2015:604872.
4. Bartelds GM, Krieckaert CM, Nurmohamed MT et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA 2011; 305(14):1460-68.
5. Bendtzen K, Geborek P, Svenson M et al. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum 2006; 54(12):3782-9.
6. Bendtzen K. Personalized medicine: theranostics (therapeutics diagnostics) essential for rational use of tumor necrosis factor-alpha antagonists. Discov Med. Apr 2013; 15(83):201-11.
7. Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. Inflamm Bowel Dis 2009; 15(8):1264-75.
8. Castillo-Gallego C, Aydin SZ, Marzo-Ortega H. Clinical utility of the new ASAS criteria for spondyloarthritis and the disease activity score. Curr Rheumatol Rep. Oct 2011; 13(5):395-401.
9. Cludts I, Spinelli FR, Morello F, et al. Anti-therapeutic antibodies and their clinical impact in patients treated with the TNF antagonist adalimumab. Cytokine. Aug 2017; 96:16-23.
10. Dubeau MF, Ghosh S. Optimizing infliximab therapy for inflammatory bowel disease-the tools are getting sharper. Gastroenterol Hepatol 2012; 8(2):134-6.
11. Eser A, Primas C, Reinisch W. Drug monitoring of biologics in inflammatory bowel disease. Curr Opin Gastroenterol. Jul 2013; 29(4):391-396.

12. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013; 369: 699-710.
13. Finckh A, Dudler J, Wermelinger F et al. Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients. Joint Bone Spine 2010; 77(4):313-8.
14. Frederiksen MT, Ainsworth MA, Brynskov J, et al. Antibodies against infliximab are associated with de novo development of antibodies to adalimumab and therapeutic failure in infliximab-to-adalimumab switchers with IBD. Inflamm Bowel Dis. Oct 2014; 20(10):1714-21.
15. Garces S, Antunes M, Benito-Garcia E, et al. A preliminary algorithm introducing immunogenicity assessment in the management of patients with RA receiving tumour necrosis factor inhibitor therapies. Ann Rheum Dis. Jun 2014; 73(6):1138-1143.
16. Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Annals of the rheumatic diseases 2012.
17. Hernandez-Breijo B, Chaparro M, Cano-Martinez D, et al. Standardization of the homogeneous mobility shift assay protocol for evaluation of anti-infliximab antibodies. Application of the method to Crohn's disease patients treated with infliximab. Biochem Pharmacol. Sep 21 2016.
18. Jani M, Chinoy H, Warren RB, et al. Clinical utility of random anti-tumor necrosis factor drug-level testing and measurement of antidrug antibodies on the long-term treatment response in rheumatoid arthritis. Arthritis Rheumatol. May 2015; 67(8):2011-9.
19. Khanna R, Sattin BD, Afif W, et al. Review article: a clinician's guide for therapeutic drug monitoring of infliximab in inflammatory bowel disease. Aliment Pharmacol Ther. Sep 2013; 38(5):447-459.
20. Kopylov U, Mazor Y, Yavzori M et al. Clinical utility of antihuman lambda chain-based enzyme-linked immunosorbent assay (ELISA) versus double antigen ELISA for the detection of anti-infliximab antibodies. Inflammatory bowel diseases 2012; 18(9):1628-33.
21. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. Mar 2010; 105(3):501-523; quiz 524.
22. Korswagen LA, Bartelds GM, Krieckaert CL et al. Venous and arterial thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies: a case series and cohort study. Arthritis and rheumatism 2011; 63(4):877-83.
23. 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. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. Am J Gastroenterol. Feb 2009; 104(2):465-483; quiz 464, 484.
25. Lichtenstein GR. Comprehensive review: antitumor necrosis factor agents in inflammatory bowel disease and factors implicated in treatment response. Therap Adv Gastroenterol. Jul 2013; 6(4):269-293.
26. Masson PL. Thromboembolic events and anti-tumor necrosis factor therapies. International immunopharmacology 2012; 14(4):444-5.

