



# A PRIMARY CARE APPROACH TO THE USE AND INTERPRETATION OF COMMON RHEUMATOLOGIC TESTS

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The results of common rheumatologic laboratory tests play an important part in the diagnosis and management of rheumatic diseases. Rheumatologic test results can often be ambiguous and can sometimes be misleading, particularly in primary care settings. Because the diagnosis of most rheumatic conditions depends on information derived from sources other than serum tests, these laboratory values are usually supportive rather than diagnostic [1]. Few serum test results are pathognomonic for a specific rheumatic disease and alone are insufficient to determine a diagnosis [2]. Test results should be interpreted in a clinical context, which includes information derived from the history and physical examination, basic laboratory tests, radiographic and other imaging studies, and synovial fluid analysis. Serum rheumatologic tests are most useful for confirming a clinically suspected diagnosis. Because there is a high incidence of false-positive results in the general population, these tests have little clinical utility when there is a low pretest probability. Furthermore, the predictive value of serum rheumatologic tests is limited when performed in settings in which the prevalence of rheumatic conditions is low.

Studies suggest that primary care physicians overuse common rheumatologic tests [3]. The practice of routinely ordering a battery of rheumatologic laboratory tests to “rule out” rheumatologic disease is not uncommon [1]. This approach rarely leads to a definitive diagnosis and

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usually increases diagnostic confusion. The significant proportion of false-positive test results, especially among elderly patients, contributes to this confusion. The misapplication of rheumatologic tests can lead to misdiagnoses, unnecessary work-ups, needless referrals and treatments, and increased health care costs. The overuse of such tests reduces their predictive value in the primary care setting.

Patients with musculoskeletal complaints and constitutional symptoms (eg, fatigue) are commonly evaluated by primary care physicians. The vast majority of these patients do not have a rheumatologic disease [4]. The use of rheumatologic tests by primary care doctors may be improved by increasing understanding regarding the indications for and value of such tests. Recognizing the limitations of rheumatologic tests may improve their utility by encouraging more selective testing and more cautious interpretation of test results [5]. This article describes the characteristics of commonly ordered rheumatologic tests and reviews examples of their application in a primary care setting.

## DEFINITIONS OF STATISTICAL TERMS

To fully understand the clinical utility of a test, it is important to have an understanding of fundamental test characteristics and their application in a clinical setting. Performance attributes of a test include sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs). Sensitivity refers to the percentage of patients with the disease who have a positive test result. For example, about 80% of patients with rheumatoid arthritis (RA) are positive for rheumatoid factor (RF). Conversely, 20% of patients with RA have a negative test result for RF (false-negative result). Specificity refers to the percentage of patients without the disease who have a negative test result. Patients without the disease with a positive test result have a false-positive result.

Sensitivity and specificity can be affected by the clinical setting in which the test is performed. For example, only about one third of RA patients develop RF in the first 3 months of illness [4]. Therefore, for the primary care physician who is likely to evaluate a patient with RA early in the course of the disease, the sensitivity of RF for RA may be lower than for a rheumatologist, who is likely to evaluate the patient at a later stage of the condition [4]. In addition, sensitivity and specificity can be affected by characteristics of patient populations. For instance, the specificity of antinuclear antibody (ANA) tests can be lower among inpatients than among outpatients because hospitalized patients are more likely to have other conditions associated with a false-positive ANA test [4]. The sensitivity and specificity of a given test can change depending on the definition of the normal and abnormal range [4]. A wider normal range may increase the specificity of a test by reducing the number of false-positive results but can reduce its sensitivity. Conversely, a wider abnormal range may increase a test's sensitivity but may decrease its specificity. Choosing

the value that distinguishes normal from abnormal involves balancing the importance of a test's sensitivity and specificity.

Although sensitivity and specificity are informative measures of test performance, they cannot inform clinicians of the probability that an individual patient has the disease in question because these test characteristics are determined from patients who are known to have or not have the disease. In practice, clinicians may not know a patient's true disease state. Therefore, the test feature of relevance to practicing clinicians is a test's ability to estimate the probability that a patient has the disease in question. The PPV is the probability that the patient has the disease given a positive test result. The NPV is the probability that the patient does not have the disease given a negative result.

The predictive value of a test is influenced by the clinical context in which it is applied. The predictive value may be calculated using Bayes' theorem, which relies upon the test sensitivity, test specificity, and the patient's pretest probability. A patient's pretest probability is estimated by using elements of the history, physical examination and other diagnostic data, and the prevalence of the disease in the population. The pretest probability has significant bearing on the ability of a test to predict the probability of disease. Even if a test has excellent sensitivity and specificity, a test used in a patient with a low pretest probability may have poor predictive value [6].

## ISSUES IN LABORATORY TESTS IN RHEUMATOLOGY

### Titers

There are a number of special features intrinsic to rheumatologic laboratory tests that should be considered when interpreting their meaning. First, many rheumatologic tests, such as RF and ANA tests, are reported in a quantitative fashion using a serum dilution titer. The reported titer represents the highest dilution of serum that yields detectable agglutination. The incidence of a positive result in a population depends on the assay system used and the titer chosen to separate positive and negative responses [7]. The titer selected to distinguish between normal and abnormal should be based on the disease prevalence in the patient's local population. Often, the cutoff dilution is intended to exclude 95% of the normal population while maintaining a test's sensitivity for disease. Each laboratory must determine the level it considers positive, and this level may vary significantly between labs. In general, the higher the titer is, the lower the false-positive rate. The converse is also true: the lower the titer is, the higher the false-positive rate of the test.

Guidelines constructed by the American College of Rheumatology Ad Hoc Committee on Immunologic Testing recommend that test results like ANA should not only be reported as "positive" or "negative" but should also give an account of the highest titer for which antibody is detected. The committee submits that laboratory reports should also disclose the

percentage of patients without any ANA-associated disease who have similar titers [8].

