2.04.119	Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis		
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Section:	2.0 Medicine	**Page:**	Page 1 of 18

Policy Statement

I. The use of a multibiomarker disease activity score for rheumatoid arthritis (RA) (e.g., Vectra® score) is considered **investigational** in **all** situations.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

There is a specific CPT code for this test:

- **81490**: Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score

Description

Assessment of disease activity in rheumatoid arthritis is an important component of management with a goal of treatment 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 test is a commercially available multibiomarker disease activity blood test that measures 12 biomarkers to construct a disease activity score. Concentrations of these 12 biomarkers are entered into a proprietary formula which, after adjustment by age, gender and adiposity (i.e., leptin) levels, generates a disease activity score ("adjusted MBDA score") that ranges from 1 (low disease activity) to 100 (high disease activity).

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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® 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.

Rationale

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 7 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 targeted treatment with historical controls. The treatment targets were heterogeneous, including symptom-based measures, joint scores on the exam, validated treatment activity measures, lab values, or combinations of these factors. In all 4 trials that randomized patients to tight control or routine management, there was a significant decrease in the Disease Activity Score (DAS) or its 28 joints version (DAS28) and in the likelihood of achieving remission for patients in the tight control group.

According to the 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, reliable and valid measurement of disease activity is necessary. 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,[4] 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 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.[5] 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:[6]

Categories of scores were constructed to correlate with the DAS28-CRP scale[5,7]:

- 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.[8] However, as the current, commercially available version of the test includes the leptin-adjusted MBDA score (now called the "adjusted MBDA score"),[6] 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),[4] 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.

Literature Review

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 Testing in Rheumatoid Arthritis

Clinical Context and Test Purpose

The purpose of the multibiomarker disease activity (MBDA), specifically the Vectra, test in patients who have rheumatoid arthritis (RA) is to determine the level of disease activity (low, medium, or high) in order to inform treatment decisions.

The question addressed in this evidence review is: Does use of an MBDA (e.g., Vectra) test, alone or as an adjunct, to predict disease activity in patients with RA, improve health outcomes compared with the use of other American College of Rheumatology (ACR)-recommended measures of disease activity?

The following PICO was 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) and/or biologic agents.

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 provides a score indicating the level of disease activity, based on blood levels of the following 12 biomarkers: interleukin-6, tumor necrosis factor (TNF) receptor type I, vascular cell adhesion molecule 1, epidermal growth factor, vascular endothelial growth factor A, YKL-40 glycoprotein, matrix metalloproteinase 1, matrix metalloproteinase 3, C-reactive protein (CRP), serum amyloid A, leptin, and resistin. The current, commercially available version of the Vectra test is adjusted for patient age, gender, and adiposity, (i.e., leptin), now referred as the "adjusted MBDA score".

Scores range from 1 to 100 (1-29=low disease activity; 30-44=medium disease activity; 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 one year. In addition, 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), 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 5 measures as “preferred” for regular use in most clinic settings: the DAS28-ESR/CRP, CDAI, DSAI, RAPID3, and Patient Activity Scale-II.

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

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

If Vectra 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 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 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 a 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 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 MBDA test (e.g., Vectra), studies would need to use the current commercially available version of the test (including the "adjusted MBDA score") 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, 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 the current commercially available version of Vectra (including the "adjusted MBDA score") used as an adjunct or as a replacement to ACR-recommended disease activity measures, with radiographic progression as a reference standard. Prognostic studies should report the probability of the outcome measure (with precision) by risk group. Studies reporting other measures (e.g., odds ratios) may be included but are less informative.

Clinically Valid

Review of Evidence
Vectra Test with Adjusted Multibiomarker Disease Activity 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 2 retrospective cohort studies (Table 1).[9,8,] A study by Curtis et al (2019) 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 trial (RCT)[10,] or the Brigham Rheumatoid Arthritis Sequential Study (BRASS) cohort study.[11,] The clinical validity of the Vectra test was compared to that of the original Vectra DA test and other measures of disease activity (Table 2).

