Quest Diagnostics™

Autoimmune Rheumatic and Related Diseases

Laboratory Support for Classification and Diagnosis

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CLINICAL BACKGROUND

Autoimmune rheumatic diseases (ARDs) are diseases in which the immune system attacks the joints and certain systems. The cause of many of these diseases is unknown. ARDs are sometimes difficult to distinguish due to overlapping signs and symptoms: joint pain, diminished joint mobility, rash, fever, malaise, fatigue, and weight loss. Laboratory testing may be useful for the differential diagnosis and classification.

This Clinical Focus provides background on the available laboratory tests and their use in diagnosis and classification of the following autoimmune rheumatic and related diseases: gout and pseudogout, juvenile idiopathic arthritis (JIA), mixed connective tissue disease (MCTD), polymyositis and dermatomyositis (PM/DM), rheumatoid arthritis (RA), sarcoidosis, Sjögren syndrome, spondyloarthropathies (SpA), systemic lupus erythematosus (SLE) and neuropsychiatric lupus, systemic scleroderma (SSc), and systemic vasculitis. It does not cover laboratory testing as it relates to prognosis or treatment. It also does not cover nonrheumatic autoimmune diseases (ie, Crohn disease, ulcerative colitis, autoimmune hepatitis) or nonautoimmune rheumatic diseases (ie, osteoarthritis, drug-induced lupus).

INDIVIDUALS SUITABLE FOR TESTING

Individuals who have signs and symptoms consistent with 1 or more ARD **(Table 1)**.

TEST AVAILABILITY

Quest Diagnostics offers many tests and panels that may be useful for classifying or diagnosing ARDs **(Appendix Table)**.

TEST SELECTION AND INTERPRETATION

Gout and Pseudogout

The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for gout **(Table 2)** include laboratory testing for monosodium urate (MSU) crystals and serum urate. However, a patient should only be tested if he or she has had at least 1 episode of pain, swelling, or tenderness in peripheral joints. If the patient has had an episode, the presence of MSU crystals in symptomatic joints indicates gout. If MSU crystals are absent, other criteria, including serum urate levels, are needed for a diagnosis. A high titer of serum urate is consistent with gout if other clinical or imaging criteria are met.[1]

Pseudogout, also known as calcium pyrophosphate dihydrate (CPPD) crystal deposition disease, is definitively diagnosed by detection of CPPD crystals in synovial fluid or biopsy; diagnosis depends upon exclusion of other causes of arthritis.[2,3]

Table 1. Common Signs and Symptoms of Autoimmune Rheumatic and Related Diseases[a]

Sign or Symptom	Gout	JIA	MCTD	PM/DM	Pseudogout	RA	Sarcoidosis
Joint-/muscle-related							
Joint pain, stiffness, or inflammation	X	X	X	X	X	X	X
Muscle weakness			X	X			
Myalgia							
Skin-/hair-related							
Alopecia							
Rash		X	X	X			X
Raynaud phenomenon			X	X		O	
Skin lesions		X		O[b]			
General							
Anorexia						X	X
Cough							X
Ear involvement	O[c]						
Eye involvement		O					X
Fatigue				X		X	X
Fever	X	X	X	X		X	X
GI involvement							
Malaise	X					X	X
Nasal symptoms							O
Nervous system involvement							O
Respiratory involvement		X					X
Weight loss				X		X	X
Other							
Adenopathy		X					
Anemia						O	
Dysphagia				X			
Swelling of hands			X	O			O

(Continued)

Table 1. Common Signs and Symptoms of Autoimmune Rheumatic and Related Diseases[a] *(Continued)*

Sign or Symptom	SjS	SLE	SpA				SSc	Systemic Vasculitis		
			AS	ReA	PsA	EA		GPA	EGPA	MPA
Joint-/muscle-related										
Joint pain, stiffness, or inflammation	X	X	X	X	X	X	X	X	X	X
Muscle weakness		O								
Myalgia		O						X	X	X
Skin-/hair-related										
Alopecia	X	X								
Rash	X	X							X	X
Raynaud phenomenon	X	X					X			
Skin lesions		O		O	X			O		O
General										
Anorexia			X							
Cough								X	X	
Ear involvement								X[c]		
Eye involvement	X	X	X	X				X		X
Fatigue		X	X	X					X	X
Fever		X	X	X				X	X	X
GI involvement						X	X		X	X
Malaise		X							X	X
Nasal symptoms								X	X	
Nervous system involvement		X						X	X	X
Respiratory involvement								X	X	
Weight loss			X	X					X	X
Other										
Adenopathy	X	X								
Anemia		X	X							
Dysphagia	X						X			
Swelling of hands					X		X			

X indicates common; O indicates less common but not rare. AS, ankylosing spondylitis; EA, enteropathic (inflammatory bowel disease-associated) arthritis; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; MPA, microscopic polyangiitis; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; PsA, psoriatic arthritis; ReA, reactive arthritis; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SpA, spondyloarthropathies; SSc, systemic scleroderma.

[a] This is not a complete list of signs and symptoms; some conditions have more signs and symptoms than could be presented here.

[b] In dermatomyositis.

[c] External ear in gout; middle ear in GPA.

Table 2. Gout Classification Criteria[1]

Classify a patient as having gout if:

1. Patient has had ≥1 episode of pain, swelling, or tenderness in peripheral joint or bursa *and* monosodium urate crystals are present in symptomatic joint or bursa or tophus *or*
2. Patient has had ≥1 episode of pain, swelling, or tenderness in peripheral joint or bursa *and* sum of points for criteria below is ≥8

Criteria	Score
Clinical	
1. Pattern of joint involvement in monoarticular or oligoarticular episode	
– Involving ankle or midfoot (without involvement of first metatarsophalangeal joint)	1
– Involving first metatarsophalangeal joint	2
2. Characteristics of symptomatic episode:	
– Erythema on affected joint – Touch or pressure on affected joint unbearable – Inability to use affected joint	1 per characteristic
3. Time course of typical episodes[a]	
– 1 typical episode	1
– Recurrent typical episodes	2
4. Presence of tophus[b]	4
Laboratory	
1. Serum uric acid: <4 mg/dL	-4
2. Serum uric acid: ≥4 to <6 mg/dL	0
3. Serum uric acid: 6 to 8 mg/dL	2
4. Serum uric acid: 8 to <10 mg/dL	3
5. Serum uric acid: ≥10 mg/dL	4
6. Monosodium urate negative in synovial fluid of symptomatic joint or bursa	-2
Imaging	
1. Ultrasound or dual-energy computed tomography (DECT) evidence of urate deposition in symptomatic joint or bursa	4
2. Radiographic evidence of gout-related joint damage (ie, erosion)	4

[a] Typical episode is defined by ≥2 of the following, regardless of anti-inflammatory treatment: 1) maximal pain occurs in <24 hours; 2) symptoms resolve in ≤14 days; 3) symptoms completely resolve between symptomatic episodes.

