

Clinical Utility of Common Serum Rheumatologic Tests

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Serum rheumatologic tests are generally most useful for confirming a clinically suspected diagnosis. Testing for rheumatoid factor is appropriate when rheumatoid arthritis, Sjögren's syndrome or cryoglobulinemia is suspected. Antinuclear antibody testing is highly sensitive for systemic lupus erythematosus and drug-induced lupus. Anti-double-stranded DNA antibodies correlate with lupus nephritis; the titer often corresponds with disease activity in systemic lupus erythematosus. Testing for anti-Ro (anti-SS-A) or anti-La (anti-SS-B) may help confirm the diagnosis of Sjögren's syndrome or systemic lupus erythematosus; these antibodies are associated with the extraglandular manifestations of Sjögren's syndrome. Cytoplasmic antineutrophil cytoplasmic antibody testing is highly sensitive and specific for Wegener's granulomatosis. Human leukocyte antigen-B27 is frequently present in ankylosing spondylitis and Reiter's syndrome, but the background presence of this antibody in white populations limits the value of testing. An elevated erythrocyte sedimentation rate (ESR) is a diagnostic criterion for polymyalgia rheumatica and temporal arteritis; however, specificity is quite low. ESR values tend to correlate with disease activity in rheumatoid arthritis and may be useful for monitoring therapeutic response. (*Am Fam Physician* 2002;65:1073-80. Copyright© 2002 American Academy of Family Physicians.)

Many serum rheumatologic tests have been available for fewer than 10 years. As a result, some physicians are not fully aware of the indications, sensitivity, specificity, cost and clinical utility of these tests. Several studies have suggested that overuse of common serum rheumatologic tests, including antinuclear antibody (ANA) and rheumatoid factor (RF) measurements, leads to unnecessary referrals and further laboratory work-ups.^{1,2} Failure to use these tests in a knowledgeable and thoughtful manner can result in diagnostic confusion and increased costs.

Definition of Terms

The essential attributes of a test are its sensitivity, specificity, and positive and negative predictive values. Sensitivity refers to the proportion of patients with a disease who have a positive test result. Specificity refers to the proportion of patients without the disease who have a negative test result.

Predictive value refers to the likelihood of disease or nondisease based on a positive or

negative test result. A positive result on a test with a high positive predictive value indicates that the patient probably has the disease in question. Similarly, a test with a high negative predictive value indicates that the patient with a negative test result most likely does not have the disease in question.

Sensitivity and specificity are independent of disease prevalence, whereas predictive value is markedly affected by disease prevalence. For example, the predictive value of a positive rheumatologic test in patients with polyarthralgia is likely to be higher in a rheumatology practice than in a family physician's office. This fact emphasizes the importance of limiting testing to patients with a reasonable pretest possibility of disease. As the pretest probability increases, so does the clinical utility of a given test.

Rheumatoid Factor

The RF detected by standard laboratory testing is an IgM antibody directed against the Fc (crystallizable fragment) portion of IgG. Laboratory tests are capable of detecting other classes of rheumatoid factors (e.g., IgG and

Rheumatoid factor is present in approximately 80 percent of patients with rheumatoid arthritis.

IgA); however, these tests are not widely used clinically.

A number of rheumatic and nonrheumatic conditions are associated with positive RF tests (Table 1).³ RF is present in approximately 80 percent of patients with rheumatoid arthritis.³ RF testing is also commonly positive in patients with Sjögren's syndrome or cryoglobulinemia. Nonrheumatic conditions frequently associated with the presence of RF include bacterial endocarditis, tuberculosis, sarcoidosis and malignancies. The prevalence of RF in healthy elderly patients may be as high as 10 percent, although the titer is usually low (1:40 or lower).³

TABLE 1
Conditions Associated with a Positive Rheumatoid Factor Test

Rheumatic conditions (prevalence)

Rheumatoid arthritis (50 to 90%)
Systemic lupus erythematosus (15 to 35%)
Sjögren's syndrome (75 to 95%)
Systemic sclerosis (20 to 30%)
Cryoglobulinemia (40 to 100%)
Mixed connective tissue disease (50 to 60%)

Nonrheumatic conditions

Aging
Infection: bacterial endocarditis, liver disease, tuberculosis, syphilis, viral infections (especially mumps, rubella and influenza), parasitic diseases
Pulmonary disease: sarcoidosis, interstitial pulmonary fibrosis, silicosis, asbestosis
Miscellaneous diseases: primary biliary cirrhosis, malignancy (especially leukemia and colon cancer)

Adapted with permission from Shmerling RH, Delbanco TL. The rheumatoid factor: an analysis of clinical utility. Am J Med 1991;91:528-34.

