



BlueCross BlueShield  
of Alabama

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**Name of Blue Advantage Policy:**

**Anti-CCP Testing for Rheumatoid Arthritis**

Policy #: 353

Latest Review Date: August 2022

Category: Medicine

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**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).*

## **POLICY:**

**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.*

## **DESCRIPTION OF PROCEDURE OR SERVICE:**

The measurement of antibodies to cyclic citrullinated peptide (anti-CCP) is highly specific testing used for the diagnosis of rheumatoid arthritis (RA). The detection of anti-CCP has been shown to be of prognostic significance in the diagnosis of RA.

Autoantibodies can cause disease by attacking the body's healthy cells by mistake. Anti-CCP target healthy tissues in the joints.

Anti-CCP targets healthy tissues in the joints. Anti-CCP is found in the blood of approximately 60-70% of people who have rheumatoid arthritis. They are almost never found in people who don't have the disease.

This testing may also be known as: Cyclic citrullinated peptide antibody, anticitrullinated peptide antibody, citrulline antibody, anti-cyclic citrullinated peptide, anti-CCP antibody, ACPA.

## **KEY POINTS:**

This policy has been updated with literature review performed through August 18, 2022.

### **Summary of Evidence**

Studies have shown a high specificity for anti-CCP testing. If testing is positive, it is likely to indicate accurately a diagnosis of rheumatoid arthritis. The evidence is sufficient to prove that this technology improves net health outcomes when used for the diagnosis of RA.

After a diagnosis of rheumatoid arthritis is made, there is a paucity of evidence to prove that anti-CCP levels demonstrate disease activity. A decreased anti-CCP level might be seen to indicate the patient has low disease activity or be in remission, but this response varies from patient to patient. Anti-CCP levels do not necessarily go down or go away, even if the disease is under

control. This technology has not been proven useful for monitoring of this disease activity or treatment response. The evidence is insufficient to that this technology improves net health outcomes for the monitoring of disease activity and/or treatment response in RA.

**Physician Guidelines and Position Statements**

**American College of Rheumatology**

Anti-CCP antibody test is predictive for having rheumatoid arthritis. According to the American College of Rheumatology, anti-CCP antibodies are found in 60% to 70% of people with rheumatoid arthritis. These antibodies are directed against cyclic citrullinated peptides (CCP) and can be present before rheumatoid arthritis symptoms ever develop.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**KEY WORDS:**

CCP, antibody testing, Cyclic citrullinated peptide antibody testing, Diastat, anti-CCP, anticitrullinated peptide antibody, citrulline antibody, anti-cyclic citrullinated peptide, ACPA.

**APPROVED BY GOVERNING BODIES:**

Siemens Healthcare Diagnostics, Tarrytown, NY, obtained FDA clearance in 2013 to offer U.S. laboratories an anticyclic citrullinated peptide (anti-CCP) IgG assay to aid diagnosis of rheumatoid arthritis (RA), a chronic, progressive autoimmune disease. 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. Axis-Shield Diagnostics obtained 501k FDA clearance for device: Antibodies, Anti-Cyclic Citrullinated Peptide (CCP). The device is used for the detection of anti-cyclic citrullinated peptide (CCP) antibodies in human serum or plasma 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.

**CURRENT CODING:**

**CPT Codes:**

86200	Cyclic citrullinated peptide (CCP), antibody
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## REFERENCES:

1. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69(9):1580-8.
2. Bose N, Calabrese LH. Q: Should I order an anti-CCP antibody test to diagnose rheumatoid arthritis? *Cleve Clin J Med*. 2012 Apr; 79(4):249-52.
3. Bukhari M, Thomson W, Naseem H, et al. The performance of anti-cyclic citrullinated peptide antibodies in predicting the severity of radiologic damage in inflammatory polyarthritis: Results from the Norfolk Arthritis Register. *Arthritis Rheum* 2007; 56(9):2929-35.
4. DeJaco C, Duftner C, Klotz W et al. Third generation anti-cyclic citrullinated peptide antibodies do not predict anti-TNF-alpha treatment response in rheumatoid arthritis. *Rheumatol Int* 2010; 30(4):451-4.
5. Fleischmann R, Connolly SE, Maldonado MA, Schiff M. Brief Report: Estimating Disease Activity Using Multi-Biomarker Disease Activity Scores in Rheumatoid Arthritis Patients Treated With Abatacept or Adalimumab. *Arthritis Rheumatol*. 2016; 68(9):2083.
6. Gao IK, Haas-Wöhrle A, Mueller KG, Lorenz HM, Fiehn C. Determination of anti-CCP antibodies in patients with suspected rheumatoid arthritis: does it help to predict the diagnosis before referral to a rheumatologist? *Ann Rheum Dis*. 2005 Oct; 64(10):1516-7.
7. Gavrilă BI, Ciofu C, Stoica V. Biomarkers in Rheumatoid Arthritis, what is new? *J Med Life*. 2016 Apr-Jun; 9(2):144-8.
8. Hwang SM, Kim JO, Yoo YM et al. Performance analysis of the ARCHITECT anti-cyclic citrullinated peptide antibody in the diagnosis of rheumatoid arthritis. *Clin Chem Lab Med* 2010; 48(2):225-30.
9. IOM (Institute of Medicine). 2011. *Clinical Practice Guidelines We Can Trust*. Washington, DC: The National Academies Press.
10. Karimifar M, Salesi M, Farajzadegan Z. The association of anti-CCP1 antibodies with disease activity score 28 (DAS-28) in rheumatoid arthritis. *Adv Biomed Res*. 2012; 1:30.
11. Landmann T, Kehl G, Bergner R. The continuous measurement of anti-CCP-antibodies does not help to evaluate the disease activity in anti-CCP-antibody-positive patients with rheumatoid arthritis. *Clin Rheumatol* 2010; 29(12):1449-53.
12. Lee YH, Bae SC, Song GG. Diagnostic accuracy of anti-MCV and anti-CCP antibodies in rheumatoid arthritis: A meta-analysis. *Z Rheumatol*. 2015; 74(10):911-918.
13. Liao KP, Batra KL, Chibnik L, Schur PH, Costenbader KH. Anti-cyclic citrullinated peptide revised criteria for the classification of rheumatoid arthritis. *Ann Rheum Dis*. 2008 Nov; 67(11):1557-61.
14. Lipinska J, Lipinska S, Kasielski M, Smolewska E. Anti-MCV and anti-CCP antibodies-diagnostic and prognostic value in children with juvenile idiopathic arthritis (JIA). *Clin Rheumatol*. 2016; 35(11):2699-2706.
15. Meyer PWA, Ally MTM, Hodgkinson B, et al. Comparison of the diagnostic potential of three anti-citrullinated protein antibodies as adjuncts to rheumatoid factor and CCP in a

