Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Measurement of Serum and Anti-Drug Antibody Levels for Selected Biologic Agents

Description/Background

Biologic agents used to treat autoimmune diseases include infliximab, adalimumab, vedolizumab, and ustekinumab. Infliximab (Remicade) is an intravenous tumor necrosis factor α blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira) is a subcutaneous tumor necrosis factor α inhibitor that is FDA approved for the treatment of rheumatoid arthritis, Crohn disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis in adults and those with juvenile idiopathic arthritis, hidradenitis suppurativa, and uveitis. Vedolizumab (Entyvio) is an intravenous integrin receptor antagonist that is FDA approved for treatment of ulcerative colitis and Crohn disease in adults. Ustekinumab (Stelara) is an intravenous and subcutaneous human interleukin-12 and -23 antagonist that is FDA approved for the treatment of, Crohn disease and ulcerative colitis in adults, and psoriatic arthritis and plaque psoriasis in children and adults. Following the primary response to these medications, some patients become secondary non-responders. The development of antidrug antibodies is considered a cause of this secondary nonresponse.

Infliximab, Adalimumab, Ustekinumab and Vedolizumab in Autoimmune Disease
Biologic agents (e.g. infliximab, adalimumab, vedolizumab, or ustekinumab) are used to treat multiple inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis; inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis), ankylosing spondylitis, and plaque psoriasis. These agents are generally given to patients who fail conventional medical therapy, and they are typically highly effective for the 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] Antidrug antibodies are also associated with injection-site reactions and acute infusion reactions and delayed hypersensitivity reactions.

Infliximab and Adalimumab in Inflammatory Bowel Disease
Drug levels are important in the management individuals with inflammatory bowel disease to determine effectiveness of treatment and to maintain remission. While symptoms can be used as a clinical guide, this is suboptimal because often by the time symptoms appear, significant damage has already been done, such as a stricture that is irreversible.

There is widespread consensus that in adults and children with IBD we should measure levels at the end of induction to adjust dosing to measure remission. There is evidence that for growing children, drug levels should be measured proactively as they grow, even if they are clinically doing well.

It is not necessary to measure anti-drug antibody levels in most patients. Most of the labs (Mayo, Esoterix, etc.) have a two-step reflexive test. They measure the drug level. Then if the level is low, then they reflexively measure antibodies. They do not measure antibodies if the drug level is high.

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 immunosorbent assays [ELISA]) can only measure antidrug antibodies in the absence of detectable drug levels due to interference of the drug with the assay, limiting clinical utility. 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 HMSA measures antidrug antibodies when infliximab is present in the serum. Studies evaluating the validation of the results between different assays are lacking, making inter-study comparisons difficult. One retrospective study by Kopylov et at (2012) which evaluated 63 patients, demonstrated comparable diagnostic accuracy between two different ELISA methods, i.e., double antigen ELISA and antihuman lambda chain ELISA.[2] This study did not include an objective, clinical and endoscopic scoring system for validation of results.

Treatment Options for Secondary Nonresponse to Biologic Agents
A diminished or suboptimal response to infliximab, adalimumab, ustekinumab or vedolizumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different biologic agent (in patients who continue to have loss of response after receiving the increased dose), or switching to a non-biologic 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 Act (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 Inc. is a College of American Pathologists-accredited lab under the Clinical Laboratory Improvement Amendments, offers four non-radiolabeled, fluid-phase HMSA tests called Anser™ IFX for infliximab, Anser™ ADA for adalimumab and Anser® VDZ for Vedolizumab, and Anser® UST for ustekinumab. The tests measure both serum drug concentrations and antidrug antibodies. They are not based on an ELISA test, and can measure antidrug antibodies in the presence of detectable drug levels, improving on a major limitation of the ELISA method.

These tests were developed, and their performance characteristics determined by Prometheus Laboratories Inc. Neither has been cleared or approved by FDA.

Medical Policy Statement

Measurement of biologic agent drug levels and, if low, anti-drug antibody levels in individuals with inflammatory bowel disease (IBD) is established.

Measurement of antidrug antibodies in other individuals being treated with a biologic agent, either alone or as a combination test, which includes the measurement of serum TNF blocking agent levels, is considered experimental/ investigational. The use of these tests have not been clinically proven to improve patient clinical outcomes or alter patient management.