RF testing may be appropriate in patients suspected of having rheumatoid arthritis.⁴ The test is most useful when there is a moderate level of suspicion for rheumatoid arthritis.³ If clinical suspicion is low (i.e., absence of joint inflammation), RF testing is unlikely to be helpful because of the high incidence of false-positive results in the general population. Even when clinical suspicion is high, 20 percent of patients with rheumatoid arthritis are seronegative.³ Furthermore, up to 40 percent of patients with rheumatoid arthritis may be seronegative early in the course of the disease.³ RF testing in these circumstances may influence the physician away from the true diagnosis.

In patients with rheumatoid arthritis, the RF titer generally correlates with extra-articular manifestations and disease severity. RF testing may have prognostic value in these patients. However, RF titers are not helpful in following disease progression. Once a patient has a positive RF result, repeating the test is of no value.

The specificity of RF for rheumatoid arthritis ranges from 80 to 95 percent, depending on the age and health of the population studied.^{5,6} The sensitivity of RF ranges from approximately 10 percent in patients with polymyositis to more than 90 percent in those with Sjögren's syndrome or cryoglobulinemia.⁵

RF testing is a useful screening tool when Sjögren's syndrome or cryoglobulinemia is suspected. Serial RF measurements can be helpful in patients with Sjögren's syndrome because the disappearance of RF may herald the onset of lymphoma.⁷

Antinuclear Antibody

Antinuclear antibody (ANA) testing involves the use of indirect immunofluorescence to detect antibodies that bind to various nuclear antigens. Most laboratories employ a HEp-2 cell line (a line of human epithelial cells) as the substrate for this test. The sensitivity of ANA tests can differ when other animal-based substrates are used.

ANAs are reported as titers, and higher

values (greater than 1:320) are more likely to represent true-positive results. Although titers of 1:20 or 1:40 are commonly reported as positive, patients with rheumatologic syndromes rarely have such low titers.⁸

ANA tests are frequently positive in patients with connective tissue diseases (Table 2).⁸ In systemic lupus erythematosus and drug-induced lupus, the sensitivity of ANA testing approaches 100 percent; the specificity for systemic lupus erythematosus is approximately 90 percent.⁸

ANA tests can be false-positive in many conditions, including rheumatoid arthritis, subacute bacterial endocarditis, human immunodeficiency virus infection, liver disease, malignancy, type 1 diabetes, pulmonary fibrosis and multiple sclerosis. False-positive tests also occur in patients with silicone gel implants, pregnant women and the elderly.⁹

When an ANA test is positive, the nuclear staining pattern is frequently reported. This pattern reflects the intracellular target of

In systemic lupus erythematosus and drug-induced lupus, the sensitivity of antinuclear antibody testing approaches 100 percent; the specificity for systemic lupus erythematosus is approximately 90 percent.

ANA. The most commonly described nuclear staining patterns are homogeneous and rim (both specific for systemic lupus erythematosus), speckled (associated with Sjögren's syndrome and mixed connective tissue disease), diffuse (nonspecific), nucleolar (associated with diffuse scleroderma) and anti-centromere (highly specific for CREST syndrome [calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias]). With more specific autoantibody tests now available, nuclear staining patterns are clinically less useful.

ANA testing is done primarily when systemic lupus erythematosus or drug-induced lupus is suspected. In patient populations with a low prevalence of systemic lupus erythematosus (i.e., the elderly), ANA testing is unlikely to be useful because of its low positive predictive value. ANA titers correlate poorly with disease activity; hence, serial measurements are not recommended.

Despite high sensitivity, a negative ANA test does not rule out systemic lupus erythematosus. Rarely, patients with isolated anti-Ro (anti-SS-A) antibodies or anti-single-stranded DNA (anti-ssDNA) have a negative ANA test. Also, patients with the systemic lupus erythematosus-like antiphospholipid syndrome may be ANA negative. Conversely, ANA results are positive in 5 percent of tested women and older patients. In these patients, the ANA titer is generally less than 1:320.⁸

Chromatin-Associated Antibodies

ANTI-DOUBLE-STRANDED DNA

High titers of anti-double-stranded DNA (anti-dsDNA) antibodies are highly specific for systemic lupus erythematosus. However,

TABLE 2
Conditions Associated with a Positive Antinuclear Antibody Test

Condition	Sensitivity (%)*
Drug-induced lupus	100
Systemic lupus erythematosus	99
Scleroderma	97
Sjögren's syndrome	96
Mixed connective tissue disease	93
Polymyositis and dermatomyositis	78
Rheumatoid arthritis	40
Systemic vasculitis	15
Healthy old age	5

*—Percentage of patients with a positive test.

