MEDICAL POLICY – 2.04.123
Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases

BCBSA Ref. Policy: 2.04.123
Effective Date: Sept. 1, 2018
Last Revised: Aug. 10, 2018
Replaces: N/A

RELATED MEDICAL POLICIES:
None

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

Connective tissue holds the body together as it surrounds and supports other tissues and organs. Tendons, ligaments, skin, blood vessels, and cartilage are examples of connective tissue. Connective tissue is also found in many organs such as the heart and lungs. Connective tissue is made up of two main proteins, elastin and collagen. If the connective tissue becomes inflamed, the inflammation can damage the elastin and collagen and it can affect the body parts they are associated with. There are many different connective tissue diseases, and their symptoms can overlap. Tests that look at several different substances in the blood at one time have been developed to try to identify specific connective tissue disorders. These tests are unproven. More studies are needed to see if they bring more health benefits than the standard ways of diagnosing these disorders.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

Testing

| Serum biomarker panel testing | 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. |

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT</td>
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</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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Related Information

Serum Biomarker Panel Tests

Tests offered by Exagen Diagnostics laboratory (see Description and Regulatory Status) include:

- Avise SLE + Connective Tissue 2.0
- Avise SLE 2.0
- Avise SLE Prognostic
Description

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease (CTD) that can be difficult to diagnose because patients often present with diverse, nonspecific symptoms that overlap with other CTDs; to further complicate matters, commonly used laboratory tests are not highly accurate. Currently, differential diagnosis depends on a combination of clinical signs and symptoms and individual laboratory tests. More accurate laboratory tests for SLE and other CTDs could facilitate diagnosis of the disease. Recently, laboratory-developed, diagnostic panel tests with proprietary algorithms and/or index scores for the diagnosis of SLE and other autoimmune CTDs have become commercially available.

Background

Connective Tissue Diseases

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease (CTD). It is one of several types of lupus, the others being cutaneous and drug-induced lupus. About 90% of lupus patients are women between the ages of 15 and 44 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 increase 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 United States 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. SLE also increases patients’ risk of infection, cancer, avascular necrosis (bone death), and pregnancy complications (eg, preeclampsia, preterm birth). The course of the disease is variable, and patients generally experience periods of mild-to-severe illness (called flares) and remission.
Other Connective Tissue Diseases

Several other CTDs may require a differential diagnosis from SLE (eg, 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.

Polymyositis and dermatomyositis are inflammatory myopathies characterized by muscle weakness and inflammation. Dermatomyositis may also have skin manifestations.

Diagnosis

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 of SLE can be made with certainty (eg, when there are typical symptoms of rash and joint symptoms, and laboratory testing shows a high-titer abnormal ANA in a pattern specific for SLE). However,
in many other patients, the symptom patterns of SLE are less clear, and ANA testing is equivocal; as a result, cascade testing with additional serologic tests may be ordered. In addition, ANA testing alone can result in false positives due to low specificity.

**Classifications**

The diagnosis of SLE has been based on a combination of clinical symptoms and laboratory results. In 1997 the American College of Rheumatology (ACR) updated 1982 criteria for the classification of SLE.²³

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 research, but they have been widely adopted in clinical care. Individuals who meet 4 or more of the 11 criteria are diagnosed with SLE. If a patient meets fewer than 4 of the criteria, lupus can still be diagnosed by clinical judgment and it is recommended that a rheumatologist confirm the diagnosis.⁴ 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 for additional laboratory testing.\textsuperscript{5} Assessments of ACR’s 1982 criteria have reported sensitivities ranging from 78\% to 95\% and specificities ranging from 89\% to 100\%, with lower accuracy in patients with mild disease.\textsuperscript{5}

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC), an international research group, developed revised criteria for diagnosing SLE.\textsuperscript{6} 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 below, including at least 1 clinical criterion and 1 immunologic criterion, or they have biopsy-confirmed 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. Table 1 outlines SLICC criteria.