[b] Clinical evidence of tophus includes draining or chalk-like nodule under transparent skin, usually located in joints, ears, olecranon bursae, finger pads, or tendons.

Juvenile Idiopathic Arthritis

The International League of Associations for Rheumatology (ILAR) classification criteria define JIA as arthritis that begins before 16 years of age, persists for ≥6 weeks, and has unknown etiology.[4] Although diagnosis of juvenile idiopathic arthritis (JIA) is primarily clinical, ILAR recommends laboratory testing to distinguish between the forms of JIA **(Table 3)**. For example, HLA-B27 antigen testing and rheumatoid factor (RF) testing can help distinguish forms of JIA. A positive HLA-B27 antigen test result is consistent with enthesitis-related arthritis. A positive RF test result differentiates RF-positive and RF-negative forms of polyarthritis. Both of these test results also serve as exclusion criteria for other forms of JIA.

Mixed Connective Tissue Disease

Patients with MCTD can present with a wide range of signs and symptoms, most of which overlap with other ARDs. Four sets of MCTD classification criteria exist: Sharp, Alarcón-Segovia, Kasukawa, and Kahn.[5] The different sets require a variety of clinical and serological criteria be met, but all 4 require either a positive result or a high titer for RNP antibody. For example, the Kasukawa criteria require a positive anti-RNP test result, whereas the Alarcon-Segovia criteria require a high RNP antibody titer **(Table 4)**. The other sets of criteria factor in different laboratory test results, including a negative result for Sm and high titers of RNP or extractable nuclear antigen antibodies.

The first indication of MCTD is often a high antinuclear antibody (ANA) titer, which occurs in 94% to 97% of MCTD patients (see Appendix for more information about ANA testing).[6] This test result should be followed by testing for antibodies to RNP, Sm, SS-A, SS-B, histone, and dsDNA.[7] Over 90% of MCTD patients are positive for antibodies to RNP, while the other antibodies occur less frequently (<20% of patients).[6,8] Antibodies to dsDNA, Sm, and SS-A can be seen transiently in MCTD, but consistent presence of these antibodies may indicate SLE.[7]

Polymyositis and Dermatomyositis

Validated diagnostic criteria for PM and DM do not exist, but the Bohan and Peter criteria[9] **(Table 5)** are commonly used and are supported by the International Myositis Assessment and Clinical Studies Group for enrollment of PM and DM patients in clinical trials.[10] Laboratory testing for muscle enzyme levels (creatine kinase, aldolase, transaminases, lactate dehydrogenase) can assist with diagnosis according to Bohan and Peter criteria.

Table 3. Juvenile Idiopathic Arthritis Classification Criteria[4]

General

1. Arthritis begins before 16 years of age
2. Arthritis persists ≥6 weeks
3. Other potential causes of arthritis are excluded

JIA Form	Inclusion Criteria	Exclusion Criteria
Systemic arthritis	1. Arthritis in ≥1 joint *and* 2. Fever for ≥2 weeks that is daily for ≥3 days *and* 3. ≥1 of the following: 1. Evanescent erythematous rash 2. Generalized adenopathy 3. Hepatomegaly, splenomegaly, or both 4. Serositis	See footnotes a, b, c, and d.
Oligoarthritis	*Persistent form*: Arthritis in 1 to 4 joints during first 6 months of disease *and* in ≤4 joints during disease course *Extended form*: Arthritis in 1 to 4 joints during first 6 months of disease *and* in >4 joints after first 6 months	See footnotes a, b, c, d, and e.
Polyarthritis (RF negative)	Arthritis in ≥5 joints during first 6 months of disease *and* negative results in RF test	See footnotes a, b, c, d, and e.
Polyarthritis (RF positive)	Arthritis in ≥5 joints during first 6 months of disease *and* positive results in ≥2 RF tests run ≥3 months apart during first 6 months	See footnotes a, b, c, and e.
Psoriatic arthritis	1. Arthritis *and* psoriasis *or* 2. Arthritis *and* ≥2 of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. 1st degree relative with psoriasis	See footnotes b, c, d, and e.
Enthesitis-related arthritis	1. Arthritis *and* enthesitis *or* 2. Arthritis *or* enthesitis *and* ≥2 of the following: 1. Sacroiliac joint tenderness *and/or* inflammatory lumbosacral pain 2. Positive for HLA-B27 antigen 3. Arthritis onset in male >6 years of age 4. Acute anterior uveitis 5. 1st degree relative with ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, reactive arthritis, *or* acute anterior uveitis	See footnotes a, d, and e.
Undifferentiated arthritis	Arthritis that fulfills criteria for none of the above or ≥2 of the above types	NA

IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; NA, not applicable; RF, rheumatoid factor.

[a] Psoriasis in patient or 1st degree relative.

[b] Arthritis beginning after 6th birthday in HLA-B27-positive male.

[c] 1st degree relative with ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, reactive arthritis syndrome, or acute anterior uveitis.

[d] Positive results in ≥2 RF tests run ≥3 months apart.

[e] Presence of systemic JIA.

