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

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

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 experimental, investigational and/or unproven**.

Policy Guidelines

None.

Description

Connective Tissue Diseases
Systemic Lupus Erythematosus
Systemic lupus erythematous (SLE) is an autoimmune connective tissue disease (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. Systemic lupus erythematous 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. Systemic lupus erythematous 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. (1) The morbidity associated with SLE is substantial. Symptoms such as joint and muscle pain can impact quality of life and functional status. Systemic lupus erythematous also increases patients' risk of infection, cancer, avascular necrosis (bone death), and pregnancy complications (e.g., preeclampsia, preterm birth). The course of the disease is variable, and patients 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.

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

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Systemic Lupus Erythematosus
Clinical Context and Test Purpose
The purpose of serum biomarker panel testing is to provide an option that is an alternative to or an improvement on existing tests for diagnosis and management, such as established systemic lupus erythematosus (SLE) classification systems and individual serum biomarker tests, in individuals with signs and/or symptoms of SLE.

The following PICO was used to select literature to inform this policy.

Populations
The population of interest is individuals with signs and/or symptoms of SLE. Individuals with SLE often present with nonspecific symptoms such as fever, fatigue, joint pain, and rash, which can make the disease difficult to diagnose. In some individuals, the diagnosis of SLE can be made with certainty (e.g., when there are typical rash and joint symptoms, and laboratory testing shows a high-titer abnormal antinuclear antibody [ANA] in a pattern specific for SLE). However, in many other individuals, 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.

Interventions
The test being considered is serum biomarker panel testing.

Systemic lupus erythematosus 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 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.

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 nuclear 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-ScI-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 individuals' 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.

Comparators

Comparators of interest include established SLE classification systems (e.g., American College of Rheumatology [ACR], Systemic Lupus International Collaborating Clinics [SLICC]) and clinical diagnosis based on clinical and laboratory findings, such as individual serum biomarker tests, with exclusion of alternative diagnoses.

The diagnosis of SLE has been based on a combination of clinical symptoms and laboratory results. Previously, the ACR published a 1982 criteria for classifying SLE. In 1997, the ACR

updated the 1982 criteria for the classification of SLE. (3, 4) In 2019, new classification criteria endorsed by the European League Against Rheumatism (EULAR) and the ACR were developed and validated. (5) The 2019 EULAR/ACR classification criteria requires a positive ANA as an entry criterion. For those with a positive ANA, additive criteria are assessed in 7 clinical and 3 immunological domains. Weighted criteria (ranging from 2 to 10 points) are evaluated within each domain, with only the highest weighted criterion in a specific domain counting towards the total score. The weighted feature allows for criteria that are more tightly associated with SLE to contribute more heavily to the overall score. A classification of SLE requires a total score of ≥10 points.

The EULAR/ACR classification criteria are as follows:

- Entry criterion: ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test.
- If entry criterion is present, apply additive criteria (weight):
    - Constitutional: fever [2];
    - Hematologic: leukopenia [2], thrombocytopenia [4], autoimmune hemolysis [4];
    - Neuropsychiatric: delirium [2], psychosis [3], seizure [5];
    - Mucocutaneous: non-scarring alopecia [2], oral ulcers [2], subacute cutaneous or discoid lupus [4], acute cutaneous lupus [6];
    - Serosal: pleural or pericardial effusion [5], acute pericarditis [6];
    - Musculoskeletal: joint involvement [6];
    - Renal: proteinuria >0.5 g/24 h [4], renal biopsy Class II or V lupus nephritis [8], renal biopsy Class III or IV lupus nephritis [10];
    - Antiphospholipid antibodies: anti-cardiolipin antibodies or anti-β2GP1 antibodies or lupus anticoagulant [2];
    - Complement proteins: low C3 or low C4 [3], low C3 and low C4 [4];
    - SLE-specific antibodies: anti-dsDNA or anti-Sm [6].

