Annals of Internal Medicine | Review

Meta-analysis: Diagnostic Accuracy of Anti–Cyclic Citrullinated Peptide Antibody and Rheumatoid Factor for Rheumatoid Arthritis

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Background: Rheumatoid factor (RF) and autoantibodies against cyclic citrullinated peptide (CCP) are markers that might help physicians diagnose rheumatoid arthritis.

Purpose: To determine whether anti-CCP antibody more accurately identifies patients with rheumatoid arthritis and better predicts radiographic progression than does RF.

Data Sources: MEDLINE through September 2006 and reference lists of retrieved studies and review articles.

Study Selection: Studies in any language that enrolled at least 10 participants and that examined the role of anti-CCP antibody and RF in the diagnosis or prognosis of known or suspected rheumatoid arthritis.

Data Extraction: Two authors independently evaluated studies for inclusion, rated methodological quality, and abstracted relevant data.

Data Synthesis: The DerSimonian–Laird random-effects method was used to summarize sensitivities, specificities, and positive and negative likelihood ratios from 37 studies of anti-CCP antibody and 50 studies of RF. The pooled sensitivity, specificity, and positive and negative likelihood ratios for anti-CCP antibody were 67% (95% CI, 62% to 72%), 95% (CI, 94% to 97%), 12.46 (CI, 9.72 to 15.98), and 0.36 (CI, 0.31 to 0.42), respectively. For IgM RF, the values were 69% (CI, 65% to 73%), 85% (CI, 82% to 88%), 4.86 (CI, 3.95 to 5.97), and 0.38 (CI, 0.33 to 0.44). Likelihood ratios among IgM RF, IgG RF, and IgA RF seemed to be similar. Results from studies of patients with early rheumatoid arthritis were similar to those from all studies. Three of 4 studies found that risk for radiographic progression was greater with anti-CCP antibody positivity than with IgM RF positivity.

Limitations: Many studies had methodological limitations. Studies of RF were heterogeneous and had wide ranges of sensitivity and specificity.

Conclusions: Anti-CCP antibodies are more specific than RF for diagnosing rheumatoid arthritis and may better predict erosive disease.

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Rheumatoid arthritis is the most common autoimmune disease, affecting approximately 1% of the world's population (1). It causes persistent synovitis, pain, joint destruction, and functional disability. Because irreversible joint destruction can be prevented by intervention during the first months of disease, early diagnosis of rheumatoid arthritis is important (2–4).

Rheumatoid factor (RF) is an antibody directed against the Fc region of IgG that has been used as a diagnostic marker for rheumatoid arthritis. However, it is nonspecific and may be present in healthy elderly persons or in patients with other autoimmune and infectious diseases (5). Other rheumatoid arthritis–associated autoantibodies known to be specific for rheumatoid arthritis include antiperinuclear factor and antikeratin antibodies (6, 7). Because of rigorous technical requirements for their detection, antiperinuclear factor and antikeratin antibodies have never been widely used as markers for rheumatoid arthritis, despite their high specificity. The epitopes of their antigens are arginyl residues citrullinated by peptidyl arginine deiminase (8–10). Some enzyme-linked immunosorbent assays (ELISAs) use linear citrulline-containing peptides that have similar sensitivity to and higher specificity than RF for diagnosing rheumatoid arthritis (11). To improve sensitivity, assays that use cyclic citrullinated peptide (CCP) were developed to detect anti-CCP antibody (12).

In this systematic review, we summarize published data on the sensitivity, specificity, and likelihood ratios of RF and anti-CCP antibodies for diagnosing rheumatoid arthritis. We also summarize results of studies that assessed the associations of these markers with development and radiographic progression of rheumatoid arthritis.

Methods

Data Sources and Searches

We developed a protocol for the review and followed standard reporting guidelines (13, 14). We searched MEDLINE for studies published in any language through September 2006 that examined autoantibodies against citrullinated proteins, rheumatoid factor, or both for the diagnosis of rheumatoid arthritis. Our searches (available

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Context

Are autoantibodies against cyclic citrullinated peptide (CCP) better serum markers for rheumatoid arthritis than rheumatoid factor (RF)?

Contribution

This meta-analysis of 86 studies found that the positive likelihood ratio for anti-CCP antibody was greater than that for IgM RF for identifying patients with rheumatoid arthritis (12.5 vs. 4.9). Sensitivity was similar for the 2 tests, although specificity of anti-CCP antibody (95%) was higher than specificity of IgM RF (85%).

Cautions

Fewer studies evaluated anti-CCP antibody than RF. There was possible publication bias for reporting positive findings regarding anti-CCP antibody.

Implication

Anti-CCP antibody positivity seems to be more specific than IgM RF positivity for identifying patients with rheumatoid arthritis.

—The Editors

on request) were based on combinations of the following index terms: *rheumatoid arthritis, antiperinuclear factor, antikeratin antibody, citrullinated protein, anti–cyclic citrullinated peptide, rheumatoid factor, sensitivity, specificity, mass screening, predictive value of tests, receiver-operating characteristic curve,* and *accuracy*. We also reviewed reference lists of retrieved studies and review articles.

Study Selection

Two reviewers independently scanned abstracts that met the inclusion criteria. We included studies that evaluated the utility of assaying anti-CCP antibody or RF for diagnosis of known or suspected rheumatoid arthritis, enrolled at least 10 participants, were published after 1987, and provided enough data to allow calculation of sensitivity and specificity for diagnosis of rheumatoid arthritis. We used the 1987 revised American College of Rheumatology (ACR) criteria as the reference standard of rheumatoid arthritis (15). In general, we regarded reports of patients with symptom duration of less than 1 year as studies of early rheumatoid arthritis, although we also used the researchers' definitions of early rheumatoid arthritis.

Data Extraction and Study Quality Assessment

We extracted data by using a standard form that included the demographic characteristics of the participants, inclusion and exclusion criteria, number of participants who were evaluated with the index test, and methods of antibody testing. Two investigators independently assessed the design of the studies by using previously developed quality criteria for studies of diagnostic tests (16–18). These assessments addressed the technical quality of the anti-CCP antibody test, technical quality of the RF test, application of the reference or index test, blinding of observers, description of the study sample, and cohort assembly. We used κ coefficients to examine interrater agreement for our initial overall quality score (19) and resolved any item discrepancies through discussion.

Data Analysis

We used a random-effects model to combine estimates of sensitivity, specificity, and positive and negative likelihood ratios (19–21). We planned analyses that were stratified by generation of anti-CCP antibody assay (first [anti-CCP1] second [anti-CCP2]) and by RF subtype (IgA, IgG, and IgM). We analyzed subgroups of relevant studies that included patients with early rheumatoid arthritis and that evaluated combination testing for anti-CCP antibody and RF. We conducted a stratified analysis for different threshold and measurement methods when we suspected heterogeneity among studies. We also conducted threshold analyses and metaregression to assess whether the threshold effect and heterogeneity among studies existed (22).

We examined funnel plots for diagnostic odds ratios to explore the possibility of publication bias (23). For analyses, we used MetaDiSc, version 1.1.4 (Hospital Universitario Ramón y Cajal, Madrid, Spain); Stata, version 8.2 (Stata Corp., College Station, Texas); and R, version 2.21 (R Foundation for Statistical Computing, Vienna, Austria).

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RESULTS

Search Results and Characteristics of Studies

We identified 302 reports, of which 86 met the inclusion criteria (11, 12, 24–106) (**Appendix Figure**, available at www.annals.org). Thirty-seven studies in 14 949 patients (11, 12, 24, 26, 29–38, 40–42, 44, 45, 47, 48, 50, 52, 54, 56, 58, 60–62, 64, 66, 67, 70, 74, 76, 97, 99, 100) reported on the diagnostic accuracy of anti-CCP antibody, whereas 50 studies in 15 286 patients (12, 24, 27, 29, 30, 32–37, 39, 40, 42–44, 47, 48, 50, 52, 54, 55, 60–62, 64, 66, 70, 72–74, 76, 80–85, 88–98, 100) reported on the diagnostic accuracy of RF.

Appendix Table 1 (available at www.annals.org) (11, 24, 26, 29–38, 40–42, 44, 45, 47, 48, 50, 52, 54, 56, 58, 60–62, 64–67, 74, 76, 97, 99, 100) and **Appendix Table 2** (available at www.annals.org) (12, 24, 27, 29, 33–35, 37, 39–43, 45, 47, 48, 52, 65, 66, 72–74, 76, 80, 81, 88, 90–92, 94–98, 100) summarize the characteristics of the

included studies. In anti-CCP antibody and IgM RF studies, respectively, the median numbers of participants were 404 and 226, their median ages were 57 years and 53 years, and the median proportions of women were 59% and 68%. Studies of anti-CCP antibody that were published after 2000 usually addressed anti-CCP2 assays.

Characteristics of control groups varied. Among the anti-CCP antibody studies, 5 used patients with undifferentiated arthritis, 13 used patients with other rheumatic diseases, 1 used healthy persons, 1 used hepatitis C carriers, and 17 used a mix of healthy persons and patients with other diseases. Among the IgM RF studies, 5 used patients with undifferentiated arthritis, 16 used patients with other rheumatic diseases, 2 used healthy persons, 1 used hepatitis C carriers, 1 used patients with polymyalgia rheumatica, and 22 used a mix of healthy persons and patients with other diseases. Three studies did not report details on the control group.

Study Quality

Only 1 study satisfied all criteria on our quality checklist. Twenty-two studies (30%) met at least 70% of the criteria, and 9 studies (10%) met fewer than 50% of the criteria. The κ coefficient for interrater agreement was 0.92 on the quality score.

Most studies adequately described the technical aspects of assaying anti-CCP antibody and RF. In 86% (32 of 37) of anti-CCP antibody studies and 82% (41 of 50) of RF studies, the 1987 revised ACR criteria were used as the reference standard for rheumatoid arthritis. Most studies did not explicitly mention blinding of investigators to the clinical assessment or to the reference standard. Most studies (90%) enrolled patients with known or suspected rheumatoid arthritis. Characteristics of these patients were fully described in just over half of the studies. Enrollment was prospective in 18 of 37 anti-CCP antibody studies and 25 of 50 RF studies.

