
Medical Policy



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Title: Multi-Biomarker Disease Activity (MBDA) Laboratory Testing (e.g., Vectra DA Blood Test) for Rheumatoid Arthritis

Description/Background

RHEUMATOID ARTHRITIS

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 for affected patients.¹

Treatment

Treatment of RA has undergone a shift from symptom management to a more proactive strategy of reducing disease activity and delaying disease progression.² 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. In a systematic review published in 2010, Schoels et al (2010) identified 7 trials that evaluated the efficacy of tight control.³ Four of these trials randomized patients to either a tight control using treatment targets or 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 4 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.

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.

Selection of Disease Activity Assessment Tools

For a strategy of tight control to be successful, a reliable and valid measurement of disease activity is important. Numerous measurements exist that assess various aspects of RA disease activity, including patient self-report of symptom severity and functional capacity, physician examination of joints for swelling and tenderness, laboratory testing of serum biomarkers, and imaging. Various assessment tools exist that range from those that rely only on single types of measurements, to composite tools that combine information from multiple measurement sources. These assessment tools vary in their psychometric properties and their feasibility of implementation and these trade-offs must be considered in their selection for use. For example, although composite tools are more comprehensive, in some cases they may be less feasible for regular use.

Based on a systematic review (2019) of the psychometric properties of 46 tools,⁵ an ACR working group determined that the following 11 measures of disease activity fulfilled a minimum standard for regular use in most clinical settings: 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 the Simplified Disease Activity Index (SDAI). Additionally, using a modified Delphi process, the ACR working group further identified the following 5 measures as “preferred” for regular use in most clinic settings: the DAS28-ESR/CRP, CDAI, DSAI, RAPID3, and Patient Activity Scale-II.

Vectra DA Test

The Vectra Test is a commercially available multibiomarker disease activity (MBDA) test that is an approach to measuring RA disease activity that uses only serum biomarkers obtained through a laboratory blood draw. The manufacturer describes Vectra as a complement to clinical judgment.⁶ 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 test measures the serum concentrations of the following 12 biomarkers: 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), and Matrix Metalloproteinase 3 (MMP-3), C-reactive protein (CRP), Serum Amyloid A (SAA), Leptin, and Resistin. The concentrations of these 12 biomarkers are measured in serum and, combined with age, gender and adiposity (i.e., leptin) information, are entered in a proprietary formula to generate a score on a scale of 1 to 100 that represents the level of RA disease activity:⁷

The Vectra DA test scores range from 1 to 100. Categories of scores were constructed to correlate with the DAS28-C-reactive protein scale.^{6,8}

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

Prior to December 2017, the Vectra test was originally referred to as Vectra DA and the original MBDA score did not include adiposity (i.e., leptin) adjustment.⁹ However, as the current, commercially available version of the test includes the leptin-adjusted MBDA score (now called the "adjusted MBDA score"),⁷ the focus of this policy will primarily be on the leptin-adjusted Vectra test.

In the ACR working group's systematic review reported by England et al (2019),⁵ they also graded feasibility of the RA disease activity measurement tools. Any measure not commercially available or requiring advanced imaging was graded as infeasible. All other measures started with 4 points (i.e., "++++") and were downgraded by 1-point for each of the following implementation considerations: requiring a provider joint count, requiring a laboratory test, not possible to complete during a routine clinic visit, not possible to complete on the same day as the clinic visit. The ACR Working Group downgraded the feasibility of the Vectra DA by 3 points (i.e., score of "++++" decreased to "+"). This was due to its requirement of a laboratory test and because its result is not available on the same day as the clinic visit. Although the current, commercially available version of the Vectra test was not assessed in the 2019 ACR guideline, because it requires the same laboratory testing that is not available on the same days as the clinic visit, likely it would have a similar feasibility rating as the older version.

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.

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[®] 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.

Medical Policy Statement

The use of a multi-biomarker disease activity score for rheumatoid arthritis (RA) (e.g., Vectra DA score) is considered experimental/investigational in all situations. There is insufficient documentation in medical literature to determine whether this testing is as good as or better

than other measures of disease activity, and its clinical utility for improving patient clinical outcomes has not been proven.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81490

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

MULTIBIOMARKER DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS

Clinical Context and Test Purpose

The purpose of the MBDA, specifically the Vectra DA, in individuals who have rheumatoid arthritis is to determine the level of disease activity (low, medium, or high), which will inform treatment decisions.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with RA who are being managed with a disease-modifying antirheumatic drug (DMARD).