## Crossreactivity

Another important issue in the ordering of rheumatologic tests is the high rate of crossreactivity [4]. Several different rheumatic conditions that share symptomatology and presentation may cause positive test results for various distinct diseases. For example, RA and systemic lupus erythematosus (SLE) may present with symmetric polyarthritis. ANA testing ordered to evaluate for SLE will be positive in 30% or more of patients with RA [4]. Thus, such cross-reactivity may lower the PPV of ANA testing for the diagnosis of SLE.

## Interlaboratory Variability

Interlaboratory variability in rheumatologic testing and in measurement error contributes to the difficult task of interpreting lab results [1,4,7]. In one study, two university immunology laboratories differed in their classification of duplicate serum samples as normal or abnormal in 11% of cases for ANA testing, in 15% of cases for DNA binding testing, and in 27% of cases for serum complement testing [9]. Heterogeneity among test results between laboratories may be a consequence of variability in methods, substrates, reagents, visualizing equipment, and the subjective component of reading results [10]. Although there are efforts to standardize laboratory technique and minimize measurement error [2], test results need to be interpreted in consideration of individual laboratory methodology. If a laboratory value does not agree with the clinical estimation, the clinician may consider laboratory error to explain the finding [1].

## Testing Bias and Generalizability

Laboratory test performance in the general population can be difficult to determine when studies evaluating such tests examine populations with dissimilar disease prevalence or varying levels of suspected disease [1,10]. For instance, many studies investigating the properties of rheumatologic tests include a selected group of patients who have been referred to a rheumatologist and who may have a specific constellation of symptoms [10]. Therefore, applying data regarding the value of these tests to the general population or to a primary care setting can be problematic.

## Rheumatoid Factor

RF is one of the most commonly ordered tests in the evaluation of patients with musculoskeletal complaints. Most RFs are IgM autoanti-

bodies, which bind to the Fc portion of IgG immunoglobulins. Although the diagnosis of RA cannot be made on the basis of RF testing alone, a positive RF is included among the American College of Rheumatology criteria for the diagnosis of RA [11]. The sensitivity of RF is about 80% in patients with RA, although studies have reported rates ranging from 30% to 90% [12]. Some authors suggest that 80% may be an overestimate due to selection bias because studies may have intended to include indisputable and possibly more severe cases of RA [5]. The specificity of RF for RA ranges from 80% to 98%, depending on the study [12] and the age and health of the population studied [6]. The titer of RF also differs among various ethnic groups [13]. Patients with elderly-onset RA and female patients are more often seronegative [5].

A false-positive RF is found in a number of other rheumatic and nonrheumatic conditions (Box 1). Several of these conditions may present

### **Box 1. Conditions Commonly Associated with a Positive Rheumatoid Factor**

#### *Rheumatic diseases (prevalence)*

- Rheumatoid arthritis (50% to 90%)
- Systemic lupus erythematosus (15% to 35%)
- Sjögren's syndrome (75% to 95%)
- Systemic sclerosis (20% to 30%)
- Polymyositis/dermatomyositis (5% to 10%)
- Cryoglobulinemia (40% to 100%)
- Mixed connective tissue disease (50% to 60%)

#### *Nonrheumatic conditions*

- Aging (>70 years) (10% to 25%)
- Infections
  - Bacterial endocarditis (25% to 50%)
  - Hepatitis (15% to 40%)
  - Tuberculosis (8%)
  - Syphilis (up to 13%)
  - Parasitic diseases (20% to 90%)
  - Leprosy (5% to 58%)
  - Viral infections (15% to 65%; including mumps, rubella, influenza, HIV, mononucleosis, and many others)
- Pulmonary diseases
  - Sarcoidosis (3% to 33%)
  - Interstitial pulmonary fibrosis (10% to 50%)
  - Silicosis (30% to 50%)
  - Asbestosis (30%)
- Miscellaneous diseases
  - Primary biliary cirrhosis (45% to 70%)
  - Malignancy (5% to 25%)

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

with similar musculoskeletal complaints, thereby adding to the diagnostic confusion. However, RF titers in patients with nonrheumatic conditions tend to be lower than in RA [13]. Unexplained positive RF titers may suggest underlying hepatitis C, multiple myeloma, lymphoma, or sarcoidosis. RF also occurs in normal individuals. The prevalence of RF in the normal population is at least 1%, although this figure may rise with age, reaching 10% to 25% in healthy elderly patients [4,5,14]. Because the prevalence of RA ranges from 0.5% to 3%, at least as many individuals who have a positive RF do not have RA as have the disease [1,5].

The presence of RF has often been misinterpreted as being diagnostic for RA. The clinician's estimated pretest probability that a patient has RA greatly affects the ability of RFs to aid in diagnosis. For instance, if a clinician were to use RF as a screening test, assuming a 1% pretest probability based on the prevalence of RA in the general population, a test sensitivity of 80%, and a specificity of 95%, the PPV of the RF is only 16%. This means that there is only a 16% chance that a patient with a positive RF has RA (Table 1). On the other hand, if a clinician estimated that the pretest probability of a patient having RA was 25%, a positive RF would increase the probability of RA to 84% (Table 1). Therefore, the selection of patients with a sufficient pretest probability improves the test's utility. RF testing is most useful when there is a moderate level of suspicion for RA.

When the clinical suspicion for RA is high, RF testing is less helpful because 20% of patients with RA are seronegative [6]. False-negative rates are even more common early in the course of RA. RF is detectable in only 33% of patients who develop RF during the first 3 months of disease and in only 60% of patients who develop RF during the first 6 months [1]. This may be particularly relevant in a primary care setting, where patients are evaluated earlier in the course of disease. Therefore, if there is a high probability that a patient has RA, that patient has a reasonable chance of having

**TABLE 1.**  
*Predictive Value of Rheumatic Factor for Rheumatoid Arthritis<sup>a</sup>*

<b>Pretest Probability</b>	<b>Post-test Probability, RF(+)</b>	<b>Post-test Probability, RF(-)</b>
1% <sup>b</sup>	16%	0.2%
15%	74%	4%
25%	84%	7%
50%	94%	17%
75%	98%	39%
90%	99%	65%

*Abbreviation:* RF, rheumatic factor.

