Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases

**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. Moreover, similar symptoms may also present themselves in patients with fibromyalgia. 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 the 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.

The Systemic Lupus International Collaborating Clinics (SLICC; 2012), classification system includes a wider range of laboratory tests than the American College of Rheumatology (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 (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) to examine the "pattern" of ANA positivity. These include antibodies 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 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 one at the surface of the invading microorganism, and the peptide diffuses away.

For example, in the first step, complement protein C3 is cleaved into C3a and C3b. 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 the 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 one multibiomarker test to aid in 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 in Table 1.

**Table 1. Avise Systemic Lupus Erythematosus Tests**

<table>
<thead>
<tr>
<th>Systemic Lupus Erythematosus Tests</th>
<th>Description</th>
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<tbody>
<tr>
<td>10-marker Avise Lupus test</td>
<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>
</tr>
<tr>
<td>Avise CTD test</td>
<td>Avise Lupus test plus the following:</td>
</tr>
<tr>
<td>Avise Lupus test</td>
<td>Auto-antibodies: U1RNP, RNP70, SS-A/Ro</td>
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</tbody>
</table>

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Rheumatoid arthritis auto-antibodies: rheumatoid factor IgM, rheumatoid factor IgA, anti-cyclic citrullinated peptide IgG

Anti-phospholipid syndrome auto-antibodies: cardiolipin IgM, cardiolipin IgG, β2-glycoprotein 1 IgG, β2-glycoprotein 1 IgM

Thyroid auto-antibodies: thyroglobulin IgG, thyroid, thyroid peroxidase

ANA: antinuclear antibody; anti-dsDNA: antibodies to double-stranded DNA; anti-Sm: antibodies to Smith nuclear antigen; CTD: connective tissue disease; Ig: immunoglobulin.

The Avise CTD test assesses all 22 markers. Avise CTD uses a three-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 anti-dsDNA, 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, antimitated citrullinated vimentin, anti-Jo-1, anti-Sci-70, anti-CENP, and anti-Ss-b/La. In other words, there are six 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 ten markers are included in both panel tests.

OBJECTIVE

The objective of this evidence review is to determine whether the use of a serum biomarker panel improves the net health outcome in patients with signs and/or symptoms of systemic lupus erythematosus or other connective tissue diseases.

POLICY STATEMENT

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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 the 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.

RATIONALE

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. The relevant outcomes are test accuracy, symptoms, and QOL. 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 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. The relevant outcomes are test accuracy, symptoms, and QOL. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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.

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REFERENCES


POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>December 2014</td>
<td>New policy</td>
<td>Policy created with literature review. Serum biomarker panel tests for systemic lupus erythematosus with proprietary algorithms and/or index scores are considered investigational.</td>
</tr>
<tr>
<td>December 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review; no references added. Policy statement unchanged.</td>
</tr>
<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 26, 2018; references 10, 13 and 15 added. The phrase “and other connective tissue diseases” added to policy statement and title.</td>
</tr>
<tr>
<td>September 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 1, 2019; no references added. Policy statement unchanged.</td>
</tr>
</tbody>
</table>

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