Anthem

Medical Policy

Subject: Multiplex Autoantigen Microarray Testing for Systemic Lupus Erythematosus
Document #: LAB.00036
Status: Reviewed
Publish Date: 09/27/2023
Last Review Date: 08/10/2023

Description/Scope

This document addresses multiplex autoantigen microarray testing for the diagnosis and management of systemic lupus erythematosus (SLE), a chronic autoimmune disease. The technology involves simultaneous testing for multiple autoantibodies associated with SLE, and may involve use of a proprietary algorithm to determine a risk score. At least one manufacturer, Exagen, Inc., is marketing such tests in the United States; the SLE-key® test (ImmunArray) is not currently available. The document does not address panels of individual tests for evaluating SLE.

Position Statement

Investigational and Not Medically Necessary:

Multiplex autoantigen microarray testing to screen for, diagnose, or manage systemic lupus erythematous is considered **investigational and not medically necessary**.

Rationale

Avise® tests

Putterman and colleagues (2014) reported on the diagnostic accuracy of the Avise Lupus test. The study included 794 individuals from 2 cohorts; 304 fulfilled ACR classification criteria, 285 were diagnosed with other rheumatic diseases and 205 were healthy volunteers. Blood samples from study participants were analyzed in a central laboratory. When a two-tiered analysis was performed that was similar to the analysis method for the commercially available test (described below in the Background/Overview section), the sensitivity for detecting SLE was 80% and the specificity was 86%.

In 2019, Wallace and colleagues published findings of a randomized controlled trial (RCT) that included individuals with suspected SLE who were referred to rheumatologists. Other eligibility criteria included having a history of ANA positivity in the past 6 months and clinical assessment within 3 months of study participation. Individuals were randomized to either undergo testing with the Avise Lupus test or to standard laboratory testing (no specific testing recommendation). All participants had venous blood collected at randomization and sent to Exagen (the manufacturer of the Avise Lupus test). A total of 145 individuals were randomized, 72 to the Avise Lupus testing arm and 73 to the standard testing arm. The primary outcome measure was the physician-reported likelihood of SLE using a 5-point Likert scale (0: very low to 4: high). At baseline, this likelihood was 1.46 in the Avise Lupus arm and 1.42 in the standard testing arm. After reviewing testing results, the physician-reported likelihood of SLE was 1.01 in the Avise Lupus group and 1.23 in the standard lab testing group; the decrease in the estimate of likelihood was significantly greater in the Avise Lupus testing group, p=0.027. Findings were similar at the 12-week follow-up; the physician-reported likelihood of SLE was 0.85 in the Avise Lupus group and 1.11 in the standard testing group, p=0.025. The study did not include a “gold standard” reference test for diagnosing Lupus, such as ACR criteria, with which to compare the physician-reported likelihood of SLE. It also did not report health outcomes in the two groups, although it was reported that individuals in the Avise Lupus group were significantly more likely to initiate prednisone compared with the standard testing group.

Alexander and colleagues (2021) reported on a retrospective review of medical records of 161 ANA-positive adults who had undergone testing with the Avise Lupus test. Individuals who had indeterminate or equivocal multianalyte assay panel (MAP) scores were excluded from the review. MAP scores, derived from the Avise Lupus test algorithm, were scored as negative, tier-2 positive or tier-1 positive. The investigators retroactively estimated the confidence in SLE diagnosis at T0 (when the test was ordered), T1 (when test results were reviewed) and T2 (a later visit that occurred at least 8 months after T1). Confidence was assessed using a 5-point Likert scale (0: very low to 4: high). At T0, physician confidence in an SLE diagnosis was low for 93 cases (58%), moderate for 49 (30%) and high for 19 (12%). At T1, among cases with a negative MAP, physician confidence in SLE diagnosis was very low for 49% of cases and low for 35%. Among cases with a tier-1 positive MAP, confidence was high for 36% and very high for 45%. At T2, for cases with a negative MAP, confidence in SLE diagnosis was very low in 74% and, for cases with a tier-1 positive MAP, confidence was very high for 83%. There were 21 cases (13%) who fulfilled the 1997 ACR criteria for SLE at T0. Hydroxychloroquine was already prescribed to 35 (22%) individuals. After MAP testing, hydroxychloroquine was prescribed more frequently in the groups that tested positive than the group that tested negative. A limitation of this study is that it was retrospective, and physicians were asked to recall their pre-test confidence in SLE diagnosis at the time of record review; this may not accurately reflect their confidence in the SLE diagnosis at T0 or T1. Moreover, although a diagnosis reference standard, in this case the ACR criteria, was reported at T0, but not at T1 or T2, it is not possible from these data to determine the accuracy of SLE diagnosis.