Inclusionary and Exclusionary Guidelines

Inclusions:

Biologic agent drug levels are established in individuals who are:

- diagnosed with inflammatory bowel disease **AND**
- being treated with either Adalimumab, Infliximab, Ustekinumab, and Vedolizumab **AND**
- being monitored for their response to the agent by biologic agent drug level

If the biologic agent drug level is below the therapeutic range, testing for the anti-drug antibody level is established.

Exclusions:

- Any condition other than inflammatory bowel disease

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

80145	80230	80280	80299[a]	82397[b]	83520[b]

Other codes (investigational, not medically necessary, etc.):

84999

[a] When this code apply to Ustekinumab drug level testing
[b] When these codes are used for anti-drug antibody level testing

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Rationale

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, ADALIMUMAB, USTEKINUMAB AND VEDOLIZUMAB

Clinical Context and Test Purpose
The purpose of testing serum antibodies to infliximab (ATI), adalimumab (ATA), ustekinumab (UST) or vedolizumab (VDZ) in patients with arthritis (e.g., rheumatoid, psoriatic, or juvenile idiopathic), inflammatory bowel disease (IBD), ankylosing spondylitis, or plaque psoriasis is to improve health outcomes.

The following **PICO** was used to select literature to inform this review

Populations
The relevant populations of interest are individuals, both pediatric and adults, with arthritis (e.g., rheumatoid, psoriatic, or juvenile idiopathic), IBD, ankylosing spondylitis, or plaque psoriasis.

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

Interventions
The test being considered is an evaluation for serum antibodies to infliximab, adalimumab, ustekinumab, or vedolizumab.

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.

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

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.

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).

Review of Evidence
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 through 3) and studies published after the search dates of those reviews,[3] as well as relevant studies not included in identified reviews (e.g., those focusing on adverse reactions and ADA).

Systematic Reviews
A systematic review (SR) published by Vermeire (2018) evaluated studies on immunogenicity to adalimumab (ADM), certolizumab pegol (CZP), golimumab, infliximab (IFX), ustekinumab, and vedolizumab in patients being treated for inflammatory bowel disease (IBD).[13] Although 122 publications covering 114 studies were noted as included in the review, all study designs and abstracts from conference proceedings were included. Greater than 90% of studies involved administration of ADM or IFX. Of the studies involving IFX administration, only 12 were RCTs and 62 were non-randomized or observational studies. Across these studies, rates of ADA formation were highly variable, ranging from 0.0–65.3% in patients with IBD. While the authors reported that the proportion of patients achieving and maintaining a response to treatment with IFX was “generally lower” for patients with detected ADA than those without detected ADA, no pooled analyses were reported for any study outcomes. No analysis informing clinically useful thresholds or timing of antibody testing was provided. This review was funded by Pfizer, Inc, a manufacturer of Inflectra, which is an infliximab biosimilar and multiple study authors are employees and/or stakeholders in Pfizer, Inc.

Six reviews published from 2012 through 2017 were identified.[4-9] 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 with meta-analysis by Pecoraro et al (2017) selected 34 studies (total N=4273), 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<.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<.001) than infliximab (RR=0.37; 95% CI, 0.2 to 0.7; p<.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=.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<.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-α response, the results should be viewed cautiously due to reported study limitations, including small numbers of studies assessed and considerable heterogeneity.

Freeman (2017) published a SR with meta-analysis evaluating the test accuracy estimates of levels of anti-tumour necrosis factor (anti-TNF) and antibodies to anti-TNF to predict loss of response or lack of regaining response in patients with anti-TNF managed Crohn's disease (CD).[16] Studies of patients with CD treated with infliximab or adalimumab as well as studies with mixed Crohn's and ulcerative colitis populations were included if the proportion of Crohn's patients was at least 70%. Twenty-four full-test reports and seven conference abstracts were included in the SR; eleven of the 31 studies examined infliximab trough levels, 20 examined levels of antibodies to infliximab and five and six studies, respectively, investigated adalimumab levels and antibodies to adalimumab. The greatest identified threat to validity of the studies was high risk of bias in patient selection, which was present in nearly 80% of the included studies. The studies were heterogeneous with respect to the type of test used (e.g., commercial or in-house ELISA, radioimmunoassay (RIA), homogeneous mobility shift assay (HMSA)), criteria for establishing response or lack of regaining response (e.g., use of the Crohn's Disease Activity Index score or the physician's global assessment score) and population examined (responders or patients with secondary loss of response). Summary point estimates for sensitivity and specificity were 56% and 79% for antibodies to infliximab, respectively, and results for antibodies to adalimumab were similar. Positive and negative predictive values across all pooled studies ranged between 70% and 80%, implying that between 20% and 30% of both positive and negative test results may be incorrect in predicting loss of response. The authors concluded that "higher quality head-to-head test accuracy studies are required to enable differentiation between different types of tests and cut-offs, with consistent outcome measurement in the same population" and "more clinical trial evidence from test–treat studies is required before the clinical utility of the tests can be reliably evaluated."

