BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Anti-CCP Testing for Rheumatoid Arthritis

Policy #: 353
Category: Medicine

Latest Review Date: September 2019
Policy Grade: **Active policy but no longer scheduled for regular literature reviews and updates.**

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Autoantibodies directed against cyclic citrullinated proteins (anti-CCP) are found in many patients with rheumatoid arthritis (RA). Citrullination refers to the post-translational modification of the amino acid arginine to citrulline by the enzyme peptidylarginine deiminase (PAD). The physiologic role of citrullination is unclear; however, it has been shown to occur during apoptosis, and is thought to play a role in the degradation of intracellular proteins by unfolding protein molecules and thereby exposing them to degradation enzymes. PAD enzymes can be found in monocytes and macrophages associated with inflammation, including in the synovial fluid of patients with active RA. In patients with RA and active joint inflammation, levels of anti-CCP are higher in the synovial fluid than in the peripheral circulation. Anti-CCP found in the serum is thought to be a result of diffusion of these antibodies from the synovial fluid into the general circulation.

Autoantibodies against CCP have been recognized and measured for several decades, by means of the anti-perinuclear factor (APF) and the anti-keratin antibody (AKA). However, these older tests were performed by a cumbersome immunofluorescence assay and were not commonly used in routine clinical practice. Following the recognition that APF and AKA activity were entirely dependent upon citrullination, attention turned toward measuring anti-CCP antibodies. Serum Anti-CCP levels are currently measured using an ELISA assay. The first generation of anti-CCP testing (CCP1) used citrullinated proteins derived from human filaggrin. This method of testing was expensive and difficult to standardize, since it required purification of sufficient quantities of the human antigen. The second generation of anti-CCP testing (CCP2) uses a synthetic peptide antigen, thus making the test cheaper and easy to standardize. CCP2 is currently the only commercially available method for testing for anti-CCP antibodies.

Policy:

Effective for dates of service on or after June 7, 2009:

Blue Advantage will treat **measurement of anti-CCP** as a **covered** benefit when used as part of the diagnostic workup for rheumatoid arthritis.

Blue Advantage will treat **measurement of anti-CCP** as a **non-covered** benefit when used to monitor disease activity and/or treatment response and as **investigational.**

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

Key Points:
A literature review was most recently performed on September 21, 2019.

Anti-CCP has been proposed both as a diagnostic test for rheumatoid arthritis, and as a potential marker of disease activity and/or treatment response. These two potential uses of anti-CCP antibodies will be discussed separately.

Anti-CCP In The Diagnosis Of Rheumatoid Arthritis
Use of the 2010 ACR/EuLAR classification criteria for RA is intended for patients who have at least one joint with clinical evidence of synovitis and for whom the synovitis is not better explained by another disease. For this patient population, a score of six or greater is considered to be definitive evidence for RA.

These guidelines are intended to permit diagnosis of RA earlier in the course of the disease. Treatment guidelines for RA support the early initiation of disease-modifying antirheumatic drug (DMARD) therapy to prevent the onset, or slow the progression, of joint damage. The current guidelines assert that early initiation of DMARD therapy leads to better control of disease activity and less joint damage over time. Early treatment with DMARDs can delay, or prevent, joint destruction and disability, thereby improving long-term functional outcomes. Therefore, DMARD therapy should be initiated within three months of diagnosis to minimize irreversible joint damage.

Utility Of Anti-CCP In Diagnosing RA
The utility of anti-CCP in diagnosing RA depends both on the performance characteristics (sensitivity, specificity, etc.) of the test and its ability to be incorporated into new diagnostic paradigms that improve on the existing classification criteria.

Whiting et al (2010) published a comprehensive systematic review of the diagnostic accuracy of anti-CCP. A total of 151 studies were identified that contained information on sensitivity and specificity of anti-CCP for diagnosing RA. There was a high degree of heterogeneity for the parameters of sensitivity and specificity across the range of studies included. The pooled sensitivity for all studies was 67% (95% confidence interval [CI]: 64-70%), and the pooled specificity was 95% (95% CI: 94-96%). When confined to cohort studies (n=27), the sensitivity was lower at 60% (95% CI: 54-64%), while the specificity was unchanged at 96% (95% CI: 94-98%). The sensitivity was higher for second generation anti-CCP tests compared to first generation tests. Limited data from third-generation testing suggested similar sensitivity for second- and third-generation testing.

