Policy Statement

The use of a multibiomarker disease activity score for rheumatoid arthritis (RA) (e.g., Vectra® DA score) is considered investigational in all situations.

Policy Guidelines

There is a specific CPT code for this test:

- **81490**: Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score

Description

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. A multibiomarker 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).

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 Amendments. The Vectra® DA test (Crescendo Bioscience, South San Francisco, CA) is available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.
Rationale

Background

Rheumatoid Arthritis

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 patients.

Treatment

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 antirheumatic drugs has made the achievement of remission, or sustained low disease activity, a feasible goal for a large proportion of patients with RA. This treatment strategy has been called a tight control approach.

The concept of tight control in the management of RA has gained wide acceptance because evidence from clinical trials have demonstrated that outcomes are improved with a tight control strategy. In a tight control strategy, treatment targets used are mainly based on measures of disease activity. In a 2010 systematic review, Schoels et al identified 7 trials that evaluated the efficacy of tight control. Four of these trials randomized patients to a tight control using treatment targets or to routine management. The treatment targets used were heterogeneous, including symptom-based measures, joint scores on exam, validated treatment activity measures, lab values, or combinations of these factors. In all 4 trials, there was a significant decrease in the Disease Activity Score (DAS) or its 28 joint version (DAS28) and in the likelihood of achieving remission for patients in the tight control group.

Validated Assessment Tools

For a strategy of tight control to be successful, a reliable and valid measurement of disease activity is necessary. There are numerous disease activity measurements that can be used in clinical care. Composite measures include information from multiple sources, including patient self-report, physician examination, and biomarker measurement. Composite measures are the most comprehensive but are more cumbersome and difficult to complete. Patient-reported measures are simpler, and rely only on information patients can provide expeditiously, but are more subjective. Measurements that rely only on biomarkers are objective and do not require patient input, but involve the cost and inconvenience of laboratory tests.

The most widely used and validated scoring system in clinical research is the DAS28 score. This is a composite measure that includes an examination of 28 joints for swelling and tenderness, combined with a patient report of disease activity and measurement of C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR). This score is often considered the criterion standard for measuring disease activity. However, it requires a thorough joint examination, patient-reported symptoms, and laboratory testing. Therefore, many attempts have been made to create a simpler, valid disease activity measure.

There is a fairly large body of evidence comparing the performance of different disease activity measures in clinical care, including a number of systematic reviews. In a 2012 systematic review of disease activity measures sponsored by the American College of Rheumatology, more than 60 measurement instruments were identified. Through a 5-stage process that included review by an expert advisory panel in RA disease activity and detailed evaluation of psychometric properties, the working group selected 6 measures that were most useful and feasible for point-of-care clinical care. They were the Clinical Disease Activity Index (CDAI), DAS28, Patient Activity Scale (PAS), Patient Activity Scale II (PAS-II), Routine Assessment of Patient Index Data 3 (RAPID3), and the Simplified Disease Activity Index (SDAI).
In another 2012 systematic review, Gaujoux-Viala et al compared 4 composite indices: the DAS, DAS28, SDAI, and CDAI.\(^4\) In general, the concordance between measures was good, with \(\kappa\) values in the range of 0.7. An exception to this level of concordance was in the definition of remission, for which the DAS28 had lower levels of concordance with other measures, with \(\kappa\) values ranging from 0.48 to 0.63. All measures had fair-to-good correlations with an independent health status measure, the Health Assessment Questionnaire, and with a radiologic examination of joint structural damage.

Salaffi et al (2012) compared the responsiveness of numerous disease activity measures, including patient self-report measures and composite indices, over a 6-month period of treatment with disease-modifying drugs.\(^5\) The composite indices evaluated were the DAS28, SDAI, CDAI, and the Mean Overall Index for RA. The patient-reported measures evaluated were the Clinical Arthritis Index, the Rheumatoid Disease Activity Index, RAPID3, and PAS. Across all measures, there was wide variability in internal responsiveness, with the highest value obtained for the DAS28 measure. There were differences in responsiveness between the measures, but all were considered suitable for use in clinical care. When comparing the patient-reported measures with the composite measures, there were no differences in internal or external responsiveness.