The systematic review and meta-analysis by Thomas et al (2015) included 68 studies (total n=14651).[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 (e.g., 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 antidrug antibody was associated with lower levels of infliximab and lower risk of disease control or remission. The presence of antidrug antibody also increased the risk of infusion reactions. When ascertained, the time to development of antidrug antibody varied from as little as 16 weeks to over a year. The time from antibodies to adalimumab (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.

Hsu (2014) published a SR of ADA in psoriasis that included 25 studies (n=7,969).[17] Inclusion criteria for the studies were: having at least 15 patients, documentation of serial assessments of psoriasis severity, and reporting ADA in patients with psoriasis receiving infliximab, etanercept, adalimumab, or ustekinumab. Ten of these studies reported on infliximab ADA: three found an association between ADA and lower serum infliximab levels, and five found an association between ADA and clinical response. Of the five studies that evaluated anti-adalimumab antibodies, four found lower treatment efficacy for those with ADA. Six studies reported on ustekinumab ADA, and two of these found an association between ADA and Psoriasis Area and Severity Index (PASI) response. The remaining six studies in the review focused on anti-etanercet antibodies.

Nanda et al (2013) conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of antidrug antibody 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, 1 prospective 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 antidrug antibody 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 antidrug antibodies 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 antidrug antibody 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 (e.g., 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 (e.g., 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 antidrug antibody, the effect of antidrug antibody on the prevalence of infusion reactions, and the effect of antidrug antibody on disease remission rates.[6] Databases were searched through October 2011, and 18 studies (total N=3326) were selected. Studies included 9 RCTs, 5 prospective cohort studies, and 4 retrospective cohort studies. The prevalence of antidrug antibody was 45.8% when episodic infusions of infliximab were given and 12.4% when maintenance infliximab was given (see Table 1). Patients with antidrug antibody were less likely to be in clinical remission (see Table 2), but this finding was not statistically significant (RR=0.90; p=.10). Rates of infusion reactions were significantly higher in patients with antidrug antibody (RR=2.07; see Table 3). Immunosuppressants resulted in a 50% reduction in the risk of developing antidrug antibody (p<.001). Reviewers concluded that patients with IBD who test positive for antidrug antibodies are at an increased risk of infusion reactions but have rates of remission similar to patients who test negative for antidrug antibodies.

Table 1. Estimated Prevalence of Antidrug Antibodies 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 Antidrug Antibodies 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 Antidrug Antibodies

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 Antidrug Antibody 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.

Nonrandomized Studies

A multicenter prospective cohort study of 137 patients with plaque-type psoriasis was published by De Keyser (2019).[35] Serum samples and Psoriasis Area and Severity Index scores were obtained at baseline, week 16, 28, 40, 52, and/or ≥64 of ustekinumab treatment. Presence of anti-ustekinumab antibodies (prevalence of 8.7%) was significantly associated with a diminished clinical response (p=.032). The median ustekinumab trough concentration was 0.3 mcg/mL (<0.02-3.80). No differences in serum concentrations were observed between moderate to good responders and nonresponders (p=.948). Although the authors found that the presence of anti-ustekinumab antibodies was associated with treatment response in this patient population, serial measurements were collected in less than half (43.8%) of the patients. Anti-ustekinumab antibodies was reported to have developed during the first 52 weeks of treatment, however, the number of observations in the first year of treatment (n=191) was significantly higher than the number of observations in patients on treatment more than one year (n=38). This may underestimate the prevalence of anti-ustekinumab antibody formation after long-term treatments. Ultimately, the authors concluded that while measurement of anti-ustekinumab antibodies should be considered if treatment response is unsatisfactory, additional research is needed to identify tools for TDM in psoriasis patients on ustekinumab treatment.

