Biomarker and Multiplex Autoantigen Microarray Testing for Autoimmune Disease

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DESCRIPTION

Note: This medical policy addresses the use of the following biomarker and multiplex autoantigen microarray testing for autoimmune disease including the following:

- *Multi-biomarker disease activity (MBDA) blood testing that produces a score designed to assess rheumatoid arthritis (RA) disease actively, an example is the Vectra blood test (Crescendo Biosicence, Inc.);* ***and***
- *Biomarker testing for systemic lupus erythematous (SLE) to assist in diagnosis, prognosis, and monitoring with proprietary algorithms and/or index scores, examples of this testing include AVISE SLE, AVISE SLE Prognostic, AVISE CTD Assay, and AVISE Lupus (Exagen, Inc);* ***and***

- *Multiplex autoantigen microarray testing for evaluation of systemic lupus erythematous (SLE), is technology that involves testing for multiple antibodies associated with SLE at the same time and may involve the use of proprietary algorithm to determine a risk score, an example of this testing includes SLE-Key Rule Out Tests (ImmunoArray).*

Rheumatoid Arthritis (RA)
Rheumatoid arthritis (RA) is characterized by chronic joint inflammation leading to painful symptoms, progressive joint destruction, and loss of function. The disorder is relatively common and associated with a high burden of morbidity for affected individuals.

Treatment of RA has undergone a shift from symptom management to a more proactive strategy of minimizing disease activity and delaying disease progression. The goal of treatment is to reduce irreversible joint damage that occurs from ongoing joint inflammation and synovitis by keeping disease activity as low as possible. The availability of an increasing number of effective disease -modifying anti-rheumatic drugs has made achievement of remission, or sustained low disease activity, a feasible goal in a large proportion of patients with RA. This treatment strategy has been called a "tight control" approach.

Selection of Disease Activity Assessment Tools for Rheumatoid Arthritis (RA)
For a strategy of tight control to be successful, reliable, and valid measurement of disease activity is necessary. Numerous measurements exist that assess various aspects of RA disease activity, including patient self-report of symptom severity and functional capacity, physician examination of joints for swelling and tenderness, laboratory testing of serum biomarkers, and imaging. Various assessment tools exist that range from those that rely only on single types of measurements, to composite tools that combine information from multiple measurement sources. These assessment tools vary in their psychometric properties and their feasibility of implementation, and these trade-offs must be considered in their selection for use. For example, although composite tools are more comprehensive, in some cases they may be less feasible for regular use.

Assessment of disease activity in rheumatoid arthritis is an important component of management because a main goal of treatment is to maintain low disease activity or remission. There are a variety of available instruments for measuring rheumatoid arthritis disease activity. They use combinations of physical exam findings, radiologic results, and serum biomarkers to construct a disease activity score. There are more than 60 methods of measuring disease activity in individuals with RA. An expert panel on RA determined the following 6 measures were the most useful and feasible in a clinical setting: Clinical Disease Activity Index [CDAI], Disease Activity Score with 28 joints (DAS28), Patient Activity Scale, Patient Activity Scale II, Routine Assessment of Patient Index Data 3 (RAPID3), and Simplified Disease Activity Index (SDAI). Rheumatologists usually use four blood tests in the diagnosis of RA. These blood tests are the Sedimentation rate (ESR), C-reactive protein (CRP), Rheumatoid Factor, and the anti-CCP. The ESR and the

CRP, both inflammatory markers, are also used in the ongoing monitoring of RA to assess your level of inflammation.

Multi-Biomarker Disease Activity (MBDA) Testing for Rheumatoid Arthritis (RA)

Vectra Test
The Vectra Test is a commercially available multibiomarker disease activity (MBDA) test that is an approach to measuring rheumatoid arthritis (RA) disease activity that uses only serum biomarkers obtained through a laboratory blood draw. The manufacturer describes Vectra as a complement to clinical judgment. Although not explicitly stated, it appears that the test may be used as an adjunct to other disease activity measures, to potentially identify patients at high-risk of progression who would, therefore, benefit from a more aggressive treatment strategy.

The Vectra test measures the serum concentrations of the following 12 biomarkers:

- Atrix metalloproteinase 3 (MMP-3)
- C-reactive protein (CRP)
- Epidermal growth factor (EGF)
- Interleukin-6 (IL-6),
- Leptin
- Matrix metalloproteinase 1 (MMP-1)
- Serum amyloid A (SAA)
- Resistin
- Tumor necrosis factor receptor type I (TNFRI)
- Vascular cell adhesion molecule 1 (VCAM-1)
- Vascular endothelial growth factor A (VEGF-A)
- YKL-40

The concentrations of these 12 biomarkers are measured in serum and, combined with age, gender, and adiposity (i.e., leptin) information, are entered in a proprietary formula to generate a score on a scale of 1 to 100 that represents the level of RA disease activity:

Categories of scores were constructed to correlate with the DAS28-CRP scale:

- 45-100: high disease activity
- 30-44: moderate disease activity
- 1-29: low disease activity

Prior to December 2017, the Vectra test was originally referred to as Vectra DA and the original MBDA score did not include adiposity (i.e., leptin) adjustment. However, as the current, commercially available version of the test includes the leptin-adjusted MBDA score (now called the "adjusted MBDA score") the focus of this policy will primarily be on the leptin-adjusted Vectra test.