**Vectra DA Test**

The Vectra DA test consists of 12 individual biomarkers:\(^6\)

- Interleukin-6
- Tumor necrosis factor receptor type I
- Vascular cell adhesion molecule 1
- Epidermal growth factor
- Vascular endothelial growth factor A
- YKL-40
- Matrix metalloproteinase 1
- Matrix metalloproteinase 3
- C-reactive protein
- Serum amyloid A
- Leptin
- Resistin

The Vectra DA test scores range from 1 to 100. Categories of scores were constructed to correlate with the DAS28-CRP scale:\(^7\):

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

**Literature Review**

Multibiomarker disease activity (MBDA) tests for disease activity in rheumatoid arthritis (RA) are best evaluated in the framework of a prognostic test because such frameworks provide prognostic information that assists in treatment decisions. Assessment of a prognostic tool typically focuses on 3 categories of evidence: (1) technical performance; (2) clinical validity (ie, statistically significant association between the test result and health outcomes); and (3) clinical utility (ie, demonstration that use of the prognostic information clinically can alter clinical management and/or improve health outcomes compared with patient management without use of the prognostic tool). In some cases, it is important to evaluate whether the test provides incremental information above the standard workup to determine if the test has utility in clinical practice.

**Testing for Rheumatoid Arthritis**

**Clinical Context and Test Purpose**

The purpose of the Vectra DA in patients who have RA is to determine the level of disease activity (low, medium, or high) that will inform treatment decisions.
The question addressed in this evidence review is: Does the use of the Vectra DA test improve the net health outcome in individuals with RA?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals with RA.

**Interventions**
Vectra DA is a blood test that includes 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, matrix metalloproteinase 1, matrix metalloproteinase 3, C-reactive protein (CRP), serum amyloid A, leptin, and resistin. Scores range from 1 to 100 (1-29=low disease activity; 30-44=medium disease activity; 45-100=high disease activity).

**Comparators**
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).

**Outcomes**
The general outcome of interest is to characterize the disease activity accurately in an individual with RA. An accurate determination of disease activity can then inform the decision on whether to approach treatment with a tight control. No single disease activity measure is considered the criterion standard; however, the DAS28 is currently the most common technique used.

**Beneficial Outcomes**
If disease activity is measured accurately, the correct treatment approach can be implemented. If disease activity is high, a tight control approach may be used, which can include increasing treatment doses or injecting steroids. The goal of treatment is to minimize disease activity and delay disease progression.

**Harmful Outcomes**
If high disease activity is not detected, treatment may be withheld. Untreated ongoing joint inflammation may cause irreversible joint damage.

**Timing**
The test may be run as often as a clinician needs disease activity information. A test immediately after diagnosis may serve as a baseline measurement.

**Setting**
The test is given at an on-site or local laboratory or in a clinician's office.

**Technical Performance**
Eastman et al (2012) described aspects of the technical performance of the Vectra DA MBDA test. The 12 biomarkers in the Vectra DA test were measured using multiplexed sandwiched immunoassays with biomarker-specific-capture antibodies. The total MBDA score had good reproducibility over time, with a coefficient of variation of less than 2%. Cross-reactivity by serum rheumatoid factor, other RA antibodies, and/or common RA therapies, was minimal.

Centola et al published a study on the development of the Vectra DA test in 2013. They described a multistage process for development and validation of the score. In the first phase
(the screening phase), proteins were identified that could be readily measured and had the potential to be associated with RA disease activity. A comprehensive total of 130 candidate biomarkers were selected. In the second phase, 4 separate patient cohorts were used to refine the biomarkers based on their correlations with multiple measures of disease activity. In the final phase (assay optimization and training), the biomarkers with the greatest predictive ability were optimized for multiplex assay. Additionally, the combined cohorts of patients were used for algorithm training using a number of statistical techniques. The final model included 12 individual biomarkers and an algorithm that generated a score between 1 (low) and 100 (high).

**Clinical Validity**

Evidence on the clinical validity consists primarily of studies that correlate the MBDA score with other disease activity measures (DAS28, CDAI, SDAI) and markers of disease progression (radiographic measures). There is also evidence on using MBDA to measure response to therapy. The studies are either observational cohort or post hoc analyses of serum samples from randomized controlled trials (RCTs). We reviewed the evidence that includes RCTs and prospective cohort studies.