Among the various disease activity measures assessed, only the new Vectra test (relative risk [RR], 8.38; 95% CI [confidence interval], 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 CI suggest at least similar prognostic performance to other disease activity 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 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 et al using combined data from 953 patients enrolled in the OPERA, BRASS, Leiden Early Arthritis Clinic (EAC), and SWEFOT (Swedish Farmacotherapy) cohorts.[9,] 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; $p = 2.65 \times 10^{-6}$) 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 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)[8,]	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)[9,]	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,

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
							prospective cohort with symptom duration <2 years at enrollment; non-biologic and biologic DMARD therapy

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 Farmacotherapy 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)[8,]	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)[9,]										
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)

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)[8],	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)[9],	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)[8],	2. Selection not random or consecutive (i.e., convenience)	1. Not blinded to results of reference or other comparator tests in some patients				
Curtis et al (2021)[9],	2. Selection not random or consecutive (i.e., 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.
[f] 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 RCTs and cohorts.[12,13,14,15,16,17,18,19,20,21,22,23,24,] 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.[25,4,26,]Overall, findings from the most comprehensive and rigorous review (Johnson et al 2019)[25,] 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. This review 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 heterogenous 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 RRs 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 ACR working group's systematic review of the psychometric properties of 46 RA disease activity measurement tools.[4,] 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 (1 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.[26,] 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 1 year for each of the measures were calculated based on high versus 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<.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=.02) and 1.7 (95% CI , 1.2 to 2.4 ; p=.002), respectively.

Additionally, findings were also mixed across 3 studies published subsequent to the above-described systematic review and pooled analyses.[18,10,24,] For example, in a post hoc analysis of 3 cohort studies by Roodenrijs et al (2018)[24,], 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, and 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 (DRESS) RCT by Bouman et al (2017),[18,] 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: 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 2 retrospective cohort studies that correlated Vectra with other measures of disease activity and with radiographic progression. Results from the 4 cohorts analyzed in these studies have shown that Vectra may be predictive of radiographic progression at 1 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, the numerous study 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. The incremental benefit of MBDA when used as an adjunct to other disease activity measures is unclear given the high prevalence of discordant results across conventional measures of disease activity. Thus, the position of the Vectra test in the management pathway is unclear.
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, more effective therapy, or avoid unnecessary therapy, or 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 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. To demonstrate equivalence with other measures directly, an RCT comparing health outcomes of 2 groups, 1 group managed using the Vectra 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 the Vectra test plus a disease activity measure with outcomes in patients receiving treatment guided only by the other disease activity measure. No RCTs were identified. No studies of the current commercially available Vectra test ("updated MBDA score") were identified. Below is a retrospective study that evaluated the original Vectra DA test and medication use among patients with RA.

Curtis et al (2018) used Medicare data from 2011 to 2015 to study the original Vectra DA test (not commercially available) scores and biologic and Janus kinase inhibitors use among patients with RA.[27] The database contained 60,596 patients with RA who had the original Vectra DA testing results. Among patients not currently taking biologics (n=33,728), statistically significant differences in adding or switching medications were detected based on the original Vectra DA 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 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 Vectra 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 test with the "updated MBDA score" or the original Vectra DA score with 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. 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 Vectra or Vectra DA are clinically valid.

Summary of Evidence
For individuals with 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 2 studies that analyzed archived serum samples using combined data from RCTs and 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 with other previously validated disease activity measures such as the DAS28 or to radiographic progression, consisted mostly of correlations. However, the PPVs that individuals with Vectra moderate to high risk disease scores had radiographic progression were low, at 4.4% and 15.8%, respectively. Additionally, due to numerous study relevance, design, and conduct limitations, 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. Given the high prevalence of discordant results across conventional measures of disease activity, the position of the Vectra test in the management pathway is unclear. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with 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, PPV, and negative predictive value (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 that the technology results in an improvement in the net health outcome.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Rheumatology
In its 2019 guidelines on recommended rheumatoid arthritis disease activity measures, the American College of Rheumatology[4,] 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