The ACR criteria were originally developed for research, but they have been widely adopted in clinical care. If an individual does not fulfill criteria for classification for SLE, lupus can still be diagnosed by clinical judgment; it is recommended that a rheumatologist confirm the diagnosis. (6) Validation of the 2019 EULAR/ACR criteria reported a sensitivity of 96.1% and a specificity of 93.4%. (5) In comparison, the validation cohort for the ACR 1997 updated criteria reported 82.8% sensitivity and 93.4% specificity. Lastly, it should be noted that the development of the 2019 EULAR/ACR criteria aimed to improve the detection of early or new onset SLE compared to older ACR criteria.

Additionally, the SLICC, an international research group, developed revised criteria for diagnosing SLE in 2012. (7) These criteria include more laboratory tests than the 1997 ACR criteria, including elements of the complement system. Individuals 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 individuals, 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 2 outlines the SLICC criteria.

Table 2. Clinical and Immunologic Criteria

Clinical Criteria
Acute cutaneous lupus (including but not limited to lupus malar rash)
Chronic cutaneous lupus (including but not limited to discoid rash)
Oral ulcers
Nonscarring alopecia in the absence of other causes
Synovitis involving ≥2 joints, characterized by swelling or effusion or and ≥30 minutes 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
Immunologic Criteria
Antinuclear antibody above laboratory reference range
Antibodies to double-stranded DNA above laboratory reference range
Antibodies to Smith nuclear antigen
Antiphospholipid antibody
Low complement (low C3, low C4, or low CH15)
Direct Coombs tests in the absence of hemolytic anemia

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. Antinuclear antibody 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 antigens against single- and dsDNA, histones, Sm, Ro, La, and ribonucleoprotein (RNP) antibodies. The presence of anti-dsDNA or anti-Sm is highly specific for SLE because few individuals without SLE test positive; however, neither test has high sensitivity. (8) 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.

Outcomes

General outcomes of interest are test accuracy, symptoms, and quality of life, as described in Table 3.

Table 3. Outcomes of Interest for Individuals with Signs and/or Symptoms of SLE

Outcomes	Details
Test accuracy	Sensitivity and specificity in detecting biomarkers for SLE [FU for several years to assess accuracy of diagnosis]
Symptoms	Malar rash, discoid rash, photosensitivity, mouth or nose ulcers, arthritis (nonerosive), among others [≥ 2 weeks]
Quality of life	Relief of symptoms [≥ 3 years] Reduction in joint and organ damage [≥ 3 years]

FU: follow-up; SLE: systemic lupus erythematosus.

More specifically, outcomes of interest for SLE include disease activity indices, organ damage, reduction in flares, and reduction in concomitant corticosteroids. (9) Patient reported outcomes are also encouraged, particularly ones that measure fatigue as most experts agree that it is one of the most important symptoms of SLE. However, the U.S. Food and Drug Administration (FDA) has not identified an existing instrument optimal for measuring fatigue in individuals with SLE. Both fatigue and pain are the most consequential and frequent symptoms in SLE, and these contribute significantly to physical functioning, sleep, and the ability to complete daily tasks, among other quality of life measures. (10) Validated instruments for measuring quality of life in SLE are mainly used in clinical trials. Systemic lupus erythematosus specific measures include the Lupus-quality-of-life and SLE-specific quality-of-life (SLEQOL) instruments; additionally general quality of life measures are also used to measure health-related quality of life (e.g., Short Form 36 [SF-36]). Recommended health outcome measures for disease activity and organ damage per FDA guidance is summarized in Table 4. (9, 11)

Table 4. Health Outcome Measures Relevant to SLE

Outcome	Measure (Units)	Assessment	Description	Clinical Interpretation (if available)
Disease activity index				
BILAG 2004 (12)	Disease activity is scored from A to E	Disease activity within last month	Ordinal scale index that assesses 9 individual organ systems. Disease activity is scored and converted into 5 levels from A to E. Grade A is very active disease requiring anticoagulation therapy, while Grade E is no current or previous disease activity.	Major clinical response as defined by the FDA as BILAG C scores or better at 6 months with no new BILAG A or B scores with maintenance of response between 6 to 12 months.

