BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.123 Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases

Effective Policy Date: October 1, 2023

Original Policy Date: December 2014

Related Policies:

2.04.119 - Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis

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

Description

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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 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 the 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 are commercially available.

At least 1 multibiomarker test to aid 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 antibody 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's disease. Specific biomarkers in the panel are listed in Table 1.

Table 1. Avise Systemic Lupus Erythematosus Tests

Systemic Lupus Erythematosus Tests
10-marker Avise Lupus test
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
Avise CTD test
Avise Lupus test plus the following:
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, 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; CENP: centromere protein; CTD: connective tissue disease; Ig: immunoglobulin; RNP: ribonucleoprotein.

The Avise CTD test assesses all 22 markers. Avise CTD uses a 3 step process.[2,] 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 antibodies to Smith nucleaer antigen (anti-Sm),erythrocyte-bound C4d (EC4d), B-cell-bound C4d (BC4d), and antibodies to double-stranded DNA (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, anti-mutated citrullinated vimentin, anti-histidyl transfer RNA synthetase (anti-Jo-1), anti-topoisomerase I (anti-Scl-70), anti-centromere protein (anti-CENP), and anti-Sjögren Syndrome-B (anti-SSB/La) antibody tests. 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.

Additionally, in 2017, Exagen released an advanced blood test that incorporates specialized lupus biomarkers to assist in evaluating SLE disease activity - the AVISE SLE Monitor. The AVISE SLE Monitor test includes EC4d, a patented lupus biomarker that measures complement activation, a novel testing method to better assess changes in anti-dsDNA levels, PC4d (a patented lupus biomarker significantly associated with a history of thrombosis), and the anti-C1q biomarker that assists in evaluating lupus activity and possible kidney damage. C3 and C4 testing is also incorporated in the AVISE SLE Monitor; low levels of these proteins may indicate increased lupus disease activity.

OBJECTIVE

The objective of this evidence review is to determine whether the use of a serum biomarker panel improves the net health outcome in individuals 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**.

POLICY GUIDELINES

None

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 (CLIA). The Avise tests (Exagen Diagnostics) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA 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 systemic lupus erythematosus (SLE) who receive serum biomarker panel testing, the evidence includes several diagnostic accuracy studies and 1 prospective evaluation of clinical utility that compared the impact of the test results on physicians' evaluation of patients with a clinical suspicion for SLE. 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 connective tissue diseases (CTDs) (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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" 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.

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

Date	Action	Description
December 2014	New policy	Policy created with literature review. Serum biomarker panel tests for systemic lupus erythematosus with proprietary algorithms and/or index scores are considered investigational.
December 2015	Replace policy	Policy updated with literature review through June 30, 2015; reference 12 added. Policy statement unchanged.
December 2016	Replace policy	Policy updated with literature review; no references added. Policy statement unchanged.
September 2018	Replace policy	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.
September 2019	Replace policy	Policy updated with literature review through April 1, 2019; no references added. Policy statement unchanged.
September 2020	Replace policy	Policy updated with literature review through May 13, 2020; references added. Policy statement unchanged.
September 2021	Replace policy	Policy updated with literature review through April 27, 2021; reference added. Policy statement unchanged
September 2022	Replace policy	Policy updated with literature review through May 11, 2022; no references added. Policy statement unchanged.
September 2023	Replace policy	Policy updated with literature review through April 24, 2023; reference added. Policy statement unchanged.