Published in final edited form as:
Arthritis Rheum. 2009 November 15; 61(11): 1472–1483. doi:10.1002/art.24827.

Anti-Citrullinated Peptide Antibody (ACPA) Assays and their Role in the Diagnosis of Rheumatoid Arthritis

Rohit Aggarwal[*,1], **Katherine Liao**[*,2], **Raj Nair**[*,3], **Sarah Ringold**[*,4], and **Karen H. Costenbader**[2]

[1]Rush University Medical Center, Chicago, IL

[2]Brigham & Women's Hospital, Boston, MA

[3]University of North Carolina, Chapel Hill, NC

[4]Seattle Children's Hospital & Regional Medical Center, Seattle, WA.

Abstract

Increasingly, assays for the detection of anti-citrullinated peptide antibodies (ACPA) are used in RA diagnosis. This review summarizes the biologic basis and development of ACPA assays, available ACPA assays and their performance characteristics, and diagnostic properties of ACPA alone and compared to rheumatoid factor (RF) in early RA. We also review correlations, precision, costs and cost-effectiveness, availability, stability and reproducibility of the available assays. Taken together, data indicate that ACPA has a higher specificity than RF for early RA, good predictive validity, high sensitivity, apparent cost-effectiveness and good stability and reproducibility. Given its superior performance characteristics and increasing availability, ACPA is emerging as the most useful single assay for the diagnosis of RA.

Keywords

anti-citrullinated peptide antibody; rheumatoid factor; anti-CCP; ACPA; RF; diagnosis; rheumatoid arthritis; early arthritis

Introduction

The diagnosis of early rheumatoid arthritis (RA) has relied upon clinical criteria, including history and physical exam findings, laboratory and radiographic results. Irreversible damage frequently occurs early in RA (1-5). With mounting evidence supporting early diagnosis and aggressive treatment to prevent damage and disability, there is need to improve identification and diagnosis of early RA (6). Until recently, assays detecting rheumatoid factor (RF), antibodies directed against the Fc portion of the immunoglobulin G (IgG) molecule, have been the primary serological tests for RA diagnosis. Anti-citrullinated peptide antibody (ACPA) assays, developed and commercialized in the past decade, are now being employed clinically. Since ACPA are present before the onset of RA symptoms and are predictive of RA development, they are a valuable diagnostic test early in the course of the disease (4).

This review synthesizes currently available data regarding the diagnostic properties of RF and ACPA for the diagnosis of early RA. We focus on ACPA given their recent

[*]The first four authors contributed equally to this manuscript and should be considered as joint first authors.

development and their potential role in the improved identification of early, undifferentiated RA. Data included in this review were obtained from medical literature searches, websites and contact with companies marketing the assays, and information and opinions obtained from experts in the field. We have included information on the biologic basis and development of ACPA assays, the available assays, and data concerning assay performance characteristics, in particular those published in peer-reviewed journals, but also those publicized by manufacturers. Diagnostic properties of these tests, including, but not limited, to sensitivity, specificity, positive and negative predictive values, are reviewed.

Rheumatoid factor (RF)

In 1940, Waaler observed that mixing serum from an RA patient with IgG-sensitized sheep erythrocytes inhibited hemolysis, but caused cell agglutination (7). Rose and colleagues later reported that RA sera agglutinated sheep erythrocytes coated with rabbit anti-sheep erythrocyte antibody more than did sera healthy individuals (8). These findings formed the basis of the earliest RA assay, the Waaler-Rose test.RF assays most commonly detect IgM antibodies directed against the Fc portion of the IgG molecule. The agglutination test measures RF IgM only and remains the most widely used assay. Agglutination assays are reported as either titers or units. Cut-offs for positivity are determined by manufacturers and based upon results from RA patients compared to healthy controls (4,9). Agglutination assays have sensitivities for RA r from 70-85% and specificities ranging from 40-90%, as agglutination in individuals without RA may occur (10-12).

Other assays for RF have been developed, including enzyme-linked immunosorbent assays (ELISAs), radioimmune assays (RIAs), and laser or rate nephelometry techniques (13). Assays for the detection of IgA and IgG RF are also available (14-19). The sensitivity of RF for RA diagnosis by these techniques is 50-90% and specificity is 50-95%. These wide ranges reflect differences in populations tested (20-26). Studies directly comparing RF detection techniques in cohorts of established RA patients, healthy controls, and patients with non-inflammatory joint disease, have reported latex agglutination test performance to be similar to that of nephelometry and radioimmune assays (12,27). In a meta-analysis of 50 studies of RF assays from 1998-2005, the pooled likelihood ratios (dependent upon both sensitivities and specificities) were quantitatively similar for IgM, IgA and IgG RF assays, and for using a higher versus lower RF titer for positivity (26) (Table 1).

False positive RF results commonly occur in the setting of chronic infections, malignancy, and other rheumatic diseases (21). RF is detected in the sera of 1-4% of healthy young persons and in a higher percentage of elderly persons without RA (28,29). The RF assay however, is widely available, relatively inexpensive, and understood by both primary care physicians and arthritis specialists (21).

Antibodies to citrullinated peptides

In 1964, Nienhuis and colleagues described an autoantibody they called anti-perinuclear factor. Detected by indirect immunofluorescence test on human buccal mucosa cells, anti-perinuclear factor recognized antigen present in keratohyaline granules surrounding the nucleus (30). Anti-perinuclear factor was present in up to 90% of established RA patients, with a 73-99% specificity (31). Young and colleagues later detected anti-keratin antibodies using indirect immunofluorescence on cryosections of rat esophagus (32). The reported sensitivity of the anti-keratin assay in RA patients of 36-59% and specificity 88-99% (31). Despite the high specificity for RA, these tests were not used widely because of difficulty in standardization of natural substrates and arbitrary interpretation of the indirect immunofluorescence pattern.

In 1995, Sebbag and colleagues demonstrated that both of these antibodies belonged to a family of autoantibodies directed against citrullinated fillagrin, an epithelial cell protein (33). Citrullination is posttranslational modification of arginine to citrulline by the enzyme peptidyl arginine deiminase (PAD). This process occurs naturally during inflammation, apoptosis and keratinization (9). While fillagrin is not present in the synovium (34), several citrullinated proteins, including fibrinogen and fibronectin, are present in RA synovium, and other citrullinated epitopes have been identified as targets of highly RA-specific autoantibodies (35-37). In 1998, Schellekens and colleagues produced synthetic linear citrullinated peptides derived from human fillagrin, easily detected by ELISA with enhanced sensitivity and no loss of specificity (35). To improve antigen composition and antibody recognition, a cyclic citrullinated peptide (CCP) was developed (38).

The first commercially available ACPA assay (1st generation or CCP1) was developed by Eurodiagnostica, used in early studies (2000–2001). This ELISA–based test employed a single cyclic citrullinated peptide derived from fillagrin.(38). The assay detected autoantibodies in 53% of established RA patients with 96% specificity (38).

Peptide libraries were then screened for better epitopes Since 2000, 2nd generation cyclic citrullinated peptide (CCP2) and 3rd generation cyclic citrullinated peptide (CCP3) assays have been developed. Several companies market these assays for RA diagnosis. CCP3 assays rely upon additional epitopes not present in the CCP2 antigen sequence (39,40). Apart from the main difference in substrate, both CCP2 and CCP3 use ELISA methods and similar dilutions (1:101), diluents, controls, conjugates, and rinterpretation. AxSYM Anti-CCP utilizes microparticle enzyme immunoassay (MEIA) for the semi-quantitative determination of the IgG class of auto-antibodies specific to CCP 2. Most studies, however, show no evident improvement of CCP3 compared to CCP2 assays (41-43). The compositions of many new CCP3 peptides are not yet publicly available as patents are pending. The anti-CCP3.1 assay marketed by INOVA detects both IgG and IgA CCP3 antibodies in an effort to increase sensitivity (41). Eurodiagnostica has developed a “point-of-care” assay, employing a finger lancet to obtain a drop of blood for rapid office-based results.

Newer assays detect non-cyclic citrullinated peptides (41); the term anti-citrullinated peptide antibody (ACPA) has thus replaced anti-cyclic citrullinated peptide (anti-CCP) antibody. Citrullinated vimentin is present in synovial fluid. Anti-Sa antibodies, directed against it, are detectable in RA synovium (44,45). Anti-Sa antibodies have reported sensitivity of 20-25% and specificity of 95% in early RA (46). An ELISA for the detection of autoantibodies against mutated citrullinated vimentin (anti-MCV) has better sensitivity than anti-Sa antibody. The sensitivity of anti-MCV is comparable (or even higher in some studies) to that of ACPA (82% vs 72%) (47), while specificity of anti-MCV is slightly lower than ACPA in several studies (90-92% vs. 96-98%) (41,48). Unlike ACPA assays, the anti-MCV levels may correlate with disease activity (47,49).

Pathogenetic role of ACPA in RA

The roles of citrullinated peptides and autoantibodies to them in RA pathogenesis remain unclear. ACPA are strongly associated with an increased risk of developing RA in healthy individuals and are detectable in the blood of healthy persons prior to clinical RA (14,50,51). Among those with RA, their presence is associated with more severe structural damage, radiographic progression and poorer response to therapy. (26,38,52-60,66). Geneticists and epidemiologists hold ACPA-positive RA to be a homogeneous phenotype of severe RA. ACPA is strongly associated with the *HLA-DRB1* shared epitope (61) and *PTPN22* (62,63), strong genetic risk factors for RA, and smoking (64,65), the strongest

known environmental risk factor for RA. Smoking by individuals with inherited *HLA-DRB1* shared epitope genes may trigger RA-specific immune reactions to citrullinated peptides, the generation of ACPAs and, ultimately, disease (64).

