



**Kaiser Foundation Health Plan
of Washington**

Clinical Review Criteria

Vectra DA (Multiple Biomarker Disease Activity [MBDA])

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	9/17/2021 Noridian retired: Billing and Coding: MoIDX: Vectra™ DA (A54505) . These services still need to meet medical necessity as outlined in the coverage article and will require review. Coverage articles are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Therefore, continue to use LCD A54505 for determining medical necessity.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or consulting specialist.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that primarily involves synovial joints. It is debilitating disease that if uncontrolled, may lead to joint destruction, functional disability, and premature death. It is thus important to detect RA early, and to control the disease as soon as possible after diagnosis to delay its progression and preserve physical function.

Treatment of RA has shifted from symptom management, to reducing the disease activity and delaying its progression. Recent guidelines recommend treating RA promptly and aggressively aiming for remission as a therapeutic target (tight control or treatment-to-target strategy). Tight control may be defined as a treatment

strategy tailored to the disease activity in individual patients with RA with the aim of achieving a predefined level of low disease activity, or preferably remission within a reasonable period of time. The availability of an increasing number of biologic and non-biologic effective disease-modifying anti-rheumatic drugs (DMARDs) has allowed the achievement of this treatment goal, but requires close monitoring of the disease activity, which is the cornerstone of tight control (Bakker 2007, Anderson 2012, Curtis 2012, Peabody 2013, Segurado 2014, Michaud 2015).

There are a number of composite tools available for assessing RA disease activity, six of which have been recommended by the American College of Rheumatology (ACR): Clinical Disease Activity Index (CDAI), Disease Activity Score with 28-joint counts (DAS28), Patient Activity Scale (PAS), PAS-II, Routine Assessment of Patient Index Data with 3 measures (RAPID-3), and Simplified Disease Activity Index (SDAI). These indices are based on information obtained from clinical, laboratory, and physical measures that include quantitative joint counts, patient reported outcomes, physician examination, and laboratory test including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These composite measurements are of great importance, but are complicated, may have intra- and inter-observer variability, are unable to detect subclinical synovial damage, and may be influenced by cumulative damage and other conditions unrelated to RA (Anderson 2012, Curtis 2012, Owens 2015).

More recently, researchers have been investigating biomarkers to complement the clinical assessment of RA and improve the evaluation of disease activity. No single biomarker has been found to accurately assess RA activity, and it is hypothesized that a combination of biomarkers that measure diverse pathways to RA may have the potential of providing objective information on disease activity (Curtis 2012, Hirata 2013).

Vectra DA (Crescendo Bioscience, South San Francisco, CA), is a commercially available blood test that measures the serum concentration of 12 biomarkers and combines them into an algorithm to generate a multibiomarker disease activity (MBDA) score. The biomarkers included in Vectra DA test are: VCAM-1 (vascular cell adhesion molecule-1), EGF (epidermal growth factor), VEGF-A (vascular endothelial growth factor A), IL-6 (interleukin-6), TNF-RI (tumor necrosis factor receptor, type 1), MMP-1 (matrix metalloproteinase-1 or collagenase-1), MMP-3 (matrix metalloproteinase-3 or stromelysin-1), YKL-40, SAA (serum amyloid), CRP (C-reactive protein), leptin, and resistin. The score generated by the test is believed to represent the level of RA disease activity on a scale of 1 (lowest activity) to 100 (greatest activity). According to the manufacturer a score between 45 and 100 indicates high level of disease activity; 30 to 44 indicates moderate disease activity; and 1 to 29 indicates a low level of disease activity. Vectra DA test is not intended or validated to diagnose RA, but as an aid in the assessment of disease activity in adults RA patients when used in conjunction with standard clinical assessment (Curtis, 2012, Peabody 2013, Michaud 2015, Vectra.com).