Management of patients with RA has changed from treatment of symptoms to a tight control strategy. The objective of a tight control strategy is to minimize disease progression and joint damage by monitoring disease activity and treating aggressively if an increase in activity is predicted.

Interventions

Vectra DA is a blood test that includes the following 12 biomarkers: 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, and resistin.

Scores range from 1-100 (1-29=low disease activity; 30-44=medium disease activity; and 45-100=high disease activity).

Comparators

The reference standard for disease activity is radiographic progression at a set point in time, typically 3 months to 1 year. In addition, an ACR expert panel on RA determined the following 6 disease activity measures were useful and feasible to implement in a clinical setting: Clinical Disease Activity Index (CDAI), Disease Activity Score with 28 joints (DAS28), Patient Activity Scale, Patient Activity Scale II, Routine Assessment of Patient Index Data 3, and Simplified Disease Activity Index.

Outcomes

The general outcomes of interest within RA are to improve quality of life and to prevent progression of the disease. Progression of disease causes irreversible joint damage.

If Vectra DA correctly assesses disease activity as low, the clinician may maintain medications at the same level or consider tapering the patient's medication.

If Vectra DA correctly assesses disease activity as moderate or high, the clinician may be more aggressive in disease management, by either increasing doses of current medications, switching medications, or adding medications to the treatment plan.

If Vectra DA incorrectly assesses disease activity as low, the clinician may maintain or decrease medication levels, which will allow progression of the disease and further joint damage.

If Vectra DA incorrectly assesses disease activity as moderate or high, the clinician may continue to manage the patient with higher levels of medication than is necessary to prevent disease progression, exposing the patient to unnecessary toxins. DMARDs may affect the liver, stomach, and intestines. Biologic agents may increase the risk of infection, lymphoma, and skin cancer.

The test may be run as often as the clinician needs disease activity information, typically every 3 to 6 months. A test immediately after diagnosis may serve as a baseline measurement.

For purposes of assessing Vectra DA against the reference standard of radiographic progression, 1 year is the typical time frame.

Study Selection Criteria

For the evaluation of the clinical utility of a multibiomarker disease activity test (e.g., Vectra DA), studies would need to use the test as either an adjunct or a replacement to current

disease activity measures to manage treatment decisions in patients with RA. Outcomes would be quality of life and measures of disease progression.

In the absence of direct evidence for the clinical utility of Vectra DA, evidence for clinical validity is evaluated, in which we can make inferences on clinical utility. For the evaluation of clinical validity, studies would need to compare Vectra DA used as an adjunct or as a replacement to ACR-recommended disease activity measures, with radiographic progression as a reference standard. Key validity outcomes of sensitivity, specificity, as well as positive (PPV) and negative (NPV) predictive values, should be reported.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Meznerics et al (2023) conducted a systematic review with meta-analysis evaluating the MBDA score as an objective tool for monitoring RA.¹⁰ The number of included studies that specifically used the Vectra test was not mentioned by the authors. An analysis of 6 studies (N=667) demonstrated a moderate correlation between baseline MBDA score and baseline DAS28-CRP (correlation, 0.45; 95% confidence interval [CI], 0.28 to 0.59). Similarly, an analysis of 2 studies (N=127) demonstrated a moderate correlation between baseline MBDA score and baseline DAS28-ESR (correlation, 0.55; 95% CI, 0.19 to 0.78). With regard to follow-up scores, an analysis of 6 studies (N=287) demonstrated a moderate correlation between follow-up MBDA score and follow-up DAS28-CRP (correlation, 0.44; 95% CI, 0.28 to 0.57). Only one study was included in an analysis investigating the correlation between follow-up MBDA score and follow-up DAS28-ESR; a moderate correlation was found (correlation, 0.49; 95% CI, 0.22 to 0.69). Additionally, based on 10 studies (N=698), a moderate correlation was identified between change in MBDA score and change in DAS-CRP (correlation, 0.40; 95% CI, 0.32 to 0.48); similarly, based on 7 studies (N=543), a moderate correlation was identified between change in MBDA score and change in DAS-ESR (correlation, 0.56; 95% CI, 0.51 to 0.60). Lastly, data from 3 studies (N=481) demonstrated a higher likelihood of radiographic progression in patients with a high as compared to a low MBDS score (>44 vs. <30) (OR, 1.03; 95% CI, 1.02 to 1.05).