(2019) England et al. reported in the ACR working group's systematic review and also graded feasibility of the RA disease activity measurement tools. Any measure not commercially available or requiring advanced imaging was graded as infeasible. All other measures started with 4 points (i.e., "++++") and were downgraded by 1-point for each of the following implementation considerations: requiring a provider joint count, requiring a laboratory test, not possible to complete during a routine clinic visit, and not possible to complete on the same day as the clinic visit. The ACR Working Group downgraded the feasibility of the Vectra DA by 3 points (i.e., score of "++++" decreased to "+"). This was due to its requirement of a laboratory test and because its result is not available on the same day as the clinic visit. Although the current, commercially available version of the Vectra test was not assessed in the 2019 ACR guideline, because it requires the same laboratory testing that is not available on the same days as the clinic visit, likely it would have a similar feasibility rating as the older version.

A multi-biomarker disease activity (MBDA) instrument is a disease activity measure that is comprised entirely of serum biomarkers. The Vectra DA test is a commercially available MBDA blood test that uses 12 biomarkers to construct a disease activity score ranging from 1 (low disease activity) to 100 (high disease activity).

(2016) Fleischmann et al. evaluated the ability of Vectra DA to measure disease activity in participants of the Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate (AMPLE) trial. In the AMPLE trial (Schiff, 2014), a total of 646 subjects naïve to biological agents were randomized to receive abatacept (n=318) or adalimumab (n=328). Multi-biomarker disease activity (MBDA) results were available for 259 and 265 subjects, respectively. No association was found between the MBDA score and disease activity as defined by American College of Rheumatology (ACR) recommended disease activity measures (CDAI, SDAI, DAS28-C-reactive protein, or Routine Assessment of Patient Index Data with 3 measures [RAPID-3]) in either treatment group. The authors concluded:

- These findings indicated that the MBDA score should not be used to guide RA management decisions, particularly in patients treated with abatacept or adalimumab as a first biologic agent. Treatment decisions in RA should be based on clinical judgment, utilizing the disease activity measures recommended by the ACR for point-of-care clinical use.

Section Summary: Vectra Test with Adjusted Multibiomarker Disease Activity Score

For individuals who have RA who receive the current commercially available Vectra test ("adjusted MBDA score") as an adjunct or as a replacement of other disease activity measures, the evidence includes 2 studies that analyzed archived serum samples using combined data from randomized controlled trials (RCTs) and cohort studies. Relevant outcomes are test validity, other test performance measures, symptoms, change in disease status, functional outcomes, and quality of life. Analyses comparing Vectra with other previously validated disease activity measures such as the Disease Activity Score with 28 joints (DAS28) or to radiographic progression, consisted mostly of correlations.

However, the positive predictive values (PPVs) that individuals with Vectra moderate- to high-risk disease scores had radiographic progression were low, at 4.4% and 15.8%, respectively. Additionally, due to numerous study relevance, design and conduct limitations, the body of evidence on the Vectra test is insufficient to determine whether it is as good as or better than other disease activity measures. Given the high prevalence of discordant results across conventional measures of disease activity, the position of the Vectra test in the management pathway is unclear. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Original Vectra Disease Activity Test
For individuals who have RA who receive the original Vectra DA test as an adjunct or as a replacement of other disease activity measures, the evidence includes analyses of archived serum samples from RCTs and prospective cohort studies. Relevant outcomes are test validity, other test performance measures, symptoms, change in disease status, functional outcomes, and quality of life. Analyses comparing Vectra DA with other previously validated disease activity measures such as the DAS28 or to radiographic progression, consisted mostly of correlations, with only 1 study providing sensitivity, specificity, and PPV and negative predictive value (NPV). The PPV from this study was 21%. Other analyses of archived serum samples evaluated the use of Vectra DA to predict treatment response. Results from those analyses were inconsistent. The body of evidence on the Vectra DA test is insufficient to determine whether it is as good as or better than other disease activity measures. Additionally, there is no evidence evaluating Vectra DA as an adjunct to other disease activity measures. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

For individuals who have rheumatoid arthritis (RA) who receive the Vectra test, the evidence includes post hoc analyses of archived serum samples from randomized controlled trials and prospective cohort studies. The published data is conflicting as to whether or not multi-biomarker disease activity (MBDA) blood tests, such as the Vectra, perform as well as other RA disease markers. There is insufficient published evidence indicating that treatment decisions can be influenced by MBDA test scores, and insufficient evidence demonstrating the effect of the MBDA testing on net health outcomes.

Clinical Context and Test Purpose
The purpose of the multibiomarker disease activity (MBDA), (e.g., Vectra) test in individuals who have rheumatoid arthritis (RA) is to determine the level of disease activity (low, medium, or high) in order to inform treatment decisions.

The question addressed in this evidence review is: Does use of an MBDA (e.g., Vectra) test, alone or as an adjunct, to predict disease activity in patients with RA, improve health outcomes compared with the use of other American College of Rheumatology (ACR)-recommended measures of disease activity?

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

Populations
The relevant population of interest is individuals with RA who are being managed with a disease-modifying antirheumatic drug (DMARD) and/or biologic agents.

Management of individuals with RA has changed from treatment of symptoms to a tight control strategy. The objective of a tight control strategy is to minimize disease progression and joint damage by monitoring disease activity and treating aggressively if an increase in activity is predicted.