As part of a RCT of treatment strategies in rheumatoid arthritis (RA), Hambardzumyan (2019) analyzed serum infliximab (sIFX) and anti-drug antibodies (ADAs) levels in study participants randomized to methotrexate + infliximab therapy and for whom serial serum sampling data at three, nine, and 21 months were available (n=101).[36] The primary and secondary outcome measures were low disease activity [LDA = 28-joint Disease Activity Score (DAS28) ≤ 3.2] and remission (DAS28 < 2.6). The frequencies of very low sIFX levels increased over time, with 15%, 23%, and 28% at 3, 9, and 21 months from IFX start, respectively, and the majority of patients with very low sIFX levels were ADA positive at these time-points [71% (10/14), 82% (18/22), and 68% (19/28), respectively]. The proportion of patients with LDA was numerically higher at all follow-up time-points among those with sIFX ≥ 0.2 µg/mL compared with patients who had sIFX < 0.2 µg/mL and positive ADAs, although only significant at 21 months (67% and 26%, p=.002). Similar results were observed when remission was the outcome measure (47% vs 11%, p=.004). The authors concluded that these findings support the monitoring of serum drug levels, however, these findings require validation in larger populations and for dose-adjustment studies.

Van den Berghe (2018) published a small study evaluating ADA to vedolizumab in a cohort of 40 patients with IBD. [37] This study included the development of an ELISA-based test to measure ADA in the presence of the drug. Anti-vedolizumab antibodies and vedolizumab trough levels were measured after six weeks of treatment and after treatment discontinuation. At the six-week follow-up, three (8%) of the patients were positive for ADA, but this appeared to be transient. None of the patients who discontinued vedolizumab were positive for ADA at the time of their last infusion or after discontinuation. The authors concluded that immunogenicity did not appear to play a major role in vedolizumab treatment failure.

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 µg/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<.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 versus ADA-negative patients were significantly worse in the adalimumab group (3.7 vs. 3.2; p=.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=.001) and among the 3 groups combined (p=.001), and a significant (p=.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.

Chiu (2015) published a prospective observational study investigating the role of ustekinumab ADA in psoriasis.[22] The study included 76 individuals with plaque psoriasis who were treated with ustekinumab for at least seven months (mean 13 months). Antibodies to ustekinumab were found in five (6.5%) of the patients, and the presence of these antibodies was associated with lower serum levels of the drug (p<.001) and lower PASI 50 response (p=.004). Among the 15 patients who switched to ustekinumab from adalimumab, no difference in ustekinumab ADA was found between patients who had previously developed adalimumab ADA and those who did not.

Menting (2015) reported on the association between serum ustekinumab trough levels, ADA, and treatment efficacy in a small prospective study that included 41 patients with RA.[23] The mean follow-up time was 32 weeks (range 4 to 52 weeks), and during this period ADA to ustekinumab were detected in three patients. No correlations were seen between ustekinumab trough levels and clinical response to the medication.

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.

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[19-21] 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).

Syversen et al (2021) reported on results of a randomized, parallel-group, open-label trial of 411 adults with RA, spondyloarthritis, psoriatic arthritis, ulcerative colitis, CD, or psoriasis who

received either proactive therapeutic drug monitoring of infliximab therapy based on serum infliximab level and ADA, or standard therapy without serum infliximab level or ADA.[23] Serum trough infliximab levels and ADA were measured at each infusion in the therapeutic drug monitoring group. The infliximab dose or interval could be adjusted based on the therapeutic range during induction and during treatment. If ADA was greater than 50 mcg/L at any point, therapy with infliximab was switched to a different agent. There was no difference between the therapeutic drug monitoring group and standard therapy group in clinical remission at week 30 (50.5% vs 53% of patients, respectively; p=.78). During infliximab treatment, 36 (18%) patients in the therapeutic drug monitoring group and 34 (17%) in the standard therapy group developed ADAs ≥15 mcg/L. Antidrug antibodies ≥50 mcg/L (the threshold for discontinuation) occurred in 20 (10%) of patients in the therapeutic drug monitoring group and 30 (15%) in the standard therapy group. The remission rate in patients who developed ADAs was 56% in the therapeutic drug monitoring group and 35% in the standard therapy groups. The trial was limited by the small sample size of subjects who developed ADAs.

