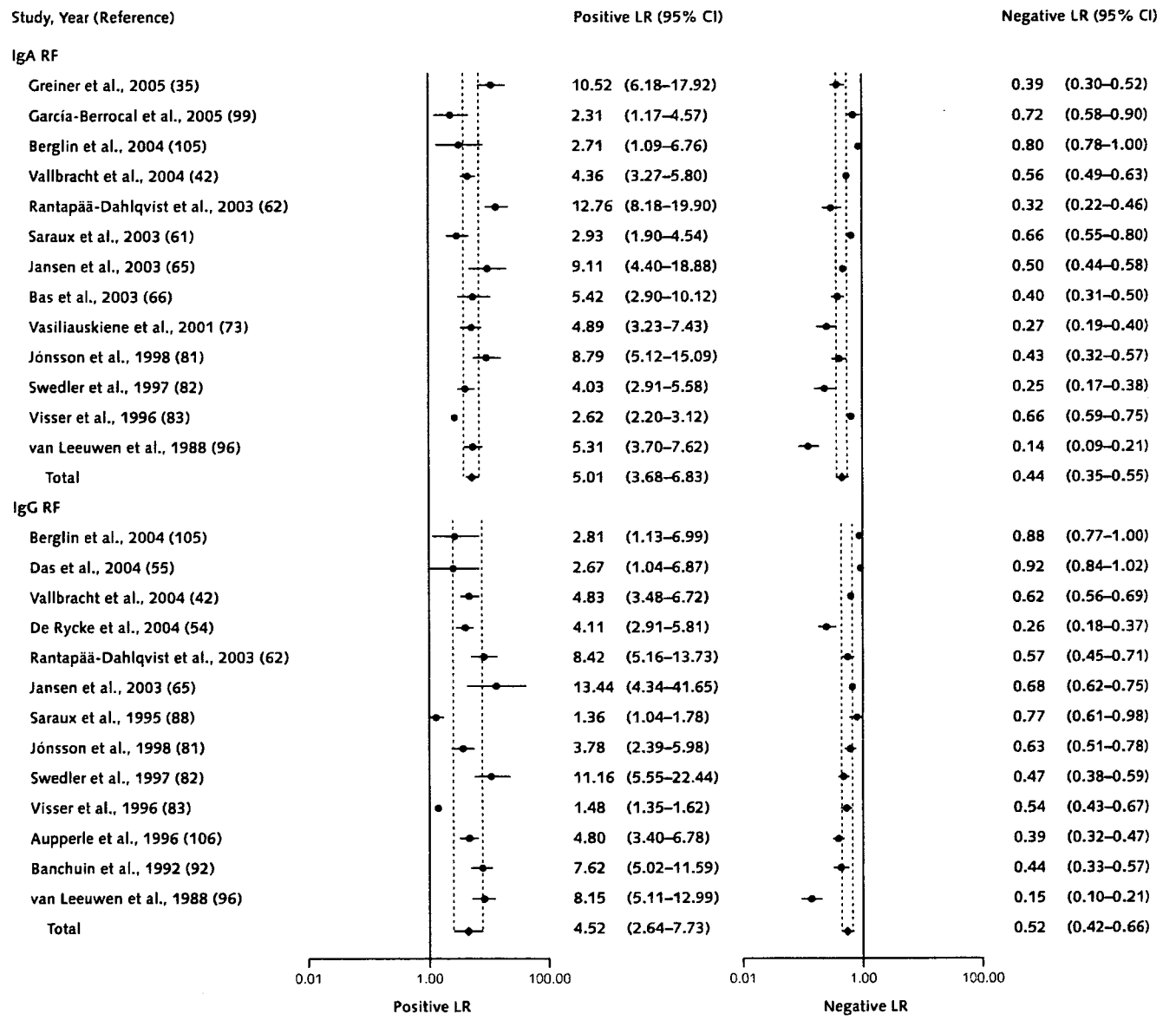
Figure 3. Likelihood ratio *(LR)* for IgA rheumatoid factor *(RF)* and IgG RF.



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).

