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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, 2024	RELATED MEDICAL POLICIES:
Last Revised:	Aug. 12, 2024	2.04.119 Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
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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	Investigational
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

Code	Description
CPT	
0062U	Autoimmune (systemic lupus erythematosus), IgG and IgM analysis of 80 biomarkers, utilizing serum, algorithm reported with a risk score (SLE-key Rule Out)
0312U	Autoimmune diseases (e.g., systemic lupus erythematosus [SLE]), analysis of 8 IgG autoantibodies and 2 cell-bound complement activation products using enzyme-linked immunosorbent immunoassay (ELISA), flow cytometry and indirect immunofluorescence, serum, or plasma and whole blood, individual components reported along with an algorithmic SLE-likelihood assessment (Avise Lupus)
0446U	Autoimmune diseases (systemic lupus erythematosus [SLE]), analysis of 10 cytokine soluble mediator biomarkers by immunoassay, plasma, individual components reported with an algorithmic risk score for current disease activity (new codes effective 4/1/2024)
0447U	Autoimmune diseases (systemic lupus erythematosus [SLE]), analysis of 11 cytokine soluble mediator biomarkers by immunoassay, plasma, individual components reported with an algorithmic prognostic risk score for developing a clinical flare (new codes effective 4/1/2024)
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry procedure

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Serum Biomarker Panel Tests

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

- Avise CTD
- Avise Lupus
- Avise SLE Monitor
- Avise SLE Prognostic

Other tests offered by other laboratories

- SLE-key Rule Out, Veracis, Inc.

Evidence Review

Description

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease (CTD) that can be difficult to diagnose because individuals 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 individuals 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 diagnosis of the disease. 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

SLE is an autoimmune CTD. It is one of several types of lupus, the others being cutaneous and drug-induced. 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.[1] 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 individuals' risk of infection, cancer, avascular necrosis (bone death), and pregnancy complications (e.g., preeclampsia, preterm birth). The course of the disease is variable, and individuals generally experience flares of mild-to-severe illness and remission.

Other Connective Tissue Diseases

Several other CTDs may require a differential diagnosis from SLE (e.g., rheumatoid arthritis, thyroid disease, 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.

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 and one prospective evaluation of clinical utility that compared the impact of the test results on physicians' evaluation of individuals with a clinical suspicion for SLE. The relevant outcomes are test accuracy, symptoms, and quality of life. Observational studies have been primarily retrospective in design, not performed in the intended-use population and lacking concurrent, appropriate comparator. Additionally, a randomized controlled trial (RCT) evaluated the influence of test results from Avise and standard diagnosis laboratory testing on rheumatologists' change in physician global assessment for the likelihood of SLE, which is not a health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 quality of life. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

A search of **ClinicalTrials.gov** in April 2024 did not identify any ongoing or unpublished trials that would likely influence this review.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No guidelines or statements were identified.

Medicare National Coverage

There is no national coverage determination.

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

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History

Date	Comments
10/13/14	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.
10/13/15	Annual Review. Added the names of the currently available SLE panel tests to the Policy Guidelines section. Policy updated with literature review through June 30, 2015; reference 12, 15 added. Policy statement unchanged. Coding update, informational CPT codes removed: 83520, 86038, 86039, 86146, 86147, 86200, 86225, 86235, 86376, 86800, 88184, 88185 and 88187.
09/01/16	Annual Review, approved August 9, 2016. Policy updated with literature review through April 29, 2016; no references added. Policy statement unchanged.
09/01/17	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.
09/01/18	Annual Review, approved August 10, 2018. Policy updated with literature review through April 2018; reference 13 added. Policy statement unchanged.
09/01/19	Annual Review, approved August 6, 2019. Policy updated with literature review through April 2019; no references added. Policy statement unchanged. Added CPT code 0062U.
09/01/20	Annual Review, approved August 20, 2020. Policy updated with literature review through May, 2020; references added. Policy statement unchanged.
09/01/21	Annual Review, approved August 3, 2021. Policy updated with literature review through April 27, 2021; reference added. Policy statement unchanged.
04/01/22	Coding update. Added new CPT code 0312U.
08/01/22	Annual Review, approved July 25. 2022. Policy updated with literature review through May 11, 2022; no references added. Policy statement unchanged.
09/01/23	Annual Review, approved August 21, 2023. Policy updated with literature review through April 24, 2023; reference added. Policy statement unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/24	Coding update. Added new CPT codes 0446U and 0447U.
09/01/24	Annual Review, approved August 12, 2024. Policy updated with literature review through April 18, 2024; no references added. Policy statement unchanged.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.