*From Shmerling R, Delbanco T. The rheumatoid factor: an analysis of clinical utility. Am J Med 1991;91:528-34; with permission.*

<sup>a</sup> Assuming that the sensitivity of RF is 80% and the specificity is 95%.

<sup>b</sup> Based on the estimated prevalence of RA in the US of 0.5% to 3%.

RA even with a negative RF (Table 1). In these cases, RF testing may lead a physician away from the diagnosis of RA, which is regrettable as more evidence demonstrates the importance of treating RA early, before end-organ damage.

In patients with RA, the RF titer generally correlates with severe articular disease and extra-articular manifestations, although this relationship is variable. RF testing may have prognostic value in these patients [6,15]. However, RF titers are not helpful in following disease progression. Once a patient has a positive RF test, repeating the test is of no value [6].

Few studies have addressed the utility of using RF testing in diseases other than RA. RF is often positive in Sjögren's syndrome and cryoglobulinemia and can be useful when these conditions are suspected. Because the presence of cryoglobulins can be difficult to confirm, RF testing can sometimes be used as a surrogate when cryoglobulinemia is suspected. It has been suggested that the disappearance of the RF in a patient with Sjögren's syndrome may indicate the onset of lymphoma [6]. In addition, RF is often ordered in the evaluation of fever of unknown origin (FUO). The utility of RF testing in FUO has been questioned in consideration of the infrequency of prolonged fever in RA and the low yield of RF testing in such cases [5].

## Antinuclear Antibody

ANA testing is the most commonly performed autoantibody test in clinical laboratories [16]. It is usually ordered to evaluate for the presence of SLE or other connective tissue diseases (CTDs). The ANA test detects antibodies that bind to various nuclear and cytoplasmic antigens. Most ANA testing uses an indirect immunofluorescence technique for the initial screening test, although ELISA tests are available. Although substrates can differ between labs, most labs use HEp-2 cells over traditional rodent tissues because of their improved sensitivity.

When an ANA test is positive (titers  $\geq 1:160$ ), the nuclear staining pattern is frequently reported. This pattern reflects the intracellular target of the nuclear antibody and may convey clinically useful information. Nuclear patterns include homogenous/diffuse, rim/peripheral, speckled, nucleolar, and centromere. These patterns have been associated with specific CTDs; however, there is substantial overlap and variation between diseases and patterns. The homogenous and rim pattern is characteristic for SLE [16]. A speckled pattern can occur with Sjögren's syndrome and mixed CTD. A nucleolar pattern is associated with diffuse scleroderma, and a centromere pattern is specific for CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) [16].

Emphasis on nuclear staining patterns has diminished over the past several years because of their lack of specificity and the availability of more specific autoantibody tests [2,17]. Furthermore, fluorescent patterns may vary with serum dilution, which may limit their reliability and

reproducibility [18,19]. In addition, traditional nuclear staining patterns may differ with ANA testing using newer HEp-2 cell substrates [2].

The nuclear pattern and titer of ANA tests do not necessarily reflect disease activity. Therefore, the ANA test is most useful for diagnostic purposes and has no utility for monitoring patients. Serial ANA testing has no known value in patients with a positive ANA. Other laboratory tests (eg, complement, anti-double-stranded DNA antibodies, and erythrocyte sedimentation rate [ESR]) are more useful in assessing disease activity. Clinical factors, including patient symptoms and physical examination findings, and the results of routine laboratory values, including a CBC, creatinine, and urinalysis, are also much more significant in assessing disease activity.

An ANA titer is the primary laboratory test used to diagnose SLE. The ANA test is sensitive for SLE, with about 95% to 100% of patients with SLE having positive results [10]. A positive ANA is included in the updated American College of Rheumatology criteria for the diagnosis of SLE [20–22]. A positive test alone is insufficient for the diagnosis. Before the diagnosis of SLE can be established, 4 of 11 clinical and laboratory criteria must be met (Box 2). The ANA test is not specific for SLE. Reported specificities range from 49% to 90% [6,10].

ANA testing has a role in the diagnosis of other CTDs. A positive ANA test is required for the diagnosis of some rheumatic conditions, including drug-induced lupus, autoimmune hepatitis, and mixed CTD [2,10]. The ANA test can be positive in other CTDs, such as scleroderma, Sjögren's syndrome, and polymyositis/dermatomyositis, in varying degrees (Table 2). In these conditions, a positive ANA test can support the diagnosis but

### **Box 2. The American College of Rheumatology Criteria for Systemic Lupus Erythematosus (abbreviated)**

- Malar rash—Flat or raised fixed erythema
- Discoid rash—Raised patches with plugging/scaling
- Photosensitivity—Photosensitive skin rash
- Oral ulcers—Usually painless
- Nonerosive arthritis—Involving two or more peripheral joints
- Serositis—Pleural or cardiac
- Renal disease—Proteinuria or cellular casts
- Neurologic disorder—Seizures or psychosis in the absence of other cause
- Hematologic disorder—Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
- Immunologic disorder—Anti-dsDNA, anti-Sm, antiphospholipid antibodies (anticardiolipin antibody, lupus anticoagulant, or a false-positive venereal disease reference laboratory test)
- Antinuclear antibody—Abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug

Data from references 19–21.