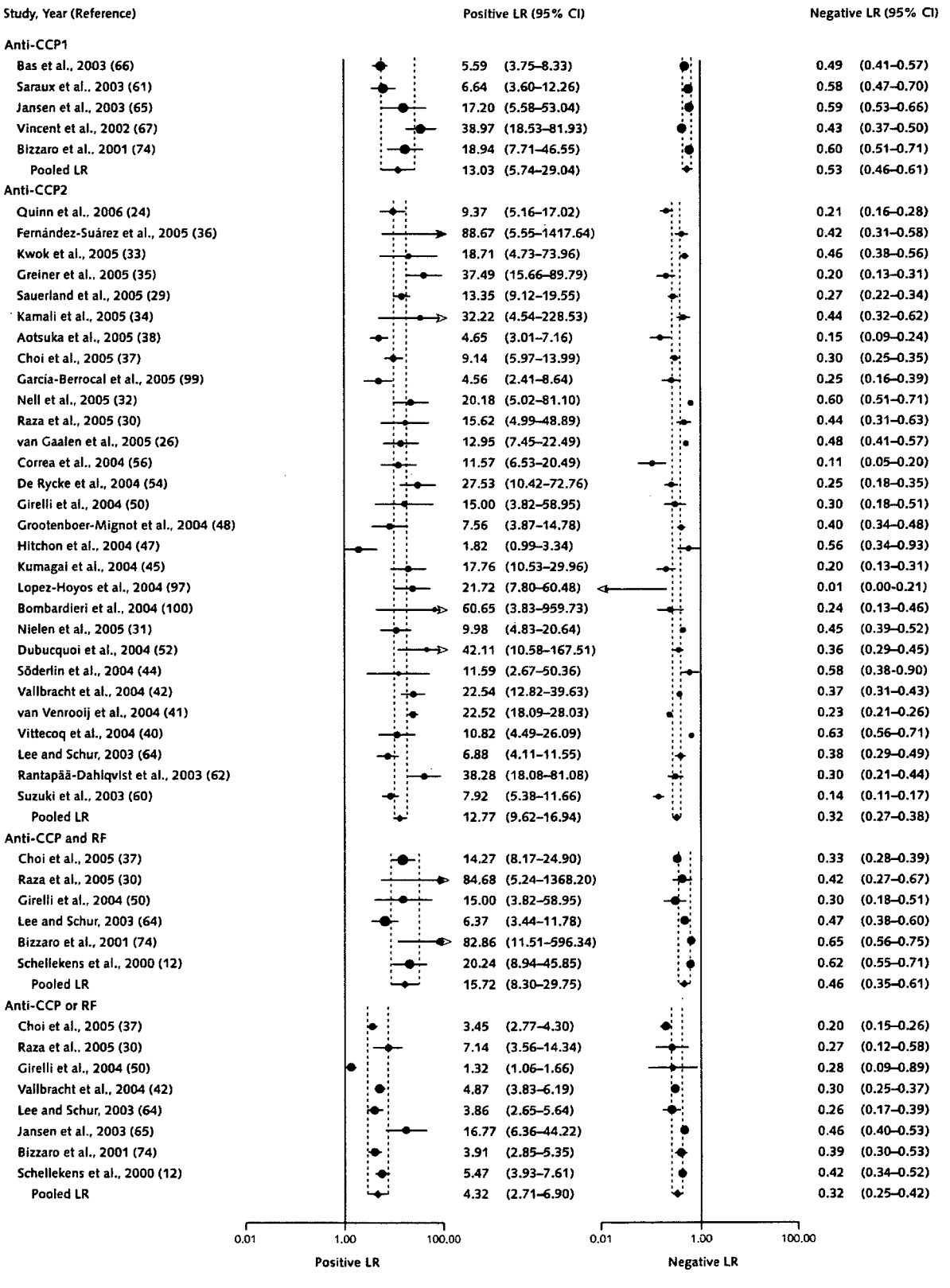
Our review has several limitations. We may have missed some pertinent studies, because we included only diagnostic studies that provided information on sensitivity

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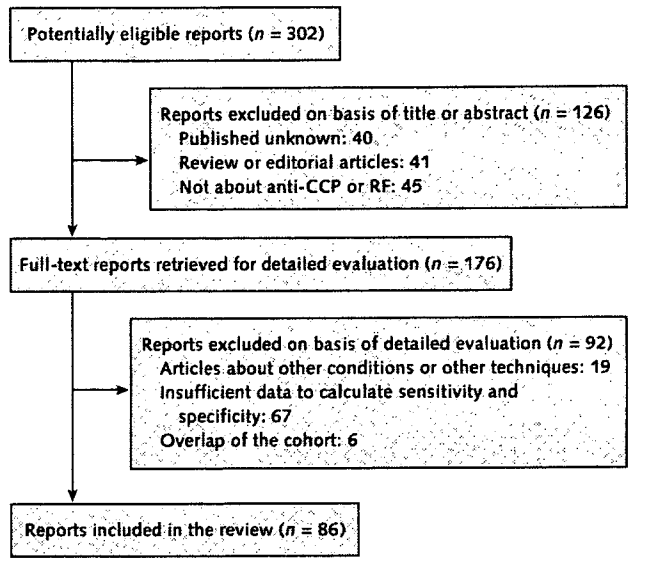
Appendix Figure. **Study flow diagram.** WEB-ON



CCP = cyclic citrullinated peptide; RF = rheumatoid factor.

