Medical Policy
Serum Biomarker Panel Testing for Systemic Lupus Erythematosus

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Policy Number: 702
BCBSA Reference Number: 2.04.123

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Serum biomarker panel testing with proprietary algorithms and/or index scores for the diagnosis of systemic lupus erythematosus is **INVESTIGATIONAL.**

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

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<tr>
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<tr>
<td>Commercial Managed Care (HMO and POS)</td>
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<td>Commercial PPO and Indemnity</td>
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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.
Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

No Specific CPT Code.

**Description**

SLE is an autoimmune connective tissue disease that affects approximately 1.5 million individuals in the United States.¹ It is one of several types of lupus, the other 2 being cutaneous and drug-induced lupus. About 90% of lupus patients are women between the ages of 15 and 45 years. SLE causes inflammation and can affect any part of the body, most commonly the skin, heart, joints, lungs, blood vessels, liver, kidneys, and nervous system. Although generally not fatal, SLE can lead to increased mortality, most commonly from cardiovascular disease due to accelerated atherosclerosis. SLE can also lead to kidney failure, which may reduce survival. The survival rate in the U.S. is approximately 95% at 5 years and 78% at 20 years.² The morbidity associated with SLE is substantial. Symptoms such as joint and muscle pain can impact quality of life and functional status. SLE also increases patients’ risk of infection, cancer, avascular necrosis (bone cancer death), and pregnancy complications (eg, preeclampsia and preterm birth). The course of the disease is variable, and patients generally experience periods of illness (called flares) and periods of remission. Flare severity can range from mild to serious.

Treatments for SLE can ameliorate symptoms, reduce disease activity, and slow progression of organ damage, however there is no cure for SLE. Muscle and joint pain, fatigue and rashes are generally initially treated with nonsteroidal anti-inflammatory drugs. Antimalerial drugs such as hydroxychloroquine can relieve some symptoms of SLE including fatigue, rashes, and joint pain. Patients with more serious symptoms, such as heart, lung or kidney involvement, can be treated with corticosteroids or immune suppressants. There are also biologic treatments, such as rituximab, which are U.S. Food and Drug Administration approved for treatment of rheumatoid arthritis and are being evaluated for treatment of SLE.

Patients with SLE often present with nonspecific symptoms such as fever, fatigue, joint pain, and rash, which can make the disease difficult to diagnose. In some patients, the diagnosis can be made with certainty, for example when there are typical symptoms of rash and joint symptoms, and laboratory testing shows a high-titer abnormal antinuclear antibody (ANA) in a pattern that is specific for SLE. However, in many other patients, the symptom patterns are less clear and laboratory testing is equivocal, and as a result, a definitive diagnosis is difficult to make.

The diagnosis of SLE has depended on a combination of clinical symptoms and laboratory results. In 1997 the American College of Rheumatology (ACR) proposed updated criteria for classification of SLE; this represented an update of 1982 criteria.

The ACR classification criteria are as follows:
1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Mouth or nose ulcers (usually painless)
5. Arthritis (nonerosive) in two or more peripheral joints, along with tenderness, swelling, or effusion.
6. Serositis: Pleuritis or pericarditis
7. Renal disorder: excessive protein in the urine, or cellular casts in the urine
8. Neurologic disorder: seizures and/or psychosis, in the absence of offending drugs or known metabolic derangements
9. Hematologic disorders: hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia
10. Immunologic disorder: antibodies to double stranded DNA (anti-dsDNA), antibodies to Smith nuclear antigen (anti-Sm), positive antiphospholipid antibody or false positive serologic test for syphilis known to be positive for at least 6 months.
11. ANA test in the absence of drugs known to induce it.
These criteria were originally developed for use in research studies, but they have been widely adopted into clinical care. Individuals who meet 4 or more of the 11 criteria receive a diagnosis of SLE. If a patient meets fewer than 4 of criteria, lupus can still be diagnosed by clinical judgment; it is generally recommended that a rheumatologist confirm the diagnosis of SLE.5 ANA testing is usually performed for patients who present with signs and symptoms involving 2 or more organ systems, and individuals who test positive are recommended to undergo additional laboratory testing.6 Studies on the 1982 ACR criteria have reported sensitivities ranging from 78% to 95% and specificities ranging from 89% to 100%, with lower accuracy in patients with mild disease.

