Serum Biomarker Panel Testing for Systemic Lupus Erythematosus

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Description of Procedure or Service

Systemic Lupus Erythematosus (SLE) is an autoimmune connective tissue disease that affects approximately 1.5 million individuals in the U.S. It is one of several types of lupus, the other two being cutaneous and drug-induced lupus. About 90% of lupus patients are 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. The morbidity associated with SLE is substantial. Symptoms such as joint and muscle pain can impact quality of life and functional status. 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.

Several other connective tissue diseases may require a differential diagnosis from SLE (e.g., rheumatoid arthritis, Sjögren syndrome, antiphospholipid syndrome, and polymyositis.

Rheumatoid arthritis is a chronic inflammatory peripheral polyarthritis. Rheumatoid arthritis can lead to deformity through stretching of tendons and ligaments and destruction of joints through erosion of cartilage and bone. Rheumatoid arthritis can also affect the skin, eyes, lungs, heart, and blood vessels.

Graves disease is an autoimmune disorder that leads to overactivity of the thyroid gland. The disease arises from thyroid-stimulating hormone receptor antibodies. It is the most common cause of hyperthyroidism. Blood tests may show raised thyroid-stimulating immunoglobulin antibodies.

Hashimoto disease, also known as chronic lymphocytic thyroiditis, is an autoimmune disorder and is the most common cause of hypothyroidism second to iodine insufficiency. It is characterized by an underactive thyroid gland and gradual thyroid failure. Diagnosis is confirmed with blood tests for thyroid stimulating hormone (T4) and antithyroid antibodies.

Sjögren syndrome is an autoimmune disorder characterized by dryness of the eyes and mouth due to diminished lacrimal and salivary gland function. Affected individuals may also have symptoms of fatigue, myalgia, and cognitive dysfunction, which may be difficult to distinguish clinically from fibromyalgia or medication side effects. Typical antibodies include antinuclear antibody (ANA), anti-Sjögren-syndrome related antigen, anti-Sjögren syndrome type B, or rheumatoid factor.

Antiphospholipid syndrome is a systemic autoimmune disorder characterized by venous or arterial thrombosis and/or pregnancy morbidity. Antiphospholipid antibodies are directed against phospholipid binding proteins.
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Polymyositis and dermatomyositis are inflammatory myopathies characterized by muscle weakness and inflammation. Dermatomyositis may also have skin manifestations.

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. Antimalarial 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. Belimumab (Benlysta), a B-lymphocyte stimulator (BlyS)-specific inhibitor, has U.S. Food and Drug Administration (FDA) approval for treatment of adult patients with active, autoantibody-positive, SLE who are receiving standard therapy. There are also biologic treatments, such as Rituximab, which are FDA 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 diagnosis. 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:

- Malar rash
- Discoid rash
- Photosensitivity
- Mouth or nose ulcers (usually painless)
- Arthritis (nonerosive) in two or more peripheral joints, along with tenderness, swelling, or effusion.
- Serositis: pleuritis or pericarditis
- Renal disorder: excessive protein in the urine, or cellular casts in the urine
- Neurologic disorder: seizures and/or psychosis, in the absence of offending drugs or known metabolic derangements
- Hematologic disorders: hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia
- 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.
- 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. ANA testing is usually performed for patients who present with signs and symptoms involving two or more organ systems, and individuals who test positive are recommended to undergo additional laboratory testing. 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. 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 one
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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)

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

Immunological criteria:

- ANA above laboratory reference range
- Anti-dsDNA above laboratory reference range
- Anti-Sm
- Antiphospholipid antibody
- Low complement (low C3, low C4, or low CH50)
- 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 (i.e., 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 Sjögren 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), e.g., 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 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 Lupus 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,

**Avise CTD 2.0 test:**
Avise Lupus test plus the following:
- Auto-antibodies: U1RNP, RNP70, SS-A/Ro.
- Rheumatoid arthritis auto-antibodies: Rheumatoid factor IgM, Rheumatoid factor IgA, Anticyclic 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 peroxidase IgG.