Papamichael, Juncadella, et al. (2019) studied the therapeutic drug monitoring of adalimumab in populations with IBD.[38] This multicenter retrospective cohort study included data from 382 patients with IBD (including 311 patients with CD). Participants received either standard of care or at least one proactive TDM. “Multiple Cox regression analyses showed that at least one proactive TDM was independently associated with a reduced risk for treatment failure” (Papamichael, Juncadella, et al., 2019).[38] This study shows that proactive TDM of adalimumab may help to decrease rates of treatment failure for IBD patients.

Kamperidis (2019) published retrospective observational study on the impact of therapeutic drug level monitoring (TDM) on outcomes of 291 patients with Crohn's disease treated with Infliximab (IFX).[39] Primary outcomes were clinicians' response to each TDM result and the rate of IFX discontinuation due to secondary loss of response or serious adverse event. Secondary outcomes included the intestinal surgery rate after IFX initiation and remission six months after TDM. Two hundred thirty-eight (81.8%) patients were tested for TDM at least once during their follow-up with 672 TDM results. 95/238 patients (39.9%) had undetectable levels and 76 (31.9%) had positive antibodies to infliximab (ATI) at least once. IFX was discontinued in 109 patients (37.5%). TDMs results were not followed by altered patient management in 526/672 (78.3%) of the observations. Treatment was discontinued in 40 (75.5%) patients never tested for TDM compared with 69 (29.0%) of those tested (p<0.01). Fewer TDM tested patients (29; 12.2%) required intestinal surgery post IFX initiation compared with those not TDM tested (15; 28.3%). In this retrospective study, data collected on clinical outcomes relied on record keeping and physician response was taken as the measure of clinical remission. These methods may be subject to interpretation bias.

Dong (2019) reported an observational study of 60 patients with ankylosing spondylitis (AS) taking a biosimilar of etanercept.[40] Serum drug levels and anti-drug antibody levels, as well as clinical measures of disease activity were assessed at baseline and after four, 12, and 24 weeks of treatment. The authors found that anti-drug antibodies had no effect on the Assessment of Spondylosis Arthritis International Society (ASAS) remission rates but reported that patients with ADA had lower drug levels and higher TNF-α levels.

Fernandes et al. (2019) examined whether TDM can improve clinical outcomes in Crohn's disease (CD) and ulcerative colitis (UC) patients.[43] A total of 205 patients were included in the study, and 56 patients were placed in a “proactive” regimen. This proactive regimen involved G2105 Immunopharmacologic Monitoring of Therapeutic Serum Antibodies Page 8 of 18

Disclaimer: These policies are clinical editing payment decisions for Blue Cross of Blue Shield of Michigan and do not apply to Blue Care Network of Michigan. measuring infliximab (IFX) trough levels and antidrug antibodies before the fourth infusion and subsequently every two infusions. The regimen aimed to establish an IFX trough level of 3-7 ug/mL for CD patients and 5-10 ug/mL for UC patients. The control group was made of patients treated with IFX but without TDM. The authors found that treatment escalation was more common in the proactive TDM (pTDM) group (76.8% vs 25.5%), mucosal healing was more common (73.2% vs 38.9%), and surgery was less common (8.9% vs 20.8%). Proactive TDM also decreased the odds of any unfavorable outcome by an odds ratio of 0.358. The authors concluded that "Proactive TDM is associated with fewer surgeries and higher rates of mucosal healing than conventional non-TDM-based management" (Fernandes et al., 2019).[43]

Negoescu et al. (2019) performed a cost-effectiveness analysis of proactive verses reactive TDM in a simulated population of individuals with CD on IFX. The proactive strategy measured IFX concentration and antibody status every 6 months, or at the time of a flare, then dosed IFX appropriately.[44] The reactive strategy measured both IFX concentration and antibodies at the time of a flare. The authors found that the proactive strategy led to fewer flares, finding an "incremental cost-effectiveness ratio of $146,494 per quality-adjusted life year." More patients stayed on IFX in the proactive strategy (63.4% vs 58.8% at year 5). The authors concluded that "assuming 40% of the average wholesale acquisition cost of biologic therapies, proactive TDM for IFX is marginally cost-effective compared with a reactive TDM strategy. As the cost of infliximab decreases, a proactive monitoring strategy is more cost-effective (Negoescu et al., 2019)."[44]

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.[24] 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)[25] 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[26] 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=.810; per-protocol, 47% in the algorithm group vs. 53% in the control group; p=.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 (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 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.[27] 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 4.9 μg/mL)[28], (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<.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<.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<.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<.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<.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.[29] 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.[29] Study limitations included the retrospective design and use ELISA testing for ATI. Because there was no control group, it cannot be determined 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.

