Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis

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.
Score | Investigational
---|---
Multi-biomarker disease activity score | 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>

**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 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).4

Two systematic reviews were published the same year as the ACR’s recommendations, one by Gaujoux-Viala et al (2012)5 and the other by Salaffi et al (2012),6 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>No. of swollen joints out of 28(^a)</td>
</tr>
<tr>
<td>CDAI and SDAI</td>
<td>No. of swollen joints out of 28(^a)</td>
</tr>
<tr>
<td>PAS</td>
<td>Patient describes ability to do each of 20 activities(^b) as “without any difficulty,” “with some difficulty,”</td>
</tr>
<tr>
<td>PAS II</td>
<td>Patient describes ability to do each of 10 activities(^c) as “without any difficulty,”</td>
</tr>
<tr>
<td>RAPID3</td>
<td>Patient describes ability to do each of 13 activities(^d) as “without any difficulty,”</td>
</tr>
<tr>
<td>Vectra DA</td>
<td>• Interleukin-6</td>
</tr>
<tr>
<td></td>
<td>• Tumor necrosis factor receptor type 1</td>
</tr>
<tr>
<td></td>
<td>• Vascular cell adhesion molecule 1</td>
</tr>
<tr>
<td></td>
<td>• Epidermal growth factor</td>
</tr>
<tr>
<td></td>
<td>• Vascular endothelial growth factor A</td>
</tr>
<tr>
<td>Recommended by ACR</td>
<td>No ACR Recommendation</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>DAS28</strong></td>
<td><strong>CDAI and SDAI</strong></td>
</tr>
<tr>
<td>“with much difficulty,” or “unable to do”</td>
<td>“with some difficulty,” “with much difficulty,” or “unable to do”</td>
</tr>
<tr>
<td>No. of tender joints out of 28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No. of tender joints out of 28&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>ESR (mm/h)</strong></td>
<td><strong>CRP (mg/L)</strong> (only in the SDAI, not part of CDAI calculation)</td>
</tr>
<tr>
<td><strong>CRP (mg/L)</strong></td>
<td><strong>Patient Global Assessment (0 [very well] to 10 [very poor])</strong></td>
</tr>
<tr>
<td><strong>Patient Global Assessment (0 [best] to 100 [worst])</strong></td>
<td><strong>Physician Global Assessment (0 [very well] to 10 [very poor])</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Recommended by ACR

<table>
<thead>
<tr>
<th>DAS28</th>
<th>CDAI and SDAI</th>
<th>PAS</th>
<th>PAS II</th>
<th>RAPID3</th>
<th>Vectra DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ACR Recommendation</td>
<td>no ACR Recommendation</td>
<td>no ACR Recommendation</td>
<td>no ACR Recommendation</td>
<td>no ACR Recommendation</td>
<td>no ACR Recommendation</td>
</tr>
</tbody>
</table>

Adapted by Anderson et al (2012).  

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.

### 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:

- **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 Table2.

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>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02832297a</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.


<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>
</tr>
<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81490, effective 1/1/16, added to policy.</td>
</tr>
</tbody>
</table>
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
لا يجوز للشركة التمييز بين الأشخاص بناءً على مسألة العرق أو الجنس أو اللغة.

Chinese (Chinese):
本通知有重要的讯息。本通知可能有关於您透过 Premera Blue Cross 提交的申请或保单的重要讯息。本通知内可能有重要日期。您可能需要在截止日期之前採取行动。保留您的健康保险或_coverage_補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

English (English):
This Notice has Important Information. This notice may have important information on your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

French (French):

Hmoob (Hmong):

Italian (Italian):
Premera Blue Cross may provide key dates that may be important in

Este aviso poderá conter informações importantes que podem

 بالإذاعة المجانية والتي تتعلق بالأعمال حسب القانون، وكمية

La prestazione può contenere informazioni importanti.

Se desempenhador de verjurado, a idade mínima de 18 anos.

The information provided may be important in relation to

inwi</code>

비치</code>

غيد</code>

فريد</code>