**TABLE 2.**  
**Conditions Associated with a Positive Antinuclear Antibody (ANA Test)**

Rheumatic Conditions <sup>a</sup>	Patients with positive ANA
Systemic lupus erthematosus	99%
Drug-induced lupus	100%
Scleroderma/systemic sclerosis	97%
Mixed connective tissue disease	93%
Polymyositis/dermatomyositis	78%
Sjögren's syndrome	96%
Rheumatoid arthritis	40%
<b>Nonrheumatic Conditions<sup>b</sup></b>	
Normal individuals: females > males, increasing age, relatives of patients with rheumatic disease, pregnancy	
Hepatic diseases: chronic active hepatitis, primary biliary cirrhosis, alcoholic liver disease	
Pulmonary diseases: idiopathic pulmonary fibrosis, asbestosis, primary pulmonary hypertension	
Chronic infections	
Malignancies: lymphoma, leukemia, melanoma, solid tumors (ovary, breast, lung, kidney)	
Hematologic disorders: idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia	
Miscellaneous: type 1 diabetes mellitus, Grave disease, multiple sclerosis, end-stage renal failure, after organ transplantation	

<sup>a</sup> Adapted from Peng S, Craft J. Antinuclear antibodies. In: Ruddy S, Harris E, Sledge C, editors. Kelly's textbook of rheumatology. 6th edition. Philadelphia: Saunders; 2001: p. 161–73; with permission.

<sup>b</sup> Adapted from Pincus T. Laboratory tests in rheumatic disorders. In: Klippel J, Dieppe P, editors. Rheumatology. 2nd edition. Philadelphia: Mosby; 1998. p. 10.5.

is not required [2]. An ANA test is positive in approximately 40% to 50% of patients with antiphospholipid antibody syndrome, and its presence may increase the likelihood that the syndrome is secondary to SLE, but a positive ANA test is not necessary for the diagnosis [2,7]. Although a positive ANA test is not uncommon in patients with RA, its presence has no diagnostic significance in RA and is not useful in patients suspected of having RA [10].

Although the ANA test is not useful for establishing the diagnosis of Raynaud's phenomenon or juvenile chronic arthritis (JCA), the presence of a positive ANA test with these conditions may provide information concerning prognosis. A positive ANA test result in a patient with Raynaud's phenomenon increases the likelihood of the development of a systemic rheumatic disease from around 19% to 30%, whereas a negative ANA test result decreases the likelihood to approximately 7% [2]. Thus, a negative ANA test in this case may be reassuring. The presence of a positive ANA test result in children with JCA may predict the development of uveitis and should prompt screening [2].

Because of the high sensitivity of the ANA test for SLE, almost all patients with SLE have a positive ANA test. However, due to the low prevalence of SLE in the general population (40–50 cases per 100,000), most patients with a positive ANA test do not have SLE [2]. ANA tests can be positive in many nonrheumatic conditions and among normal individuals, particularly in women and in elderly persons (Table 2). Positive ANA tests have been noted during pregnancy and in patients with silicone gel implants [6]. In addition, up to 30% of relatives of patients with CTD may have high titers of ANA without having manifestations of disease [10,19]. Studies have shown that nearly 32% of normal individuals have a positive ANA at a 1:40 serum dilution, 13% have a positive ANA at a 1:80 serum dilution, 5% have a positive ANA at a 1:160 serum dilution, and 3% have a positive ANA at a 1:320 serum dilution [7,10,23]. Although the American College of Rheumatology criteria refer to an “abnormal” ANA titer, there is no set titer value that can distinguish between those with and without SLE. Titers  $> 1:320$  are more likely to represent true-positive results [2]. Each laboratory must determine the level that it considers positive, and this level may vary significantly among laboratories depending on various methodologic variables [16]. In most laboratories, the level of a positive ANA titer is 1:40 to 1:80. In laboratories where HEP-2 cells are used as substrates to perform an ANA test, titers of 1:80 or higher are considered positive [2]. Although each laboratory should establish its own reference intervals, guidelines suggest that titers  $< 1:40$  are negative and that titers  $\geq 1:160$  are positive [24]. Titers  $\geq 1:40$  and  $< 1:160$  are weakly positive and are common in healthy individuals. Such titers need to be interpreted in their clinical context. In the absence of specific symptoms suggesting CTD, further diagnostic study is not advised [24,25]. Although using higher cutoffs to define a positive ANA titer may improve the specificity of the test for the diagnosis of SLE, this practice would decrease its diagnostic sensitivity.

False-positive results of ANA testing constitute one of the most common reasons for rheumatology consultations [1]. If one considers that positive ANAs appear in at least 5% of the normal population and that SLE occurs in only about 40 to 50 cases per 100,000 persons, the likelihood of a positive ANA result indicating the presence of SLE is low. Studies estimate that the PPV of the ANA test in the general population is only 11% [9]. This means that a positive ANA is indicative of rheumatic disease in only 11% of patients and may have no clinical significance in nearly 90% of patients. An ANA test should be ordered if the clinician feels there is a reasonable clinical suspicion of SLE or another CTD based on the patient's history, physical examination findings, and results of other laboratory tests or studies [2]. Because most patients with a positive ANA test do not have SLE or any other rheumatic disease, ANA testing is not recommended as a screening test to rule out rheumatic disease, particularly when the suspicion for disease is low.

A negative ANA test has a high NPV and usually indicates the absence of SLE or other CTDs. Evidence suggests that testing for specific autoantibodies after a negative ANA result or after a weakly positive ANA ( $< 1:160$ ) is not helpful and yields positive results in fewer than 5% of

cases [25]. A proportion of patients can have a negative ANA titer early in the course of disease and eventually develop a positive ANA titer [20]. Therefore, it can be worthwhile to repeat the ANA test if the patient's clinical course develops features consistent with a CTD. In rare instances, patients with SLE can have a negative ANA test. This can occur if the substrate used in the fluorescent ANA test did not contain sufficient antigen to allow for detection of those antibodies, usually the antigen Ro/SS-A. However, with more routine use of HEp-2 cell substrates, virtually all SLE patients have a positive ANA test [2]. If the clinical picture strongly suggests CTD and if the ANA is negative, further investigation should include testing for specific assays for Ro, La, Jo-1, and phospholipids [18]. Complement studies, including testing for C3, C4, and CH50, may be indicated because complement deficiencies can cause an ANA-negative, lupus-like syndrome [26].