Studies of RF showed a wide range of sensitivities and specificities (**Appendix Table 1**, available at www.annals.org). One study (35) reported very low sensitivity and specificity. In this study, 57% of control patients had conditions that can present with RF-positive arthritis (primarily the Sjögren syndrome or Wegener granulomatosis).

Laboratory techniques for measuring RF varied across studies. Fifteen studies used nephelometry, 16 used latex agglutination, and 16 used ELISA. Twenty-two studies used less than 20 U/mL as the cutoff value for negative test results, 11 used less than 40 U/mL as the cutoff value, and 17 did not report cutoff values.

Diagnostic Accuracy of Anti-CCP Antibody and IgM RF, IgA RF, and IgG RF

The summary positive and summary negative likelihood ratios, respectively, were 12.46 (95% CI, 9.72 to 15.98) and 0.36 (0.31 to 0.42) for anti-CCP antibody and 4.86 (CI, 3.95 to 5.97) and 0.38 (CI, 0.33 to 0.44) for IgM RF (**Figure 1** and **Figure 2**). The pooled sensitivity and specificity were 67% (CI, 65% to 68%) and 95% (CI, 95% to 96%), respectively, for anti-CCP antibody and 69% (CI, 68% to 70%) and 85% (CI, 84% to 86%) for IgM RF. Data that were limited to studies of patients with early rheumatoid arthritis were similar to those from all studies (data available from the authors on request).

Studies published before 2000 tended to report high sensitivity and specificity for RF compared with studies published from 2000 onward. More recent studies reported favorable specificities for anti-CCP antibody. Summary likelihood ratios for studies that directly compared anti-CCP antibody and IgM RF (11, 12, 24, 26, 29–38, 40–42, 44, 45, 47, 48, 50, 52, 54, 56, 58, 60–62, 64, 66, 67, 70, 74, 76, 97, 99, 100) were similar to summary data from all studies. Positive likelihood ratios for anti-CCP antibody and IgM RF were 12.32 and 3.86, respectively. Negative likelihood ratios for anti-CCP antibody and IgM RF were 0.40 and 0.41, respectively. Positive and negative likelihood ratios for IgA RF and IgG RF seemed to be qualitatively similar to those for IgM RF (**Figure 3**). Stratified analyses for IgM RF showed no major differences for positive summary likelihood ratios or negative likelihood ratios across the strata of cutoff values and measurement methods (**Table**). The threshold effect for IgM RF is not statistically significant, and no covariate was statistically significant in the metaregression model.

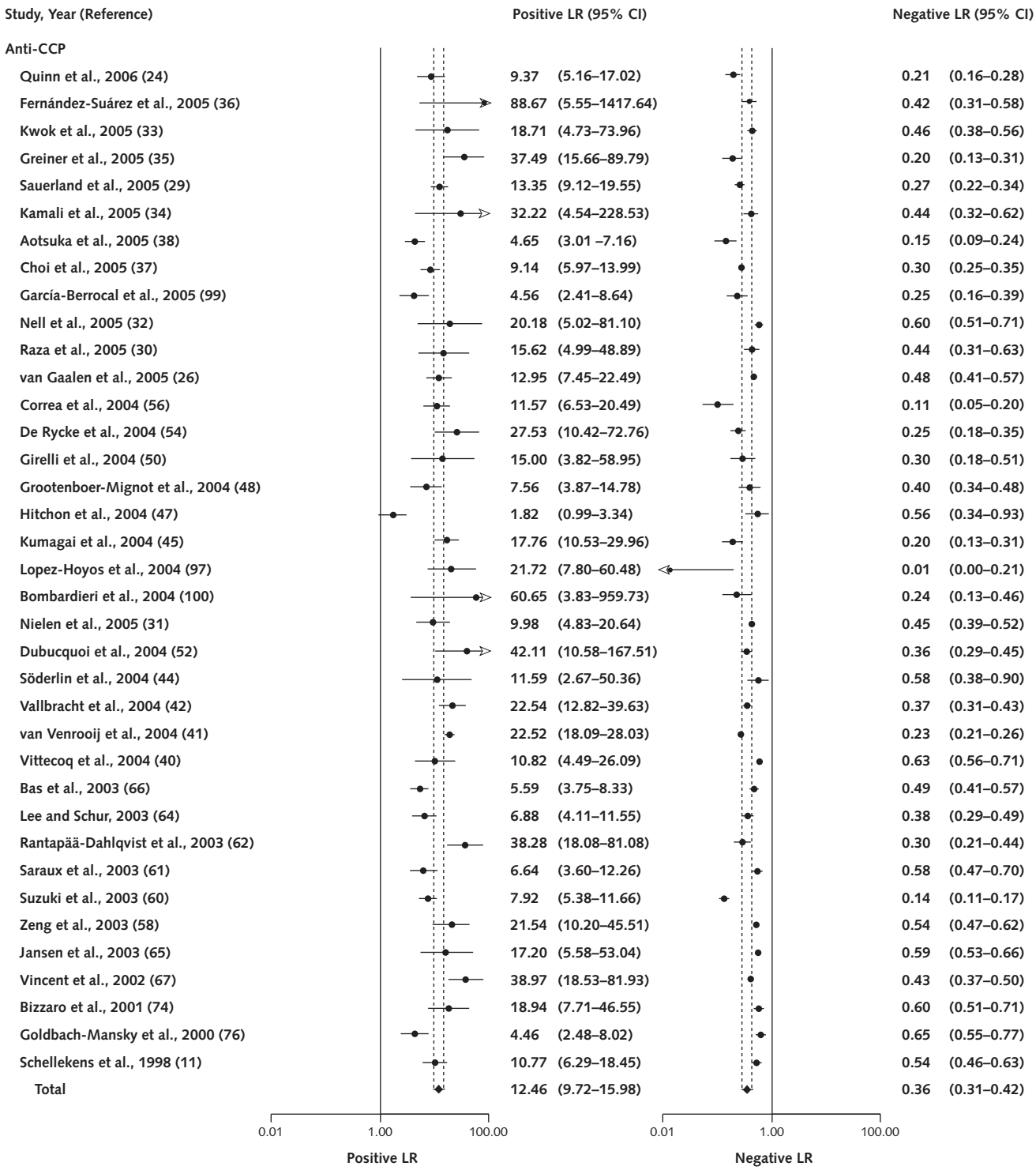
Diagnostic Accuracy of Anti-CCP1, Anti-CCP2, and Both Anti-CCP Antibody and IgM RF

Twenty-nine studies in 11 821 patients (24, 26, 29–38, 40–42, 44, 45, 47, 48, 50, 52, 54, 56, 60, 62, 64, 97, 99, 100) assessed anti-CCP2, whereas 5 studies in 2098 patients (61, 66, 67, 70, 74) assessed anti-CCP1.

Although the sensitivities and specificities were similar to those in the anti-CCP1 studies, 3 studies (12, 58, 76) that used an in-house ELISA were excluded because incorporating them introduced a positive threshold effect and caused heterogeneity among the studies. The summary positive and negative likelihood ratios were 12.77 (CI, 9.62 to 16.94) and 0.32 (CI, 0.27 to 0.38), respectively, for anti-CCP2 and 13.03 (CI, 5.74 to 29.04) and 0.53 (CI, 0.46 to 0.61) for anti-CCP1 (**Figure 4**).

Six studies in 1753 patients (12, 30, 37, 50, 64, 74) simultaneously measured anti-CCP antibody and RF, whereas 8 studies in 2837 patients (12, 30, 37, 42, 50, 64, 70, 74) performed 1 of the tests only when the results on the other test were positive. For studies that required the presence of both anti-CCP antibody and IgM RF for a positive result, the summary positive and negative likelihood ratios were 15.72 (CI, 8.30 to 29.75) and 0.46 (CI, 0.35 to 0.61), respectively. For studies that considered a result positive if either anti-CCP antibody or IgM RF was detected, the positive and negative summary likelihood ratios were 4.32 (CI, 2.71 to 6.90) and 0.32 (CI, 0.25 to 0.42), respectively.

Figure 1. **Likelihood ratio *(LR)* for autoantibodies against cyclic citrullinated peptides *(anti-CCP).***



Prognostic Value of Anti-CCP Antibody and IgM RF

Appendix Table 3 (available at www.annals.org) summarizes the results of 5 studies of the association between rheumatoid arthritis and anti-CCP antibody. The odds ratio for rheumatoid arthritis was 16.1 to 38.99 for anti-CCP antibody positivity and 1.2 to 8.7 for RF positivity.