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
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
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
Teaching hospital	CCP2	Euroimmun	ACR	Prospective	Not reported	NA	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 469)	171	26	60
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
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
Primary care	CCP2	Tosho	ACR	Not reported	Not reported	Not reported	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 251)	236	20	88
Teaching hospital	CCP2	Euro-Diagnostica	ACR	Retrospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	Other diseases (n = 49)	69	8	18
Cohort study	CCP2	Axis-Shield	ACR	Prospective	Not reported	<12 mo	Yes	No	NA	NA	0.125	UA (n = 98)	42	2	60
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
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
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
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
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
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
Teaching hospital	CCP2	Inter-medico	ACR	Prospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	UA (n = 23)	26	8	15
Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	Not reported	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 307)	64	14	15
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
Teaching hospital	CCP2	Axis-Shield	ACR	Prospective	Not reported	Not reported	Yes	Yes	58.8	NA	10	HCV infection (n = 10)	23	0	7
Rheumatology clinic	CCP2	Euro-Diagnostica	ACR	Prospective	Yes	1 y	Yes	Yes	56.1	0.686	0.4	UA (n = 121)	149	7	109
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
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
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
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
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
Teaching hospital	CCP1	Euro-Diagnostica	ACR	Cross-sectional	Not reported	Not reported	Yes	Yes	62	0.71	NA	Other rheumatic diseases (n = 160), spondylo-arthropathies (n = 79)	110	24	86
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

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
Rheumatology clinic	CCP1	Euro-Diagnostica	Clinical diagnosis	Prospective	Not reported	Not reported	Yes	Yes	57	69	NA	UA (n = 121)	110	3	148
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
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
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
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

CP = 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.
: 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).

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	2
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	5
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	1
Teaching hospital	Nephelometry	Dade Behring	20	ACR	Prospective	Not reported	NA	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 469)	161	89	
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	2
Rheumatology clinic	LA	Tulip Diagnostics	8	ACR	Not reported	Not reported	Not reported	Yes	No	NA	NA	NA	Healthy persons (n = 155)	482	2	8
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	
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	6
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	4
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	2
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	1
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	2
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	
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	2
Teaching hospital	Nephelometry	Intermedico	20	ACR	Prospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	UA (n = 23)	32	10	
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	
Teaching hospital	Nephelometry	Dade Behring	15	ACR	Prospective	Not reported	Not reported	Yes	Yes	58.8	NA	10	HCV infection (n = 10)	27	6	
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	5
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	1
Teaching hospital	Nephelometry	Beckman Instruments	20	ACR	Prospective	Yes	Not reported	Yes	Yes	50.75	62	NA	Other rheumatic diseases (n = 102)	57	9	3
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	9
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	11
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	5
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	2
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	2
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	5
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	16
Rheumatology clinic	Nephelometry	Dako Diagnostics	30	Clinical diagnosis	Prospective	Not reported	Not reported	Yes	yes	57	69	NA	UA (n = 121)	130	8	12
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	61	36	3

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
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
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
Rheumatology clinic	Nephelometry	Dade Behring	20	ACR	Retrospective	Not reported	Not reported	Yes		NA	NA	NA	Mixed	89	3	9
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
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
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
Teaching hospital	ELISA	In-house	Not reported	Clinical diagnosis	Retrospective	Not reported	<2 mo	Yes	Yes	48	67.3	12	Mixed	157	287	78
Teaching hospital	LA	Fumouze Diagnostics	100	ACR	Prospective	Yes	Not reported	Yes		NA	NA	NA	Not reported	80	50	39
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
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
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
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
Teaching hospital	ELISA	In-house	87	Not reported	Not reported	Not reported	Not reported	Yes		NA	NA	NA	OA (n = 56), healthy persons (n = 76)	60	8	20
Teaching hospital	ELISA	Dade MicroScan	Not reported	ACR	Prospective	Not reported	Same period	Yes		NA	70	NA	Other rheumatic diseases (n = 55)	18	3	31
Rheumatology clinic	LA	Polysciences	Not reported	Not reported	Not reported	Not reported	Not reported	Yes		NA	NA	NA	Not reported	113	19	29
Teaching hospital	ELISA	In-house	Not reported	Not reported	Not reported	Not reported	Not reported	Yes		NA	NA	NA	Not reported	163	10	28

LISA = 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
h 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 Sacr
ostics (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).

	cohort	study		other ACR criteria							
lish	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
lish	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
lish	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
lish	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

KA = 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.