Vectra Test with Adjusted Multibiomarker Disease Activity Score (MBDA)

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 1 retrospective cohort study (Table 1).^{9,11} This study by Curtis et al (2018) evaluated the clinical validity of the Vectra test in predicting radiographic progression at 1 year using a convenience sample of combined data from 533 patients enrolled in either the Optimized Treatment in early Rheumatoid Arthritis (OPERA) randomized controlled trial¹² or the Brigham Rheumatoid Arthritis Sequential Study (BRASS) cohort study.¹³ The clinical validity of the Vectra test was compared to that of the original Vectra DA test and other measures of DA (Table 2). Among the various disease activity measures assessed, only the new Vectra test (RR 8.38; 95% 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 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 by Curtis et al (2018) are initially supportive of the Vectra test’s ability to predict radiographic progression at 1 year, its numerous relevance, design and conduct limitations (Tables 3 and 4) provide an insufficient basis to conclude the clinical validity of the Vectra test.

In 2021, updated clinical validity data on the Vectra test with an adjusted MBDA score was published by Curtis and coworkers using combined data from 953 patients enrolled in the OPERA, BRASS, Leiden Early Arthritis Clinic (EAC), and SWEFOT (Swedish Farmacotherapy) cohorts.¹¹ The adjusted MBDA score was validated in the Leiden and SWEFOT cohorts and compared with conventional disease activity measures across all 4 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 = .24) and 9.37 (2.34 to 37.5; p = 2.65 x 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 x 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 4 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. Study relevance, design, and conduct limitations are summarized in Tables 3 and 4.

Table 1. Characteristics of Vectra Adjusted Multibiomarker Disease Activity Score Clinical Validity Studies

Study	Study Population	Design	Outcome Measure	Threshold(s) for Risk Categories of Index Test	Timing of Enrollment with respect to course of disease	Blinding of Assessors	Comment
Curtis et al (2019) ⁹ .	OPERA, BRASS cohorts	Retrospective cohorts with convenience samples	RP (mTSS >5 units) at 1 y	Low (<30), moderate (30-44), and high (>44)	OPERA: RA <6 months BRASS: mean disease duration, 13.82 y	OPERA: Yes BRASS: No	OPERA involved treatment-naïve patients randomized to MTX plus placebo or MTX plus adalimumab; BRASS: large, single-center, prospective and observational cohort recruited from the practices of rheumatologists; Hand and wrist radiographs only were adjusted by a factor of 1.6 to equal mTSS for all joints; DMARD therapy Combined cohort included 555 (92%) of 604 with “suitable radiographic data”
Curtis et al (2021) ¹¹ .	OPERA, BRASS, Leiden EAC, SWEFOT cohorts	Retrospective cohorts with convenience samples	RP (mTSS >5 units) at 1 y	Low (<30), moderate (30-44), and high (>44)	OPERA, BRASS: see above SWEFOT: RA <12 months Leiden: mean disease duration, 4.6 y	OPERA, BRASS: see above SWEFOT: No Leiden: Yes	SWEFOT: open-label, multicenter trial comparing conventional DMARD combination therapy to MTX + anti-TNF in patients with <1 year symptom duration and inadequate response to MTX Leiden: population-based, single-

										center, prospective cohort with symptom duration <2 years at enrollment; Non-biologic and biologic DMARD therapy
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BRASS: Brigham Rheumatoid Arthritis Sequential Study; DMARD: disease-modifying anti-rheumatic drugs; EAC: Early Arthritis Clinic; mTSS: maximal modified total Sharp score; MTX: methotrexate; OPERA: Optimized Treatment in Early Rheumatoid Arthritis; RA: rheumatoid arthritis; RP: radiographic progression; SWEFOT: Swedish Farmaco-therapy Trial; TNF: tumor necrosis factor

Table 2. Results of Vectra Adjusted Multibiomarker Disease Activity Score Clinical Validity Studies