Fifteen studies examined associations between marker positivity and radiographic progression (**Appendix Table 4**,

Figure 2. **Likelihood ratio *(LR)* for autoantibodies against IgM rheumatoid factor *(RF).***

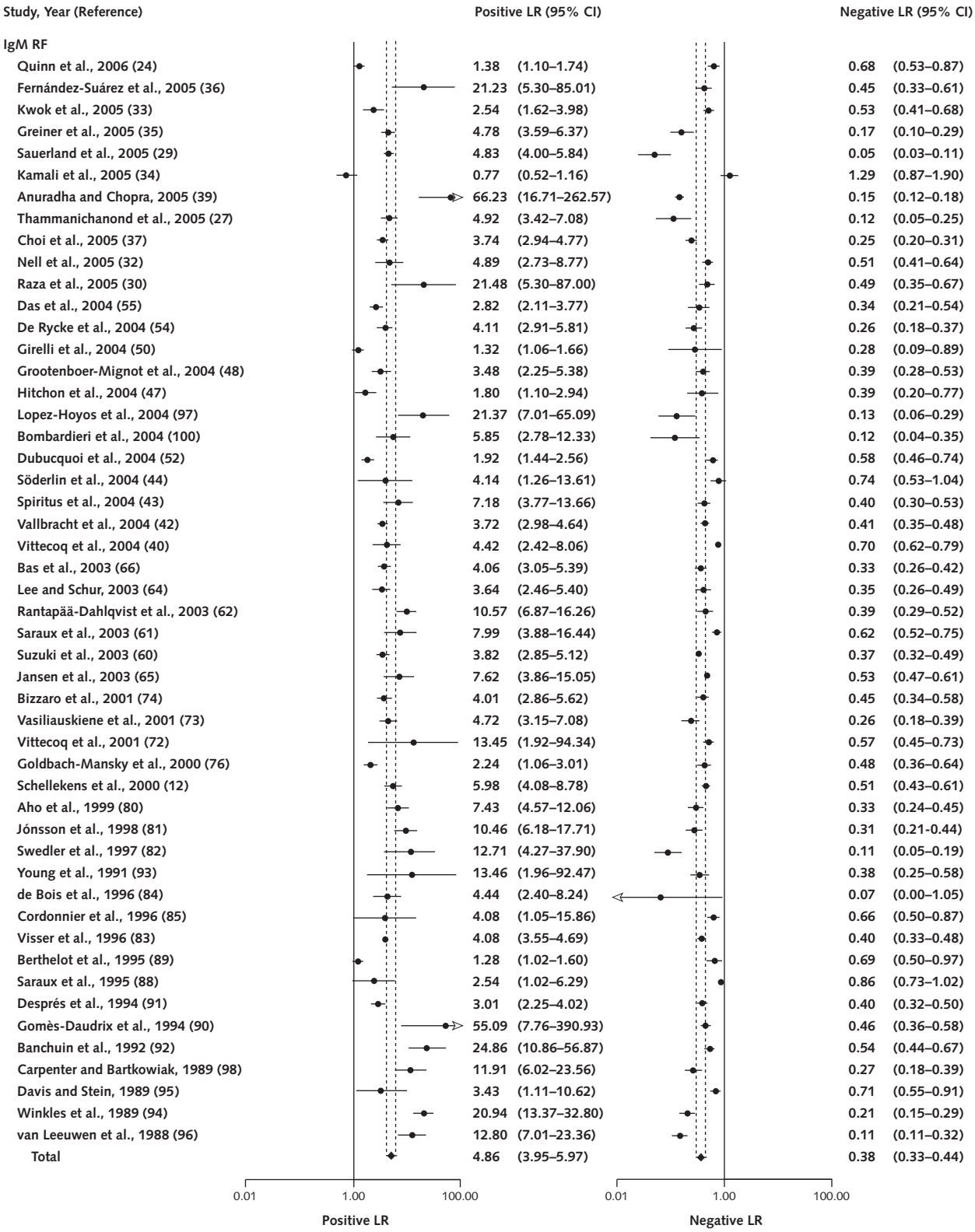
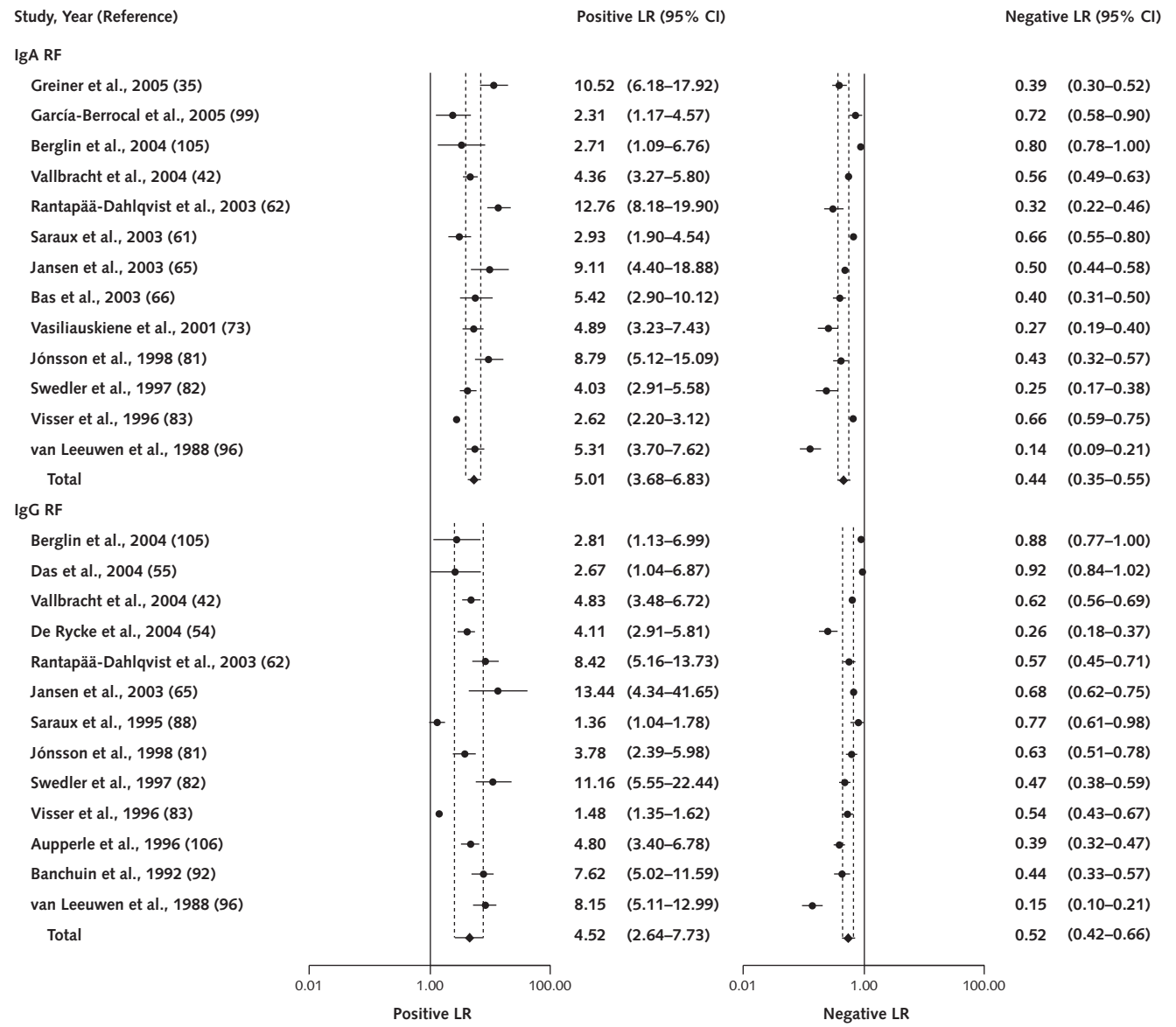


Figure 3. **Likelihood ratio *(LR)* for IgA rheumatoid factor *(RF)* and IgG RF.**



available at www.annals.org). Six studies assessed associations with anti-CCP antibody positivity; 3 of these studies used an anti-CCP1 assay. All 6 studies reported that anti-CCP antibody positivity was a statistically significant risk factor for radiographic progression. Of the 4 studies that examined anti-CCP antibody and RF, 3 reported that the risk for radiographic progression was greater for patients with anti-CCP antibody positivity than for those with IgM RF positivity.

Discussion

We identified several issues that had not been addressed systematically or quantitatively in past narrative reviews (107, 108). Anti-CCP antibody positivity was more specific than IgM RF, IgG RF, or IgA RF positivity for rheumatoid arthritis and was more specific than IgM RF for early rheumatoid arthritis. Because pooled sensitivities were similar for anti-CCP antibody and RF, the better diagnostic accuracy of anti-CCP antibody was mainly due to its higher specificity. Anti-CCP2 was a more sensitive marker than anti-CCP1. Assaying anti-CCP antibody alone and assaying combinations of anti-CCP antibody and IgM RF provided similar results. Anti-CCP antibody positivity, especially anti-CCP2, was superior to IgM RF positivity for predicting development of rheumatoid arthritis and radiographic progression.

Some experts believe that immunity against citrulline

plays a crucial role in the pathogenesis of rheumatoid arthritis (109). Anti-CCP antibodies and anticitrullinated filaggrin antibodies are locally produced in inflamed joints, and citrullinated fibrin is found in the synovia of patients with rheumatoid arthritis (110).

Anti-CCP antibody is present before symptoms develop, which suggests that citrullination and production of anti-CCP antibody are early processes in rheumatoid arthritis (62). As we show, anti-CCP antibody is highly specific for rheumatoid arthritis. However, the biological function of RF is unclear: It is found in some apparently healthy elderly persons and in persons who have conditions other than rheumatoid arthritis (111). Substantial differences exist among RF test kits, and the reliability of some RF assays is questionable (112). The varying techniques for measuring RF might partly explain the heterogeneous study results for RF.

Some studies have reported conflicting results on whether IgG RF and IgA RF are better diagnostic markers than IgM RF (82, 87, 92). We found no major diagnostic differences among IgG RF, IgA RF, and IgM RF, whereas anti-CCP antibody was a better diagnostic marker than all 3 RF subclasses. Our findings are compatible with those of earlier studies of the sensitivity of different generations of anti-CCP antibody assays. Filaggrin-derived cyclic peptide anti-CCP1 assays had very high specificity (98%) and moderate sensitivity that was lower than that of RF (12, 113). To overcome this problem, various cyclic epitopes that mimic true conformational epitopes were selected from libraries of citrullinated peptides to develop more sensitive anti-CCP2 assays (41, 62).

Some studies suggested that the diagnostic accuracy of both anti-CCP antibody and IgM–RF positivity was not markedly better than that of anti-CCP antibody positivity alone. The combination of anti-CCP antibody and IgM RF positivity improved specificity over RF positivity alone. Persons without rheumatoid arthritis who had false-positive results for RF did not have positive results for anti-CCP antibody and were regarded as healthy. The sensitivity, however, was reduced because positivity for anti-CCP antibody and RF is a more stringent criterion than is positivity for anti-CCP antibody or IgM RF alone. As a result, combining anti-CCP antibody and RF testing offered little improvement.