SLEDAI-2K (13)	Scale from 0 to 105	Disease activity within last 10 days	A 24-item assessment of 16 clinical symptoms and 8 laboratory results that covers 9 organ systems. Items are weighted giving individual item scores ranging from 1 to 8. Categories of activity range from inactive (score of 0) to very active (score >12).	A score of 6 is considered clinically important and affects the decision to treat.
SLAM-R (14)	Scale from 0 to 81	Disease activity within last month	Evaluates 9 organ systems plus 7 laboratory features. Each organ item is scored 0 to 3 points. Laboratory categories can score a maximum of 21 points. Higher scores indicate higher disease activity.	A score of 7 is considered clinically important and affects the decision to treat.
ECLAM (15)	Scale from 0 to 17.5	Disease activity within last month	A 33-item assessment that is organized into 12 categories, including 10 organ symptoms plus ESR and complement levels. Individual item scores range from 0.5 to 2. Higher scores indicate higher disease activity.	
Organ damage assessment				
SLICC/ACR damage index (16)	Scale from 0 to 46	Disease damage present for ≥ 6 months or after irreversible event.	Captures items of permanent change after a diagnosis of SLE that covers specific manifestations in 12 organ systems. The 41-item assessment scores the presence of organ damage from 1 to 3 points. Higher scores indicate higher damage.	Organ damage is considered if the score is ≥1. Cumulative damage is a poor prognostic sign and a predictor of mortality.

ACR: American College of Rheumatology; BILAG: British Isles Lupus Assessment Group; ECLAM: European Consensus Lupus Activity Measure; ESR: erythrocyte sedimentation rate; FDA: U.S. Food and Drug Administration; SLAM-R: Systemic Lupus Erythematosus Activity Measure revised; SELENA: Safety of Estrogen in Lupus Erythematosus National Assessment Trial; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics.

Lastly, a quicker diagnosis of SLE could allow the initiation of treatments for SLE sooner. 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. Anti-maltimes drugs such as hydroxychloroquine can relieve some symptoms of SLE including fatigue, rashes, and joint pain. Individuals with more severe symptoms (e.g., heart, lung, or kidney involvement) can be treated with corticosteroids or immune suppressants. There are also biologic treatments (e.g., rituximab) approved by the FDA for the treatment of rheumatoid arthritis and are being evaluated for SLE.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic [ROC], area under receiver operating characteristic [AUROC], c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.
- Studies involving panel testing should report on commercially-marketed tests.

Several studies were excluded from the evaluation of the clinical validity of serum biomarker panel testing because they did not use the marketed version of the test (17) or only evaluated the cell-bound complement activation products (CB-CAPs) component of commercially available multianalyte tests. (18, 19)

Clinical Validity

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Retrospective Studies

Putterman et al. (2014) published data from a large cross-sectional, industry-sponsored study evaluating serum biomarkers for the diagnosis of SLE. (20) They analyzed the 10 markers in the Avise Lupus test (plus ANA) using a 2-tier testing logic similar to that employed in the

commercially available panel. The study evaluated 2 cohorts (N=794); 593 participants were enrolled between April and August 2010, and 201 participants enrolled between June 2011 and September 2013. Together, the 2 cohorts consisted of 304 patients who met ACR classification criteria for SLE, 161 patients diagnosed with other rheumatic diseases, and 205 healthy volunteers. Results of serum testing were available for 764 (96%) of 794 participants. A total of 140 (46%) patients with SLE, 9 (3%) patients with other diseases, and 1 healthy volunteer tested positive for at least 1 of the 4 tier 1 markers. Patients testing negative for tier 1 tests underwent tier 2 testing and an index score was calculated. A total of 102 (62%) of 164 patients with SLE analyzed in tier 2 had an index score greater than 0 (i.e., suggestive of SLE). Moreover, 245 of 276 patients with other rheumatic diseases had an index score of less than 0 (i.e., not suggestive of SLE). When the results of tier 1 and 2 tests were combined, the overall sensitivity for SLE was 80% (242/304) and the overall specificity for distinguishing SLE from other diseases was 86% (245/285). The specificity for distinguishing between SLE and healthy volunteers was 98% (201/205). A limitation of Putterman et al. (2014) is that the study sample population included patients with SLE who met ACR classification criteria, but not patients with symptoms suggestive of SLE who failed to meet ACR criteria. It is not known how the diagnostic accuracy of the panel test compares with the ACR classification criteria or with concurrent clinician diagnosis (the mean time since SLE diagnosis was 11 years).