Interventions
Vectra provides a score indicating the level of disease activity, based on blood levels of the following 12 biomarkers: interleukin-6, tumor necrosis factor (TNF) receptor type I, vascular cell adhesion molecule 1, epidermal growth factor, vascular endothelial growth factor A, YKL-40 glycoprotein, matrix metalloproteinase 1, matrix metalloproteinase 3, C-reactive protein (CRP), serum amyloid A, leptin, and resistin. The current, commercially available version of the Vectra test is adjusted for patient age, gender, and adiposity, (i.e., leptin), now referred as the "adjusted MBDA score".

Scores range from 1 to 100 (1-29=low disease activity; 30-44=medium disease activity; 45-100=high disease activity).

Comparators
The reference standard for disease activity is radiographic progression at a set point in time, typically 3 months to one year. In addition, an ACR working group determined that the following 11 measures of disease activity fulfilled a minimum standard for regular use in most clinical settings: Disease Activity Score (DAS), Routine Assessment of Patient Index Data 3 (RAPID3), Routine Assessment of Patient Index Data 5 (RAPID5), Clinical Disease Activity Index (CDAI), Disease Activity Score with 28 joints (DAS28-ESR/CRP), Patient Derived DAS28, Hospital Universitario La Princesa Index (HUPI), the original and no longer commercially available Multibiomarker Disease Activity Score (MBDA score, Vectra DA), Rheumatoid Arthritis Disease Activity Index (RADAI),Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5), and the Simplified Disease Activity Index (SDAI). Additionally, using a modified Delphi process, the ACR working group further identified the following 5 measures as “preferred” for regular use in most clinic settings: the DAS28-ESR/CRP, CDAI, DSAI, RAPID3, and Patient Activity Scale-II.

Outcomes
The goal of treating patients with RA is to improve quality of life and to prevent progression of the disease. Progression of disease causes irreversible joint damage.

If Vectra correctly assesses disease activity as low, the clinician may maintain medications at the same level or consider tapering the patient's medication.

If Vectra correctly assesses disease activity as moderate or high, the clinician may be more aggressive in disease management, by either increasing doses of current medications, switching medications, or adding medications to the treatment plan.

If Vectra incorrectly assesses disease activity as low, the clinician may maintain or decrease medication levels, which will allow progression of the disease and further joint damage.

If Vectra incorrectly assesses disease activity as moderate or high, the clinician may continue to manage the patient with higher levels of medication than is necessary to prevent disease progression, exposing the patient to unnecessary toxins. DMARDs may affect the liver, stomach, and intestines. Biologic agents may increase the risk of infection, lymphoma, and skin cancer.

The test may be run as often as a clinician needs disease activity information, typically every 3 to 6 months. A test immediately after diagnosis may serve as a baseline measurement.

For purposes of assessing Vectra against the reference standard of radiographic progression, 1 year is the typical time frame.

Study Selection Criteria
For the evaluation of the clinical utility of a multibiomarker disease activity test (e.g., Vectra), studies would need to use the current commercially available version of the test (including the "adjusted MBDA score") as either an adjunct or a replacement to current disease activity measures to manage treatment decisions in patients with RA. Outcomes would be quality of life and measures of disease progression.

In the absence of direct evidence for the clinical utility of Vectra, evidence for clinical validity is evaluated, in which we can make inferences on clinical utility. For the evaluation of clinical validity, studies would need to compare the current commercially available version of Vectra (including the "adjusted MBDA score") used as an adjunct or as a replacement to ACR-recommended disease activity measures, with radiographic progression as a reference standard. Prognostic studies should report the probability of the outcome measure (with precision) by risk group. Studies reporting other measures (e.g., odds ratios) may be included but are less informative.

Clinically Valid - Review of Evidence
Vectra Test with "adjusted MBDA score"
Evidence on the evaluation of clinical validity of the current commercially available version of the Vectra test (including the “adjusted MBDA score”) in individuals with RA, consists of two retrospective cohort studies.

(2021) Curtis et al. updated clinical validity data on the Vectra test with an adjusted MBDA score was using combined data from 953 patients enrolled in the OPERA,