However, anti-CCP antibody positivity or IgM RF positivity is more permissive in terms of sensitivity because the antibodies complement each other in patients with false-negative results. In this case, specificity is reduced substantially because all persons with false-positive results for RF are counted as having positive results for rheumatoid arthritis. Because the improvement and deterioration of sensitivity were balanced, the overall diagnostic accuracy of RF is less than that of anti-CCP antibody alone. Together, these results show that anti-CCP antibody positivity is as effective a diagnostic indicator as anti-CCP antibody and RF positivity combined and is a less accurate indicator than positivity for either antibody alone.

In clinical practice, most rheumatologists recommend measuring anti-CCP antibody and RF because anti-CCP antibody has moderate sensitivity, and clinicians try to maximize sensitivities by combining the 2 markers, especially for early rheumatoid arthritis (32, 47, 48, 52, 59, 61, 63, 64, 66). Also, rheumatologists measure RF because it is included in the 1987 ACR criteria, and both anti-CCP antibody and RF are recommended screening tests for rheumatoid arthritis (114). In any case, comparison of anti-CCP antibody only with testing for anti-CCP antibody and RF involves a tradeoff between overall sensitivity and specificity. If we want to maximize sensitivity, then both tests are better, although this may prompt us to treat patients who are anti-CCP antibody negative but RF positive. Because it is harmful and costly to treat persons with false-positive results who do not have rheumatoid arthritis, we need to consider the risks and the benefits of such an approach. Clinical trials and cost-effectiveness studies of these tradeoffs are needed.

When should we measure both anti-CCP antibody and RF? If the prior probability of rheumatoid arthritis is relatively low, such as in patients who have knee pain only in primary care or those who meet no other ACR criteria, measuring anti-CCP antibody alone seems to be a reasonable strategy that avoids too many false-positive results. If, however, the prior probability of rheumatoid arthritis is relatively high, such as in patients seen in rheumatology clinics or those who meet other ACR criteria, measuring anti-CCP antibody or IgM RF seems to be a reasonable strategy that avoids missing potentially treatable patients.

We found that the presence of anti-CCP antibody is associated with development of rheumatoid arthritis and greater radiographic progression, and we confirmed that RF is a major predictor of bone damage (58, 88).

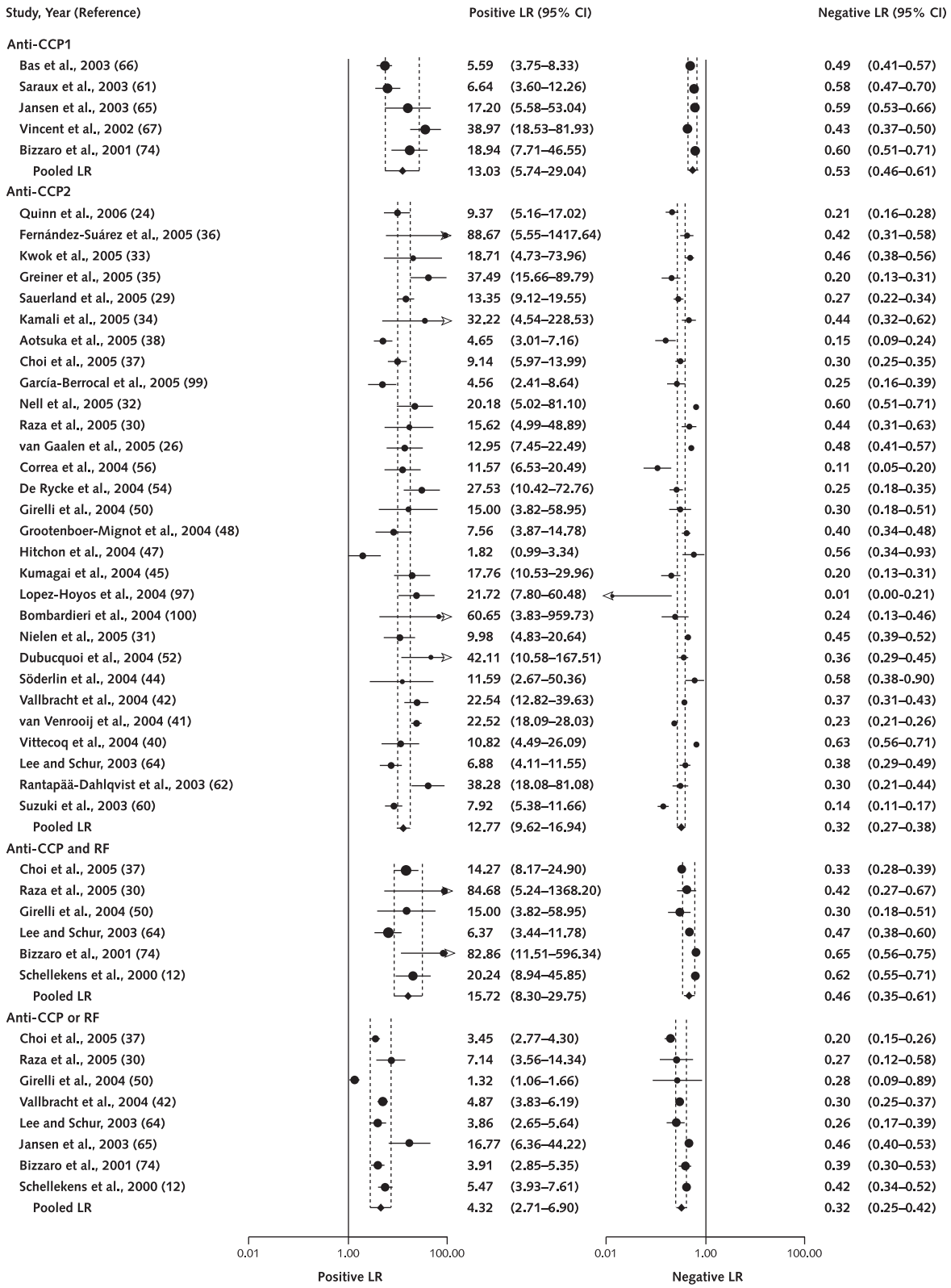
Our review has several limitations. We may have missed some pertinent studies, because we included only diagnostic studies that provided information on sensitivity

Table. **Summary Likelihood Ratios of IgM Rheumatoid Factor***

Variable	Positive LR (95% CI)	Negative LR (95% CI)
All studies	4.86 (3.96–5.97)	0.38 (0.33–0.44)
Cutoff value		
≥20 U/mL	4.42 (3.02–6.47)	0.39 (0.31–0.50)
≥40 U/mL	5.49 (2.25–13.38)	0.50 (0.37–0.69)
≥80 U/mL	4.57 (1.36–15.09)	0.44 (0.29–0.68)
Measurement method		
Nephelometry	4.15 (2.95–5.84)	0.32 (0.25–0.41)
Latex agglutination	5.05 (3.01–8.50)	0.39 (0.27–0.56)
ELISA	6.13 (4.60–8.17)	0.42 (0.34–0.51)

* ELISA = enzyme-linked immunosorbent assay; LR = likelihood ratio.

Figure 4. **Pooled likelihood ratio *(LR)* for first-generation assays for autoantibodies against cyclic citrullinated peptide *(CCP1)*, second-generation assays *(CCP2)*, anti-CCP antibody and rheumatoid factor *(RF)*, and anti-CCP antibody or RF.**



and specificity. Our funnel plots suggested some publication bias for favorable anti-CCP antibody studies (data not shown). Because RF is incorporated into the current diagnostic criteria of rheumatoid arthritis, diagnostic studies of IgM RF might have some incorporation bias that could have increased the apparent sensitivity of this marker (115).

In conclusion, anti-CCP antibody positivity is more specific than IgM RF positivity for diagnosing rheumatoid arthritis and early rheumatoid arthritis. Anti-CCP antibody positivity should be included among the diagnostic criteria of these 2 conditions.

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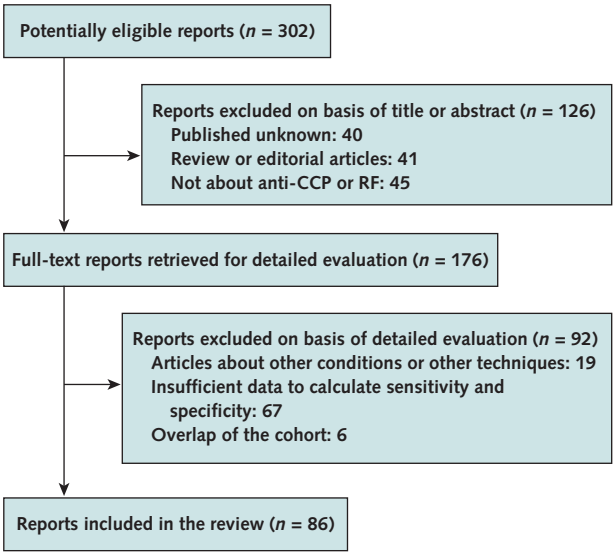
Appendix Figure. **Study flow diagram.** WEB-ONLY



CCP = cyclic citrullinated peptide; RF = rheumatoid factor.