Wallace et al. (2016) analyzed serum biomarkers as well as an algorithm for diagnosing SLE. (21) This study analyzed markers in the Avise Lupus (plus ANA) test using a 2-tier testing logic to evaluate SLE patients who met ACR criteria (n=75) and patients with primary fibromyalgia (n=75). Use of a multianalyte assay with the algorithm, including CB-CAP levels, generated indeterminate results in 12 of the 150 subjects enrolled. For the remainder of patients, use of the algorithm to diagnosis SLE was 60% sensitive and 100% specific. Study limitations included a selection of patients with a well-established diagnosis and long duration of disease.

Mossell et al. (2016) reported on an industry-sponsored retrospective case-control study of 23 patients who had a positive Avise Lupus test result and 23 patients who had a negative result. (22) All patients were ANA-positive but negative for auto-antibodies specific for SLE, representing cases difficult to diagnose. Each positive Avise test case was matched to a control (negative test) from the same clinic with the same ANA level. A chart review was performed by a nonblinded rheumatologist approximately 1 year after the test results were available. Of the cases with a positive Avise Lupus test, 20 (87%) were diagnosed with SLE during follow-up. This compared with 4 (17%) individuals who had a negative result on the Avise Lupus test, resulting in a sensitivity of 83.3% and specificity of 86.4%. Interpretation of this study is limited due to its retrospective design, relatively short follow-up to monitor the progression of the disease, and the lack of an independent reference standard, because the diagnosis was based in part on the results of that test.

Liang et al. (2020) conducted a retrospective single-center study of 117 patients in a rheumatology clinic without a confirmed SLE diagnosis who had received an Avise CTD test as part of their clinical care between April 2014 and November 2016. (23) The study aimed to determine whether the Avise test would aid in assessing the risk of developing SLE in patients

who had undifferentiated findings presenting in a real-world setting. At the clinic, patients who had inflammatory arthritis, undifferentiated CTD, or other diagnoses or features suggestive of SLE received Avise testing. In this cohort of patients without a diagnosis of SLE at baseline, the diagnosis at 2 years from baseline changed in 80% (16/20) of patients who had a positive test as opposed to only 28.9% (28/97) who had a non-positive test. Of the 20 patients who had a positive test, 13 (65%) had their diagnosis changed to SLE at 2 years. The Avise test was associated with a specificity of 93%, with a sensitivity of 57%, positive predictive value of 65%, and negative predictive value of 90%. The study also observed that patients with a positive Avise test had a significant accrual of clinical features, as defined by SLICC and ACR criteria, as well as organ damage, as defined by the SLICC Damage Index, compared to those without a positive test over the 2-year period. Additionally, there were no significant differences in medication regimens received by positive versus non-positive patients at baseline or at 2 years, except for more frequent use of mycophenolate mofetil in positive patients at year 2. Limitations of the study include its retrospective design and the potential for confirmation bias as treating physicians were aware of the Avise results and were potentially less likely to diagnose SLE in a patient with a negative Avise test.