Because specific autoantibody tests possess diagnostic significance, a positive ANA usually warrants follow-up with specialized assays (Table 3) [40]. If SLE is suspected, further work-up may include tests for anti-dsDNA, anti-Sm, anti-U1 snRNP, anti-Ro, and anti-La antibodies [18]. If mixed CTD is suspected, the serum should be tested for anti-U1 RNP antibodies; for Sjögren's syndrome, the serum should be tested for anti-Ro and anti-La antibodies; in scleroderma, the serum should be tested for anti-Scl-70 (or topoisomerase I) and anti-centromere antibodies; and in polymyositis/dermatomyositis, the serum should be tested for anti-Jo-1 antibodies. The ordering of specific autoantibodies should be targeted to address a suspected diagnosis, rather than including a large panel of tests with uncertain significance.

## **INFLAMMATORY MARKERS: ERYTHROCYTE SEDIMENTATION RATE AND C-REACTIVE PROTEIN**

The systemic response to tissue injury, regardless of the cause, is characterized by a cytokine-mediated alteration in the hepatic synthesis of a number of different plasma proteins, known collectively as "acute phase reactants" [27]. These proteins, which include fibrinogen, C-reactive protein (CRP), serum amyloid A protein, and many others, rise in proportion to the severity of tissue injury, although the magnitude of each component varies. Because some systemic rheumatic conditions cause tissue inflammation and injury, assessment of the acute phase response can play an important part in the diagnosis and management of these diseases [27].

Laboratory tests, including erythrocyte sedimentation rate (ESR) and CRP, are commonly used to measure systemic inflammation or the acute phase response. These tests may help assess the degree of disease activity in some rheumatic conditions and monitor disease activity and response to treatment over time [28]. ESR and CRP levels may have prognostic value in conditions such as RA. Studies suggest that ESR and CRP levels are associated with long-term outcomes of RA, such as work disability [29,30]

**TABLE 3.**  
***Other Autoantibodies Detected in Patients with Connective Tissue Diseases***

<b>Autoantibody</b>	<b>Disease (percentage)</b>	<b>Comments</b>
Anti-dsDNA	Active SLE (60–70) Inactive SLE (20) Absent in drug-induced lupus	Specific but less sensitive for SLE; correlates with lupus nephritis and disease activity. Tests for single-stranded DNA are nonspecific and should not be ordered.
Anti-histone	Drug-induced lupus (95) Idiopathic SLE (> 50)	Sensitive but nonspecific for drug-induced lupus
Anti-U1 snRNP	SLE (35–40), mixed connective tissue disease (100)	Nonspecific; part of the criteria for MCTD; associated with milder disease and less nephritis
Anti-Sm	SLE (20–30)	Highly specific but not sensitive for SLE
Anti-Ro (anti-SS-A)	Sjögren's syndrome (60–75), SLE (40)	Associated with "ANA-negative" SLE, cutaneous involvement, congenital heart block in babies of mothers with this antibody [17]
Anti-La (anti-SS-B)	Sjögren's syndrome (50), SLE (10–15)	Usually occurs with anti-Ro; associated with late-onset SLE, secondary Sjögren's, neonatal lupus syndrome [6]
Anti-ribosome	SLE (10–20)	Highly specific but not sensitive for SLE; correlated with neuropsychiatric SLE [6]

Anti-centromere	Scleroderma (22–36) [6] CREST variant (80–90) PSS (25)	Associated with limited scleroderma (CREST) and Raynaud's phenomenon
Anti-topoisomerase I (Anti-Scl-70)	Scleroderma (22–40) [6] PSS (30)	Specific but not sensitive for scleroderma; correlated with progressive systemic sclerosis
Anti-Jo 1	Polymyositis and dermatomyositis (20–30)	Highly specific but not sensitive for polymyositis/dermatomyositis; associated with pulmonary fibrosis and Raynaud's phenomenon [6]
Antiphospholipid ACA, Lupus anticoagulant	ACA: SLE (12–30) [40] Lupus anticoagulant: SLE (15–34) [40]	Associated with thrombosis, thrombocytopenia, recurrent fetal loss, livedo reticularis

*Abbreviations:* ACA, anticardiolipin; ANA, antinuclear antibody; MCTD, mixed connective tissue disease; PSS, progressive systemic sclerosis; SLE, systemic lupus erythematosus.

*Adapted from* Snow C. Laboratory testing for musculoskeletal diseases. In: Harris E, Genovese M, editors. Primary care rheumatology. Philadelphia: WB Saunders; 2000; p. 55; with permission.

and radiologic progression of RA [30,31]. These inflammatory markers could allow physicians to identify patients at greatest risk for progressive disease so they can be treated more aggressively.

Generally, ESR and CRP are nonspecific indicators of inflammation and are not useful as screening tests for rheumatic conditions [32]; nor are they helpful for differentiating various rheumatic diseases [32]. However, in addition to assessing disease activity, they can be helpful for supporting the diagnosis of some rheumatic diseases, such as temporal/giant cell arteritis, polymyalgia rheumatica (PMR), and RA.

## Erythrocyte Sedimentation Rate

ESR is a simple and inexpensive laboratory test that is commonly ordered in clinical medicine [33]. Although a single ESR test is inexpensive to perform, the test is ordered so frequently that it becomes expensive in the aggregate [32]. The ESR is an indirect measure of inflammation. The test measures the distance that erythrocytes have fallen after 1 hour in a vertical column of anticoagulated blood under the influence of gravity [27]. The most accurate method of performing the ESR was introduced by Westergren in 1921 [33].

**TABLE 4.**  
**Factors that May Influence the Erythrocyte Sedimentation Rate**

Increase ESR	Decrease ESR
Anemia	Red blood cell abnormalities: sickle cell disease, anisocytosis
Hypercholesterolemia	Spherocytosis: acanthocytosis, microcytosis
Female sex	Extreme leukocytosis
Pregnancy	Polycythemia
Old age	Bile salts
Technical factors: dilutional problem, tilted ESR tube, increased temperature of specimen	Technical factors: dilutional problem, inadequate mixing, clotting of blood sample, short ESR tube, vibration during test, > 2 h delay in running the test, low temperature of specimen
Elevated fibrinogen level: infection, inflammation, malignancy, chronic renal failure, tissue damage (MI, CVA)	Protein abnormalities: hypofibrinogenemia, hypogammaglobulinemia, dysproteinemia with hyperviscosity
Red blood cell abnormalities: macrocytosis	High doses of adrenal steroids

*Abbreviations:* CVA, cerebrovascular accident; ESR, erythrocyte sedimentation rate; MI, myocardial infarction.