**Post Hoc Analyses of Completed Randomized Controlled Trials**

Post hoc analyses of at least 5 RCTs have evaluated the clinical validity of the Vectra DA score. These RCTs were conducted for different reasons and, therefore, have different patient populations and interventions.

**BeST Trial**

Two publications have reported results from the BeST trial, a multicenter RCT of 508 patients with early RA randomized to 4 different treatment strategies. For both of these studies, a subset of patients who had serum samples available were included. Of the 508 patients, 125 patients had serum samples, 91 had baseline samples, 89 had 1-year follow-up samples, and 55 patients had both baseline and follow-up serum samples available. Comparison of patients who had and did not have samples available revealed that the population with serum samples differed from the population that did not by sex (75% vs 65% female, p=0.04), median number of tender joints (11 vs 14, p<0.001), and median number of erosions seen on imaging (1.0 vs 2.0, p=0.005).

In the first study, Hirata et al (2013) studied the correlation between the Vectra DA score and scores for other validated measures of disease activity.\(^{10}\) Validated measures were the DAS28, SDAI, CDAI, and the Health Assessment Questionnaire Disease Index (HAQ-DI). MBDA scores correlated significantly with DAS28 scores at baseline (Spearman ρ=0.66, p<0.001) and at 1 year (Spearman ρ=0.55, p<0.001). Vectra DA scores correlated significantly with SDAI, CDAI, and HAQ-DI scores at the p<0.001 level at baseline. MBDA measures of change in scores after 1 year correlated with those for the SDAI, but not CDAI. The 1-year follow-up analyses were limited by small sample sizes.

The second study by Markusse et al (2014) evaluated how well the Vectra DA score predicted the progression of radiographic joint damage and compared the predictive ability of the Vectra DA score with the DAS28 score.\(^{11}\) Radiographic progression was defined as a change of at least 5 points on the Sharp/van der Heijde Score over a 1-year period. Receiver operating characteristic analysis was performed, with an area under the curve (AUC) for the Vectra DA test of 0.77 (95% confidence interval [CI], 0.64 to 0.90), which was higher than the AUC for the DAS28 (0.52; 95% CI, 0.39 to 0.66).

**Computer-Assisted Management in Early Rheumatoid Arthritis Trial**

Bakker et al (2012) examined the correlation between MBDA (Vectra DA) scores and DAS28 scores plus response to therapy in a subset of patients from the Computer-Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial.\(^{12}\) In the larger CAMERA trial, 299 patients were randomized to standard or to intensive management of RA. In the Bakker subset, 74 (24.7%) of the 299 patients had blood drawn and 20 biomarkers, including the 12 comprising the MBDA test, were measured. Seventy-two samples were collected at baseline and 48 at 6 months. The
total test score, between 1 and 100, was calculated using a proprietary algorithm. The Vectra DA score correlated significantly with the DAS28 score at baseline (Pearson r = 0.72, p < 0.001). When using the DAS28-CRP cutoff of 2.7 as the criterion standard, the MBDA score discriminated between remission/low disease activity and moderate/high disease activity with an AUC of 0.86. The κ score for agreement with the DAS28-CRP cutoff for classifying disease activity was 0.34 (95% CI, 0.19 to 0.49). The MBDA (SD) score decreased following therapy, from a baseline of 53 (18) to 39 (16) at 6 months.

Swedish Farmacotherapy Trial
Hambardzumyan et al (2015) performed a post hoc analysis from the Swedish Farmacotherapy (SWEFOT) trial, an RCT that randomized 487 patients to 2 treatment regimens.13 A total of 235 (48%) patients had serum samples available and complete clinical and radiographic data. The authors evaluated the Vectra DA score as a predictor of radiographic progression, defined as a change of at least 5 points on the Sharp/van der Heijde Score. The Vectra DA score was a univariate predictor of radiographic progression (odds ratio [OR], 1.05 per unit increase; 95% CI, 1.02 to 1.08; p < 0.001), and was an independent predictor of progression in a variety of multivariate models. For patients with a low or moderate Vectra DA score (<44), radiographic progression was uncommon, occurring in 1 (2.5%) in 40 patients.