Study	Initial N	Final N	Excluded Samples	RP Prevalence	Study Population in Risk Group, n (%)			Clinical Validity: Proportion of Patients with RP, % (95% CI)		
					Low Risk	Intermediate Risk	High Risk	Low Risk	Intermediate Risk	High Risk
Curtis et al (2019) ⁹ .	604	533	49 (9%) initially excluded for “unsuitable” samples; 22 (4%) excluded for unspecified reasons	6.3%						
Vectra (adjusted MBDA score)					90 (16.9%)	153 (28.7%)	290 (54.4%)	1.1% (0% to 6.0%)	3.9% (1.5% to 8.3%)	9.3% (6.2% to 13.3%)
Original Vectra DA (unadjusted, not commercially available)					111 (20.8%)	144 (27.0%)	278 (52.2%)	1.8% (0.2% to 6.4%)	3.5% (1.1% to 7.9%)	9.7% (6.5% to 13.8%)
Curtis et al (2021) ¹¹ .										
Leiden	163	NR	NR	17.2%	25 (15.3%)	59 (36.2%)	79 (48.5%)	1/25 (4.0%)	4/59 (6.8%)	23/79 (29.1%)
SWEFOT	235	NR	NR	18.3%	3 (1.3%)	27 (11.5%)	205 (87.2%)	0/3 (0%)	1/27 (3.7%)	42/205 (20.5%)
OPERA	154	NR	NR	8.4%	4 (2.6%)	18 (11.7%)	132 (85.7%)	0/4 (0%)	0/18 (0%)	13/132 (9.9%)
BRASS	401	NR	NR	5.2%	87 (21.7%)	146 (36.4%)	168 (41.9%)	1/87 (1.2%)	6/146 (4.1%)	14/168 (8.3%)

Combined	953	NR	NR	11.0%	119 (12.5%)	250 (26.2%)	584 (61.3%)	1.7% (NR)	4.4% (NR)	15.8% (NR)
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BRASS: Brigham Rheumatoid Arthritis Sequential Study; CI: confidence interval; MBDA: multibiomarker disease activity; NR: not reported; OPERA: Optimized Treatment in Early Rheumatoid Arthritis; RP: radiographic progression; SWEFOT: Swedish Farmacotherapy Trial.

Table 3. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Curtis et al (2019) ⁹ .	2. Position in clinical pathway unclear; 4. Unclear if population with low-risk of clinical progression is representative of intended use	3. Not consistent with current use, which is as an adjunct to other disease activity measures		3. Rationale for selecting radiographic progression definition not provided	
Curtis et al (2021) ¹¹ .	2. Position in clinical pathway unclear; 4. Unclear if population with low-risk of clinical progression is representative of intended use	3. Unclear how discordant test results impact use of test as an adjunct to other disease activity measures		3. Rationale for selecting radiographic progression definition not provided	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest (e.g., older version of test, not applied as intended).

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (see template Results tables; 4. Reclassification of diagnostic or prognostic risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 4. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Curtis et al (2019) ⁹ .	2. Selection not random or consecutive (ie, convenience)	1. Not blinded to results of reference or other comparator tests in some patients				
Curtis et al (2021) ¹¹ .	2. Selection not random or consecutive (ie, convenience)	1. Not blinded to results of reference or other comparator tests in some patients				1. Incomplete reporting of confidence intervals.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss

to follow-up or missing data.

[†] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported; 3: Insufficient consideration of potential confounding.

Original Vectra DA Test (not commercially available)

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.¹⁴⁻²⁶ 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 3 recent systematic reviews and pooled analyses.²⁷⁻²⁸ Overall, findings from the most comprehensive and rigorous review (Johnson et al, 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.

The most comprehensive review was conducted by Johnson et al (2019),²⁷ which reported on the results of a systematic review of 22 studies of the clinical validity of the original Vectra DA test. Among those, 9 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 were significant in only 6 studies. Additionally, results of 8 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 ($r = 0.41$; 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.