ACPA reproducibility and stability over time

In stored blood bank samples, Nielen and colleagues detected ACPA antibodies present up to 14 years prior to RA onset, with gradually increasing prevalence and increased sensitivity and specificity for RA compared to RF (51). The duration of the preclinical autoantibody positive, symptom-free period prior to RA may iincrease with increasing age (60). In a 3-year study off 97 individuals with RA, ACPA status was relatively stable: three ACPA positive subjects became negative, while two ACPA negative subjects became positive (67). Decreases in ACPA may be observed with some RA therapies, but generally patients do not lose their positive results (68-72). Although in some small studies ACPA levels paralleled RA disease activity (68,69,73-75), this has not been corroborated in subsequent studies and ACPA assay results are not employed clinically to monitor disease activity (70-72).

Currently Available ACPA Assay Performance Characteristics

Several ACPA assays are currently approved by the U.S. Food and Drug Administration (FDA) (Table 2). The ACPA assays employed by European and Canadian early arthritis cohorts are mainly CCP2 assays (Diastat™ from Axis–Shield, Immunoscan-CCP Plus™ from Eurodiagnostica, and ELIA-CCP™ from Phadia, and Quanta Lite from Inova, etc). Most currently available assays are kits employing a substrate derived from the synthetic cyclic peptide described by Schellekens and colleagues (38,41), but differ in incubation time, volume and dilution of serum, type of conjugate and of enzymatic substrate, and range of units reported and thresholds for positive results (41,42,76-78). To determine the diagnostic performance, manufacturers have tested established RA patients meeting the 1987 ACR criteria (79), and healthy individuals. Sensitivities range from 60-80% and specificities from 85-99%. CCP2 assays have slightly higher sensitivity than CCP1 assays; the newest non-cyclic ACPA assays report similar performance compared to CCP2 (42,76-78,80,81).

As ACPA assays are based on detection of autoantibodies by ELISA or MEIA or immuno-enzymofluorimetry, reactivity is related to the quantity of antibody present in a non-linear fashion. While changes in antibody concentration are reflected in a corresponding rise or fall in results, the change is not proportional in most assays (i.e. a doubling of the antibody concentration will not double the reactivity) (41). In a head-to-head comparison of the technical performance of six different commercially available ACPA assays, Inova, Eurodiagnostica and Genesis (41) demonstrated significant deviation from linearity; the best linearity was achieved by Euroimmun.

ACPA assay precision

Studies comparing different ACPA assays have concluded that the majority of assays are precise, with within-assay (intra-assay) coefficient of variations (CVs) for most available assays ranging from 4-19% (41,78). In a study by Coenen and colleagues comparing six ACPA assays, the greatest precision was found with Genesis (4.8-5.9% intra-assay CV) and Inova assays (3.7-5.1% intra-assay CV) and the lowest with the Eurodiagnostica assay (12.6-34.3% intra-assay CV) (41,78).

ACPA Assay correlation

Although different antigens and methods are employed to quantitate and report ACPA, the results, expressed as positive or negative values, are highly correlated among commercially

available ACPA assays, with correlation coefficients from 0.59 to 0.96 (Table 3) (41,78). Vander Cruyssen and colleagues studied four ACPA assays, including INOVA's CCP3 assay. They found that discrepancy between the ACPA assays was due to borderline results, inter-assay variability and inter-test variability. The lowest intertest discrepancy is observed between tests using the same substrate (82). If one false positive ACPA was found in an individual without RA, there was a high probability that ACPA would be negative in a different ACPA assay (82).

Development of an international reference range for standardized ACPA reporting

Given the variety of ACPA assays, quantitative results are not currently comparable between studies. Work is underway to develop standardized ACPA units. (83). Results were promising, but require additional confirmation in large numbers of samples and acceptance by assay manufacturers (84).

ACPA assays in other diseases

While the specificity of ACPA assays for RA compared to healthy individuals is good, the potential for lower specificity in the setting of other inflammatory disorders, such as psoriatic arthritis, scleroderma, systemic lupus erythematosus (SLE) and seronegative spondyloarthropathies is of concern (85). The presence of immune complexes or other immunoglobulin aggregates can cause increased non-specific binding and false positive results.

We identified and reviewed 63 studies that examined the cross-reactivity rate of ACPA in non-RA rheumatic diseases and common infections. The highest frequency of ACPA positivity in non-RA autoimmune conditions are found in psoriatic arthritis (9%), SLE (8%), and juvenile idiopathic arthritis (JIA) (8%), as well as scleroderma and CREST syndrome (7%), followed by Sjögren's syndrome (6%) and vasculitis (5%) (Table 4). As many patients in these studies do not have long-term follow-up, they may have ultimately been diagnosed with ACPA-positive RA or an overlap syndrome. For example, 7 of 126 psoriatic arthritis patients with detectable ACPA had more severe, erosive disease and high prevalence of the RA-associated *HLA-DRB1* shared epitope (86). A high frequency of ACPA positivity has been observed in patients with erosive arthritis and overlap syndromes with features of scleroderma and SLE (41,43,78,82,87-91). ACPA in JIA has been associated with RF-positive disease similar to RA in adults (92).

The surprisingly high prevalence of ACPA in active tuberculosis has been studied by Kakamanu and colleagues (93). They reported that reactivity to uncitrullinated arginine-containing residues was common in tuberculosis, but not in RA. The mechanism of induction of ACPA in active pulmonary tuberculosis known. ACPA levels decreased somewhat, but not rapidly, after treatment for tuberculosis (93).

Comparison of 1st, 2nd, and 3rd Generation and newer ACPA assays

Given the rapid evolution of ACPA assays, establishing the comparative sensitivity and specificity of the three "generations" of assays is crucial if they are to be used interchangeably. CCP2 and CCP3 assays offer slightly improved sensitivity over that of CCP1 assays (85,94), although they have similar specificity for RA (86-96%). CCP2 and CCP3 assays in most (41-43), but not all studies (91), have had similar performance characteristics with sensitivities 68-79% and specificities 86-96% (26,43,75,78,81,95).

New anti-MCV assays also have similar performance, with sensitivities 70-82% and specificities 90-98% (47,48,96,97). Higher false positives rates have been reported with Orgentec™ (anti-MCV) and Inova Quantalite™ (CCP3) assays (41). There is some lack of agreement between the results obtained from different ACPA assays on same subjects, which could be partially attributed to borderline results and inter-assay variability. One study has shown 18% discrepancy between two different ACPA assays tested on RA patients (82).

Cost and availability of RF and ACPA assays

RF assays have been widely used for years and are familiar to general practitioners. They are relatively inexpensive and easy to obtain. Since 2000, when ACPA assays were first introduced, the availability of these tests has drastically increased and costs have decreased. They are now marketed almost worldwide by a variety of companies. The Diastat™ CCP2 assay from Axis-Shield, for example, is sold globally. It has the approval of the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMEA) and the Japanese Ministry of Health and Welfare (MOHW). The price per kit varies from market to market, but is approximately $US 250-300 per 96 well kit. Immunoscan™ 2nd generation ACPA assay 96 well kits from Euro-Diagnostica are currently marketed for 350-400€, $US 500-600, or £250-300 in Great Britain. Fully automated and point-of-care assays are beginning to be marketed by several companies.

Konnopka and colleagues performed a cost effectiveness analysis to address the incremental benefit of testing for ACPA in addition to the current ACR criteria for RA classification (98). They developed a Markov model of the 10-year progression of RA in patients presenting with undifferentiated arthritis, and estimated the effects of ACPA testing on incremental costs and quality-adjusted life years, including the impact of late diagnosis and treatment. Their analysis revealed that up-front use of ACPA testing, rather than waiting and testing after a few years of symptoms, was cost effective, and, when indirect costs were incorporated, saved in the range of 1000€ per quality-adjusted life year. While based on multiple assumptions, this study does provide evidence for changing the current approach to early inflammatory arthritis.

Diagnostic accuracy of ACPA assays

More than 300 studies have been published concerning the diagnostic accuracy of ACPA assays in RA diagnosis (26). These studies vary substantially in focus: some have addressed technical aspects, while others have compared the diagnostic accuracy in different populations of individuals (early or established RA; patients with other diseases or healthy controls). The studies are heterogeneous in their comparison of ACPA assay utility to other tests, including IgM, IgA and IgG RF (26) and their use of a gold standard for RA diagnosis (most often the existing 1987 American College of Rheumatology criteria for the classification of RA (79)).

In studies of early or undifferentiated RA, ACPA testing is generally more specific and equally sensitive to RF (Table 5). In cohorts containing both established and early RA, the performance characteristics of the two tests are comparable (Table 4). The definition of early arthritis or early RA has varied in these studies. In the majority, early arthritis has been defined as symptom duration of less than 2 years (median of approximately 2 months) and initial serologies of patients who developed RA have been compared to those who did not (14,26,38-40,46,51,56,59,76,99-102,103,104,105,106,107-111). Most of these data are from the prospective follow-up of early arthritis cohorts in Japan, the Netherlands, and Austria.

