**Vectra DA Blood Test for Rheumatoid Arthritis**

**Effective:** August 1, 2018

**Next Review:** June 2019
**Last Review:** June 2018

**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

The Vectra DA test is a commercially available multi-biomarker disease activity blood test that uses 12 biomarkers to construct a disease activity score ranging from 0 to 100 for the assessment of disease activity in rheumatoid arthritis (RA).

**MEDICAL POLICY CRITERIA**

The use of a multi-biomarker disease activity score for rheumatoid arthritis (RA) (e.g., Vectra DA score) is considered **investigational** for all indications.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

**CROSS REFERENCES**

None

**BACKGROUND**

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

The concept of “tight control” in the management of RA has gained wide acceptance as evidence from clinical trials have demonstrated that outcomes are improved with a tight control strategy. In a tight control strategy, treatment targets are used that are mainly based on measures of disease activity. 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/or biomarker measurement. Composite measures are the most comprehensive but have the disadvantage of being more cumbersome and difficult to complete. Patient reported measures are intended to be simpler, and rely only on information that patients can provide expeditiously, but have the disadvantage of being more subjective. Measurements that rely only on biomarkers are objective and do not require patient input but do involve the cost and inconvenience of laboratory tests.

The Disease Activity Score 28 (DAS28) is the most widely used and validated composite measure and includes examination of 28 joints for swelling and tenderness, combined with a patient report of disease activity and measurement of C-reactive protein (CRP) (or erythrocyte sedimentation rate). This score is often considered the criterion standard for measuring disease activity; however, it requires a thorough joint examination, information obtained from the patient, and laboratory testing. Therefore, there have been many attempts to create a valid disease activity measure that is simpler. Some measures include only patient self-report and thus can be completed quickly in the setting of an office visit. An example of this type of measure is the Simplified Disease Activity Index (SDAI). Another approach is to use only serum biomarkers, which requires a blood draw, such as the Vectra DA. Proponents of a biomarker approach have argued that this is simpler and avoids the subjectivity of physical examination and patient report.

**VECTRA DA TEST**

The Vectra DA test (Crescendo Bioscience) is a commercially available MBDA blood test that uses 12 biomarkers to construct a disease activity score ranging from 0 to 100. These biomarkers include:

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

The Vectra DA test scores range from 1 to 100. Categories of scores were constructed to correlate with the DAS28-C-reactive protein scale.[3]

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

REGULATORY STATUS

There are no U.S. Food and Drug Administration (FDA)-approved multibiomarker disease activity (MBDA) tests for measuring disease activity in RA. Commercially available tests are laboratory-developed tests that are not subject to FDA approval. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

EVIDENCE SUMMARY

Validation of the clinical use of any prognostic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a disease marker of interest that is present or in excluding a disease marker that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes. The clinical utility of both positive and negative tests must be established.

ANALYTIC VALIDITY

Nonrandomized Studies

Centola (2013) published a study on the development of the Vectra DA test in 2013.[4] This publication 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, four separate patient cohorts were utilized to refine the biomarkers by 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. In addition, 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 0 and 100.

Eastman (2012) described aspects of the technical performance of the MBDA Vectra test in 2012.[5] The 12 individual biomarkers in the Vectra 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.

**Section Summary**

Evidence for the analytical validity of the Vectra DA test consists of studies that demonstrate the technical accuracy and feasibility of the test. However, the above studies were limited and do not provide sufficient evidence that Vectra DA test results contribute to changes in the clinical management of RA patients.

**CLINICAL VALIDITY**

**Nonrandomized Studies**

**Post-hoc Analysis of Completed Randomized Controlled Trials**

Reiss (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.[6] Patients were included in the analysis if they had DAS28-CRP and Clinical Disease Activity Index (CDAI) scores at baseline and 24 weeks follow-up and sufficient serum for MBDA testing at the same time points. Disease activity level (low, moderate, high) agreement between DAS28-CRP and MBDA at baseline was 77%; however, the agreement between the two measures at 24 weeks of follow-up was 24%. Agreement between 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).