Published in 2018 and updated in 2020, the NICE guidance on the management of adult patients with rheumatoid arthritis does not include a discussion on the use of a MBDA test to monitor patients.[28,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There are no Medicare national coverage determinations for the Vectra test. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03810144[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 (CareFirst)	500	Oct 2022 (active)
NCT03631225[a]	Vectra InVolved Informed Decision Outcome Study (VIVID): A Prospective Randomized Controlled Trial Evaluating the Effect of Guided Care With Vectra Compared to Treatment as Usual in Patients With Rheumatoid Arthritis	1500	Sept 2023 (recruiting)
NCT02832297[a]	Prospective Outcomes Study: Vectra® DA Guided Care Compared to Usual Care	318	Aug 2022 (recruiting)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. Upchurch KS, Kay J. Evolution of treatment for rheumatoid arthritis. Rheumatology (Oxford). Dec 2012; 51 Suppl 6: vi28-36. PMID 23221584
2. Schoels M, Knevel R, Aletaha D, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis. Apr 2010; 69(4): 638-643. PMID 20237123
3. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). Jul 2021; 73(7): 924-939. PMID 34101387
4. England BR, Tiong BK, Bergman MJ, et al. 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res (Hoboken). Dec 2019; 71(12): 1540-1555. PMID 31709779
5. Crescendo Bioscience. Vectra DA Patient Guide: Understanding results. n.d.; https://vectrascore.com/know-your-results/. Accessed May 9, 2022.
6. Labcorp. Vectra. 2021. https://www.labcorp.com/tests/504965/vectra. Accessed May 9, 2022.
7. Centola M, Cavet G, Shen Y, et al. Development of a multi-biomarker disease activity test for rheumatoid arthritis. PLoS One. 2013; 8(4): e60635. PMID 23585841
8. Curtis JR, Flake DD, Weinblatt ME, et al. Adjustment of the multi-biomarker disease activity score to account for age, sex and adiposity in patients with rheumatoid arthritis. Rheumatology (Oxford). May 01 2019; 58(5): 874-883. PMID 30590790
9. Curtis JR, Weinblatt ME, Shadick NA, et al. Validation of the adjusted multi-biomarker disease activity score as a prognostic test for radiographic progression in rheumatoid