A systematic review of the performance characteristics of anti-CCP in the diagnosis of RA was recently published by Avouac. This study identified 68 publications that evaluated the diagnostic accuracy of anti-CCP in patients that met the American College of Rheumatology (ACR) criteria for RA, and used a control population of either patients with other rheumatologic disorders, or healthy controls. A total of 42 studies evaluated anti-CCP2 while the remainder evaluated anti-CCP1, the first generation version of anti-CCP that is not commercially available. The pooled sensitivity for anti-CCP2 was 68 +/- 15%, and the pooled specificity was 95 +/- 5%. The

specificity of anti-CCP2 in healthy controls was greater than 99%, and when the analysis of specificity was confined to patients with other rheumatologic diseases, the specificity ranged from 91–99%. This systematic review included 11 studies that evaluated the predictive ability for anti-CCP in patients with early undifferentiated arthritis. Anti-CCP was not a sensitive marker for RA in these patients with early arthritis, being present initially in only 23% of patients who eventually developed RA. However, the presence of anti-CCP was a powerful predictor of future RA, conferring a 25-fold increased risk of eventually developing RA (95% CI: 18–35).

Another systematic review by Avouac evaluated the accuracy of a subset of anti-CCP antibodies, anti-mutated citrullinated vimentin (anti-MCV). These auto-antibodies are considered by some experts to have higher sensitivities than that of general anti-CCP autoantibodies. These authors included 16 observational studies in their review. Pooled sensitivity was calculated at 77% (95% CI: 75-78%), and pooled specificity was estimated at 89% (95% CI: 87-90%). The area under the curve (AUC) on summary receiver operating characteristics (ROC) analysis was 0.92.

Some research studies have attempted to incorporate anti-CCP into new models for diagnosing RA, although no such model has achieved widespread acceptance as a replacement for the ACR criteria. In the largest study of this type, Visser et al. evaluated 524 consecutive patients with early inflammatory arthritis. The researchers used a gold standard of persistent erosive arthritis after two years of follow-up as a proxy for RA diagnosis, and determined how well their proposed models differentiated between self-limited arthritis, persistent non-erosive arthritis, and persistent erosive arthritis.

This study reported that anti-CCP was a strong predictor of both persistent, non-erosive arthritis, and persistent erosive arthritis. For persistent non-erosive arthritis, symptom duration prior to presentation was the most powerful predictor (OR 5.49) and anti-CCP was the second most powerful predictor of outcome (OR 4.58). For persistent erosive arthritis, anti-CCP was the most powerful predictor of outcome with an odds ratio of 4.58. Based on these findings, the authors constructed a diagnostic model that included anti-CCP as well as six other parameters (symptom duration, morning stiffness, arthritis in three or more joint groups, bilateral pain in metatarsophalangeal joints, rheumatoid factor, and erosions on radiography). By receiver-operating characteristic (ROC) analysis, this model was superior to the ACR classification for discriminating between self-limited and persistent RA, with an area under the curve (AUC) of 0.84 compared with 0.78 for the ACR classification. It was also superior in discriminating between erosive and non-erosive arthritis, with an AUC of 0.91, compared with 0.78 for the ACR criteria.

The standard methods for diagnosing RA have limited sensitivity for patients with early inflammatory arthritis. Confirming the diagnosis of RA early in the course of inflammatory arthritis may be important, given that early initiation of treatment with DMARDs can minimize joint damage and improve functional outcomes. Anti-CCP has high specificity and moderate sensitivity in diagnosing RA. In addition, multivariate predictive models have demonstrated the potential utility of anti-CCP testing in combination with other known clinical, laboratory and radiologic parameters. However, there are currently no prospectively validated prediction models that demonstrate the additional predictive value of anti-CCP for this purpose.

Some studies have reported higher sensitivities associated with more recent assays of anti-CCP. These have included third generation anti-CCP tests, as well as variants of anti-CCP autoantibodies such as mutated citrullinated vimentin (MCV). Wagner et al as well as other researchers, have reported that measurement of anti-MCV improves the sensitivity of anti-CCP testing. In 193 patients with RA, sensitivity of anti-MCV testing was 71%. Shidara et al reported sensitivities of 88.7% and 89.5% associated with kits for anti-CCP2 and anti-CCP3, respectively. Ryu et al reported a sensitivity of 85% for anti-CCP2 by ELISA. Hwang et al reported accuracy of a commercially available automated chemiluminescent immunoassay. The sensitivity and specificity were 76.8% and 95.3% with an AUC of 0.90.