BRASS, Leiden Early Arthritis Clinic (EAC), and SWEFOT (Swedish Farmacotherapy) cohorts. The adjusted MBDA score was validated in the Leiden and SWEFOT cohorts and compared with conventional disease activity measures across all 4 cohorts. Among the various baseline disease activity measures, only the adjusted MBDA score (odds ratio [OR] 1.05; 95% CI, 1.03 to 1.06), seropositivity (OR 6.20; 95% CI, 2.90 to 16.1), CRP (OR 1.57; 95% CI, 1.29 to 1.91), baseline joint damage (total Shape score [TSS]) (OR 1.01; 95% CI, 1.00 to 1.01), and DAS28-CRP (OR 1.24; 95% CI, 1.05 to 1.46) were significantly predictive of radiographic progression. Risk ratios (95% CI) for change in TSS > 5 units were 2.62 (0.59 to 11.6; p =.24) and 9.37 (2.34 to 37.5; p = 2.65 x 10-6) in the moderate and high adjusted MBDA score categories compared to the low category. The risk ratio was 4.47 (2.54 to 7.87; p = 5.26 x 10-10) for the high category compared to combined low and moderate categories. Adjusted MBDA scores from the combined cohorts were cross classified with conventional disease activity measures to evaluate discordances. The frequency of radiographic progression was low when the adjusted MBDA score was low and highest when high regardless of DAS28-CRP, CRP, swollen joint count, and CDAI score categories. These trends were not observed within conventional disease activity measures. However, while individual analysis of the 4 cohorts with cross-classification by DAS28-CRP and adjusted MBDA score were generally consistent with these trends, they should be interpreted with caution due to the limited number of progressors. Overall, the frequency of radiographic progression corresponded more consistently with the category of adjusted MBDA score than the category of DAS28-CRP, CRP, swollen joint count, or CDAI scores. Bivariable logistic regression analysis identified the adjusted MBDA score as the strongest single, independent predictor of radiographic progression. A risk curve for radiographic progression for change in TSS > 5 was generated for the adjusted MBDA score. While the risk of radiographic progression exceeded 40% at the highest adjusted MBDA score in the model, at the high-risk cutoff score (> 44) the risk of radiographic progression is less than 10%. While the Leiden and SWEFOT cohorts contributed a higher proportion of patients with radiographic progression in the moderate and high-risk groups, there continues to be insufficient support for the use of the test to “rule in” moderate- to high-risk disease. Furthermore, given the high prevalence of discordant results across conventional disease activity measures, the position of the adjusted MBDA score in the clinical management pathway is unclear. Study relevance, design, and conduct limitations.

(2019) Curtis et al. evaluated the clinical validity of the Vectra test in predicting radiographic progression at 1 year using a convenience sample of combined data from 533 patients enrolled in either the Optimized Treatment in early Rheumatoid Arthritis (OPERA) randomized controlled trial (RCT) or the Brigham Rheumatoid Arthritis Sequential Study (BRASS) cohort study. The clinical validity of the Vectra test was compared to that of the original Vectra DA test and other measures of DA (Table 2). Among the various disease activity measures assessed, only the new Vectra test (relative risk [RR] 8.38; 95% CI, 1.15 to 60.8), the original Vectra Disease Activity (DA) test (RR 5.39; 95% CI, 1.3 to 22.29), and CRP (RR 4.15; 95% CI, 1.58 to 10.95) significantly differentiated between the risk of radiographic progression for the high-risk groups

versus the low-risk groups. Based on these outcomes, the study authors concluded that the new Vectra test ("adjusted MBDA score") may offer "improved clinical utility" over the original and not commercially available Vectra DA test. Although the overlapping confidence intervals suggest at least similar prognostic performance to other DA measures, they indicate uncertainty as to whether Vectra provides prognostic performance superior to the original Vectra DA or CRP. Additionally, the low proportions of patients with radiographic progression in the moderate to high-risk patient groups (3.9% to 9.3% for the new Vectra test and 3.5% to 9.7% for the original Vectra DA test group) do not support the use of the test to "rule in" moderate- to high-risk disease. These low rates of patients with radiographic progression in the moderate to high-risk patient groups suggest that 9 out of 10 patients identified as moderate or high risk could receive intensification of therapy unnecessarily. Likely this is due at least in part to the fact that the overall prevalence of radiographic progression was notably low in this study cohort (6.3%). Although the results from this study are initially supportive of the Vectra test's ability to predict radiographic progression at 1 year, its numerous relevance, design, and conduct limitations provide an insufficient basis to conclude the clinical validity of the Vectra test.

Section Summary: Clinically Valid: Rheumatoid Arthritis
Evidence for the clinical validity of the current commercially available version of the Vectra test (including the "adjusted MBDA score") in patients with RA, consists of 2 retrospective cohort studies that correlated it with other measures of disease activity and with radiographic progression. Results from the 4 cohorts analyzed in these studies have shown that Vectra may be predictive of radiographic progression at 1 year. However, its low positive predictive value (PPV) (4.4% to 15.8%) indicates that 9 out of 10 patients identified as moderate- to high-risk disease could unnecessarily receive intensification of therapy. Additionally, the numerous study relevance, design, and conduct limitations provide an insufficient basis to conclude the clinical validity of the Vectra test.

Evidence for the clinical validity of the original Vectra DA test consists of analyses of archived serum samples from RCTs as well as prospective cohort studies that have correlated the original Vectra DA with other measures of disease activity and with radiographic progression. Results from studies comparing the original Vectra DA with other disease activity measures have shown a positive correlation; however, results from studies comparing the original Vectra DA with radiographic progression are inconsistent. Only 1 study reported sensitivity and specificity, with a PPV of 21%, indicating that 4 out of 5 patients identified as positive would receive intensification of therapy unnecessarily.

Currently, MBDA is used as an adjunct to other disease activity measures. The incremental benefit of MBDA when used as an adjunct to other disease activity measures is unclear given the high prevalence of discordant results across conventional measures of disease activity. Thus, the position of the Vectra test in the management pathway is unclear.

Overall, the evidence is insufficient to conclude the clinical validity of Vectra compared with ACR-recommended measures of disease activity.

Clinically Useful: Rheumatoid Arthritis
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: Rheumatoid Arthritis
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 RCTs.

To demonstrate clinical utility, there should be evidence that the Vectra score is at least as good a measure of disease activity as other available measures or that the Vectra score demonstrates an incremental benefit when used as an adjunct with other disease activity measures. To demonstrate equivalence with other measures directly, an RCT comparing health outcomes of two groups, one group managed using the Vectra test and the other group managed by another disease activity measure is needed.