A second publication from the SWEFOT trial presented repeat scores at multiple time points.14 Of the 487 patients enrolled in the SWEFOT trial, 220 (45.2%) had baseline Vectra DA scores, 205 (42.1%) had scores at 3 months, and 133 (27.3%) had scores at 1 year. Patients with low initial scores, or with a decrease in scores over time into the low range, had the lowest rate of radiographic progression at 1 year. Cross-tabulation of Vectra DA results with the DAS28 results, erythrocyte sedimentation rate (ESR), and CRP values were presented, but statistics addressing the comparative accuracy of the different measures were not reported.

Abatacept versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate Trial
The Abatacept versus Adalimumab Comparison in Biologic-Naive RA Subjects With Background Methotrexate (AMPLE) trial randomized patients with active RA and an inadequate response to methotrexate, to abatacept, or to adalimumab and followed patients for 2 years.15 Eligibility criteria included a DAS28-CRP score of at least 3.2 and a positive test for antibodies to cyclic citrullinated peptide or to rheumatoid factor. Vectra DA scores were analyzed from stored serum samples at baseline, 3 months, 1 year, and 2 years, and correlated with other measures of disease activity (DAS28-CRP, CDAI, SDAI, RAPID3). A total of 646 patients enrolled and 524 (81%) had results for the Vectra DA test. The concordance of disease activity states was examined for the different measures. There was little concordance in the high, moderate, and low disease classifications, but quantitative measures of association were not reported. The Vectra DA score was not found to be a significant predictor of radiographic progression, while the CDAI score was a significant predictor (see Table 1).

Table 1. Comparing Rheumatoid Arthritis Classification Systems15

<table>
<thead>
<tr>
<th>Classification</th>
<th>Baseline</th>
<th>3 Months</th>
<th>1 Year</th>
<th>2 Years</th>
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<td>Tx 1</td>
<td>Tx 2</td>
<td>Tx 1</td>
<td>Tx 2</td>
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<td>Remission/low disease activity, %</td>
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<td></td>
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<td>Moderate disease activity, %</td>
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<tr>
<td>DAS28-CRP</td>
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<td>1 Year</td>
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<td>High disease activity, %</td>
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</table>

CDAI: Clinical Disease Activity Index; DAS28-CRP: Disease Activity Score in 28 joints using C-reactive protein; MBDA: multibiomarker disease activity; RAPID3: Routine Assessment of Patient Index Data 3; SDAI: Simplified Disease Activity Index; Tx 1: abatacept; Tx 2: adalimumab.

This post hoc analysis by Fleischmann et al was accompanied by an editorial by Davis. Davis summarized the evidence for the validity of the MBDA test:

- The test measures biologic pathways and therefore provides unique information that complements clinical assessments (face validity)
- Relevant biomarker components were chosen for the test (content validity)
- Correlation with other measures of disease is inconsistent, ranging from discordant to strong, because there is a lack of a criterion standard in measuring RA disease activity (criterion validity)
- Sensitivity to change following different RA treatments was inconsistent with other disease activity measures (discriminant validity)
- High MBDA scores were predictive of radiographic progression, despite clinical measures showing no disease progression (construct validity)

Davis concluded that the clinical value of MBDA remains unclear. He pointed out that the manufacturer does not propose that MBDA replace current tests, but rather the test should be used as a complement to clinical evaluations.

In 2017, Curtis et al published a response to the Fleischmann study. The authors explained that one of the reasons for discordance between MBDA and the other RA disease activity measures in the Fleischmann study was the use of incorrect cutoff points defining low, moderate, and high disease activity (DAS28-ESR cutoff points were used to compare MBDA and DAS28-CRP measures). Also, Curtis et al proposed looking at the relation between radiographic outcomes and MBDA by evaluating radiographic progressors rather than nonprogressors, which is how Fleischmann conducted the analysis. In a rebuttal, Fleischmann et al (2017) justified their use of nonprogressors on 2 bases: (1) nonprogressors are important patient-level assessments of therapeutic response; and (2) nonprogressors were much more common in the AMPLE database (after 1-year follow-up, there were 327 nonprogressors and 40 progressors).

