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Medical Policy Manual

Laboratory, Policy No. 67

Multi-biomarker Disease Activity Blood Test for Rheumatoid Arthritis

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The Vectra® test is a commercially available multi-biomarker disease activity blood test that measures 12 biomarkers to construct a disease activity score ranging from 0 to 100 for the assessment of disease activity in rheumatoid arthritis (RA).

MEDICAL POLICY CRITERIA

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

Rheumatoid arthritis (RA) is a disorder 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.

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 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 as evidence from clinical trials have demonstrated that outcomes are improved with a tight control strategy. In a tight control strategy, treatment targets are used that are mainly based on measures of disease activity. 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 have the disadvantage of being more cumbersome and difficult to complete. Patient reported measures are intended to be simpler and rely only on information that patients can provide expeditiously but have the disadvantage of being more subjective. Measurements that rely only on biomarkers are objective and do not require patient input but do involve the cost and inconvenience of laboratory tests.

The Disease Activity Score 28 (DAS28) is the most widely used and validated composite measure and includes examination of 28 joints for swelling and tenderness, combined with a patient report of disease activity and measurement of C-reactive protein (CRP) (or erythrocyte sedimentation rate). This score is often considered the criterion standard for measuring disease activity; however, it requires a thorough joint examination, information obtained from the patient, and laboratory testing. Therefore, there have been many attempts to create a valid disease activity measure that is simpler. Some measures include only patient self-report and thus can be completed quickly in the setting of an office visit. An example of this type of measure is the Simplified Disease Activity Index. Another approach is to use only serum biomarkers, which requires a blood draw, such as the Vectra® test. Proponents of a biomarker approach have argued that this is simpler and avoids the subjectivity of physical examination and patient report.

VECTRA® TEST

The Vectra® test (Labcorp, previously Myriad and Crescendo Bioscience) is a commercially available multibiomarker disease activity (MBDA) blood test that uses 12 biomarkers to construct a disease activity score ranging from 0 to 100. These biomarkers include:^[2]

- Interleukin-6 (IL-6)
- Tumor necrosis factor receptor type I (TNFRI)
- 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)
- Matrix metalloproteinase 3 (MMP-3)

- C-reactive protein (CRP)
- Serum amyloid A (SAA)
- Leptin
- Resistin

The Vectra® DA test scores range from 1 to 100. Categories of scores were constructed to correlate with the DAS28-C-reactive protein scale.

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

REGULATORY STATUS

There are no U.S. Food and Drug Administration (FDA)-approved MBDA tests for measuring disease activity in RA. Commercially available tests are laboratory-developed tests that are not subject to FDA approval. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

EVIDENCE SUMMARY

Validation of the clinical use of any prognostic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a disease marker of interest that is present or in excluding a disease marker that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes. The clinical utility of both positive and negative tests must be established.

This evidence review focuses on clinical validity and utility.

CLINICAL VALIDITY

The reference standard for disease activity is radiographic progression at a set point in time, typically three months to one year. In addition, an American College of Radiology (ACR) working group determined that the following 11 measures of disease activity fulfilled a minimum standard for regular use in most clinical settings:^[3] Disease Activity Score (DAS), Routine Assessment of Patient Index Data 3 (RAPID3), Routine Assessment of Patient Index Data 5 (RAPID5), Clinical Disease Activity Index (CDAI), Disease Activity Score with 28 joints (DAS28-ESR/CRP), Patient Derived DAS28, Hospital Universitario La Princesa Index (HUPI), the original and no longer commercially available Multibiomarker Disease Activity Score (MBDA score, Vectra® DA), Rheumatoid Arthritis Disease Activity Index (RADAI), Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5), and the Simplified Disease Activity Index (SDAI). Additionally, using a modified Delphi process, the ACR working group further identified the

following five measures as “preferred” for regular use in most clinic settings: the DAS28-ESR/CRP, CDAI, DSAI, RAPID3, and Patient Activity Scale-II.

