Autoimmune disease diagnostic panel testing

Clinical Policy ID: CCP.1562

Recent review date: 6/2026

Next review date: 10/2027

Policy contains: autoimmune disease diagnostic panel testing, multianalyte assay panel, AVISE, AVISE Lupus, AVISE Connective Tissue Disease, cell-bound complement activation products.

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Coverage policy

Autoimmune disease diagnostic panel testing, including multianalyte assay panels, proprietary algorithm-based autoimmune panels, AVISE-type autoimmune diagnostic panels, cell-bound complement activation product panels is investigational/not clinically proven and, therefore, not medically necessary for members for the diagnosis, differentiation, prognosis, risk stratification, or management of autoimmune disease, including systemic lupus erythematosus and related connective tissue diseases.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Autoimmune disease diagnostic panel testing refers to blood-based testing that combines multiple serum or cell-associated biomarkers with an interpretive score or proprietary algorithm. These panels are intended to support evaluation of individuals with suspected systemic autoimmune disease, particularly systemic lupus erythematosus and related connective tissue diseases.

The biomarkers included in these panels may include antinuclear antibody testing, antibodies to double-stranded deoxyribonucleic acid, antibodies to Smith antigen, other disease-associated autoantibodies, soluble complement proteins, and cell-bound complement activation products. Some newer panels or investigational approaches also evaluate complement fragment deposition on erythrocytes, B lymphocytes, or T lymphocytes, as well as anti-T-lymphocyte autoantibodies. The test result is generally reported as a composite score or tiered result intended to supplement, rather than replace, clinical assessment (Alexander, 2021; Clarke, 2020; Kyttaris, 2025).

Systemic lupus erythematosus diagnosis remains based on clinician assessment of symptoms, physical findings, laboratory results, and disease evolution over time. Conventional serologic evaluation commonly includes antinuclear antibody testing, disease-specific autoantibodies, and complement proteins. These tests have recognized limitations: antinuclear antibody testing is sensitive but nonspecific, while antibodies to double-stranded deoxyribonucleic acid and Smith antigen are more specific but less sensitive. Classification criteria may support consistent research classification, but they are not designed to function as stand-alone diagnostic criteria for individual clinical decision-making. The 2019 European League Against Rheumatism and American College of Rheumatology systemic lupus erythematosus criteria are classification criteria, use antinuclear antibody positivity as an entry criterion, and are intended to support consistent classification rather than replace clinician diagnosis for individual clinical decision-making (Aringer, 2019; American College of Rheumatology, 2026).

The proposed role of multianalyte autoimmune diagnostic panels is to provide additional laboratory information when clinical findings and conventional serologic testing are inconclusive. In this context, the panel result may be used to support consideration of systemic lupus erythematosus, distinguish systemic lupus erythematosus from other autoimmune or nonautoimmune conditions, or estimate likelihood of future classification in individuals with probable or incomplete disease. The referenced evidence describes AVISE Lupus as commercially available through a laboratory accredited by the College of American Pathologists and certified under the Clinical Laboratory Improvement Amendments; the same source reports approval by the New York State Clinical Laboratory Evaluation Program. Laboratory certification or state laboratory approval is distinct from evidence that a test improves clinical outcomes. The Food and Drug Administration and the Centers for Medicare and Medicaid Services have stated that the Clinical Laboratory Improvement Amendments program and Food and Drug Administration oversight are separate in scope and purpose: the Clinical Laboratory Improvement Amendments program establishes laboratory quality standards, while Food and Drug Administration oversight addresses whether tests work, including analytical and clinical validity (Alexander, 2021; Food and Drug Administration and Centers for Medicare and Medicaid Services, 2024).
Food and Drug Administration regulatory history for laboratory-developed tests has changed recently and should be distinguished from clinical utility evidence. On May 6, 2024, the Food and Drug Administration issued a final rule amending the definition of “in vitro diagnostic products” in title 21 of the Code of Federal Regulations, section 809.3(a), to add the words “including when the manufacturer of these products is a laboratory.” On March 31, 2025, a federal district court vacated the May 2024 final rule. On September 19, 2025, the Food and Drug Administration issued a final rule reverting the regulation to the text that existed before the effective date of the May 2024 final rule (Food and Drug Administration, 2025).

Findings

The direct evidence base for proprietary multianalyte autoimmune biomarker panels is concentrated in systemic lupus erythematosus and probable systemic lupus erythematosus populations. It consists mainly of diagnostic-performance studies, short-term decision-impact studies, retrospective medical record or registry analyses, and

economic modeling. These studies show associations with diagnostic confidence, diagnosis coding, medication initiation, and selected diagnostic-performance measures, but they do not establish that panel-guided testing improves independently confirmed diagnosis, disease flares, organ damage, hospitalization, quality of life, medication toxicity, mortality, or other net health outcomes compared with standard clinical evaluation and conventional laboratory testing. Evidence is limited for other connective tissue diseases and for broader autoimmune disease evaluation. Many studies also used selected rheumatology populations, enriched case-control designs, or participants with established disease, which may overestimate diagnostic performance compared with use in individuals with nonspecific symptoms or low pretest probability. In addition, studies relying on clinician diagnosis, classification criteria, diagnosis codes, or treatment initiation as outcomes may be subject to incorporation bias when clinicians are aware of panel results. Financial sponsorship or author employment by the test manufacturer was reported in several key studies and should be considered when interpreting the evidence base.