RF and ACPA: One, either or both in Early, Inflammatory Arthritis?

Given the substantial overlap between the diagnostic performance and utility of RF and ACPA for the diagnosis of RA, the marginal diagnostic value of adding one test to the other and the added value of performing both must be addressed. In particular, the challenge is to decide on the combination of assay or assays that offers superior performance for the identification of RA among patients presenting with early, undifferentiated inflammatory arthritis. Although correlated, RF and ACPA assays detect different underlying biological phenomena in RA, and thus agreement between assay results is not static, but likely fluctuates during disease course (103).

In our review of data from early RA cohorts, ACPA was slightly more specific than RF, but the two assays have equivalent sensitivity (Table 5). The positive predictive value for ACPA in the setting of early undifferentiated arthritis is 78-96% in t early RA cohorts, with most values in the low to mid 90% range and the negative predictive value is 62-96% (38,46,58,76,101,102,104,111). The positive predictive value for RF is broader, from 36-97% with most values in 70-80%, and the negative predictive value is 69-95%. Positive ACPA results may be particularly helpful in the setting of a negative RF. The positive predictive value of a positive ACPA test was 91.7% among 260 IgM-RF negative early arthritis patients followed for one year (76). Employing both ACPA *and* RF positivity further increases specificity and positive predictive value to above 95%, but decreases sensitivity substantially. When either ACPA *or* RF positivity are required, the sensitivity is somewhat increased (52-67%), but specificity is similar to that of RF alone (72-82%) (102,104).

In cohorts containing both established and early RA, the performance characteristics of RF and ACPA are comparable and the sensitivity of both RF and ACPA is improved,,(although the ranges of performance characteristics are large and tdata are mixed). A strategy requiring either ACPA *or* RF may improve sensitivity for both early and established RA. In one study, the presence of either ACPA *or* RF increased testing sensitivity for RA from 66% (ACPA) and 72% (RF) to 81%, with a good specificity of 91% (9). The specificity of requiring both to be present is comparable to that of ACPA alone.

The addition of ACPA testing improved the sensitivity of the 1987 ACR criteria (which rely upon the presence of RF as one of the 11 possible criteria, 4 of which must be present) for the correct classification of early RA subjects (112). Adding ACPA results to the 1987 criteria increased sensitivity for early RA (≤ 6 month disease duration) from 25 to 44% and did not change the specificity of 86%. ACPA also played an important role in a rule developed by Van der Helm-van Mil and colleagues to predict which patients with undifferentiated arthritis would progress to RA (113). Five hundred and seventy patients with undifferentiated arthritis in the Leiden Early Arthritis Center were selected and reassessed at one year for RA development. The prediction rule consisted of nine variables: sex, age, location of symptoms, morning stiffness, tender joint count, swollen joint count, C-reactive protein, and RF and ACPA positivity. ACPA was one of the strongest predictors, and if positive, a subject received 2 points (113). A modified form of this prediction rule was validated in three cohorts of patients with recent onset undifferentiated arthritis and was found to have excellent discriminative ability to assess progression to RA (114).

ACPA assays are increasingly available and affordable. The assays have good predictive validity as ACPA are associated with known genetic and epidemiologic risk factors for RA and therefore identify a population of RA patients with more severe, erosive joint disease that is at high risk for rapid joint destruction. Positive and negative results are highly correlated between current assays. International standardization of reporting units is

underway and will facilitate inter-assay comparisons. Both CCP2 and CCP3 assays have improved upon CCP1 assays, and have comparable diagnostic utility, with sensitivities of 68-79% and specificities from 86-96% for RA (26,75,78,81,95)

We did not obtain all data, published and unpublished, from past comparisons of RF and ACPA assay performance or perform a formal meta-analysis. We did review published studies and presented sensitivity and specificity ranges of assays, alone and in combination in both early and established RA cohorts. Our results suggest that ACPA assays offer a slight advantage over RF (including high titer RF and combined IgM, IgA and IgG RF levels) due to higher specificity. RF and ACPA are two different autoantibody systems that do not measure or reflect the same underlying biology (103). While there is substantial correlation between ACPA and RF seropositivity within patients, the ACPA assay may be especially valuable in predicting RA in patients who are RF-negative but nevertheless have a high probability of RA (76). If the role of the assay is to aid in the identification of patients developing RA among those presenting with early undifferentiated symptoms, a high-risk population with a high prevalence of disease (rather than screening the general population), the positive predictive value of the ACPA assay is on the order of 95% (76).

ACPA assays have high specificity, high predictive validity, high specificity, apparent cost-effectiveness and good reproducibility for the diagnosis of early RA. In prior studies, accepting *either* ACPA *or* RF positive assay results for the diagnosis of RA did not improve upon testing for RF alone and requiring both assays to be positive for diagnosis is a very specific, but not extremely, sensitive approach. Ultimately, the decision to use one or both tests depends upon the population tested, the indications for the testing, and the inherent trade-off between sensitivity and specificity.

Summary and Overall Recommendations

- ACPA assays have good predictive validity in that they are associated with the known genetic and epidemiologic risk factors for RA and identify a population of RA patients with more severe, erosive joint disease, at high risk for more rapid joint destruction.
- RF and ACPA are two different autoantibody systems and do not measure or reflect the same underlying biology.
- ACPA assays are becoming increasingly available and less expensive. Cost-effectiveness analyses suggest that up-front testing of ACPA in patients presenting with undifferentiated arthritis is cost-effective, in particular in terms of the saved indirect costs of delayed diagnosis.
- ACPA offers similar sensitivity, but higher specificity for RA than RF in early RA. When used in the identification of patients potentially developing RA among those presenting with early undifferentiated symptoms, a high risk population, (rather than screening the entire population), the prevalence of disease will be high and the positive predictive value of the ACPA assay is on the order of 95% (76).
- In the setting of a relatively high clinical suspicion (pre-test probability) and a positive ACPA result, the patient has a high likelihood of having or developing RA. If ACPA is negative, further testing may be indicated depending on the level of clinical suspicion.

Acknowledgments

This publication was made possible in part by the ACR-EULAR RA Classification Criteria Committee. We thank Gillian Hawker, MD, MSc; David Felson, MD, MPH; and Josef Smolen,,MD for their expert opinions and input.

Dr. Aggarwal is the recipient of RUSH-CCH collaborative research grant 2008. Dr. Liao is supported by NIH grant T32 AR 055885. Dr. Nair is supported by NIH grant T32 AR007416. Dr. Ringold receives support from the Mentored Scholar Program through the Seattle Children's Hospital Research Institute's Center for Clinical and Translational Research. Dr. Costenbader is supported by an Arthritis Foundation/American College of Rheumatology Arthritis Investigator Award, and NIH grants P60 AR047782 and BIRCWH K12 HD051959 (funded by NIMH, NIAID, NICHD, and OD).

REFERENCES

1. Bukhari MA, Wiles NJ, Lunt M, Harrison BJ, Scott DG, Symmons DP, et al. Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. Arthritis Rheum. 2003; 48(1):46–53. [PubMed: 12528102]
2. Landewe RB. The benefits of early treatment in rheumatoid arthritis: confounding by indication, and the issue of timing. Arthritis Rheum. 2003; 48(1):1–5. [PubMed: 12528097]
3. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001; 111(6):446–51. [PubMed: 11690569]
4. Rantapaa-Dahlqvist S. Diagnostic and prognostic significance of autoantibodies in early rheumatoid arthritis. Scand J Rheumatol. 2005; 34(2):83–96. [PubMed: 16095003]
5. Kim JM, Weisman MH. When does rheumatoid arthritis begin and why do we need to know? Arthritis Rheum. 2000; 43(3):473–84. [PubMed: 10728739]
6. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007; 146(6):406–15. [PubMed: 17371885]
7. Waaler E. On the Occurrence of a Factor in Human Serum Activating the Specific Agglutination of Sheep Red Blood Corpuscles. Acta path microbiol scand. 1940; 17:172–188.
8. Rose H. Differential Agglutination of Normal and Sensitized Sheep Erythrocytes by Sera of Patients with Rheumatoid Arthritis. Proceedings of the Society for Experimental Biology and Medicine. 1948; 68(1):1–6. [PubMed: 18863659]
9. Lee DM, Schur PH. Clinical utility of the anti-CCP assay in patients with rheumatic diseases. Ann Rheum Dis. 2003; 62(9):870–4. [PubMed: 12922961]
10. Bas S, Perneger TV, Seitz M, Tiercy JM, Roux-Lombard P, Guerne PA. Diagnostic tests for rheumatoid arthritis: comparison of anti-cyclic citrullinated peptide antibodies, anti-keratin antibodies and IgM rheumatoid factors. Rheumatology (Oxford). 2002; 41(7):809–14. [PubMed: 12096232]
11. Bas S, Perneger TV, Kunzle E, Vischer TL. Comparative study of different enzyme immunoassays for measurement of IgM and IgA rheumatoid factors. Ann Rheum Dis. 2002; 61(6):505–10. [PubMed: 12006322]
12. Prentice AG, Hickling P, Wiseman IC, Holwill CJ, Northwood J. Prospective comparison of laser nephelometry with standard agglutination techniques for detection of rheumatoid factor. J Clin Pathol. 1987; 40(2):216–20. [PubMed: 3493266]
13. [accessed 9/12/2008]. http://www.fda.gov/cdrh/oivd/
14. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum. 2003; 48(10):2741–9. [PubMed: 14558078]
15. Bas S, Genevay S, Meyer O, Gabay C. Anti-cyclic citrullinated peptide antibodies, IgM and IgA rheumatoid factors in the diagnosis and prognosis of rheumatoid arthritis. Rheumatology (Oxford). 2003; 42(5):677–80. [PubMed: 12709545]
16. Jonsson T, Steinsson K, Jonsson H, Geirsson AJ, Thorsteinsson J, Valdimarsson H. Combined elevation of IgM and IgA rheumatoid factor has high diagnostic specificity for rheumatoid arthritis. Rheumatol Int. 1998; 18(3):119–22. [PubMed: 9833253]
17. Swedler W, Wallman J, Froelich CJ, Teodorescu M. Routine measurement of IgM, IgG, and IgA rheumatoid factors: high sensitivity, specificity, and predictive value for rheumatoid arthritis. J Rheumatol. 1997; 24(6):1037–44. [PubMed: 9195506]