To directly demonstrate an incremental benefit when used as an adjunct, an RCT should compare health outcomes in patients receiving treatment guided by the Vectra test plus a disease activity measure with outcomes in patients receiving treatment guided only by the other disease activity measure. No RCTs were identified. No studies of the current commercially available Vectra test ("updated MBDA score") were identified. Below is a retrospective study that evaluated the original Vectra DA test and medication use among patients with RA.

(2018) Curtis et al. used Medicare data from 2011 to 2015 to study the original Vectra DA test (not commercially available) scores and biologic and Janus kinase inhibitors use among patients with RA. The database contained 60,596 patients with RA who had the original Vectra DA testing results. Among patients not currently taking biologics (n=33,728), statistically significant differences in adding or switching medications were detected based on the original Vectra DA scores: 9.0% of patients with low scores, 11.8% with moderate scores, and 19.7% with high scores. Similarly, among patients currently taking biologics, statistically significant differences in switching medications were detected among the different levels of scores: 5.2% of patients with low scores, 8.3% with moderate scores, and 13.5% with high scores.

Chain of Evidence: Rheumatoid Arthritis
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.

Because there is insufficient evidence that the Vectra score is clinically valid, direct evidence is needed to prove clinical utility. No trials were identified that provided direct evidence of clinical utility.

Section Summary: Clinically Useful: Rheumatoid Arthritis
There are no RCTs comparing the use of the Vectra test with the "updated MBDA score" or the original Vectra DA score with an alternative method of measuring disease activity. Additionally, there are no RCTs of Vectra or Vectra DA as an adjunct to other disease activity measures compared with using the disease activity measures alone. Absent direct evidence for clinical utility, a chain of evidence could be constructed with indirect evidence proving clinical validity. However, there is insufficient evidence that Vectra or Vectra DA are clinically valid.

Summary of Evidence: Rheumatoid Arthritis
Vectra Test with Adjusted Multibiomarker Disease Activity Score: Rheumatoid Arthritis
For individuals who have RA who receive the current commercially available Vectra test ("adjusted MBDA score") as an adjunct or as a replacement of other disease activity measures, the evidence includes 2 studies that analyzed archived serum samples using combined data from RCTs and cohort studies. Relevant outcomes are test validity, other test performance measures, symptoms, change in disease status, functional outcomes, and quality of life. Analyses comparing Vectra with other previously validated disease activity measures such as the DAS28 or to radiographic progression, consisted mostly of correlations. However, the PPVs that individuals with Vectra moderate- to high-risk disease scores had radiographic progression were low, at 4.4% and 15.8%, respectively. Additionally, due to numerous study relevance, design, and conduct limitations, the body of evidence on the Vectra test is insufficient to determine whether it is as good as or better than other disease activity measures. Given the high prevalence of discordant results across conventional measures of disease activity, the position of the Vectra test in the management pathway is unclear. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Original Vectra Disease Activity Test: Rheumatoid Arthritis
For individuals who have RA who receive the original Vectra DA test as an adjunct or as a replacement of other disease activity measures, the evidence includes analyses of archived serum samples from RCTs and prospective cohort studies. Relevant outcomes are test validity, other test performance measures, symptoms, change in disease status, functional outcomes, and quality of life. Analyses comparing Vectra DA with other previously validated disease activity measures such as the DAS28 or to radiographic progression, consisted mostly of correlations, with only one study providing sensitivity, specificity, and PPV and negative predictive value (NPV). The PPV from this study was 21%. Other analyses of archived serum samples evaluated the use of Vectra DA to predict treatment response. Results from those analyses were inconsistent. The body of evidence on the Vectra DA test is insufficient to determine whether it is as good as or better than other disease activity measures. Additionally, there is no evidence evaluating

Vectra DA as an adjunct to other disease activity measures. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
Systemic Lupus Erythematosus (SLE)

Systemic Lupus Erythematosus (SLE)
Biomarker Panel Testing for Systemic Lupus Erythematosus (SLE)
Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease (CTD) that is one of several types of lupus. About 90% of lupus patients are women between the ages of 15 and 44 years. It 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.

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. 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.

Currently, differential diagnosis depends on a combination of clinical signs and symptoms and individual laboratory tests. In 2019, new classification criteria endorsed by the European League Against Rheumatism (EULAR) and the ACR were developed and validated. The 2019 EULAR/ACR classification criteria require, a positive ANA as an entry criterion. For those with a positive ANA, additive criteria are assessed in 7 clinical and three 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: antibodies to double stranded DNA (anti-dsDNA) or antibodies to Smith antigen (anti-sm) (6)

To date, the most common laboratory tests performed in the diagnosis of SLE are serum ANA, and if this is positive, tests for anti-dsDNA and anti-Sm. ANA 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, or ENAs) to examine the "pattern" of ANA positivity. These include antigens against single and double-stranded DNA, histones, Sm, Ro, La, and RNP. The presence of anti-dsDNA or anti-Sm is highly specific for SLE because few patients without SLE test positive; however, neither of these tests have high sensitivity (Suresh, 2007). The presence of other antibody patterns may indicate the likelihood of alternate diagnoses. For example, the presence of Ro and La antibodies suggests Sjogren syndrome, while the presence of antihistone antibodies suggests drug-induced lupus.