*Adapted from* Bridgen M. Clinical utility of the erythrocyte sedimentation rate. *Am Fam Physician* 1999;60:1443–50; with permission.

An elevated ESR is a nonspecific finding. There are many conditions and factors that influence the level of ESR (Table 4). Sedimentation of erythrocytes is facilitated by certain plasma proteins that neutralize the negative charge on the erythrocyte surface, permitting them to aggregate and fall more rapidly as a clump rather than as individual cells [32]. Fibrinogen is among the plasma proteins associated with the acute phase response that acts in this regard. The amount of fibrinogen in the blood directly correlates with the ESR. Conditions that elevate fibrinogen (eg, pregnancy, diabetes, renal failure, heart disease, CTD, or malignancy) may elevate the ESR [33]. Other proteins not associated with the acute phase response (eg, immunoglobulins) can elevate the ESR. Monoclonal or polyclonal gammopathies, including multiple myeloma, can cause an elevated ESR. Anemia and macrocytosis increase the ESR.

Normal ESR values span a wide range, with women, elderly individuals, and obese individuals tending to have higher ESR values. Many individuals 70 years of age and older may have ESRs in the range of 40 to 50 mm/h without apparent inflammation or tissue injury, which limits the utility of ESR testing in the elderly population. Researchers have developed an empirical formula to estimate the value of ESR that includes 98% of healthy individuals: For men, age in years is divided by two; for women, age in years plus 10 is divided by two [32]. As with other laboratory tests, the reference range used for the ESR should be established by the laboratory performing the test (Table 5) [41]. There are several technical factors regarding the performance of the ESR test that may produce erroneous values (Table 4).

Because an elevated ESR may occur in many different clinical settings, this finding may be irrelevant as an isolated laboratory value [33]. The cause of most ESR elevations can be revealed through a detailed history, physical examination, and collection of routine laboratory data [32,33]. Most unexplained ESR elevations are short lived and are not associated with a specific underlying process [32]. An unexplained elevated ESR returns to normal in most cases. Therefore, unexplained

**TABLE 5.**  
*Reference Ranges for the Erythrocyte Sedimentation Rate in Healthy Adults*

<b>Adults</b>	<b>Upper Limit of Reference Range (mm/h)</b>
Age < 50 yr	
Men	0–15
Women	0–25
Age > 50 yr	
Men	0–20
Women	0–30

*Data from Bottiger L, Svedberg C. Normal erythrocyte sedimentation rate and age. Br Med J 1967;2:85–7; with permission.*

elevated ESR levels can be rechecked in 1 to 3 months, rather than triggering an extensive search for a cause [32].

The false-positive rate is lower for an extreme elevation of ESR, defined as  $>100$  mm/h. In most of these cases, the condition causing the elevated ESR is clinically apparent; no obvious cause is identified in  $<2\%$  of patients [32]. An exhaustive search for an occult malignancy in patients with ESR levels  $>100$  mm/h is not recommended because if cancer is present it is almost always metastatic [32]. Conversely, an ESR test is often normal in the presence of various diseases, including malignancies and rheumatic conditions. Therefore, it has limited value as a test to exclude serious conditions [32].

An elevated ESR remains an important diagnostic criterion for two rheumatic conditions: PMR and temporal/giant cell arteritis [33]. Most patients with these conditions have an elevated ESR [32]. Occasionally, patients may present with a normal value. If there is good clinical evidence for these conditions, a normal ESR should not preclude the diagnosis [32].

An ESR of at least 40 mm/h has been included in the diagnostic criteria of PMR [34,35]. However, some studies have reported that the percentage of patients with PMR who have an ESR lower than 40 mm/h is about 20% [34,35]. Patients with PMR with low ESRs were more likely to be men, were generally younger, had fewer systemic manifestations, and had a lower frequency of laboratory test result abnormalities [35]. These data suggest that ESR may be related not only to the clinical activity of PMR but also to its severity. The need for corticosteroid therapy and the frequency of relapses were similar in patients with high and low ESRs [35]. Other studies have suggested that CRP levels are more sensitive than ESR levels in the assessment of disease activity in PMR [34].

Patients with temporal/giant cell arteritis almost always have elevated ESRs, with the mean ESR exceeding 90 mm/h [32]. Studies may have underestimated the rate of false-negative results [32]. This may occur because patients with a normal ESR are not likely to undergo temporal artery biopsy, which is the gold standard for establishing the diagnosis of temporal arteritis [32]. The false-positive rate of the ESR in patients who are suspected of having temporal arteritis is not known [32]. Therefore, the interpretation of an ESR depends on the clinician's estimate of the pretest probability for having temporal arteritis. When the clinical suspicion for temporal arteritis is low, a normal ESR reduces the probability of the disease to  $<1\%$  [32]. When clinical evidence supports the diagnosis of temporal arteritis, the disease may be present despite a normal ESR [32].

The American College of Rheumatology criteria for the classification of RA include an elevated ESR as one of 20 findings that may be present with the disease. An elevated ESR is not required for the diagnosis of RA. The ESR is a component of the remission criteria for RA and disease activity scores [36]. The role of ESR in distinguishing inflammatory articular disorders (eg, RA) from noninflammatory conditions (eg, osteoarthritis) is questionable [4]. One study found that in patients with RA, only



50% had an ESR that exceeded 30 mm/h [4,32]. This rate was considerably higher than the rate in patients without RA with signs of osteoarthritis (14%). Therefore, an abnormal ESR may increase the probability of RA, but it is not diagnostic. Furthermore, a normal ESR provides little evidence for or against the diagnosis of RA. A careful history and physical examination is far more significant than an ESR in establishing the diagnosis.