Appendix Table 1. **Characteristics of Studies of Autoantibodies against Cyclic Citrullinated Peptide***

Study, Year (Reference)	Location	Language	Setting	Generation of CCP	Assay Manufacturer†	Reference Standard‡	Design‡	Blind Interpretation of Test Result‡	Interval between Test and Reference Standard	Technical Quality of Anti-CCP Antibody Reported‡	Clinical Description of Sample Reported‡	Mean or Median Age, *y*	Women, %	Mean Duration of Illness, *y*	Control Participants	Result				Sensitivity, %	Specificity, %	Positive LR	Negative LR
																TP	FP	FN	TN				
Quinn et al., 2006 (24)	England	English	Rheumatology clinic	CCP2	Axis-Shield	ACR	Prospective	Not reported	Not reported	Yes	Yes	58	64.2	0.58	Other rheumatic diseases (n = 116)	147	10	35	106	80.8	91.4	9.37	0.21
Fernández-Suárez et al., 2005 (36)	Spain	English	Primary care	CCP2	Inova	ACR	Prospective	Not reported	Not reported	Yes	Yes	52	45.5	NA	Other rheumatic diseases (n = 25), healthy persons (n = 50)	31	0	22	75	58.5	100	88.67	0.42
Kwok et al., 2005 (33)	Korea	English	Rheumatology clinic	CCP2	Inova	ACR	Retrospective	Not reported	NA	Yes	Yes	56	86.8	13.2	Other rheumatic diseases (n = 68), healthy persons (n = 60)	71	2	58	66	55.0	97.1	18.71	0.46
Greiner et al., 2005 (35)	Germany	English	Teaching hospital	CCP2	Euro-Diagnostica	ACR	Not reported	Not reported	NA	Yes	Yes	54.8	NA	NA	Other rheumatic diseases (n = 233)	70	5	17	228	80.5	97.9	37.49	0.20
Sauerland et al., 2005 (29)	Germany	English	Teaching hospital	CCP2	Euroimmun	ACR	Prospective	Not reported	NA	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 469)	171	26	60	443	74.0	94.5	13.35	0.28
Kamali et al., 2005 (34)	Turkey	English	Teaching hospital	CCP2	Euroimmun	ACR	Not reported	Not reported	Not reported	Yes	No	NA	NA	NA	Progressive systemic sclerosis (n = 32), Wegener granulomatosis (n = 22)	26	1	20	56	56.5	98.2	32.20	0.44
Aotsuka et al., 2005 (38)	Japan	English	Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	0–24 y	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 90), healthy persons (n = 200)	115	17	16	73	87.8	81.1	4.65	0.15
Choi et al., 2005 (37)	Korea	English	Primary care	CCP2	Tosho	ACR	Not reported	Not reported	Not reported	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 251)	236	20	88	231	72.8	92.0	9.14	0.25
García-Berrocal et al., 2005 (99)	Spain	English	Teaching hospital	CCP2	Euro-Diagnostica	ACR	Retrospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	Other diseases (n = 49)	69	8	18	38	79.3	82.6	4.56	0.25
Nell et al., 2005 (32)	Austria	English	Cohort study	CCP2	Axis-Shield	ACR	Prospective	Not reported	<12 mo	Yes	No	NA	NA	0.125	UA (n = 98)	42	2	60	96	41.2	98.0	20.18	0.60
Raza et al., 2005 (30)	England	English	Rheumatology clinic	CCP2	Axis-Shield	ACR	Prospective	Not reported	<18 mo	Yes	Yes	59.5	53.7	0.1	Osteoarthritis (n = 10), hyperlipidemia (n = 20), other rheumatic diseases (n = 52)	24	3	18	79	57.1	96.3	15.62	0.45
van Gaalen et al., 2005 (26)	Netherlands	English	Cohort study	CCP2	Euro-Diagnostica	ACR	Prospective	Not reported	<12 mo	Yes	Yes	49	0.55	3	UA (n = 107), other rheumatic diseases (n = 207)	82	13	71	301	53.6	95.9	12.95	0.48
Correa et al., 2004 (56)	Colombia	Spanish	Teaching hospital	CCP2	Inova Diagnostics	ACR	Retrospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 131), healthy persons (n = 10)	74	11	8	130	90.2	92.2	11.57	0.11
De Rycke et al., 2004 (54)	Belgium	English	Rheumatology clinic	CCP2	Euro-Diagnostica	ACR	Prospective	Not reported	Same period	Yes	Yes	63.5	34.7	5	Other rheumatic diseases (n = 146)	89	4	29	142	75.4	97.3	27.53	0.25
Girelli et al., 2004 (50)	Italy	English	Rheumatology clinic	CCP2	Axis-Shield	ACR	Prospective	Not reported	Same period	Yes	Yes	62.9	0.779	NA	HCV infection (n = 14), other rheumatic diseases (n = 28)	25	2	10	40	71.4	95.2	15.00	0.30
Grootenboer-Mignot, et al., 2004 (48)	France	English	Teaching hospital	CCP2	Euro-Diagnostica	Not reported	Not reported	Not reported	Not reported	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 91)	167	8	98	88	63.0	91.7	7.56	0.40
Hitchon et al., 2004 (47)	Canada	English	Teaching hospital	CCP2	Inter-medico	ACR	Prospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	UA (n = 23)	26	8	15	15	63.4	65.2	1.82	0.56
Kumagai et al., 2004 (45)	Japan	Japanese	Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	Not reported	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 307)	64	14	15	293	81.0	95.4	17.77	0.20
Lopez-Hoyos et al., 2004 (97)	Spain	English	Teaching hospital	CCP2	Euro-Diagnostica	ACR	Prospective	Not reported	Not reported	Yes	Yes	62.5	64.8	NA	Polymyalgia rheumatica (n = 48)	38	3	0	73	100	96.1	21.72	0.01
Bombardieri et al., 2004 (100)	Italy	English	Teaching hospital	CCP2	Axis-Shield	ACR	Prospective	Not reported	Not reported	Yes	Yes	58.8	NA	10	HCV infection (n = 10)	23	0	7	39	76.7	100	60.65	0.25
Nielen et al., 2005 (31)	Netherlands	English	Rheumatology clinic	CCP2	Euro-Diagnostica	ACR	Prospective	Yes	1 y	Yes	Yes	56.1	0.686	0.4	UA (n = 121)	149	7	109	114	57.8	94.2	9.98	0.45
Dubucquoi et al., 2004 (52)	France	English	Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	6–18 mo	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 98), healthy persons (n = 33)	90	2	50	129	64.3	98.5	42.10	0.36
Söderlin et al., 2004 (44)	Sweden	English	Health care centers	CCP2	Euro-Diagnostica	Clinical diagnosis	Prospective	Yes	2 y	Yes	Yes	49.6	63.7	0.3	Reactive arthritis (n = 28), UA (n = 10), other arthritis (n = 15)	7	2	9	51	43.8	96.2	11.59	0.59
Vallbracht et al., 2004 (42)	Germany	English	Teaching hospital	CCP2	Euro-Diagnostica	ACR	Not reported	Not reported	Not reported	Yes	Yes	56.8	0.712	8.3	Degenerative joint disease (n = 163), other rheumatic diseases (n = 103), healthy persons (n = 154)	190	12	105	408	64.4	97.1	22.54	0.37
van Venrooij et al., 2004 (41)	Netherlands	English	Teaching hospital	CCP2	Not reported	Not reported	Not reported	Not reported	Not reported	No	Yes	NA	NA	NA	Other rheumatic diseases (n = 2297)	865	79	252	2218	77.4	96.6	22.51	0.23
Vittecoq et al., 2004 (40)	France	English	Cohort study	CCP2	Euroimmun	ACR	Prospective	Not reported	Not reported	Yes	Yes	51.7	10.5	0.33	Other rheumatic diseases (n = 225)	69	5	107	133	39.2	96.4	10.80	0.63
Bas et al., 2003 (66)	Switzerland	English	Teaching hospital	CCP1	Euro-Diagnostica	ACR	Cross-sectional	Not reported	Not reported	Yes	Yes	62	0.71	NA	Other rheumatic diseases (n = 160), spondyloarthropathies (n = 79)	110	24	86	215	56.1	90.0		
Lee and Schur, 2003 (64)	United States	English	Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	Not reported	Yes	Yes	47.5	79.1	NA	Other rheumatic diseases (n = 113), noninflammatory arthritis (n = 23)	68	14	35	132	66.0	90.4	6.89	0.38
Rantapää-Dahlqvist, et al., 2003 (62)	Netherlands	English	Cohort study	CCP2	Euro-Diagnostica	ACR	Nested case–control	Not reported	6.1 y	Yes	Yes	NA	NA	3	Healthy age- and sex-matched persons (n = 382)	47	7	20	375	70.1	98.2	38.28	0.30
Saraux et al., 2003 (61)	France	English	Cohort study	CCP1	Euro-Diagnostica	Clinical diagnosis	Prospective	Not reported	Not reported	Yes	Yes	49.4	66.6	NA	UA (n = 157)	40	11	46	146	46.5	93.0	6.64	0.58

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Appendix Table 1—**Continued**

Study, Year (Reference)	Location	Language	Setting	Generation of CCP	Assay Manufacturer†	Reference Standard‡	Design‡	Blind Interpretation of Test Result‡	Interval between Test and Reference Standard	Technical Quality of Anti-CCP Antibody Reported‡	Clinical Description of Sample Reported‡	Mean or Median Age, *y*	Women, %	Mean Duration of Illness, *y*	Control Participants	Result				Sensitivity, %	Specificity, %	Positive LR	Negative LR
																TP	FP	FN	TN				
Suzuki et al., 2003 (60)	Japan	English	Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	Not reported	Yes	Yes	57.18	85.2	9.4	Other rheumatic diseases (n = 208)	481	23	68	185	87.6	88.9	7.92	0.14
Zeng et al., 2003 (58)	China	English	Teaching hospital	CCP1	In-house ELISA	ACR	Not reported	Not reported	Not reported	Yes	Yes	46.14	71.7	NA	Other rheumatic diseases (n = 132), nonrheumatic diseases (n = 98), healthy persons (n = 90)	90	7	101	313	47.1	97.8	21.50	0.54
Jansen et al., 2003 (65)	Netherlands	English	Rheumatology clinic	CCP1	Euro-Diagnostica	Clinical diagnosis	Prospective	Not reported	Not reported	Yes	Yes	57	69	NA	UA (n = 121)	110	3	148	118	42.6	97.5	17.20	0.59
Vincent et al., 2002 (67)	France	English	Rheumatology clinic	CCP1	Euro-Diagnostica	ACR	Not reported	Not reported	Not reported	Yes	Yes	58.06	79.6	NA	Other rheumatic diseases (n = 157), nonrheumatic arthritis (n = 314)	139	7	101	464	57.9	98.5	38.9	0.43
Bizzaro et al., 2001 (74)	Italy	English	Rheumatology clinic	CCP1	Euro-Diagnostica	ACR	Prospective	Yes	Not reported	No	Yes	65	89.7	NA	Other rheumatic diseases (n = 174), healthy persons (n = 58)	40	5	58	227	40.8	97.8	18.94	0.61
Goldbach-Mansky et al., 2000 (76)	United States	English	Cohort study	CCP1	In-house ELISA	ACR	Prospective	Not reported	12 mo	Yes	Yes	42.1	0.66	NA	UA (n = 85), other rheumatic diseases (n = 57)	43	12	63	120	40.6	90.9	4.46	0.65
Schellekens et al., 1998 (11)	Netherlands	English	Teaching hospital	CCP1	In-house ELISA	ACR	Retrospective	Yes	Not reported	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 329), infectious diseases (n = 366), healthy persons (n = 120)	72	14	77	298	48.3	95.5	10.77	0.54