The second most comprehensive systematic review was reported by England et al (2019), which 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.⁵ 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 ≥ 3 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 1 of the following: (a) level of evidence suggesting at least moderate positive results in at least 1 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 2 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 et al (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 et al (2019) conducted a pooled analysis on data from studies of Vectra DA and radiographic progression.²⁸ 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 5 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 vs not high (low and moderate combined) categories. Of the 3 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 3 studies published subsequent to the above-described systematic review and pooled analyses.^{12,20,26} For example, in a post hoc analysis of 3 cohort studies by Roodenrijs et al (2018)²⁶ 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. Additionally, change in the original Vectra DA score from baseline to 6 months was significantly associated with European League Against Rheumatism (EULAR) response (good or moderate) versus non-response at 6 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 et al (2017),²⁰ among 167 randomized, RP 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 RP.

Section Summary: Clinically Valid

Evidence for the clinical validity of the current commercially available version of the Vectra test (including the “adjusted MBDA score”) in patients with RA, consists of 1 retrospective cohort study that correlated it with other measures of disease activity and with radiographic progression. Results from this study have shown a positive correlation between Vectra and other disease activity measures and have shown that Vectra may be predictive of radiographic progression at 1 year. However, its low PPV (3.9% to 9.3%) indicates that 9 out of 10 patients identified as moderate- to high-risk disease could unnecessarily receive intensification of therapy. Additionally, the study’s numerous relevance, design and conduct limitations provide an insufficient basis to conclude the clinical validity of the Vectra test.

Evidence for the clinical validity of the original Vectra DA test consists of analyses of archived serum samples from RCTs as well as prospective cohort studies that have correlated the original Vectra DA with other measures of disease activity and with radiographic progression. Results from studies comparing the original Vectra DA with other disease activity measures have shown a positive correlation; however, results from studies comparing the original Vectra DA with radiographic progression are inconsistent. Only 1 study reported sensitivity and specificity, with a PPV of 21%, indicating that 4 out of 5 patients identified as positive would receive intensification of therapy unnecessarily.

Currently, MBDA is used as an adjunct to other disease activity measures. No evidence was identified that evaluated the incremental benefit of MBDA when used as an adjunct to other disease activity measures.

Overall, the evidence is insufficient to conclude the clinical validity of Vectra compared with ACR-recommended measures of disease activity.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

To demonstrate clinical utility, there should be evidence that the MBDA score is at least as good a measure of disease activity as other available measures or that the MBDA score demonstrates an incremental benefit when used as an adjunct with other disease activity measures. To demonstrate equivalence with other measures directly, an RCT comparing health outcomes of 2 groups, 1 group managed using the Vectra DA test and the other group managed by another disease activity measure is needed.

To directly demonstrate an incremental benefit when used as an adjunct, an RCT should compare health outcomes in patients receiving treatment guided by MBDA plus a disease activity measure with outcomes in patients receiving treatment guided only by the other disease activity measure.

Curtis et al (2018) used Medicare data from 2011 to 2015 to study MBDA scores and biologic and Janus kinase inhibitors use among patients with RA.²⁹ The database contained 60596 patients with RA who had MBDA testing results. Among patients not currently taking biologics (n=33728), 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.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because there is insufficient evidence that the MBDA score is clinically valid, direct evidence is needed to prove clinical utility. No trials were identified that provided direct evidence of clinical utility.

Section Summary: Clinically Useful

There are no RCTs comparing the use of the Vectra DA score with an alternative method of measuring disease activity. Additionally, there are no RCTs of Vectra DA as an adjunct to other disease activity measures compared with using the disease activity measures alone. Absent direct evidence for clinical utility, a chain of evidence could be constructed with indirect evidence proving clinical validity. However, there is insufficient evidence that MBDA is clinically valid.

SUMMARY OF EVIDENCE

For individuals who have RA who receive the current commercially available Vectra test ("adjusted MBDA score") as an adjunct or as a replacement of other disease activity measures, the evidence includes 1 study that analyzed archived serum samples using combined data from an RCT and a cohort study. Relevant outcomes are test validity, other test performance measures, symptoms, change in disease status, functional outcomes, and quality of life. Analyses comparing Vectra with other previously validated disease activity measures such as the DAS28 or to radiographic progression, consisted mostly of correlations. However, the PPV's that individuals with Vectra moderate- to high-risk disease scores had radiographic progression were low, at 3.9% and 9.3%, respectively. Additionally, due to numerous relevance, design and conduct limitations of this study, the body of evidence on the Vectra 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 as an adjunct to other disease activity measures. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have RA who receive the original 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 PPV and NPV. The PPV 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.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Rheumatology (ACR)

