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 investigational.

Measurement of antibodies to adalimumab in a patient receiving treatment with adalimumab, either alone or as a combination test, which includes the measurement of serum adalimumab levels, is considered investigational.

Coding
According to materials from Prometheus on Anser™ IFX and Anser™ ADA, these tests will be reported using 1 unit of the following CPT code:

- 84999: Unlisted chemistry procedure

Description
Infliximab (Remicade) is an intravenous tumor necrosis factor α (TNF-α) blocking agent approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis, Crohn disease, 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.

Related Policies

- Infliximab

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Measurement of Serum Antibodies to Infliximab and Adalimumab

date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Prometheus Laboratories (San Diego, CA), a College of American Pathologists-accredited lab under the Clinical Laboratory Improvement Amendments, offers non-radio-labeled, fluid-phase homogenous mobility shift assay 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 ADA in the presence of detectable drug levels, improving on a major limitation of the ELISA method. Both tests measure serum drug concentrations and ADA.

Rationale

Background

Infliximab and Adalimumab in Autoimmune Diseases

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. Therapy with monoclonal antibodies has revolutionized therapy for patients with inflammatory diseases such as inflammatory bowel disease (IBD; 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 out of 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). 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 Antidrug Antibodies

The detection and quantitative measurement of ADA 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 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 method and, more recently, the homogenous mobility shift assay using high-performance liquid chromatography. Disadvantages of the radioimmunoassay 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 serum. Studies evaluating the validation of results among different assays are lacking, making interstudy comparisons difficult. One retrospective study (2012) in 63 patients demonstrated comparable diagnostic accuracy between 2 different ELISA methods in patients with IBD (i.e., double-antigen ELISA and antihuman lambda chain–based ELISA). This study did not include an objective clinical and endoscopic scoring system for validation of results.

Treatment Options for Secondary Nonresponse to Anti-Tumor Necrosis Factor Therapy

A diminished or suboptimal response to infliximab and 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.

Literature Review

The most recent literature update was performed through September 11, 2017.
Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

**Antibodies to Infliximab and Adalimumab**

Blue Cross Blue Shield Association assessed the literature to identify studies on the analytic validity, clinical validity, and clinical utility of measuring serum antidrug antibodies (ADA). Most studies evaluating antibodies to infliximab (ATI) or to adalimumab (ATA) have reported serum drug together with ADA levels, and correlate levels to disease response. Serum drug levels and disease response are not addressed in this evidence review, which focuses instead on the data reported on ADA.

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

**Analytic Validity**

**Measurement of Antibodies to Infliximab**

**Wang et al** (2012) developed and validated a non-radio-labeled homogeneous mobility shift assay (HMSA) to measure ATI and infliximab levels in serum samples. Full method validation was performed on both the ATI-HMSA and infliximab HMSA, and the clinical sample test results were compared with those obtained from a bridging enzyme-linked immunosorbent assay (ELISA) method to evaluate the difference in performance between the 2 assays. Intra- and interassay precision rates (as indicated by the coefficient of variation [CV]) for the ATI-HMSA and infliximab HMSA were less than 4% and less than 15% respectively; and less than 6% and less than 15% respectively, are considered to be robust. Hernandez-Breijo et al (2016) described the use of the HMSA protocol in measuring ATI in 50 infliximab-treated Crohn disease (CD) patients, using methods similar to Wang et al.

Sera from 100 healthy subjects (blood bank donors) were tested to determine assay cut points, defined to have an upper limit of approximately 97.5%. Using receiver operating characteristic analysis, a cut point of 1.19 μg/mL was calculated for ATI, yielding a sensitivity of 95% (95% confidence interval [CI], 89% to 98%) with a false-positive rate of 3%. For serum infliximab levels, a cut point of 0.98 μg/mL was calculated; the false-positive rate with this cut point was 5%. One hundred serum samples that previously tested positive with ELISA were reanalyzed by the new method. There was a high correlation between the 2 methods for ATI levels (p<0.001). The new method identified five false-positive samples from the bridging ELISA method, thought to be due to a higher rate of nonspecific binding in the ELISA method.