Fleischmann (2016) published results from a post-hoc analysis from the Abatacept versus adalimumab comParison in bioLogic-naïve RA (AMPLE) study, a randomized controlled trial (RCT) that compared different administrations of adalimumab in the treatment of patients with RA who are biologic naïve. [7] In this post-hoc analysis the authors assessed the ability of an MBDA score to reflect clinical measures of disease in patients with RA. Six hundred and forty-six participants were enrolled in the AMPLE study, and MBDA data were available on 524. Participants MBDA score was analyzed in serum samples collected at baseline, month three, and years one and two. Cross-tabulation was used to compare the MBDA score and clinical measures of disease activity: CDAI, Simplified Disease Activity Index (SDAI), DAS28-CRP, and Routine Assessment of Patient Index Data (RAPID)-3. The authors found no association between the MBDA score and disease activity and recommended that the MBDA score not be used to guide decision-making in the management of patients with RA, although this result may be taken with caution as another group re-analyzed the same data with different results.[8]

A 2016 publication from the Swedish Farmocotherapy (SWEFOT) trial, an RCT that randomized 487 patients to two different treatment regimens, reported repeat scores at multiple time points.[9] Of 487 patients enrolled in the SWEFOT trial, 220 had baseline Vectra DA scores (45.2%), 205 had scores at three months (42.1%), and 133 had scores at one year (27.3%). 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 one year. Cross tabulation of Vectra DA results with the DAS28, ESR, and CRP values was presented, but no statistics that addressing the comparative accuracy of the different measures were reported.
In an earlier publication from the SWEFOT trial, Hambardsumyan (2015) performed a post-hoc analysis of, a total of 235 patients (48%) who 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 five points on the Van der Heijde Sharp score. The Vectra DA score was a univariate predictor of radiographic progression (odds ratio [OR], 1.05 per unit increase, 95% confidence interval [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 in 34 (3.4%) patients during year one.

The RETRO trial enrolled patients treated with disease modifying antirheumatic drugs (DMARDs) in clinical remission, and randomized participants to tapering DMARD or standard maintenance care. Eligibility criteria included a DAS28-ESR score lower than 2.6 for at least six months and follow-up was for 12 months. Of 101 patients enrolled in RETRO, Vectra DA data was available for 94 (93%). The Vectra DA score was higher in patients experiencing a relapse (32.0 ±2.3) compared with patients who did not experience a relapse (22.6 ±1.2, p=0.0001). 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-CCP status (odds ratio 24.5, 95% CI 3.1 to 194.0).

Marcuse (2014) also used samples from the BeST trial to evaluate how well the Vectra DA score predicted the progression of radiographic joint damage and compared the predictive ability of Vectra DA with the DAS28. Radiographic progression was defined as a change of at least five points on the Sharp van der Heijde Score over a one-year period. ROC analysis was performed, with an area under the curve (AUC) for the Vectra DA test of 0.77 (95% CI 0.64 to 0.90), which was higher than the AUC for the DAS28 (0.52, 95% CI 0.39 to 0.66). Comparison of patients who had samples available from the BeST trial and those who did not revealed that the population with serum available differed from those who did not on sex (75% vs. 65% female, p=0.04), the median number of tender joints (11 vs. 14, p<0.001), and the median number of erosions seen on imaging (1.0 vs. 2.0, p=0.005).

Hirata (2013) studied the correlation of the Vectra DA score with other validated measures of disease activity in 125 patients from the BeST trial, which was a multicenter RCT of 508 patients with early RA, randomized to four different treatment strategies. Blood samples were available from 179 visits, 91 baseline visits and 88 visits at one-year follow-up. Validated disease activity measures were DAS28, SDAI, CDAI, and the HAQ Disability Index (DI). The Vectra DA scores were significantly correlated with the DAS28 measure (Spearman correlation coefficient ρ=0.66, p<0.001), as were the changes in scores between baseline and one year (Spearman ρ=0.55, p<0.001). The Vectra scores were also significantly correlated with the SDAI, CDAI, and HAQ-DI at the p<0.001 level. This study was limited by the retrospective study design and small sample size. The authors noted, “Effective comparison of the MBDA score with other biomarkers will require additional studies using independent disease outcomes such as joint damage progression or functional disability.”

