This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
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<tr>
<td>Individuals: • With rheumatoid arthritis</td>
<td>Interventions of interest are: • Vectra DA test</td>
<td>Comparators of interest are: • Alternative disease activity measures (e.g., Disease Activity Score 28, Clinical Disease Activity Index, Patient Activity Scale)</td>
<td>Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Symptoms • Change in disease status • Functional outcomes • Quality of life</td>
</tr>
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Description

Assessment of disease activity in rheumatoid arthritis (RA) is an important component of management, because a main goal of treatment is to maintain low disease activity or remission. There are a variety of available instruments for measuring RA disease activity. They use combinations of physical exam findings, radiologic results, and serum biomarkers to construct a disease activity score. A multi-biomarker disease activity (MBDA) instrument is a disease activity measure that is comprised entirely of serum biomarkers. The Vectra DA test is a commercially available MBDA blood test that uses 12 biomarkers to construct a disease activity score ranging from 0 (low) to 100 (high).

Summary of Evidence

For individuals who have RA who are evaluated with the Vectra DA test, the evidence includes post hoc analyses of randomized controlled trials and prospective cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, change in disease status, functional outcomes, and quality of life. Evidence from the available studies correlates Vectra DA with disease progression, response to therapy, and/or other previously validated disease activity measures such as the Disease Activity Score with 28 joints (DAS28). These studies have established that the Vectra DA score is a predictor of disease progression and that decreases in the score correlate with disease response. They have also shown moderate correlations between Vectra and the DAS28. A smaller number of studies have evaluated clinical utility by examining changes in decision making associated with use of Vectra, but these studies are limited by the design because they used
simulated cases or physician surveys and did not report any outcomes data. This 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, and it is uncertain whether it is as accurate as the DAS28. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

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

Medicare Advantage

For Medicare Advantage the use of VECTRA™ DA is considered **medically necessary** to obtain a disease activity score for rheumatoid arthritis.

Medicare Advantage Policy Guidelines

This test should be limited to two services per patient per year.

Background

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 of RA has undergone a shift from symptom management to a more proactive strategy of minimizing disease activity and delaying disease progression. The goal of treatment is to reduce 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 achievement of remission, or sustained low disease activity, a feasible goal in 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 because evidence from clinical trials have demonstrated that outcomes are improved with a tight control strategy. In a tight control strategy, treatment targets used are mainly based on measures of disease activity. In a systematic review published in 2010, Schoels et al identified seven trials that evaluated the efficacy of tight control. Four of these trials randomized patients to a tight control using treatment targets or to routine management. The treatment targets used were heterogeneous, including symptom-based measures, joint scores on exam, validated treatment activity measures, lab values, or combinations of these factors. In all four trials, there was a significant decrease in the Disease Activity Score (DAS) and in the likelihood of achieving remission for patients in the tight control group.

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. Composite measures include information from multiple sources, including patient self-report, physician examination, and/or biomarker measurement. Composite measures are the most comprehensive but are more cumbersome and difficult to complete. Patient-reported measures are simpler, and rely only on information patients can provide expeditiously, but are more subjective. Measurements that rely only on biomarkers are objective and do not require patient input, but involve the cost and inconvenience of laboratory tests.
The most widely used and validated scoring system in clinical research is the DAS28 score. This is a composite measure that includes examination of 28 joints for swelling and tenderness, combined with a patient report of disease activity and measurement of C-reactive protein or and erythrocyte sedimentation rate. This score is often considered the criterion standard for measuring disease activity. However, it requires a thorough joint examination, patient-reported symptoms, and laboratory testing. Therefore, there have been many attempts to create a valid disease activity measure that is simpler.

There is a fairly large body of evidence comparing the performance of different disease activity measures in clinical care, including a number of systematic reviews. In a 2012 systematic review of disease activity measures sponsored by the American College of Rheumatology, more than 60 measurement instruments were identified. Through a five-stage process that included review by an expert advisory panel in RA disease activity and detailed evaluation of psychometric properties, the working group selected six measures that were most useful and feasible for point-of-care clinical care. These were the 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).

In another systematic review, Gaujoux-Viala et al compared four composite indices: the DAS, DAS28, SDAI, and CDAI. In general, the concordance between measures was good, with κ values in the range of 0.7. An exception to this level of concordance was in the definition of remission, for which the DAS28 had lower levels of concordance with other measures, with κ values ranging from 0.48 to 0.63. All measures had fair-to-good correlations with an independent health status measure, the Health Assessment Questionnaire, and with radiologic examination of joint structural damage.

Salaffi et al compared the responsiveness of numerous disease activity measures, including patient self-report measures and composite indices, over a six-month period of treatment with disease-modifying drugs. The composite indices evaluated were the DAS28, SDAI, CDAI, and the Mean Overall Index for RA. The patient-reported measures evaluated were the Clinical Arthritis Index, the Rheumatoid Disease Activity Index, RAPID3, and PAS. Across all measures, there was wide variability in internal responsiveness, with the highest value obtained for the DAS28 measure. There were differences in responsiveness between the measures, but all were considered suitable for use in clinical care. When comparing the patient-reported measures with the composite measures, there was no difference in internal or external responsiveness.

**Vectra DA Test**

The Vectra DA test consists of 12 individual biomarkers. They are:

- Interleukin-6
- Tumor necrosis factor receptor type I
- Vascular cell adhesion molecule 1
- Epidermal growth factor
- Vascular endothelial growth factor A
- YKL-40
- Matrix metalloproteinase 1
- Matrix metalloproteinase 3
- C-reactive protein
- Serum amyloid A
- Leptin
- Resistin.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The Vectra® DA test (Crescendo Bioscience, South San Francisco, CA) is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity
testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


20. Noridian Healthcare Solutions, LLC, (Jurisdiction - California - Entire State) Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35160), Revision Effective Date for services performed on or after 10/01/2015.