Table 4. Mixed Connective Tissue Disease Diagnostic Criteria[a,5]

Kasukawa Criteria	Alarcón-Segovia Criteria
Diagnose MCTD if: 1. RNP antibody test is positive *and* 2. ≥1 common symptom is present *and* 3. ≥1 mixed symptom in ≥2 disease categories *Common Symptoms* 1. Raynaud phenomenon 2. Swollen fingers or hands *Mixed Symptoms* 1. SLE-like symptoms (polyarthritis, lymphadenopathy, facial erythema, pericarditis or pleuritis, leukothrombocytopenia) 2. SSc-like findings (sclerodatyly, pulmonary fibrosis, restrictive changes of lung, reduced diffusion capacity, hypomotility or dilation of esophagus) 3. PM-like findings (muscle weakness, elevated serum levels of muscle enzymes [creatinine phosphokinase], myogenic pattern on electromyogram)	**Diagnose MCTD if:** 1. RNP antibody titer >1:1,600 *and* 2. ≥3 clinical criteria present, including synovitis or myositis *Clinical Criteria* 1. Edema in hands 2. Synovitis 3. Myositis 4. Raynaud phenomenon 5. Acrosclerosis

MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; SSc, systemic scleroderma; PM, polymyositis.
[a] Two of 4 existing MCTD criteria are shown here; they were selected because of their higher reported sensitivity and specificity (though the Kahn criteria perform similarly to Alarcón-Segovia criteria).[5,6]

ANA testing is not included in the Bohan and Peter criteria, but it can support diagnosis (see Appendix for more information about ANA testing). Between 40% and 80% of PM and DM patients test positive for ANAs.[11] Eleven percent to 20% test positive for the autoantibody Jo-1[12]; Jo-1 is rare in patients with other ARDs. Thus, a positive test result for Jo-1 antibody is consistent with PM and DM in a symptomatic patient.

Table 5. Polymyositis and Dermatomyositis Diagnostic Criteria[9]

Classify patient as having definite DM if ≥3 of the following criteria *and* rash[a] are present.[b]

Classify patient as having definite PM if all 4 of the following criteria (without rash[a]) are present.[b]

Criteria

1. Progressive proximal muscle weakness
2. Elevated muscle enzyme levels in serum (creatine kinase, aldolase, transaminases, lactate dehydrogenase)
3. Abnormal electrical activity on electromyography (polyphasic, short, and small action potentials; fibrillations, positive sharp waves, and insertional irritability; high-frequency repetitive discharges)
4. Muscle biopsy findings consistent with PM or DM (necrosis, phagocytosis, regeneration, inflammation)

[a] Heliotrope rash, Göttron sign, or Göttron papules.
[b] Classify patient as having probable DM if 2 of the criteria *and* rash are present; classify patient as having probable PM if 3 of the criteria (without rash) are present.

Rheumatoid Arthritis

Rheumatoid Factor and Cyclic Citrullinated Peptide

The ACR/EULAR classification criteria for RA **(Table 6)** include testing for autoantibodies to RF and cyclic citrullinated peptide (CCP).[13] RF is a widely used laboratory marker of RA. The reported sensitivity of RF is 57% for early RA[14] and ranges from 60% to 86% for established RA.[15,16] Positive RF results are suggestive of RA, but the relatively low specificity (70%-85%) precludes a definitive diagnosis for either early or established disease.[14,16-20] Negative RF results are consistent with conditions other than RA but do not rule out RA; 14% to 43% of patients with RA are seronegative.[14-16]

The sensitivity of CCP antibody is comparable to that of RF in early (59%)[14] and established RA (64%-88%).[15,18] Unlike RF, CCP antibody is highly specific (90%-98%) for early and established RA.[14,17,19,21] Most side-by-side comparisons

Table 6. Rheumatoid Arthritis Classification Criteria[13]

Classify a patient as having RA if sum of points is ≥6.	
Criteria	**Points**
Joint involvement	
1. 1 large joint	0
2. 2-10 large joints	1
3. 1-3 small joints, with or without large joint	2
4. 4-10 small joints, with or without large joint	3
5. >10 joints with ≥1 small joint	5
Symptom duration	
1. <6 weeks	0
2. ≥6 weeks	1
RF and CCP antibody	
1. Normal RF and CCP antibody	0
2. Low-positive RF or CCP antibody	2
3. High-positive RF or CCP antibody	3
CRP and ESR	
1. Normal CRP and ESR	0
2. Elevated CRP or ESR	1

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

demonstrate that CCP antibody is at least as sensitive as and more specific than RF in various clinical situations.[15-18,20,22] Thus, positive CCP antibody results are highly suggestive of RA[14,17,19,21]; however, patients with other rheumatic diseases may also have elevated titers. Negative results are consistent with RA and other rheumatic diseases. They do not rule out a diagnosis of RA; 12% to 41% of patients with RA are CCP seronegative.[14,18] In RF-positive patients with chronic HCV or other infections associated with polyarticular arthritis, a positive CCP antibody result suggests a likely diagnosis of coexisting RA; HCV patients with cryoglobulinemia, but not RA, typically have negative CCP antibody results.[23]

The combination of RF and CCP antibodies provides greater sensitivity than either assay alone[15,16,20] and is commonly used in the diagnostic evaluation of suspected RA. The combination of a positive IgM RF *and* CCP antibody result is highly suggestive of RA (~90%-100%). However, this test result may be found in some patients with other rheumatic diseases such as SLE, scleroderma, and psoriatic arthritis. Patients with negative RF and positive CCP antibody results are also likely to have RA. Patients with positive RF and negative CCP results are less likely to have RA, but RA remains a possibility. Negative results on both assays indicate a low likelihood of RA but do not exclude the diagnosis. Between 28% and 44% of patients with early disease test negative for both RF and CCP antibodies,[24,25] which has led to the search for other RA markers.

14-3-3η

The 14-3-3η protein is elevated in serum and synovial fluid during joint inflammation and is a relatively new RA marker.[26] Although it is not yet included in the ACR/EULAR classification criteria, 14-3-3η antibody test sensitivity (64%) was higher than that of RF (57%) or CCP antibody (59%) in early RA patients in a side-by-side comparison.[14] In patients with established RA, the sensitivity of 14-3-3η (77%) was comparable to that of RF or CCP antibody and specificity (93%) fell between that of RF and CCP antibody.[14] Thus, positive 14-3-3η results are suggestive of RA.[14] However, negative results do not rule out RA; 23% to 36% of patients with RA are 14-3-3η seronegative.[12] In a patient with a personal or family history of psoriasis, nail changes, and back or heel pain along with peripheral joint polyarthritis, a positive 14-3-3η result is consistent with a diagnosis of psoriatic arthritis.

Adding 14-3-3η testing to RF and CCP antibody testing provides greater sensitivity for early RA: 78% with 14-3-3η versus 72% without 14-3-3η.[14] In seronegative patients, 14-3-3η detects 21% of patients with early RA and 67% of patients with established RA.[14] This increased sensitivity may translate into treatment earlier in the course of disease, which can minimize irreversible joint damage. In patients with suspected RA, a positive/elevated result of RF, CCP antibody, and/or 14-3-3η protein suggests an RA diagnosis. Negative/normal results for all 3 markers indicate that an RA diagnosis is less likely.