Bakker (2012) examined the correlation of the MBDA score (Vectra DA score) with the DAS28 and response to therapy, in a subset of patients from the CAMERA trial. In the larger CAMERA trial, 299 patients were randomized to standard or intensive management of RA. For the Bakker substudy, 74 of 299 patients (24.7%) had blood drawn for measurement of the 20 biomarkers, including the 12 comprising the MBDA test. There were 72 samples collected at
baseline and 48 samples collected at six months. The total test score was a number between 0 and 100, calculated through use of a proprietary algorithm.

The MBDA score was significantly correlated with the DAS28 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 kappa score for agreement with the DAS28-CRP for classifying disease activity was 0.34 (95% CI 0.19 to 0.49). The MBDA score decreased following therapy, from a baseline of 53 (standard deviation [SD]=18) to 39 (SD=16) at six months. The authors note this study was not adequately powered to compare the effectiveness of the treatment strategies. Further, the authors concluded that, “more measurements over time should be evaluated, and ultimately a trial evaluating the effect of a tight control strategy using the MBDA score (as compared with a clinical DAS) could be performed.”

**Prospective Cohort Studies**

A publication from the Leiden Early Arthritis Clinic Cohort (Index for Rheumatoid Arthritis Measurement, Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study) was published in 2016.[15] This study used the Vectra DA score and other measures of disease activity to predict radiographic progression of disease at one year. There were 163 patients in this cohort that had complete information on Vectra DA 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, and 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 one year ($p=0.005$).

Hirata (2014) published results from a study 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.[16] The relationship between baseline scores and response to treatment was measured for the Vectra DA test and for a number of other disease activity scores (DAS28, SDAI, CDAI). A good response, as defined by the European League Against Rheumatism clinical criteria, was achieved by 56% of patients. The mean Vectra DA score decreased from 64 to 34 over the course of 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) compared to those with a moderate response (-21 points, $p<0.001$), and decreased more in patients with a moderate response compared to nonresponders (+2 points, $p<0.007$). There was a positive correlation of the Vectra DA score with the DAS28-CRP ($r=0.46$) and the DAS28-ESR ($r=0.48$), but not with the SDAI or the CDAI. A 2016 publication presents results from an analysis of this cohort after one year of TNF-inhibitor therapy (adalimumab, etanercept, infliximab).[17] Results showed that higher MBDA and DAS28 scores at 24 weeks were predictive of greater radiographic progression over one year of TNF-inhibitor therapy.

A study by Curtis (2012) used blood samples from three cohorts of arthritis patients from the Leiden Early Arthritis Clinic to validate the Vectra DA MBDA against the DAS28-CRP and other known markers of disease activity.[2] There was a positive correlation of the Vectra Score with the DAS28-CRP score, with a Pearson correlation coefficient ($r$) of 0.56 in seropositive RA patients and 0.43 in seronegative patients. The AUC 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 score was also correlated with other measures of disease activity, including the SDAI, the CDAI, and the RAPID3, with $r$ values ranging from 0.47 to 0.55 for seropositive patients and 0.21 to 0.29 for seronegative patients. Limitations of this study include the retrospective study design and the patients examined in the validation studies were diverse in terms of geographic origin and disease characteristics, and were not selected except for their clinical disease activity levels.

**Section Summary**

Evidence regarding the clinical validity of the Vectra DA test consisted of studies that correlated the score with other measures of disease activity, including the DAS28. However, the above studies were limited by retrospective study design, small patient populations that were underpowered or were post-hoc analysis of RCTs with methodological short-comings. Without large, well-designed prospective clinical trials, conclusion regarding the diagnostic performance of the Vectra DA test cannot be reached.

**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. An RCT that compared a management strategy using Vectra DA score with an alternate management strategy, and that reported clinical outcomes such as symptoms, functional status, quality of life, or disease progression on radiologic imaging may demonstrate the clinical utility of Vectra DA. Indirect measures of clinical utility could be obtained from high-quality evidence that clinical validity of the MBDA 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).