More accurate laboratory tests for systemic lupus erythematosus (SLE) could facilitate diagnosis, prognosis, and management. Recently, laboratory-developed, diagnostic panel tests with proprietary algorithms and/or index scores for the diagnosis of SLE have become commercially available. AVISE testing offers next-generation insight autoimmune lab tests to include the following:

- **AVISE CTD Assay**: All markers reported in AVISE CTD are carefully selected to provide maximum performance in the diagnosis of SLE and diseases that mimic lupus. The AVISE CTD assay 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 and a 12- marker panel that focuses on connective tissue diseases (CTDs) to help distinguish SLE from other CTDs. 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.
- **AVISE Lupus:** The AVISE Lupus test is a 10-marker diagnostic test containing Cell-Bound Complement Activation Products (CB-CAPs) and other SLE

associated markers designed to aid healthcare providers in a timely differential diagnosis of SLE.

- **AVISE SLE Monitor**: The AVISE SLE Monitor is a unique combination of 6 specialized biomarkers include EC4d and PC4d to help assess patients with SLE.
- **AVISE SLE Prognostic:** The AVISE SLE Prognostic test is a 10-marker panel developed to help assess an SLE patient's risk for their potential risk for thrombosis, cardiovascular events, lupus nephritis and neuropsychiatric lupus.

Panel tests for systemic lupus erythematosus (SLE) include markers that are standard in the work-up of SLE, but also contain novel markers, most notably cell-bound complement activation products (CB-CAPs). The accuracy of CB-CAPs in establishing a diagnosis of SLE is not known, nor is the use of these novel biomarkers recommended in clinical practice guidelines. In addition to reporting the results of the panel of tests, an index score is reported that rates how suggestive the results of the panel are of a diagnosis of SLE. Information is not available on how this index score is calculated, nor is it known how this score performs in diagnosing SLE compared with currently accepted clinical and laboratory criteria. Finally, the utility of assessing multiple biomarkers simultaneously, rather than the more commonly performed sequential testing, is unknown. The evidence is insufficient to determine the effects of the technology on net health outcomes.

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 patients with signs and/or symptoms of SLE. The question addressed in the evidence review is does the use of a serum biomarker panel improve the net health outcome in patients with signs and/or symptoms of SLE?

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

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 symptoms of 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 (SLE) is an autoimmune connective tissue disease CTD that can be difficult to diagnose because patients 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 patients 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 the table below.

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 autoantibodies: thyroglobulin IgG, thyroid, thyroid peroxidase

ANA: antinuclear antibody; anti-dsDNA: antibodies to double-stranded DNA; anti-Sm: antibodies to Smith nuclear antigen; CTD: connective tissue disease; Ig: immunoglobulin.

The Avise Connective Tissue Disease (CTD)Test
The Avise CTD test assesses all 22 markers. Avise CTD uses a 3-step process. 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 anti-Sm, EC4d, BC4d, and 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, antimutated citrullinated vimentin, anti-Jo-1, anti-Sci-70, anti-CENP, and anti-Ss-B/La. 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.

Avise Lupus Prognostic Test
The Avise Lupus Prognostic test (Exagen), a 10-marker panel that can be ordered with the Avise Lupus and Avise connective tissue disease (CTD) panels. The prognostic test focuses on patients' 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.

The AVISE SLE Monitor
The AVISE SLE Monitor (Exagen) released an advanced blood test in 2017 that incorporates specialized lupus biomarkers to assist in evaluating SLE disease activity. 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 1982 criteria for classifying SLE. In 1997, the ACR updated the 1982 criteria for the classification of SLE. In 2019, new classification criteria endorsed by the European League Against Rheumatism (EULAR) and the ACR were developed and validated. The 2019 EULAR/ACR classification criteria require 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: antibodies to double stranded DNA (anti-dsDNA) or antibodies to Smith antigen (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. 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. These criteria include more laboratory tests than the 1997 ACR criteria, including elements of the complement system. Patients 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 patients, 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. The table below outlines the SLICC criteria.

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 min 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 CH150)

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 RNP antibodies. The presence of anti-dsDNA or anti-Sm is highly specific for SLE because few patients without SLE test positive; however, neither test has high sensitivity. 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.

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

Outcomes	Details
Test accuracy	Sensitivity and specificity in detecting biomarkers for SLE [Follow up 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]

More specifically, outcomes of interest for SLE include disease activity indices, organ damage, reduction in flares, and reduction in concomitant corticosteroids. Individual 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. 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 (eg, Short Form 36 [SF-36]). Recommended health outcome measures for disease activity and organ damage per FDA guidance is summarized in the table below.

Health Outcome Measures Relevant to SLE

Outcome	Measure (Units)	Assessment	Description	Clinical Interpretation (if available)
Disease Activity Index				
BILAG 2004	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	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	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	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	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.

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. 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 U.S. Food and Drug Administration 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. 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, or only evaluated the cell-bound complement activation products (CB-CAPs) component of commercially available multianalyte tests.

Clinically Valid
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).

Review of Evidence

Serum Biomarker Panel Tests
(2021) Ramsey-Goldman et al. reviewed 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. 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.

(2020) Liang et al. 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. 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. The authors concluded that the Avise CTD may be useful in predicting the development of SLE.