arthritis: a combined analysis of multiple studies. Arthritis Res Ther. Jan 04 2021; 23(1): 1. PMID 33397438
10. Brahe CH, Ostergaard M, Johansen JS, et al. Predictive value of a multi-biomarker disease activity score for clinical remission and radiographic progression in patients with early rheumatoid arthritis: a post-hoc study of the OPERA trial. Scand J Rheumatol. Jan 2019; 48(1): 9-16. PMID 29985080
11. Iannaccone CK, Lee YC, Cui J, et al. Using genetic and clinical data to understand response to disease-modifying anti-rheumatic drug therapy: data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study. Rheumatology (Oxford). Jan 2011; 50(1): 40-6. PMID 20847201
12. Bakker MF, Cavet G, Jacobs JW, et al. Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. Ann Rheum Dis. Oct 2012; 71(10): 1692-7. PMID 22596166
13. Markusse IM, Dirven L, van den Broek M, et al. A multibiomarker disease activity score for rheumatoid arthritis predicts radiographic joint damage in the BeSt study. J Rheumatol. Nov 2014; 41(11): 2114-9. PMID 25128518
14. Hambardzumyan K, Bolce R, Saevarsdottir S, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis. Jun 2015; 74(6): 1102-9. PMID 24812287
15. Hambardzumyan K, Bolce RJ, Saevarsdottir S, et al. Association of a multibiomarker disease activity score at multiple time-points with radiographic progression in rheumatoid arthritis: results from the SWEFOT trial. RMD Open. 2016; 2(1): e000197. PMID 26958364
16. Fleischmann R, Connolly SE, Maldonado MA, et al. Brief Report: Estimating Disease Activity Using Multi-Biomarker Disease Activity Scores in Rheumatoid Arthritis Patients Treated With Abatacept or Adalimumab. Arthritis Rheumatol. Sep 2016; 68(9): 2083-9. PMID 27111089
17. Hirata S, Li W, Kubo S, et al. Association of the multi-biomarker disease activity score with joint destruction in patients with rheumatoid arthritis receiving tumor necrosis factor-alpha inhibitor treatment in clinical practice. Mod Rheumatol. Nov 2016; 26(6): 850-856. PMID 26873570
18. Bouman CAM, van der Maas A, van Herwaarden N, et al. A multi-biomarker score measuring disease activity in rheumatoid arthritis patients tapering adalimumab or etanercept: predictive value for clinical and radiographic outcomes. Rheumatology (Oxford). Jun 01 2017; 56(6): 973-980. PMID 28339738
19. Hambardzumyan K, Saevarsdottir S, Forslind K, et al. A Multi-Biomarker Disease Activity Score and the Choice of Second-Line Therapy in Early Rheumatoid Arthritis After Methotrexate Failure. Arthritis Rheumatol. May 2017; 69(5): 953-963. PMID 27992691
20. van der Helm-van Mil AH, Knevel R, Cavet G, et al. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. Rheumatology (Oxford). May 2013; 52(5): 839-46. PMID 23287359
21. Li W, Sasso EH, van der Helm-van Mil AH, et al. Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis. Rheumatology (Oxford). Feb 2016; 55(2): 357-66. PMID 26385370
22. Krabbe S, Bolce R, Brahe CH, et al. Investigation of a multi-biomarker disease activity score in rheumatoid arthritis by comparison with magnetic resonance imaging, computed tomography, ultrasonography, and radiography parameters of inflammation and damage. Scand J Rheumatol. Sep 2017; 46(5): 353-358. PMID 27682742
23. Reiss WG, Devenport JN, Low JM, et al. Interpreting the multi-biomarker disease activity score in the context of tocilizumab treatment for patients with rheumatoid arthritis. Rheumatol Int. Feb 2016; 36(2): 295-300. PMID 26026604
24. Roodenrijs NMT, de Hair MJH, Wheater G, et al. The multi-biomarker disease activity score tracks response to rituximab treatment in rheumatoid arthritis patients: a post hoc analysis of three cohort studies. Arthritis Res Ther. Nov 20 2018; 20(1): 256. PMID 30458871
25. Johnson TM, Register KA, Schmidt CM, et al. Correlation of the Multi-Biomarker Disease Activity Score With Rheumatoid Arthritis Disease Activity Measures: A Systematic Review

and Meta-Analysis. Arthritis Care Res (Hoboken). Nov 2019; 71(11): 1459-1472. PMID 30320973
26. Curtis JR, Brahe CH, Ostergaard M, et al. Predicting risk for radiographic damage in rheumatoid arthritis: comparative analysis of the multi-biomarker disease activity score and conventional measures of disease activity in multiple studies. Curr Med Res Opin. Sep 2019; 35(9): 1483-1493. PMID 30777458
27. Curtis JR, Xie F, Yang S, et al. Uptake and Clinical Utility of Multibiomarker Disease Activity Testing in the United States. J Rheumatol. Mar 2019; 46(3): 237-244. PMID 30442830
28. National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management [NG100]. October 2020, https://www.nice.org.uk/guidance/ng100. Accessed May 9, 2022.

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
09/30/2015	New Policy Adoption
08/01/2016	Policy revision without position change
08/01/2017	Policy revision without position change
08/01/2018	Policy title change from Vectra® DA Blood Test for Rheumatoid Arthritis Policy revision without position change
08/01/2019	Policy revision without position change
08/01/2020	Annual review. No change to policy statement. Literature review updated.
08/01/2021	Annual review. No change to policy statement. Literature review updated.
08/01/2022	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis 2.04.119 **Policy Statement:** The use of a multibiomarker disease activity score for rheumatoid arthritis (RA) (e.g., Vectra® score) is considered **investigational** in **all** situations.	**Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis 2.04.119** **Policy Statement:** I. The use of a multibiomarker disease activity score for rheumatoid arthritis (RA) (e.g., Vectra® score) is considered **investigational** in **all** situations.