Reduction of Therapy in Patients with Rheumatoid Arthritis in Ongoing Remission Trial
The Reduction of Therapy in Patients with Rheumatoid Arthritis in Ongoing Remission (RETO) trial enrolled patients treated with disease-modifying antirheumatic drugs (DMARDs) in clinical remission and randomized participants to tapering DMARD or to standard maintenance care. Eligibility criteria included a DAS28 ESR cutoff score lower than 2.6 for at least 6 months, and follow-up for 12 months. Of 101 patients enrolled in the RETRO trial, Vectra DA data were available for 94 (93%). Vectra DA scores were higher in patients experiencing a relapse (32.0) than in patients who did not (22.6; p=0.001). On multivariate analysis, the Vectra DA score was a significant predictor of relapse (OR=8.54; 95% CI, 2.0 to 36.4), along with treatment arm (OR=5.94; 95% CI, 1.3 to 26.7) and anti-cyclic citrullinated peptide status (OR=24.5; 95% CI, 3.1 to 194.0).

ACT-RAY Trial of Patients with Active Rheumatoid Arthritis
Reiss et al (2016) conducted a post hoc analysis on patients from the ACT-RAY trial in which patients who did not respond to methotrexate therapy were randomized to add-on tocilizumab therapy or placebo. Patients were included in the analysis if they had DAS28-CRP and CDAI scores at baseline and 24-week follow-up and sufficient serum for MBDA testing at the same time points. Disease activity level (low, moderate, high) agreement between the DAS28-CRP and MBDA at baseline was 77%; however, the agreement between the 2 measures at 24 weeks of
follow-up was 24%. Agreement between the MBDA and CDAI followed a similar pattern: 72% agreement at baseline and 22% agreement after 24 weeks of tocilizumab therapy. DAS28-CRP and CDAI had high levels of agreement, both at baseline and 24 weeks (87% and 85%, respectively).

**Prospective Cohort Studies**

Curtis et al (2012) used blood samples from 3 cohorts of arthritis patients (Index for Rheumatoid Arthritis Measurement, Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study, Leiden Early Arthritis Clinic) to validate the Vectra DA test against the DAS28-CRP and other known markers of disease activity.6 There was a positive correlation between the Vectra DA score and the DAS28-CRP score, with a Pearson r correlation coefficient of 0.56 in seropositive RA patients and 0.43 in seronegative patients. The AUC curve for discriminating low disease activity from moderate-to-high disease activity was 0.77 in seropositive patients and 0.70 in seronegative patients, using the DAS28-CRP as the criterion standard. The Vectra DA score also correlated with other measures of disease activity, including the SDAI, CDAI, and RAPID3, with r values ranging from 0.47 to 0.55 for seropositive patients and from 0.21 to 0.29 for seronegative patients.

An additional report from the Leiden Early Arthritis Clinic Cohort was published in 2016.21 This study used the Vectra DA score and other measures of disease activity to predict radiologic progression of disease at 1 year. One hundred sixty-three patients in this cohort had complete information on Vectra DA test and other disease activity measures. The proportion of patients with radiographic progression increased as Vectra DA scores increased. For patients with a score of less than 29, 2% met criteria for radiographic progression; for patients with a score of 60 or greater, 41% met criteria for radiographic progression. Vectra DA scores and other measures of disease activity (DAS28-CRP, swollen joint count, CRP) were predictors of radiographic progression on univariate analysis. On multivariate analysis, only the Vectra DA score was a significant predictor of progression at 1 year (p=0.005).