In 2014, Steenholdt et al published a post hoc comparison of different ATI assays. Blood samples were collected from 66 (96%) of 69 patients enrolled in a 2014 randomized controlled trial (RCT) that assessed a algorithmic treatment for CD relapse during infliximab therapy. Samples were analyzed by 3 binding assays (radioimmunoassay [RIA], ELISA, HMSA) and by a reporter gene assay (a functional cell-based technique). ATI were detected in 18 (27%) patients by RIA, in 6 (9%) patients by ELISA, and in 22 (33%) patients by HMSA. The reporter gene assay detected anti-infliximab activity, most likely due to ATI, in 7 (11%) patients. As observed by the authors, findings suggested that ATI detected by RIA and HMSA are not necessarily functionally active or neutralizing. Five (8%) patients were ATI-positive, and 43 (65%) patients were ATI-negative by all 4 assays. Correlations were statistically significant (p<0.001) for all pairwise comparisons (r range, 0.77-0.96). However, statistical agreement between assays could not be estimated accurately.
Measurement of Serum Antibodies to Infliximab and Adalimumab

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Measurement of Adalimumab

Wang et al (2013) developed and validated a non-radio-labeled HMSA to measure ATA and adalimumab levels in serum samples. Analytic validation of performance characteristics (i.e., calibration standards, assay limits, intra- and interassay precision, linearity of dilution, substance interference) was performed for both the ATA-HMSA and adalimumab HMSA. Because the elimination half-life of adalimumab (10-20 days) overlaps the dosing interval (every 2 weeks), ATA-positive sera to provide calibration standards were difficult to collect (i.e., the drug-free interval for antibody formation is short). Therefore, antisera from rabbits immunized with adalimumab were pooled to form calibration standards. Serial dilutions of these ATA calibration standards then generated a standard curve against which test samples were compared. Over 29 experimental runs, intra-assay precision and accuracy for the adalimumab HMSA (as indicated by the CV) were less than 20% and 3%, respectively; interassay (run-to-run, analyst-to-analyst, instrument-to-instrument) precision and accuracy were less than 12% and less than 22%, respectively. For the ATA-HMSA, CVs for intra-assay precision and accuracy were less than 3% and 13%, respectively; CVs for interassay precision and accuracy were less than 9% and 18%, respectively. ELISA could not be used as a standard comparator due to competition from circulating drug.

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

Section Summary: Analytic Validity

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

Clinical Validity

There is a substantial body of evidence (numerous systematic reviews and meta-analyses) examining associations between ADA and nonresponse as well as injection- or infusion-site reactions. Accordingly, Blue Cross Blue Shield Association 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, as well as relevant studies not included in identified reviews (e.g., those focusing on adverse reactions and ADA).
**Systematic Reviews**

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

Lee et al (2012) conducted a meta-analysis of patients with IBD receiving infliximab to estimate the prevalence of ATI, effect of ATI on the prevalence of infusion reactions, and the effect of ATI on disease remission rates. Database searches were conducted 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 (relative risk [RR], 0.90; 95% CI, 0.79 to 1.02; p=0.10). Rates of infusion reactions were significantly higher in patients with ATI (RR=2.07; 95% CI, 1.61 to 2.67; see Table 3). Immunosuppressants resulted in a 50% reduction in the risk of developing ATI (p<0.001). Reviewers concluded that patients with IBD who test positive for ATIs are at an increased risk of infusion reactions but have rates of remission similar to patients who test negative for ATIs.

