

## Corporate Medical Policy

### Vectra DA Blood Test for Rheumatoid Arthritis AHS – G2127

**File Name:** vectra\_da\_blood\_test\_for\_rheumatoid\_arthritis  
**Origination:** 01/01/2019  
**Last CAP Review:** n/a  
**Next CAP Review:** 01/01/2020  
**Last Review:** 4/2019

#### Description of Procedure or Service

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**Definition**

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder which results from a complex interaction between genes and environment, leading to a breakdown of immune tolerance and synovial inflammation in a characteristic symmetric pattern. RA usually leads to destruction of joints due to erosion of cartilage and bone, causing joint deformities (Firestein, 2017).

Vectra DA is an multi-biomarker disease activity (MBDA) blood test which employs an algorithm to combine the levels of 12 serum biomarkers into a single score from 1 to 100 to provide an objective measure of RA disease activity intended for use in conjunction with existing symptom-based disease activity measures with the objective of improving long-term outcomes for RA patients (van der Helm-van Mil, Knevel, Cavet, Huizinga, & Haney, 2013).

This policy does not pertain to general inflammation; for guidance on general inflammation testing, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), see policies General Inflammation Testing and ANA/ENA Testing.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

#### Policy

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**The use of a multi-biomarker disease activity score for rheumatoid arthritis (e.g., Vectra DA score) is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

#### When a multi-biomarker disease activity score for rheumatoid arthritis (Vectra DA) is covered

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Not applicable.

## When a multi-biomarker disease activity score for rheumatoid arthritis (Vectra DA) is not covered

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The use of a multi-biomarker disease activity score for rheumatoid arthritis (e.g., Vectra DA score) is considered investigational.

## Policy Guidelines

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### Background

RA affects over 1.3 million people in the US and over 4 million worldwide. Despite the availability of potent biologic treatments, substantial disease activity persists in many patients, with accompanying progressive bone and soft tissue damage, extra-articular consequences, disability, and increased mortality (Centola et al., 2013). The condition usually involves stiffness and swelling joints all around the body, pain, and eventually the destruction of the affected joints. This typically leads to significant motor disability in patients who do not respond to treatment (Venables, 2017).

Measuring disease activity has become important for the management of patients with RA (Curtis et al., 2012). As RA is a chronic illness, earlier and more aggressive treatment may provide significant benefit, especially for patients with more severe forms of the illness (Taylor & Maini, 2017). Tighter control, such as more frequent monitoring and actively striving to meet a disease activity level, has been shown to be helpful in several studies (Bakker, Jacobs, Verstappen, & Bijlsma, 2007; Mease, 2010). However, there is no gold standard for disease activity assessment in RA. Multiple measures are used, and no single best measure of disease activity was recommended in U.S. or international RA guidelines (Centola et al., 2013). Disease activity indices are based on clinical, laboratory, and physical measures. Most of these indices, such as the Disease Activity Score (DAS) and the Routine Assessment of Patient Index Data-3 (RAPID-3) rely on either clinical evaluation of joints, patient-reported outcomes (PROs), or both in assessing disease activity. However, high intra- and inter-observer variability occurs. Furthermore, prior damage to joints or other conditions may influence these measurements (Curtis et al., 2012). Other commonly used tools for diagnosing RA have significant weaknesses; for example, blood tests may be used but are completely normal for many RA patients. MRI may be used due to its ability to identify early signs, but it is expensive and time consuming (Li, Sasso, van der Helm-van Mil, & Huizinga, 2016).

Biologic markers or “biomarkers” can provide objective measurements that reflect underlying pathophysiological processes, pathogenic processes, or responses to treatment. Most measures of monitoring disease and treatment progress rely on subjective measurements, such as joint evaluation, so biomarkers may be a useful complement in patient management (Taylor & Maini, 2017). Joint damage at the molecular level may be occurring before any clinical signs appear, so identifying any indications of disease activity could allow clinical interventions to be taken earlier (Mc Ardle, Flatley, Pennington, & FitzGerald, 2015). Markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are part of clinical measures such as the DAS. However, these two biomarkers are nonspecific; abnormal amounts of these markers may be due to other reasons apart from RA and may even be completely normal in patients with RA (Centola et al., 2013; Curtis et al., 2012). This nonspecificity is not limited to these two biomarkers as well. For example, antibodies (usually called rheumatoid factors and abbreviated RF) produced against immunoglobulin G (IgG) are often tested to diagnose RA, but these antibodies may be produced in response to another rheumatic condition or a separate chronic infection (Shmerling, 2018). RA is a heterogenous condition, and no single biomarker is a reliable predictor of RA disease activity (Mc Ardle et al., 2015). However, the combined assessment of multiple biomarkers, such as through MBDA, may be useful for predicting disease activity and progression (Taylor & Maini, 2017).

### *Validity and Utility*

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The MBDA algorithm (Vectra DA) was developed by screening 396 candidate biomarkers and creating an algorithm to generate a composite score based on the 12 most correlated to RA clinical disease activity which are as follows:

- interleukin-6 [IL-6]
- tumor necrosis factor receptor type I [TNFR1]
- 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]
- MMP-3
- CRP
- serum amyloid A [SAA]
- leptin
- resistin.

These biomarkers represent several processes related to RA, such as cartilage remodeling and cytokine signaling pathways. A score of  $\leq 29$  is considered “low” activity, between 29 and 44 is “moderate” activity, and  $>44$  is “high” activity. The MBDA is intended to provide separate information from a clinical evaluation of joints and should be used as a complement, not as a replacement (Curtis et al., 2012).

