BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Medical Policy

Title: Measurement of Serum Antibodies to Infliximab and Adalimumab

Professional
Original Effective Date: March 5, 2013
Revision Date(s): June 7, 2013;
January 23, 2015; February 9, 2016;
May 10, 2017; December 20, 2017;
February 27, 2019
Current Effective Date: January 23, 2015

Institutional
Original Effective Date: July 8, 2013
Revision Date(s): July 8, 2013;
January 23, 2015; February 9, 2016;
May 10, 2017; December 20, 2017;
February 27, 2019
Current Effective Date: January 23, 2015

Populations	Interventions	Comparators	Outcomes
Individuals: • With rheumatoid, psoriatic, or juvenile idiopathic arthritis; inflammatory bowel diseases; ankylosing spondylitis; psoriasis	Interventions of interest are: • Evaluation for anti–tumor necrosis factor α inhibitor antibodies to infliximab or adalimumab	Comparators of interest are: • Standard of care	Relevant outcomes include: • Test validity • Change in disease status • Health status measures • Quality of life • Treatment-related morbidity

DESCRIPTION

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 (RA), Crohn disease (CD), ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira) is a subcutaneous TNF-α inhibitor that is approved by the Food and Drug Administration for treatment of Crohn 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 a cause of this secondary nonresponse.

Objective

The objective of this evidence review is to evaluate and compare the net health outcome of 2 types of treatment: the first, when serum antibody testing for infliximab and/or adalimumab is used in patients being managed with those drugs; the second, when a patient receives standard of care to manage conditions (eg, rheumatoid arthritis, Crohn disease, ulcerative colitis) associated with the aforementioned drugs.

Background

Infliximab and Adalimumab in Autoimmune Disease

Infliximab is a chimeric (mouse/human) anti-tumor necrosis factor α (TNF-α) monoclonal antibody. Adalimumab is a fully human monoclonal antibody to TNF-α. Use of monoclonal antibodies has revolutionized therapy for patients with inflammatory diseases such as inflammatory bowel disease (eg, 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. It is estimated that 1 in 3 patients do not respond to induction therapy (primary nonresponse), further, among initial responders, response wanes over time in approximately 20% to 60% of patients (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to antidrug antibodies (ADA).[1] ADA are also associated with injection-site reactions (adalimumab) and acute infusion reactions and delayed hypersensitivity reactions (infliximab). As a fully human antibody, adalimumab is considered less immunogenic than chimeric antibodies, like infliximab.

Detection of ADA

The detection and quantitative measurement of ADA is difficult, owing to drug interference and identifying when antibodies likely to have a neutralizing effect. First-generation assays, (ie, enzyme-linked immunosorbent assays [ELISA]) can measure only ADA 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, along with safety concerns related to the handling of radioactive material. The homogenous mobility shift assay measures ADA when infliximab is present in the serum. Studies evaluating the validation of results among different assays are lacking, making interstudy comparisons difficult. One retrospective study by Kopylov et al (2012) which evaluated 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with IBD (ie, double antigen ELISA and antihuman lambda chain-based ELISA).[2] 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.

Regulatory Status
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 Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA 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, a College of American Pathologists–accredited lab under CLIA, offers non-radio-labeled, fluid-phase homogenous mobility shift assay (HMSA) tests called Anser™ IFX (for infliximab) and Anser™ ADA (for adalimumab). Neither is based on an enzyme-linked immunosorbent assay (ELISA) test, and each can measure antidrug antibodies (ADA) in the presence of detectable drug levels, improving on a major limitation of the ELISA method. Both tests measure serum drug concentrations and antidrug antibodies.

POLICY

A. 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, is considered **experimental / investigational**.

B. 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, is considered **experimental / investigational**.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through September 6, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Antibodies to Infliximab and Adalimumab
Clinical Context and Test Purpose
The purpose of testing anti-tumor necrosis factor α (TNF-α) inhibitor antibodies to infliximab (ATI) or adalimumab (ATA) in patients with arthritis (eg, rheumatoid, psoriatic, or juvenile idiopathic), inflammatory bowel disease (IBD), ankylosing spondylitis, or plaque psoriasis is to improve health outcomes.