O'Malley et al. (2022) reported results of the CAPSTONE retrospective study (N=44,605) of electronic health record data from 2016 to 2020 from 300 U.S. rheumatologists. (24) The study compared the likelihood of SLE diagnosis and SLE treatment initiation between AVISE testing and an ANA testing strategy. The testing results from the AVISE test were obtained directly from the laboratory vendor. The test results for the ANA tests were obtained from the electronic health record by searching for all variants of ANA and related test names. The study participants had a mean age in the early- to mid-50s, were mostly female (>80%), and mostly White (>55%). AVISE positive patients were more likely to initiate SLE medications compared with ANA positive patients (adjusted odds ratio [OR], 2.1; 95% confidence interval [CI], 1.9 to 2.4). AVISE positive patients were more likely to be diagnosed with SLE, as compared with the ANA patients (31% vs 8%; adjusted OR, 4.8; 95% CI, 4.0 to 5.7). The study is limited by its retrospective, non-paired design. The ANA comparator is only a subset of the standard diagnostic information used in practice.

Prospective Studies

Ramsey-Goldman et al. (2020) evaluated a multianalyte assay panel (MAP) in patients with suspected SLE to predict progression to SLE as classified by ACR criteria in an industry-sponsored prospective observational study at 7 academic institutions. (25) Patients with probable SLE as suspected by lupus experts who also met 3 ACR criteria (n=92) were enrolled along with patients with established SLE based on ACR and SLICC criteria (n=53). A control group of patients with primary Sjögren's syndrome and other rheumatic diseases (n=101) were also included. The multianalyte panel with algorithm evaluated was the Avise Lupus test. The sensitivity of MAP at enrollment was higher compared to anti-dsDNA levels or low complement levels. The ability of positive MAPs to predict fulfillment of the ACR criteria at 9 to 18 months after enrollment was also analyzed. In the subgroup of 20 patients with probable SLE who fulfilled ACR criteria within 18 months, 8 (40%) had a MAP score >0.8 at enrollment. Kaplan-Meier estimates found that a MAP score >0.8 was predictive of progression

to classifiable SLE (hazard ratio, 3.11; 95% CI, 1.26 to 7.69). A limitation of the study was the relatively small population of patients with probable SLE. Ramsey-Goldman et al. (2021) continued to follow patients with probable SLE from their original report to better determine whether more patients transitioned to classifiable SLE and whether the MAP score retained its ability to predict this transition. (26) Of the 92 patients with probable SLE, 74 had 1 or 2 follow-up visits 9 to 35 months after enrollment (total follow-up visits: 128). Twenty-eight patients with probable SLE (30.4%) were found to transition to ACR-classifiable SLE. This included 16 individuals in the first year and 12 afterwards. A MAP score >0.8 at enrollment continued to predict a transition to classifiable SLE during follow-up (hazard ratio, 2.72; p=.012); individual biomarkers or fulfillment of SLICC criteria did not.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence – Randomized Controlled Trials

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Serum biomarker panel tests should be compared with usual clinical diagnosis assessments. Clinical diagnosis for SLE is not standardized, but generally consists of assessments of individual biomarkers in patients with signs and symptoms suspicious of SLE. One RCT is available directly comparing serum biomarker panel tests to standard diagnosis laboratory testing.
(27) Characteristics of the trial are shown in Table 5.

Table 5. Summary of RCT Characteristics

Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Wallace et al. (2019); CARE for Lupus trial (27)	United States	32	July 2017 to December 2018	145 patients who were referred to a rheumatologist with a clinical suspicion for SLE, including a history of ANA positivity Participant demographics: • ~94% female	Avise Lupus test (n=72)	Standard diagnosis laboratory testing (n=73)

				• Race: ~70% White, ~21% Black, ~2.7% Asian, ~5.6% Other		

ANA: antinuclear antibody; CI: confidence interval; CARE: Clinical Laboratory Assessment and Recommendations for Lupus; RCT: randomized controlled trials; SLE: systemic lupus erythematosus

Health outcome results for RCTs are summarized in Table 6. Wallace et al. (2019) reported quality of life measures with the 5-level EuroQOL-5 Dimension index; however, outcomes were not reported by treatment group.