The ESR can be helpful for measuring disease activity and response to treatment for some rheumatic diseases, including PMR, temporal arteritis, and RA, but the ESR level does not always reflect disease activity. Many patients started on corticosteroid therapy for polymyalgia rheumatic or temporal arteritis have an elevated ESR even when their clinical status has significantly improved [32]. Conversely, patients can have relapses of these conditions with a normal ESR level. Therefore, steroid therapy should not be based on the ESR level alone [32].

In RA, the ESR tends to reflect disease activity, but clinical symptoms and joint examination findings are considered more useful in assessing disease activity [32]. Although studies have correlated elevated ESRs with increased disease activity, evidence suggests that a significant proportion of patients in clinical remission may have an elevated ESR value and that a significant proportion of patients with a relapse may have an ESR <30 mm/h [32]. Therefore, although an increased ESR may be used as additional evidence of disease activity for RA, the ESR value alone should not be the reason for altering therapy [32].

The ESR is not helpful in following disease activity in SLE. The ESR often remains elevated even when the disease is controlled, usually due to a persistent polyclonal gammopathy [37].

## **C-Reactive Protein**

Of the several acute-phase reactants, CRP is another commonly ordered test measuring systemic inflammation and is often compared with ESR. The CRP is named for its binding of the pneumococcal C-polysaccharide. The CRP is a rapid responder to inflammation and may be a better indicator of the acute-phase response during the first 24 hours in an inflammatory process than ESR [30]. CRP concentrations increase within 4 hours after an appropriate stimulus, peak within 24 to 72 hours, and may increase as much as 1000-fold [36]. They promptly return to normal when the underlying inflammation resolves. ESR levels rise over 24 to 48 hours and may not return to normal for weeks [38]. CRP levels can remain elevated in chronic inflammatory states, such as active RA. The CRP test is more expensive, less widely available, and more time-consuming to perform than the ESR. It usually needs to be sent to a well-equipped central laboratory, which may delay availability of results. CRP is directly measured and therefore is not affected by the variety of factors that influence ESR levels. CRP levels, as opposed to ESR levels, can be measured on stored or frozen sera. Many methods have been used to assay levels of CRP, and reporting

units can vary. It is unclear whether these differences in laboratory techniques affect reported CRP levels.

Several conditions can cause elevated CRP levels. Examples of clinical conditions associated with CRP elevations in various degrees are shown in Table 6. CRP concentrations below 1 mg/dL but higher than seen in most normal subjects (0.2 mg/dL) have been found in patients with osteoarthritis. Such levels have been found to predict subsequent coronary events, indicating participation of inflammation in these disorders. Mild CRP elevations have been noted with increasing age [27].

Most rheumatic diseases, including RA, JCA, Reiter disease, ankylosing spondylitis, and psoriatic arthritis, are associated with high levels of CRP (1–10 mg/dL) when they are active [1]. However, studies have shown that CRP, unlike ESR, is usually not elevated in active SLE. Elevated CRP levels in patients with SLE are usually an indicator of infection rather than inflammation [1,27].

Whether CRP or ESR correlate better with disease activity in RA has been vigorously debated. The literature on the comparative value of the CRP and ESR tests is inconclusive, with studies suggesting that one or the other, or neither, is better [38,39]. CRP is used extensively in Europe, where it is believed to be the better test [38]. In the United States, 78% of rheumatologists use ESR to evaluate patients with RA, compared with 30% who use CRP [38]. CRP and ESR are often correlated, but in some situations CRP and ESR give different results. Although different studies suggest the superiority of one test over the other, the combined use of CRP and ESR most likely offers the most information [30].

**TABLE 6.**  
*Conditions Associated with Elevated C-Reactive Protein Levels*

<b>Normal or Insignificant Elevation (&lt; 1 mg/dL)</b>	<b>Moderate Elevation (1–10 mg/dL)</b>	<b>Marked Elevation (&gt; 10 mg/dL)</b>
Vigorous exercise	Myocardial infarction	Acute bacterial infection (80% to 85%)
Common cold	Malignancies	Major trauma
Pregnancy	Pancreatitis	Systemic vasculitis
Gingivitis	Mucosal infection (bronchitis, cystitis)	
Cerebrovascular accident	Most rheumatic diseases	
Seizures		
Angina		

*From* Ballou S, Kushner I. Laboratory evaluation of inflammation. In: Ruddy S, Harris E, Sledge C, editors. Kelley's textbook of rheumatology. 6th edition. Philadelphia: WB Saunders; 2001; p. 698; with permission.

## **COMMONLY ASKED QUESTIONS REGARDING RHEUMATOLOGIC TESTING**

### **When Is it Appropriate to Order an Antinuclear Antibody Test?**

An ANA test is appropriate to order if the clinician has a reasonable clinical suspicion for SLE or another CTD based on the patient's history, physical findings, and results of other laboratory tests. Because of the large number of conditions associated with a positive ANA and the significant number of normal, healthy persons with a positive ANA, the ANA test should not be used for random screening for SLE or other CTDs. Ideally, clinicians use information collected from the history, physical examination, and previous laboratory work to estimate a pretest probability for disease. If patients have few signs or symptoms suggestive of disease, their pretest probability is low. A positive ANA in this case does little to increase the probability of disease and may lead to diagnostic confusion and unnecessary work-ups. On the other hand, if patients have signs and symptoms suggestive of disease, their pretest probability is higher. In this scenario, a positive ANA result can be helpful for supporting a diagnosis.

### **How Would You Evaluate an Unexplained Positive Antinuclear Antibody Test?**

An ANA test should be used primarily as a confirmatory test when the physician strongly suspects SLE or another CTD. A positive ANA in isolation never makes a specific diagnosis. Many different rheumatologic conditions and nonrheumatologic conditions can cause a positive ANA, and a substantial number of normal individuals have a positive ANA test. Therefore, a positive ANA test alone does not necessitate further work-up unless the clinical context suggests the presence of SLE or another CTD. If the ANA titer is significantly elevated, it may be worthwhile to re-evaluate the titer in 6 to 12 months.