Diagnostic accuracy and comparison with conventional serologic testing

A multicenter validation study of 400 adult participants evaluated T-lymphocyte autoantibodies and cell-bound complement biomarkers in participants with systemic lupus erythematosus, autoimmune rheumatic disease controls, apparently healthy volunteers, and other disease controls. In antinuclear antibody-positive participants with systemic lupus erythematosus compared with autoimmune rheumatic disease controls, area under the curve values were 0.81 for T-lymphocyte autoantibody immunoglobulin G, 0.80 for B lymphocyte-bound complement fragment, and 0.79 for T-lymphocyte-bound complement fragment. These values exceeded the reported performance for antibodies to double-stranded deoxyribonucleic acid, complement protein three, complement protein four, and antibodies to Smith antigen. At 95% specificity against apparently healthy volunteers, sensitivity was 58.1% for T-lymphocyte-bound complement fragment, 31.4% for T-lymphocyte autoantibody immunoglobulin G, and 29.5% for T-lymphocyte autoantibody immunoglobulin M (Kyttaris, 2025).

The same multicenter validation study reported that T-lymphocyte biomarkers identified a subset of participants with systemic lupus erythematosus who were negative for conventional systemic lupus erythematosus autoantibodies and had normal complement protein levels. This finding shows diagnostic discrimination in a selected validation cohort that included participants with established disease and disease controls, but it does not establish clinical utility in undifferentiated diagnostic populations or improved outcomes from panel-guided care. The study did not evaluate a general population with undifferentiated symptoms, did not measure long-term clinical outcomes, and included participants with established disease, mild disease activity, and medication exposure that may limit applicability to early diagnostic settings. Interpretation should account for Exagen funding and reported funder involvement in study design, study oversight, data analysis, interpretation, and manuscript drafting (Kyttaris, 2025).

A retrospective cohort study of 117 participants without a prior systemic lupus erythematosus diagnosis evaluated an AVISE connective tissue disease panel over two years. AVISE positivity had 57% sensitivity, 93% specificity, 65% positive predictive value, and 90% negative predictive value for systemic lupus erythematosus diagnosis at two years. Conventional markers showed different tradeoffs: elevated antibodies to double-stranded deoxyribonucleic acid and low complement protein levels had specificity greater than 90% but sensitivity below 20%, while antinuclear antibody positivity had 87% sensitivity and 39% specificity. These findings suggest improved discrimination in a selected rheumatology cohort, but some participants with negative AVISE results later developed systemic lupus erythematosus (Liang, 2020).

A smaller retrospective chart review reported sensitivity of 83% and specificity of 86% for an AVISE Lupus result compared with rheumatologist diagnosis among antinuclear antibody-positive participants who were negative for systemic lupus erythematosus-specific autoantibodies. This study was not emphasized because it included 46 participants, used a retrospective design, and investigators were not blinded to the test result (Mossell, 2016).

Clinical utility and decision-making

The most directly relevant randomized decision-impact study was a prospective study of 145 antinuclear antibody-positive participants with low to moderate clinician-assessed likelihood of systemic lupus erythematosus. Participants were randomized to standard diagnostic laboratory testing or multianalyte panel testing with cell-bound complement activation products and followed for 12 weeks. The primary outcome was change in physician likelihood of systemic lupus erythematosus on a five-point scale. Multianalyte panel testing produced a larger reduction in post-test likelihood of systemic lupus erythematosus than standard testing, both after review of results and at 12 weeks. Positive panel results were associated with prednisone initiation, while hydroxychloroquine initiation showed a nonsignificant trend. The study measured short-term diagnostic impressions and treatment decisions rather than independent diagnostic confirmation or long-term health outcomes. The study was funded by Exagen and reported multiple Exagen-related conflicts (Wallace, 2019).

A retrospective medical record review of 161 antinuclear antibody-positive participants with suspected systemic lupus erythematosus found that higher multianalyte panel scores were associated with greater physician confidence in systemic lupus erythematosus diagnosis. Follow-up at eight months or longer after test-result review was available for 90 participants. Odds of higher diagnostic confidence increased 1.74-fold per unit increase in panel score. Compared with participants who had negative panel and negative antibodies to double-stranded deoxyribonucleic acid, the hazard of assigning a systemic lupus erythematosus diagnosis code and initiating hydroxychloroquine increased across positive panel tiers. These outcomes reflect clinician behavior after test result availability and do not establish that testing improved health outcomes (Alexander, 2021).