18. van Leeuwen MA, Westra J, van Riel PL, Limburg PC, van Rijswijk MH. IgM, IgA, and IgG rheumatoid factors in early rheumatoid arthritis predictive of radiological progression? Scand J Rheumatol. 1995; 24(3):146–53. [PubMed: 7777825]
19. van Leeuwen MA, Westra J, Limburg PC, de Jong HJ, Marrink J, van Rijswijk MH. Quantitation of IgM, IgA and IgG rheumatoid factors by ELISA in rheumatoid arthritis and other rheumatic disorders. Scand J Rheumatol Suppl. 1988; 75:25–31. [PubMed: 3070726]
20. Shmerling RH. Diagnostic tests for rheumatic disease: clinical utility revisited. South Med J. 2005; 98(7):704–11. quiz 712-3, 728. [PubMed: 16108239]
21. Shmerling RH, Delbanco TL. The rheumatoid factor: an analysis of clinical utility. Am J Med. 1991; 91(5):528–34. [PubMed: 1951415]
22. Shmerling RH, Delbanco TL. How useful is the rheumatoid factor? An analysis of sensitivity, specificity, and predictive value. Arch Intern Med. 1992; 152(12):2417–20. [PubMed: 1456851]
23. Lichtenstein MJ, Pincus T. Rheumatoid arthritis identified in population based cross sectional studies: low prevalence of rheumatoid factor. J Rheumatol. 1991; 18(7):989–93. [PubMed: 1920334]
24. Dorner T, Egerer K, Feist E, Burmester GR. Rheumatoid factor revisited. Curr Opin Rheumatol. 2004; 16(3):246–53. [PubMed: 15103252]
25. Sauerland U, Becker H, Seidel M, Schotte H, Willeke P, Schorat A, et al. Clinical utility of the anti-CCP assay: experiences with 700 patients. Ann N Y Acad Sci. 2005; 1050:314–8. [PubMed: 16014547]
26. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007; 146(11):797–808. [PubMed: 17548411]
27. Anuradha V, Chopra A. In the era of nephelometry, latex agglutination is still good enough to detect rheumatoid factor. J Rheumatol. 2005; 32(12):2343–4. [PubMed: 16331760]
28. Shmerling RH. Rheumatic disease: choosing the most useful diagnostic tests. Geriatrics. 1996; 51(11):22–6. 29–30, 32. [PubMed: 8918481]
29. Wolfe F, Cathey MA, Roberts FK. The latex test revisited. Rheumatoid factor testing in 8,287 rheumatic disease patients. Arthritis Rheum. 1991; 34(8):951–60. [PubMed: 1859489]
30. Nienhuis RL, Mandema E. A New Serum Factor in Patients with Rheumatoid Arthritis; the Antiperinuclear Factor. Ann Rheum Dis. 1964; 23:302–5. [PubMed: 14178016]
31. Hoet RM, Boerbooms AM, Arends M, Ruiter DJ, van Venrooij WJ. Antiperinuclear factor, a marker autoantibody for rheumatoid arthritis: colocalisation of the perinuclear factor and profilaggrin. Ann Rheum Dis. 1991; 50(9):611–8. [PubMed: 1718228]
32. Young BJ, Mallya RK, Leslie RD, Clark CJ, Hamblin TJ. Anti-keratin antibodies in rheumatoid arthritis. Br Med J. 1979; 2(6182):97–9. [PubMed: 111762]
33. Sebbag M, Simon M, Vincent C, Masson-Bessiere C, Girbal E, Durieux JJ, et al. The antiperinuclear factor and the so-called antikeratin antibodies are the same rheumatoid arthritis-specific autoantibodies. J Clin Invest. 1995; 95(6):2672–9. [PubMed: 7539459]
34. Baeten D, Peene I, Union A, Meheus L, Sebbag M, Serre G, et al. Specific presence of intracellular citrullinated proteins in rheumatoid arthritis synovium: relevance to antifilaggrin autoantibodies. Arthritis Rheum. 2001; 44(10):2255–62. [PubMed: 11665966]
35. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest. 1998; 101(1):273–81. [PubMed: 9421490]
36. Nogueira L, Sebbag M, Vincent C, Arnaud M, Fournie B, Cantagrel A, et al. Performance of two ELISAs for antifilaggrin autoantibodies, using either affinity purified or deiminated recombinant human filaggrin, in the diagnosis of rheumatoid arthritis. Ann Rheum Dis. 2001; 60(9):882–7. [PubMed: 11502616]
37. Vincent C, Nogueira L, Sebbag M, Chapuy-Regaud S, Arnaud M, Letourneur O, et al. Detection of antibodies to deiminated recombinant rat filaggrin by enzyme-linked immunosorbent assay: a highly effective test for the diagnosis of rheumatoid arthritis. Arthritis Rheum. 2002; 46(8):2051–8. [PubMed: 12209508]

38. Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000; 43(1):155–63. [PubMed: 10643712]
39. Vittecoq O, Incaurgarat B, Jouen-Beades F, Legoedec J, Letourneur O, Rolland D, et al. Autoantibodies recognizing citrullinated rat filaggrin in an ELISA using citrullinated and non-citrullinated recombinant proteins as antigens are highly diagnostic for rheumatoid arthritis. Clin Exp Immunol. 2004; 135(1):173–80. [PubMed: 14678280]
40. Saraux A, Berthelot JM, Devauchelle V, Bendaoud B, Chales G, Le Henaff C, et al. Value of antibodies to citrulline-containing peptides for diagnosing early rheumatoid arthritis. J Rheumatol. 2003; 30(12):2535–9. [PubMed: 14719190]
41. Coenen D, Verschueren P, Westhovens R, Bossuyt X. Technical and diagnostic performance of 6 assays for the measurement of citrullinated protein/peptide antibodies in the diagnosis of rheumatoid arthritis. Clin Chem. 2007; 53(3):498–504. [PubMed: 17259232]
42. Correia ML, Carvalho S, Fortuna J, Pereira MH. Comparison of Three Anti-CCP Antibody Tests and Rheumatoid Factor in RA and Control Patients. Clin Rev Allergy Immunol. 2008; 34(1):21–5. [PubMed: 18270853]
43. Santiago M, Baron M, Miyachi K, Fritzler MJ, Abu-Hakima M, Leclercq S, et al. A comparison of the frequency of antibodies to cyclic citrullinated peptides using a third generation anti-CCP assay (CCP3) in systemic sclerosis, primary biliary cirrhosis and rheumatoid arthritis. Clin Rheumatol. 2008; 27(1):77–83. [PubMed: 17570008]
44. Despres N, Boire G, Lopez-Longo FJ, Menard HA. The Sa system: a novel antigen-antibody system specific for rheumatoid arthritis. J Rheumatol. 1994; 21(6):1027–33. [PubMed: 7932409]
45. Vossenaar ER, Despres N, Lapointe E, van der Heijden A, Lora M, Senshu T, et al. Rheumatoid arthritis specific anti-Sa antibodies target citrullinated vimentin. Arthritis Res Ther. 2004; 6(2):R142–50. [PubMed: 15059278]
46. Goldbach-Mansky R, Lee J, McCoy A, Hoxworth J, Yarboro C, Smolen JS, et al. Rheumatoid arthritis associated autoantibodies in patients with synovitis of recent onset. Arthritis Res. 2000; 2(3):236–43. [PubMed: 11056669]
47. Bang H, Egerer K, Gauliard A, Luthke K, Rudolph PE, Fredenhagen G, et al. Mutation and citrullination modifies vimentin to a novel autoantigen for rheumatoid arthritis. Arthritis Rheum. 2007; 56(8):2503–11. [PubMed: 17665451]
48. Soos L, Szekanecz Z, Szabo Z, Fekete A, Zeher M, Horvath IF, et al. Clinical evaluation of anti-mutated citrullinated vimentin by ELISA in rheumatoid arthritis. J Rheumatol. 2007; 34(8):1658–63. [PubMed: 17611988]
49. Szekanecz Z, Soos L, Szabo Z, Fekete A, Kapitany A, Vegvari A, et al. Anti-Citrullinated Protein Antibodies in Rheumatoid Arthritis: As Good as it Gets? Clin Rev Allergy Immunol. 2008; 34(1): 26–31. [PubMed: 18270854]
50. Berglin E, Padyukov L, Sundin U, Hallmans G, Stenlund H, Van Venrooij WJ, et al. A combination of autoantibodies to cyclic citrullinated peptide (CCP) and HLA-DRB1 locus antigens is strongly associated with future onset of rheumatoid arthritis. Arthritis Res Ther. 2004; 6(4):R303–8. [PubMed: 15225365]
51. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 2004; 50(2):380–6. [PubMed: 14872479]
52. Berglin E, Johansson T, Sundin U, Jidell E, Wadell G, Hallmans G, et al. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. Ann Rheum Dis. 2006; 65(4):453–8. [PubMed: 16176994]
53. Vencovsky J, Machacek S, Sedova L, Kafkova J, Gatterova J, Pesakova V, et al. Autoantibodies can be prognostic markers of an erosive disease in early rheumatoid arthritis. Ann Rheum Dis. 2003; 62(5):427–30. [PubMed: 12695154]