**Randomized Controlled Trials**

Hambardzumyan (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 (MTX) therapy.[18] As described earlier, patients ($n=157$) in the SWEFOT trial were randomized into two groups: triple therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus infliximab. MBDA categories were defined as: $<30 =$ low disease activity, 30 to 44 = moderate disease activity, and $>44 =$ high disease activity. Responders after one-year follow-up were defined as patients with DAS28 less than 3.2. The investigators compared MBDA scores at three months with DAS28-ESR measures at one year to determine if MBDA scores at three months could accurately predict the patients' response to therapy at one-year follow-up. Among patients with low MBDA scores at three months, 88% (seven of eight) subsequently had a clinical response to triple therapy, and 18% (2 of 11) had a clinical response to MTX plus infliximab at one-year follow-up. Among patients with high MBDA scores at three months, 35% (15 of 43) subsequently responded to triple therapy, and 58% (26 of 46) responded to MTX plus infliximab. The three-month low and high MBDA scores were better predictors of clinical response to therapy than clinical and inflammatory markers. The authors conclude that three-month MBDA scores have the potential to inform the decision on which type of therapy to recommend to patients who do not respond to initial methotrexate therapy.
An RCT by Peabody (2013) tested the impact of the Vectra DA score on simulated decision making by experienced rheumatologists.[19] A total of 81 rheumatologists without previous experience with the Vectra DA test were randomized to decision making with and without the Vectra DA score, using three 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% compared with 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 of 12% (p<0.01), and more appropriate use of biologics and disease modifying drugs (p<0.01). This study contained the following limitations:

- patient sample size was relatively small and thus limited the statistical power for the secondary outcomes;
- the control group received neither MBDA training, nor MBDA test results and therefore the study did not directly address the independent effect of training alone;
- the long-term impact of use of the MBDA test on physician practice and resulting improvements in patient outcomes were not analyzed;
- a single time point was assessed in this study and therefore the MBDA test was not fully assessed for its impact on routine practice; and
- the test results were hypothetical and may differ from those obtained for actual patients.

Nonrandomized Studies

In a study using physician surveys, Li (2013) examined the impact of a MBDA score on treatment decisions for patients with RA.[20] The study examined the treatment decisions made by six health care providers, all who had shown previous interest in using the MBDA score. A total of 108 patients were enrolled who were at least 18 years old, had a diagnosis of RA, completed a 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 was provided. After receiving the MBDA score, treatment plans were changed in 38 of 101 cases (38%, 95% CI 29% to 48%). Changes in treatment decisions were a change in the type of drug in 21 of 38 cases, and a change in the dose or route of administration of a drug in 17 of 38 cases. There was no data collected on outcomes associated with the different treatment decisions. The study was limited by the following: small sample size; lack of control group; and no longitudinal follow-up.

Section Summary

The available evidence regarding the impact of the Vectra DA score upon treatment decisions is limited to analysis of archived RCT serum samples, simulated cases, and surveys of physician behavior. There are no RCTs that compare use of the Vectra DA score to an alternative method of measuring disease activity, and as a result there is no direct evidence that Vectra DA improves outcomes. There is insufficient evidence to determine whether Vectra DA is as efficient as other more established disease activity measures in improving outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF RHEUMATOLOGY

In the 2015 American College of Rheumatology guidelines on the treatment of rheumatoid arthritis, the American College of Rheumatology endorses the following measures of disease activity: Patient Activity Scale, Routine Assessment of Patient Index Data 3, Clinical Disease Activity...
Activity Index, Disease Activity Score 28, and Simplified Disease Activity Index.[21] The authors acknowledge that other measures are available to clinicians, but that including the new measures was beyond the scope of the review.

SUMMARY

There is not enough research to show how the Vectra DA test changes clinical management or improves health outcomes in patients with rheumatoid arthritis. In addition, no evidence-based clinical practice guidelines recommend the Vectra DA test. Therefore, the Vectra DA test is considered investigational for use as a measure of disease activity in the patients with rheumatoid arthritis.

REFERENCES


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81490</td>
<td>Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>agent antigen; qualitative or semiquantitative, multiple step method;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>quantitative, not otherwise specified</td>
<td></td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
<td></td>
</tr>
<tr>
<td>86140</td>
<td>C-reactive protein</td>
<td></td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*Date of Origin: June 2014*