The question addressed in this evidence review is: Does testing anti-TNF-α inhibitor ATI or ATA in patients with arthritis (eg, rheumatoid, psoriatic, or juvenile idiopathic), IBD, ankylosing spondylitis, or psoriasis improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with arthritis (eg, rheumatoid, psoriatic, or juvenile idiopathic), IBD, ankylosing spondylitis, or plaque psoriasis.

Interventions
The test being considered is an evaluation for anti-TNF-α inhibitor ATI or ATA.

Comparators
The following practice is currently being used to manage arthritis, IBD, ankylosing spondylitis, or plaque psoriasis: standard of care.

Outcomes
The general outcomes of interest are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity.

Timing
Follow-up over months to years is of interest for the relevant outcomes.

Setting
Patients are actively managed by rheumatologists, gastroenterologists, and primary care providers in an outpatient setting.

Study Selection Criteria
For the evaluation of clinical validity of this test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

There is a substantial body of evidence (numerous systematic reviews and meta-analyses) examining associations between antidrug antibodies (ADA) and nonresponse as well as injection- or infusion-site reactions. Accordingly, this review of the evidence on clinical validity focuses on the most current systematic reviews (see Tables 1-3) and studies published after the search dates of those reviews,[3] as well as relevant studies not included in identified reviews (eg, those focusing on adverse reactions and ADA).

Systematic Reviews
Six reviews published from 2012 through 2017 were identified.[4,5,6,7,8,9] The number of studies included ranged from 11[7] to 68,[8] varying by review objectives and conditions of interest. Although not delineated here, there was considerable overlap in selected studies across reviews.

The systematic review and meta-analysis by Pecoraro et al (2017) selected 34 studies (total N=4273 patients), including randomized controlled trials (RCTs; n=4), prospective observational (n=22), retrospective observational (n=6), and cross-sectional (n=2).[9] Studies evaluated rheumatoid arthritis (RA; n=18), ulcerative colitis (n=2), Crohn disease (CD; n=5), psoriatic arthritis (n=4), ankylosing spondylitis (n=5), plaque psoriasis (n=4), and spondyloarthritis (SpA; n=1). Most 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), or poor (n=1). The effect of ADA was evaluated in 19 studies, showing a significant ($p<0.05$) reduction of response (relative risk [RR], =0.43; 95% confidence interval [CI], 0.3 to 0.63) in ADA-positive patients relative to ADA-negative patients, with adalimumab therapy demonstrating a greater reduction (RR=0.40; 95% CI, 0.25 to 0.65; $p<0.001$) than infliximab (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 on 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 methotrexate therapy relative to treated those without methotrexate (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-tumor necrosis factor α (TNF-α) serum concentration (see Table 5). Of the 20 studies (n>2800 patients) 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 events, and 5% (n=1 study) developed serious adverse events. Although ADA significantly reduced TNF-αresponse, the results should be viewed cautiously due to reported study limitations, including small numbers of studies assessed and considerable heterogeneity.

The systematic review and meta-analysis by Thomas et al (2015) included 68 studies (total N=14651 patients).[8,] 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 enzyme-linked immunosorbent assays (ELISA). 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. 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). Evaluation of potential publication bias and overall assessment (eg, GRADE or similar) for the body of evidence were 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).[4,] 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 radioimmunoassay (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 (eg, 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.

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.[7,] Several databases were searched to February 2012 (one was searched to August 2012). Eleven studies involving 707 patients were selected. Six studies (2 RCTs, 1prospective cohort study, 3 retrospective cohort studies) were included. Selected studies failed at least 1 quality domain (study eligibility criteria, measurement of exposure and outcome, control for confounders, completeness of follow-up), and all studies had a 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 a 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 the requirement for surgery or presence of a nonhealing fistula. Patients with ATIs had a 3-fold greater risk of loss of response than those without ATIs (RR=3.2; 95% CI, 2.0 to 5.0; shown in Table 2 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 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 was limited by variability in the method of ATI detection (double-antigen ELISA, antihuman lambda chain-based ELISA, fluid-phase RIA).

