Multibiomarker Disease Activity 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®‡ score) in all situations to be **investigational.***

Background/Overview

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 the 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. Evidence from clinical trials has demonstrated that outcomes are improved with a tight control strategy, in which treatment targets are mainly based on measures of disease activity. In a systematic review,

Schoelsetet al (2010) identified 7 studies that evaluated the efficacy of tight control. Four of these trials randomized patients to tight control using treatment targets or to routine management, 2 studies compared different treatment targets, and 1 study compared results from targeted treatment with historical controls. The treatment targets were heterogeneous, including symptom-based measures, joint scores on the exam, validated treatment activity measures, lab values, or combinations of these factors. In all 4 trials that randomized patients to tight control or routine management, there was a significant decrease in the Disease Activity Score (DAS) or its 28 joints version (DAS28) and in the likelihood of achieving remission for patients in the tight control group.

According to the American College of Rheumatology (ACR) guidelines, initial treatment of patients with RA is monotherapy (usually a disease-modifying antirheumatic drug). Treatment may progress to combination therapy if disease activity remains moderate or high despite monotherapy. Combination therapy may consist of additional disease-modifying antirheumatic drugs or the addition of tumor necrosis factors or non-tumor necrosis factor biologics.

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

Based on a systematic review (2019) of the psychometric properties of 46 tools, an ACR working group determined that the following 11 measures of disease activity fulfilled a minimum standard for regular use in most clinical settings: Disease Activity Score (DAS), Routine Assessment of Patient Index Data 3 (RAPID3), Routine Assessment of Patient Index Data 5 (RAPID5), Clinical Disease Activity Index (CDAI), Disease Activity Score with 28 joints (DAS28-ESR/CRP), Patient Derived DAS28, Hospital Universitario La Princesa Index (HUPI), Multibiomarker Disease Activity Score (MBDA score, Vectra DA), Rheumatoid Arthritis Disease Activity Index (RADAI),Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5), and the Simplified Disease

Activity Index (SDAI). Additionally, using a modified Delphi process, the ACR working group further identified the following 5 measures as "preferred" for regular use in most clinic settings: the DAS28-ESR/CRP, CDAI, DSAI, RAPID3, and Patient Activity Scale-II.

Vectra Test

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

The Vectra test measures the serum concentrations of the following 12 biomarkers: 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), atrix metalloproteinase 3 (MMP-3), C-reactive protein (CRP), serum amyloid A (SAA), leptin, and resistin. The concentrations of these 12 biomarkers are measured in serum and, combined with age, gender, and adiposity (i.e., leptin) information, are entered in a proprietary formula to generate a score on a scale of 1 to 100 that represents the level of RA disease activity:

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

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

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

In the ACR working group's systematic review reported by England et al (2019), they also graded feasibility of the RA disease activity measurement tools. Any measure not commercially available

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

Rationale/Source

Assessment of disease activity in RA is an important component of management with a goal of treatment to maintain low disease activity or achieve remission. There are a variety of instruments for measuring RA disease activity. The instruments use combinations of physical exam findings, radiologic results, and serum biomarkers to construct a disease activity score. A MBDA instrument is a disease activity measure that is comprised entirely of serum biomarkers. The Vectra test is a commercially available MBDA blood test that measures 12 biomarkers to construct a disease activity score. Concentrations of these 12 biomarkers are entered into a proprietary formula which, after adjustment by age, gender, and adiposity (i.e., leptin) levels, generates a disease activity score ("adjusted MBDA score") that ranges from 1 (low disease activity) to 100 (high disease activity).

Summary of Evidence

Vectra Test with Adjusted Multibiomarker Disease Activity Score

For individuals who have RA who receive the current commercially available Vectra test ("adjusted MBDA score") as an adjunct or as a replacement of other disease activity measures, the evidence includes 2 studies that analyzed archived serum samples using combined data from randomized controlled trials (RCTs) and cohort studies. Relevant outcomes are test validity, other test performance measures, symptoms, change in disease status, functional outcomes, and quality of life. Analyses comparing Vectra with other previously validated disease activity measures such as the Disease Activity Score with 28 joints (DAS28) or to radiographic progression, consisted mostly of correlations. However, the positive predictive values (PPVs) that individuals with Vectra moderate- to high-risk disease scores had radiographic progression were low, at 4.4% and 15.8%, respectively.

Additionally, due to numerous study relevance, design and conduct limitations , the body of evidence on the Vectra test is insufficient to determine whether it is as good as or better than other disease activity measures. Given the high prevalence of discordant results across conventional measures of disease activity, the position of the Vectra test in the management pathway is unclear. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Rheumatology
In its 2019 guidelines on the treatment of rheumatoid arthritis, the American College of Rheumatology[4.] identified the following 11 measures of disease activity as fulfilling a minimum standard for regular use in most clinical settings: Disease Activity Score (DAS), Routine Assessment

of Patient Index Data 3 (RAPID3), Routine Assessment of Patient Index Data 5 (RAPID5), Clinical Disease Activity Index (CDAI), Disease Activity Score with 28 joints (DAS28-ESR/CRP), Patient Derived DAS28, Hospital Universitario La Princesa Index (HUPI), Multibiomarker Disease Activity Score (MBDA score, Vectra DA), Rheumatoid Arthritis Disease Activity Index (RADAI), Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5), Simplified Disease Activity Index (SDAI). Although the original Vectra DA test is included in this list, the current commercially available version of the test that is now called Vectra and that includes the leptin-adjusted MBDA score (now called the "adjusted MBDA score") was not addressed in the 2019 ACR guideline. This is because evidence on Vectra with the adjusted MBDA score was published subsequent to the ACR review end date.

National Institute for Health and Care Excellence
Published in 2018 and updated in 2020, the National Institute for Health and Care Excellence guidance on the management of adult patients with rheumatoid arthritis does not include a discussion on the use of a multibiomarker disease activity blood test to monitor patients.

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

Medicare National Coverage
There are no Medicare national coverage determinations for the Vectra test. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT03810144[a]	Impact of Guided Care with the Vectra DA Multi-Biomarker Disease Activity (MBDA) Blood Test on Clinical Outcomes and Pharmaceutical Utilization in Patients with Rheumatoid Arthritis: a Prospective Randomized Study (CareFirst)	500	Mar 2021 (recruiting)
NCT03631225[a]	Vectra InVolved Informed Decision Outcome Study (VIVID): A Prospective Randomized Controlled Trial Evaluating the Effect of Guided Care With Vectra Compared to Treatment as Usual in Patients With Rheumatoid Arthritis	1200	Oct 2021 (recruiting)
NCT02832297[a]	Prospective Outcomes Study: Vectra® DA Guided Care Compared to Usual Care	318	Aug 2022 (recruiting)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 08/20/2014
Current Effective Date: 10/11/2021

08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. New policy.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. No change to coverage.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. No change to coverage. Title changed.
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. No change to coverage.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. No change to coverage.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 09/2022

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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	81490, 83520, 84999
HCPCS	No codes
ICD-10 Diagnosis	M05.0-M05.9, M06.00-M06.9, M08.00-M08.9A, M12.00-M12.09

*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. Food and Drug Administration (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:
    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
    3. Reference to federal regulations.

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