



MEDICAL POLICY STATEMENT

| Original Effective Date | Next Annual Review Date | Last Review / Revision Date |
|---|-------------------------|-----------------------------|
| 10/06/2015 | 10/06/2016 | 10/06/2015 |
| Policy Name | Policy Number | |
| Serum Biomarker Panel Testing in Systemic Lupus Erythematosus and Rheumatoid Arthritis | MM-0037 | |

Medical Policy Statements prepared by CSMG Co. and its affiliates (including CareSource) are derived from literature based on and supported by clinical guidelines, nationally recognized utilization and technology assessment guidelines, other medical management industry standards, and published MCO clinical policy guidelines. Medically necessary services include, but are not limited to, those health care services or supplies that are proper and necessary for the diagnosis or treatment of disease, illness, or injury and without which the patient can be expected to suffer prolonged, increased or new morbidity, impairment of function, dysfunction of a body organ or part, or significant pain and discomfort. These services meet the standards of good medical practice in the local area, are the lowest cost alternative, and are not provided mainly for the convenience of the member or provider. Medically necessary services also include those services defined in any Evidence of Coverage documents, Medical Policy Statements, Provider Manuals, Member Handbooks, and/or other policies and procedures.

Medical Policy Statements prepared by CSMG Co. and its affiliates (including CareSource) do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

For Medicare plans please reference the below link to search for Applicable National Coverage Descriptions (NCD) and Local Coverage Descriptions (LCD):

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 are 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 developed by analysis of clinical disease activity (DAS28) and the levels of serum immune markers. Utilizing a weighted algorithm a single number (ranging from 0 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 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.

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™ 2.0 (Exagen Diagnostics) is a commercially available panel of 22 biomarkers combining a 10 marker panel of immune tests that may be utilized in the diagnosis of SLE (Avise SLE 2.0™) with a 12 marker panel directed toward other autoimmune disorders (Avise SLE + Connective Tissue 2.0™) utilizing a tiered protocol. The collection of biomarkers included in this panel include various auto-antibodies (ANA, Anti-dsDNA, Anti-mutated citrullinated vimentin (Anti-MCV), C4d erythrocyte-bound complement fragment (EC4d), C4d lymphocyte-bound complement (BC4d), Anti-Sm, Jo-1, Sci-70, CENP, SS-B/La, U1RNP, RNP70 and SS-A/Ro); Rheumatoid auto antibodies (Rheumatoid factor IgM, Rheumatoid factor IgA, Anti-cyclic citrullinated peptide IgG), antiphospholipid antibodies (Cardiolipin IgM, Cardiolipin IgG, B2-glycoprotein 1 IgG, B2-glycoprotein 1 IgM), and anti-thyroid antibodies (Thyroglobulin IgG, Thyroid peroxidase IgG).

A panel designed to offer prognostic information related to thrombotic and other cardiovascular complications of SLE such as lupus cerebritis and nephritis is offered by Exagen (Avise SLE Prognostic Reflex™). This panel measures: anti-C1q, anti-ribosomal P, anti-



phosphatidylserine/prothrombin IgM and IgG, anti-cardiolipin IgM, IgG and IgA and anti-B2-glycoprotein 1 IgM, IgG and IgA.

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 leads 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. Immunologic abnormalities, especially the production of a number of antinuclear antibodies (ANA), are a prominent feature of the disease.
- **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 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.
- II. Based on a lack of evidence in current peer reviewed medical literature CareSource considers the Avise SLE 2.0™, the Avise SLE + Connective Tissue 2.0™, and the Avise SLE Prognostic Reflex™ panels for the diagnosis, prognosis and/or management of SLE and other indications to be experimental, investigational and not medically necessary.

For Medicare Plan members, reference the Applicable National Coverage Determinations (NCD) and Local Coverage Determinations (LCD). Compliance with NCDs and LCDs is required where applicable.

CONDITIONS OF COVERAGE

HCPCS

CPT 81479 – Unlisted Molecular procedure

AUTHORIZATION PERIOD

E. RELATED POLICIES/RULES

F. REVIEW/REVISION HISTORY

Date Issued: 10/06/2015
Date Reviewed: 10/06/2015
Date Revised:



G. REFERENCES

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4. *Clin Pharmacol Ther*. 2001 Mar;69(3):89-95. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework
5. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64:2677.
6. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40:1725.
7. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69:1580
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12. Biomarkers Definition Working Group, convened by the National Institutes of Health Director's Initiative on Biomarkers and Surrogate Endpoints. *Clin Pharmacol Therapeutics*. 2001;69: 89-95.

This guideline contains custom content that has been modified from the standard care guidelines and has not been reviewed or approved by MCG Health, LLC.

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