Vectra® Test with “Adjusted MBDA Score”

Evidence on the evaluation of clinical validity of the current commercially available version of the Vectra® test (including the “adjusted MBDA score”) in patients with RA, consists of two retrospective cohort studies. A study by Curtis (2019)^[4] evaluated the clinical validity of the Vectra® test in predicting radiographic progression at one year using a convenience sample of combined data from 533 patients enrolled in either the Optimized Treatment in early Rheumatoid Arthritis (OPERA) randomized controlled trial,^[5] or the Brigham Rheumatoid Arthritis Sequential Study (BRASS) cohort study.^[6] The clinical validity of the Vectra® test was compared to that of the original Vectra® DA test and other measures of disease activity. MBDA scores were adjusted for age, sex, and either leptin levels or BMI, with scores ranging from 1 to 100. The thresholds for low-, moderate-, and high-risk groups were < 30, 30-44, and > 44, respectively. Among the various disease activity measures assessed, only the new Vectra® test with the leptin-adjusted score (relative risk [RR] 8.38, 95% confidence interval [CI] 1.15 to 60.8), the original Vectra® DA test (RR 5.39, 95% CI 1.3 to 22.29) and CRP (RR 4.15, 95% CI 1.58 to 10.95) significantly differentiated between the risk of radiographic progression for the high-risk groups versus the low-risk groups.

Based on these outcomes, the study authors concluded that the new Vectra® test (“adjusted MBDA score”) may offer “improved clinical utility” over the original and not commercially available Vectra® DA test. Although the overlapping confidence intervals suggest at least similar prognostic performance to other DA measures, they indicate uncertainty as to whether Vectra® provides prognostic performance superior to the original Vectra® DA or CRP. Additionally, the low proportions of patients with radiographic progression in the moderate to high-risk patient groups (3.9% to 9.3% for the new Vectra® test and 3.5% to 9.7% for the original Vectra® DA test group) do not support the use of the test to “rule in” moderate- to high-risk disease. These low rates of patients with radiographic progression in the moderate to high-risk patient groups suggest that 9 out of 10 patients identified as moderate or high risk could receive intensification of therapy unnecessarily. Likely this is due at least in part to the fact that the overall prevalence of radiographic progression was notably low in this study cohort (6.3%). Although the results from this study are initially supportive of the Vectra® test’s ability to predict radiographic progression at one year, its numerous relevance, design and conduct limitations provide an insufficient basis to conclude the clinical validity of the Vectra® test. For example, it is unclear if the low risk for clinical progression population represents the patients for whom the test would be intended, and the rationale for selecting the definition of radiographic progression in the study was not provided. Additionally, the study used a convenience sample that lacked randomization.

Updated clinical validity data on the Vectra® test with an adjusted MBDA score was published by Curtis (2021) and used combined data from 953 patients enrolled in the OPERA, BRASS, Leiden Early Arthritis Clinic (EAC), and SWEFOT (Swedish Farmaco-therapy) cohorts.^[7] The adjusted MBDA score was validated in the Leiden and SWEFOT cohorts and compared with conventional disease activity measures across all four cohorts. Among the various baseline disease activity measures, only the adjusted MBDA score (odds ratio [OR] 1.05, 95% CI 1.03 to 1.06), seropositivity (OR 6.20, 95% CI 2.90 to 16.1), CRP (OR 1.57, 95% CI 1.29 to 1.91), baseline joint damage (total Shape score [TSS]) (OR 1.01; 95% CI 1.00 to 1.01), and DAS28-CRP (OR 1.24, 95% CI 1.05 to 1.46) were significantly predictive of radiographic progression.

Risk ratios (95% CI) for change in TSS > 5 units were 2.62 (0.59 to 11.6, $p=0.24$) and 9.37 (2.34 to 37.5, $p=2.65 \times 10^{-6}$) in the moderate and high adjusted MBDA score categories compared to the low category. The risk ratio was 4.47 (2.54 to 7.87, $p=5.26 \times 10^{-10}$) for the high category compared to combined low and moderate categories. Adjusted MBDA scores from the combined cohorts were cross-classified with conventional disease activity measures to evaluate discordances. The frequency of radiographic progression was low when the adjusted MBDA score was low and highest when high regardless of DAS28-CRP, CRP, swollen joint count, and CDAI score categories. These trends were not observed within conventional disease activity measures. However, while individual analysis of the four cohorts with cross-classification by DAS28-CRP and adjusted MBDA score were generally consistent with these trends, they should be interpreted with caution due to the limited number of progressors. Overall, the frequency of radiographic progression corresponded more consistently with the category of adjusted MBDA score than the category of DAS28-CRP, CRP, swollen joint count, or CDAI scores. Bivariable logistic regression analysis identified the adjusted MBDA score as the strongest single, independent predictor of radiographic progression. A risk curve for radiographic progression for change in TSS > 5 was generated for the adjusted MBDA score. While the risk of radiographic progression exceeded 40% at the highest adjusted MBDA score in the model, at the high-risk cutoff score (> 44) the risk of radiographic progression is less than 10%. While the Leiden and SWEFOT cohorts contributed a higher proportion of patients with radiographic progression in the moderate and high-risk groups, there continues to be insufficient support for the use of the test to “rule in” moderate- to high-risk disease. Furthermore, given the high prevalence of discordant results across conventional disease activity measures, the position of the adjusted MBDA score in the clinical management pathway is unclear.