	cohort study	study								
nglish	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
nglish	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
nglish	Rheumatology clinic		Larsen erosive scores at 3 y	<2	3	866/866	Followed UK guidelines for RA	NA	64	ACR
nglish	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
nglish	Population-based cohort study	Prospective cohort study	Larsen score	<1	2	333/379	DMARDs (66%), MTX (36%), sulfasalazine (51%)	55	65	ACR
nglish	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
nglish		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
nglish	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
nglish	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
nglish	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
nglish	Teaching hospital	Prospective cohort study	Sharp–van der Heijde score	<1	6	Not reported	Not reported	51.5	65.9	ACR
nglish	Teaching hospital	Prospective cohort study	Modified Sharp score	<1	3	Not reported	Not reported	NA	NA	ACR
nglish	Teaching hospital	Retrospective cohort study	Probability of predicting erosion (Larsen score ≥ grade 2)	3	1	175/175	Not reported	59	71	ACR
nglish	Teaching hospital	Prospective cohort study	Physician opinion	1.6	6 (median)	Not reported	Not reported	NA	NA	ACR

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Accuracy of Anti–Ribosomal P Protein Antibody Testing for the Diagnosis of Neuropsychiatric Systemic Lupus Erythematosus

An International Meta-Analysis

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Objective. **To quantitatively evaluate the diagnostic accuracy of antibodies to ribosomal P proteins (anti-P) for neuropsychiatric systemic lupus erythematosus (NPSLE) in general, for psychosis, mood disorder, or both, and for other diffuse manifestations.**

Methods. **This international meta-analysis combined standardized data from 1,537 lupus patients contributed by 14 research teams. Weighted estimation of sensitivity and specificity with fixed-effects and random-effects models, as well as summary receiver operating characteristic (SROC) curve analysis, was used to summarize test performance. The robustness of the overall estimates was examined in sensitivity analyses that included additional studies published up to November 1, 2004 in the Medline, EMBase, and Cochrane databases.**

Results. **Combining the data from the 14 teams, the weighted sensitivity and specificity estimates for the diagnosis of NPSLE were 26% (95% confidence interval [95% CI] 15–42%) and 80% (95% CI 74–85%), respectively. For psychosis, mood disorder, or both, the sensitivity and specificity were 27% (95% CI 14–47%) and 80% (95% CI 74–85%), respectively. For other diffuse manifestations, the sensitivity was 24% (95% CI 12–42%), and the specificity was 80% (95% CI 73–85%). The proportion of patients with anti-P antibodies did not vary markedly across different presentations of NPSLE. Between-study heterogeneity was substantial, but the SROC curves were consistent with the weighted estimates. In further analyses that included another 24**

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published studies, only the sensitivity for psychosis and/or mood disorder was slightly improved, but it was still suboptimal (42% [95% CI 30–53%]); the specificity remained essentially the same (81% [95% CI 76–85%]).

Conclusion. **Anti-P antibody testing has limited diagnostic value for NPSLE, and it is not helpful in differentiating among various disease phenotypes.**

Neuropsychiatric manifestations occur in approximately one-half of patients with systemic lupus erythematosus (SLE) and may cause substantial impairment of quality of life as well as disability (1–3). Moreover, multiple neuropsychiatric events during the disease course are associated with adverse long-term prognosis (4,5) and may lead to death, with a mortality rate of 7–19% (2,5,6). Neuropsychiatric SLE (NPSLE) encompasses a multitude of symptoms involving the central, peripheral, and autonomic nervous systems as well as psychiatric disorders (7). Recently, an ad hoc committee of the American College of Rheumatology (ACR) proposed a standard nomenclature for 19 neuropsychiatric syndromes associated with SLE (7), yet NPSLE is difficult to diagnose and is challenging to treat. Secondary factors, such as drugs, metabolic abnormalities, or infections, can also cause neuropsychiatric disturbances in lupus patients (3,7). Manifestations reflecting diffuse cerebral involvement pose the foremost difficulty in differentiating their exact origin, since psychiatric disorders may merely be reactive psychological disturbances (2,3,7).

During the last 2 decades, several studies have explored the utility of antibodies to ribosomal P proteins (anti-P) in detecting NPSLE (6,8–35). These antibodies are directed toward 3 large-subunit ribosomal phosphoproteins, called P0 (38 kd), P1 (19 kd), and P2 (17 kd), which share a common linear determinant in the carboxyl-terminal 22–amino acid sequence (36). Early studies claimed that serum anti-P antibodies were highly accurate for the diagnosis of SLE-mediated psychosis and depression (9,26), but subsequent reports were less optimistic (11–13,18,20,25,27,31). Other studies expanded the spectrum of neuropsychiatric features that could be correlated with anti-P to include active disease, diffuse manifestations, or NPSLE overall (6,25,28,30), making even more unclear their clinical value for this entity. Methodologic shortcomings, including the criteria used to define NPSLE, the approaches adopted for detecting anti-P antibodies, and the small sample size of isolated studies, may have contributed to the uncertainty.