**Table 1. Clinical and Immunological Criteria**

<table>
<thead>
<tr>
<th>Clinical and Immunologic Criteria</th>
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<tbody>
<tr>
<td><strong>Clinical Criteria</strong></td>
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<tr>
<td>Acute cutaneous lupus (including but not limited to lupus malar rash)</td>
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</tr>
<tr>
<td>Chronic cutaneous lupus (including but not limited to discoid rash)</td>
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</tr>
<tr>
<td>Oral ulcers</td>
<td></td>
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<tr>
<td>Nonscarring alopecia in the absence of other causes</td>
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<tr>
<td>Synovitis involving ≥2 joints, characterized by swelling or effusion and ≥30 min of morning stiffness</td>
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</tr>
<tr>
<td>Serositis</td>
<td></td>
</tr>
<tr>
<td>Renal: excessive protein in the urine or cellular casts in the urine</td>
<td></td>
</tr>
<tr>
<td>Neurologic disorder: seizures, psychosis, mononeuritis complex, or peripheral, or cranial neuropathy</td>
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<tr>
<td>Seizures</td>
<td></td>
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<tr>
<td>Hemolytic anemia</td>
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<tr>
<td>Leukopenia or lymphopenia</td>
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<tr>
<td>Thrombocytopenia</td>
<td></td>
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<tr>
<td><strong>Immunologic Criteria</strong></td>
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<tr>
<td>Antinuclear antibody above laboratory reference range</td>
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</table>
Clinical and Immunologic Criteria

<table>
<thead>
<tr>
<th>Antibodies to double-stranded DNA above laboratory reference range</th>
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<tbody>
<tr>
<td>Antibodies to Smith nuclear antigen</td>
</tr>
<tr>
<td>Antiphospholipid antibody</td>
</tr>
<tr>
<td>Low complement (low C3, low C4, or low CH150)</td>
</tr>
<tr>
<td>Direct Coombs tests in the absence of hemolytic anemia</td>
</tr>
</tbody>
</table>

As 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 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, called ENAs) to examine the “pattern” of ANA positivity. These include antigens against single and dsDNA, histones, Sm, Ro, La, and RNP antibodies. The presence of anti-dsDNA or anti-Sm is highly specific for SLE because few patients without SLE test positive; however, neither test has high sensitivity. The presence of other antibody patterns may indicate the likelihood of other 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 and other CTDs 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 an inactive form until activated by a trigger (eg, an infection) and when the protein molecules are activated, 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 (eg, C3a, C5a, C4d) have been considered as SLE biomarkers. More recently, cell-bound complement activation products, which live longer than circulating complement activation products, have been investigated as biomarkers of SLE.

In addition to exploration of individual biomarkers with higher accuracy than accepted markers (eg, ANA, 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 the diagnosis of SLE and other CTDs is commercially available. This panel, Avise CTD (Exagen Diagnostics), contains 22 different tests. It combines 2 smaller panels, a 10-marker panel that includes common SLE tests, as well as cell-bound complement activation products (known as Avise Lupus) and a 12-marker panel that focuses on CTDs other than SLE (known as Avise CTD). Avise CTD includes nuclear antigen antibodies markers to help distinguish CTD, a rheumatoid arthritis panel to rule-in or rule-out rheumatoid arthritis, an antiphospholipid syndrome panel to assess risk for thrombosis and cardiovascular events, and a thyroid panel to help rule-in or rule-out Graves disease and Hashimoto disease. Specific biomarkers in the panel are listed below in Table 2.