Anti-CCP For Monitoring Disease Activity In RA

Some experts have proposed that levels of anti-CCP may serve as a marker of disease severity, and/or as a measure of treatment response. Several studies have examined whether the presence of anti-CCP correlates with the severity of future joint erosions. Bongi et al reported that the presence of anti-CCP antibodies was associated with a worse prognosis, as defined by the severity of joint erosions. Raza et al reported similar findings, and also that the combination of anti-CCP positivity and anti-rheumatoid factor positivity was associated with the greatest severity of erosive bone lesions. However, in patients with anti-CCP antibodies, there is little or no evidence that the absolute levels of anti-CCP are important prognostic indicators of disease activity or severity of joint erosions.

Landmann et al correlated the level of anti-CCP and disease activity using the DAS-28, a measure of disease activity that includes the clinical examination of 28 joints, a patient-reported visual analog scale (VAS) score, and the ESR. Forty patients with RA were followed over a mean of 31 months. There was only a weak correlation found between anti-CCP levels and DAS-28 score ($r=0.19$, $p=0.001$), although there was wide variability among individual patients. Other measures, such as clinical symptoms or the ESR, showed a stronger correlation with overall disease activity than did anti-CCP.

Numerous studies have evaluated whether anti-CCP positivity, and the levels of anti-CCP, correlate with treatment response. These studies have generally followed patients with established RA who are being treated with DMARDs, primarily methotrexate and anti-TNF agents, and have generally found little correlation between treatment, anti-CCP levels and other measures of disease activity.

In the largest study of this type, Ronnelid et al followed 379 patients with RA under treatment for a total of five years. Anti-CCP positivity was reversed in only 3.9% of patients. There was a small but significant decrease in the mean anti-CCP level during the first year of treatment, and this decrease correlated with sulfasalazine treatment but not with other treatment agents. During the subsequent years of follow-up there was no significant change in anti-CCP levels, and no correlation between treatment response, disease activity, and anti-CCP levels.

Dejaco et al evaluated changes in anti-CCP2 and anti-CCP3 in 42 RA patients treated with infliximab, etanercept, or adalimumab. Serum levels of anti-CCP were measured before treatment and following six months of treatment. Neither changes in anti-CCP2 nor anti-CCP3 levels were predictive of treatment response with anti-TNF agents.

At least six other smaller studies of similar type have also evaluated this question. Only one of these studies reported that clinical improvement was correlated with a decrease in anti-CCP levels. In the other studies, there was either a small reduction in anti-CCP levels that did not correlate with treatment response, or no significant change in anti-CCP levels associated with treatment.

In a study by Maksymowych (2014) a quantitative ELISA was used to assess 14-3-3ηlevels. Early (n=99) and established patients with RA (n=135) were compared to all controls (n=385), including healthy subjects (n=189). The sensitivity, specificity, positive and negative predictive values of 14-3-3η, and the likelihood ratios (LR) for RA were determined through receiver-operator curve analysis. The incremental value of adding 14-3-3ηto anticitrullinated protein antibody (ACPA) and rheumatoid factor (RF) in diagnosing early and established RA was assessed. Serum 14-3-3ηdifferentiated established patients with RA from healthy individuals and all controls ($p<0.0001$). A serum 14-3-3ηcutoff of≥0.19 ng/ml delivered a sensitivity and specificity of 77% and 93%, respectively, with corresponding LR positivity of 10.4. At this cutoff in early RA, 64% of patients with early RA were positive for 14-3-3η, with a corresponding specificity of 93% (LR+ of 8.6), while 59% and 57% were positive for ACPA or RF, respectively. When ACPA, RF, and 14-3-3ηpositivity were used in combination, 77 of the 99 patients (78%) with early RA were positive for any one of the three markers. Serum 14-3-3ηdid not correlate with C-reactive protein, erythrocyte sedimentation rate, or Disease Activity Score, but patients who were 14-3-3η-positive had significantly worse disease.

