



MASSACHUSETTS

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Medical Policy

Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis

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Policy Number: 677

BCBSA Reference Number: 2.04.119 (For Plan internal use only)

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The use of a multi-biomarker disease activity score for rheumatoid arthritis (eg, Vectra® DA score) is considered **INVESTIGATIONAL** in all situations.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is not a covered service.
Commercial PPO and Indemnity	This is not a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

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

Description

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. Most epidemiological studies and clinical trials on RA have predominantly focused on White patients.¹ As a result, there are limited data informing the epidemiology and clinical outcomes of patients from other races and ethnicities with RA.

Treatment

Treatment of RA has undergone a shift from symptom management to a more proactive strategy of minimizing disease activity and delaying disease progression.² 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.³ 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.⁴ Combination therapy may consist of additional disease-modifying antirheumatic drugs or the addition of tumor necrosis factor inhibitors 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-reporting 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,⁵ an ACR working group determined that the following 11 measures of disease activity fulfilled a minimum standard for regular use in most clinical settings: 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-erythrocyte sedimentation rate [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.⁶ 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 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), matrix 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.⁷

Categories of scores were constructed to correlate with the DAS28-CRP scale^{6,8}:

- 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.⁹ 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 review will primarily be on the leptin-adjusted Vectra test.⁷

In the ACR working group's systematic review reported by England et al (2019),⁵ 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.

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 (CLIA). The Vectra test (Myriad, formerly Crescendo Bioscience) is available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA

for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Summary

Assessment of disease activity in rheumatoid arthritis (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 multibiomarker disease activity (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

For individuals with rheumatoid arthritis (RA) who receive the current commercially available Vectra test ("adjusted multibiomarker disease activity [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 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.

For individuals with 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 randomized controlled trials (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, 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.

Policy History

Date	Action
8/2024	Annual policy review. Summary and references updated. Policy statements unchanged.
8/2023	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
8/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.

8/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
8/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
8/2018	Annual policy review. Policy statement clarified. Title changed to “Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis.”
7/2017	Annual policy review. New references added.
7/2016	Annual policy review. New references added.
1/2016	Clarified coding information.
9/2014	New medical policy describing investigational indications. Effective 9/1/2014.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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