



BlueCross BlueShield
of Alabama

Name of Policy:

Anti-CCP Testing for Rheumatoid Arthritis

Policy #: 353
Category: Medicine

Latest Review Date: August 2011
Policy Grade: Active Policy but no
longer scheduled for
regular literature reviews
and updates.

Background/Definitions:

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

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

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

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

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

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.

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. According to the FDA statement for the Diastat, “autoantibody levels represent one parameter in a multi-criterion diagnostic process, encompassing both clinical and laboratory-based assessments.” Additional anti-CCP tests have received 510(k) marketing clearance since 2002.

Policy:

Measurement of anti-CCP meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used as part of the diagnostic workup for rheumatoid arthritis.

Measurement of anti-CCP does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage when used to monitor disease activity and/or treatment response and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best

medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

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

Current guidelines for the diagnosis of rheumatoid arthritis: The traditional guidelines for diagnosing RA were developed in 1987 and depended on a combination of clinical, laboratory, and radiographic features (Table). This classification system was criticized as suboptimal for use as a diagnostic tool, especially regarding the low sensitivity for patients with early arthritis. In 2010, a new set of criteria for diagnosis were developed jointly by the American College of Rheumatology (ACR) and the European League against Rheumatism (EuLAR), which incorporate anti-CCP as a diagnostic criterion for RA:

Table: The 2010 ACR/EuLAR classification criteria for RA (adapted from Aletaha et al. 2010)

Criterion	Points
A. Joint involvement a. One large joint b. 2-10 large joints c. 1-3 small joints (with or without involvement of large joints) d. 4-10 small joints (with or without involvement of large joints) e. >10 joints (with at least one small joint)	0 1 2 3 5
B. Serology a. Negative RF and negative anti-CCP b. Low-positive RF or low-positive anti-CCP c. High-positive RF or high-positive anti-CCP	0 2 3
C. Acute-phase reactants a. Normal CRP and normal ESR b. Abnormal CRP or abnormal ESR	0 1
D. Duration of symptoms a. <6weeks b. >6weeks	0 1

RF=rheumatoid factor; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate
Use of this classification system is intended for patients who have at least 1 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 6 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 3 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 published a comprehensive systematic review of the diagnostic accuracy of anti-CCP in 2010. 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 2 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 6 other parameters (symptom duration, morning stiffness, arthritis in 3 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 5 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 6 months of treatment. Neither changes in anti-CCP2 nor anti-CCP3 levels were predictive of treatment response with anti-TNF agents.

At least 6 other smaller studies of similar type have also evaluated this question. Only 1 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.

Summary

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 10-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 5 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 3 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 6 and CCP 7 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 6 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 3-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 3 months. The specificity of anti-CCP testing alone was highest in patients with symptoms for less than 3 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.

Physician Specialty Society and Academic Medical Center Input

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. The input while this policy was under review in late 2008 uniformly supported the use of this testing in the diagnosis of rheumatoid arthritis and did not support its use in monitoring disease activity.

The new 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.

2011 Update

The policy statement remains unchanged.

Key Words:

CCP, antibody testing, Cyclic citrullinated peptide antibody testing, Diastat

Approved by Governing Bodies:

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.

ITS: Home Policy provisions apply

FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.

Pre-certification requirements: Not applicable

Current Coding:

CPT Codes:

86200

Cyclic citrullinated peptide (CCP), antibody

References:

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Policy History:

Medical Policy Group, April 2009 (3)

Medical Policy Administration Committee, May 2009

Available for comment May 12-June 25, 2009

Medical Policy Group, April 2011; Updated Key Points

Medical Policy Group, August 2011; (3) Updated Key Points & References

Medical Policy Group, August 2012 (3): Active Policy but no longer scheduled for regular literature reviews and updates.

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

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