All 22 markers are assessed when the Avise CTD test is ordered. Avise uses a 3-step process. The 10-marker panel is done in 2 tiers and the third step involves the add-on 12-marker panel to further assist with the differential diagnosis of connective tissue disease. In addition, ANA testing is done by ELISA and by indirect immunofluorescence (IIF). The 2 tiered testing approach to the 10 marker panel is described next:

**Tier 1:** Tests for anti-sm, EC4d, BC4d and anti-dsDNA. If any of the tests are positive, the result is considered suggestive of SLE and no further testing is done. Cutoffs for positivity are >10 U/ml for anti-sm, >75 U/ml for EC4d, >200 U/ml for BC4d and >301 U/ml for anti-dsDNA. Positive findings for anti-dsDNA are confirmed with a *Crithidia luciliae* assay.

**Tier 2:** If the Tier 1 tests are negative, an index score is created, consisting of results of tests for ANA, Ec4d/BC4d, anti-MCV, anti-Jo-1, Anti-Sci-70, Anti-CENP, anti Ss-B/La. (In other words, there are 6 additional markers and the ratio of Ec4d to Bc4d, both of which were measured in Tier 1).

The index score, calculated using a proprietary algorithm, rates how suggestive results of tests are of SLE. Although information on cutoffs used to indicate positivity for individual markers, information is not available as to precisely how the 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 Lupus 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-phoshatidylserine/prothrombin IgM and IgG.
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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.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The Avise tests (Exagen Diagnostics, Vista, CA) are available under the auspices of CLIA. To date, the FDA has chosen not to require any regulatory review of this test.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
Serum biomarker panel testing with proprietary algorithms and/or index scores for the diagnosis of systemic lupus erythematosus is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Serum Biomarker Panel Testing for Systemic Lupus Erythematosus is covered
Not applicable.

When Serum Biomarker Panel Testing for Systemic Lupus Erythematosus is not covered
Serum biomarker panel testing with proprietary algorithms and/or index scores for the diagnosis of systemic lupus erythematosus and other connective tissue diseases is considered investigational.

Policy Guidelines
Clinical Utility:
No studies were identified that provide direct evidence on the impact of serum biomarker panel testing for SLE on patient outcomes. A more accurate and timelier diagnosis of SLE (i.e., before multiorgan system involvement) and other connective tissue diseases could lead to better patient management (e.g., more appropriate medical treatment). This, in turn, could improve health outcomes (e.g., less joint or organ damage, improved survival).

Summary of Evidence:
For individuals with signs and/or symptoms of systemic lupus erythematosus (SLE) or connective tissue disease (besides SLE) who receive serum biomarker panel testing, the evidence includes several diagnostic accuracy studies. Relevant outcomes are test accuracy, symptoms, and quality of life. One study evaluated a panel similar to a commercially available test; it found that the panel test had somewhat higher specificity and lower sensitivity than the most common currently used biomarkers. The clinical significance of this degree of difference in diagnostic accuracy is unclear. One case-control study found a high sensitivity and specificity for a commercially available test for diagnosing SLE, but
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This retrospective analysis has several limitations, and prospective studies are therefore needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

**Applicable service codes:** There is no specific CPT code for these testing panels.

There are specific codes for some of the component tests:
83520, 86038, 86039, 86146, 86147, 86200, 86225, 86235, 86376, 86800, 88184, 88185, 88187, 84999

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Senior Medical Director review 8/2014


Specialty Matched Consultant Advisory Panel review 8/2015


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## Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>10/14/14</td>
<td>New policy developed. Serum biomarker panel testing for systemic lupus erythematosus is considered investigational. Senior Medical Director review 8/2014. (lpr)</td>
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<tr>
<td>9/1/15</td>
<td>Updated Description and Policy Guidelines sections. Added the following CPT codes to the Billing/Coding section: 86038, 86146, 86147, 86376, 86800. Reference added. Specialty Matched Consultant Advisory Panel review 8/26/2015. (lpr)</td>
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<tr>
<td>4/1/16</td>
<td>Specialty Matched Consultant Advisory Panel review 2/24/16. No change to policy. (an)</td>
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<tr>
<td>12/30/16</td>
<td>Minor change to description section. No change to policy statement. (an)</td>
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<tr>
<td>11/10/17</td>
<td>Non-coverage statement revised to read: Serum biomarker panel testing with proprietary algorithms and/or index scores for the diagnosis of systemic lupus erythematosus and other connective tissue diseases is considered investigational. Description section and Policy Guidelines updated. Reference added. (an)</td>
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