54. Meyer O, Labarre C, Dougados M, Goupille P, Cantagrel A, Dubois A, et al. Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. Ann Rheum Dis. 2003; 62(2):120–6. [PubMed: 12525380]
55. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis. 2004; 63(9):1090–5. [PubMed: 15308518]
56. Quinn MA, Gough AK, Green MJ, Devlin J, Hensor EM, Greenstein A, et al. Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. Rheumatology (Oxford). 2006; 45(4):478–80. [PubMed: 16287917]
57. del Val del Amo N, Bosch R Ibanez, Manteca C Fito, Polo R Gutierrez, Cortina E Loza. Anti-cyclic citrullinated peptide antibody in rheumatoid arthritis: relation with disease aggressiveness. Clin Exp Rheumatol. 2006; 24(3):281–6. [PubMed: 16870095]
58. Panchagnula R, Rajiv SR, Prakash J, Chandrashekara S, Suresh KP. Role of anticyclic citrullinated peptide in the diagnosis of early rheumatoid factor-negative suspected rheumatoid arthritis: is it worthwhile to order the test? J Clin Rheumatol. 2006; 12(4):172–5. [PubMed: 16891919]
59. Machold KP, Stamm TA, Nell VP, Pflugbeil S, Aletaha D, Steiner G, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatology (Oxford). 2007; 46(2):342–9. [PubMed: 16899498]
60. Majka DS, Deane KD, Parrish LA, Lazar AA, Baron AE, Walker CW, et al. Duration of preclinical rheumatoid arthritis-related autoantibody positivity increases in subjects with older age at time of disease diagnosis. Ann Rheum Dis. 2008; 67(6):801–7. [PubMed: 17974596]
61. Snir O, Widhe M, von Spee C, Lindberg J, Padyukov L, Lundberg K, et al. Multiple antibody reactivities to citrullinated antigens in sera from rheumatoid arthritis patients - association with HLA-DRB1 alleles. Ann Rheum Dis. 2008
62. Kokkonen H, Johansson M, Innala L, Jidell E, Rantapaa-Dahlqvist S. The PTPN22 1858C/T polymorphism is associated with anti-cyclic citrullinated peptide antibody-positive early rheumatoid arthritis in northern Sweden. Arthritis Res Ther. 2007; 9(3):R56. [PubMed: 17553139]
63. Orozco G, Pascual-Salcedo D, Lopez-Nevot MA, Cobo T, Cabezon A, Martin-Mola E, et al. Auto-antibodies, HLA and PTPN22: susceptibility markers for rheumatoid arthritis. Rheumatology (Oxford). 2008; 47(2):138–41. [PubMed: 18156150]
64. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006; 54(1):38–46. [PubMed: 16385494]
65. Kallberg H, Padyukov L, Plenge RM, Ronnelid J, Gregersen PK, van der Helm-van Mil AH, et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. Am J Hum Genet. 2007; 80(5):867–75. [PubMed: 17436241]
66. Potter C, Hyrich KL, Tracey A, Lunt M, Plant D, Symmons DP, et al. Association of RF and anti-CCP positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-TNF response in RA. Ann Rheum Dis. 2008
67. Kastbom A, Strandberg G, Lindroos A, Skogh T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis. 2004; 63(9):1085–9. [PubMed: 15308517]
68. Alessandri C, Bombardieri M, Papa N, Cinquini M, Magrini L, Tincani A, et al. Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNFalpha therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement. Ann Rheum Dis. 2004; 63(10):1218–21. [PubMed: 15361374]
69. Atzeni F, Sarzi-Puttini P, Dell' Acqua D, de Portu S, Cecchini G, Cruini C, et al. Adalimumab clinical efficacy is associated with rheumatoid factor and anti-cyclic citrullinated peptide antibody titer reduction: a one-year prospective study. Arthritis Res Ther. 2006; 8(1):R3. [PubMed: 16356192]

70. Bobbio-Pallavicini F, Alpini C, Caporali R, Avalle S, Bugatti S, Montecucco C. Autoantibody profile in rheumatoid arthritis during long-term infliximab treatment. Arthritis Res Ther. 2004; 6(3):R264–72. [PubMed: 15142273]
71. Nissinen R, Leirisalo-Repo M, Peltomaa R, Palosuo T, Vaarala O. Cytokine and chemokine receptor profile of peripheral blood mononuclear cells during treatment with infliximab in patients with active rheumatoid arthritis. Ann Rheum Dis. 2004; 63(6):681–7. [PubMed: 15140775]
72. Bos WH, Bartelds GM, Wolbink GJ, de Koning MH, van de Stadt RJ, van Schaardenburg D, et al. Differential Response of the Rheumatoid Factor and Anticitrullinated Protein Antibodies During Adalimumab Treatment in Patients with Rheumatoid Arthritis. J Rheumatol. 2008
73. Chen HA, Lin KC, Chen CH, Liao HT, Wang HP, Chang HN, et al. The effect of etanercept on anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis. Ann Rheum Dis. 2006; 65(1):35–9. [PubMed: 15975966]
74. Aotsuka S, Okawa-Takatsuji M, Nagatani K, Nagashio C, Kano T, Nakajima K, et al. A retrospective study of the fluctuation in serum levels of anti-cyclic citrullinated peptide antibody in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005; 23(4):475–81. [PubMed: 16095115]
75. Kogure T, Tatsumi T, Fujinaga H, Niizawa A, Terasawa K. Insights to clinical use of serial determination in titers of cyclic citrullinated peptide autoantibodies. Mediators Inflamm. 2007; 2007:12367. [PubMed: 17497027]
76. Nielen MM, van der Horst AR, van Schaardenburg D, van der Horst-Bruinsma IE, van de Stadt RJ, Aarden L, et al. Antibodies to citrullinated human fibrinogen (ACF) have diagnostic and prognostic value in early arthritis. Ann Rheum Dis. 2005; 64(8):1199–204. [PubMed: 15640269]
77. Kitahara K, Takagi K, Kusunoki Y, Nishio S, Nozaki T, Inomata H, et al. Clinical value of second- and third-generation assays of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis. Ann Rheum Dis. 2008; 67(7):1059–60. [PubMed: 18556455]
78. Lutteri L, Malaise M, Chapelle JP. Comparison of second- and third-generation anti-cyclic citrullinated peptide antibodies assays for detecting rheumatoid arthritis. Clin Chim Acta. 2007; 386(1-2):76–81. [PubMed: 17826752]
79. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31(3):315–24. [PubMed: 3358796]
80. Reed GF, Lynn F, Meade BD. Use of coefficient of variation in assessing variability of quantitative assays. Clin Diagn Lab Immunol. 2002; 9(6):1235–9. [PubMed: 12414755]
81. van Gaalen FA, Visser H, Huizinga TW. A comparison of the diagnostic accuracy and prognostic value of the first and second anti-cyclic citrullinated peptides (CCP1 and CCP2) autoantibody tests for rheumatoid arthritis. Ann Rheum Dis. 2005; 64(10):1510–2. [PubMed: 15800005]
82. Vander Cruyssen B, Nogueira L, Van Praet J, Deforce D, Elewaut D, Serre G, et al. Do all anti-citrullinated protein/peptide antibody tests measure the same? Evaluation of discrepancy between anti-citrullinated protein/peptide antibody tests in patients with and without rheumatoid arthritis. Ann Rheum Dis. 2008; 67(4):542–6. [PubMed: 17644546]
83. Bizzaro, N. Evaluation of the World Health Organization Standard for Anti-citrullinated peptide antibody assays [abstract presentation]. 6th International Conference on Autoimmunity Porto; Portugal. 2008;
84. Bizzaro, N. 2008. personal communication
85. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. Ann Rheum Dis. 2006; 65(7):845–51. [PubMed: 16606649]
86. Korendowych E, Owen P, Ravindran J, Carmichael C, McHugh N. The clinical and genetic associations of anti-cyclic citrullinated peptide antibodies in psoriatic arthritis. Rheumatology (Oxford). 2005; 44(8):1056–60. [PubMed: 15901902]
87. Sghiri R, Bouagina E, Zaglaoui H, Mestiri H, Harzallah L, Harrabi I, et al. Diagnostic performances of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis. Rheumatol Int. 2007; 27(12):1125–30. [PubMed: 17447069]

88. Ingegnoli F, Galbiati V, Zeni S, Meani L, Zahalkova L, Lubatti C, et al. Use of antibodies recognizing cyclic citrullinated peptide in the differential diagnosis of joint involvement in systemic sclerosis. Clin Rheumatol. 2007; 26(4):510–4. [PubMed: 16670827]