This MBDA has been shown to correlate significantly ( $r=0.72$ ;  $p<0.001$ ) with a disease activity score based on the DAS-28-CRP and has been validated for clinical use as a disease activity marker in RA (Curtis et al., 2012). Both Hirata et al. and Bakker et al. found the MBDA score to correlate well with disease activity and could complement other existing measures of RA assessment (Bakker et al., 2012; Hirata et al., 2013). Remission based on the MBDA score was a significant predictor of radiographic non-progression, whereas remission defined by traditional DAS28-CRP or ACR/EULAR criteria was not. The MBDA test was also useful in assessing the risk of radiographic progression among patients who met clinical remission criteria. MBDA results may provide an important addition to clinical assessment, however, further studies are needed to confirm its clinical utility in the management of RA (van der Helm-van Mil et al., 2013).

Li and colleagues evaluated the impact of an MBDA blood test for rheumatoid arthritis (RA) on treatment decisions made by six health care providers (HCPs) in 101 patients. HCPs completed surveys before and after viewing the MBDA test result, recording dosage and frequency for all RA medications and assessment of disease activity. Frequency and changes in treatment plan that resulted from viewing the MBDA test result were determined. The MBDA test results were found to have changed 38% of patients’ treatment plans. Furthermore, treatment plans were changed 63% of the time the MBDA test results were found to be “not consistent” or “somewhat consistent” with the clinical assessment of disease activity. However, any improvement in clinical outcomes caused was not reported, and the overall amount of drug use was not affected (Li, Sasso, Emerling, Cavet, & Ford, 2013).

Another study assessed the correlation between MBDA score and disease progression in 163 RA patients. The study found that low radiographic progression was associated with low MBDA scores and higher scores were associated with more frequent and severe progression. Notably, MBDA scores correlated with progression even when a conventional measure such as the DAS28 indicated otherwise. For example, low risk of progression was associated with a low MBDA score, even when a concurrent DAS28 score was high. The authors concluded that MBDA may be a good complement for conventional measures, as well as provide information on changing treatment plans (Li et al., 2016).

### Applicable Federal Regulations

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There are no U.S. Food and Drug Administration (FDA)-approved multibiomarker disease activity (MBDA) tests for measuring disease activity in RA, Vectra included. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

## **Guidelines and Recommendations**

### **Practice Guidelines and Position Statements**

#### **American College of Rheumatology (ACR)**

The ACR convened a Working Group (WG) to evaluate the validity, feasibility, and acceptability of available RA disease activity measures.

The WG recommended the following measures:

- Clinical Disease Activity Index
- Disease Activity Score with 28-joint counts (erythrocyte sedimentation rate or C-reactive protein)
- Patient Activity Scale (PAS) and PAS-II
- Routine Assessment of Patient Index Data (3 measures)
- Simplified Disease Activity Index

According to the WG, these measures were recommended because “they are accurate reflections of disease activity; are sensitive to change; discriminate well between low, moderate, and high disease activity states; have remission criteria; and are feasible to perform in clinical settings.” The WG also recognized “there is no ideal measure of disease activity” and acknowledged that some measures excluded in their review may be superior to the six recommended measures. However, they believed they identified the best measures of disease activity in RA (Anderson et al., 2012).

#### **European League Against Rheumatism (EULAR), Managing Early Arthritis (2016)**

EULAR recommends clinical examination as the method of detecting arthritis, but if a definite diagnosis cannot be reached, other risk factors such as rheumatoid factor or swollen joints should be considered.

EULAR states that the main goal of disease-modifying antirheumatic drugs (DMARDs) is clinical remission and regular monitoring of adverse events, disease activity and comorbidities should occur. Monitoring should include joint counts, patient and physician global assessment, and ESR and CRP measurements. Other measures such as radiographics can complement the main measures.

EULAR notes that several combinations of biomarkers have been evaluated, but not validated. Additionally, EULAR states that current data is not convincing and further study is required (Combe et al., 2017).

#### **National Institute for Care and Excellence, Quality Standard, Rheumatoid arthritis in over 16s (NICE, 2018)**

NICE recommends monthly monitoring of CRP and disease activity until remission or low disease activity. Remission is defined as a DAS28 score of under 2.6, and low is defined as a DAS28 score of under 3.2. NICE does not mention biomarkers in its recommendations for research (NICE, 2018).

#### **Treat to Target Task Force (2014 Update to 2010 Guidelines)**

The task force states that remission or low disease activity is the goal of treatment. Remission is defined as absence of clinical signs and symptoms of disease activity.

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The task force was reconvened to update their previously issued guidelines from 2010. The task force recommended regular monitoring and documentation of disease activity. The frequency may depend on activity; for higher disease activity, the frequency may be as high as monthly whereas a lower activity patient may only need be re-evaluated every six months (Smolen et al., 2016).

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcsnc.com](http://www.bcsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81490*

Code Number	PA Required	PA Not Required	Not Covered
81490			X

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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### Policy Implementation/Update Information

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| 1/1/19  | New policy developed. The use of a multi-biomarker disease activity score for rheumatoid arthritis (e.g., Vectra DA score) is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an) |
| 5/14/19 | Reviewed by Avalon for 1 <sup>st</sup> Quarter 2019 CAB. Updated Description section. Revised Policy Guidelines section. Added reference. No change to investigational statement. Medical Director review 4/2019. (an)                                                                                                             |

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