### **If an Antinuclear Antibody Test Result is Negative, Should the Test Be Repeated, or Should Other Tests Be Done?**

Immediately repeating a negative ANA test is not necessary unless an error in testing is strongly suspected. Because systemic rheumatic diseases tend to evolve over time, if an ANA test is negative, it can be worthwhile to repeat the ANA test if the patient's clinical course develops new features consistent with a CTD.

Further antibody testing after a negative ANA test is generally not indicated. The use of HEp-2 cells as substrate has virtually eliminated false-negative ANA results. In rare instances where a CTD is strongly suspected, testing for specific autoantibodies (eg, anti-Ro, La, Jo-1, and phospholipids) and complement studies may be indicated (**Box 3**).

### Box 3. Algorithm for the Use of ANA Testing

If clinician suspects SLE or other rheumatic disease: perform ANA test

#### ANA Negative

- No further autoantibody testing is indicated. Follow patient clinically and consider repeating testing if clinically indicated.
- If there is still high clinical suspicion for:
  - SLE, consider anti-Ro/SS-A and anti-La/SS-B testing and complement studies
  - Polymyositis/dermatomyositis, consider anti-Jo-1 testing
  - Hypercoagulable state, consider antiphospholipid testing

#### ANA Positive

- If clinician suspects SLE but the diagnosis needs to be confirmed, consider testing for anti-dsDNA and anti-Sm.
- If SLE has been diagnosed and information is desired regarding prognosis or disease activity, consider testing for anti-dsDNA and anti-Ro/SS-A.
- If Sjögren's syndrome is suspected, consider testing for anti-Ro/SS-A and anti-La/SS-B.
- If polymyositis or dermatomyositis is suspected, consider testing for anti-Jo-1.
- If scleroderma is suspected, consider testing for anti-Scl-70 and anti-centromere.
- If drug-induced lupus is suspected, no further testing is indicated.
- If mixed connective tissue disease is suspected, consider testing for anti-U1 RNP.

Data from references 18–20.

## Is It Helpful to Obtain Rheumatologic Tests to Rule Out Rheumatic Disease?

Although negative rheumatologic test results can be helpful and reassuring, the frequent occurrence of false-positive results renders these tests poor screening tools. The overuse and the nonselective ordering of rheumatologic tests have not only reduced the PPV of these tests but have led to unnecessary diagnoses, treatments, referrals, and work-ups. Thus, these tests should be ordered only to confirm a suspected diagnosis. Tests ordered in a setting of low pretest probability in an effort to rule out rheumatic disease will more likely add to diagnostic confusion rather than resolution. The American College of Rheumatology recommends ANA testing in patients who have unexplained signs or symptoms involving two or more organ systems [20]. Because of the high incidence of false-positive ANA titers, testing for ANA is not indicated in patients with isolated myalgias or arthralgias in the absence of other specific clinical and laboratory findings.

## **What Testing Should Be Ordered After a Positive Antinuclear Antibody Test Result?**

Testing for specific autoantibodies after a positive ANA test result should be guided by the clinical circumstances and the suspicion of specific diseases (Box 3). The practice of “reflex” or “cascade” testing when an ANA test is positive, whereby large panels of tests are performed including various autoantibodies, is discouraged. This approach has little empirical evidence, can be costly, and can lead to erroneous diagnoses [10]. Guidelines from the College of American Pathologists suggest that for patients who meet the diagnostic criteria for SLE and have a positive ANA result, no further laboratory tests are necessary to make the diagnosis [10].

## **Which Is Better for Testing for Rheumatic Disease, C-Reactive Protein or Erythrocyte Sedimentation Rate? When Should Either One Be Ordered?**

Both tests measure components of the acute phase response and are useful for measuring generalized inflammation. The ESR is measured indirectly and is affected by multiple variables (Table 5). It is therefore less precise. However, it is inexpensive and easy to perform. The CRP is directly measured and is unaffected by the factors influencing the ESR. It rises more quickly and falls more rapidly than the ESR. The CRP is more costly, difficult to perform, and less available. Although both tests can be helpful for assessing the degree of inflammation and disease activity in rheumatic conditions, their results do not always agree. This discordance can be attributed to the variables affecting ESR levels and the different sensitivities of each test to various conditions. Many authors seem to agree that information gathered from both tests may be more helpful than either alone. The literature expresses significant contention regarding which is the better test for different rheumatic conditions.

## **What Do You Do when a Patient Has an Elevated Erythrocyte Sedimentation Rate?**

A clinician can perform a history, physical examination, and routine screening laboratory tests (complete blood count, chemistries, liver enzymes, and urinalysis) to explain an elevated ESR. Although many clinicians find an unexplained elevated ESR difficult to ignore, most of these patients do not have serious disease [32]. Most unexplained increases in ESR are transitory. If there is no obvious cause for the elevated ESR, recheck it in 1 to 3 months. The ESR level in up to 80% of patients normalizes with that time [26,32]. Follow patients for development of other signs or symptoms of disease if ESR remains elevated [26]. Consider checking a serum protein electrophoresis to rule out myeloma or polyclonal gammopathy and checking a CRP for additional evidence of an activated acute phase response [26].

### Key Points

- The results of common rheumatologic laboratory tests play an important part in the diagnosis and management of rheumatic diseases.
- Rheumatologic test results can often be ambiguous and can sometimes be misleading, particularly in primary care settings.
- Test results should be interpreted in a clinical context, which includes information derived from the history, physical examination, basic laboratory tests, radiographic and other imaging studies, and synovial fluid analysis.
- Serum rheumatologic tests are most useful for confirming a clinically suspected diagnosis.
- Because there is a high incidence of false-positive results in the general population, these tests have limited clinical utility when there is a low pretest probability.
- Recognizing the limitations of rheumatologic test may improve their utility by encouraging more selective testing and more cautious interpretation of test results.

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