MEDICAL POLICY – 2.04.119
Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis

BCBSA Ref. Policy: 2.04.119
Effective Date: Sept. 1, 2018
Last Revised: Aug. 10, 2018
Replaces: N/A

RELATED MEDICAL POLICIES:
None

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

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT 81490</td>
<td>Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score</td>
</tr>
</tbody>
</table>

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### Related Information

N/A

### Evidence Review

### Description

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 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).
Background

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 is 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 approach of minimizing disease activity and delaying disease progression. 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, 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. Four of these trials randomized patients to either tight control using treatment targets or 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 joint 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. Combination therapy may consist of additional disease-modifying antirheumatic drugs or the addition of tumor necrosis factors or non-tumor necrosis factors biologics.
Validated 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 (PAS), Patient Activity Scale II (PAS-II), Routine Assessment of Patient Index Data 3 (RAPID3), and the Simplified Disease Activity Index (SDAI).

Two systematic reviews were published the same year as the ACR’s recommendations, one by Gaujoux-Viala et al (2012) and the other by Salaffi et al (2012), 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 multibiomarker 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

<table>
<thead>
<tr>
<th>Recommended by ACR</th>
<th>No ACR Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>CDAI and SDAI</td>
</tr>
<tr>
<td>No. of swollen joints out of 28a</td>
<td>No. of swollen joints out of 28a</td>
</tr>
<tr>
<td>Patient describes ability to do each of 20 activitiesb as &quot;without any difficulty,&quot; “with some difficulty,”</td>
<td>Patient describes ability to do each of 10 activitiesc as &quot;without any difficulty,&quot;</td>
</tr>
<tr>
<td>Patient describes ability to do each of 13 activitiesd as &quot;without any difficulty,&quot;</td>
<td>Patient describes ability to do each of 13 activitiesd as &quot;without any difficulty,&quot;</td>
</tr>
<tr>
<td>Vectra DA</td>
<td></td>
</tr>
<tr>
<td>• Interleukin-6</td>
<td></td>
</tr>
<tr>
<td>• Tumor necrosis factor receptor type 1</td>
<td></td>
</tr>
<tr>
<td>• Vascular cell adhesion molecule 1</td>
<td></td>
</tr>
<tr>
<td>• Epidermal growth factor</td>
<td></td>
</tr>
<tr>
<td>• Vascular endothelial growth factor A</td>
<td></td>
</tr>
<tr>
<td>Recommended by ACR</td>
<td>No ACR Recommendation</td>
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<tr>
<td>--------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>DAS28</strong></td>
<td><strong>Vectra DA</strong></td>
</tr>
<tr>
<td>CDAI and SDAI</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td></td>
</tr>
<tr>
<td>PAS II</td>
<td></td>
</tr>
<tr>
<td>RAPID3</td>
<td></td>
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</tbody>
</table>

| **No. of tender joints out of 28** | **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 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)** |                        |

- YKL-40 glycoprotein
- MMP-1
- MMP-3
- C-reactive protein
- Serum amyloid A
- Leptin
- Resistin
### Vectra DA test

The manufacturer describes Vectra DA as a complement to clinical judgment. 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:\(^7\)\(^8\):

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

### Summary of Evidence

For individuals who have rheumatoid arthritis who receive a MBDA (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 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 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.

Ongoing and Unpublished Clinical Trials

There is currently an ongoing trial that might influence this review listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
<td>Prospective Outcomes Study: Vectra® DA Guided Care Compared to Usual Care</td>
<td>318</td>
<td>Aug 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

*American College of Rheumatology*

In its 2015 guidelines on the treatment of rheumatoid arthritis, the American College of Rheumatology endorsed the following measures of disease activity: Patient Activity Scale, Routine Assessment of Patient Index Data 3, Clinical Disease Activity Index, Disease Activity
Score with 28 joints, and Simplified Disease Activity Index. The guidelines indicated that other measures are available to clinicians, but that including the new measures was out of their scope.

**European League Against Rheumatism**

The European League Against Rheumatism (2017) updated its guidelines on the management of early arthritis. The League recommended that arthritis activity be assessed at 1- to 3-month intervals to determine target treatment. “Monitoring of disease activity should include tender and swollen joint counts, patient and physician global assessments, erythrocyte sedimentation rate, and C reactive protein, usually by applying a composite measure.” Composite measures recommended include the Disease Activity Score with 28 joints, Clinical Disease Activity Index, and Simplified Disease Activity Index. One item on the research agenda recommended by the League was to evaluate new biomarkers and multibiomarkers for the prognosis and treatment in early arthritis.

**Medicare National Coverage**

There are no Medicare National Coverage Determinations for the Vectra DA test. In July 2013, Palmetto GBA, the Medicare contractor in California, issued a coverage decision for the Vectra DA test. Because all Vectra DA tests are processed out of the Crescendo Bioscience Laboratory in California, the test will be covered for Medicare patients in the United States.

**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. The Vectra® DA test (Crescendo Bioscience) is available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.


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<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/12/14</td>
<td>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.</td>
</tr>
<tr>
<td>06/17/15</td>
<td>Annual Review. Policy updated with literature review through March 22, 2015. References 9 and 11-12 added. No change to policy statement.</td>
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<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81490, effective 1/1/16, added to policy.</td>
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