- cohort of South African rheumatoid arthritis patients. *Rheumatol Int*. 2018; 38(6):993-1001.
16. Niewold TB, Harrison MJ, Paget SA. Anti-CCP antibody testing as a diagnostic and prognostic tool in rheumatoid arthritis. *QJM*. 2007 Apr; 100(4):193-201.
  17. Qin X, Deng Y, Xu J et al. Meta-analysis: diagnostic value of serum anti-mutated citrullinated vimentin antibodies in patients with rheumatoid arthritis. *Rheumatol Int* 2011; 31(6):785-94.
  18. Raza K, Breese M, Nightingale P, et al. Predictive value of antibodies to cyclic citrullinated peptide in patients with very early inflammatory arthritis. *J Rheumatol* 2005; 32(2):231-8.
  19. Rönnelid J, Wick MC, Lampa J, Lindblad S, Nordmark B, Klareskog L, van Vollenhoven RF. Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression. *Ann Rheum Dis*. 2005 Dec; 64(12):1744-9.
  20. Ryu HJ, Takeuchi F, Kuwata S et al. The diagnostic utilities of anti-agalactosyl IgG antibodies, anti-cyclic citrullinated peptide antibodies, and rheumatoid factors in rheumatoid arthritis. *Rheumatol Int* 2011; 31(3):315-9.
  21. Sghiri R, Bouagina E, Zaglaoui H, et al. Diagnostic performances of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis. *Rheumatol Int* 2007; 27(12):1125-30.
  22. Shidara K, Inoue E, Tanaka E et al. Comparison of the second and third generation anti-cyclic citrullinated peptide antibody assays in the diagnosis of Japanese patients with rheumatoid arthritis. *Rheumatol Int* 2011; 31(5):617-22.
  23. Son JJ, Ishimori M, Mirocha J, Weisman MH, Forbess LJ. Low levels of anti-cyclic citrullinated peptide (CCP) 3.1 associated with diseases other than rheumatoid arthritis. *Medicine (Baltimore)*. 2021 Apr 23; 100(16):e25558.
  24. Syversen SW, Gaarder PI, Goll GL, et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. *Ann Rheum Dis* 2008; 67(2):212-7.
  25. Vis M, Bos WH, Wolbink G, et al. IgM-rheumatoid factor, anti-cyclic citrullinated peptide, and anti-citrullinated human fibrinogen antibodies decrease during treatment with the tumor necrosis factor blocker infliximab in patients with rheumatoid arthritis. *J Rheumatol* 2008; 35(3):425-8.
  26. Wagner E, Skoumal M, Bayer PM, Klaushofer K. Antibody against mutated citrullinated vimentin: a new sensitive marker in the diagnosis of rheumatoid arthritis. *Rheumatol Int*. 2009 Sep; 29(11):1315-21.
  27. Whiting PF, Smidt N, Sterne JA et al. Systematic review: accuracy of anti-citrullinated Peptide antibodies for diagnosing rheumatoid arthritis. *Ann Intern Med* 2010; 152(7):456-64; W155-66.
  28. Yamane T, Hashiramoto A, Tanaka Y, et al. Easy and accurate diagnosis of rheumatoid arthritis using anti-cyclic citrullinated peptide 2 antibody, swollen joint count, and C-reactive protein/rheumatoid factor. *J Rheumatol* 2008; 35(3):414-20.

29. Zendman AJ, van Venrooij WJ and Pruijn GJ. Use and significance of anti-CCP autoantibodies in rheumatoid arthritis. *Rheumatology*, 2006; 45(1):20-5.

### **POLICY HISTORY:**

Adopted for Blue Advantage, April 2009

Available for comment April 23-June 6, 2009

Medical Policy Group, April 2011

Medical Policy Group, August 2011

Medical Policy Group, September 2019

Medical Policy Group, August 2021

Medical Policy Group, October 2021: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.

Medical Policy Group, August 2022: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.

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*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.*