Original Vectra® DA Test

Numerous studies of the validity of the original Vectra® DA test (not commercially available) have been conducted based on records and archived samples from randomized controlled trials and cohorts.^[8-19] Although the Original Vectra® DA test is no longer commercially available, for historical purposes, here we will provide a summary of the key findings from these studies.

The majority of the studies of the original Vectra® DA have been previously summarized in four recent systematic reviews and pooled analyses.^[3, 20-22] Overall, findings from the most comprehensive and rigorous review, published by Johnson (2019), indicated that although the original Vectra® DA test has shown a positive correlation with other disease activity measures, results from studies comparing MBDA with radiographic progression are inconsistent.

Meznerics (2023) conducted the most recent systematic review with meta-analysis of 32 studies evaluating the MBDA score as an objective tool for monitoring RA. The number of studies that specifically used the Vectra® DA test was not mentioned by the authors. Analysis of six studies demonstrated a moderate correlation between baseline MBDA score and baseline DAS28-CRP (r 0.45, 95% CI 0.28 to 0.59). Similarly, analysis of two studies demonstrated a moderate correlation between baseline MBDA score and baseline DAS28-ESR (r 0.55, 95% CI 0.19 to 0.78). Analysis of six studies demonstrated a moderate correlation between follow-up MBDA score and follow-up DAS28-CRP (r 0.44, 95% CI 0.28 to 0.57). Analysis of a single study demonstrated a moderate correlation between follow-up MBDA score and follow-up DAS28-ESR (r 0.49, 95% CI 0.22 to 0.69). Among 10 studies, a moderate correlation was identified between change in MBDA score and change in DAS28-CRP (r 0.40,

95% CI 0.32 to 0.48). Similarly, based on seven studies, a moderate correlation was observed between change in MBDA score and change in DAS28-ESR (r 0.56, 95% CI 0.51 to 0.60). Finally, data from three studies demonstrated a higher likelihood of radiographic progression in patients with high as compared to low MBDS score (> 44 vs. < 30) (OR 1.03, 95% CI 1.02 to 1.05). The authors acknowledged the following limitations of their study: heterogeneity across study populations, inclusion of a wide range of anti-rheumatic drugs across studies, and varying follow-up times for assessment of disease activity.^[22]

The most comprehensive review was conducted by Johnson (2019), which reported on the results of a systematic review of 22 studies of the clinical validity of the original Vectra® DA test.^[20] Among those, nine studies evaluated the ability of the original Vectra® DA to predict radiographic progression. Studies were highly heterogeneous in their radiographic progression thresholds and definitions, analytic methods, and results. For example, for the comparison of patients with a Vectra® DA high-risk score versus patients with Vectra® DA low-risk scores, the range of relative risks of radiographic progression was 1.04 to 14.30 and these were significant in only six studies. Additionally, results of eight studies that reported correlations of Vectra® DA with other RA disease activity measures were included in a meta-analysis ($n=3,242$). The original Vectra® DA test demonstrated modest correlations with the DAS28-CRP (correlation coefficient [r] 0.41, 95% CI 0.36 to 0.46) and the DAS28-ESR (r 0.48, 95% CI 0.38 to 0.58). It demonstrated weaker correlations with the SDAI (r 0.35, 95% CI 0.26 to 0.43), CDAI (r 0.26, 95% CI 0.19 to 0.33), and RAPID3 (r 0.23, 95% CI 0.19 to 0.27). Systematic review authors expressed concern that inadequate information about sample handling prevented them from ruling out the potential confounding effects of biased biomarker measurement due to variation in collection, processing, and storage of serum samples. The authors concluded that the findings need further validation in light of the high level of variability in methods and results.

