



MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an independent  
Licensee of the Blue Cross and Blue Shield Association

## Medical Policy

### Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis

#### Table of Contents

- [Policy: Commercial](#)
- [Policy: Medicare](#)
- [Authorization Information](#)
- [Coding Information](#)
- [Description](#)
- [Policy History](#)
- [Information Pertaining to All Policies](#)
- [References](#)

#### Policy Number: 677

BCBSA Reference Number: 2.04.119

NCD/LCD: N/A

Local Coverage Article: MoIDX: Vectra™ DA Coding and Billing Guidelines (A53110)

#### 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.

##### Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

Medical necessity and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the link below.

[Local Coverage Article: MoIDX: Vectra™ DA Coding and Billing Guidelines \(A53110\)](#)

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at <https://www.cms.gov>.

#### 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 <b>not</b> a covered service.
Commercial PPO and Indemnity	This is <b>not</b> a covered service.
Medicare HMO Blue <sup>SM</sup>	Prior authorization is <b>not required</b> .
Medicare PPO Blue <sup>SM</sup>	Prior authorization is <b>not required</b> .

## 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.

### Treatment

Treatment of RA has undergone a shift from symptom management to a more proactive strategy of minimizing disease activity and delaying disease progression.<sup>1</sup> 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, Schoels et al (2010) identified 7 studies that evaluated the efficacy of tight control.<sup>2</sup> 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 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 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 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.<sup>3</sup> Combination therapy may

consist of additional disease-modifying antirheumatic drugs or the addition of tumor necrosis factors or non-tumor necrosis factors biologics.

### Validated Disease Activity Assessment Tools

For a strategy of tight control to be successful, a reliable and valid measurement of disease activity is necessary. There are numerous disease activity measurements that can be used in clinical care. Through a 5-stage process that included review by an expert advisory panel in RA disease activity and detailed evaluation of psychometric properties, an ACR working group determined that 6 measures were accurate reflections of disease activity: Clinical Disease Activity Index (CDAI), DAS28, Patient Activity Scale, Patient Activity Scale II, Routine Assessment of Patient Index Data 3, and the Simplified Disease Activity Index (SDAI).<sup>4</sup>

Two systematic reviews were published the same year as the ACR’s recommendations, one by Gaujoux-Viala et al (2012)<sup>5</sup> and the other by Salaffi et al (2012),<sup>6</sup> which compared disease activity measures for patients with RA. Results from the systematic reviews were consistent with the ACR working group recommendations, citing the DAS28, SDAI, and CDAI as appropriate disease activity measures for RA. Table 1 summarizes the clinical and laboratory measurements included in each of the 6 disease activity measures recommended by ACR. The table also includes the laboratory measures included in the Vectra DA, a multi-biomarker disease activity (MBDA) test which currently does not have a recommendation from ACR.

**Table 1. Clinical and Laboratory Components of Rheumatoid Arthritis Disease Activity Measurements**

Recommended by ACR					No ACR Recommendation
DAS28	CDAI and SDAI	PAS	PAS II	RAPID3	Vectra DA
No. of swollen joints out of 28 <sup>a</sup>	No. of swollen joints out of 28 <sup>a</sup>	Patient describes ability to do each of 20 activities <sup>b</sup> as “without any difficulty,” “with some difficulty,” “with much difficulty,” or “unable to do”	Patient describes ability to do each of 10 activities <sup>c</sup> as “without any difficulty,” “with some difficulty,” “with much difficulty,” or “unable to do”	Patient describes ability to do each of 13 activities <sup>d</sup> as “without any difficulty,” “with some difficulty,” “with much difficulty,” or “unable to do”	<ul style="list-style-type: none"> <li>• Interleukin-6</li> <li>• Tumor necrosis factor receptor type I</li> <li>• Vascular cell adhesion molecule 1</li> <li>• Epidermal growth factor</li> <li>• Vascular endothelial growth factor A</li> <li>• YKL-40 glycoprotein</li> <li>• MMP-1</li> <li>• MMP-3</li> <li>• C-reactive protein</li> <li>• Serum amyloid A</li> <li>• Leptin</li> <li>• Resistin</li> </ul>