Table 6. Summary of RCT Results

	Disease activity	**Initiation of SLE-specific treatment**	**Quality of life**
Wallace et al. (2019) (27)	*Change in PGA from baseline to week 12*	*Initiation of hydroxychloroquine*	*Change from baseline to week 12 for EQ5D-5L*
N	145	145	145
Avise Lupus test	-0.39 ± 0.08	25%	Not reported by treatment group
Standard diagnosis laboratory testing	-0.29 ± 0.06	14%	
Difference (95% CI)	Not reported (p=.39)	Not reported (p=.14)	

CI: confidence interval; EQ5D-5L: 5-level EuroQOL-5 Dimension; PGA: physician global assessment; RCT: randomized controlled trial; SLE: systemic lupus erythematosus.

Wallace et al. (2019) evaluated the clinical utility of the Avise Lupus test for the diagnosis of lupus as compared to standard diagnosis laboratory testing. (27) The primary endpoint of the trial was the change in the physicians' estimate of likelihood of SLE before and after testing (12 weeks after enrollment). Physicians estimated the likelihood on a 5-point Likert scale ranging from 0 (very low) to 4 (very high). At baseline, pretest likelihood was similar between the standard diagnosis laboratory testing group and the Avise Lupus test group and the likelihood of SLE decreased in both groups after testing, but the magnitude of the decrease was greater in the Avise Lupus test group. The change in likelihood of SLE from randomization to post-test was -0.44 ± 0.10 in the Avise Lupus test group versus -0.19 ± 0.07 in the standard diagnosis laboratory testing group (p=.027). The corresponding changes from baseline to end of study at week 12 was -0.31 ± 0.10 versus -0.61 ± 0.10 (p=.025), for each group respectively. Study limitations are outlined in Tables 7 and 8.

Table 7. Study Relevance Limitations

Study	**Population[a]**	**Intervention[b]**	**Comparator[c]**	**Outcomes[d]**	**Follow-Up[e]**
Wallace et al. (2019) (27)			2. In the standard diagnosis	1. Formal diagnosis or fulfillment of	1. Short follow-up did not allow for

			laboratory group, physicians were not directed to order any specific laboratory test	classification of SLE not included	confirmation of SLE diagnosis or impact on longer term health outcomes

SLE: systemic lupus erythematosus.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5. Enrolled study populations do not reflect relevant diversity; 6. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest; 5. Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective reporting[c]	Data completeness[d]	Power[e]	Statistical[f]
Wallace et al. (2019) (27)		1. No blinding was used in the study 3. Post-test likelihood of SLE assessed by the treating physician	2. Between group differences in quality of life measures were not reported		1. Power calculations were not performed	4. Median differences and 95% confidence intervals between treatment groups for outcomes was not reported

SLE: systemic lupus erythematosus.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A more accurate and timelier diagnosis of SLE (i.e., before multiorgan system involvement) and other CTDs 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).

Section Summary: Systemic Lupus Erythematosus
The diagnostic accuracy of the serum biomarker panel test was primarily evaluated in observational studies in patients with established SLE. The intended use population is patients with signs and/or symptoms suggestive of SLE. Including only patients who meet ACR criteria in studies may overestimate performance characteristics compared to the broader population of those with suggestive symptoms. Several retrospective studies did not include statistical comparison to appropriate comparator methods of diagnosis performed concurrently with the Avise test. One RCT evaluated the influence of test results from Avise and standard diagnosis laboratory testing on rheumatologists' likelihood of diagnosing SLE, which found that physicians were less likely to diagnosis SLE in a patient with a negative Avise test. The short follow-up period of the study limits an assessment on how this information would impact health outcomes. Additionally, the comparator arm in the trial, which was not standardized, may not be reflective of current practice where classification criteria are used widely. Regarding ongoing SLE monitoring/management, the AVISE SLE Monitor provides additional information for the assessment of lupus disease activity, risk for kidney damage (lupus nephritis), and potential improvement in SLE symptoms; however, clinical data evaluating use of the test are lacking.

Connective Tissue Diseases Other Than Systemic Lupus Erythematosus
Clinical Context and Test Purpose
The purpose of serum biomarker panel testing is to provide a diagnostic option that is an alternative to or an improvement on existing tests, such as clinical diagnosis and individual serum biomarker tests, in individuals with signs and/or symptoms of CTDs other than SLE.