A large retrospective registry study compared AVISE Lupus testing with a traditional antinuclear antibody testing strategy using electronic health record data from rheumatology practices and linked claims subsets. The main cohort included 21,827 AVISE testing episodes and 22,778 traditional antinuclear antibody testing episodes. Positive AVISE results were associated with higher likelihood of systemic lupus erythematosus medication initiation compared with positive traditional testing, 43% versus 32%, adjusted odds ratio 2.13, 95% confidence interval 1.85 to 2.44. Positive AVISE results were also associated with higher likelihood of a systemic lupus erythematosus diagnosis, 31% versus 8%, odds ratio 5.11, 95% confidence interval 4.43 to 5.89. The observational design leaves residual confounding, including differences in test selection, practice patterns, and follow-up ascertainment. These findings demonstrate associations between AVISE test results and clinician behavior in registry and claims data, but they do not prove that the test independently improves diagnostic accuracy or patient outcomes. Interpretation should account for incomplete follow-up, small linked claims subsets, medication use for conditions other than confirmed systemic lupus erythematosus, and Exagen funding and author disclosures (O'Malley, 2022).

Economic evidence consisted of a budget impact model rather than a clinical outcomes study or cost-effectiveness study. The model compared a multivariate assay panel with standard diagnostic laboratory testing in a hypothetical health plan of one million enrollees and assumed earlier diagnosis based on published test-performance inputs. Over four years, modeled total direct costs were lower with the multivariate assay panel than with standard testing. The model was sensitive to assumptions about diagnostic timing, specificity, test cost,

and disease prevalence among individuals suspected of systemic lupus erythematosus. These modeled estimates do not independently demonstrate improved clinical outcomes (Clarke, 2020).

Risk stratification and disease progression

A prospective study of probable systemic lupus erythematosus evaluated whether a multianalyte assay panel with cell-bound complement activation products predicted transition to American College of Rheumatology-classified systemic lupus erythematosus. The study enrolled 92 participants with probable systemic lupus erythematosus, defined by antinuclear antibody positivity, two additional classification criteria, and high suspicion by a lupus expert; 74 participants had one or two follow-up visits over nine to 35 months. Overall, 28 participants, or 30.4%, transitioned to classifiable systemic lupus erythematosus. A baseline panel score greater than 0.8 predicted transition, hazard ratio 2.72, 95% confidence interval 1.25 to 5.93, p value = 0.012. Individual biomarkers and Systemic Lupus International Collaborating Clinics criteria did not predict transition. Generalizability is limited because participants were highly selected and renal disease was excluded (Ramsey-Goldman, 2021). Transition to classification is an intermediate outcome and may not translate into fewer flares, less organ damage, improved survival, or safer treatment compared with standard clinical evaluation.

The retrospective two-year AVISE connective tissue disease cohort also addressed risk stratification. Among participants without a previous systemic lupus erythematosus diagnosis, 65% of participants with positive AVISE results developed systemic lupus erythematosus at two years compared with 10.3% with nonpositive results. AVISE positivity was the only biomarker significantly associated with confirmed systemic lupus erythematosus diagnosis in multivariable analysis, odds ratio 10.7, 95% confidence interval 2.6 to 44.9, p value = 0.001. This finding supports prognostic association in a selected rheumatology cohort, but it does not establish that panel-guided care improves organ damage, flares, survival, or treatment safety compared with standard evaluation (Liang, 2020).

Indirect evidence from immune checkpoint inhibitor toxicity studies

Two reviewed studies evaluated autoantibodies for prediction of immune-related adverse events in individuals receiving immune checkpoint inhibitors for cancer. These studies are indirect for this policy because they did not evaluate AVISE-type systemic autoimmune diagnostic panels, Current Procedural Terminology code 0312U, or diagnosis of systemic autoimmune disease. A prospective single-center study of 221 participants found that grade two or higher immune-related adverse events were more frequent in participants with preexisting autoantibodies, 50% versus 22%, odds ratio 3.5, 95% confidence interval 1.8 to 6.8, p value < 0.001 (Daban, 2023). A retrospective study of 626 participants found that a speckled antinuclear antibody pattern was associated with grade two or higher immune-related adverse events, odds ratio 1.74, 95% confidence interval 1.20 to 2.54, p value = 0.0038, with modest model discrimination (Kohno, 2025). Because these studies do not evaluate the proprietary autoimmune panels addressed by this policy, they provide contextual immunology evidence only and were not used as direct evidence for the coverage determination.

References

5/2026"autoimmune disease diagnostic panel" OR "multianalyte assay panel" OR "AVISE Lupus" On , we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were: We included the best available evidence according to established

evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

Initial review date: 5/2026 and clinical policy effective date: 7/2026

6/2026: Policy created.

Related codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1562. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code description
0062U	Autoimmune (systemic lupus erythematosus), IgG and IgM analysis of 80 biomarkers, utilizing serum, algorithm reported with a risk score.
0312U	Autoimmune diseases (e.g., 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.
0446U	Autoimmune diseases (systemic lupus erythematosus [SLE]), analysis of 10 cytokine soluble mediator biomarkers by immunoassay, plasma, individual components reported with an algorithmic risk score for current disease activity.
0447U	Autoimmune diseases (systemic lupus erythematosus [SLE]), analysis of 11 cytokine soluble mediator biomarkers by immunoassay, plasma, individual components reported with an algorithmic prognostic risk score for developing a clinical flare.
81599	Unlisted multianalyte assay with algorithmic analysis.