89. Alexiou I, Germenis A, Ziogas A, Theodoridou K, Sakkas LI. Diagnostic value of anti-cyclic citrullinated peptide antibodies in Greek patients with rheumatoid arthritis. BMC Musculoskelet Disord. 2007; 8:37. [PubMed: 17448247]

90. Chan MT, Owen P, Dunphy J, Cox B, Carmichael C, Korendowych E, et al. Associations of erosive arthritis with anti-cyclic citrullinated peptide antibodies and MHC Class II alleles in systemic lupus erythematosus. J Rheumatol. 2008; 35(1):77–83. [PubMed: 18085741]

91. Wu R, Shovman O, Zhang Y, Gilburd B, Zandman-Goddard G, Shoenfeld Y. Increased prevalence of anti-third generation cyclic citrullinated peptide antibodies in patients with rheumatoid arthritis and CREST syndrome. Clin Rev Allergy Immunol. 2007; 32(1):47–56. [PubMed: 17426360]

92. van Rossum M, van Soesbergen R, de Kort S, ten Cate R, Zwinderman AH, de Jong B, et al. Anti-cyclic citrullinated peptide (anti-CCP) antibodies in children with juvenile idiopathic arthritis. J Rheumatol. 2003; 30(4):825–8. [PubMed: 12672206]

93. Kakumanu P, Yamagata H, Sobel ES, Reeves WH, Chan EK, Satoh M. Patients with pulmonary tuberculosis are frequently positive for anti-cyclic citrullinated peptide antibodies, but their sera also react with unmodified arginine-containing peptide. Arthritis Rheum. 2008; 58(6):1576–81. [PubMed: 18512773]

94. Grootenboer-Mignot S, Nicaise-Roland P, Delaunay C, Meyer O, Chollet-Martin S, Labarre C. Second generation anti-cyclic citrullinated peptide (anti-CCP2) antibodies can replace other anti-filaggrin antibodies and improve rheumatoid arthritis diagnosis. Scand J Rheumatol. 2004; 33(4): 218–20. [PubMed: 15370715]

95. Bizzaro N, Tonutti E, Tozzoli R, Villalta D. Analytical and diagnostic characteristics of 11 2nd- and 3rd-generation immunoenzymatic methods for the detection of antibodies to citrullinated proteins. Clin Chem. 2007; 53(8):1527–33. [PubMed: 17586589]

96. Dejaco C, Klotz W, Larcher H, Duftner C, Schirmer M, Herold M. Diagnostic value of antibodies against a modified citrullinated vimentin in rheumatoid arthritis. Arthritis Res Ther. 2006; 8(4):R119. [PubMed: 16859519]

97. Mathsson L, Mullazehi M, Wick MC, Sjoberg O, van Vollenhoven R, Klareskog L, et al. Antibodies against citrullinated vimentin in rheumatoid arthritis: higher sensitivity and extended prognostic value concerning future radiographic progression as compared with antibodies against cyclic citrullinated peptides. Arthritis Rheum. 2008; 58(1):36–45. [PubMed: 18163519]

98. Konnopka A, Conrad K, Baerwald C, Konig HH. Cost effectiveness of the determination of autoantibodies against cyclic citrullinated peptide in the early diagnosis of rheumatoid arthritis. Ann Rheum Dis. 2008; 67(10):1399–405. [PubMed: 18192304]

99. Kroot EJ, de Jong BA, van Leeuwen MA, Swinkels H, van den Hoogen FH, van't Hof M, et al. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2000; 43(8):1831–5. [PubMed: 10943873]

100. Jansen AL, van der Horst-Bruinsma I, van Schaardenburg D, van de Stadt RJ, de Koning MH, Dijkmans BA. Rheumatoid factor and antibodies to cyclic citrullinated Peptide differentiate rheumatoid arthritis from undifferentiated polyarthritis in patients with early arthritis. J Rheumatol. 2002; 29(10):2074–6. [PubMed: 12375314]

101. Nell VP, Machold KP, Stamm TA, Eberl G, Heinzl H, Uffmann M, et al. Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. Ann Rheum Dis. 2005; 64(12): 1731–6. [PubMed: 15878904]

102. Raza K, Breese M, Nightingale P, Kumar K, Potter T, Carruthers DM, et al. Predictive value of antibodies to cyclic citrullinated peptide in patients with very early inflammatory arthritis. J Rheumatol. 2005; 32(2):231–8. [PubMed: 15693082]

103. Matsui T, Shimada K, Ozawa N, Hayakawa H, Hagiwara F, Nakayama H, et al. Diagnostic utility of anti-cyclic citrullinated peptide antibodies for very early rheumatoid arthritis. J Rheumatol. 2006; 33(12):2390–7. [PubMed: 16924694]

104. Ates A, Karaaslan Y, Aksaray S. Predictive value of antibodies to cyclic citrullinated peptide in patients with early arthritis. Clin Rheumatol. 2007; 26(4):499–504. [PubMed: 16670828]

105. Kudo-Tanaka E, Ohshima S, Ishii M, Mima T, Matsushita M, Azuma N, et al. Autoantibodies to cyclic citrullinated peptide 2 (CCP2) are superior to other potential diagnostic biomarkers for predicting rheumatoid arthritis in early undifferentiated arthritis. Clin Rheumatol. 2007; 26(10): 1627–33. [PubMed: 17286215]

106. Silveira IG, Burlingame RW, von Muhlen CA, Bender AL, Staub HL. Anti-CCP antibodies have more diagnostic impact than rheumatoid factor (RF) in a population tested for RF. Clin Rheumatol. 2007; 26(11):1883–9. [PubMed: 17410320]

107. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum. 2002; 46(2):357–65. [PubMed: 11840437]

108. El Miedany Y, Youssef S, Mehanna AN, El Gaafary M. Development of a scoring system for assessment of outcome of early undifferentiated inflammatory synovitis. Joint Bone Spine. 2008; 75(2):155–62. [PubMed: 17980637]

109. Lakos G, Soos L, Fekete A, Szabo Z, Zeher M, Horvath IF, et al. Anti-cyclic citrullinated peptide antibody isotypes in rheumatoid arthritis: association with disease duration, rheumatoid factor production and the presence of shared epitope. Clin Exp Rheumatol. 2008; 26(2):253–60. [PubMed: 18565246]

110. Yamane T, Hashiramoto A, Tanaka Y, Tsumiyama K, Miura Y, Shiozawa K, 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. [PubMed: 18203327]

111. Nell-Duxneuner V, Machold K, Stamm T, Eberl G, Heinzl H, Hoefler E, et al. Autoantibody profiling in patients with very early rheumatoid arthritis - a follow-up study. Ann Rheum Dis. 2009

112. Liao KP, Batra KL, Chibnik L, Schur PH, Costenbader KH. Anti-CCP revised criteria for the classification of rheumatoid arthritis. Ann Rheum Dis. 2008

113. van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum. 2007; 56(2):433–40. [PubMed: 17265478]

114. van der Helm-van Mil AH, Detert J, le Cessie S, Filer A, Bastian H, Burmester GR, et al. Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: moving toward individualized treatment decision-making. Arthritis Rheum. 2008; 58(8):2241–7. [PubMed: 18668546]

115. Thammanichanond D, Kunakorn M, Kitiwanwanich S, Attamasirikul K, Nantiruj K. Raising rheumatoid factor cutoff helps distinguish rheumatoid arthritis. Asian Pac J Allergy Immunol. 2005; 23(2-3):165–8. [PubMed: 16252848]

116. Kwok JS, Hui KH, Lee TL, Wong W, Lau YL, Wong RW, et al. Anti-cyclic citrullinated peptide: diagnostic and prognostic values in juvenile idiopathic arthritis and rheumatoid arthritis in a Chinese population. Scand J Rheumatol. 2005; 34(5):359–66. [PubMed: 16234183]

117. Kamali S, Polat NG, Kasapoglu E, Gul A, Ocal L, Aral O, et al. Anti-CCP and antikeratin antibodies in rheumatoid arthritis, primary Sjogren's syndrome, and Wegener's granulomatosis. Clin Rheumatol. 2005; 24(6):673–6. [PubMed: 15926038]

118. Greiner A, Plischke H, Kellner H, Gruber R. Association of anti-cyclic citrullinated peptide antibodies, anti-citrullin antibodies, and IgM and IgA rheumatoid factors with serological parameters of disease activity in rheumatoid arthritis. Ann N Y Acad Sci. 2005; 1050:295–303. [PubMed: 16014545]

119. Fernandez-Suarez A, Reneses S, Wichmann I, Criado R, Nunez A. Efficacy of three ELISA measurements of anti-cyclic citrullinated peptide antibodies in the early diagnosis of rheumatoid arthritis. Clin Chem Lab Med. 2005; 43(11):1234–9. [PubMed: 16232091]

120. Choi SW, Lim MK, Shin DH, Park JJ, Shim SC. Diagnostic performances of anti-cyclic citrullinated peptides antibody and antifilaggrin antibody in Korean patients with rheumatoid arthritis. J Korean Med Sci. 2005; 20(3):473–8. [PubMed: 15953872]

121. Girelli F, Foschi FG, Bedeschi E, Calderoni V, Stefanini GF, Martinelli MG. Is Anti Cyclic citrullinated peptide a useful laboratory test for the diagnosis of rheumatoid arthritis? Eur Ann Allergy Clin Immunol. 2004; 36(4):127–30. [PubMed: 15180353]