Nanda et al (2013) conducted a meta-analysis of studies that reported on clinical outcomes according to the presence or absence of ATI in patients with IBD. Several databases were searched to February 2012 (one was searched to August 2012). Eleven studies involving 707 patients were selected. Six studies (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 high risk of bias. The prevalence of detectable ATI in the included studies ranged from 22.4% to 46% (see Table 1). The outcome of interest was loss of response to infliximab, defined as “relapse of clinical symptoms in patients who were in clinical remission from, or had responded to, infliximab.” Measures of loss of response varied across studies and included clinician assessment, standardized scales (Crohn’s Disease Activity Index [CDAI], Harvey-Bradshaw Index, Simple Clinical Colitis Activity Index), and the requirement for surgery or presence of 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 1 as the RR of clinical response in treated vs untreated patients to allow comparison with other meta-analyses). This result was influenced primarily by 532 patients with CD (RR=3.2; 95% CI, 1.9 to 5.5); pooled results for 86 patients with ulcerative colitis 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, and psoriasis. Data sets 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 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 spondyloarthropathy; 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; 95% CI, 0.22 to 0.48). 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.

A systematic review and meta-analysis by Thomas et al (2015) included 68 studies (total N=14,651 patients). Patients had RA (n=6766), SpA (n=1534), or IBD (n=4351). Immunogenicity was examined for infliximab (39 comparisons), adalimumab (15), etanercept (5), golimumab...
2.04.84  
Measurement of Serum Antibodies to Infliximab and Adalimumab
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(14), and certolizumab (8). Reviewers identified studies published through December 2013 and included 38 RCTs and 30 observational studies (study quality rated as good [n=32], moderate [n=26], poor [n=10]). The pooled prevalence of ADA varied by disease and drug (see Table 1, highest with infliximab: 25.3%). Duration of exposure (reported in 60 studies) was examined for its potential effect on the development of ADA, and most studies employed ELISA assays. The presence of ADA was associated with lower odds of response across most drugs and diseases (see Table 2). An exception was in studies of IBD (similar to that reported by Lee et al). Use of immunosuppressive agents substantially decreased the risk of ADA (odds ratio [OR], 0.26; 95% CI, 0.21 to 0.32). Finally, infusion reactions and injection-site reactions were more common (see Table 3) when ADA were detectable (OR=3.25; 95% CI, 2.35 to 4.51). Evaluation of potential publication bias 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). Studies primarily included patients with IBD and RA, but also SpA and psoriasis. Most had prospective cohort designs (n=42), and a formal assessment of study quality (bias) was not reported. Reviewers noted considerable variability in the time from drug administration to ADA and drug bioavailability testing across studies. Various antibody testing assay methods were used and included solid-phases RIA, traditional ELISA, fluid-phase RIA, and bridging ELISA; cutoffs for positive test results were also inconsistently reported. The ranges of patients with detectable ADA varied substantially (see Table 1) but were consistent with other reviews. Qualitatively, the presence of ATI was associated with lower levels of infliximab and lower risk of disease control or remission. The presence of ATI also increased the risk of infusion reactions. When ascertainment, the time to development of ATI varied from as little as 16 weeks to over a year. The time to ATA positivity varied (e.g., 50% of patients with detectable ATA at 28 weeks to a median time of 1 year). Finally, for both infliximab and adalimumab, immunosuppression was associated with less ADA positivity. Reviewers concluded that “...the lack of homogeneity in study design and methodologies used ... limited the opportunity to establish the time-course and clinical consequences of anti-drug antibody development....” Although qualitative, reviewers included many studies and provided a detailed review of each not reported by the other meta-analyses.

Table 1. Estimated Prevalence of Antidrug Antibodies from Meta-Analyses

<table>
<thead>
<tr>
<th>Author</th>
<th>Included Studies</th>
<th>Drugs</th>
<th>Disease</th>
<th>Prevalence of ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IFX</td>
<td>ADL</td>
<td>Othera</td>
</tr>
<tr>
<td>Lee et al (2012)</td>
<td>11</td>
<td>18b</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Episodic</td>
<td>5</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>10</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Nanda et al (2013)</td>
<td>12</td>
<td>11</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Thomas et al (2015)</td>
<td>13</td>
<td>39c</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15c</td>
<td>20</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>11</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>●</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADA: antidrug antibodies; ADL: adalimumab; CI: confidence interval; IBD: inflammatory bowel disease; IFX: infliximab; RA: rheumatoid arthritis; SpA: spondyloarthritis.