Adapted with permission from Peng SL, Hardin JA, Craft J. Antinuclear antibodies. In: Kelley WN, et al, eds. *Textbook of rheumatology*. 5th ed. Philadelphia: Saunders, 1997:250-66.

only about 60 percent of patients with the disease have high anti-dsDNA titers.¹⁰ Hence, absence of anti-dsDNA should not be used to exclude the diagnosis of systemic lupus erythematosus.

Low titers of anti-dsDNA can be present in normal persons and in patients with Sjögren's syndrome, rheumatoid arthritis and other disorders. The presence of anti-dsDNA tends to correlate with lupus nephritis, and the anti-dsDNA level often correlates with disease activity in systemic lupus erythematosus.¹⁰

Testing for anti-dsDNA may be useful in patients with a positive ANA test and clinical suspicion (i.e., skin and/or joint involvement) for systemic lupus erythematosus. Testing is not recommended in patients with a negative ANA test.

Anti-ssDNA antibodies are nonspecific and have little clinical utility.

ANTI-HISTONE

Anti-histone antibodies are sensitive but nonspecific for drug-induced lupus. Because these antibodies may also be present in patients with systemic lupus erythematosus, testing has limited diagnostic utility. However, anti-histone antibody testing may be useful in patients with a positive ANA test and a history

of exposure to medications associated with drug-induced lupus, such as procainamide (Pronestyl) and isoniazid (INH).

Ribonucleoproteins

ANTI-SMALL NUCLEAR RIBONUCLEOPROTEINS

Several autoantibodies against small nuclear ribonucleoproteins (anti-snRNPs) have been described. Anti-Sm (anti-Smith) antibodies are specific for systemic lupus erythematosus, although they are detected in only 20 to 30 percent of such patients.¹¹

Anti-U1 snRNP is present in 30 to 40 percent of patients with systemic lupus erythematosus and is associated with disease activity, myositis, esophageal hypomotility, sclerodactyly, Raynaud's phenomenon, arthralgias and arthritis.¹¹ In addition, mixed connective tissue disease is frequently defined by the presence of anti-U1 snRNP in patients with features of multiple overlapping autoimmune diseases.¹² Testing for anti-U1 snRNP should be limited to patients with a positive ANA test who are suspected of having systemic lupus erythematosus or mixed connective tissue disease.

ANTI-RO AND ANTI-LA

Anti-Ro and anti-La (anti-SS-B) are commonly identified in patients with Sjögren's syndrome, and their presence is associated with extraglandular manifestations of the disease. Anti-Ro activity is also found in approximately 40 percent of patients with systemic lupus erythematosus and is associated with photosensitive skin rash, pulmonary disease and lymphopenia.¹³ Anti-La activity is detected in 10 to 15 percent of patients with systemic lupus erythematosus and is associated with late-onset disease, secondary Sjögren's syndrome and neonatal lupus syndrome.¹⁴

Anti-Ro and anti-La testing may help to confirm the diagnosis of Sjögren's syndrome. These tests may also be useful in patients with a positive ANA test and suspected systemic lupus erythematosus.

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ANTI-RIBOSOME

Anti-ribosome antibody is highly specific for systemic lupus erythematosus, although it is present in only 10 to 20 percent of patients with the disease.¹⁵ The antibody is also associated with lupus psychosis. Testing, however, is rarely useful in diagnosing central-nervous-system systemic lupus erythematosus.

Scleroderma Antibodies**ANTI-CENTROMERE**

Anti-centromere antibodies are found in 22 to 36 percent of patients with scleroderma.¹¹ Their presence is correlated with Raynaud's phenomenon, CREST syndrome and limited skin involvement.⁸ Anti-centromere antibodies are also present in some patients with primary biliary cirrhosis. Testing may be helpful when scleroderma is suspected.