C-reactive Protein and Erythrocyte Sedimentation Rate

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) measurements are also included in the ACR/EULAR classification criteria for RA **(Table 6)**. Elevated levels are consistent with an RA diagnosis if other laboratory and clinical criteria are met **(Table 6)**. In patients with RA, elevated levels of CRP or ESR indicate heightened disease activity. However, elevations may also be due to other inflammatory conditions. Normal CRP and ESR results indicate relatively low disease activity. In patients with discordant CRP and ESR results, CRP levels may be the more reliable marker of RA disease activity.[27]

Sarcoidosis

According to the American Thoracic Society (ATS), diagnosis of sarcoidosis requires 3 criteria **(Table 7)**.[28] The identification of noncaseating granulomas via biopsy is a strong indication of sarcoidosis; however, other causes of granulomatous disease must be excluded.[28] Because other diseases must be excluded, laboratory tests may indirectly help with diagnosis.

No laboratory tests are diagnostic for sarcoidosis due to lack of specificity, but some tests can support diagnosis. The following lab results are consistent with sarcoidosis: leukopenia, anemia, thrombocytopenia, elevated urinary calcium:creatinine ratio, and elevated serum levels of calcium, blood urea nitrogen (BUN), liver enzymes, immunoglobulins, or angiotensin-converting enzyme (ACE).[29] The ATS recommends including peripheral blood counts, urine analysis, and serum levels of calcium, liver enzymes, creatinine, and BUN as part of a work-up once a diagnosis is confirmed.[28]

Sjögren Syndrome

The American College of Rheumatology (ACR) classification criteria for Sjögren syndrome require 2 out of 3 criteria be met **(Table 8)**.[31] One criterion involves a relatively invasive procedure (labial salivary gland biopsy) and may not be necessary if the other clinical and laboratory results are consistent with Sjögren syndrome.[32] Laboratory evaluation can include testing for SS-A/Ro and SS-B/La antibodies. A positive result for either test is consistent with Sjögren syndrome; a test for anti-SS-A or anti-SS-B has a sensitivity of 84% and specificity of 92%.[31] Alternatively, a positive RF test result (sensitivity, 72%; specificity, 86%) in addition to an ANA titer ≥1:320 (sensitivity, 73%; specificity, 80%) is consistent with the Sjögren syndrome (see Appendix for more information about ANA testing).[31]

Table 7. Sarcoidosis Diagnostic Criteria[28]

Diagnose sarcoidosis if patient has all of the following criteria:

1. Clinical or radiological presentation[a]
2. Presence of noncaseating granulomas
3. Absence of alternative diseases[b]

[a] Chest x-ray or CT can identify hilar or mediastinal lymphadenopathy, upper lobe disease, subpleural reticulonodular infiltrates, peribronchial thickening, or traction bronchiectasis of the upper lobe.[30]

[b] Sarcoidosis shares signs and symptoms with other conditions including tuberculosis, prescription drug use (eg, methotrexate), granulomatous lesions of unknown significance (GLUS) syndrome, lymphoma, idiopathic pulmonary fibrosis, berylliosis, and multiple other infectious diseases.[28,29]

Table 8. Sjögren Syndrome Classification Criteria[31]

Classify a patient as having Sjögren syndrome if ≥2 of the following criteria are met:

1. SS-A/Ro antibody, SS-B/La antibody, or both are positive *or* RF is positive and ANA titer ≥1:320
2. Labial salivary gland biopsy exhibits focal lymphocytic sialadenitis (focus score ≥1 focus/4 mm^2)
3. Keratoconjunctivitis sicca (ocular staining score ≥3)[a]

Exclusion criteria: radiation treatment of head and neck, hepatitis C infection, AIDS, sarcoidosis, amyloidosis, graft versus host disease, IgG4-related disease

[a] If patient is not using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in last 5 years.

Spondyloarthropathies

The term "spondyloarthropathies" (SpA) encompasses a group of inflammatory rheumatic diseases that cause arthritis; these include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease-associated arthritis. SpA can be subdivided into axial SpA, which involves the spine and sacroiliac joints, and peripheral SpA, which involves peripheral arthritis, enthesitis, and dactylitis.[33,34] Overlapping presentations involving both axial and peripheral joints may occur.

The Assessment of SpondyloArthritis International Society (ASAS) has released classification criteria for axial SpA and peripheral SpA.[33,34] Laboratory testing for human leukocyte antigen (HLA)-B27 can help identify individuals with SpA.[33,34] The axial SpA criteria have radiographic (imaging) and clinical arms, both of which incorporate HLA-B27 testing **(Table 9)**; these criteria (ie, fulfilling criteria of either arm) have a sensitivity of 83% and a specificity of 84%.[2] The peripheral SpA criteria also incorporate HLA-B27 testing and have a sensitivity of 78% and a specificity of 82%.[33]

A positive HLA-B27 result is consistent with any type of SpA (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, or inflammatory bowel disease-associated arthritis), acute anterior uveitis, or juvenile idiopathic arthritis. However, most people who are HLA-B27 positive do not develop an associated condition. Thus, diagnosis and classification should be based on multiple criteria.[33,34] A negative HLA-B27 result does not rule out conditions associated with HLA-B27; the allele is not always present in patients with these conditions.

CRP levels can also assist with classification of axial SpA. Elevated levels are consistent with axial SpA in the presence of other criteria. A negative result does not rule out a classification of SpA since other criteria may be met.

Systemic Lupus Erythematosus and Neuropsychiatric Lupus

According to the Systemic Lupus International Collaborating Clinics (SLICC), a combination of clinical and immunologic criteria must be met for classification as SLE **(Table 10)**.[35] Laboratory testing can help assess some clinical criteria (anemia, leukopenia, lymphopenia, thrombocytopenia) and all immunologic criteria derived from ANA, dsDNA, Sm, and antiphospholipid antibody testing and from C3, C4, CH50, and direct Coombs testing. Laboratory testing can also help assess SLE based on the 1997 ACR classification criteria, which include proteinuria, anemia, leukopenia, lymphopenia, thrombocytopenia, and antibodies to DNA, Sm, antiphospholipids, and ANA.[36,37]

When considered individually, most of the laboratory tests included in the SLICC classification criteria provide high specificity (86% to 99%) and low to medium sensitivity for SLE (7% to 59%). The exception is ANA testing, which has medium specificity (45%) and high sensitivity (96%)[35]; a negative ANA test can help rule out SLE because ANA-negative SLE is rare (see Appendix for more information about ANA testing).[38]