* ACR = American College of Rheumatology criteria; CCP = cyclic citrullinated peptide; ELISA = enzyme-linked immunosorbent assay; FN = false negative; FP = false positive; HCV = hepatitis C virus; LR = likelihood ratio; NA = not available; TN = true negative; TP = true positive; UA = undifferentiated arthritis.
† The locations of the assay manufacturers are as follows: Axis-Shield (Dundee, United Kingdom), Euro-Diagnostica (Arnhem, the Netherlands), Euroimmun (Luebeck, Germany), Inova Diagnostics (San Diego, California), Intermedico (Markham, Ontario, Canada), and Tosho (Tokyo, Japan).
‡ Included for evaluation of study quality.

Appendix Table 2. **Characteristics of Studies of Rheumatoid Factor***

Study, Year (Reference)	Location	Language	Setting	Method of Measurement	Assay Manufacturer†	Cutoff Value, *U/mL*	Reference Standard‡	Design‡	Blind Interpretation of Test Result‡	Interval between Test and Reference Standard	Technical Quality of RF Reported‡	Clinical Description of Sample Reported‡	Mean or Median Age, *y*	Women, %	Mean Duration of Illness, y	Control Participants	Result				Sensitivity, %	Specificity, %	Positive LR	Negative LR
																	TP	FP	FN	TN				
Quinn et al., 2006 (24)	England	English	Rheumatology clinic	Not reported	Not reported	Not reported	ACR	Prospective	Not reported	Not reported	No	Yes	58	64.2	7 mo	Other rheumatic diseases (n = 116)	115	53	67	63	63.0	54.00	1.38	0.68
Fernández-Suárez et al., 2005 (36)	Spain	English	Primary care	Nephelometry	Dade Behring	50	ACR	Prospective	Not reported	Not reported	Yes	Yes	52	45.5	NA	Other rheumatic diseases (n = 25), healthy persons (n = 50)	30	2	23	73	56.6	97.1	21.23	0.45
Kwok et al, 2005 (33)	Korea	English	Rheumatology clinic	Nephelometry	Dade Behring	15	ACR	Retrospective	Not reported	NA	Yes	Yes	56	86.8	13.2	Other rheumatic diseases (n = 68), healthy persons (n = 60)	77	16	52	52	–	–	2.54	0.53
Greiner et al., 2005 (35)	Germany	English	Teaching hospital	Nephelometry	Dade Behring	Not reported	ACR	Not reported	Not reported	NA	Yes	Yes	54.8	NA	NA	Other rheumatic diseases (n = 233)	75	42	12	191	–	–	4.78	0.17
Sauerland et al., 2005 (29)	Germany	English	Teaching hospital	Nephelometry	Dade Behring	20	ACR	Prospective	Not reported	NA	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 469)	161	89	7	360	69.7	81	4.84	0.05
Kamali et al., 2005 (34)	Turkey	English	Teaching hospital	LA	Not reported	20	ACR	Not reported	Not reported	Not reported	Yes	No	NA	NA	NA	Progressive systemic sclerosis (n = 32), Wegener granulomatosis (n = 22)	20	32	26	25	43.5	43.9	1.29	0.78
Anuradha and Chopra, 2005 (39)	India	English	Rheumatology clinic	LA	Tulip Diagnostics	8	ACR	Not reported	Not reported	Not reported	Yes	No	NA	NA	NA	Healthy persons (n = 155)	482	2	82	153	85.5	98.7	66.20	0.15
Thammanichanond et al., 2005 (27)	Thailand	English	Teaching hospital	LA	Dade Behring	20	ACR	Retrospective	Not reported	Not reported	Yes	Yes			NA	OA (n = 15), other rheumatic diseases (n = 10), healthy persons (n = 110)	57	25	6	111	90.5	97.3	4.92	0.12
Choi et al., 2005 (37)	Korea	English	Primary care	LA	Hitachi	9	ACR	Not reported	Not reported	Not reported	Yes	Yes	NA	NA	14.6	Other rheumatic diseases (n = 251)	261	54	63	197	80.6	78.5	3.74	0.25
Nell et al., 2005 (32)	Austria	English	Cohort study	Not reported	Not reported	Not reported	ACR	Prospective	Not reported	<12 mo	Yes	No	NA	NA	0.125	UA (n = 98)	56	11	46	87	54.9	88.8	4.89	0.51
Raza et al., 2005 (30)	England	English	Rheumatology clinic	LA	Mast Diagnostics	30	ACR	Prospective	Not reported	<18 mo	Yes	Yes	59.5	53.7	0.1	OA (n = 10), hyperlipidemia (n = 20), other rheumatic diseases (n = 52)	22	2	20	80	52.4	97.6	21.48	0.49
Das et al., 2004 (55)	Japan	English	Teaching hospital	Nephelometry	Dade Behring	16.3		Prospective	Not reported	Same period	Yes	Yes	47.24	93	NA	Other rheumatic diseases (n = 206)	42	46	14	127	75.0	73.4	2.82	0.34
De Rycke et al., 2004 (54)	Belgium	English	Rheumatology clinic	LA	Difco Laboratories	3.125	ACR	Prospective	Not reported	Same period	Yes	Yes	63.5	34.7	5	Other rheumatic diseases (n = 146)	93	28	25	118	78.8	80.8	4.11	0.26
Girelli et al., 2004 (50)	Italy	English	Rheumatology clinic	Nephelometry	Dade Behring	20	ACR	Prospective	Not reported	Same period	Yes	Yes	62.9	77.9	NA	HCV infection (n = 14), other rheumatic diseases (n = 28)	32	29	3	13	91.4	31.0	1.32	0.28
Grootenboer-Mignot et al., 2004 (48)	France	English	Teaching hospital	Nephelometry	Dade Behring	20	Not reported	Not reported	Not reported	Not reported	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 91)	64	18	29	73	68.8	80.2	3.48	0.39
Hitchon et al., 2004 (47)	Canada	English	Teaching hospital	Nephelometry	Intermedico	20	ACR	Prospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	UA (n = 23)	32	10	9	13	78.0	43.0	1.80	0.39
Lopez-Hoyos et al., 2004 (97)	Spain	English	Teaching hospital	Nephelometry	Dade Behring	22	ACR	Prospective	Not reported	Not reported	Yes	Yes	62.5	64.8	NA	Polymyalgia rheumatica (n = 48)	36	3	5	70	88.0	96.0	21.37	0.13
Bombardieri et al., 2004 (100)	Italy	English	Teaching hospital	Nephelometry	Dade Behring	15	ACR	Prospective	Not reported	Not reported	Yes	Yes	58.8	NA	10	HCV infection (n = 10)	27	6	3	33	90.0	85.0	5.85	0.12
Dubucquoi et al., 2004 (52)	France	English	Teaching hospital	ELISA	Biomedical Diagnostics	20	ACR	Retrospective	Not reported	6–18 mo	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 98), healthy persons (n = 33)	84	41	56	90	60.0	69.0	1.92	0.58
Söderlin et al., 2004 (44)	Sweden	English	Health care centers	LA	Not reported	Not reported	Clinical diagnosis	Prospective	Yes	2 y	No	Yes	49.6	63.7	0.3	Reactive arthritis (n = 28), UA (n = 10), other arthritis (n = 15)	5	4	11	49	31.0	93.0	4.14	0.74
Spiritus et al., 2004 (43)	Belgium	English	Teaching hospital	Nephelometry	Beckman Instruments	20	ACR	Prospective	Yes	Not reported	Yes	Yes	50.75	62	NA	Other rheumatic diseases (n = 102)	57	9	33	93	63.0	91.0	7.18	0.40
Vallbracht et al., 2004 (42)	Germany	English	Teaching hospital	ELISA	Aesku.lab Diagnostika	15	ACR	Not reported	Not reported	Not reported	Yes	Yes	56.8	71.2	8.3	Degenerative joint disease (n = 163), other rheumatic diseases (n = 103), healthy persons (n = 154)	196	75	99	345	66.0	82.0	3.72	0.41
Vittecoq et al., 2004 (40)	France	English	Cohort study	ELISA	In-house	16	ACR	Prospective	Not reported	Not reported	Yes	Yes	51.7	10.5	0.33	Other rheumatic diseases (n = 225)	62	11	114	127	35.2	92.0	4.42	0.70
Bas et al., 2003 (66)	Switzerland	English	Teaching hospital	ELISA	In-house	Not reported	ACR	Cross-sectional	Not reported	Not reported	Yes	Yes	62	71	NA	Other rheumatic diseases (n = 160), spondylo-arthropathies (n = 79)	143	43	53	196	73.0	82.0	4.06	0.33
Lee and Schur, 2003 (64)	United States	English	Teaching hospital	LA	Difco Laboratories	80	ACR	Retrospective	Not reported	Not reported	Yes	Yes	47.5	79.1	NA	Other rheumatic diseases (n = 113), noninflammatory arthritis (n = 23)	73	22	29	90	71.6	80.4	3.64	0.35
Rantapää-Dahlqvist et al, 2003 (62)	Netherlands	English	Cohort study	ELISA	In-house	20	ACR	Nested case–control studies	Not reported	6.1 y	Yes	Yes	NA	NA	3	Healthy persons (n = 382)	49	23	28	359	63.6	94.0	10.57	0.39
Saraux et al., 2003 (61)	France	English	Cohort study	ELISA	Not reported	Not reported	Clinical diagnosis	Prospective	Not reported	Not reported	Yes	Yes	49.4	66.6	NA	UA (n = 157)	35	8	51	149	41.0	95.0	2.54	0.63
Suzuki et al., 2003 (60)	Japan	English	Teaching hospital	Nephelometry	Dade Behring	15	ACR	Retrospective	Not reported	Not reported	Yes	Yes	57.18	85.2	9.4	Other rheumatic diseases (n = 208)	383	38	166	170	69.8	81.7	3.82	0.37
Jansen et al., 2003 (65)	Netherlands	English	Rheumatology clinic	Nephelometry	Dako Diagnostics	30	Clinical diagnosis	Prospective	Not reported	Not reported	Yes	yes	57	69	NA	UA (n = 121)	130	8	128	113	50.4	93.4	7.62	0.53
Bizzaro et al., 2001 (74)	Italy	English	Rheumatology clinic	Nephelometry	Not reported	Not reported	ACR	Prospective	Yes	Not reported	No	yes	65	89.7	NA	Other rheumatic diseases (n = 124), healthy persons (n = 58)	61	36	37	196	62.2	84.5	4.01	0.45
Vasiliauskiene et al., 2001 (73)	Lithuania	English	Teaching hospital	ELISA	In-house	17	ACR	Prospective	Not reported	Not reported	Yes	Yes	53.54	75.8	7.8	Other rheumatic diseases (n = 90), healthy persons (n = 37)	75	21	21	106	78.1	83.5	4.73	0.26
Vittecoq et al., 2001 (72)	France	English	Rheumatology clinic	LA	Not reported	80	ACR	Prospective	Not reported	Not reported	Yes	Yes	51.4	68	0.33	Other rheumatic diseases (n = 30)	26	1	32	29	44.8	96.7	0.57	13.45