ANTI-TOPOISOMERASE I

Anti-topoisomerase I (or anti-Scl-70) is highly specific and is found in 22 to 40 percent of patients with scleroderma.⁸ Its presence is correlated with diffuse cutaneous disease, pulmonary fibrosis, cardiac involvement and longer disease duration.⁸ Testing for anti-topoisomerase I may be useful in patients with suspected scleroderma.

Other Antibody Tests**ANTI-JO1**

Anti-Jo1 (histidyl-tRNA synthetase) antibody is found in 30 percent of patients with polymyositis or dermatomyositis.¹¹ It is associated with pulmonary fibrosis and Raynaud's phenomenon.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

Antineutrophil cytoplasmic antibodies (ANCA) are directed against a number of antigens located in the cytoplasm of neutrophils. ANCA testing currently distinguishes between cytoplasmic ANCA (cANCA) and perinuclear ANCA (pANCA).

A positive cANCA test result indicates the presence of antibodies to the enzyme proteinase 3. The cANCA test has high specificity and sensitivity for the detection of Wegener's granulomatosis.¹⁶ However, the test has limited clinical utility in primary care settings, where the prevalence of this condition is quite low. Testing for cANCA should be limited to patients in whom Wegener's granulomatosis is strongly suspected.

The pANCA test targets myeloperoxidase, an antigen frequently associated with microscopic polyangiitis and necrotizing glomerulonephritis.¹⁶ However, the sensitivity of pANCA for these diseases is quite low. Although pANCA has been identified in several rheumatic autoimmune diseases, the sensitivity and specificity are quite low.

Human Leukocyte Antigen B27

The human leukocyte antigen-B27 (HLA-B27) allele is associated with spondyloarthropathies, especially ankylosing spondylitis. HLA-B27 has a sensitivity of approximately 95 percent for ankylosing spondylitis, 80 percent for Reiter's syndrome, 70 percent for spondylitis with psoriasis, and 50 percent for spondylitis associated with inflammatory bowel disease.⁵ However, the usefulness of HLA-B27 is limited by its background prevalence in approximately 6 to 10 percent of white populations.⁵ Testing is rarely useful and is only recommended when spondylitis is strongly suspected.

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate (ESR) is a measurement of the height of the layer of red blood cells that settle in a tube of anticoagulated blood in a specific unit of time, most commonly one hour.¹⁷ The upper limit of normal for persons 50 years of age and younger is 15 mm per hour in men and 20 mm per hour in women. Over the age of 50, the upper limit of normal for the ESR is 20 mm per hour in men and 30 mm per hour in women.¹⁸ Factors that

In rheumatoid arthritis, the erythrocyte sedimentation rate tends to correlate with clinical disease activity, although joint examination is far more useful in assessing synovitis.

may increase or decrease ESR values are summarized in *Table 3*.¹⁹

The ESR is a diagnostic criterion in polymyalgia rheumatica and temporal arteritis.²⁰ An elevated ESR value has a sensitivity of approximately 80 percent for polymyalgia rheumatica and greater than 95 percent for temporal arteritis.^{21,22}

The ESR is a means for staging rheumatoid arthritis, rather than a major diagnostic criterion. The ESR value tends to correlate with clinical disease activity and to parallel such symptoms as morning stiffness and fatigue, although joint examination is far more useful in assessing synovitis.²¹ The sensitivity of an elevated ESR value is approximately 50 percent in patients with signs of rheumatoid arthritis.²³ However, the specificity of an elevated ESR is quite low, limiting its use as a diagnostic test.

Final Comment

Selective ordering can improve the clinical usefulness and cost-effectiveness of serum rheumatologic tests (*Table 4*).¹¹ These tests should be ordered and interpreted cautiously—and only within the context of the patient's clinical situation. The practice of ordering a rheumatologic panel or an arthritis panel is discouraged. Such panels often include tests that have little or no sensitivity for the suspected condition. Physicians are often perplexed about how to interpret abnormal results within the panels.

In general, rheumatologic tests are most helpful in confirming a clinical diagnosis. Several tests are also useful for prognostic purposes. As with all tests, physicians need to be familiar with the predictive value and implications of a positive result.