Though not included in the SLICC classification criteria, chromatin antibodies have relatively high sensitivity for SLE (64% to 69%) and high specificity (92% to 99%)[39,40] and may provide value when diagnosing SLE. RNP antibodies are also present in SLE patients, but are not specific to SLE; RNP antibodies are more useful for identifying MCTD.[41,42]

Neuropsychiatric lupus has a broad range of symptoms in the central or peripheral nervous systems. Validated diagnostic criteria do not exist, but diagnosis usually involves a clinical evaluation that is supported by results from brain MRI, serology and cerebrospinal fluid (CSF) testing, and neuropsychiatric assessment; diagnosis also requires the exclusion of other potential causes of neuropsychiatric signs and symptoms.[38] Laboratory testing can indirectly help diagnose neuropsychiatric lupus by excluding other causes, including infectious diseases. In addition, compared to SLE patients without neuropsychiatric disease, patients with neuropsychiatric lupus often have higher serum levels of neuronal antibodies or antibodies to ribosomal P, cardiolipin, lupus anticoagulants, or phospholipids.[43]

Systemic Scleroderma

The ACR/EULAR classification criteria for systemic scleroderma (SSc, **Table 11**) include mainly clinical criteria, but laboratory testing for autoantibodies is included.[44] A positive test for centromere, Scl-70 (topoisomerase I), or RNA polymerase III antibodies is consistent with SSc but is not diagnostic by itself. A positive ANA test supports testing for specific autoantibodies if clinical symptoms are consistent with SSc; 85% to 97% of patients with SSc are ANA-positive (see Appendix for more information about ANA testing).[45,46]

The 2 most common types of SSc are diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc), also called CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome. The type of SSc can affect prognosis and treatment. Differentiation may be possible based on location of skin fibrosis (proximal vs distal extremities) and clinical manifestations, but laboratory test results can support differentiation. Scl-70 antibody is found in approximately 40% of patients with dcSSc, whereas centromere antibody is found in up to 90% of patients with lcSSc.[47] When detected by indirect immunofluorescence,

Table 9. Spondyloarthropathy Classification Criteria

Classify patient as having **axial SpA**[34] if the patient:		Classify patient as having **peripheral SpA**[33] if the patient:
1. Has back pain for ≥3 months *and*		1. Has only peripheral manifestations *and*
2. Is <45 years at onset *and*		2. Arthritis, enthesitis, or dactylitis *and*
3. Meets criteria in clinical or imaging arm		3. ≥1 SpA feature from footnote b or ≥2 other SpA features from footnote c
Clinical Arm	**Imaging Arm**	
1. HLA-B27 *and* 2. ≥2 other SpA features from footnote a	1. Sacroiliitis on imaging *and* 2. ≥1 SpA feature from footnote a	

[a] HLA-B27, inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn disease or ulcerative colitis, response to NSAIDs, family history of SpA, elevated C-reactive protein levels.
[b] HLA-B27, uveitis, psoriasis, Crohn disease or ulcerative colitis, preceding infection, sacroiliitis on imaging.
[c] Arthritis, enthesitis, dactylitis, inflammatory back pain, family history of SpA.

Table 10. SLE Classification Criteria[35]

Classify a patient as having SLE if:

1. 4 criteria are met, including ≥1 clinical and ≥1 immunologic criterion *or*
2. Biopsy-proven nephritis compatible with SLE *and* ANA *or* dsDNA antibodies are present

Clinical Criteria

1. Acute cutaneous lupus in the absence of dermatomyositis *or* subacute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral ulcers[a] *or* nasal ulcers[a]
4. Nonscarring alopecia[a]
5. Synovitis of ≥2 joints *or* tenderness of ≥2 joints and >30 minutes morning stiffness
6. Pleurisy (>1 day), pleural effusion, or pleural rub[a] *or* pericardial pain (>1 day), pericardial effusion, pericardial rub, or pericarditis by ECG[a]
7. Urine protein-to-creatinine ratio indicates 500 mg protein/24 hours *or* red blood cell casts
8. Seizures, psychosis, myelitis, mononeuritis multiplex [a], peripheral or cranial neuropathy,[a] or acute confusional state[a]
9. Hemolytic anemia
10. Leukopenia (<4,000/mm^3)[a] *or* lymphopenia (<1,000/mm^3)[a]
11. Thrombocytopenia (<100,000/mm^3)[a]

Immunologic Criteria

1. ANA level above reference range
2. dsDNA antibody level above reference range (or > twice reference range if tested by ELISA)
3. Sm antibody positive
4. Antiphosopholipid antibody positive[b]
5. Low C3, C4, or CH50
6. Direct Coombs test if hemolytic anemia is absent

[a] If no other cause is present.

[b] As determined by positive result for lupus anticoagulant; false-positive result for rapid plasma reagin; medium- to high-titer of cardiolipin antibody; or positive results for β2-glycoprotein I antibody.

immunoprecipitation, or immunodiffusion, Scl-70 and centromere antibodies are almost always mutually exclusive in SSc patients: only 0.5% test positive for both.[47] Thus, a positive test result for Scl-70 antibody is consistent with dcSSc if clinical symptoms are present, and a positive test result for centromere antibody is consistent with lcSSc if clinical symptoms are present.

Systemic Vasculitis

The ACR has created classification criteria for 2 autoimmune systemic vasculitis disorders **(Table 12)**: granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis)[48] and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome).[49] Laboratory tests are included in both sets of criteria. If GPA is suspected, testing for microhematuria can assist with classification. If EGPA is suspected, testing for eosinophilia can assist with classification. Other routine laboratory test results can suggest systemic vasculitis. Anemia, leukocytosis, thrombocytosis, and elevated ESR and CRP levels are consistent with an acute phase response.[50]

Diagnosis should be confirmed via biopsy of the affected tissue when possible; this is true for GPA, EGPA, and another autoimmune systemic vasculitis disorder, microscopic polyangiitis (MPA). Classification criteria for MPA are

Table 11. Systemic Scleroderma Classification Criteria[44]

Classify a patient as having systemic sclerosis if sum of points is ≥9.