No. of tender joints out of 28 <sup>a</sup>	No. of tender joints out of 28 <sup>a</sup>	Patient indicates need for cane, crutches, walker, wheelchair, or devices to assist with dressing or eating	Patient rates pain on scale of 0 (no pain) to 10 (severe pain)	Patient rates pain on scale of 0 (no pain) to 10 (severe pain)	
ESR (mm/h)	CRP (mg/L) (only in the SDAI, not part of CDAI calculation)	Patient indicates need for assistance in dressing, rising, eating, walking, hygiene, reaching, gripping, or chores	Patient rates how they are doing on scale of 0 (very well) to 10 (very poor)	Patient rates how they are doing on scale of 0 (very well) to 10 (very poor)	
CRP (mg/L)	Patient Global Assessment (0 [very well] to 10 [very poor])	Patient indicates if special devices needed in bathroom or kitchen			
Patient Global Assessment (0 [best] to 100 [worst])	Physician Global Assessment (0 [very well] to 10 [very poor])	Patient rates pain on scale of 0 (no pain) to 10 (severe pain)			
		Patient rates how they are doing on scale of 0 (very well) to 10 (very poor)			

Adapted by Anderson et al (2012).<sup>4</sup>

ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score 28; ESR: erythrocyte sedimentation rate; MMP: matrix metalloproteinase; PAS: Patient Activity Scale; RAPID3: Routine Assessment of Patient Index Data 3; SDAI: Simplified Disease Activity Index.

<sup>a</sup> Twenty-eight joints: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees.

<sup>b</sup> Dress self; shampoo hair; stand from chair; get in and out of bed; cut meat; bring cup to mouth; open milk carton; walk outdoors on flat ground; climb 5 steps; wash and dry body; take tub bath; get on and off toilet; reach and bring down 5 pound object from above head; bend and pick up clothing from floor; open car door; open new jar; turn faucets on and off; run errands; get in and out of car; do chores (eg, vacuum or yard work).

<sup>c</sup> Stand from chair; walk outdoors on flat ground; get on and off toilet; reach and bring down 5 pound object from above head; open car door; do outside work such as yard work; wait in line for 15 minutes; lift heavy objects; move heavy objects; climb 2 or more flights of stairs.

<sup>d</sup> Dress self; get in and out of bed; bring cup to mouth; walk outdoors on flat ground; wash and dry body; bend and pick up clothing from floor; turn faucets on and off; get in and out of car; walk 2 miles; participate in recreational activities; sleep well; deal with feelings of anxiety or nervousness; deal with feelings of depression or sadness.

### **Vectra DA Test**

The manufacturer describes Vectra DA as a complement to clinical judgment.<sup>7</sup> 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 DA test scores range from 1 to 100. Categories of scores were constructed to correlate with the DAS28-CRP scale <sup>7,8</sup>:

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

## **Summary**

Assessment of disease activity in rheumatoid arthritis is an important component of management with a goal of treatment being to maintain low disease activity or achieve remission. There are a variety of instruments for measuring rheumatoid arthritis 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 instrument is a disease activity measure that is comprised entirely of serum biomarkers. The Vectra DA test is a commercially available multibiomarker disease activity blood test that uses 12 biomarkers to construct a disease activity score ranging from 1 (low disease activity) to 100 (high disease activity).

For individuals who have rheumatoid arthritis who receive a multibiomarker disease activity (eg, 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 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 Disease Activity Score with 28 joints or to radiographic progression, consisted mostly of correlations, with only 1 study providing sensitivity, specificity, and positive and negative predictive values. The positive predictive value 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 the effects of the technology on health outcomes.