Hirata et al (2014) reported on the correlation between the Vectra DA score and response to treatment in 147 patients treated with anti-TNF medications for at least a year.22 The relationship between baseline scores and response to treatment was measured for the Vectra DA test and for a number of other scores (DAS28, SDAI, CDAI). As defined by the European League Against Rheumatism clinical criteria, a good response was achieved by 56% of patients. The mean Vectra DA score decreased from 64 to 34 during the study, and 37% of patients met the threshold for low activity (Vectra score, <30). The Vectra DA score decreased more in patients with a good clinical response (-29 points) than in those with a moderate response (-21 points, p<0.001) and decreased more in patients with a moderate response compared with nonresponders (+2 points, p<0.007). There was a positive correlation between the Vectra DA score and the DAS28-CRP score (r=0.46) and the DAS28-ESR score (r=0.48), but not with the SDAI or CDAI scores. A 2016 publication by Hirata et al presented results from an analysis of this cohort after 1 year of TNF inhibitor therapy (adalimumab, etanercept, infliximab).23 Results showed that higher MBDA and DAS28 scores at 24 weeks were predictive of greater radiographic progression over 1 year of TNF inhibitor therapy.

**Section Summary: Clinical Validity**

Evidence for the clinical validity of the MBDA test consists of post hoc analyses of archived serum samples from RCTs as well as prospective cohort studies that have correlated the score with other measures of disease activity. These studies have shown a positive correlation between MBDA and other measures in the moderate range, with reported r values ranging from 0.46 to 0.72. One study reported a κ value of 0.34 for DAS28 and MBDA scores, indicating a moderate level of agreement above chance. For discriminating levels of disease activity, 2 studies that used the DAS28 as the criterion standard reported an AUC curve in the moderate-to-high range, with values ranging from 0.70 to 0.86 for different populations. Another study compared the discriminatory ability of MBDA and DAS28 scores using radiographic disease progression as the reference standard and reported that the AUC curve was higher for MBDA than for DAS28.
Post hoc analysis of at least 5 RCTs have also examined whether the MBDA score is correlated with treatment response and/or radiographic progression of disease. Results from these analyses were inconsistent. Correlation of MBDA scores with other disease activity measures differed by duration and type of treatment.

Clinical Utility
To demonstrate clinical utility, there should be evidence that the MBDA score is at least as good a measure of disease activity as other available measures. This could be demonstrated directly by an RCT comparing a management strategy using the Vectra DA test with an alternative management strategy using another measure of disease activity and reporting clinical outcomes such as symptoms, functional status, quality of life, or disease progression on radiologic imaging. Indirect measures of clinical utility could be obtained from high-quality evidence that clinical validity of the MBDA score is equivalent to other measures used in clinical care, together with guidance on the optimal use of the score in decision-making (i.e., evidence linking management changes to specific results on the MBDA score).

Hambardzumyan et al (2017) analyzed a subset of data from the SWEFOT trial to investigate the use of MBDA as a predictor of optimal treatment in patients with early RA who did not respond to methotrexate therapy.24 Patients (N=157) in the SWEFOT trial were randomized to 2 groups: triple therapy (methotrexate, sulfa salazine, plus hydroxychloroquine) or double therapy (methotrexate plus infliximab). MBDA categories were defined as low disease activity (<30), moderate disease activity (30-44), and high disease activity (>44). Responders after 1 year of follow-up were defined as patients with DAS28 score of 3.2 or less. The investigators compared MBDA scores at 3 months with DAS28-ESR scores at 1 year to determine whether MBDA scores at 3 months could accurately predict patient response to therapy at the 1-year follow-up. Among patients with low MBDA scores at 3 months, 88% (7/8) subsequently had a clinical response to triple therapy, and 18% (2/11) had a clinical response to methotrexate plus infliximab. MBDA scores were better predictors of clinical response to therapy than clinical and inflammatory markers. The authors concluded that 3-month MBDA scores have the potential to inform decisions on which type of therapy to recommend to patients who do not respond to initial methotrexate therapy.

One RCT by Peabody et al (2013) tested the impact of the Vectra DA score on simulated decision-making by experienced rheumatologists.25 Eighty-one rheumatologists without previous experience with the Vectra DA test were randomized to decision-making with and without the Vectra DA score, using 3 validated clinical vignettes representing typical clinical care in RA. A quality score for each vignette was calculated using predefined criteria. Quality scores in the group receiving the Vectra DA score improved by 3% over the control group (p=0.02). The largest benefits in the Vectra DA group were improvements in the quality of disease activity and treatment decisions in 12% of patients (p<0.01), and more appropriate use of biologics and disease-modifying antirheumatic drugs (p<0.01).