Garces et al (2013) performed a meta-analysis of studies of infliximab and adalimumab used to treat RA, IBD, SpA, and psoriasis.[5] Databases were searched to August 2012, and reviewers selected 12 prospective cohort studies involving 860 patients (540 with RA, 132 with SpA, 130 with IBD, 58 with psoriasis). The outcome of interest was a response, assessed using standard assessment scales for rheumatologic diseases (eg, European League Against Rheumatism criteria for RA; 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 RR=0.32). Significant heterogeneity was introduced by varying use of immunosuppressant therapy (eg, methotrexate) across studies. To assess ADA, most studies used RIA, which is less susceptible than ELISA to drug interference and may be more accurate.

Lee et al (2012) conducted a meta-analysis of patients with IBD receiving infliximab to estimate the prevalence of ATI, the effect of ATI on the prevalence of infusion reactions, and the effect of ATI on disease remission rates.[6,] Databases were searched through October 2011, and 18 studies (total N=3326 patients) were selected. Studies included 9 RCTs, 5 prospective cohort studies, and 4 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 (see Table 1). Patients with ATI were less likely to be in clinical remission (see Table 2), but this finding was not statistically significant (RR=0.90; p=0.10). Rates of infusion reactions were significantly higher in patients with ATI (RR=2.07; 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.

Table 1. Estimated Prevalence of ADA From Meta-Analyses

Study	Included Studies	Drugs			Disease			Prevalence of ADA	
		IFX	ADL	Other[a]	IBD	RA	SpA	Pooled (95% CI), %	Range in Studies, %
Lee et al (2012) [6],	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 et al (2013)[7],	11	•			•				22.4-46
Thomas et al (2015)[8],	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 et al (2015)[4],	14	•				•			19-47
	14	•			•				15-61
	5	•					•[d]		26-50
	12		•			•			5-54
	3		•		•				9-46
	3		•				•[d]		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-Analyses of ADA and Clinical Response

Study	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 et al (2012)[6],	18	•			•			0.90 (0.79 to 1.02)		37%
Nanda et al (2013)[7],	11	•			•			0.33 (0.20 to 0.40)		70%
Garces et al (2013)[5],	12	•	•		•	•	•[b]	0.32 (0.22 to 0.48)		46%
Thomas et al (2015)[8],	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 ADA

Study	Included Studies	Drugs			Disease			Adverse Reactions: ADA vs None	
		IFX	ADL	Other[a]	IBD	RA	SpA	OR (95% CI)	RR (95% CI)
Lee et al (2012)[6]	18	●			●				2.07 (1.61 to 2.67)[a]
Thomas et al (2015)[8,]	NR	●	●	●	●	●	●	3.25 (2.35 to 4.51)	

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] Infusion reaction.

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	<0.001
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

Adapted from Pecoraro et al (2017).[9,]
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; I^2: heterogeneity measure; MD: mean difference; NR: not reported.

Table 5. Evaluation of Anti-TNF-a Concentration

Outcome Measures	No. of Studies	MD, mg/L	95% Confidence Interval	I^2, %	p
ADA-positive vs ADA-negative	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).[9,]
ADA: antidrug antibodies; DAS28: Disease Activity Score in 28 joints; I^2: heterogeneity measure; MD: mean difference; TNF: tumor necrosis factor.

Cohort Studies

BCBSA identified several publications not included in a systematic review. The results of the most recent publications are consistent with conclusions of the systematic reviews.