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Appendix Table 2—**Continued**

Study, Year (Reference)	Location	Language	Setting	Method of Measurement	Assay Manufacturer†	Cutoff Value, *U/mL*	Reference Standard‡	Design‡	Blind Interpretation of Test Result‡	Interval between Test and Reference Standard	Technical Quality of RF Reported‡	Clinical Description of Sample Reported‡	Mean or Median Age, *y*	Women, %	Mean Duration of Illness, y	Control Participants	Result				Sensitivity, %	Specificity, %	Positive LR	Negative LR
																	TP	FP	FN	TN				
Goldbach-Mansky et al., 2000 (76)	United States	English	Cohort study	Nephelometry	Not reported	20	ACR	Prospective	Not reported	12 mo	Yes	Yes	42.1	66	NA	UA (n = 85), other rheumatic diseases (n = 57)	70	39	36	93	66.0	70.5	2.24	0.48
Schellekens et al., 2000 (12)	Netherlands	English	Teaching hospital	ELISA	Not reported	Not reported	ACR	Retrospective	Yes	Same period	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 329), infectious diseases (n = 366), healthy persons (n = 120)	80	28	69	284	53.7	91.0	5.98	0.51
Aho et al., 1999 (80)	Finland	English	Rheumatology clinic	LA	Not reported	Not reported	ACR	Retrospective	Not reported	Not reported	Yes		NA	NA	NA	Other rheumatic diseases (n = 108), miscellaneous disorders (n = 56)	64	16	27	153	70.3	90.5	7.43	0.33
Jónsson et al., 1998 (81)	Iceland	English	Teaching hospital	ELISA	In-house	Not reported	ACR	Not reported	Not reported	Not reported	Yes	Yes	NA	NA	NA	OA (n = 50), UA (n = 74), other rheumatic diseases (n = 81)	50	14	20	191	71.4	93.2	10.46	0.31
Swedler et al., 1997 (82)	United States	English	Rheumatology clinic	Nephelometry	Dade Behring	20	ACR	Retrospective	Not reported	Not reported	Yes		NA	NA	NA	Mixed	89	3	9	39	90.8	92.9	12.71	0.10
Young et al., 1991 (93)	England	English	Rheumatology clinic	Rheumatoid arthritis hemagglutination	Not reported	40	ACR	Prospective	Not reported	Not reported	Yes	Yes	51.1	66.6	0.66	Other arthritis (n = 21)	25	1	14	20	64.1	95.2	13.50	0.38
de Bois et al., 1996 (84)	Netherlands	English	Teaching hospital	ELISA	Not reported	3	ACR	Not reported	Not reported	Not reported	Yes	Yes	42	84.5	NA	UA (n = 39)	8	8	0	31	100	79.5	4.44	0.07
Cordonnier et al., 1996 (85)	France	English	Teaching hospital	LA	Pasteur Production	40	ACR	Prospective	Not reported	12–24 mo	Yes	Yes	50	75.4	0.5	UA (n = 15), other arthritis (n = 5)	20	2	29	18	40.8	90.0	4.08	0.66
Visser et al., 1996 (83)	Netherlands	English	Teaching hospital	ELISA	In-house	Not reported	Clinical diagnosis	Retrospective	Not reported	<2 mo	Yes	Yes	48	67.3	12	Mixed	157	287	78	1466	66.8	83.6	4.08	0.40
Berthelot et al., 1995 (89)	France	English	Teaching hospital	LA	Fumouze Diagnostics	100	ACR	Prospective	Yes	Not reported	Yes		NA	NA	NA	Not reported	80	50	39	45	67.2	47.4	1.23	0.69
Saraux et al., 1995 (88)	France	English	Teaching hospital	LA	Biolyon	40	ACR	Retrospective	Not reported	Not reported	Yes	Yes	51.98	59	NA	Other rheumatic diseases (n = 99)	8	8	31	91	20.5	91.9	2.54	0.87
Després et al., 1994 (91)	Canada	English	Teaching hospital	LA	Not reported	Not reported	ACR	Prospective	Not reported	Not reported	Yes		NA	NA	NA	Other rheumatic diseases (n = 165), other arthritis (n = 65), healthy persons (n = 36), infectious mononucleosis (n = 10)	143	39	63	130	69.4	76.9	3.01	0.40
Gomès-Daudrix et al., 1994 (90)	France	English	Teaching hospital	ELISA	Cogent Diagnostics	Not reported	ACR	Not reported	Not reported	Not reported	Yes		NA	NA	NA	Other rheumatic diseases (n = 100)	48	1	40	99	54.5	99.0	55.1	0.46
Banchuin et al., 1992 (92)	Thailand	English	Teaching hospital	ELISA	In-house	Not reported	ACR	Not reported	Not reported	Not reported	Yes	Yes	NA	NA	NA	Healthy persons (n = 200), cancer (n = 30), infectious diseases (n = 56), other rheumatic diseases (n = 29)	36	6	41	313	46.8	98.1	24.9	0.54
Carpenter and Bartkowiak, 1989 (98)	United States	English	Teaching hospital	ELISA	In-house	87	Not reported	Not reported	Not reported	Not reported	Yes	NA	NA	NA	NA	OA (n = 56), healthy persons (n = 76)	60	8	20	119	75.0	93.7	11.91	0.27
Davis and Stein, 1989 (95)	Zimbabwe	English	Teaching hospital	ELISA	Dade MicroScan	Not reported	ACR	Prospective	Not reported	Same period	Yes	NA	70	NA	NA	Other rheumatic diseases (n = 55)	18	3	31	25	36.7	89.3	3.43	0.71
Winkles et al., 1989 (94)	England	English	Rheumatology clinic	LA	Polysciences	Not reported	Not reported	Not reported	Not reported	Not reported	Yes	NA	NA	NA	NA	Not reported	113	19	29	481	79.6	96.2	20.94	0.21
van Leeuwen et al., 1988 (96)	Netherlands	English	Teaching hospital	ELISA	In-house	Not reported	Not reported	Not reported	Not reported	Not reported	Yes	NA	NA	NA	NA	Not reported	163	10	28	140	85.3	93.3	12.80	2.07

* ACR = American College of Rheumatology criteria; ELISA = enzyme-linked immunosorbent assay; FN = false negative; FP = false positive; HCV = hepatitis C virus; LA = latex agglutination; LR = likelihood ratio; NA = not available; OA = osteoarthritis; RF = rheumatoid factor; TN = true negative; TP = true positive; UA = undifferentiated arthritis.
† The manufacturers of the assays are as follows: Aesku.lab Diagnostika (Wendelsheim, Germany), Beckman Instruments (Fullerton, California), Biolyon (Lyon, France), Biomedical Diagnostics (Marne-la-Vallée, France), Cogent Diagnostics (Penicuik, United Kingdom), Dade Behring (Marburg, Germany), Dade MicroScan (West Sacramento, California), Dako Diagnostics (Glostrup, Denmark), Difco Laboratories (Detroit, Michigan), Fumouze Diagnostics (Asnières, France), Hitachi (Tokyo, Japan), Intermedico (Markham, Ontario, Canada), Mast Diagnostics (Bootle, United Kingdom), Pasteur Production (Paris, France), Polysciences (Northampton, United Kingdom), Tulip Diagnostics (Goa, India).
‡ Included for evaluation of study quality.