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 antidrug antibody or ATA in this population has not been established, a chain of evidence supporting clinical utility cannot be constructed.

Section Summary: Antibodies to Infliximab, Adalimumab, Ustekinumab and Vedolizumab
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.

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 (Crohn's disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for serum antibodies to infliximab, adalimumab, ustekinumab or vedolizumab the evidence includes multiple systematic reviews, a randomized controlled trial (RCT), and observational studies. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. Antibodies to biologic agents 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 antidrug antibodies (ADA) and secondary nonresponse as well as injection site and infusion reactions. The clinical usefulness of measuring ADA hinges on whether results inform management changes leading to improved outcomes compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. There is some evidence that, in individuals with inflammatory bowel disease who have lost response to infliximab or adalimumab, measurement of serum drug antibodies can impact patient care decisions. Evidence-based clinical practice guidelines recommend reactive monitoring of serum drug levels and anti-drug antibodies to guide treatment changes in patients with active inflammatory bowel disease who are being treated with an anti-TNF agent. Therefore, measurement of serum antibodies to infliximab, adalimumab or vedolizumab, either alone or as a combination test that includes serum drug levels, is considered established for patients with inflammatory bowel disease (i.e., Crohn's disease or ulcerative colitis) when there is documentation of a loss of response to these medications.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology

In 2019, the American College of Gastroenterology published a guideline on ulcerative colitis (UC).[30,] The guideline stated: "In patients with moderately to severely active UC who are responders to anti-TNF [tumor necrosis factor] therapy and now losing response, we suggest

measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response (conditional recommendation, very low quality of evidence)."
In 2018, the American College of Gastroenterology published a guideline on Crohn disease (CD).[31,] Although acknowledging that a detailed review of therapeutic drug monitoring was beyond the scope of the guideline, it stated: "If active CD is documented, then assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered."

American College of Gastroenterology Institute
The American College of Gastroenterology Institute (2017) published guidelines on therapeutic drug monitoring in inflammatory bowel disease.[32] The guidelines note that

“"In the presence of sufficient trough concentrations, results of antibody testing should not guide treatment decisions. If the trough concentration is low (below the suggested threshold, in patients with active IBD) and no anti-drug antibodies are present, then the index drug should be optimized using any of the following techniques: shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. If there is no detectable drug (zero trough concentration) and high-titer anti-drug antibodies are present, then the patient should consider switching to a different drug within the class or to a different drug class. If there is no detectable drug and low-titer antibodies are present, then one can consider trying to optimize the index drug by shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. Typically, optimizing the drug will be attempted before changing to a different drug within the class or switching to a new drug class, although some might opt to change to a different drug within the class or switch to a new drug class. It should be noted that 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.”

The guidelines did not address therapeutic drug monitoring in patients treated with vedolizumab or ustekinumab.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION
In 2017, the American Gastroenterological Association published an evidence-based clinical practice guideline on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD).[42] The guideline was developed according to the GRADE framework to evaluate certainty of evidence, and a Technical Review was published to accompany the recommendations.[41] Regarding measurement of anti-drug antibodies, the Association made the following statement:

> “In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes.” *Conditional recommendation, very low quality of evidence.*

According to the GRADE method, *very low quality* is defined as: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
The guideline also stated:

"In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring." *No recommendation, knowledge gap.*

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.[33] 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."

In 2019, the National Institute for Health and Care Excellence issued guidance on therapeutic monitoring of tumor necrosis factor α inhibitors in the treatment of patients with rheumatoid arthritis.[34] The Institute stated: "Enzyme-linked immunosorbent assay (ELISA) tests for therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors (drug serum levels and antidrug antibodies) show promise but there is currently insufficient evidence to recommend their routine adoption in rheumatoid arthritis." It also recommended that "laboratories currently using ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis should do so as part of research and further data collection."