Criteria	Points
Skin thickened on fingers of both hands, extending proximal to the metacarpophalangeal joints	9
Skin on fingers thickened (only count highest score)	
– Puffy fingers	2
– Sclerodactyly[a]	4
Lesions on fingertips (only count highest score)	
– Ulcers on tip of digits	2
– Pitting scars on fingertips	3
Telangiectasia	2
Abnormal nailfold capillaries	2
Pulmonary arterial hypertension and/or interstitial lung disease (max score is 2)	
– Pulmonary arterial hypertension	2
– Interstitial lung disease	2
Raynaud phenomenon	3
Presence of any SSc-related autoantibodies[b]	3

[a] Distal to metacarpophalangeal joints but proximal to proximal interphalangeal joints.

[b] 3 points for 1 or more of the following antibodies: centromere, Scl-70, or RNA polymerase III antibody; maximum score is 3.

Table 12. Granulomatosis with Polyangiitis and Eosinophilic Granulomatosis with Polyangiitis Classification Criteria

Classify patient as having **granulomatosis with polyangiitis** if ≥2 of the following are present[48]:	Classify patient as having **eosinophilic granulomatosus with polyangiitis** if ≥4 of the following are present[49]:
1. Oral ulcers or bloody or purulent nasal discharge	1. Asthma
2. Nodules, fixed infiltrates, or cavities on chest radiograph	2. Eosinophilia >10%
3. Microhematuria or red cell casts in urine sediment	3. Mono- or polyneuropathy
4. Granulomatous inflammation in wall of artery or peri- or extra-vascular area	4. Nonfixed pulmonary infiltrates
	5. Paranasal sinus abnormality
	6. Extravascular esoinophils

not published, but clinical and histological findings in patients with MPA include fibrinoid necrotizing vasculitis of predominantly small vessels without immune deposits, focal segmental necrotizing glomerulonephritis, pulmonary capillaritis, and neutrophilic infiltration of the alveolar wall.[50]

Differential diagnosis of GPA, EGPA, and MPA can be aided by testing for specific antineutrophil cytoplasmic antibodies (ANCA).[51] Each disorder is associated with predominance of a specific ANCA type.[52] The ANCA types are revealed by fluorescent patterns obtained in an indirect immunofluorescence ANCA screen. For example, the cytoplasmic pattern (C-ANCA) is very common in GPA, but not MPA or EGPA. The perinuclear pattern (P-ANCA), on the other hand, is rare in GPA, common in MPA, and moderately common in EGPA cases. The atypical P-ANCA pattern is rare in all 3 of these; it is usually associated with nonvasculitic conditions such as inflammatory bowel disease.[53] The sensitivity and specificity of these markers for the various disorders are summarized in **(Table 13)**.[54-56]

The diagnostic accuracy of the ANCA screen can be improved by combining it with immunoassays specific for myeloperoxidase (MPO) and proteinase-3 (PR3) antibodies. An international consensus group recommends this approach.[52] Though the C-ANCA pattern typically reflects specificity to PR3, there is not 100% concordance between C-ANCA and PR3 antibody as C-ANCA has multiple targets. Similarly, the P-ANCA pattern predominantly reflects MPO specificity.

A positive ANCA screen supports a diagnosis of autoimmune-related systemic vasculitis in a symptomatic patient **(Table 13)**. Positive results are also seen in inflammatory bowel disease (ulcerative colitis) and occasionally in other autoimmune diseases (SLE, RA, autoimmune hepatitis). Exposure to certain drugs (eg, propylthiouracil, hydralazine, methimazole) and infectious agents (eg, hepatitis C virus) can result in secondary vasculitis and an ANCA-positive screen result.[57,58] A negative ANCA, MPO antibody, and/or PR3 antibody result does not rule out systemic vasculitis.

Owing to limitations in sensitivity and specificity, ANCA, MPO antibody, and PR3 antibody test results should be interpreted carefully in light of clinical and other laboratory data.

Table 13. Diagnostic Accuracy of Antibodies for Systemic Vasculitis

Markers	% Sensitivity (Specificity)		
	GPA[a,56]	MPA[a,56]	EGPA[54]
ANCA	85 (93)	68 (87)	31
C-ANCA	81 (100)	3 (93)	5
C-ANCA+/PR3+	69 (100)	0	1
P-ANCA	4 (94)	65 (94)	21
P-ANCA+/MPO+	2 (99)	48 (100)	20

GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis.

[a] Sensitivity and specificity based on patients tested for ANCA in a rheumatology clinic.

APPENDIX
Antinuclear Antibody Testing

The laboratory work-up for patients with suspected rheumatic disease often begins with an antinuclear antibody (ANA) screen. The classic ANA testing approach uses HEp-2 human tissue culture cells in an immunofluorescence assay (IFA) to detect autoantibodies directed against antigens in the cell cytoplasm and nucleus. Because it is highly sensitive, this method is considered by the American College of Rheumatology (ACR) to be the current gold standard.[41]

The high sensitivity of IFA stems from inclusion of a large number of antigens; however, these antigens are not very disease specific. Analyte-specific immunoassays are more disease specific owing to the use of antigens strongly associated with particular rheumatic diseases.

Multiplex immunoassays can identify multiple autoantibodies simultaneously, but the number of antibodies detected is fewer than in the IFA; this difference results in lower sensitivity. Thus, the IFA and immunoassay methods complement each other for the initial evaluation of suspected rheumatic disorders. When ANA is positive by IFA, especially with high titer, testing for disease-specific antibodies can help with differential diagnosis.

Samples with an IFA titer <1:40 are considered negative for ANA antibodies; follow-up with more specific testing is not needed. Higher titers are generally associated with greater likelihood of rheumatic disease, but do not reflect disease activity. When results are positive, various fluorescent staining patterns are observed in the nucleus or the cytoplasm. These patterns can aid in the differential diagnosis of rheumatic disease and guide selection of further testing for specific autoantibodies.