Cludts et al (2017) conducted a single-center retrospective cohort analysis of patients with RA (n=18), psoriatic arthritis (n=9), or ankylosing spondylitis (n=12) in Italy.[10,] Serum samples were taken prior to adalimumab therapy and after 12 and 24 weeks of treatment. Psoriatic arthritis and ankylosing spondylitis patients were grouped together (SpA) due to axial involvement in all psoriatic arthritis patients. Although adalimumab levels varied among patients (0 to 30 mg/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 adalimumab. 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 adalimumab interference. There was a negative correlation between ATA levels and adalimumab in all groups, with 43.6% and 41% of the adalimumab-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 between adalimumab trough levels and Disease Activity Score in 28 joints (DAS28) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores ($p<0.001$). There were no significant differences in BASDAI scores between ATA-positive and ATA-negative patients at 12 or 24 weeks. Study findings are consistent with others, suggesting that adalimumab levels can serve as an indicator of ATA; however, limitations included small sample size, retrospective research design, and failure to confirm neutralization 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.[11] All patients experienced secondary nonresponse to adalimumab (n=65), etanercept (n=47), and infliximab (n=19) after 6 or more months of treatment. Serum ADA was identified in 48%, 0%, and 42% 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 (>2). Physician Global Assessment values for ADA-positive vs ADA-negative patients were significantly worse in the adalimumab group (3.7 vs3.2; $p=0.02$) but not in the infliximab group. There was a significant negative linear correlation between serum drug concentrations and ADA in the adalimumab group ($p=0.001$) and among the 3 groups combined ($p=0.001$), and a significant ($p=0.019$) correlation between serum ADA titer and body surface area. Unlike the other studies, in this study, the use of concomitant antirheumatic drugs was not associated with anti-TNF immunogenicity in any of the groups. This study provided 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 were 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) evaluated possible confounding factors by analyzing adalimumab treatment for psoriasis in 5 distinct groups, including individuals who received: biologic therapies after switching from adalimumab (n=20); ongoing adalimumab therapy (n=30); novel adalimumab therapy (n=30); biologic therapies other than adalimumab (n=15); and no treatment with immunosuppressants or biologics (n=15), serving as a quasi-control.[12,] The clinical severity of psoriasis was scored using the PASI. At 12-month follow-up, ADA was highest (87%) in patients who received biologic therapies after switching from adalimumab. The false-positive rate was 23% for adalimumab detection and 22% for anti-adalimumab antibodies in individuals who were never treated with adalimumab. There were no significant differences in median PASI scores between the anti-adalimumab antibody-negative patients (1.1) and the anti-adalimumab 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 adalimumab. Additionally, there were no significant differences in TNF-α and C-reactive protein concentrations. Study limitations included the observational design, small sample size, use of ELISA to measure ADA, and high variability of results. The authors concluded that the assay has limited clinical utility.

Arstikyte et al (2015) prospectively evaluated the association between ADA and adverse events, clinical response, and serum drug levels in 143 symptomatic patients (62 with RA, 81 with SpA; mean age, 45 years) treated with TNF blockers in Lithuania.[13] All patients receiving adalimumab or infliximab were tested and 1 in 3 patients was given etanercept (because it is more commonly used). A response in RA patients was defined as either good, moderate, or low using European League Against Rheumatism criteria[14]; SpA disease activity was considered inactive, moderate, high, or very high by established criteria,[15] with inactive and moderately active disease defined as a response. At least 3 months after therapy initiation, a single serum sample was obtained prior to dosing between 2012 and 2013; disease activity and other patient characteristics (eg, 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 a 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). ATI 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 were the small number of nonresponders and lack of specificity on whether any eligible participants declined enrollment.

Jani et al (2015) measured ADA and RIA together, with drug levels in 331 RA patients treated with adalimumab (n=160) or etanercept (n=171) between 2008 and 2013.[16] Patients were participants in the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate, conducted in 60 centers across the United Kingdom. Disease activity was assessed using the DAS28. Response was evaluated using European League Against Rheumatism 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 6 months) and were associated with lower serum drug levels. Both routine (nontrough) drug levels and ATA were associated with DAS28 scores at 12 months. In predicting European League Against Rheumatism nonresponse, the area under the curve for an adalimumab concentration less than 5 mg/mL at 3 months was 0.66 (95% CI, 0.55 to 0.77) and 0.68 (95% CI, 0.54 to 0.81) for the presence of ADA. 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 serum levels were not used to inform treatment decisions. Study results corroborated other research findings.

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.[17] 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: the positive predictive value was 91% (95% CI, 59% to 100%), sensitivity was 50% (95% CI, 27% to 73%); the 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.

While many studies have evaluated the clinical validity using single ADA measurements, at least one assessed their persistence over time. Vande Casteele et al (2013) analyzed infliximab trough and ATI levels using a homogeneous mobility shift assay with banked serum obtained from 90 IBD patients treated between 1999 and 2011.[18] 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 C-reactive protein levels. ATI were detected in 53 (59%) of 90 patients but subsequently were nondetectable in 15 (28%) of the 53. Persistent ATIs were associated with discontinuation of infliximab (RR=5.1; 95% CI, 1.4 to 19.0), but the wide CI reflects considerable uncertainty. Although the transience of ATI in IBD has not been carefully scrutinized, if replicated, these results would suggest interpreting a single ATI result cautiously.