In the AMPLE trial (Fleischmann, 2016) patients were assessed regarding the ability of a multi-biomarker disease activity (MBDA) test (Vectra DA) to reflect clinical measures of disease activity in patients enrolled in the AMPLE (Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate) trial. In the AMPLE trial, patients with active rheumatoid arthritis (RA) who were naive to biologic agents and had an inadequate response to methotrexate were randomized (1:1) to receive subcutaneous abatacept (125 mg every week) or subcutaneous adalimumab (40 mg every two weeks), with background methotrexate, for two years. The MBDA score was determined using serum samples collected at baseline, month three, and years one and two. The adjusted mean change from baseline in the MBDA score was compared between the abatacept and adalimumab treatment groups. Cross-tabulation was used to compare the MBDA score with the following clinical measures of disease activity: Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP), and Routine Assessment of Patient Index Data 3 (RAPID-3). The results in total showed, 318 patients were randomized to receive abatacept, and 328 were randomized to receive adalimumab; MBDA data were available for 259 and 265 patients, respectively. No association between the MBDA score and disease activity defined by the CDAI, SDAI, DAS28-CRP, or RAPID-3 in the abatacept and adalimumab treatment groups was observed.

Summary of Evidence

Anti-CCP positivity has prognostic potential, but the absolute level of anti-CCP has not been demonstrated to be a useful measure of future severity of disease. Treatment with DMARDs may reduce anti-CCP to a small degree, but there is no convincing evidence that the reduction in anti-CCP levels correlates with disease activity and/or treatment response. Therefore, the use

of anti-CCP for monitoring disease activity is investigational.

Some publications continued to assess the sensitivity and specificity of anti-CCP testing for the diagnosis of RA. A number of related studies assessed the utility of anti-CCP in predicting future erosive arthritis. Several studies evaluated the incremental utility of incorporating anti-CCP into existing and/or new algorithms for diagnosing RA. Finally, a small number of articles evaluated anti-CCP as a marker of disease activity. Studies that evaluated the sensitivity and specificity of anti-CCP testing in the diagnosis of RA generally agreed with research noted above in demonstrating a modest sensitivity and a high specificity.

Studies that assessed the predictive ability of anti-CCP for erosive arthritis confirmed that anti-CCP is a strong independent predictor of future erosive arthritis. In a cohort of 238 patients with the diagnosis of RA followed for a ten year period, Syversen et al evaluated the predictive ability of anti-CCP, rheumatoid factor, erythrocyte sedimentation rate, C-reactive protein, and other clinical variables. They reported that anti-CCP was the strongest independent predictor of erosive arthritis. Patients with low or moderate anti-CCP levels were 2.6 times (95% CI: 0.9–7.2) more likely to exhibit radiographic progression of joint damage and patients with high levels of anti-CCP were 9.9 times (95% CI: 2.7–36.7) more likely to have radiographic progression. Bukhari et al reported data from the Norfolk Arthritis registry, which followed an inception cohort of 427 patients with inflammatory polyarthritis for five years. This study also reported that anti-CCP was a strong independent predictor of erosive arthritis (OR 10.2, 95% CI: 6.2–16.9). The authors also concluded that anti-CCP testing was most useful in patients who are rheumatoid factor negative, since 63% of patients who were rheumatoid factor negative and anti-CCP positive developed erosive arthritis. In this population, anti-CCP testing may result in an earlier diagnosis of RA, earlier administration of DMARD therapy, and an improvement in long-term functional status.

Other relevant publications attempted to determine the utility of incorporating anti-CCP into existing or new diagnostic algorithms for RA. These studies offer insights into the incremental diagnostic information provided by anti-CCP testing. Liao et al performed a retrospective analysis of 292 patients seen in their arthritis center, who had both rheumatoid factor and anti-CCP drawn. Using the final diagnosis assigned by the treating rheumatologist, these authors tested the diagnostic accuracy of the original ACR criteria for RA, and compared three alternate methods for incorporating anti-CCP. These were 1) adding anti-CCP to ACR criteria, 2) substituting anti-CCP for rheumatoid nodules (CCP 7 criteria), and 3) substituting anti-CCP for both rheumatoid nodules and radiographic joint changes (CCP 6 criteria).