Table. Laboratory Tests for Classification and Diagnosis of Autoimmune Rheumatic and Related Diseases[a]

Test Code	Test Name	Clinical Use
Gout and Pseudogout		
4563	Crystals, Synovial Fluid	Diagnose gout and pseudogout
Juvenile Idiopathic Arthritis		
4420	C-Reactive Protein (CRP)	Diagnose axial spondyloarthritis and assess disease activity
528	HLA-B27 Antigen	Diagnose spondyloarthropathies
Mixed Connective Tissue Disease		
19875[b]	ANA Screen, IFA, with Reflex to Titer and Pattern (Mixed Connective Panel 1) Includes ANA screen (IFA) with a reflex to titer and pattern and RNP antibody.	Diagnose MCTD
90074[b]	ANA Screen, IFA, with Reflex to Titer and Pattern (Mixed Connective Panel 2) Includes ANA screen (IFA) with reflexes to titer and pattern; dsDNA, RNP, and Scl-70 antibodies.	Diagnose MCTD
19887	RNP Antibody	Diagnose SLE or MCTD
38567	Sm/RNP Antibody	Diagnose SLE or MCTD
Polymyositis and Dermatomyositis		
227	Aldolase	Diagnose PM/DM
374	Creatine Kinase (CK), Total	Diagnose PM/DM
5810(X)	Jo-1 Antibody	Diagnose PM/DM
593	Lactate Dehydrogenase (LD)	Diagnose PM/DM

(Continued)

Table. Laboratory Tests for Classification and Diagnosis of Autoimmune Rheumatic and Related Diseases[a] *(Continued)*

Test Code	Test Name	Clinical Use
10185(X)[c]	Myositis AssessR™ plus Jo-1 Antibodies Includes PL-7 (test code 1226), PL-12 (test code 1224), Mi-2 (test code 3241), Ku (test code 1222), EJ (test code 1225), OJ (test code 1223), SRP (test code 1227), and Jo-1 (test code 5810[X]) antibodies.	Diagnose PM/DM
7809(X)[d]	Polymyositis/Dermatomyositis Antibody Panel 1 Includes Jo-1 (test code 5810[X]) and PM-Scl (test code 37103) antibodies.	Diagnose PM/DM
Rheumatoid Arthritis		
91455[e]	14-3-3 eta Protein	Diagnose RA; more sensitive than either RF or CCP for early RA[14]
90071[b]	ANA Screen, IFA, with Reflex to Titer and Pattern (Rheumatoid Arthritis Panel 1) Includes ANA screen (IFA) with reflex to titer and pattern; cyclic citrullinated peptide (CCP) IgG; rheumatoid factor antibody.	Diagnose RA
92813[b,e]	ANA Screen, IFA, with Reflex to Titer and Pattern (Rheumatoid Arthritis Panel 2) Includes ANA screen (IFA) with reflex to titer and pattern, 14-3-3 eta protein; cyclic citrullinated peptide (CCP) IgG; rheumatoid factor.	Diagnose RA
4420	C-Reactive Protein (CRP)	Diagnose RA and assess disease activity
11173	Cyclic Citrullinated Peptide (CCP) Antibody (IgG)	Diagnose and determine prognosis of RA; more specific than RF
809	Erythrocyte Sedimentation Rate (ESR)	Diagnose RA and assess disease activity
657	Mucin Clot, Synovial Fluid	Differential diagnosis of diseases of joints and joint fluid
91472[e]	Rheumatoid Arthritis Diagnostic IdentRA® Panel 2 Includes 14-3-3 eta protein, cyclic citrullinated peptide (CCP) IgG, and rheumatoid factor.	Diagnose RA; provides additional diagnostic and prognostic value relative to each assay alone
92812[e]	Rheumatoid Arthritis Diagnostic IdentRA® Panel 4 Includes 14-3-3 eta protein, cyclic citrullinated peptide (CCP) IgG, rheumatoid factor antibodies (IgA, IgG, IgM), and SS-A and SS-B antibodies.	Diagnose RA; may help differentiate RA from RA with secondary Sjögren syndrome
17669(X)	Rheumatoid Arthritis Diagnostic Panel 1 Includes cyclic citrullinated peptide (CCP) IgG and rheumatoid factor.	Diagnose RA
19878(X)	Rheumatoid Arthritis Diagnostic Panel 3 Includes cyclic citrullinated peptide (CCP) IgG; rheumatoid factor (IgA, IgG, and IgM); and SS-A and SS-B antibodies.	Diagnose RA; may help differentiate RA from RA with secondary Sjögren syndrome
4418	Rheumatoid Factor	Diagnose and determine prognosis of RA; detects primarily IgM RF
15682	Rheumatoid Factor (IgA)	Diagnose RA; provides added specificity when used in combination with other RF or CCP antibody assays; may help predict severity of disease course
19705(X)	Rheumatoid Factor (IgA, IgG, IgM)	Diagnose RA; detecting all 3 isotypes improves specificity and predictive value

(Continued)

Table. Laboratory Tests for Classification and Diagnosis of Autoimmune Rheumatic and Related Diseases[a] *(Continued)*

Test Code	Test Name	Clinical Use
15683	Rheumatoid Factor (IgG)	Diagnose RA; provides added specificity when used in combination with other RF or CCP antibody assays
15384[b]	Rheumatoid Factor Screen with Reflex to Titer, Synovial Fluid	Diagnose RA and determine prognosis
Sarcoidosis		
8561	Absolute Lymphocyte Count	Support diagnosis of sarcoidosis
683	Angiotensin Converting Enzyme (ACE)	Support diagnosis of sarcoidosis
303	Calcium	Support diagnosis of sarcoidosis
1635(X)	Calcium, 24-Hour Urine with Creatinine	Support diagnosis of sarcoidosis
6399	CBC (Includes Differential and Platelets)	Support diagnosis of sarcoidosis
375(X)	Creatinine	Support diagnosis of sarcoidosis and determine extent of organ involvement
7083	Immunoglobulins Panel, Serum Includes IgA, IgG, and IgM.	Support diagnosis of sarcoidosis
294	Urea Nitrogen (BUN)	Support diagnosis of sarcoidosis and determine extent of organ involvement
Sjögren Syndrome		
90077[b]	ANA Screen, IFA, with Reflex to Titer and Pattern (Sjögren's Panel 1) Includes ANA screen (IFA) with reflex to titer and pattern; rheumatoid factor; and SS-A and SS-B antibodies.	Diagnose Sjögren syndrome
19880(X)[b]	ANA Screen, IFA, with Reflex to Titer and Pattern (Sjögren's Panel 2) Includes ANA screen (IFA) with reflex to titer and pattern (test code 249); mitochondrial antibody screen with reflex to titer (test code 259); rheumatoid factor (test code 4418); and SS-A (test code 38568), SS-B (test code 38569), and thyroid peroxidase (test code 5081) antibodies.	Diagnose Sjögren syndrome
4418	Rheumatoid Factor	Diagnose Sjögren syndrome
38568	Sjögren's Antibody (SS-A)	Diagnose Sjögren syndrome
38569	Sjögren's Antibody (SS-B)	Diagnose Sjögren syndrome
7832	Sjögren's Antibodies (SS-A, SS-B)	Diagnose Sjögren syndrome
Systemic Lupus Erythematosus		
8561	Absolute Lymphocyte Count	Detect lymphopenia
90072[b]	ANA Screen, IFA, with Reflex to Titer and Pattern (Lupus Panel 1) Includes ANA screen (IFA) with reflex to titer and pattern and chromatin (nucleosomal), dsDNA, and Sm antibodies.	Diagnose SLE
29839[b]	ANA Screen, IFA, with Reflex to Titer and Pattern (Lupus Panel 2) Includes ANA screen (IFA) with reflex to titer and pattern; also includes dsDNA, scleroderma (Scl-70), Sm, Sm/RNP, SS-A, and SS-B antibodies.	Diagnose SLE