(2020) Ramsey-Goldman et al. evaluated the usefulness of CB-CAPs and a multianalyte assay 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. 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 Sjogren'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 CB-CAPs and MAP at enrollment was higher compared to anti-dsDNA levels or low complement levels. The MAP was more sensitive and specific than CB-CAPs in patients with probable SLE (40% vs 28% and 96% vs 86%, respectively). The ability of positive CB-CAPs and 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., 95% confidence interval 1.26 to 7.69). A limitation of the study was the relatively small population of patients with probable SLE.

(2016) Mossell et al. 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. 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. The authors noted that prospective studies would be performed.

(2014) Putterman et al. published data from a large cross-sectional, industry-sponsored study evaluating serum biomarkers for the diagnosis of SLE. 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 (see the Background section). The study evaluated 2 cohorts (N=794 patients); 593 participants were enrolled between April and August 2010, and 201 participants enrolled between June 2011 and September 2013. Together, the two 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.

The diagnostic accuracy of the CB-CAP EC4d and BC4d were compared with reduced complement (C3, C4) and anti-dsDNA. The AUROC curve was significantly higher for EC4d (0.82) and BC4d (0.84) than for C3 (0.73) and C4 (0.72) ($p<0.001$). The AUROC curve was significantly higher for BC4d than for anti-dsDNA (0.79; $p=.009$) but the difference was not statistically significant between EC4d and anti-dsDNA.

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 (ie, not suggestive of SLE). When the results of tier 1 and 2 testings 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).

As shown in the table below, the specificity and area under the curve were higher for models including CB-CAPs than in those without these markers; sensitivity was slightly lower.

Diagnostic Accuracy of Various Combinations of Markers

Measures	dsDNA, Sm, and ANA	dsDNA, Sm, ANA, Plus Antibody Specificity Components but Not CB-CAPs	Two-Tiered Testing Using All Markers, Including CB-CAPs EC4d and BC4d
Sensitivity, %	89	83	80
Specificity, %	53	76	86
Area under the curve	0.78	0.80	0.91

Putterman and colleagues noted a limitation of 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).

(2016) Wallace et al. reviewed a subsequent industry-sponsored study by analyzed serum biomarkers as well as an algorithm for diagnosing SLE. 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). High expression of CB-CAP EC4d or BC4d had 43% sensitivity and 96% specificity for the diagnosis of SLE. 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.

Summary of Evidence for Diagnosing and Management of Systemic Lupus Erythematosus

The diagnostic accuracy of the serum biomarker panel test was initially established in observational studies that evaluated the sensitivity and specificity of the test in

individuals with established SLE. However, the more relevant question of whether the Avise test can aid in the diagnosis or exclusion of SLE in a population with suspected SLE or undifferentiated findings in a real-world setting was examined in more recent studies. One retrospective evaluation found that patients with undifferentiated CTD positive Avise test results increased the likelihood of a SLE diagnosis within two years. Another prospective observational study reported similar results in individuals with probable SLE were more likely to fulfill ACR criteria for SLE within 9 to 18 months after a positive Avise test result. These studies are limited by a lack of a comparator. 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.

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

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 (e.g., 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).

Randomized Controlled Trials
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

(2019) Wallace et al. evaluated the clinical utility of the Avise Lupus test for the diagnosis of lupus as compared to standard diagnosis laboratory testing. 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.

Summary of Evidence: Multiplex Autoantigen Microarray Testing for Systemic Lupus Erythematosus (SLE)

The diagnostic accuracy of the serum biomarker panel test was initially established in observational studies that evaluated the sensitivity and specificity of the test in individuals with established for Systemic Lupus Erythematosus (SLE). However, the more relevant question of whether the Avise test can aid in the diagnosis or exclusion of SLE in a population with suspected SLE or undifferentiated findings in a real-world setting was examined in more recent studies. Currently one test the SLE-key rule-out test (ImmunoArray) is designed to rule-out the likelihood of a systemic lupus erythematous (SLE) diagnosis. The index score, 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.

Two industry-funded studies evaluating the SLE-key test have been published. The available published literature on the SLE-key rule-out test is limited in that it includes samples only from individuals already diagnosed with SLE or healthy people, and not from the population most likely to be tested in clinical practice, individuals with suspected SLE. A development and validation study included an even more selected population, females between the ages of 18 and 60. Moreover, the impact of the test on individual management such as reducing the need for other tests or permitting an earlier diagnosis has not been studied.

Another prospective observational study reported similar results in individuals with probable SLE were more likely to fulfill ACR criteria for SLE within 9 to 18 months after a positive Avise test result. These studies are limited by a lack of a comparator. A 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 an individual 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. Furthermore, data are not available on the impact of SLE-key Rule-Out testing on health outcomes. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American Academy of Pediatrics (AAP)
(Released 2019; Last reviewed 2022) The AAP released guidelines through *Choosing Wisely*. In it, they state:

- "Do not order antinuclear antibody (ANA) and other autoantibody testing on a child unless there is strong suspicion or specific signs of autoimmune disease" (*Accessed May 2022*)

American College of Rheumatology (ACR)
(2021) The ACR noted in the updated guideline for the treatment of rheumatoid arthritis the following statement:

- Because the ACR has in a separate project, endorsed several disease activity measures for use in clinical practice, this guideline does not define levels of disease activity or the instruments a clinician should use to measure it. (*Accessed May 2022*)

