Protocol

Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis

(204119)

Medical Benefit		**Effective Date**: 01/01/17	**Next Review Date**: 09/20
Preauthorization	No	**Review Dates**: 09/16, 09/17, 09/18, 09/19	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With rheumatoid arthritis	Interventions of interest are: • Multibiomarker disease activity (e.g., Vectra DA) test an adjunct or as a replacement of other disease activity measures	Comparators of interest are: • Alternative disease activity measures (e.g., Disease Activity Score 28, Clinical Disease Activity Index, Patient Activity Scale)	Relevant outcomes include: • Test validity • Other test performance measures • Symptoms • Change in disease status • Functional outcomes • Quality of life

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 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 one (low disease activity) to 100 (high disease activity).

SUMMARY OF EVIDENCE

For individuals who have rheumatoid arthritis who receive a multibiomarker disease activity (e.g., 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 one 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. Addi-

tionally, 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

The use of a multibiomarker 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

Treatment of RA has undergone a shift from symptom management to a more proactive strategy of minimizing disease activity and delaying disease progression.[1] 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 seven studies that evaluated the efficacy of tight control.[2] Four of these trials randomized patients to tight control using treatment targets or to routine management, two studies compared different treatment targets, and one 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 four 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.[3] 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 five-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 six 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).[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 six 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[a]	No. of swollen joints out of 28[a]	Patient describes ability to do each of 20 activities[b] as "without any difficulty," "with some difficulty," "with much difficulty," or "unable to do"	Patient describes ability to do each of 10 activities[c] as "without any difficulty," "with some difficulty," "with much difficulty," or "unable to do"	Patient describes ability to do each of 13 activities[d] as "without any difficulty," "with some difficulty," "with much difficulty," or "unable to do"	• Interleukin-6 • Tumor necrosis factor receptor type I • Vascular cell adhesion molecule 1 • Epidermal growth factor • Vascular endothelial growth factor A • YKL-40 glycoprotein • MMP-1 • MMP-3 • C-reactive protein • Serum amyloid A • Leptin • Resistin
No. of tender joints out of 28[a]	No. of tender joints out of 28[a]	Patient indicates need for cane, crutches, walker, wheelchair, or devices to assist with dressing or eating	Patient rates pain on scale of zero (no pain) to 10 (severe pain)	Patient rates pain on scale of zero (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 zero (very well) to 10 (very poor)	Patient rates how they are doing on scale of zero (very well) to 10 (very poor)	

Recommended by ACR			No ACR Recommendation
CRP (mg/L)	Patient Global Assessment (zero [very well] to 10 [very poor])	Patient indicates if special devices needed in bathroom or kitchen	
Patient Global Assessment (zero [best] to 100 [worst])	Physician Global Assessment (zero [very well] to 10 [very poor])	Patient rates pain on scale of zero (no pain) to 10 (severe pain)	
		Patient rates how they are doing on scale of zero (very well) to 10 (very poor)	

Adapted by Anderson et al (2012).[4]

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.

[a] Twenty-eight joints: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees.

[b] 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 abovehead; 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 (e.g., vacuum or yard work).

[c] 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.

[d] 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 two 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.[7] 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 one 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
- one-29: low disease activity.

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.

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.

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