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MEDICAL POLICY – 2.04.119

Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis

BCBSA Ref. Policy:	2.04.119	
Effective Date:	Sept. 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	Aug. 12, 2024	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

A biomarker is something in the body that can reflect the presence or activity of a disease. Different diseases may have different biomarkers. A blood test called Vectra DA looks at 12 different biomarkers for rheumatoid arthritis (RA) and combines the results into a single score. This single score can be followed over time in an attempt to show how active the arthritis could be and how it might be responding to therapy. Blood tests that measure many biomarkers to try to assess the RA activity level are investigational (unproven). Current medical studies do not answer whether these multi-biomarker tests are as good as or better than the standard tests.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Score	Investigational
Multi-biomarker disease activity score	**The use of a multi-biomarker disease activity score for rheumatoid arthritis (e.g., Vectra score) is considered investigational in all situations.**

Coding

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

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review

Description

Assessment of disease activity in rheumatoid arthritis (RA) is an important component of management, with a goal of treatment being to maintain low disease activity or 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 uses 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).

Background

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 is associated with a high burden of morbidity for affected individuals. Most epidemiological studies and clinical trials on RA have predominantly focused on White individuals.[1] As a result, there are limited data informing the epidemiology and clinical outcomes of individuals 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 individuals 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, Schoels et al (2010) identified 7 studies that evaluated the efficacy of tight control.[3] Four of these trials randomized individuals to either tight control using treatment targets or routine management, two studies compared different treatment targets, and one study compared results from a 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 individuals to tight control or routine management, there was a significant decrease in the Disease Activity Score (DAS) or its 28 joint version (DAS28), and in the likelihood of achieving remission for individuals in the tight control group.

According to American College of Rheumatology (ACR) guidelines, initial treatment of individuals 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 factors or non-tumor necrosis factors biologics.

Selection of Disease Activity Assessment Tools

For a strategy of tight control to be successful, a reliable and valid measurement of disease activity is necessary. Numerous measurements exist that assess various aspects of RA disease activity, including individual 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[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:

- 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)

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:

- DAS28-ESR/CRP
- CDAI
- DSAI
- RAPID3
- Patient Activity Scale-II

Vectra Test

The Vectra Test is a commercially available 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 individuals 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), and 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 policy 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 (i.e., "++++") 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, 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 (i.e., 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.

Summary of Evidence

Vectra Test with Adjusted MBDA 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 two studies that analyzed archived serum samples using combined data from RCTs and cohort studies. The 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in **Table 2**.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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	1500	Sept 2025 (recruiting)

NCT02832297[a]	Prospective Outcomes Study: Vectra® DA Guided Care Compared to Usual Care	318	Aug 2022 (status unknown)
Unpublished			
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)	444	Oct 2022

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or the 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 RA, the American College of Rheumatology[5] 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 RA does not include a discussion on the use of a MBDA blood test to monitor patients.[30]

Medicare National Coverage

There are no Medicare National Coverage Determinations for the Vectra test.

Regulatory Status

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 US Food and Drug Administration has chosen not to require any regulatory review of this test.

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History

Date	Comments
05/12/14	New Policy. New policy created with literature review through March 6, 2014. The Vectra DA test for measuring disease activity in rheumatoid arthritis is investigational.
07/23/14	Update Related Policies. Remove 12.04.91.
06/17/15	Annual Review. Policy updated with literature review through March 22, 2015. References 9 and 11-12 added. No change to policy statement.
01/19/16	Coding update. New CPT code 81490, effective 1/1/16, added to policy.
09/01/16	Annual Review, approved August 9, 2016. Policy updated with literature review through April 26, 2016; references 12-15 added. Policy statement unchanged. Removed codes 83520 and 86140.
09/01/17	Annual Review, approved August 1, 2017. Policy moved into new format. Policy updated with literature review through April 25, 2017; references 16, 18, 20, and 23-24 added. Policy statement unchanged. Removed unlisted CPT code 84999.
09/01/18	Annual Review, approved August 10, 2018. Policy updated with literature review through April2018; references 15-16, 19, and 23-24 added. Policy statement unchanged. Title changed from "Vectra® DA Blood Test for Rheumatoid Arthritis" to "Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis."

Date	Comments
09/01/19	Annual Review, approved August 6, 2019. Policy updated with literature review through April 2019; references added. Policy statement unchanged.
09/01/20	Annual Review, approved August 4, 2020. Policy updated with literature review through April, 2020; references added. Policy statement unchanged.
09/01/21	Annual Review, approved August 3, 2021. Policy updated with literature review through May 7, 2021; reference added. Policy statement unchanged.
09/01/22	Annual Review, approved August 8, 2022. Policy updated with literature review through May 9, 2022; references added. Policy statement unchanged.
09/01/23	Annual Review, approved August 21, 2023. Policy updated with literature review through April 25, 2023; references added. Policy statement unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
09/01/24	Annual Review, approved August 12, 2024. Policy updated with literature review through April 18, 2024; no references added. Policy statement unchanged.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.