England (2019) detailed the results of an American College of Rheumatology working group's systematic review of the psychometric properties of 46 RA disease activity measurement tools.^[3] The objective of this ACR review was to determine which measures of disease activity fulfilled a minimum standard for regular use in most clinical settings. The ACR's definition of minimum standard was: (1) that the tool provided a numerical value, (2) categorized to greater than or equal to three disease states that separate low, moderate, and high disease activity, (3) was feasible for regular measurement in the clinic, and (4) possessed adequate psychometric properties. The ACR defined the adequacy of psychometric properties as having a level of evidence that suggested at least moderate positive results in hypothesis testing plus one of the following: (a) level of evidence suggesting at least moderate positive results in at least one of the following additional areas: internal consistency, reliability, measurement error, content validity, structural validity, or responsiveness; (b) level of evidence suggesting at least limited positive results in at least two of those additional areas (one of which must be responsiveness), or, (c) a defined minimum important difference/minimum clinically important difference. The ACR systematic review included 14 studies of the original version of the MBDA test, Vectra® DA, that were published between 2012 and 2016. The review by England (2019) provided data abstraction of performance characteristic results from the individual studies but did not draw any conclusions about specific clinical validity measures. Based on an overall qualitative assessment of the findings, including correlations and associations to other DA measures and radiographic progression, the ACR workgroup concluded that the original Vectra® DA met their criteria for a moderate level of hypothesis testing, based on consistent findings in multiple studies of fair methodologic quality.

Finally, Curtis (2019) conducted a pooled analysis on data from studies of Vectra® DA and radiographic progression.^[21] To be included in the analysis, the cohort studies needed to have patient-level data, more than 100 patients, and the following measures: Vectra® DA scores (low/moderate/high: < 30, 30-44, > 44), DAS28-CRP (low/moderate/high: < 2.67, > 2.67 to 4.09, > 4.09), and CRP (low/moderate/high: < 10, > 10 to 30, > 30 mg/L). Four studies containing five cohorts (n=929 patients) were included in the analysis. Relative risks for radiographic progression at one year for each of the measures were calculated based on high versus not high (low and moderate combined) categories. Of the three measures, Vectra® DA scores best predicted radiographic progression, with a relative risk of 4.6 (95% CI 2.4 to 8.9, p<0.0001), though DAS28-CRP and CRP alone also reliably predicted radiographic progression, with a relative risk of 1.7 (95% CI 1.1 to 2.6, p=0.02) and 1.7 (95% CI 1.2 to 2.4, p=0.002), respectively. Additionally, findings were also mixed across studies published subsequent to the above-described systematic reviews and pooled analyses.^[5, 15, 19, 23] For example, in a post hoc analysis of three cohort studies by Roodenrijs (2018) of 57 RA patients treated with rituximab 1000 mg and methylprednisolone 200 mg, among those with an original Vectra® DA score of low, moderate and high MBDA scores, radiographic progression (change in SHS ≥ 5) was observed in 0 (0%), 0 (0%) and 5 (56%) patients, respectively.^[19] Additionally, change in the original Vectra® DA score from baseline to six months was significantly associated with European League Against Rheumatism (EULAR) response (good or moderate) versus non-response at six months (OR 0.93, 95% CI 0.88 to 0.98) per unit change). This association remained statistically significant even after adjustment by age, gender, smoking status, rheumatoid factor (RF) status, autoantibodies against citrullinated peptides (ACPA) status (OR 0.89, 95% CI 0.81 to 0.98 per unit change). However, in contrast, in the Dose REduction Strategies of Subcutaneous TNF Inhibitors trial (DRESS) RCT by Bouman (2017),^[15] among 167 randomized, radiographic progression occurred in 31% in the dose tapering group and in 16% in the usual care group and the original Vectra® DA score was not predictive of successful tapering, flare occurrence, or radiographic progression.