**Table 2. Avise Systemic Lupus Erythematosus Tests**

<table>
<thead>
<tr>
<th>Systemic Lupus Erythematosus Tests</th>
<th>10-marker Avise Lupus test</th>
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</thead>
<tbody>
<tr>
<td>Auto-antibodies: ANA, anti-dsDNA, antimutated citrullinated vimentin, C4d erythrocyte-bound complement fragment, C4d lymphocyte-bound complement, anti-Sm, Jo-1, Sci-70, CENP, SS-B/La</td>
<td></td>
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<table>
<thead>
<tr>
<th>Avise CTD Test</th>
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<tbody>
<tr>
<td>Avise Lupus test plus the following:</td>
</tr>
<tr>
<td>Auto-antibodies: U1RNP, RNP70, SS-A/Ro</td>
</tr>
<tr>
<td>Rheumatoid arthritis auto-antibodies: rheumatoid factor IgM, rheumatoid factor IgA, anticyclic citrullinated peptide IgG</td>
</tr>
<tr>
<td>Anti-phospholipid syndrome auto-antibodies: cardiolipin IgM, cardiolipin IgG, β2-glycoprotein 1 IgG, β2-glycoprotein 1 IgM</td>
</tr>
<tr>
<td>Thyroid auto-antibodies: thyroglobulin IgG, thyroid peroxidase IgG</td>
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ANA: antinuclear antibody; anti-dsDNA: Antibodies to double-stranded DNA; anti-Sm: antibodies to Smith nuclear antigen; Ig: immunoglobulin.

The Avise CTD test assesses all 22 markers. Avise CTD uses a 3-step process. The 10-marker panel is done in 2 tiers, and the add-on 12-marker panel is done in a third step to further assist with the differential diagnosis of CTD. In addition, ANA testing is done by enzyme-linked immunosorbent assay and by indirect immunofluorescence. 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 tests are positive, the result is considered suggestive of SLE and no further testing is done. Cutoffs for positivity are greater than 10 U/mL for anti-Sm, greater than 75 U/mL for EC4d, greater than 200 U/mL for BC4d, and
greater than 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 and BC4d, antimutated citrullinated vimentin, anti-Jo-1, anti-Sci-70, anti-CENP, and 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 (tier 2), calculated using a proprietary algorithm, rates how suggestive test results are of SLE. Although there is information on cutoffs used to indicate positivity for individual markers, information is not available on how precisely 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 indeterminate.

Exagen also offers the Avise Lupus Prognostic test, a 10-marker panel that can be ordered with the Avise Lupus and Avise CTD 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-phosphatidylserine/prothrombin immunoglobulin (Ig) M and IgG, anti-cardiolipin IgM, IgG, and IgA and anti-β2-glycoprotein 1 IgM, IgG, and IgA. Four of the 10 markers are included in both panel tests.

**Treatment**

Treatments for SLE can ameliorate symptoms, reduce disease activity, and slow progression of organ damage; however, there is no cure. Muscle and joint pain, fatigue, and rashes are generally treated initially 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 severe symptoms (eg, heart, lung, or kidney involvement) can be treated with corticosteroids or immune suppressants. There are also biologic treatments (eg, rituximab) approved by the U.S. Food and Drug Administration for treatment of rheumatoid arthritis and are being evaluated for SLE.

**Summary of Evidence**

For individuals with signs and/or symptoms of 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 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.

For individuals with signs and/or symptoms of CTD (besides SLE) who receive serum biomarker panel testing, more studies are needed. Relevant outcomes are test accuracy, symptoms, and quality of life. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in April 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

Practice Guidelines and Position Statements

No guidelines or statements were identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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 Amendments. The Avise® tests (Exagen Diagnostics) are available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement
Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

References

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<td>10/13/14</td>
<td>New policy, add to Pathology/Laboratory section. Policy created with literature review through July 23, 2014. Serum biomarker panel tests for systemic lupus erythematosus with proprietary algorithms and/or index scores are considered investigational.</td>
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<td>09/01/16</td>
<td>Annual Review, approved August 9, 2016. Policy updated with literature review through April 29, 2016; no references added. Policy statement unchanged.</td>
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<tr>
<td>09/01/17</td>
<td>Annual Review, approved August 22, 2017. Policy updated with literature review through April 25, 2017; references 10 and 15 added. The phrase “and other connective tissue diseases” added to policy statement and title.</td>
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