Medical Technology Assessment Committee (MTAC)

12/21/2015: MTAC REVIEW

Vectra DA Test for Rheumatoid Arthritis

Evidence Conclusion: *Analytic validity* - Eastman and colleagues (2012), evaluated the analytical performance of each of the individual biomarker assays that comprise the MBDA test and the generated MBDA score. The investigators quantified the 12 serum biomarkers and found that all 12 individual assays exhibit a high level of precision with minimal cross-reactivity and interference by substances commonly seen in RA patients. The total MBDA score had good reproducibility over time with a median coefficient of variation of <2% across the score range. The same MBDA score was observed in different subjects with different biomarker profiles (Eastman 2012). *Clinical validity* - The published literature on the clinical validity of the MBDA Vectra DA test consists of observational cohort studies and posthoc analyses of randomized controlled trials performed for other reasons and among patients for whom serum samples were available to retrospectively evaluate the Vectra DA test. The studies correlated the MBDA score with other validated measures used for disease activity (mainly DAS28-CRP), radiographic joint progression, or response to therapy, and had no long-term follow-up to determine the test ability to predict clinical outcomes. Curtis and colleagues (2012), prospective cohort study (Evidence table 1): The authors used blood samples for 371 patients from 3 diverse RA cohorts in North America and Europe to validate the MBDA scores against DAS28-CRP (Disease Activity Score in 28 joints using the C-reactive protein level) as the reference measure for disease activity. The analysis of the results showed that MBDA score was positively, but moderately correlated with DAS28-CRP in both seropositive and seronegative patients (correlation coefficient $r=56$ and 43 respectively). The area under the receiver operating characteristic curve (AUROC) for discriminating low disease activity from moderate disease activity was 0.77 for seropositive patients and 0.70 for seronegative patients. The analysis also showed that changes in the MBDA scores at 6-12 weeks were significantly correlated with the corresponding changes in DAS28-CRP (Spearman's correlation coefficient $r_s = 0.51$). The study did not adjust for confounding factors, and did not evaluate the ability of the test to predict long-term outcomes of RA. In addition, it was partially supported by Crescendo Bioscience, the company manufacturing the laboratory test, and the authors had financial ties to the company. Bakker, et al (2012), Posthoc analysis of a completed randomized controlled trial (Evidence table 2): The investigators evaluated the performance of individual biomarkers and a