Because SLE is a relatively uncommon disease and NPSLE is even more uncommon, no single study can reliably assess the operating characteristics of anti-P antibodies. Yet, a rigorous appraisal of a diagnostic test may reduce the number of unwanted clinical consequences related to misleading estimates of the accuracy of that test. Ideally, one would like to assess the diagnostic accuracy of a test across a large study population and use similar, standardized, and reproducible methods. In the absence of a single very large study that could do this, an attractive alternative is to standardize data across existing cohorts of lupus patients. Therefore, the aim of this study was to evaluate the diagnostic performance of anti-P antibodies for NPSLE in general, for diffuse NPSLE manifestations, and for particular psychiatric syndromes (psychosis, mood disorder, or both) in the context of an international collaborative meta-analysis, with standardization of the data contributed by a large number of investigators.

PATIENTS AND METHODS

Eligibility criteria. The meta-analysis included lupus patients with and without NPSLE who had undergone serum anti-P antibody testing by immunoblotting, a standard enzyme-linked immunosorbent assay (ELISA), or both (37–39).

To ensure consistency, participating investigators were asked to comply with the following rules. Patients had to fulfill the ACR criteria for the classification of SLE (40) and had to be evaluated for the presence or absence of neuropsychiatric lupus syndromes according to the ACR nomenclature and case definitions (7). Patients with a neuropsychiatric syndrome during any time in the course of SLE were classified into 3 subgroups: those with psychosis, mood disorders, or both; those with other diffuse (2,6) manifestations (including acute confusional state, generalized seizures, cognitive dysfunction, anxiety disorder, and headache other than migraine or cluster headache), and those with focal (2,6) neurologic events (including cerebrovascular disease, partial seizures, migraine or cluster headache, myelopathy, demyelinating syndrome, movement disorder, aseptic meningitis, and syndromes of the peripheral nervous system) (7). When both diffuse and focal events occurred in the same patient, the designation was made according to the predominant manifestation. Severe, sustained, or progressive presentations requiring more-aggressive

treatment with cytotoxic immunosuppressive agents were considered to be predominant.

Collaborating investigators provided a clear description of the immunoassay(s) used for anti-P determination, with sufficient detail to permit replication (41). When both immunoblotting and ELISA had been used, data were reported separately for each method. Patients who had undergone testing for anti-P multiple times were considered to have this autoantibody specificity if at least 1 of the determinations yielded positive results. Investigators were also asked to specify whether immunoassays were performed without knowledge of the clinical condition of the patients and whether the diagnosis of NPSLE, as well as the assignment of neuropsychiatric syndromes, was accomplished without knowledge of the anti-P status of the participants.

Organization of the international database. Research teams who have previously published data on cohorts of SLE patients were invited to participate in this meta-analysis, provided that the study patients met the eligibility criteria defined above. Collaborating teams were identified through searches of the Medline, EMBase, and Cochrane databases conducted in January 2003, using combinations of index terms (systemic lupus erythematosus, rheumatic diseases, connective tissue disease, or autoimmune disease, as well as ribosomal, antiribosomal, anti-P, or antineuronal), cited references of eligible studies and review articles, abstracts of major rheumatology conferences, and consultation with experts in the field. We e-mailed invitations to investigators working on SLE. The meta-analysis was also announced at an autoimmune disease–related scientific meeting (42). Pertinent data were contributed on a standard reporting form. The database remained open until July 2004.

Research teams from 14 centers (8 European, 4 Asian, and 2 South American) agreed to participate. We accepted data that were already available as well as data that were prospectively generated specifically by some of the participating teams for the purposes of the collaborative project. The effort was coordinated by the Clinical and Molecular Epidemiology Unit of the Department of Hygiene and Epidemiology at the University of Ioannina School of Medicine. The coordinating center was responsible for giving instructions to participating investigators on how to standardize and summarize their individual-level databases. The contributed data sets were assessed for potential errors or inconsistencies and then assembled at the coordinating center, which was also responsible for conducting the analyses. Queries were clarified through communications with the participating investigators.

Data synthesis and statistical analysis. Measures of diagnostic performance included sensitivity and specificity of anti-P antibodies for various forms of NPSLE. The main analysis involved the following 4 comparisons: NPSLE overall and each subgroup of NPSLE (psychosis and/or mood disorder, other diffuse manifestations, and focal events) versus the non-NPSLE group; all diffuse manifestations versus focal events; and psychosis and/or mood disorder versus other diffuse manifestations. These analyses address the discriminatory ability of the test for NPSLE in general, for each disease subtype, and for different neuropsychiatric presentations. To further pursue the possibility that anti-P may be specifically associated with particular psychiatric disorders (8,9,16,22,26), we evaluated the diagnostic accuracy of anti-P antibody for patients with psychosis and/or mood disorder versus all other lupus patients.

Test performance was estimated separately from studies that used immunoblotting for the detection of anti-P antibodies and from studies that used ELISA. In the overall analysis, when both immunoblotting and ELISA data were available from the same study, the results from the ELISA were used for the calculations. Diagnostic accuracy was also evaluated for subgroups defined by race.