For all patients, the ACR criteria had a low sensitivity of 51% and a high specificity of 91%, as expected. The addition of anti-CCP improved the sensitivity slightly to 55% with no change in specificity. For the CCP six and CCP seven criteria, the sensitivity was increased further to 74% and 77% respectively, with a corresponding decrease in specificity of 81% and 79%. Anti-CCP appeared to have greater utility in the subgroup of patients with symptoms for less than six months. For these patients, the addition of anti-CCP resulted in a larger improvement in sensitivity from 25–44% with no decrease in specificity.

In a prospective study, Yamane et al assessed the diagnostic utility of anti-CCP in 435 patients

seen with arthritic symptoms over a three-year period, 209 of which were diagnosed with RA. These authors compared numerous permutations of anti-CCP, rheumatoid factor, C-reactive protein, and the presence of swollen joints as means of diagnosing RA, using clinician diagnosis as the gold standard. They also examined the variability in diagnostic performance by length of symptoms, with particular emphasis on patients with symptom duration of less than three months. The specificity of anti-CCP testing alone was highest in patients with symptoms for less than three months (95.4%, 95% CI: 91.4–99.3), with a correspondingly high positive predictive value of 87.8%. Therefore, the authors concluded that for this patient population, a positive anti-CCP by itself is sufficient to confirm a diagnosis of RA. The combination of anti-CCP with other clinical and lab markers resulted in a diagnostic algorithm that had a high specificity, ranging from 90.7–98.7 and a low sensitivity, ranging from 19.4–65.6. None of the tested combinations were clearly superior to the others, nor were they demonstrably superior to the ACR criteria.

A few studies evaluated the utility of anti-CCP as a marker of disease activity and/or treatment response. These studies were consistent with previous research reporting that anti-CCP was not useful for monitoring disease activity or response to treatment.

Serum 14-3-3ηis a novel RA mechanistic marker that is highly specific, associated with worse disease, and complements current markers, enabling a more accurate diagnosis of RA. The MBDA score did not reflect clinical disease activity in patients enrolled in AMPLE and should not be used to guide decision-making in the management of RA, particularly for patients who receive abatacept or adalimumab as the first biologic agent.

Physician Guidelines and Position Statements
In response to requests, input was received from one Physician Specialty Society (American College of Rheumatology) and two Academic Medical Centers while this policy was under review. While the various Physician Specialty Societies and Academic Medical Centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the Physician Specialty Societies or Academic Medical Centers, unless otherwise noted. Evidence corroborates prior studies in concluding that anti-CCP has a modest sensitivity, a high sensitivity, and is a strong predictor of future erosive arthritis. Some evidence exists suggesting that anti-CCP offers unique diagnostic information that may aid in the diagnosis of RA, especially for patients with short duration of symptoms. Thus, it may be considered medically necessary in the diagnosis of rheumatoid arthritis. The evidence suggests that anti-CCP is not useful as a measure of disease activity and/or response to treatment.

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

Key Words:
CCP, antibody testing, Cyclic citrullinated peptide antibody testing, Diastat, anti-CCP

Approved by Governing Bodies:

Siemens Healthcare Diagnostics obtained FDA clearance in 2013 to offer U.S. laboratories an anti-cyclic citrullinated peptide (anti-CCP) IgG assay to aid diagnosis of rheumatoid arthritis (RA), a chronic, progressive autoimmune disease affecting approximately 1.3 million Americans. Available on the company's IMMULITE® 2000/2000 XPi immunoassay systems, the anti-CCP IgG assay affords laboratories the ability to integrate RA testing onto an automated, random-access analyzer.

With a clinical specificity of 97 percent, the IMMULITE anti-CCP IgG assay offers laboratories and clinicians a highly accurate diagnostic tool for fast and early RA diagnosis. The assay also helps rule out other inflammatory and arthritic conditions, enabling physicians to determine an appropriate treatment path.

The INOVA Diagnostics QUANTA Lite™ CCP IgG ELISA and the Axis-Shield Diagnostics Diastat™ anti-CCP ELISA test received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA) in 2002 for use as an aid in the diagnosis of rheumatoid arthritis.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Coding:

CPT Codes:

86200 Cyclic citrullinated peptide (CCP), antibody

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Policy History:

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