In 2022, O’Malley and colleagues published findings of the CAPSTONE study evaluating data from a large patient registry. The investigators compared rates of initiation of SLE medication in two groups of individuals; 21,827 individuals tested with the AVISE test and 27,778 individuals treated with standard care that included ANA testing. Mean follow-up after testing was 285 days for the AVISE cohort and 303 days for the ANA testing cohort. A total of 2437 (11.2%) individuals had a positive AVISE test and 5364 (23.5%) had a positive ANA test. Individuals with a positive AVISE test were significantly more likely to initiate SLE medications than those with a positive ANA test (43% versus 32%, unadjusted odds ratio [OR]=1.57; 95% CI, 1.41 to 1.76). The difference between groups remained statistically significant after multivariate adjustment for potential confounding variables (OR, 2.13; 95% CI, 1.85 to 2.44). Limitations of the analysis include that individuals were not randomized to testing strategy and that the diagnostic accuracy of the Avise test was not measured directly.

Background/Overview

Systemic lupus erythematosus (SLE), is a chronic autoimmune disorder that can affect multiple body systems, particularly the joints, skin, brain, kidneys, lungs and blood vessels. The etiology of SLE is unknown; genetic and epigenetic factors and ethnic origin and environmental factors may all contribute to its development.

SLE affects individuals of all ages, but women between the ages of 15 and 44 are at greatest risk of developing the condition. The Centers for Disease Control (CDC, 2018) estimates that approximately 161,000 individuals in the U.S. have definite SLE and about 322,000 have definite or probable SLE (CDC, 2018). The ratio of females to males diagnosed with SLE is approximately 9:1 (Weckerle, 2011).

SLE can be difficult to diagnose because affected individuals present with a variety of nonspecific symptoms and there are no definitive tests for the disease. Presenting symptoms commonly include fatigue, weight loss, joint pain and fever. SLE can be confused with conditions such as Sjogren's syndrome, early rheumatoid arthritis, fibromyalgia, and idiopathic thrombocytopenic purpura. Currently, the diagnosis of SLE is based on a combination of clinical signs and symptoms and immunological laboratory test results. Diagnosis begins by identifying individuals with a high clinical suspicion of the condition. SLE is suspected when there is involvement of at least two organ systems and the presence of characteristic symptoms such as malar rash, discoid rash, unexplained seizures and photosensitivity (Lam, 2016).

SLE is associated with the presence of autoantibodies directed against a range of intracellular autoantigens; collectively these autoantibodies are known as antinuclear antibodies (ANAs). In individuals with suspected SLE, laboratory testing involves a sequence of tests starting with an ANA test. Several methods are available for ANA testing. A 2015 position statement from the ACR stated that the organization supports ANA testing using Human Epithelial type 2 (HEp-2) substrate. Serum ANA testing is highly sensitive, with a positive result in approximately 95% of individuals with SLE (ACR 2015; Lam, 2016). However, ANA tests have a low positive predictive value (PPV) since individuals with positive ANA tests could have other autoimmune diseases and some medications or other diseases such as cancer can lead to a positive ANA test (ACR, 2017; Egner 2000).