Summary estimates were obtained with 2 meta-analytic methods: weighted independent estimation of sensitivity and specificity, and summary receiver operating characteristic (SROC) curve analysis.

Sensitivity and specificity estimates for each comparison were independently combined across studies, using both fixed-effects (Mantel-Haenszel) and random-effects (DerSimonian-Laird) models (43,44). Fixed-effects models weigh each study by the inverse of its variance. Random-effects models also incorporate between-study variation. The random-effects approach tends to provide wider confidence intervals (CIs) and is preferable in the presence of between-study heterogeneity. Except where indicated otherwise, random-effects estimates are provided below. Between-study heterogeneity was examined with Fisher's exact test.

Because sensitivity and specificity are interdependent, independent weighting may sometimes underestimate both measures. Hence, we used SROC curve analysis to account for this mutual dependence (45,46). The method fits a curve describing the tradeoff between sensitivity and specificity across studies, with different characteristics and thresholds for an abnormal test result. The regression is calculated as follows: $D = \alpha + \beta S$, where D is the difference in the logits of the true-positive rate (sensitivity) and the false-positive rate (1 – specificity), and S is the sum of these logits. When β is not significantly different from 0, the SROC curve is symmetric around the diagonal that runs from the top left corner to the bottom right corner of the diagram. Conversely, when β is significantly different from 0, the SROC curve is not symmetric, and the overall diagnostic performance varies in different parts of the curve, with an uneven tradeoff between sensitivity and specificity across studies. This may indicate significant between-study variation in the selected test threshold, study population, or other parameters. SROC curves should not be extrapolated outside the range of observed values. Both nonweighted and weighted SROC curves were estimated (46,47); nonweighted curves consider all studies equally in the calculations, whereas weighted curves weigh each study by the variance of D.

Inclusion of other published data. Sensitivity analyses were conducted to examine whether the addition of further relevant published studies affected our summary estimates of the operating characteristics of anti-P antibodies. Only the following 2 comparisons were examined, since articles focused on these patient groups: the entire group of NPSLE

patients versus the non-NPSLE patient group, and patients with psychosis and/or mood disorder versus either the non-NPSLE patients or all other lupus patients. Finally, we evaluated the available data to compare active NPSLE versus non-NPSLE.

Eligible studies published in any language were retrieved during the stage of identification of pertinent articles and collaborating investigators, as described above. We updated the literature search of the 3 computerized databases in November 2004 to identify additional relevant studies published up to November 1, 2004. Meeting abstracts were not included because the results may not be final and may not have been subjected to formal peer review. Duplicate or overlapping data were counted only once. The inclusion criteria were similar to those of the collaborative meta-analysis, with no restriction on patient age or study location. Nevertheless, in these analyses, we did not use the stringent criteria regarding the method of antibody determination and classification of neuropsychiatric disease; studies were combined regardless of the assay used to detect anti-P antibodies and regardless of the criteria used to diagnose NPSLE.

Other sensitivity analyses. We also performed sensitivity analyses to assess the robustness of the quantitative estimates derived from the collaborative meta-analysis. These analyses were limited to studies that used the ACR criteria for NPSLE syndromes and limited to studies that specified blinding.

Software. Analyses were conducted with the use of the following software: SPSS, version 12.0 (SPSS, Chicago, IL), Meta-Test, version 0.6, New England Medical Center, Boston, MA, 1997 (Joseph Lau, Tufts–New England Medical Center, Boston, MA) and Meta-Analyst, version 0.991 (Joseph Lau, Boston, MA).

RESULTS

General characteristics. We sent inquiries to 104 investigators working on SLE. Of those 104 investigators, 65 did not reply, 18 did not have any data and could not produce such data for the project, and 4 declined to participate. Of the last group, 2 investigators had published studies that were included in the sensitivity analysis.

The collaborative meta-analysis considered 1,537 lupus patients from 14 teams of investigators. Of these, 1,295 patients underwent both anti-P antibody testing by immunoblotting or standard ELISA and evaluation for NPSLE according to the ACR case definitions. The median sample size per study was 91 patients (interquartile range [IQR] 48–162). Women accounted for 80–97% of each study population. Although more than one-half of the participants were of European descent, patients of other ancestries were also included (Table 1). The mean age of the patients at study entry ranged from 29.8 years to 41.6 years, and the median of the mean disease durations across study cohorts was 7.3 years (IQR 6.2–7.8).

Most studies used a solid-phase ELISA, with highly purified synthetic peptides of the carboxyl-terminal 22–amino acid sequence (n = 4), a multiple-antigen peptide format (n = 3), and purified native (n = 2) or recombinant (n = 3) proteins as coating antigen to detect anti-P antibodies. Seven studies designated a positive anti-P result as >2 SD (n = 1) or >3 SD (n = 6) above the mean value obtained in a normal population, whereas 5 studies reported results according to the suggested threshold for the commercial ELISA systems they used. Only 4 studies used Western blotting on cell extracts from various sources for the detection of this autoantibody specificity. A single study used a line immunoassay, which is an ELISA-based multianalyte assay (Table 1).