In its 2019 guidelines recommended for rheumatoid arthritis disease activity measures, the American College of Rheumatology⁵ identified the following 11 measures of disease activity as fulfilling a minimum standard for regular use in most clinical settings: 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), 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 subsequent to the ACR review end date.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2018) and updated in 2020 published guidance on the management of adult patients with rheumatoid arthritis.³⁰ There is no discussion on the use of a multibiomarker disease activity blood test to monitor patients with rheumatoid arthritis.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Currently ongoing trials that might influence this review is listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02832297 ^a	Prospective outcomes study: Vectra® guided care compared to usual care	318	Aug 2022
MCT03810144 ^a	Impact of Guided Care with the Vectra DA Multi-Biomarker Disease Activity (MBDA) Blood Test on Clinical Outcomes and Pharmaceutical Utilization in Patients with Rheumatoid Arthritis: a Prospective Randomized Study	500	Oct 2022
NCT03631225 ^a	Prospective Randomized Controlled Trial Evaluating the Effect of Guided Care with Vectra DA on Radiographic Outcomes in Patients with Rheumatoid Arthritis	1500	Sep 2023

NCT: national clinical trial

^a Denotes industry-sponsored or cosponsored trial

Government Regulations

National:

There is no Medicare National Coverage Determination for the Vectra DA test.

Local:

WPS. Local Coverage Article (A55223), effective 10/01/2020. Retired 02/24/2022.

The MoIDX Team has completed the **VECTRA** DA assessment and determined that the test meets criteria for analytical and clinical validity, and clinical utility as a reasonable and necessary Medicare benefit. As per the conclusion of the clinical utility study, MoIDX will reimburse **VECTRA** DA tests performed for dates of service on and after 06/30/12. Based on the developer's recommendation, this test should be limited to two services per patient per year.

To report a **VECTRA** DA service, please submit the following claim information:

- For services prior to 01/01/2016, BCBSM code 81479– unlisted molecular pathology procedure
- 2016 CPT code 81490-Autoimmune (RA), analysis of 12 biomarkers
- Labs may either use the SV101-7 or SV202-7 (preferred) or the NTE field to submit this required information.
- Enter assigned DEX Z-Code™ Identifier in the comment/narrative field for the following Part B claim field/types:
 - Loop 2400 or SV101-7 for the 5010A1 837P
 - Box 19 for paper claim
- Enter the appropriate DEX Z-Code™ identifier adjacent to CPT code in the comment/narrative field for the following Part A claim field/types:
 - Line SV202-7 for 837I electronic claim
 - Block 80 for the UB04 claim form
- Select the appropriate ICD-10-CM diagnosis.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

None

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2023, the date the research was complete.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/15	10/21/14	11/7/14	Joint policy established
3/1/16	12/10/15	12/10/15	Routine maintenance Procedure code 81490 (effective 1/1/16) added to policy
3/1/17	12/13/16	12/13/16	Routine policy maintenance. Updated references and rationale.
3/1/18	12/12/17	12/12/17	Updated rationale section. Added references 16-18, 20, and 23-24. Policy status unchanged.
3/1/19	12/11/18		Routine policy maintenance, reference # 15-16, 19, and 23-24. Policy status unchanged.
3/1/20	12/17/19		Routine policy maintenance, reference # 22-24 and 26. Policy status unchanged.
3/1/21	12/15/20		Rationale reorganized, no new references added. Policy status unchanged.
3/1/22	12/14/21		Updated rationale, added reference #11. No change in policy status.
3/1/23	12/20/22		Routine policy maintenance, no change in policy status.
3/1/24	12/19/23		Routine policy maintenance, added reference 10. No change in policy status. Vendor managed: Avalon (ds)

Next Review Date: 4th Qtr. 2024

**BLUE CARE NETWORK BENEFIT COVERAGE
 POLICY: MULTI-BIOMARKER DISEASE ACTIVITY (MBDA) LABORATORY TESTING (E.G.,
 VECTRA DA BLOOD TEST) FOR RHEUMATOID ARTHRITIS**

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A