Section Summary: Clinically Valid
A large body of evidence has evaluated the clinical validity of ADA testing. ADA has been associated with secondary nonresponse in RA, SpA, and possibly IBD. The presence of ADA has been consistently associated with an increased risk of an 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 adalimumab to treat psoriasis.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Several algorithms have been developed to manage patients with IBD[19,20,21] and RA[22] 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).

Steenholdt et al (2014) reported on 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.[23] Patients were randomized to infliximab dose intensification (5 mg/kg every 4 weeks) or algorithmic treatment based on serum infliximab level and ATI. Patients with subtherapeutic infliximab level (<0.5 μg/mL[24]) had the 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 were unaware, but investigators were aware of test results). Randomized groups were similar at baseline; overall, 55 (80%) of 69 patients had nonfistulizing disease. Most patients (70%) had therapeutic serum infliximab levels without detectable ATI; revised diagnoses in 6 (24%) of 25 such patients in the algorithm arm[25,] included bile acid malabsorption, strictures, and irritable bowel syndrome. 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 score for patients with nonfistulizing 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 intention-to-treat 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 the 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 (ie, 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 nonfistulizing disease), only a subjective measure of treatment response was used (minimum 70-point reduction from baseline CDAI).

Roblin et al (2014) conducted a single-center, prospective observational study of 82 patients with IBD (n=45 CD, n=27 ulcerative colitis) with clinical relapse (CDAI score >220 or Mayo Clinic score >5) during treatment with adalimumab 40 mg every 2 weeks.[26,] 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 score <150 or Mayo score <2) within 4 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 6 months were compared across 3 groups: (1) those with a therapeutic adalimumab level (>4.9 μg/mL[27]), (2) those with a subtherapeutic adalimumab level and undetectable ATA; and (3) those with a 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 1 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 ulcerative colitis) 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 1 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 included 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. A subsequent study comparing the management using the algorithm proposed with usual care is needed. Finally, the lead author of the study received lecture fees from the ADA test provider (Theradiag).

Afif et al (2010) evaluated the clinical utility of measuring ATI (referred to as human antichimeric antibodies in the study) and infliximab concentrations by retrospectively reviewing patient medical records.[28] 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 a 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.[28] Study limitations included the retrospective design and use of 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 aremeasured.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of testing anti-TNF-α inhibitor ATI or ATA in this population has not been established, a chain of evidence supporting clinical utility cannot be constructed.

Section Summary: Clinically Useful

Convincing evidence for the clinical utility of ADA testing is currently 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 included a lack of clinical follow-up after treatment decisions were made and lack of clinical assessments to guide treatment decisions. 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. Methodologic 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, the Lichtenstein (2013) systematic review of infliximab-related infusion reactions concluded: "…there is a paucity of systematic and controlled data on the risk, prevention, and management of infusion reactions to infliximab."[21,]

Summary of Evidence

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (eg, Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for anti-TNF-α inhibitor ATI or to ATA, the evidence includes multiple systematic reviews, a randomized controlled trial, and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. ATI or ATA 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.

Practice Guidelines and Position Statements

American College of Gastroenterology Institute

The American College of Gastroenterology Institute (2017) published guidelines on therapeutic drug monitoring in inflammatory bowel disease.[29,] The guidelines note that "When anti-drug antibodies are detected, it is unclear what antibody level is clinically meaningful…. the reporting of anti-drug antibodies is variable between commercial assays, with some assays being very sensitive for detecting very-low-titer antibodies of limited clinical significance. Uniform thresholds for clinically relevant antibody titers are lacking. At this time, it is unclear how antibodies affect drug efficacy when both active drug and antibodies are detected.

In cases of low trough concentrations and low or high anti-drug antibodies, the evidence to clarify optimal management is lacking."