a Includes etanercept, golimumab, certolizumab.
Table 2. Results from Meta-Analyses of Antidrug Antibodies and Clinical Response

<table>
<thead>
<tr>
<th>Author</th>
<th>Included Studies</th>
<th>Drugs</th>
<th>Disease</th>
<th>Clinical Response: ADA vs None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee (2012)</td>
<td>18</td>
<td>IFX</td>
<td>ADL</td>
<td>0.90 (0.79 to 1.02)</td>
</tr>
<tr>
<td>Nanda (2013)</td>
<td>11</td>
<td></td>
<td></td>
<td>0.33 (0.20 to 0.40)</td>
</tr>
<tr>
<td>Garmes (2013)</td>
<td>12</td>
<td></td>
<td></td>
<td>0.32 (0.22 to 0.48)</td>
</tr>
<tr>
<td>Thomas (2015)</td>
<td>13</td>
<td></td>
<td></td>
<td>1.16 (0.66 to 2.03) NR</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td></td>
<td></td>
<td>0.27 (0.20 to 0.36) NR</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td>0.18 (0.09 to 0.37) NR</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td>0.42 (0.30 to 0.58) NR</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Included Studies</th>
<th>Drugs</th>
<th>Disease</th>
<th>Adverse Reactions: ADA vs None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee (2012)</td>
<td>18</td>
<td>IFX</td>
<td>ADL</td>
<td>2.07 (1.61 to 2.67)</td>
</tr>
<tr>
<td>Thomas (2015)</td>
<td>NR</td>
<td></td>
<td></td>
<td>3.25 (2.35 to 4.51)</td>
</tr>
</tbody>
</table>

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 systematic review and meta-analysis by Pecoraro et al (2017) selected 34 studies (total N=4273 patients), including RCTs (n=4), prospective observational (n=22), retrospective observational (n=6), and cross-sectional (n=2).14 Studies evaluated RA (n=18), ulcerative colitis (n=2), CD (n=5), psoriatic arthritis (n=4), ankylosing spondylitis (n=5), plaque psoriasis (n=4), spondyloarthritis (n=1). Most of the patients (45%) received infliximab, 35% received adalimumab, and 21% received etanercept. None received golimumab or certolizumab. Reviewers identified studies published through August 2016 and rated study quality as good (n=17), fair (n=16), and poor (n=1). The effect of ADA was evaluated in 19 studies, showing a significant (p<0.05) reduction of response (RR=0.43; 95% CI, 0.3 to 0.63) in ADA-positive patients relative to ADA-negative patients, with 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 concurrent 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) discontinued treatment due to adverse events, and 5% (n=1 study) developed serious adverse events (5%). Although ADA significantly reduced TNF-α response, the results should be viewed cautiously due to reported study limitations, including small numbers of studies included and considerable heterogeneity.

Table 4. Effect of Antidrug Antibodies on Clinical Response

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>No. Studies</th>
<th>MD</th>
<th>95% Confidence Interval</th>
<th>I², %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Activity Score 28</td>
<td>9</td>
<td>0.93</td>
<td>0.41 to 1.44</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BASDAI</td>
<td>2</td>
<td>-0.62</td>
<td>-1.51 to 0.27</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>ASDAS</td>
<td>2</td>
<td>0.96</td>
<td>-0.27 to 2.2</td>
<td>0</td>
<td>0.13</td>
</tr>
<tr>
<td>Psoriasis Area Severity Index</td>
<td>1</td>
<td>4.7</td>
<td>-1.15 to 9.25</td>
<td>NR</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adapted from Pecoraro et al (2017).14

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; I²: heterogeneity measure; MD: mean difference; NR: not reported.