## **Policy History**

<b>Date</b>	<b>Action</b>
8/2018	BCBSA National medical policy review. Policy statement clarified. Title changed to “Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis.”
7/2017	New references added from BCBSA National medical policy.

7/2016	New references added from BCBSA National medical policy.
1/2016	Clarified coding information.
6/2015	New references added from BCBSA National medical policy. Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.
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. Upchurch KS, Kay J. Evolution of treatment for rheumatoid arthritis. *Rheumatology (Oxford)*. Dec 2012;51 Suppl 6:vi28-36. PMID 23221584
2. 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
3. Singh JA, Saag KG, Bridges SL, Jr., et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. Jan 2016;68(1):1-26. PMID 26545940
4. Anderson J, Caplan L, Yazdany J, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res (Hoboken)*. May 2012;64(5):640-647. PMID 22473918
5. Gaujoux-Viala C, Mouterde G, Baillet A, et al. Evaluating disease activity in rheumatoid arthritis: which composite index is best? A systematic literature analysis of studies comparing the psychometric properties of the DAS, DAS28, SDAI and CDAI. *Joint Bone Spine*. Mar 2012;79(2):149-155. PMID 21680221
6. Salaffi F, Ciapetti A, Gasparini S, Carotti M, Bombardieri S, New Indices study g. The comparative responsiveness of the patient self-report questionnaires and composite disease indices for assessing rheumatoid arthritis activity in routine care. *Clin Exp Rheumatol*. Nov-Dec 2012;30(6):912-921. PMID 22935335
7. Crescendo Bioscience. Vectra DA Patient Guide: Understanding results. n.d.; <https://vectrada.com/health-care-professionals/understanding-results/?gclid=CMqLnbrTiNQCFQcaaQodcE4JRg>. Accessed May 22, 2018.
8. Centola M, Cavet G, Shen Y, et al. Development of a multi-biomarker disease activity test for rheumatoid arthritis. *PLoS One*. Apr 2013;8(4):e60635. PMID 23585841
9. 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):1692-1697. PMID 22596166
10. 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):2114-2119. PMID 25128518
11. 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):1102-1109. PMID 24812287
12. 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*. Mar 2016;2(1):e000197. PMID 26958364
13. Fleischmann R, Connolly SE, Maldonado MA, Schiff M. 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):2083-2089. PMID 27111089
14. 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*. Mar 30 2016;1-7. PMID 26873570
15. Bouman CAM, van der Maas A, van Herwaarden N, Sasso EH, van den Hoogen FHJ, den Broeder AA. 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 1 2017;56(6):973-980. PMID 28339738
  16. 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
  17. van der Helm-van Mil AH, Knevel R, Cavet G, Huizinga TW, Haney DJ. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. *Rheumatology (Oxford)*. May 2013;52(5):839-846. PMID 23287359
  18. Li W, Sasso EH, van der Helm-van Mil AH, Huizinga TW. 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):357-366. PMID 26385370
  19. 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
  20. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst*. Nov 4 2009;101(21):1446-1452. PMID 19815849
  21. Hirata S, Dirven L, Shen Y, et al. A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study. *Rheumatology (Oxford)*. Jul 2013;52(7):1202-1207. PMID 23392591
  22. Hirata S, Li W, Defranoux N, et al. A multi-biomarker disease activity score tracks clinical response consistently in patients with rheumatoid arthritis treated with different anti-tumor necrosis factor therapies: A retrospective observational study. *Mod Rheumatol*. May 2015;25(3):344-349. PMID 25295918
  23. Combe B, Landewe R, Daien CI, et al. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis*. Jun 2017;76(6):948-959. PMID 27979873
  24. Palmetto GBA. Vectra DA Coding and Billing Guidelines (M00031, V10). <https://www.palmettogba.com/palmetto/MoIDx.nsf/DocsCat/MoIDx%20Website~MoIDx~Browse%20By%20Topic~Covered%20Tests~97KMQ68675?open&navmenu=%7C%7C>. Accessed May 24, 2018.