In addition to the serum immunologic tests

TABLE 3

Factors That May Influence the Erythrocyte Sedimentation Rate*

Increase in erythrocyte sedimentation rate

Old age
Female gender
Pregnancy
Anemia
Macrocytosis
Technical factors: dilutional problem, increased specimen temperature, tilted tube
Elevated fibrinogen level: infection, inflammation, malignancy

Decrease in erythrocyte sedimentation rate

Extreme leukocytosis
Polycythemia
Sickle cell disease
Anisocytosis
Spherocytosis
Acanthocytosis
Microcytosis
Technical factors: dilutional problem, inadequate mixing, clotting of blood sample, short tube, vibration during testing
Protein abnormalities: hypofibrinogenemia, hypogammaglobulinemia, dysproteinemia with hyperviscosity state

*—Factors with no clinically significant effect or a questionable effect include obesity, body temperature, recent meal and use of aspirin or other non-steroidal anti-inflammatory drugs.

Adapted from Brigden ML. Clinical utility of the erythrocyte sedimentation rate. Am Fam Physician 1999;60:1443-50.

reviewed in this article, more routine tests, including urinalysis and synovial fluid analysis, are often useful in the diagnosis of rheumatologic disease. These tests should be performed when clinically appropriate.

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TABLE 4
Autoantibodies Detected in Patients with Connective Tissue Diseases

<i>Autoantibody</i>	<i>Disease (frequency of autoantibody)</i>	<i>Cost (\$)*</i>	<i>Comments</i>
RF	Rheumatoid arthritis (80%), other connective tissue diseases (see Table 1)	15	Sensitive but not specific for rheumatoid arthritis; correlates with prognosis of disease severity (not disease activity)
ANA	Systemic lupus erythematosus (99%), drug-induced lupus (100%), other connective tissue diseases (see Table 2)	30	Sensitive but not specific for connective tissue diseases; correlates poorly with disease activity
Anti-dsDNA	Systemic lupus erythematosus (60%)	30	Specific but not sensitive for systemic lupus erythematosus; correlates with lupus nephritis and disease activity
Anti-ssDNA	Infrequent	200†	Nonspecific and of little clinical utility
Anti-histone	Drug-induced lupus (90%), systemic lupus erythematosus (50%)		Sensitive but not specific for drug-induced lupus
Anti-Smith	Systemic lupus erythematosus (20 to 30%)		Specific but not sensitive for systemic lupus erythematosus
Anti-U1 snRNP	Systemic lupus erythematosus (30 to 40%), mixed connective tissue disease (100%)		Associated with disease activity in systemic lupus erythematosus
Anti-Ro (anti-SS-A)	Sjögren's syndrome (75%), systemic lupus erythematosus (40%)		Associated with photosensitive skin rash, pulmonary disease and lymphopenia in systemic lupus erythematosus
Anti-La (anti-SS-B)	Sjögren's syndrome (40%), systemic lupus erythematosus (10 to 15%)		Associated with late-onset systemic lupus erythematosus, secondary Sjögren's syndrome and neonatal lupus syndrome
Anti-ribosome	Systemic lupus erythematosus (10 to 20%)	30	Highly specific but not sensitive for systemic lupus erythematosus; associated with lupus psychosis
Anti-centromere	Scleroderma (22 to 36%)	30	Associated with CREST syndrome and Raynaud's phenomenon
Anti-topoisomerase I (anti-Scl-70)	Scleroderma (22 to 40%)	40	Highly specific but not sensitive for scleroderma
Anti-Jo1	Polymyositis and dermatomyositis (30%)	40	Associated with pulmonary fibrosis and Raynaud's phenomenon
c-ANCA	Wegener's granulomatosis (>90%)	30	Highly specific and sensitive for Wegener's granulomatosis; correlates with disease activity
p-ANCA	Wegener's granulomatosis (10%), microscopic polyangiitis, glomerulonephritis	30	Sensitivity and specificity quite low in Wegener's granulomatosis

RF = rheumatoid factor; ANA = antinuclear antibody; anti-dsDNA = anti-double-stranded DNA; anti-ssDNA = anti-single-stranded DNA; anti-Smith = anti-Smith; anti-U1 snRNP = autoantibodies against small nuclear ribonucleoprotein U1; CREST = calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias; c-ANCA = cytoplasmic antineutrophilic cytoplasmic antibodies; p-ANCA = perinuclear antineutrophilic cytoplasmic antibodies.

*—Costs based on those at Hallmark Health's laboratory, Melrose, Mass.

†—Cost for entire panel (anti-ssDNA, anti-histone, anti-Smith, anti-U1 snRNP, anti-Ro, anti-La).

Adapted with permission from Moder KG. Use and interpretation of rheumatologic tests: a guide for clinicians. *Mayo Clin Proc* 1996;71:391-6.

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