In a study using physician surveys, Li et al (2013) examined the impact of an MBDA score on treatment decisions for patients with RA.26 This study examined the treatment decisions made by 6 health care providers, all of whom had shown previous interest in using the MBDA score. A total of 108 patients 18 years and older were enrolled if they had a diagnosis of RA, had completed an MBDA test, and had a survey completed by a physician. Surveys of treatment decisions were done before and after the results of the MBDA score were provided. After receiving the MBDA score, treatment plans were changed in 38 (38%) of 101 cases (95% CI, 29% to 48%). Changes in treatment decisions included the type of drug in 21 of 38 cases and the dose or route of administration of a drug in 17 of 38 cases. No data were collected on outcomes associated with the different treatment decisions.
Section Summary: Clinical Utility
There is limited evidence that treatment decisions can be influenced by the Vectra DA score. The evidence comes from analysis of archived RCT serum samples, simulated cases, and surveys of physician behavior. There are no RCTs comparing the use of the Vectra DA score with an alternative method of measuring disease activity; as a result, there is no direct evidence that the Vectra DA test improves outcomes. Other disease activity measures have been associated with improvements in health outcomes in clinical trials. Thus, the evidence from RCTs on other measures, together with the correlation of the Vectra DA test with these measures, is indirect evidence that outcomes may be improved with use of the test. However, there is insufficient indirect evidence to determine whether the Vectra DA test is as good as other more established disease activity measures in improving outcomes.

Summary of Evidence
For individuals who have rheumatoid arthritis who receive the Vectra DA test, the evidence includes post hoc analyses of archived serum samples from randomized controlled trials and prospective cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, change in disease status, functional outcomes, and quality of life. Evidence from the available studies has correlated Vectra DA with disease progression and other previously validated disease activity measures such as the Disease Activity Score with 28 joints (DAS28). These studies have shown that the Vectra DA score has moderate correlations with other disease activity measures (e.g., DAS28). Other post hoc analyses of archived serum samples have evaluated the use of multibiomarker disease activity (MBDA) to measure treatment response. Correlation of MBDA scores with other disease activity measures differed by the duration and type of treatment. A smaller number of studies have evaluated clinical utility by examining changes in decision-making associated with the use of Vectra, but these studies are limited by the design because they used archived serum samples, simulated cases, or physician surveys and did not report any health outcomes data. This 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, and it is uncertain whether it is as accurate as the DAS28. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements
In the 2015 American College of Rheumatology guidelines on the treatment of rheumatoid arthritis, ACR endorsed the following measures of disease activity: Patient Activity Scale, Routine Assessment of Patient Index Data 3, Clinical Disease Activity Index, Disease Activity Score 28, and Simplified Disease Activity Index.27 The guidelines indicated that other measures are available to clinicians, but that including the new measures was out of scope.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There are no Medicare national coverage determinations for the Vectra DA test. In July 2013, Palmetto GBA, the Medicare contractor in California, issued a positive coverage decision for the Vectra DA test. Because all Vectra DA tests are processed out of the Crescendo Bioscience Laboratory in California, the test will be covered for Medicare patients in the United States.

Ongoing and Unpublished Clinical Trials
A currently ongoing trial that might influence this review is listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
<td></td>
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### NCT trials for Vectra® DA Blood Test for Rheumatoid Arthritis

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<th>NCTNo.</th>
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<td>NCT02832297a</td>
<td>Prospective Outcomes Study: Vectra® DA Guided Care Compared to Usual Care</td>
<td>318</td>
<td>Aug 2018</td>
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</table>

NCT: national clinical trial.

*a* Denotes industry-sponsored or cosponsored trial.

### References


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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</thead>
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<tr>
<td>CPT®</td>
<td>81490</td>
<td>Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using</td>
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</table>
2.04.119  Vectra® DA Blood Test for Rheumatoid Arthritis

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<table>
<thead>
<tr>
<th>Type</th>
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<tr>
<td>ICD-10 Procedure</td>
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<tr>
<td>ICD-10 Diagnosis</td>
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<td>immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score</td>
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</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>09/30/2015</td>
<td>New Policy Adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.