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC), an international group of researchers developed revised criteria for diagnosing SLE.7 These criteria include more laboratory tests than the earlier ACR criteria, including elements of the complement system. Patients are classified as having SLE if they satisfy 4 or more of the 18 criteria, including at least 1 clinical criterion and 1 immunologic criterion or they have biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies. In a sample of 690 patients, the SLICC criteria had a sensitivity of 97% and a specificity of 84% for diagnosing SLE, whereas the ACR criteria applied to the same sample had a sensitivity of 83% and a specificity of 96%. It is not clear how well accepted the SLICC recommendations are in the practice setting. The SLICC criteria are as follows:

Clinical criteria (in the absence of other known causes)
1. Acute cutaneous lupus (including but not limited to lupus malar rash)
2. Chronic cutaneous lupus (including but not limited to discoid rash)
3. Oral ulcers
4. Non-scarring alopecia in the absence of other causes
5. Synovitis involving two or more joints, characterized by swelling or effusion or and thirty minutes or more of morning stiffness.
6. Serositis
7. Renal: excessive protein in the urine, or cellular casts in the urine
8. Neurologic disorder: seizures, psychosis, mononeuritis complex or peripheral or cranial neuropathy
9. Seizures
10. Hemolytic anemia
11. Leukopenia or lymphopenia
12. Thrombocytopenia

Immunological criteria:
1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range
3. Anti-Sm
4. Antiphospholipid antibody
5. Low complement (low C3, low C4, or low CH150)
6. Direct Coombs tests in the absence of hemolytic anemia.

As previously noted, the SLICC classification system includes a wider range of laboratory tests than the ACR criteria. To date, the most common laboratory tests performed in the diagnosis of SLE are serum ANA, and if this is positive, tests for anti-dsDNA and anti-Sm. ANA tests are highly sensitive (ie, with a high negative predictive value) but have low specificity and relatively low positive predictive value, particularly when the ANA is positive at a low level. Specificity of testing can be increased by testing for specific antibodies against individual nuclear antigens (extractable nuclear antigens, or ENAs) to examine the “pattern” of ANA positivity. These include antigens against single and double-stranded DNA, histones, Sm, Ro, La, and RNP. The presence of anti-dsDNA or anti-Sm is highly specific for SLE because few patients without SLE test positive; however, neither of these tests have high sensitivity. The presence of other antibody patterns may indicate the likelihood of alternate diagnoses. For example, the presence of Ro and La antibodies suggests Sjogren syndrome, while the presence of antihistone antibodies suggests drug-induced lupus.
Better diagnostic tests for SLE would be useful in clinical practice. A variety of biomarkers, including markers associated with the complement system, are being explored to aid in the diagnosis of lupus. The complement system is part of the immune system and consists of 20 to 30 protein molecules that circulate in the blood in inactive form until activated by a trigger. When activated, as in by an infection, a sequence of events known as the complement cascade is initiated. This cascade involves the proteolysis of a complement protein into a smaller protein and a peptide. The smaller protein is able to bind to the complex at the surface of the invading microorganism and the peptide diffuses away. For example, in the first step, complement protein C3 is cleaved into C3b and C3a. C3b binds to the surface of the microorganism and activates the next step in the cascade, the proteolysis of C5, and the small peptide, C3a diffuses away. The precursors C3 and C4 and the complement activation products (CAPs), eg, C3a, C5a and C4d, have been considered as SLE biomarkers. More recently, cell-bound complement activation products (CB-CAPs), which are longer-lived than circulating CAPs, have been investigated as biomarkers of SLE. It is as yet unclear what advantages CB-CAPs may have over measuring circulating CAPs.