The following PICO was used to select literature to inform this policy.

Populations
The population of interest is individuals with signs and/or symptoms of CTD (other than SLE). Presenting clinical features of CTD are highly variable and can be non-specific, which contributes to the difficulty in diagnosis.

Interventions
The test being considered is serum biomarker panel testing.

Comparators
Comparators of interest include clinical diagnosis and individual serum biomarker tests.

Outcomes
General outcomes of interest are test accuracy, symptoms, and quality of life. Details are described below in Table 9.

Table 9. Outcomes of Interest for Individuals With Signs and/or Symptoms of CTD (Besides SLE)

Outcomes	Details
Test accuracy	Sensitivity and specificity in detecting biomarkers for CTDs other than SLE [FU for several years to assess accuracy of diagnosis]
Symptoms	Dry eyes and mouth, fatigue, cognitive dysfunction, muscle weakness, and inflammation [≥ 2 weeks]
Quality of life	Symptom relief [≥ 3 years] Reduction in joint and organ damage [≥ 3 years]

CTD: connective tissue disease; FU: follow-up; SLE: systemic lupus erythematosus.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.
- Studies involving panel testing should report on commercially-marketed tests.

As previously discussed, Putterman et al. (2014) published data from a large cross-sectional, industry-sponsored study evaluating serum biomarkers for the diagnosis of SLE. (20) They analyzed the 10 markers in the Avise Lupus (plus ANA) using a 2-tier testing logic similar to that

employed in the commercially available panel. Of the 794 patients in the study, 161 were diagnosed with rheumatic diseases other than SLE.

A total of 140 (46%) patients with SLE, 9 (3%) patients with other diseases, and 1 healthy volunteer tested positive for at least 1 of the 4 tier 1 markers. Patients testing negative for tier 1 tests underwent tier 2 testing and an index score was calculated. A total of 245 of 276 patients with other rheumatic diseases had an index score of less than 0 (i.e., not suggestive of SLE). When the results of tier 1 and tier 2 testings were combined, the overall specificity for distinguishing SLE from other diseases was 86% (245/285).

An earlier study by Kalunian et al. (2012) reported on the first cohort of 593 individuals included in the Putterman et al. (2014) analysis. (17) Out of 593 participants, 178 patients had rheumatic diseases, 210 had SLE, and 205 were healthy volunteers. Authors evaluated the performance of a 7-marker biomarker panel for the diagnosis of SLE; some markers are included in a commercially available panel test. The biomarkers included ANA, anti-dsDNA, antimutated citrullinated vimentin, and the CB-CAPs (EC4d, PC4d, BC4d). In relation to SLE, the combination of anti-dsDNA and the multivariate logistic regression analysis index score yielded 87% specificity against other rheumatic diseases.

Section Summary: Connective Tissue Diseases Other Than Systemic Lupus Erythematosus
All studies found centered around diagnosing SLE with other CTDs as comparators and did not assess the sensitivity of the biomarker tests to detect CTDs other than SLE. For individuals with signs and/or symptoms of CTD (besides SLE) who receive serum biomarker panel testing, more studies are needed.

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 individuals 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.

Practice Guidelines and Position Statements

No guidelines or statements were identified.

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 medical policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	81599, 83520, 84999, 86038, 86039, 86146, 86147, 86200, 86225, 86235, 86376, 86800, 88184, 88185, 88187, 88188, 88189, 0039U, 0062U, 0312U
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change

10/15/2025	Reviewed. No changes.
11/15/2024	Document updated with literature review. Coverage unchanged. Added reference 24.
12/01/2023	Reviewed. No changes.
12/01/2022	Document updated with literature review. Coverage unchanged. Added reference 25.
01/01/2022	Reviewed. No changes.
12/15/2020	Document updated with literature review. Coverage unchanged. Added references 5, 9-16, and 23-25.
09/15/2019	Reviewed. No changes.
10/01/2018	New medical document. 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 experimental, investigational and/or unproven.