MEDICAL POLICY STATEMENT

INDIANA MARKETPLACE PLANS

Policy Name	Policy Number	Date Effective
Serum Biomarker Panel Testing in Systemic Lupus Erythematosus and Rheumatoid Arthritis	MM-0904	04/01/2020 - 12/31/2020

Policy Type			
MEDICAL	Administrative	Pharmacy	Reimbursement

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A. Subject

Serum Biomarker Panel Testing in Systemic Lupus Erythematosus and Rheumatoid Arthritis

B. Background

Rheumatic diseases such as Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis contribute significantly to many who are affected through reduced quality of life, increased disability, and premature mortality. The Centers for Disease Control and Prevention (CDC) estimate for SLE an incidence between 1.8 and 7.6 per 100,000 persons per year in the continental United States. Estimates for RA from 2005, suggest prevalence among women 9.8 per 1000 and 4.1 per 1000 for men.

The widely variable clinical expression of these disorders combined with the limited specificity and sensitivity in many diagnostic tests can contribute to the challenge of unequivocally and promptly establishing a specific diagnosis in these disorders. Clinical societies have established classification criteria for clinical trials and epidemiologic studies. Their utility in clinical practice however may be limited and requires further investigation.

The diagnosis of SLE or RA is often based upon clinical judgement, careful integration of the patient's history and physical findings combined with selected laboratory and radiographic tests, often with serial assessments over time.

With the development of effective disease-modifying anti-rheumatic drugs (DMARDS) and their early introduction into treatment regimens as a standard of care in RA the importance of early and accurate diagnosis and the ability to monitor treatment response has been heightened.

A variety of scoring systems are utilized to assess disease activity in RA (including but not limited to: Disease Activity Score (DAS), Disease Activity Score employing 28 joint counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and Routine Assessment of Patient Index Data-3 (RAPID3).

In establishing the diagnosis of SLE, routine laboratory tests are often supplemented with more specialized tests including: erythrocyte sedimentation rate (ESR), C - reactive protein (CRP), complement levels (C3, C4 and CH50), antiphospholipid antibodies and antinuclear antibodies (ANA). Among the latter is a constellation of antibodies that include anti-double-stranded DNA (anti-dsDNA), anti-smooth muscle antibodies (Anti-Sm Abs), anti-Ro/SSA, and anti-La/SSB, anti-U1 RNP antibodies, anti-ribosomal P protein antibodies.

In RA rheumatoid factor (RF) and anti-citrullinated peptide/protein antibodies (anti CCP antibodies) are often measured along with ESR and CRP.

The sensitivity and specificity of these serum immune biomarkers varies considerably among patients, limiting their value. As a result investigative laboratories have sought to

establish proprietary algorithms and index scoring methodologies to assist in establishing a diagnosis, estimating prognosis, and monitoring disease activity. Among these include, but are not limited to, the following:

The Vectra DA™ test (Crescendo Bioscience Inc.) is a multi-biomarker panel blood test developed by analysis of clinical disease activity (DAS28) and the levels of serum immune markers. Utilizing a weighted algorithm a single number (ranging from zero to 100) reflecting the multi-biomarker disease activity (MBDA) is calculated. This value is proposed to correlate with disease activity. (i.e. low =1 to 29, moderate =30 to 44, or high > 44). While Vectra DA™ is not a diagnostic test and does not guide selection of specific pharmacologic agents or therapies, it has been suggested that results may inform treatment decisions of rheumatologists in the outpatient setting when used in combination with more standard clinical assessments. The MBDA score may provide a baseline assessment of disease activity, corroborate other clinical findings, and clarify disease activity when clinical assessment is challenging or when laboratory findings, symptoms, or other test results are conflicting.

A single prospective cohort study (N=101) and 7 retrospective studies (n+74 to 235) have addressed the predictive capacity of this panel to assess prognosis and manage early disease in RA. While evidence suggested some degree of correlation between the MBDA and these functions, the overall quality of the evidence is low (retrospective design in 7 of the 8 studies). Further, there was some conflicting data and none of the studies assessed long-term outcomes.

The Avise CTD (Exagen Diagnostics) is a commercially available panel containing 22 different biomarkers. Avise CTD is a combination of two smaller panels, Avise Lupus, a 10-marker panel that includes common SLE tests, as well as CB-CAPs and Avise CTD, a 12-marker panel that focuses on connective tissue diseases/autoimmune disorders other than SLE. The collection of biomarkers in Avise CTD includes nuclear antigen antibodies markers to help distinguish connective tissue disease, a RA panel to rule-in or rule-out RA, 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.

The 10-marker Avise Lupus test consists of various auto-antibodies (ANA, anti-dsDNA, antimutated citrullinated vimentin (Anti-MCV), C4d erythrocyte-bound complement fragment, C4d lymphocyte-bound complement, anti-Sm, Jo-1, Sci-70, CENP, SS-B/La).

The Avise CTD test consists of the Avise Lupus test plus the following: Auto-antibodies (U1RNP, RNP70, SS-A/Ro); Rheumatoid arthritis auto-antibodies (rheumatoid factor IgM, rheumatoid factor IgA, anticyclic citrullinated peptide IgG); Anti-phospholipid syndrome auto-antibodies (cardiolipin IgM, cardiolipin IgG, β2-glycoprotein 1 IgG, β2-glycoprotein 1IgM); 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); Ig (immunoglobulin); CTD)connective tissue disease).