122. De Rycke L, Peene I, Hoffman IE, Kruithof E, Union A, Meheus L, et al. Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: diagnostic value, associations with radiological progression rate, and extra-articular manifestations. Ann Rheum Dis. 2004; 63(12): 1587–93. [PubMed: 15547083]

123. Das H, Atsumi T, Fukushima Y, Shibuya H, Ito K, Yamada Y, et al. Diagnostic value of antiagalactosyl IgG antibodies in rheumatoid arthritis. Clin Rheumatol. 2004; 23(3):218–22. [PubMed: 15168148]

124. Vallbracht I, Rieber J, Oppermann M, Forger F, Siebert U, Helmke K. Diagnostic and clinical value of anti-cyclic citrullinated peptide antibodies compared with rheumatoid factor isotypes in rheumatoid arthritis. Ann Rheum Dis. 2004; 63(9):1079–84. [PubMed: 15308516]

125. Spiritus T, Verschueren P, Westhovens R, Bossuyt X. Diagnostic characteristics of a gelatin based Waaler-Rose assay (Serodia-RA) for the detection of rheumatoid factor. Ann Rheum Dis. 2004; 63(9):1169–71. [PubMed: 15308531]

126. Soderlin MK, Kastbom A, Kautiainen H, Leirisalo-Repo M, Strandberg G, Skogh T. Antibodies against cyclic citrullinated peptide (CCP) and levels of cartilage oligomeric matrix protein (COMP) in very early arthritis: relation to diagnosis and disease activity. Scand J Rheumatol. 2004; 33(3):185–8. [PubMed: 15228190]

127. Lopez-Hoyos M, de Alegria C Ruiz, Blanco R, Crespo J, Pena M, Rodriguez-Valverde V, et al. Clinical utility of anti-CCP antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. Rheumatology (Oxford). 2004; 43(5):655–7. [PubMed: 14970400]

128. Hitchon CA, Alex P, Erdile LB, Frank MB, Dozmorov I, Tang Y, et al. A distinct multicytokine profile is associated with anti-cyclical citrullinated peptide antibodies in patients with early untreated inflammatory arthritis. J Rheumatol. 2004; 31(12):2336–46. [PubMed: 15570632]

129. Dubucquoi S, Solau-Gervais E, Lefranc D, Marguerie L, Sibilia J, Goetz J, et al. Evaluation of anti-citrullinated filaggrin antibodies as hallmarks for the diagnosis of rheumatic diseases. Ann Rheum Dis. 2004; 63(4):415–9. [PubMed: 15020336]

130. Bombardieri M, Alessandri C, Labbadia G, Iannuccelli C, Carlucci F, Riccieri V, et al. Role of anti-cyclic citrullinated peptide antibodies in discriminating patients with rheumatoid arthritis from patients with chronic hepatitis C infection-associated polyarticular involvement. Arthritis Res Ther. 2004; 6(2):R137–41. [PubMed: 15059277]

131. Suzuki K, Sawada T, Murakami A, Matsui T, Tohma S, Nakazono K, et al. High diagnostic performance of ELISA detection of antibodies to citrullinated antigens in rheumatoid arthritis. Scand J Rheumatol. 2003; 32(4):197–204. [PubMed: 14626625]

132. Jansen LM, van Schaardenburg D, van der Horst-Bruinsma I, van der Stadt RJ, de Koning MH, Dijkmans BA. The predictive value of anti-cyclic citrullinated peptide antibodies in early arthritis. J Rheumatol. 2003; 30(8):1691–5. [PubMed: 12913923]

133. Bizzaro N, Mazzanti G, Tonutti E, Villalta D, Tozzoli R. Diagnostic accuracy of the anti-citrulline antibody assay for rheumatoid arthritis. Clin Chem. 2001; 47(6):1089–93. [PubMed: 11375296]

134. Aho K, Palosuo T, Lukka M, Kurki P, Isomaki H, Kautiainen H, et al. Antifilaggrin antibodies in recent-onset arthritis. Scand J Rheumatol. 1999; 28(2):113–6. [PubMed: 10229141]

135. Visser H, Gelinck LB, Kampfraath AH, Breedveld FC, Hazes JM. Diagnostic and prognostic characteristics of the enzyme linked immunosorbent rheumatoid factor assays in rheumatoid arthritis. Ann Rheum Dis. 1996; 55(3):157–61. [PubMed: 8712877]

136. de Bois MH, Arndt JW, Speyer I, Pauwels EK, Breedveld FC. Technetium-99m labelled human immunoglobulin scintigraphy predicts rheumatoid arthritis in patients with arthralgia. Scand J Rheumatol. 1996; 25(3):155–8. [PubMed: 8668958]

137. Cordonnier C, Meyer O, Palazzo E, de Bandt M, Elias A, Nicaise P, et al. Diagnostic value of anti-RA33 antibody, antikeratin antibody, antiperinuclear factor and antinuclear antibody in early

rheumatoid arthritis: comparison with rheumatoid factor. Br J Rheumatol. 1996; 35(7):620–4. [PubMed: 8670593]

138. Saraux A, Valls I, Voisin V, Koreichi A, Baron D, Youinou P, et al. How useful are tests for rheumatoid factors, antiperinuclear factors, antikeratin antibody, and the HLA DR4 antigen for the diagnosis of rheumatoid arthritis? Rev Rhum Engl Ed. 1995; 62(1):16–20. [PubMed: 7540486]
139. Berthelot JM, Maugars Y, Audrain M, Youinou P, Prost A. Specificity of antiperinuclear factor for rheumatoid arthritis in rheumatoid factor-positive sera. Br J Rheumatol. 1995; 34(8):716–20. [PubMed: 7551653]
140. Gomes-Daudrix V, Sebbag M, Girbal E, Vincent C, Simon M, Rakotoarivony J, et al. Immunoblotting detection of so-called 'antikeratin antibodies': a new assay for the diagnosis of rheumatoid arthritis. Ann Rheum Dis. 1994; 53(11):735–42. [PubMed: 7529986]
141. Banchuin N, Janyapoon K, Sarntivijai S, Parivisutt L. Re-evaluation of ELISA and latex agglutination test for rheumatoid factor detection in the diagnosis of rheumatoid arthritis. Asian Pac J Allergy Immunol. 1992; 10(1):47–54. [PubMed: 1418183]
142. Young A, Sumar N, Bodman K, Goyal S, Sinclair H, Roitt I, et al. Agalactosyl IgG: an aid to differential diagnosis in early synovitis. Arthritis Rheum. 1991; 34(11):1425–9. [PubMed: 1953820]
143. Davis P, Stein M. Evaluation of criteria for the classification of SLE in Zimbabwean patients. Br J Rheumatol. 1989; 28(6):546–7. [PubMed: 2686803]
144. Carpenter AB, Bartkowiak CD. Rheumatoid factors determined by fluorescence immunoassay: comparison with qualitative and quantitative methods. Clin Chem. 1989; 35(3):464–6. [PubMed: 2646034]
145. Winkles JW, Lunec J, Gray L. Automated enhanced latex agglutination assay for rheumatoid factors in serum. Clin Chem. 1989; 35(2):303–7. [PubMed: 2914380]
146. Vittecoq O, Salle V, Jouen-Beades F, Krzanowska K, Menard JF, Gayet A, et al. Autoantibodies to the 27 C-terminal amino acids of calpastatin are detected in a restricted set of connective tissue diseases and may be useful for diagnosis of rheumatoid arthritis in community cases of very early arthritis. Rheumatology (Oxford). 2001; 40(10):1126–34. [PubMed: 11600742]
147. Vasiliauskiene L, Wiik A, Hoier-Madsen M. Prevalence and clinical significance of antikeratin antibodies and other serological markers in Lithuanian patients with rheumatoid arthritis. Ann Rheum Dis. 2001; 60(5):459–66. [PubMed: 11302867]
148. Garcia-Berrocal B, Gonzalez C, Perez M, Navajo JA, Moreta I, Davila C, et al. Anti-cyclic citrullinated peptide autoantibodies in IgM rheumatoid factor-positive patients. Clin Chim Acta. 2005; 354(1-2):123–30. [PubMed: 15748608]
149. Snijders GF, Broeder AA, Bevers K, Jeurissen ME, van Eerd JE, van den Hoogen FH. Measurement characteristics of a new rapid anti-CCP2 test compared to the anti-CCP2 ELISA. Scand J Rheumatol. 2008; 37(2):151–4. [PubMed: 18415774]
150. Vossenaar, ER. Overview of CCP Sensitivity and Specificity. University of Nijmejen; 2004. p. 24
151. http://www.eurodiagnostica.com/pdf.asp?id=1836&volgnummer=14
152. Inanc N, Dalkilic E, Kamali S, Kasapoglu-Gunal E, Elbir Y, Direskeneli H, et al. Anti-CCP antibodies in rheumatoid arthritis and psoriatic arthritis. Clin Rheumatol. 2007; 26(1):17–23. [PubMed: 16538391]
153. Alenius GM, Berglin E, Dahlqvist S Rantapaa. Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without joint inflammation. Ann Rheum Dis. 2006; 65(3): 398–400. [PubMed: 16096328]
154. Helliwell PS, Porter G, Taylor WJ. Polyarticular psoriatic arthritis is more like oligoarticular psoriatic arthritis, than rheumatoid arthritis. Ann Rheum Dis. 2007; 66(1):113–7. [PubMed: 16840501]
155. Nikolaisen C, Rekvig OP, Nossent HC. Diagnostic impact of contemporary biomarker assays for rheumatoid arthritis. Scand J Rheumatol. 2007; 36(2):97–100. [PubMed: 17476614]
156. Candia L, Marquez J, Gonzalez C, Santos AM, Londono J, Valle R, et al. Low frequency of anticyclic citrullinated peptide antibodies in psoriatic arthritis but not in cutaneous psoriasis. J Clin Rheumatol. 2006; 12(5):226–9. [PubMed: 17023808]