(Continued)

Table. Laboratory Tests for Classification and Diagnosis of Autoimmune Rheumatic and Related Diseases[a] *(Continued)*

Test Code	Test Name	Clinical Use
19881(X)[b]	ANA Screen, IFA, with Reflex to Titer and Pattern (Lupus Panel 3) Includes ANA screen (IFA) with reflex to titer and pattern; also includes chromatin (nucleosomal), dsDNA, RNP, Sm, SS-A, and SS-B antibodies; complement components C3 and C4 and total complement (CH50).	Diagnose SLE
37491[b,e]	ANA Screen, IFA, with Reflex to Titer and Pattern (Lupus Panel 5) Includes ANA screen (IFA) with reflex to titer and pattern (test code 249); also includes actin (IgG, test code 15043), gastric parietal cell (test code 15114), rheumatoid factor (test code 4418), ribosomal P (test code 34283), Scl-70 (test code 4942), Sm (test code 37923), Sm/RNP (test code 38567), SS-A (test code 38568), SS-B (test code 38569), and thyroid peroxidase (test code 5081) antibodies; dsDNA (Crithidia, test code 37092); mitochondrial (test code 259), myocardial (test code 261), reticulin (test code 37520), and striated muscle antibody (test code 266) screens with reflex to titers; and C3 and C4 complement components (test code 5704).	Diagnose SLE
30340	Beta-2-Glycoprotein I Antibodies (IgG, IgA, IgM)	Diagnose SLE
7352	Cardiolipin Antibodies (IgA, IgG, IgM)	Diagnose SLE
34088	Chromatin (Nucleosomal) Antibody	Diagnose SLE
37859(X)	Complement Component C3, C4, CH50	Diagnose SLE
361	Direct Antiglobulin Test (DAT)	Determine presence of autoimmune hemolytic anemia
255	DNA (ds) Antibody	Diagnose SLE
427	Erythropoietin	Determine presence of hemolytic anemia
19654	Lupus Anticoagulant and Antiphospholipid Confirmation (non-Coumadin) with Consultation	Diagnose SLE
91740	Platelet Antibody, Direct (IgG)	Detect autoimmune thrombocytopenia
34283	Ribosomal P Antibody	Diagnose neuropsychiatric SLE
19887	RNP Antibody	Diagnose SLE or MCTD
38567	Sm/RNP Antibody	Diagnose SLE or MCTD
37923	Sm Antibody	Diagnose SLE
937	White Blood Cell Count (WBC)	Determine presence of leukopenia
Systemic Scleroderma		
90073[b]	ANA Screen, IFA with Reflex to Titer and Pattern (Systemic Sclerosis Panel 1) Includes ANA screen (IFA) with reflexes to titer and pattern and centromere B and Scl-70 antibodies.	Diagnose systemic sclerosis
16088	Centromere B Antibody	Diagnose limited cutaneous systemic sclerosis (CREST)
19899(X)	RNA Polymerase III Antibody	Diagnose systemic sclerosis
4942	Scleroderma Antibody (Scl-70)	Diagnose systemic sclerosis

(Continued)

Table. Laboratory Tests for Classification and Diagnosis of Autoimmune Rheumatic and Related Diseases[a] *(Continued)*

Test Code	Test Name	Clinical Use
Systemic Vasculitis		
10547(X)[b]	ANA Multiplex with Reflex to dsDNA	Differentially diagnose ARDs
70159(X)[b]	ANCA Screen with MPO and PR3, with Reflex to ANCA Titer	Differentiate types of systemic vasculitis
4420	C-Reactive Protein (CRP)	Identify inflammatory conditions
375(X)	Creatinine	Assess renal function
425	Eosinophil Count, Blood	Assess eosinophilia
427	Erythropoietin	Determine presence of hemolytic anemia
809	Erythrocyte Sedimentation Rate (ESR)	Determine disease severity
723	Platelet Count, EDTA	Assess thrombocytopenia
294	Urea Nitrogen (BUN)	Assess renal function
8563	Urinalysis, Microscopic	Determine presence of microhematuria
937	White Blood Cell Count (WBC)	Assess leukopenia
ANA Screening Panels		
249[b]	ANA Screen, IFA, with Reflex to Titer and Pattern	Differentially diagnose ARDs
16814[b]	ANA Screen, IFA, with Reflex Titer and Pattern, and Reflex to Multiplex 11 Ab Cascade Antibody cascade includes chromatin, dsDNA, RNP, Sm, Sm/RNP antibodies; if all 5 antibodies are negative, reflex to SS-A, SS-B, Scl-70, and Jo-1 antibodies; if all 4 of these antibodies are negative, reflex to ribosomal P and centromere B antibodies.	Differentially diagnose ARDs
19946[b]	ANA Multiplex with Reflex to 11 Antibody Cascade Includes ANA multiplex test with reflex to chromatin, dsDNA, RNP, Sm, Sm/RNP antibodies; if all 5 antibodies are negative, reflex to SS-A, SS-B, Scl-70, and Jo-1 antibodies; if all 4 of these antibodies are negative, reflex to ribosomal P and centromere B antibodies.	Differentially diagnose ARDs

[a] Panel components may be ordered separately.
[b] Reflex tests are performed at an additional charge and are associated with an additional CPT code.
[c] Individual components available from Quest Diagnostics Nichols Institute, Valencia, CA.
[d] This test was developed and its performance characteristics have been determined by Quest Diagnostics Nichols Institute. Performance characteristics refer to the analytical performance of the test.
[e] This test was developed and its performance characteristics have been determined by Quest Diagnostics Nichols Institute. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.

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