In individuals with clinical suspicion of SLE and a positive ANA test, additional laboratory tests are generally performed including measurement of anti-double-stranded DNA (anti-dsDNA), anti-Smith (Anti-Sm), anti-RNP, anticardiolipin and beta-2 glycoprotein antibodies (Lam, 2016).

In its 2015 position statement on the methodology for ANA testing, the ACR stated that it supported use of specific tests in individuals with suspected SLE rather than panels of tests, as follows:

> Healthcare providers should avoid ordering panels of ANA subserologies (double stranded DNA, Smith, RNP, SS-A, SS-B Scl-70, centromere) when not appropriately indicated. Instead, ordering healthcare professionals should select specific ANA subserologies based on a patient's signs and symptoms and when there is a high pretest suspicion for a specific condition.

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) published criteria for diagnosing SLE that were based on a revision of the ACR criteria. The classification system included 18 items. They comprise criteria similar to the ACR classification system, with the addition of more antiphosolipid antibody testing options and testing for elements of the complement system and the direct Coombs test. A diagnosis of SLE required fulfillment of at least four criteria, including at least one clinical and one immunologic criterion, or the presence of lupus nephritis only in the presence of ANA or anti-dsDNA antibodies. Results of a validation study found a sensitivity of 97% and specificity of 84% for the SLICC criteria in classifying individuals as having or not having SLE. This compared to a sensitivity of 83% and a specificity of 97% for the 1997 ACR criteria (Petri, 2012).

In 2019, the ACR, along with the European League Against Rheumatism (EULAR) published an updated classification system for SLE (Aringer, 2019). The new criteria include 7 clinical domains and 3 immunology domains. The immunology domains include antiphospholipid antibodies, the complement proteins C3 and C4, and the SLE-specific antibodies, anti-dsDNA antibody and the anti-Smith antibody. In a validation study, the authors found a sensitivity of 85% and specificity of 95% for the 1997 ACR criteria, a sensitivity of 97% and specificity of 90% for the 2012 SLICC criteria and a sensitivity of 98% and specificity of 96% for the 2019 ACR criteria.

The diagnosis of SLE remains complex and no single test or combination of tests are completely accurate. There is a need for additional tests that are simple to use and have high sensitivity and specificity. Emerging technologies for SLE testing include development of improved ANA testing methods, panel testing for multiple serum biomarkers and point of care testing (Olsen, 2017). Another novel approach to SLE testing is multiplexed autoantibody arrays that can detect a large number of autoantibodies. Whereas most laboratory tests are designed to detect 10 to 15 types of ANA-related autoantibodies, multiplexed autoantibody arrays can detect hundreds of types of autoantibodies. Several multiplexed autoantibody arrays, both planar arrays and bead-based arrays, have been studied.

Exagen, Inc. (Vista, CA) markets the Avise tests for diagnosis and management of SLE. The Avise Lupus test is intended to be used in individuals with suspected SLE. It includes, among other markers, Exagen's proprietary biomarkers, elevated B lymphocyte complement 4 derived ligand (BC4d) and erythrocyte complement 4 derived ligand (EC4d) (Mossell, 2016). Testing uses a two-tiered approach. In Tier 1, levels of anti-dsDNA, anti-Smith, C4d bound to B cells (BC4d), erythrocytes (EC4d), and BC4d are measured. If levels of these biomarkers meet strong positive criteria, the test is considered positive. When there is a negative result in Tier 1, the testing moves on to Tier 2 markers. These are ANA, EC4d, BC4d and the autoantibody specificity components (anti-CCP, anti-SS-B/La, CENP, Jo-1, and Scl-70). Findings are aggregated using a proprietary algorithm. The AVISE CTD test is intended for the differential diagnosis of SLE and The Avise SLE Monitor test is intended to monitor individuals with SLE. Like the Avise Lupus test, these panel tests include, among other markers, Exagen's patented biomarkers. The Avise tests are laboratory-developed test and, as such, clearance or approval from the Food and Drug Administration (FDA) is not required.