Table 5. Evaluation of Anti-Tumor Necrosis Factor-α Concentration

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>No. Studies</th>
<th>MD, mg/L</th>
<th>95% Confidence Interval</th>
<th>I², %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA-positive vs ADA-negative</td>
<td>8</td>
<td>-7.07</td>
<td>-8.9 to -5.25</td>
<td>98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Responders vs no responders</td>
<td>13</td>
<td>2.77</td>
<td>1.97 to 3.58</td>
<td>82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adalimumab therapy</td>
<td>6</td>
<td>5.07</td>
<td>3.77 to 6.36</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infliximab</td>
<td>4</td>
<td>2.74</td>
<td>0.59 to 4.89</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Etanercept</td>
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Adapted from Pecoraro et al (2017).14

ADA: antidrug antibodies; DAS28: Disease Activity Score in 28 joints; I²: heterogeneity measure; MD: mean difference; TNF: tumor necrosis factor.

Cohort Studies

Blue Cross Blue Shield Association identified 3 recent publications, which were not included in a systematic review.15-17 The results of the 3 publications were consistent with conclusions of the systematic reviews.

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.15 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 (EULAR) criteria;18 SpA disease activity was considered inactive, moderate, high, or very high by established criteria,19 with inactive and moderately active disease defined as 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 (e.g., symptom duration, health status) were assessed concurrently. Serum adalimumab, infliximab, and etanercept levels were obtained; ADA was assayed using a bridging ELISA. Of 57 patients receiving infliximab, 14 (24.6%) had detectable antibodies, with 13 of the 14 undetectable infliximab trough levels. Disease activity at baseline was unassociated with the development of ADA in either disease. In patients achieving response, infliximab and adalimumab trough levels were higher, but not significantly (p=0.09 and p=0.14, respectively). However, adalimumab concentrations were significantly higher in nonresponders (p<0.001). All were associated with infusion reactions but with little certainty (OR=5.9; 95% CI, 1.0 to 33.3) as was stopping infliximab treatment or changing agent. Study strengths included its prospective design, standardized assessments, and responder definition. Limitations involved the small number of nonresponders and no indication whether any eligible participants declined enrollment.
Frederiksen et al (2014) conducted a single-center retrospective cohort study of IBD patients treated with infliximab (n=187) or adalimumab (n=57) in Denmark. ADA were assayed using fluid-phase RIA; 49% of infliximab-treated patients developed antibodies compared with 21% of those treated with adalimumab. Development of ATA was associated with secondary nonresponse: 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.

Jani et al (2015) measured ADA RIA together with drug levels in 331 RA patients treated with adalimumab (n=160) or etanercept (n=171) between 2008 and 2013. Patients were participants in the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate, conducted in 60 centers across the United Kingdom. Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28). Response was evaluated using EULAR response criteria or change in DAS28 score. Following 12 months of adalimumab therapy, ADA were detectable in 24.8% of patients (almost all were detectable by 6 months) and were associated with lower drug levels. Both routine (nontrough) drug levels and ATA were associated with DAS28 at 12 months. In predicting EULAR 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 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 levels were not used to inform treatment decisions. Study results corroborated other research findings.

While many studies have evaluated 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 an HMSA with banked serum obtained from 90 IBD patients treated between 1999 and 2011. ATI levels had been previously assayed using an ELISA-based test. A total of 1232 samples were evaluated (mean, 14 per patient). Treatment decisions were made solely on clinical evaluation and 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 confidence interval 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.

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. 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 DAS28 and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores (p<0.001). There were no significant differences between BASDAI in ATA-positive compared with ATA-negative patients at 12 or 24 weeks. The study is consistent with others suggesting that adalimumab levels can serve as an indicator of ATA; however, limitations...
Measurement of Serum Antibodies to Infliximab and Adalimumab

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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 2014.22 All patients experienced secondary nonresponse to a 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 of patients treated with adalimumab, etanercept, and infliximab, respectively. Loss of efficacy was assessed using the Psoriasis Area and Severity Index (PASI; >5), 75% improvement in PASI score from baseline (PASI75), and/or the Physician Global Assessment (PGA, >2). PGA values for ADA-positive vs ADA-negative patients were significantly worse in the adalimumab group (3.7 vs 3.2; p=0.02) but not in the infliximab group. There was a significant negative linear correlation between serum drug concentrations and ADA in both the adalimumab group (p=0.001) and among the 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) excludes 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.23 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 was no significant difference in median PASI score 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 its 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.