Government Regulations
National:
There is no NCD or LCD on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 3, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/14	10/15/13	10/25/13	Joint policy established
3/1/15	12/12/14	12/29/14	Routine maintenance
3/1/16	12/10/15	12/10/15	Routine policy maintenance with reference updates. No change in policy status.
3/1/17	12/13/16	12/13/16	Updated rationale and added references (4, 33). No change in policy status.
3/1/18	12/12/17	12/12/17	Routine maintenance
5/1/18	2/20/18	2/20/18	Added Vedolzumab to title and body of policy. Added reference #31. No change in policy status.
5/1/19	2/19/19		Rationale section reorganized, no new references. No change in policy status.
5/1/20	2/18/20		Title changed to “Measurement of Serum Antibodies to Selected Biologic Agents”. Ustekinumab added to policy; Rationale updated; MPS reworded. No change in policy status.
5/1/21	TABLED		No references added. Updated terminology throughout the policy to reflect the addition of the interleukin-2 and -23 antagonist ustekinumab. Added “antidrug” to MPS in front of “antibodies. Policy statement otherwise unchanged.
9/1/21	8/12/21		• Per committee’s request from February 26, 21 JUMP – policy updated to EST for children with IBD; all other indications considered experimental and investigational. • Medical policy name updated from Measurement of Serum Antibodies for Select Biologic Agents to Measurement of Serum and Anti-Drug

			Antibody Levels for Selected Biologic Agents. • 8/12/21 discussion with Dr. Johnson, Ann, and Nancy – determined that only codes 80145 Adalimumab and 80230 Infliximab are EST for children with IBD under 21 years old. • Payable diagnosis codes: ICD-10 codes: K50.00, K50.011-K50.019, K50.10, K50.111-K50.119, K50.80, K50.811-K50.819, K50.90, K50.911-K50.919 Crohn's Disease code range • K51.00, K51.011-K51.019, K51.20, K51.211-K51.219, K51.30, K51.311-K51.319, K51.40, K51.411-K51.419, K51.50, K51.511-K51.519, K51.80, K51.811-K51.819, K51.90, K51.911-K51.919 Ulcerative Colitis code range • Added the below to the Inclusions/Exclusions: Biologic agent drug levels are established in children (under the age of 21 years) who are: • diagnosed with inflammatory bowel disease and • being treated with either Adalimumab and Infliximab and • being monitored for their response to the agent by biologic agent drug level If the biologic agent drug level is below the therapeutic range, anti-drug antibody level is established.

			Exclusions: • Individuals over 21 years of age • Any condition other than inflammatory bowel disease
9/1/22	6/21/22		Routine policy maintenance, added references #23 and 32. No change in policy status.
9/1/23	6/13/23		Routine policy maintenance (ky) Vendor: Avalon (AHS). AHS doesn't specify adult or pediatric and covers TNF inhibitors in specific situations, MI covers it only in children. Per discussion at EWG on 5/18/23 to update policy and align with vendor Avalon to cover for individuals over 21 years of age. JUMP policy to include adults over the age of 21 who are diagnosed with IBD and being treated with either adalimumab and infliximab and being monitored for their response to the agent by biologic agent drug level. To reflect this change, updated medical policy statement, inclusion section, section summary, deleted and added references. Per Record of Inquiry 151069 – code 80280 Vedolizumab is to be made EST from E/I. Jump policy is reflecting this change. Code 80280 Vedolizumab is moved from E/I to EST. This is also in alignment with our vendor Avalon. Added Vedolizumab under the inclusions section as well as in the summary of evidence section. Post JUMP: Added the following codes 80299* and 83520* as EST *when these codes apply to Ustekinumab drug level testing. Added Ustekinumab to the second bullet under the Inclusions section and added in bold to this statement: If the biologic agent drug level is below

			the therapeutic range, testing for the anti-drug antibody level is established. (ky)
9/1/24	6/11/24		Routine maintenance No change in policy status Vendor: Avalon (ky)
11/1/24	8/20/24		Per discussion with Dr. Finn – adding code 82397 Chemiluminescent assay under EST– when this code is used for anti-drug antibody level testing. Also added when this code is used for anti-drug antibody level testing to code 83520. This policy will go back to June JUMP date. Vendor: Avalon (ky)

Next Review Date: 2nd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE POLICY: MEASUREMENT OF SERUM AND ANTI-DRUG ANTIBODY LEVELS FOR SELECTED BIOLOGIC AGENTS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered criteria applied.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A