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Vectra DA Blood Test for Rheumatoid Arthritis

Policy # 00442
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of a multi-biomarker disease activity score for rheumatoid arthritis (RA) (e.g., Vectra DA score) in all situations to be **investigational.***

Background/Overview

Assessment of disease activity in RA is an important component of treatment management, as one of the main goals of treatment is to maintain low disease activity or remission. There are a variety of available instruments for measuring RA disease activity. One potential approach is the use of a multibiomarker disease activity (MBDA) score. The Vectra DA test is a commercially available MBDA blood test that uses 12 biomarkers to construct a disease activity score ranging from 0 to 100.

Rheumatoid arthritis 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 a high burden of morbidity for affected patients.

Treatment of RA has undergone a shift from symptom management to a more proactive strategy of reducing 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. In a systematic review published in 2010, Schoels et al identified 7 trials that evaluated the efficacy of tight control. Four of these trials randomized patients to either a tight control using treatment targets or 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) and in the likelihood of achieving remission for patients in the tight control group.

For a strategy of tight control to be successful, a reliable and valid measurement of disease activity is important. 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 most widely used and validated in clinical research is the DAS28 score. This is a composite measure that 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 has been widely validated and used for both research and clinical care and 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 only requires a blood draw. The Vectra DA is this type of biomarker-based measure. Proponents of a biomarker approach have argued that this is simpler and avoids the subjectivity of physical examination and patient report.

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 systematic review of disease activity measures sponsored by the American College of Rheumatology in 2012, 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 workgroup selected 6 that were most useful and feasible for point-of-care clinical care. These were the Clinical Disease Activity Index (CDAI), DAS28, Patient Activity Scale (PAS), Patient Activity Scale II (PAS-II), Routine Assessment of Patient Index (RAPI) data with 3 measures, and the SDAI.

In another systematic review, Gaujoux-Viala et al compared 4 composite indices, DAS, DAS28, SDAI, and CDAI. 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 of the measures had fair-to-good correlations with an independent health status measure, the Health Assessment Questionnaire (HAQ) and with radiologic examination of joint structural damage.

Salaffi et al 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. The composite indices evaluated were 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, the Routine Assessment of Patient Index Data (RAPID3), and PAS. Across all measures, there was wide variability in internal responsiveness, with the highest value obtained for the DAS28 measure. There were some 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 was no difference in internal or external responsiveness.

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Vectra DA test
The Vectra DA test (Crescendo Bioscience, South San Francisco, CA) consists of 12 individual biomarkers. These are:

- 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)
- CRP
- Serum amyloid A (SAA)
- Leptin
- Resistin

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
There are no U.S. FDA-approved 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.

Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source

Multibiomarker disease activity tests for disease activity in RA are best evaluated in the framework of a prognostic test, as they 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 whether the test has utility in clinical practice.

Technical Performance
Eastman et al described aspects of the technical performance of the MBDA Vectra test in 2012. 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.

Centola et al published a study on the development of the Vectra DA test in 2013. 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, 4 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.

Clinical Validity
Curtis et al 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 MBDA against the Disease Activity Score with 28 joints (DAS28)-CRP (C-reactive protein) and other known markers of disease activity. There was a positive correlation of the Vectra Score with the DAS28-CRP score, with a Pearson product-moment correlation coefficient (*r*) of 0.56 in seropositive RA patients and 0.43 in seronegative patients. The area under the curve (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.

Hirata et al studied the correlation of the Vectra DA score with other validated measures of disease activity in 125 patients from the Behandel Strategieen study. Blood samples were available from 179 visits, 91 baseline visits and 88 visits at 1-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 $\rho=0.66$, $p<0.001$), as were the changes in scores between baseline and 1 year (Spearman $\rho=0.55$, $p<0.001$). The Vectra scores were also significantly correlated with the SDAI, CDAI, and HAQ-DI at the $p<0.001$ level.

Bakker et al examined the correlation of the MBDA score (Vectra DA score) with the DAS28 score 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 6 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 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 kappa score for agreement with the DAS28-CRP for classifying disease activity was 0.34 (95% confidence interval [CI], 0.19 to 0.49). The MBDA score decreased following therapy, from a baseline of 53 (SD=18) to 39 (SD=16) at 6 months.

Section Summary
Evidence for the clinical validity of the Vectra DA test consists of studies that correlate the score with other measures of disease activity, including the DAS28 score. These studies show a positive correlation that is in the moderate range, with reported r values ranging from 0.5 to 0.7. One study reported a kappa value of 0.34 for the DAS28 and Vectra DA, indicating a moderate level of agreement above chance. There is also some evidence that the Vectra DA score correlates with response to treatment. For discriminating levels of disease activity, 2 studies that used the DAS28 as the criterion standard reported an AUC in the moderate to high range, with values ranging from 07 to 0.86 for different populations.

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 a randomized controlled trial (RCT) that compared a management strategy using Vectra DA score with an alternate management strategy using another measure of disease activity, and that reported 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 is equivalent to other measures used in clinical care, together with guidance on the optimal use of the score in decision making, ie, evidence linking management changes to specific results on the MBDA score.

One RCT was identified that tested the impact of the Vectra DA score on simulated decision making by experienced rheumatologists. 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 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% 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).

In a study using physician surveys, Li et al examined the impact of a MBDA score on treatment decisions for patients with RA. This study examined the treatment decisions made by 6 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.

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Section Summary
There is some evidence that treatment decisions can be influenced by the Vectra DA score. This evidence comes from simulated cases and/or 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. 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 Vectra DA with these measures is indirect evidence that outcomes may be improved with use of the Vectra DA test. However, there is insufficient evidence to determine whether Vectra DA is as good as other more established disease activity measures in improving outcomes.

Summary
The Vectra DA is a biomarker-based measurement of disease activity in RA that uses results of 12 serum biomarkers to construct a score ranging from 0 to 100. It is one of numerous disease activity measures that are available for use in clinical care, and there are other disease activity scores (eg, Disease Activity Score with 28 joints [DAS28]) that have been more extensively validated. Evidence of validity for the measure consists of several studies that correlate Vectra DA with other previously validated measures such as the DAS28. These studies show moderate correlations of Vectra with the DAS28. A small number of studies evaluate clinical utility by examining changes in decision making associated with use of Vectra, but these are limited by the design of using simulated cases or physician surveys and do not report any outcome data. This limited body of evidence on the Vectra DA test is not sufficient to determine whether it is as good as or better than other disease activity measures, and it is possible that it is not as accurate as the DAS28. As a result, the Vectra DA test is considered investigational for use as a measure of disease activity in the patients with RA.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	84999, 83520, 86140
HCPCS	No codes
ICD-9 Diagnosis	714.0 thru 714.9
ICD-9 Procedure	No codes

Policy History

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08/20/2014 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 08/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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