MBDA (Vectra DA) test score in a subset of RA patient population enrolled in the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) tight control study. Only patients with available serum samples were included in the study evaluating the performance MBDA test (72 patients out of the 299 enrolled in CAMERA trial). There were significant differences between the patients with available samples versus those without. Blood samples were obtained from 72 patients at baseline and from 46 patients after treatment. MBDA scores were calculated and the performance of the Vectra DA test was evaluated relative to DAS28-CRP. The analysis showed that MBDA score had a significant correlation with DAS28-CRP ($r=0.72$; $p<0.001$) and an area under the receiver operating characteristic curve for distinguishing remission/low from moderate/high disease activity of 0.86 ($p<0.001$) using a DAS28-CRP cut-off of 2.7. The agreement of MBDA score with DAS28-CRP for classifying disease activity was fair (kappa score =0.34, 95% CI 0.19-0.49). The results also showed that MBDA score decreased from 53 ± 18 at baseline to 39 ± 16 at 6 months in response to study therapy ($p<0.0001$). Neither MBDA score nor DAS28-CRP was predictive of radiographic progression. The study was based on posthoc analysis of data from a completed trial, did not adjust for confounding factors, and did not evaluate the ability of the test to predict long-term outcomes of RA. The study was supported by Crescendo Bioscience, and the authors had financial ties to the company. [Hirata and colleagues \(2013\)](#) evaluated MBDA score in 125 patients with RA from the Behandel Strategieën (BeSt) study. Data and serum samples were available from 179 visits (91 at baseline and 88 at year 1). The results showed that the MBDA scores was significantly correlated with DAS28-ESR (Spearman's rank correlation coefficient $r_s=0.66$). It was also correlated with simplified disease activity index (SDAI), clinical disease activity index (CDAI). Changes in MBDA between baseline and year 1 were also correlated with changes in DAS28-ESR (assessed in a subgroup of 54 patients, $r_s=0.55$). The study was also a posthoc analysis of patients enrolled in BeSt study, was supported by Crescendo Bioscience, Inc., and the authors had financial ties to the company. *Prediction of radiographic joint progression* - Posthoc analyses of two RCTs: SWEFOT (Hambardzumyan et al, 2015) and BeSt [Markusse et al, 2014] suggest that MBDA scores may predict radiographic damage progression in patients with RA. These analyses had their limitations including, but not limited to the use of data obtained from RCTs designed primarily to compare different RA therapies, the patients included in the trials do not represent all RA patients as those with low DAS28 were excluded, patients were not randomized to therapy based on their MBDA scores, these scores were only available at baseline, and after 1 year (in one trial). In addition, patients in SWEFOT trial switched from one drug to another during the trial, which could affect radiographic outcomes, and the treatment-to-target strategy in BeSt trial suppressed inflammation and progression of radiographic joint damage in the majority of patients. A more recently published retrospective observational study (Li, 2015) with its limitations also suggest that MBDA score may enhance the ability to predict radiographic progression in patients with RA treated with non-biologic DMARDs. In conclusion, the published studies on the relationship between MBDA and radiographic joint damage had their limitations and do not provide sufficient evidence to determine the value of MBDA in predicting progression of radiographic joint damage in patients with rheumatoid arthritis. *Clinical utility*- There are no published RCTs, to date, that compared a management strategy using the MBDA score versus another established measure of disease activity, and reported clinical outcomes such as disease progression, functional status, or quality of life. The studies that evaluated the impact of Vectra DA test on clinical-decision making used simulated cases or physician surveys and did not report outcome data. [Li and colleagues \(2013\)](#), assessed the impact of MBDA, Vectra DA blood test on RA treatment decisions in 101 patients with RA. The health care providers (HCP) completed surveys before and after viewing the MBDA test result, recorded the dosage and frequency for all planned RA medications and the physician global assessment of disease activity. Frequency and types of change in treatment plan that resulted from viewing the MBDA test result were determined. The results of the study showed that, after reviewing MBDA test results treatment decisions were changed in 38 cases (38%), of which 18 involved starting, discontinuing, or switching a biologic or non-biologic DMARD. Other changes involved drug dosage, frequency or route of administration. The total frequency of use of the major classes of drug therapy changed by <5%. Treatment plans changed 63% of the time when the MBDA test result was perceived as being not consistent or somewhat consistent with the HCP assessment of disease activity. The study had its limitations including the small sample size, lack of a control group, and absence of follow-up to determine the impact on patient outcomes. [Rech and colleagues \(2015\)](#) analyzed the role of MBDA score in predicting disease relapse in patients with RA in sustained remission with tapered disease modifying antirheumatic drug (DMARD) therapy in RETRO trial. This was a RCT that evaluated the possibility of tapering or stopping DMARDs in patients fulfilling classification criteria for RA. The participants were randomized to 3 arms: 1. continuing DMARDs for 12 months, 2. Tapering the treatment by 50%, or 3. Reducing the dose by 50% for the first 6 months before entirely discontinuing the treatment. MBDA scores were calculated from the analysis of baseline serum samples of 94 patients participating in the RETRO trial. Retrospective analysis of data showed that baseline MBDA levels were significantly higher in patients experiencing a relapse vs. those in sustained remission. The analysis was retrospective and does not provide sufficient evidence to determine utility of MBDA in predicting the disease relapse and tapering or discontinuing the use of DMARDs accordingly. Conclusion There is insufficient evidence to determine whether MBDA is as good as or better than other established indices used to measure RA disease activity. The published studies show a

moderate correlation between Vectra DA and DAS28-CRP in classifying patients into low vs. moderate to high disease. There is insufficient evidence to determine the clinical validity of Vectra DA test and its ability to predict outcomes. There is insufficient evidence to determine that Vectra DA test results have an impact on the management of patients with rheumatoid arthritis and/or improve their health outcomes.

Articles: The literature search revealed a study on the analytic validity of MBDA test score, four studies on the clinical validity of the MBDA Vectra Da test, and few small simulating studies or surveys on the clinical utility of the test. The following two studies on the clinical validity of MBDA test studies were selected for critical appraisal: Bakker MF, Cavet G, Jacobs JW, et al. Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. *Ann Rheum Dis*. 2012 Oct; 71(10):1692-1697. See [Evidence Table 1](#). Curtis JR, van der Helm-van Mil AH, Knevel R, et al. Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken)*. 2012 Dec; 64(12):1794-1803. See [Evidence Table 2](#).

The use of Vectra DA (Multiple Biomarker Disease Activity [MBDA]) test for monitoring disease activity in patients with rheumatoid arthritis does not meet the *Kaiser Permanente Technology Assessment Criteria*.

Applicable Codes

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met

Non-Medicare - Considered Not Medically Necessary

CPT® Codes	Description
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

**To verify authorization requirements for a specific code by plan type, please use the [Pre-authorization Code Check](#).

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Revision History	Description