157. Sene D, Ghillani-Dalbin P, Limal N, Thibault V, van Boekel T, Piette JC, et al. Anti-cyclic citrullinated peptide antibodies in hepatitis C virus associated rheumatological manifestations and Sjogren's syndrome. Ann Rheum Dis. 2006; 65(3):394–7. [PubMed: 16474032]

158. Liu FC, Chao YC, Hou TY, Chen HC, Shyu RY, Hsieh TY, et al. Usefulness of anti-CCP antibodies in patients with hepatitis C virus infection with or without arthritis, rheumatoid factor, or cryoglobulinemia. Clin Rheumatol. 2008; 27(4):463–7. [PubMed: 17876647]

159. Lee SI, Yoo WH, Yun HJ, Kim DS, Lee HS, Choi SI, et al. Absence of antibody to cyclic citrullinated peptide in sera of non-arthritic patients with chronic hepatitis B virus infection. Clin Rheumatol. 2007; 26(7):1079–82. [PubMed: 17136313]

160. Dewint P, Hoffman IE, Rogge S, Joos R, Union A, Dehoorne J, et al. Effect of age on prevalence of anticitrullinated protein/peptide antibodies in polyarticular juvenile idiopathic arthritis. Rheumatology (Oxford). 2006; 45(2):204–8. [PubMed: 16188943]

161. Brunner J, Sitzmann FC. The diagnostic value of anti-cyclic citrullinated peptide (CCP) antibodies in children with Juvenile Idiopathic Arthritis. Clin Exp Rheumatol. 2006; 24(4):449–51. [PubMed: 16956438]

162. Brunner JK, Sitzmann FC. Anticyclic citrullinated peptide antibodies in juvenile idiopathic arthritis. Mod Rheumatol. 2006; 16(6):372–5. [PubMed: 17164999]

163. Ceccato F, Roverano S, Barrionuevo A, Rillo O, Paira S. The role of anticyclic citrullinated peptide antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. Clin Rheumatol. 2006; 25(6):854–7. [PubMed: 16514472]

164. Elkayam O, Segal R, Lidgi M, Caspi D. Positive anti-cyclic citrullinated proteins and rheumatoid factor during active lung tuberculosis. Ann Rheum Dis. 2006; 65(8):1110–2. [PubMed: 16361276]

165. Hill JA, Al-Bishri J, Gladman DD, Cairns E, Bell DA. Serum autoantibodies that bind citrullinated fibrinogen are frequently found in patients with rheumatoid arthritis. J Rheumatol. 2006; 33(11):2115–9. [PubMed: 16924693]

Table 1

Positive and Negative Likelihood Ratios for IgM Rheumatoid Factor in the Diagnosis of Rheumatoid Arthritis

	Positive LR (95% CI)	Negative LR (95% CI)	References
Pooled LR	4.86 (3.96-5.97)	0.38 (0.33-0.44)	(9,14-17,19,25,27,39,40,44, 56,94,101,102,115-145)
RF Assay Type			
Nephelometry	4.15 (2.95-5.84)	0.32 (0.25-0.41)	(17,25,46,94,116,118,119, 121,123,125,127,128,130-133)
Latex Agglutination	5.05 (3.01-8.50)	0.39 (0.27-0.56)	(9,27,44,102,115,117,120, 122,126,134,137-139,145, 146)
ELISA	6.13 (4.6-8.17)	0.42 (0.34-0.51)	(14-16,19,38-40,124,129, 135,136,140,141,143,144, 147)
RF Value			
≥ 20 U/ml	4.42 (3.02-6.47)	0.39 (0.31-0.50)	(26)
≥ 40 U/ml	5.49 (2.25-13.38)	0.50 (0.37-0.69)	(26)
≥ 80 U/ml	4.57 (4.60-8.17)	0.42 (0.34-0.51)	(26)

LR: Likelihood ratio; RF: Rheumatoid factor.

Adapted from Nishimura K, et al (26).

Reprinted with permission from Annals of Internal Medicine.

Table 2

Available ACPA assays on the market (1987 ACR Criteria for RA used for calculating sensitivity and specificity in most studies).

Name	Manufacturer	Type of Assay (generation)	Sensitivity for RA *	Specificity for RA *	Within-run assay CV *
Diastat	**Axis-Shield Diagnostics** Scotland, UK	ELISA (2nd)	76.5%(77)	86.1%(77)	13.6%(148)
CCPoint	**Euro-diagnostica** Netherlands	Colloidal gold immunoassay (2nd)	56.0%(149)	98.8%(149)	N/A
CCPlus	**Euro-diagnostica** Netherlands	ELISA (2nd)	70%(150)	97.5%(150)	0.4-5.1%(151)
EDIA	**Euro-diagnostica** Netherlands	ELISA (2nd)	66.7%(78)	97%(78)	1.9-7.9%(151)
RA anti-CCP ELISA	**Euro-diagnostica** Netherlands	ELISA (2nd)	76.5%(41)	95.4%(41)	12.6-34.3%(41)
Euroimmun	**Euroimmun** Germany	ELISA (2nd)	72.5%(41)	96.4%(41)	6.4-12.1%(41)
Quanta Lite	**Inova** United States	ELISA (2nd)	70%(77)	91.3%(77)	6%(148)
ELIA CCP	**Phadia** Sweden, Germany	Immunocap method (2nd)	77.5%(41)	95.9%(41)	7.2-9.8%(41)
Quanta Lite CCP3	**Inova** United States	ELISA (3rd)	77.5%(41)	87.8%(41)	3.7-5.1%(41)
Quanta Lite CCP3.1	**Inova** United States	ELISA (3rd)	74%(133)	89.6%(133)	0.5-4.8%(133)
Org 548 anti-MCV	**Orgentec** Germany	ELISA mutated citrullinated vimentin	74.5%(41)	90.3%(41)	8.4-12.3%(41)

*Value in parenthesis represents the respective reference numbers.

Table 3

Spearman Rho Correlations Comparing Quantitative Anti-Citrullinated Peptide Antibody Assays

	INOVA CCP	INOVA 3 CCP	Euroimmun CCP	Euro-Diagnostica CCP	Axis-Shield CCP	Edia CCP	Pharmacia CCP	Triturus CCP
INOVA 3 CCP	0.86							
Euroimmun CCP	0.84	0.76						
Euro-Diagnostica CCP	0.96	0.83	0.8					
Axis-Shield CCP	0.83	0.71	0.81	0.8				
Edia CCP	0.86	0.82	0.93	0.62	0.93			
Pharmacia CCP	0.82	0.66	0.71	0.79	0.8	0.87		
Triturus CCP	0.75	0.74	0.77	0.71	0.67	0.7	0.59	
IgM RF Nephelometry	0.67	0.64	0.63	0.65	0.59	0.73	0.58	0.48

RF: Rheumatoid factor

Reprinted with permission from *Clinica Chimica Acta*(78)

Table 4

Detection of ACPA in other diseases

	n	ACPA+ (n, %)	Refs.
Psoriatic arthritis	1343	115 (8.6%)	(41,78,82,86,87,152-156)
SLE	1078	84 (7.8%)	(41,78,82,89-91)
Sjögren's syndrome	609	35 (5.7%)	(41,78,87,89,91)
Spondyloarthropathy	431	10 (2.3%)	(78,89,104,149,155)
Scleroderma/CREST	380	26 (6.8%)	(41,43,78,87,88,91)
Hepatitis C/cryoglobulinemia	285	10 (3.5%)	(87,157,158)
Osteoarthritis	182	4 (2.2%)	(78,87,89,91,149)
Hepatitis B	176	1 (0.6%)	(159)
Juvenile idiopathic arthritis	169	13 (7.7%)	(87,91,152,160-162)
Polymyalgia rheumatica	146	0 (0%)	(89,91,149,163)
Vasculitis/ Wegener's granulomatosis	107	5 (4.7%)	(78,87,89,91,104)
Tuberculosis	96	33 (34.3%)	(93,164)
Polymyositis/dermatomyositis	75	0 (0%)	(41,78,82,87)
Fibromyalgia	74	2 (2.7%)	(78,149)
Gout and pseudogout	58	0 (0%)	(87,89,149)

Table 5

Comparison of performance characteristics of RF and ACPA (CCP2) assays in early RA cohorts and cohorts containing both early and established RA

	ACPA (CCP2)	IgM RF	ACPA (CCP2) or IgM RF	ACPA (CCP2) and IgM RF
Early RA Cohorts (38,46,58,76,101,102,104,106,111,119)				
Sensitivity range, %	41-63	41-66	52-67	33-58
Specificity range, %	91-100	87-97	72-82	98-100
Early and Established RA Cohorts (9,41,82,96,102,106,120,124,133,155,165)				
Sensitivity range, %	41-77	62-87	70-81	33-57
Specificity range, %	88-98	43-96	80-91	91-99