The median prevalence of anti-P antibodies was 18.2% (IQR 9.7–28.6%). These antibodies were more prevalent in lupus patients of Asian descent than among those of other racial ancestries. The study-specific frequencies of anti-P antibodies were 23.8–45.5% in 320 patients of Chinese, Japanese, Taiwanese, and Filipino ancestry and 6.4–25.4% in 1,212 patients of other ancestry.

Approximately one-third of the 1,537 lupus patients had NPSLE that manifested as syndromes described in the ACR case definitions (median prevalence 32% [IQR 12–42%]). In 1 study (Table 1), neuropsychiatric involvement was determined according to prespecified criteria other than the ACR case definitions. Eight research teams provided individual patient data; in these studies, 8% of patients had >1 neuropsychiatric disorder, but only 5% had both focal and diffuse presentations. The other 6 teams directly collected data on only the most prominent manifestation. More than one-half of the NPSLE patients presented with disorders reflecting diffuse cerebral involvement (median prevalence 54.5% [IQR 47.6–68.2%]). The median prevalence of psychosis, mood disorder, or both was 24.9% (IQR 17.1–38.4%). In most studies, NPSLE was diagnosed without knowledge of the anti-P antibody status, and test interpreters were blinded to the clinical condition of the patients (Table 1).

Diagnostic performance of anti-P antibody testing. Substantial heterogeneity was found in both the sensitivity and the specificity of anti-P antibody testing

Table 1. Characteristics of the studies and patient populations included in the collaborative meta-analysis*

Study ID	Investigator, country, year (ref.)	Study setting	No. of patients	% women	Ethnicity (%)†	Mean age, years	Mean disease duration, years	Anti-P antibody assay	Prevalence of NPSLE, %	NPSLE manifestation			Blinding‡
										Psychosis and/or mood disorder	Other diffuse manifestations	Focal events	
1	Doria A, Italy, 2004	University	101	88	Italian (98), African (2)	29.8	6.7	WB/ELISA	21	8	6	7	T, C
2	Morozzi G, Galeazzi M, Italy, 2004	University	20§	90	Italian (85), Chinese/Filipino (15)	35.7	7.6	ELISA	15	0	0	3	T, C
3	Afeltra A, Italy, 2004	University	43	88	Italian	41.6	8	ELISA	93	2	16	22	T, C
4	Mathieu A, Italy; Sanna G, UK, 2000 (24)	University	68¶	96	Italian	38.4	7.7	ELISA	49	7	9	17	T, C
5	Hoffman I, De Keyser F, Belgium, 2004 (14)	University	235#	88	Belgian, Dutch, Slovak, English	40	7.2	LIA	59	33	32	51	NS
6	Tzioufas A, Greece, 2000 (30)	University	185	96	Greek	34.7	4.3	ELISA	9	2	7	8	NS
7	Ambrozic A, Slovenia, 2003	University	150	91	Slovenian	38.1	7.8	WB	39	11	14	33	T, C
8	Inanc M, Turkey, 2004	University	218	89	Turkish	38.5	7.8	ELISA	23	20	5	26	T, C
9	Chang D-M, Taiwan, 2003	Community	80	91	Taiwanese	35	9.4	ELISA	6	1	3	1	NS
10	Mok CC, China, 2004	Community	33	97	Chinese	36.2	7	WB/ELISA	33	3	5	3	T, C
11	Hirohata S, Japan, 2003	University	50	80	Japanese	40.8	2.6	ELISA	32	5	7	4	T, C
12	Yoshio T, Japan, 2003 (35)	University	154**	90	Japanese	34.6	4.7	ELISA	40	14	24	24	T, C
13	Massardo L, Chile, 2002 (21)	University	141††	90	Chilean	33	7	WB/ELISA	9	5	1	6	T, C
14	Spindler AJ, Argentina, 2003	University	59	92	Argentinean	36	7.3	ELISA	44	11	4	11	T, C

* References and publication dates (when the contributed data were derived from published studies) are provided; otherwise, the year the data were collected and sent to the coordinating center are shown. See Patients and Methods for a full description of the 3 subgroups of neuropsychiatric systemic lupus erythematosus (NPSLE). Anti-P = anti–ribosomal P; WB = Western blotting; ELISA = enzyme-linked immunosorbent assay; LIA = line immunoassay.

† Percentages are given for studies that included patients of different ethnicities, when known.

‡ NPSLE was diagnosed without knowledge of the results of the anti-P antibody testing (T), and test interpreters were blinded to the clincial data (C). NS = not specified.

§ In this study, 3 patients had indeterminate results for anti-P antibodies and were not included in the quantitative synthesis.