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2016) issued guidance on therapeutic monitoring of tumor necrosis factor α inhibitors in the treatment of patients with Crohn disease.[30,] The Institute recommended that laboratories monitoring tumor necrosis factor α inhibitors in patients with Crohn disease who have lost response to the treatment should "work with clinicians to collect data through a prospective study, for local audit, or for submission to an existing registry."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01638715	A Randomized, Multi-Center Biomarker Trial to Predict Therapeutic Responses of Patients With Rheumatoid Arthritis to a Specific Biologic Mode of Action	200	Jun 2018 (ongoing)
Unpublished			
NCT01971918	Comparative Analysis of Two Therapeutic Strategies in Patients With Spondyloarthritis Treated With Anti-TNF Biologics (STRADA)	104	Apr 2017 (terminated)
NCT01895764	Effect of the Combination of Methotrexate and Adalimumab on Reduction of Immunization in Ankylosing Spondylitis (COMARIS)	110	Apr 2015 (completed)

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

84999 Unlisted chemistry procedure

- According to materials from Prometheus Laboratories on Anser™IFX, and Anser™ ADA, these tests will be reported using 1 unit of CPT code 84999.

DIAGNOSES

Experimental / investigational for all diagnoses related to this policy.

REVISIONS	
06-07-2013	Policy added to the bcbsks.com web site.
	Effective for Institutional providers 30 days after the Revision Date, 07-08-2013.
01-23-2015	Title updated from "Measurement of Serum Antibodies to Infliximab" to "Measurement of Serum Antibodies to Infliximab and Adalimumab"
	Description section updated
	In Policy section: ▪ Added the indication of "B. 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, is considered experimental / investigational."
	Rationale section updated
	In Coding section: ▪Updated coding comments
	References updated
02-09-2016	Description section updated
	Rationale section updated
	References updated
05-10-2017	Description section updated
	Rationale section updated
	References updated
12-20-2017	Description section updated
	Rationale section updated
	References updated
02-27-2019	Description section updated
	Rationale section updated
	References updated

REFERENCES

1. Bendtzen K. Personalized medicine: theranostics (therapeutics diagnostics) essential for rational use of tumor necrosis factor-alpha antagonists. Discov Med. Apr 2013;15(83):201-211. PMID 23636137
2. 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. Inflamm Bowel Dis. Sep 2012;18(9):1628-1633. PMID 22038899
3. 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: Agency for Healthcare Research and Quality; 2008.
4. 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):812-829. PMID 25985765
5. 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. Ann Rheum Dis. Dec 2013;72(12):1947-1955. PMID 23223420
6. 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. May 27 2012;24(9):1078-1085. PMID 22647738
7. 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. Jan 2013;108(1):40-47; quiz 48. PMID 23147525

8. 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):241-258. PMID 26280210
9. 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. PMID 28411169
10. 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. PMID 28279855
11. 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. PMID 28274164
12. Lombardi G, Perego S, Sansoni V, et al. Anti-adalimumab antibodies in psoriasis: lack of clinical utility and laboratory evidence. BMJ Open. Dec 09 2016;6(12):e011941. PMID 27940624
13. 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. Jun 2015;2015:604872. PMID 26064930
14. 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. PMID 8546736
15. 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. PMID 21748416
16. 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):2011-2019. PMID 26109489
17. 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):1714-1721. PMID 25069030
18. 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):962-971. PMID 23419382
19. Eser A, Primas C, Reinisch W. Drug monitoring of biologics in inflammatory bowel disease. Curr Opin Gastroenterol. Jul 2013;29(4):391-396. PMID 23703367
20. 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. PMID 23848220
21. 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. PMID 23814608
22. 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. PMID 23666932
23. 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. PMID 23878167
24. 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. Mar 2011;46(3):310-318. PMID 21087119
25. Tan M. Importance of defining loss of response before therapeutic drug monitoring. Gut. Mar 2015;64(3):516-517. PMID 25031226
26. 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. PMID 24913041

27. 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. PMID 23891927
28. 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. May 2010;105(5):1133-1139. PMID 20145610
29. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology. Sep 2017;153(3):827-834. PMID 28780013
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) [DG22]. 2016; https://www.nice.org.uk/guidance/dg22/chapter/1-Recommendations. Accessed October 28, 2018.