Section Summary: Clinical Validity

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

Clinical Utility

Several algorithms have been developed to manage patients with IBD24-26 and RA27 who have relapsed during TNF-inhibitor therapy. These algorithms are generally based on evidence that
has indicated an association between ADA, reduced serum drug levels, and relapse. None of the algorithms has included evidence demonstrating improved health outcomes, such as reduced time to recovery from relapse (response).

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

The authors concluded that measurement of ATI and infliximab concentration had a clinically useful effect on patient management. The strategy of increasing infliximab dose in patients with ATI was ineffective whereas in patients with subtherapeutic infliximab concentrations this strategy was a good alternative to changing to another anti-TNF agent. Study limitations included the retrospective design and 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 are measured.

In 2014, Steenholdt et al reported results of a noninferiority trial and cost-effectiveness analysis of 69 patients with CD who relapsed (CDAI ≥220 and/or ≥1 draining perianal fistula) during infliximab therapy. Patients were randomized to infliximab dose intensification (5 mg/kg every 4 weeks) or algorithmic treatment based on serum infliximab level and ATI: Patients with subtherapeutic infliximab level (<0.5 μg/mL) had infliximab dose increased if ATI were undetectable or were switched to adalimumab if ATI were detectable; patients with therapeutic infliximab level underwent repeat testing of infliximab and ATI levels if ATI were detectable or diagnostic reassessment if ATI were undetectable. Serum infliximab and ATI levels were measured in all patients using RIA in single-blind fashion (patients 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 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 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 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 >220 or Mayo Clinic >5)
during treatment with adalimumab 40 mg every 2 weeks. For all patients, trough adalimumab
levels and ADA were measured in a blinded fashion using EUSA, and adalimumab dose was
optimized to 40 mg weekly. Those who did not achieve clinical remission (CDAI <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) (32), (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 include its use of subjective and objective measures of
remission and blinded serum drug level and ATA monitoring. However, results were influenced by
the small sample size, use of ELISA for antibody testing, and lack of ADA levels for decision
making. Subsequent study comparing the management using the algorithm proposed with
usual care is needed. Ideally, using more than 1 method of assaying antibodies would further
assessment of analytic validity. Finally, the lead author of the study received lecture fees from
the ADA test provider (Theradiag).

Section Summary: Clinical Utility

Convincing evidence for the clinical utility of ADA testing currently is lacking. Uncontrolled
retrospective studies in IBD have demonstrated the impact of ADA testing on treatment
decisions but cannot demonstrate improved patient outcomes compared with a no-testing
strategy. Additional limitations of these studies include lack of clinical follow-up after treatment
decisions were made (in Afif et al) and lack of clinical assessments to guide treatment
decisions (in Steenholdt et al). 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

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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 2013 Lichtenstein 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.” He added that “[m]ore randomised controlled trials are needed in order to investigate the efficacy of the proposed preventive and management algorithms.”

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 adalimumab, the evidence includes multiple systematic reviews, a randomized controlled trial, and observational studies. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. ATI or antibodies to adalimumab develop in a substantial proportion of treated patients and are believed to neutralize or enhance clearance of the drugs. Considerable evidence has demonstrated an association between ADA and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring ADA hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring ADA. A small randomized controlled trial in patients with Crohn disease comparing ATI-informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the ATI-informed approach. Additionally, many assays—some having significant limitations—have been used in studies; ADA threshold values that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

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

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

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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

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<td>NCT01638715</td>
<td>A Randomized, Multi-Center Biomarker Trial to Predict Therapeutic Responses of Patients with Rheumatoid Arthritis to a Specific Biologic Mode of Action</td>
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<td>Effect of the Combination of Methotrexate and Adalimumab on Reduction of Immunization in Ankylosing Spondylitis (COMARIS)</td>
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<td>NCT01971918</td>
<td>Comparative Analysis of Two Therapeutic Strategies in Patients with Spondyloarthritis Treated with Anti-TNF Biologics (STRADA)</td>
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NCT: national clinical trial.

References


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.