All 22 of the markers are assessed when the Avise CTD is ordered. The Avise CTD uses a three-step process. The ten-marker panel is done as follows:

- Tier 1 Lupus assessments: includes tests for anti-Sm, EC4d, BC4d, and anti-dsDNA. If any of these tests are positive, the results are considered suggestive of SLE and further testing is not done. Test results 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 are considered to be positive findings. Positive findings for anti-dsDNA are confirmed with a Crithidialuciliae assay.
- Tier 2 Lupus assessments: If Tier 1 tests are negative, an index score consisting of results of tests for ANA, EC4d/BC4d, anti-MCV, anti-Jo-1, Anti-Sci-70, Anti-CENP, anti Ss-B/La is formulated. The index score is a rating of how strongly SLE is suggested from the test results. The score is devised using a proprietary algorithm and can range from -5 (highly nonsuggestive of SLE) to +5 (highly suggestive of SLE). Scores in the range of -0.1 to 0.1 are considered nonconclusive.
- The 12-marker panel is done as an added-on third step to further assist with the differential diagnosis of connective tissue disease. In addition, ANA testing is done by enzyme-linked immunosorbent assay and by indirect immunofluorescence (IIF).

Exagen also offers the Avise Lupus Prognostic test, a ten-marker panel that can be ordered with the Avise Lupus/Avise CTD panels. The prognostic test focuses on patients' risk of lupus nephritis, neuropsychiatric SLE, thrombosis, and cardiovascular events. This 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.

A multicenter cross sectional study of 210 patients with SLE reported on a 5 marker panel that included the components of the Avise test for SLE. This study, which was co-authored by investigators from Exagen Diagnostics, has not been independently validated in order to assess the safety or impact on health outcomes or patient management.

Clinical laboratories may develop, validate, and market tests under the regulatory standards of the Centers for Medicare & Medicaid Services (CMS) Clinical Laboratory Improvement Act (CLIA) of 1988. The above reference tests comply with CLIA specifications.

C. Definitions

- **Rheumatoid Arthritis:** (RA) is a symmetric, inflammatory, peripheral polyarthritis of unknown etiology. It typically leas to deformity through the stretching of tendons and ligaments and destruction of joints through the erosion of cartilage and bone. If it is untreated or unresponsive to therapy, inflammation and joint destruction lead to loss of physical function, inability to carry out daily tasks of living, and difficulties in maintaining employment.
- **Systemic Lupus Erythematosus:** (SLE) is a chronic inflammatory disease of unknown cause that can affect virtually any organ of the body most commonly the skin, heart, joints, lungs, blood vessels, liver, kidneys, and nervous system. Immunologic abnormalities, especially the production of a number of antinuclear

antibodies (ANA), are a prominent feature of the disease. SLE is not usually but common increases in mortality occur from cardiovascular disease due to atherosclerosis. SLE can also cause kidney failure. Symptoms such as joint and muscle pain can impact quality of life and ability to function. SLE also increases risks of infection, cancer, avascular necrosis, and complications in pregnancy such as preeclampsia and preterm birth.

- **Biomarkers:** a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

D. Policy

I. Based on a lack of evidence in current peer-reviewed medical literature and insufficient evidence of clinical validity, CareSource considers the Vectra DA™ panel for the diagnosis, prognosis and/or management of RA and other indications to be experimental, investigational and not medically necessary in all situations. There is insufficient documentation in medical literature to determine whether this testing is as good as or better than other measures of disease activity, and its clinical utility for improving patient clinical outcomes has not been proven.

II. Based on a lack of evidence in current peer reviewed medical literature CareSource considers the following panels for the diagnosis, prognosis, and/or management of SLE and other indications to be experimental, investigational, and not medically necessary:

- Diagnostic tests: Avise CTD (SLE and Connective Tissue Disease test), Avise Lupus (SLE Diagnostic test), Avise APS (Antiphospholipid Syndrome test)
- Prognostic tests: Avise SLE Prognostic (SLE Prognostic test), AVISE PC4D (History of SLE thrombosisAvise Anti-CarP (RA diagnosis and prognosis)
- Monitoring tests: Avise SLE Monitor (SLE disease monitoring test), Avise MTX (methotrexate polyglutamates test), Avise HCQ (hydroxychloroquine measuring test)

E. Conditions of Coverage

HCPCS
AUTHORIZATION PERIOD

F. Related Polices/Rules

AD-0006 Experimental or Investigative Technologies

G. Review/Revision History

	DATE	ACTION
Date Issued	10/06/2015	Original Policy
Date Revised	10/06/2016	Revised
Date Revised	01/08/2020	Revised
Date Effective	04/01/2020	
Date Archived	12/31/2020	This Policy is no longer active and has been archived. Please note that there could be other Policies that may have some of the same rules incorporated and CareSource reserves the right to follow CMS/State/NCCI guidelines without a formal documented Policy.

H. References

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The Medical Policy Statement detailed above has received due consideration as defined in the Medical Policy Statement Policy and is approved.