Section Summary

Evidence regarding the clinical validity of the Vectra® DA test consisted of studies that correlated the score with other measures of disease activity, including the DAS28, and have shown that Vectra® may be predictive of radiographic progression at one year. However, its low positive predictive value (PPV) (4.4% to 15.8%) indicates that 9 out of 10 patients identified as moderate- to high-risk disease could unnecessarily receive intensification of therapy. Additionally, studies were limited by retrospective study design, small patient populations that were underpowered, or were post-hoc analysis of RCTs with methodological shortcomings. Without large, well-designed prospective clinical trials, conclusion regarding the diagnostic performance of the Vectra® DA test cannot be reached.

CLINICAL UTILITY

To demonstrate clinical utility, there should be evidence that the Vectra® score is at least as good a measure of disease activity as other available measures or that the Vectra® score demonstrates an incremental benefit when used as an adjunct with other disease activity measures. An RCT that compared a management strategy using Vectra® score with an alternate management strategy, and that reported clinical outcomes such as symptoms, functional status, quality of life, or disease progression on radiologic imaging may demonstrate the clinical utility of the Vectra® score. No RCTs were identified. Indirect measures of clinical utility could be obtained from high-quality evidence that clinical validity of the Vectra® score is

equivalent to other measures used in clinical care, together with guidance on the optimal use of the score in decision making, (i.e., evidence linking management changes to specific results on the Vectra® score). No studies of the current commercially available Vectra® test ("updated MBDA score") were identified. Below is a retrospective study conducted that evaluated the original Vectra® DA test and medication use among patients with RA.

Curtis (2019) used Medicare data from 2011 to 2015 to study MBDA scores and biologic and Janus kinase inhibitors use among patients with RA.^[24] The database contained 60,596 patients with RA who had MBDA testing results. Among patients not currently taking biologics (n=33,728), statistically significant differences in adding or switching medications were detected based on MBDA scores: 9.0% of patients with low scores, 11.8% with moderate scores, and 19.7% with high scores. Similarly, among patients currently taking biologics, statistically significant differences in switching medications were detected among the different levels of MBDA scores: 5.2% of patients with low scores, 8.3% with moderate scores, and 13.5% with high scores.

Section Summary

The available evidence regarding the impact of the Vectra® score upon treatment decisions is limited. There are no RCTs that compare use of the Vectra® test with the "adjusted MBDA score" or the original Vectra® DA test to an alternative method of measuring disease activity. Additionally, there are no RCTs of Vectra® or Vectra® DA as an adjunct to other disease activity measures compared with using the disease activity measures alone. There is insufficient evidence to determine whether the Vectra® test is as efficient as other more established disease activity measures in improving outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF RHEUMATOLOGY

In its 2019 consensus guidelines on the treatment of rheumatoid arthritis, the American College of Rheumatology identified the following 11 measures of disease activity as fulfilling a minimum standard for regular use in most clinical settings:^[3] Patient Activity Scale, Disease Activity Score (DAS), Routine Assessment of Patient Index Data 3 (RAPID3), Routine Assessment of Patient Index Data 5 (RAPID5), Clinical Disease Activity Index (CDAI), Disease Activity Score with 28 joints (DAS28-ESR/CRP), Patient Derived DAS28, Hospital Universitario La Princesa Index (HUPI), Multibiomarker Disease Activity Score (MBDA score, Vectra® DA), Rheumatoid Arthritis Disease Activity Index (RADAI), Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5), and Simplified Disease Activity Index (SDAI). Although the original Vectra® DA test is included in this list, the current commercially available version of the test that is now called Vectra® and that includes the leptin-adjusted MBDA score (now called the "adjusted MBDA score"), was not addressed in the 2019 ACR guideline. This is because evidence on Vectra® with the adjusted MBDA score was published after the ACR review end date.

SUMMARY

There is not enough research to show how the Vectra® DA test changes clinical management or improves health outcomes in patients with rheumatoid arthritis. In addition, no evidence-based clinical practice guidelines recommend the Vectra® DA test. Therefore, the Vectra® DA test is considered investigational for use as a measure of disease activity in

the patients with rheumatoid arthritis.

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CODES

Codes	Number	Description
CPT	81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method; quantitative, not otherwise specified

84999	Unlisted chemistry procedure
86140	C-reactive protein
HCPCS	None

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