In addition to exploration of individual biomarkers with higher accuracy than accepted markers such as ANA and anti-dsDNA, there is interest in identifying a panel of tests with high sensitivity and specificity for SLE diagnosis. At least 1 multibiomarker test to aid in the diagnosis of SLE is commercially available. This panel, Avise™ 2.0 (Exagen Diagnostics), contains a total of 22 different tests. It combines 2 smaller panels, a 10-marker panel that includes common SLE tests, as well as CB-CAPs (known as Avise SLE 2.0) and a 12-marker panel that includes focuses on connective tissue diseases other than SLE (known as Avise SLE + Connective Tissue 2.0™).

Specific biomarkers in the panel are as follows.

10 marker Avise SLE 2.0 test:

**Auto-antibodies:** ANA, Anti-dsDNA, Anti-mutated citrullinated vimentin (Anti-MCV), C4d erythrocyte-bound complement fragment (EC4d), C4d lymphocyte-bound complement (BC4d), Anti-Sm, Jo-1, Sci-70, CENP, SS-B/La,

12 marker Avise SLE + Connective Tissue 2.0 test:

**Auto-antibodies:** U1RNP, RNP70, SS-A/Ro

**Rheumatoid arthritis auto-antibodies:** Rheumatoid factor IgM, Rheumatoid factor IgA, Anti-cyclic citrullinated peptide IgG.

**Anti-phospholipid syndrome auto-antibodies:** Cardiolipin IgM, Cardiolipin IgG, B2-glycoprotein 1 IgG, B2-glycoprotein 1 IgM.

**Thyroid auto-antibodies:** Thyroglobulin IgG, Thyroid peroxididase IgG.

In addition to reporting individual test results, an index score is reported that rates how suggestive results of tests are of SLE. Information is not available as to how this index score is calculated. The score can range from -5 (highly nonsuggestive of SLE) to 5 (highly suggestive of SLE) and a score of -0.1 to 0.1 is considered to be in the indeterminate zone.

Exagen also offers the Avise SLE Prognostic test, a 10-marker panel that can be ordered in conjunction with the Avise SLE 2.0/Avise SLE + Connective Tissue 2.0 panels. The prognostic test focuses on patients’ risk of lupus nephritis, neuropsychiatric SLE, thrombosis and cardiovascular events. The test includes anti-C1q, anti-ribosomal P, anti-phosphatidylerine/prothrombin IgM and IgG, anti-cardiolipin IgM, IgG and IgA and anti-B2-glycoprotein 1 IgM, IgG and IgA. Four of the 10 markers are included in the Avise SLE + Connective Tissue 2.0 panel. Company materials do not state that Exagen reports a summary score for the prognostic test.
Summary
Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease that can be difficult to
diagnose because patients often present with diverse, nonspecific symptoms, and commonly used
laboratory tests are not highly accurate. Currently, the diagnosis of SLE depends on a combination of
clinical signs and symptoms and individual laboratory tests. More accurate laboratory tests for SLE could
facilitate diagnosis of the disease in many patients. Recently, laboratory-developed, diagnostic panel
tests with proprietary algorithms and/or index scores for the diagnosis of SLE have become commercially
available.

Panel tests for SLE include markers that are standard in the work-up of SLE, but also contain novel
markers, most notably cell-bound complement activation products (CB-CAPs). The accuracy of CB-CAPs
in establishing a diagnosis of SLE is not known, nor is the use of these novel biomarkers recommended
in clinical practice guidelines. In addition to reporting the results of the panel of tests, an index score is
reported that rates how suggestive the results of the panel are of a diagnosis of SLE. Information is not
available on how this index score is calculated, nor is it known how this score performs in diagnosing SLE
compared with currently accepted clinical and laboratory criteria. Finally, the utility of assessing multiple
biomarkers simultaneously, rather than the more commonly performed sequential testing, is unknown.
Therefore, serum biomarker panel testing with proprietary algorithms and/or index scores for the
diagnosis of SLE is considered investigational.

Policy History

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<tr>
<td>11/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References
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   2012;64(8):2677-2686. PMID 22553077
   2007;68(10):538-541. PMID 17974296