Appendix Table 3. **Value of Autoantibodies against Cyclic Citrullinated Peptide and Rheumatoid Factor in Predicting Development of Rheumatoid Arthritis***

Study, Year (Reference)	Location	Language	Setting	Design	Cohort	Outcome Measure	Mean or Median Duration of Illness before Study	Follow-up, *y*	Patients Who Completed Follow-up, *n/n*	Treatments Received	Mean or Median Age, *y*	Women, %	Reference Standard	Diagnostic Test	Effect Size
van Gaalen et al., 2005 (26)	Netherlands	English	Population-based cohort	Prospective cohort study	936 patients with UA	OR for RA, adjusted for other ACR criteria	3 mo	3	127/318	Not reported	49	55	ACR	Anti-CCP IgM RF Arthritis in >3 joints Erosion on radiographs	OR, 38.9 (95% CI, 9.9–151.0) OR, 8.7 (CI, 2.4–31.2) OR, 5.0 (CI, 1.8–13.2) OR, 8.7 (CI, 2.4–31.2)
Nielen et al., 2004 (101)	Netherlands	English	Population-based cohort	Retrospective cohort study	79 blood donors with RA	Cumulative percentage of positive test results before onset of symptoms	7.5 y	15 (maximum)	79/79	Not reported	51.4	62	ACR	Anti-CCP IgM RF IgM RF or anti-CCP	40.5% (32/79) 27.8% (22/79) 49.4% (39/79)
Söderlin et al., 2004 (44)	Sweden	English	Population-based cohort	Prospective cohort study	69 patients with RA	PPV for rheumatoid factor	3 mo	2	69/69	Not reported	49.6	63.7	Clinical judgment	Anti-CCP	PPV, 78
Rantapää-Dahlqvist, 2003 (62)	Netherlands	English	Population-based cohort	Nested case–control studies	83 blood donors with RA adjusted in multivariate logistic regression	OR for RA	3	10.9	Not reported	Not reported	Not available	Not available	ACR	Anti-CCP (≤1.5 y before symptom onset) IgM RF (≤1.5 y before symptom onset) IgG RF (≤1.5 y before symptom onset) IgA RF (≤1.5 y before symptom onset) Anti-CCP (>1.5 y before symptom onset) IgM RF (>1.5 y before symptom onset) IgG RF (>1.5 y before symptom onset) IgA RF (>1.5 y before symptom onset)	OR, 28.9 (CI, 4.3–192.6) OR, 1.2 (CI, 0.1–22.1) OR, 6.2 (CI, 0.6–61.0) OR, 11.4 (CI, 1.3–98.0) OR, 16.1 (CI, 3.3–76.7) OR, 1.3 (CI, 0.6–2.4) OR, 0.5 (CI, 0.1–2.4) OR, 5.1 (CI, 1.6–16.0)
Saraux et al., 2002 (69)	France	English	Primary care	184 patients with UA	Prediction of RA	<1	2.5 (median)	Not reported	Not reported	49.5	68.9	ACR	Prospective cohort study	IgM RF (latex agglutination) IgM RF (ELISA) IgG AKA	OR, 3.6 (CI, 1.2–10.4) OR, 4.0 (CI, 1.6–10.1) OR, 6.6 (CI, 2.7–16.0)

* ACR = American College of Rheumatology criteria; AKA = antikeratin antibody; CCP = cyclic citrullinated peptide; ELISA = enzyme-linked immunosorbent assay; OR = odds ratio; PPV = positive predictive value; RA = rheumatoid arthritis; RF = rheumatoid factor; UA = undifferentiated arthritis.

Appendix Table 4. **Value of Autoantibodies against Cyclic Citrullinated Peptide and Rheumatoid Factor in Predicting Radiographic Progression of Rheumatoid Arthritis***

Study, Year (Reference)	Location	Language	Setting	Design	Outcome Measure	Mean Duration of Illness before Study, *mo*	Follow-up, *y*	Patients Who Completed Follow-up, *n/n*	Treatment Received	Mean or Median Age, *y*	Women, %	Reference Standard	Diagnostic Test	Effect Size
Nell et al., 2005 (32)	Austria	English	Population-based cohort study	Prospective cohort study	Larsen score	<0.25	3	66/102	Not reported	50	Not reported	ACR	CCP2 RF	PPV, 88% PPV, 78%
Meyer et al., 2006 (25)	France	English	Population-based cohort study	Prospective cohort study	Sharp–van der Heijde score	4.3	5	99/99	MTX (n = 38), sulfasalazine (n = 31), both MTX and sulfasalazine (n = 27), corticosteroids (n = 33)	50	73	ACR	CCP2 (first 3 y) IgM RF (first 3 y)	OR, 3.17 (95% CI, 1.3–7.7) OR, 0.88 (CI, 0.30–2.58)
Tanaka et al., 2005 (28)	Japan	English	Teaching hospital	Prospective cohort study	Sharp–van der Heijde score	<1	10	114/130	DMARDs (95%), MTX (35%), sulfasalazine (47%), bucillamine (13%), gold (7%), auranofin (2%)	54	69	ACR	RF CRP Synovial membrane enhancement on MRI	OR, 2.07 (CI, 1.01–3.11) OR, 2.86 (CI, 1.01–5.88) OR, 3.59 (CI, 1.53–8.39)
Dixey et al., 2004 (53)	United Kingdom	English	Rheumatology clinic		Larsen erosive scores at 3 y	<2	3	866/866	Followed UK guidelines for RA	NA	64	ACR	RF Nodules HLA-DR shared epitopes	OR, 2.43 (CI, 1.72–3.44) OR, 2.09 (CI, 1.08–4.05) OR, 2.57 (CI, 1.72–3.85)
Goronzy et al., 2004 (49)	United States	English	Teaching hospital	Prospective cohort study	Sharp–van der Heijde score	<1	2	94/111	Followed the algorithm created by the authors	51.5	70.3	ACR	RF Age Number of erosions	OR, 3.14 (CI, 1.41–7.00) OR, 1.45 (CI, 1.08–1.94) OR, 4.31 (CI, 1.78–10.42)
Forslind et al., 2004 (51)	Sweden	English	Population-based cohort study	Prospective cohort study	Larsen score	<1	2	333/379	DMARDs (66%), MTX (36%), sulfasalazine (51%)	55	65	ACR	Larsen score >3 Anti-CCP2 ESR >28 mm/h	OR, 9.3 (CI, 5.3–16.1) OR, 3.0 (CI, 1.7–5.2) OR, 1.8 (CI, 1.0–3.1)
Meyer et al., 2003 (63)	France	English	Teaching hospital	Prospective cohort study	Progression of total Sharp score Progression of erosion Sharp score Progression of total Sharp score Progression of erosion Sharp score	<1	5	156/191	DMARDs or NSAIDs (100%)	50.5	73	ACR	CCP1 CCP1 RF RF	OR, 2.5 (CI, 1.2–5.0) OR, 3.4 (CI, 1.6–7.2) OR, 0.7 (CI, 0.3–1.5) OR, 1.2 (CI, 0.5–2.8)
Vencovský et al., 2003 (59)	Czech Republic	English		Prospective cohort study	Larsen score progression >10 vs. <10 Larsen score progression >10 vs. <10 Larsen score progression >10 vs. <10 Larsen score progression >10 vs. <10	<2	2	104/104	Not reported	NA	NA	ACR	CCP1 IgM RF IgG RF IgA RF	OR, 4.8 (CI, 2.0–11.4) OR, 2.7 (CI, 1.2–6.2) OR, 2.7 (CI, 1.2–6.2) OR, 2.9 (CI, 1.2–6.7)
Jansen et al., 2001 (102)	Netherlands	English	Population-based cohort study	Prospective cohort study	Difference of Sharp–van der Heijde score from multiple logistic regression	0.25	1	114/130	Not reported	64	68	ACR	IgM RF CRP Joint damage at study entry	OR, 2.58 (CI, 1.11–5.97) OR, 3.59 (CI, 1.53–8.39) OR, 1.07 (CI, 1.02–1.12)
Aman et al., 2000 (78)	Finland	English	Rheumatology clinic	Prospective cohort study	Larsen score progression >20	<1	3	63/63	Gold (83%), sulfasalazine (12%), hydroxychloroquine (5%)	43.5	0.83	Clinical judgment	RF Cross-linked carboxyl telopeptide of type 1 collagen	OR, 3.9 (CI, 1.0–15.5) OR, 3.9 (CI, 1.3–11.9)
Bas et al., 2000 (77)	Switzerland	English	Rheumatology clinic	Prospective cohort study	Larsen score progression/y	Not reported	12 (by exploration of linear regression model)	Not reported	Not reported	59	71.6	ACR	RF Antifilaggrin antibody	2.0 points/y (CI, 1.3–2.6) 1.6 points/y (CI, 1.1–2.2)
Kroot et al., 2000 (75)	Netherlands	English	Teaching hospital	Prospective cohort study	Sharp–van der Heijde score	<1	6	Not reported	Not reported	51.5	65.9	ACR	Anti-CCP1 (damage score at 6 y) Anti-CCP1 (damage score at 3 y) IgM RF (damage score at 6 y) IgM RF (damage score at 3 y)	Regression coefficient, 0.918 ($P < 0.05$) Regression coefficient, 0.209 (NS) Regression coefficient, 2.477 ($P < 0.001$) Regression coefficient, 1.964 ($P < 0.001$)
van Jaarsveld et al., 1999 (103)	Netherlands	English	Teaching hospital	Prospective cohort study	Modified Sharp score	<1	3	Not reported	Not reported	NA	NA	ACR	Anti-CCP vs. IgM RF	NS
Brennan et al., 1996 (86)	United Kingdom	English	Teaching hospital	Retrospective cohort study	Probability of predicting erosion (Larsen score ≥ grade 2)	3	1	175/175	Not reported	59	71	ACR	RF Disease duration ≥3 mo Involvement of ≥2 joints	Probability of developing erosions, 0.46 Probability of developing erosions, 0.26 Probability of developing erosions, 0.37
van Zeben et al., 1993 (104)	Netherlands	English	Teaching hospital	Prospective cohort study	Physician opinion	1.6	6 (median)	Not reported	Not reported	NA	NA	ACR	RF Agalactosyl IgG Ritchie score	OR, 8.26 (CI, 2.8–24.3) OR, 3.34 (CI, 1.03–10.9) OR, 1.09 (CI, 1.01–1.19)

* ACR = American College of Rheumatology criteria; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; DMARDs = disease-modifying antirheumatic drugs; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; MTX = methotrexate; NA = not available; NS = not significant; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio; PPV = positive predictive value; RA = rheumatoid arthritis; RF = rheumatoid factor.