Canadian Rheumatology Association (CRA)
(2018) The CRA guidelines and recommendations for assessing and monitoring SLE, they state,

- "Best clinical practice includes a complete history and physical examination at baseline, with laboratory monitoring possibly including but not limited to complete blood count (CBC), liver enzymes, creatine kinase, creatinine and estimated glomerular filtration rate (eGFR), urine routine/microscopic (urinalysis), urine protein-creatinine ratio, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complements (C3, C4), anti-dsDNA, antinuclear antibodies, antibodies to extractable nuclear antigens, antiphospholipid antibodies (aPL), lupus anticoagulant (LAC), anticardiolipin (aCL), anti-β2-glycoprotein I (anti-β2-GPI), and lipid profile. Follow-up (sic) laboratory monitoring will depend on the patient's clinical status and may include CBC, eGFR, urinalysis, urine protein-creatinine ratio, CRP, and/or ESR, C3, C4, and anti-dsDNA antibodies." (*Accessed May 2022*)

European League Against Rheumatism
(2017) The European League Against Rheumatism guidelines on the management of early arthritis recommended arthritis activity be assessed at 1- to 3-month intervals to determine target treatment.

- "Monitoring of disease activity should include tender and swollen joint counts, patient and physician global assessments, erythrocyte sedimentation rate, and C reactive protein, usually by applying a composite measure." Composite measures recommended include the Disease Activity Score with 28 joints, Clinical Disease Activity Index, and Simplified Disease Activity Index. One item on the research agenda recommended by the League was to evaluate new biomarkers and multibiomarkers for the prognosis and treatment in early arthritis. (*Accessed May 2022*)

National Institute for Health and Clinical Excellence (NICE)
(Published 2018; updated in 2020) The National Institute for Health and Care Excellence guidance on the management of adult patients with rheumatoid arthritis does not include a discussion on the use of a multibiomarker disease activity blood test to monitor individuals. (*Accessed May 2022*)

Systemic Lupus International Collaborating Clinics (SLICC)
(2012) The Systemic Lupus International Collaborating Clinics (SLICC), an international group of researchers, developed revised criteria for diagnosing SLE. These criteria include more laboratory tests than the earlier ACR criteria, including elements of the complement system. Patients 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-DNA antibodies. In a sample of 690 patients, 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. The SLICC criteria are outlined below:

- **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)
    - Hemolytic anemia
    - Leukopenia or lymphopenia
    - Neurologic disorder: seizures, psychosis, mononeuritis complex, or peripheral, or cranial neuropathy
    - Nonscarring alopecia in the absence of other causes
    - Synovitis involving ≥ 2 joints, characterized by swelling or effusion or and ≥ 30 min of morning stiffness
    - Oral ulcers
    - Renal: excessive protein in the urine or cellular casts in the urine
    - Serositis

    - Seizures
    - 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 CH50)
    - Direct Coombs tests *in the absence of hemolytic anemia*

As previously noted, the SLICC classification system includes a wider range of laboratory tests than the ACR criteria. 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.
(*Accessed May 2022*)

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 Act (CLIA). These tests are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA Clinical for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

- The Avise® tests (Exagen Diagnostics) are available under the auspices of the CLIA.
- The original Vectra DA test is no longer commercially available.

PRIOR APPROVAL

Not applicable.

POLICY

Rheumatoid Arthritis (RA)
The use of multi-marker biomarker disease activity (MBDA) testing (e.g., Vectra) for rheumatoid arthritis (RA) is considered **investigational** for all indications. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Systemic Lupus Erythematosus (SLE)
Serum biomarker panel testing with proprietary algorithms and/or index scores for the diagnosis, prognosis, or management of systemic lupus erythematosus (SLE), including, but not limited to the following tests are considered **investigational** for all indications because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- AVISE CTD Assay
- AVISE Lupus
- AVISE SLE Monitor
- AVISE SLE Prognostic

Multiplex autoantigen microarray testing to screen for, diagnose or manage systemic lupus erythematous (SLE) using SLE-key rule-out test is considered **investigational** for all indications. The evidence is insufficient to determine the effects of the technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81479 Unlisted molecular pathology procedure (*may be utilized for the following: AVISE CTD Assay, AVISE Lupus, AVISE SLE Monitor, AVISE SLE Prognostic*)
- 81490 Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score (*may be utilized for Vectra DA*)
- 81599 Unlisted multi-analyte assay with algorithmic analysis (*may be utilized for the following: AVISE CTD Assay, AVISE Lupus, AVISE SLE Monitor, AVISE SLE Prognostic*)
- 84999 Unlisted chemistry procedure (*may be utilized for the following: AVISE CTD Assay, AVISE Lupus, AVISE SLE Monitor, AVISE SLE Prognostic*)
- 0062U Autoimmune (systemic lupus erythematosus), IgG and IgM analysis of 80 biomarkers, utilizing serum, algorithm reported with a risk score (*may be utilized for SLE-Key Rule-Out Test*)
- 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 (*may be utilized for Avise Lupus*)

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POLICY HISTORY		
Date	**Reason**	**Action**
June 2022	Annual Review	Policy Revised
June 2021	Annual Review	Policy Revised
June 2020	Annual Review	Policy Revised
September 2019	Annual Review	Policy Revised
September 2018	Annual Review	Policy Revised
September 2017	New Policy	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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