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 <u>Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:</u>

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 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 (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
8/2023	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

References

1. Yip K, Navarro-Millán I. Racial, ethnic, and healthcare disparities in rheumatoid arthritis. Curr Opin Rheumatol. Mar 01 2021; 33(2): 117-121. PMID 33394602
2. Upchurch KS, Kay J. Evolution of treatment for rheumatoid arthritis. Rheumatology (Oxford). Dec 2012; 51 Suppl 6: vi28-36. PMID 23221584
3. Schoels M, Knevel R, Aletaha D, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis. Apr 2010; 69(4): 638-643. PMID 20237123
4. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). Jul 2021; 73(7): 924-939. PMID 34101387
5. England BR, Tiong BK, Bergman MJ, et al. 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res (Hoboken). Dec 2019; 71(12): 1540-1555. PMID 31709779
6. Crescendo Bioscience. Vectra DA Patient Guide: Understanding results. n.d.; https://vectrascore.com/know-your-results/. Accessed April 23, 2023.
7. Labcorp. Vectra. 2021. https://www.labcorp.com/tests/504965/vectra. Accessed April 26, 2023.
8. Centola M, Cavet G, Shen Y, et al. Development of a multi-biomarker disease activity test for rheumatoid arthritis. PLoS One. 2013; 8(4): e60635. PMID 23585841
9. Curtis JR, Flake DD, Weinblatt ME, et al. Adjustment of the multi-biomarker disease activity score to account for age, sex and adiposity in patients with rheumatoid arthritis. Rheumatology (Oxford). May 01 2019; 58(5): 874-883. PMID 30590790
10. Meznerics FA, Kemény LV, Gunther E, et al. Multibiomarker disease activity score: an objective tool for monitoring rheumatoid arthritis? A systematic review and meta-analysis. Rheumatology (Oxford). Jun 01 2023; 62(6): 2048-2059. PMID 36575983
11. Curtis JR, Weinblatt ME, Shadick NA, et al. Validation of the adjusted multi-biomarker disease activity score as a prognostic test for radiographic progression in rheumatoid arthritis: a combined analysis of multiple studies. Arthritis Res Ther. Jan 04 2021; 23(1): 1. PMID 33397438
12. Brahe CH, Østergaard M, Johansen JS, et al. Predictive value of a multi-biomarker disease activity score for clinical remission and radiographic progression in patients with early rheumatoid arthritis: a post-hoc study of the OPERA trial. Scand J Rheumatol. Jan 2019; 48(1): 9-16. PMID 29985080
13. Iannaccone CK, Lee YC, Cui J, et al. Using genetic and clinical data to understand response to disease-modifying anti-rheumatic drug therapy: data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study. Rheumatology (Oxford). Jan 2011; 50(1): 40-6. PMID 20847201
14. 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. Oct 2012; 71(10): 1692-7. PMID 22596166

15. Markusse IM, Dirven L, van den Broek M, et al. A multibiomarker disease activity score for rheumatoid arthritis predicts radiographic joint damage in the BeSt study. J Rheumatol. Nov 2014; 41(11): 2114-9. PMID 25128518
16. Hambardzumyan K, Bolce R, Saevarsdottir S, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis. Jun 2015; 74(6): 1102-9. PMID 24812287
17. Hambardzumyan K, Bolce RJ, Saevarsdottir S, et al. Association of a multibiomarker disease activity score at multiple time-points with radiographic progression in rheumatoid arthritis: results from the SWEFOT trial. RMD Open. 2016; 2(1): e000197. PMID 26958364
18. Fleischmann R, Connolly SE, Maldonado MA, et al. Brief Report: Estimating Disease Activity Using Multi-Biomarker Disease Activity Scores in Rheumatoid Arthritis Patients Treated With Abatacept or Adalimumab. Arthritis Rheumatol. Sep 2016; 68(9): 2083-9. PMID 27111089
19. Hirata S, Li W, Kubo S, et al. Association of the multi-biomarker disease activity score with joint destruction in patients with rheumatoid arthritis receiving tumor necrosis factor-alpha inhibitor treatment in clinical practice. Mod Rheumatol. Nov 2016; 26(6): 850-856. PMID 26873570
20. Bouman CAM, van der Maas A, van Herwaarden N, et al. A multi-biomarker score measuring disease activity in rheumatoid arthritis patients tapering adalimumab or etanercept: predictive value for clinical and radiographic outcomes. Rheumatology (Oxford). Jun 01 2017; 56(6): 973-980. PMID 28339738
21. Hambardzumyan K, Saevarsdottir S, Forslind K, et al. A Multi-Biomarker Disease Activity Score and the Choice of Second-Line Therapy in Early Rheumatoid Arthritis After Methotrexate Failure. Arthritis Rheumatol. May 2017; 69(5): 953-963. PMID 27992691
22. van der Helm-van Mil AH, Knevel R, Cavet G, et al. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. Rheumatology (Oxford). May 2013; 52(5): 839-46. PMID 23287359
23. Li W, Sasso EH, van der Helm-van Mil AH, et al. Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis. Rheumatology (Oxford). Feb 2016; 55(2): 357-66. PMID 26385370
24. Krabbe S, Bolce R, Brahe CH, et al. Investigation of a multi-biomarker disease activity score in rheumatoid arthritis by comparison with magnetic resonance imaging, computed tomography, ultrasonography, and radiography parameters of inflammation and damage. Scand J Rheumatol. Sep 2017; 46(5): 353-358. PMID 27682742
25. Reiss WG, Devenport JN, Low JM, et al. Interpreting the multi-biomarker disease activity score in the context of tocilizumab treatment for patients with rheumatoid arthritis. Rheumatol Int. Feb 2016; 36(2): 295-300. PMID 26026604
26. Roodenrijs NMT, de Hair MJH, Wheater G, et al. The multi-biomarker disease activity score tracks response to rituximab treatment in rheumatoid arthritis patients: a post hoc analysis of three cohort studies. Arthritis Res Ther. Nov 20 2018; 20(1): 256. PMID 30458871
27. Johnson TM, Register KA, Schmidt CM, et al. Correlation of the Multi-Biomarker Disease Activity Score With Rheumatoid Arthritis Disease Activity Measures: A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken). Nov 2019; 71(11): 1459-1472. PMID 30320973
28. Curtis JR, Brahe CH, Østergaard M, et al. Predicting risk for radiographic damage in rheumatoid arthritis: comparative analysis of the multi-biomarker disease activity score and conventional measures of disease activity in multiple studies. Curr Med Res Opin. Sep 2019; 35(9): 1483-1493. PMID 30777458
29. Curtis JR, Xie F, Yang S, et al. Uptake and Clinical Utility of Multibiomarker Disease Activity Testing in the United States. J Rheumatol. Mar 2019; 46(3): 237-244. PMID 30442830
30. National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management [NG100]. October 2020, https://www.nice.org.uk/guidance/ng100. Accessed April 26, 2023