27. Meroni PL, Valentini G, Ayala F, et al. New strategies to address the pharmacodynamics and pharmacokinetics of tumor necrosis factor (TNF) inhibitors: A systematic analysis. Autoimmun Rev. Sep 2015; 14(9):812-29.
28. 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. The American journal of gastroenterology 2013; 108(1):40-7; quiz 48.
29. National Institute for Health and Care Excellence (NICE). 2015; www.nice.org.uk/news/press-and-media/nice-says-more-research-needed-on-tests-to-help-guide-treatment-of-digestive-disorder.
30. National Institute for Health and Care Excellence (NICE). Therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits). www.nice.org.uk/guidance/dg22/chapter/1-Recommendations. Accessed October 31, 2016.
31. National Institute for Health and Care Excellence. Crohn's disease: management in adults, children and young people. NICE guidelines [CG152], October 2012. www.nice.org.uk/guidance/CG152.
32. National Institute for Health and Care Excellence. Infliximab (review) and adalimumab for the treatment of Crohn's disease. NICE technology appraisals [TA187], May 2010. www.nice.org.uk/Guidance/TA187.
33. Ordas I, Mould DR, Feagan BG et al. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther 2012; 91(4):635-46.
34. Pecoraro V, De Santis E, Melegari A, et al. The impact of immunogenicity of TNFalpha inhibitors in autoimmune inflammatory disease. A systematic review and meta-analysis. Autoimmun Rev. Jun 2017; 16(6):564-575.
35. Plasencia C, Pascual-Salcedo D, Nuno L et al. Influence of immunogenicity on the efficacy of longterm treatment of spondyloarthritis with infliximab. Annals of the rheumatic diseases 2012; 71(12):1955-60.
36. Raine T. Vedolizumab for inflammatory bowel disease: Changing the game, or more of the same? United European Gastroenterology 2014; Vol. 2(5) 333-344.
37. Roblin X, Marotte H, Rinaudo M, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. Jan 2014; 12(1):80-84 e82.
38. Roblin X, Rinaudo M, Del Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. Am J Gastroenterol. Aug 2014; 109(8):1250-1256.
39. Sanborn WJ, Feagan BG, Rutgeerts P, et. al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013; 369:711-721.
40. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment had failed. Gastroenterology 2014; 147: 618-627.
41. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: A multi-center cohort. Inflamm Bowel Dis. 2015 Aug 17. MPID 26288002

42. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). May 2012; 64(5):625-39.
43. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. Mar 2014; 73(3):492-509.
44. Steenholdt C, Bendtzen K, Brynskov J et al. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. Scand J Gastroenterol 2011; 46(3):310-8.
45. Steenholdt C, Bendtzen K, Brynskov J, et al. Clinical implications of measuring drug and anti-drug antibodies by different assays when optimizing infliximab treatment failure in Crohn's disease: post hoc analysis of a randomized controlled trial. Am J Gastroenterol. Jul 2014; 109(7):1055-1064.
46. Steenholdt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut. Jun 2014; 63(6):919-927.
47. Tan M. Importance of defining loss of response before therapeutic drug monitoring. Gut. Jul 16 2014.
48. Thomas SS, Borazan N, Barroso N, et al. Comparative immunogenicity of TNF inhibitors: impact on clinical efficacy and tolerability in the management of autoimmune diseases. A systematic review and meta-analysis. BioDrugs. Aug 2015; 29(4):241-58.
49. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League against Rheumatism Criteria. Arthritis Rheum. Jan 1996; 39(1):34-40.
50. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol. Jun 2013; 108(6):962-71.
51. Wang SL, Hauenstein S, Ohrmund L et al. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. Journal of pharmaceutical and biomedical analysis 2013; 78-79:39-44.
52. 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(1-2):177-88.
53. White CM, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews methods guide for effectiveness and comparative effectiveness reviews. Rockville MD 2008.

Policy History:

Medical Policy Group, August 2012 **(1):** New policy adopted from MPP update
Medical Policy Administration Committee, October 2012
Available for comment October 24 through December 10, 2012
Medical Policy Panel, September 2013

Medical Policy Group, September 2013 **(1):** Title changed to add "and Adalimumab;" "Measurement of antibodies to adalimumab in a patient receiving adalimumab, either alone or as a combination test which includes the measurement of serum adalimumab levels" added to the policy statement; considered investigational; update to Key Points and References related to infliximab with no change to policy statement
Medical Policy Administration Committee September 2013
Available for comment September 19 through November 2, 2013
Medical Policy Panel, October 2014
Medical Policy Group, October 2014 **(1):** No policy change. Update to Key Points and References.
Medical Policy Panel, November 2015
Medical Policy Group, November 2015 **(3):** 2015 Updates to Description, Key Points, Approved by Governing Bodies & References; no change to policy statement.
Medical Policy Panel, November 2016
Medical Policy Group, November 2016 **(3):** 2016 Updates to Key Points & References; no change to policy statement.
Medical Policy Panel, November 2017
Medical Policy Group, November 2017 **(3):** 2017 Updates to Description, Key Points & References; no change to policy statement.
Medical Policy Group, July 2018 **(5)**: 2018 updated policy statement to clarify that Measurement of antibodies to vedolizumab is considered investigational. This has always been considered investigational; Updated Key Points, Key Words: (serum vedolizumab, antibodies to vedolizumab, Anser VDZ, Entyvio), and References.
Medical Policy Administration Committee July 2018
Available for comment July 11 through August 24, 2018

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.