Definitions

Antinuclear Antibodies (ANA): Antibodies to human proteins within the nucleus of a cell.

Autoantibodies: Antibodies to human proteins.

Microarray testing: A microchip-based testing platform that permits the identification and analysis of many pieces of DNA or protein at the same time.

Multiplex: Many elements that are in a complex relationship to one another.

Systemic lupus erythematosus (SLE) (also known simply as lupus): A chronic autoimmune disease that can affect any part of the body.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the procedure codes listed below, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

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, Veracis Inc, Veracis Inc
0312U	Autoimmune diseases (eg, 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, Exagen Inc, Exagen Inc
ICD-10 Diagnosis	
	All diagnoses

References

Peer Reviewed Publications:

1. Alexander RV, Rey DS, Conklin J et al. A multianalyte assay panel with cell-bound complement activation products demonstrates clinical utility in systemic lupus erythematosus. Lupus Sci Med. 2021; 8(1):e000528.
2. Egner W. The use of laboratory tests in the diagnosis of SLE. J Clin Pathol. 2000; 53(6):424-432.
3. Lam NC, Ghetu MV, Bieniek ML. Systemic lupus erythematosus: primary care approach to diagnosis and management. Am Fam Physician. 2016; 94(4):284-294.
4. Olsen NJ, Choi MY, Fritzler MJ. Emerging technologies in autoantibody testing for rheumatic diseases. Arthritis Res Ther. 2017; 19(1):172.
5. O'Malley T, Xie F, Su Y et al. Complement activation products vs standard ANA testing: Treatment outcomes, diagnosis, and economic impact (CAPSTONE) in systemic lupus erythematosus. J Manag Care Spec Pharm. 2022 28(9):1021-1032.
6. Putterman C, Furie R, Ramsey-Goldman R et al. Cell-bound complement activation products in systemic lupus erythematosus: comparison with anti-double-stranded DNA and standard complement measurements. Lupus Sci Med. 2014; 1(1):e000056.
7. Wallace DJ, Alexander RV, O'Malley T et al. Randomised prospective trial to assess the clinical utility of multianalyte assay panel with complement activation products for the diagnosis of SLE. Lupus Sci Med. 2019; 6(1):e000349.
8. Weckerle CE, Niewold TB. The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. Clin Rev Allergy Immunol. 2011; 40(1):42-49.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American College of Rheumatology. 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus. Available at: https://www.rheumatology.org/Portals/0/Files/1997%20Update%20of%201982%20Revised.pdf. Accessed on June 28, 2023.
2. American College of Rheumatology. Last updated 2015. Position Statement: Methodology of Testing for Antinuclear Antibodies. Available at: https://rheumatology.org/policy-position-statements. Accessed on June 28, 2023.
3. American College of Rheumatology. Antinuclear Antibodies (ANA) Last updated March 2017. Available at: https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Antinuclear-Antibodies-ANA. Accessed on June 28, 2023.
4. Aringer M, Costenbader K, Daikh D et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019; 78(9):1151-1159.
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(8):2677-86.

Websites for Additional Information

1. Centers for Disease Control. Lupus Detailed Fact Sheet (updated July 2022). Available at: https://www.cdc.gov/lupus/facts/detailed.html. Accessed on June 28, 2023.
2. U.S. Dept of Health and Human Services. Office of Women's Health. Lupus (updated February 2021). Available at: https://www.womenshealth.gov/lupus. Accessed on June 28, 2023.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Rationale, Background/Overview, References and Index sections updated.
Reviewed	08/11/2022	MPTAC review. Rationale, Background/Overview, References and Index sections updated.
	04/01/2022	Updated Coding section with 04/01/2022 CPT changes; added 0312U.
Reviewed	08/12/2021	MPTAC review. Background/Overview and References sections updated.
Reviewed	08/13/2020	MPTAC review. References section updated.
Reviewed	11/07/2019	MPTAC review. References section updated.
New	01/24/2019	MPTAC review. Initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.