¶ In this study, 5 patients who were not tested for anti-P antibodies were not included in the quantitative synthesis.

In this study, sufficient clinical information for NPSLE was available for 196 patients; the presence or absence of NPSLE was assessed using prespecified criteria other than the American College of Rheumatology case definitions (7); and data for disease duration were available for 197 patients.

** Only 44 patients were included in the published study.

†† In this study, 2 patients in addition to the ones listed under NPSLE manifestations had NPSLE, but the type of involvement was not known.

Table 2. Summary results of the collaborative meta-analysis*

Comparison	No. of studies	No. of subjects	Weighted sensitivity (95% CI)	Weighted specificity (95% CI)
NPSLE versus non-NPSLE	13	1,340	0.26 (0.15–0.42)	0.80 (0.74–0.85)
Psychosis and/or mood disorder versus non-NPSLE	12	1,024	0.27 (0.14–0.47)	0.80 (0.74–0.85)
Other diffuse neuropsychiatric manifestations versus non-NPSLE	12	1,034	0.24 (0.12–0.42)	0.80 (0.73–0.85)
Focal neurologic events versus non-NPSLE	13	1,110	0.29 (0.15–0.48)	0.80 (0.74–0.85)
All diffuse neuropsychiatric manifestations versus focal neurologic events	12	406	0.26 (0.14–0.43)	0.70 (0.50–0.84)
Psychosis and/or mood disorder versus other diffuse neuropsychiatric manifestations	12	228	0.28 (0.15–0.46)	0.75 (0.57–0.88)
Patients with psychosis and/or mood disorder versus all other lupus patients	12	1,322	0.27 (0.14–0.47)	0.80 (0.72–0.86)

* Weighted sensitivity and specificity were determined according to the random-effects model. Between-study heterogeneity was statistically significant for all comparisons ($P < 0.01$). 95% CI = 95% confidence interval; NPSLE = neuropsychiatric systemic lupus erythematosus.

using ELISA (Table 2). In the random-effects model, the overall weighted sensitivity and specificity estimates for the diagnosis of NPSLE were 26% (95% CI 15–42%) and 80% (95% CI 74–85%), respectively (Table 2).

Diagnostic performance for neuropsychiatric disease appeared to be somewhat better in studies that used Western blotting to detect anti-P antibodies (summary sensitivity 36% [95% CI 16–63%]; summary specificity 84% [95% CI 70–92%]), but significant between-study heterogeneity was still present ($P = 0.0001$ for heterogeneity in sensitivity estimates and $P = 0.0007$ for heterogeneity in specificity estimates), and data were too limited to be conclusive (4 studies; 424 patients). Test performance was poor for NPSLE in Asian patients (4 studies; 317 patients, yielding a summary sensitivity of 55% [95% CI 45–65%] and a summary specificity of 68% [95% CI 59–76%]). The weighted specificity tended to be higher in all other lupus patients, which were mostly of European descent, but there was low sensitivity (9 studies; 1,023 patients, yielding a summary sensitivity of 17% [95% CI 9–32%] and a summary specificity of 85% [95% CI 81–88%]).

SROC analyses suggested similar performance for identifying SLE-induced neuropsychiatric disease. Weighted and nonweighted curves were practically coincident (Figure 1A). Anti-P antibodies had an almost equally meager discriminating ability for the diagnosis of either psychiatric syndromes or other forms of neuropsychiatric involvement in SLE (Table 2). Weighted random-effects independent estimates stand very close to the weighted SROC curves for these comparisons (Figures 1B–D), suggesting that they are appropriate approximations of the overall diagnostic performance. Statistically significant asymmetry was found in all these curves (Figure 1), indicating that an improvement in specificity was accompanied by a disproportionately large decrease in sensitivity.

Within the group with NPSLE (Table 2), anti-P antibody testing could not accurately discriminate patients presenting with diffuse manifestations from those presenting with focal events (summary sensitivity 26%; summary specificity 70%) (Figure 2A) or patients presenting with psychiatric disorders from those presenting with any other diffuse symptom (summary sensitivity 28%; summary specificity 75%) (Figure 2B). Test characteristics remained unchanged for the identification of patients with psychiatric disorders compared with all other lupus patients (with or without neuropsychiatric dysfunction) (Table 2). Significant asymmetry was found in the corresponding SROC curve (Figure 2C), implying that an improvement in specificity was accompanied by an uneven, large decrease in sensitivity.

Findings of additional analyses. Our search of the 3 databases identified a total of 306 potentially relevant articles, of which 243 studies were excluded upon reading the titles and abstracts. Another 39 studies were excluded after reviewing the complete reports: 8 were editorials, comments without original data, or review articles, 11 were case reports, 7 studies presented duplicate or overlapping data, 8 evaluated anti-P antibody testing for other SLE manifestations or other autoimmune diseases, 3 focused on isolated neuropsy-