Anthem

Medical Policy

Subject: Multi-biomarker Disease Activity Blood Tests for Rheumatoid Arthritis
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Description/Scope

This document addresses the use of multi-biomarker disease activity (MBDA) blood testing that produces a score designed to assess rheumatoid arthritis (RA) disease activity. An example is the Vectra® DA blood test (Crescendo Bioscience, Inc., South San Francisco, CA).

Position Statement

Investigational and Not Medically Necessary:

The use of multi-biomarker disease activity blood testing for rheumatoid arthritis (for example, Vectra DA) is considered **investigational and not medically necessary** in all situations.

Rationale

The published evidence evaluating MBDA testing, such as the Vectra DA blood test, includes post hoc analyses of randomized controlled trials (RCTs) and prospective cohort studies. A 2012 analysis by Bakker and colleagues reported an association between MBDA (Vectra DA) scores and disease activity score 28 (DAS28) in a subset of participants from the Computer-Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial, a 2-year, multicenter, prospective, open-label study. A total of 299 subjects had been randomized to standard or intensive management of RA. For the subset analysis, 74 (24.7%) of the 299 subjects had blood drawn for measurement of 20 biomarkers, using 12 biomarkers to calculate the MBDA test, including biomarkers both individually associated and not associated with disease activity. There were 72 samples collected at baseline and 48 samples collected at 6 months. The Vectra DA score correlated with the DAS28 score at baseline with a receiver operating curve area (r) of 0.72 ($p<0.001$). When using the DAS28 C-reactive protein (CRP) cutoff of 2.7 as the criterion standard, the MBDA score discriminated between remission/low disease activity and moderate/high disease activity with an r value of 0.86 ($p<0.001$). In multivariate analysis, the MBDA score, but not CRP, appeared to be an independent predictor of disease activity measures. Responding to the treatment used in the CAMERA study (n=46), the mean (SD) MBDA score decreased from a baseline of 53 (18) to 39 (16) at 6 months ($p<0.0001$). Neither the MBDA score nor clinical variables were predictive of radiographic progression. From this small study, the authors concluded that “further studies are needed to define the optimal use of biomarkers in the management of RA.”

Other authors (Hirata, 2013; Markusse, 2014) evaluated the Vectra DA MBDA test from the Behandel Strategieën (BeSt) (Dutch acronym for treatment strategies) study, a multicenter controlled trial of 508 subjects with early RA, randomized to four different treatment options. For both of these studies, a subset of subjects who had serum samples available were included. Of the 508 total subjects, 125 had serum samples, 91 had baseline samples, 89 had 1-year follow-up samples, and 55 had both baseline and follow-up serum samples available. While Hirata found that the MBDA score demonstrated an r value of 0.83 ($p<0.0001$) when compared to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean remission, a comparison of subjects who had samples available and those who did not revealed that the population with serum samples differed from the population that did not on sex (75% vs 65% female, $p=0.04$), median number of tender joints that were lower (11 vs 14, $p<0.001$), and median number of erosions seen on imaging (1.0 vs 2.0, $p=0.005$).

Hirata and colleagues (2013) studied the correlation between the Vectra DA score and scores for other validated measures of disease activity, specifically, the DAS28, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and the Health Assessment Questionnaire Disease Index (HAQ-DI). Vectra DA scores correlated significantly with DAS28 scores (Spearman $\rho=0.66$, $p<0.001$), as did the changes in scores between baseline and 1 year (Spearman $\rho=0.55$, $p<0.001$). The authors reported that Vectra DA scores also correlated significantly with SDAI, CDAI, and HAQ-DI scores at the $p<0.001$ level.

Markusse and colleagues (2014) evaluated the ability of the Vectra DA score to predict the progression of radiographic joint damage and also compared the predictive ability of the Vectra DA score with the DAS28 score. Radiographic progression was defined as a change of at least 5 points on the Sharp/van der Heijde Score (SHS) over a 1-year period. Receiver operating characteristic analysis was performed, with an area under the curve (AUC) for the Vectra DA test of 0.77 (95% confidence interval [CI], 0.64 to 0.90), which was higher than the AUC for the DAS28 (0.52; 95% CI, 0.39 to 0.66).

In the “Reduction of Therapy in Patients With Rheumatoid Arthritis in Ongoing Remission” (RETRO) trial, Rech and colleagues (2015) enrolled subjects treated with disease-modifying antirheumatic drugs (DMARDs) in clinical remission, and they randomized participants to tapering DMARD or standard maintenance care. MBDA (Vectra DA) scores were determined for 94 (93%) of 101 enrollees. Moderate-to-high MBDA scores were observed in 33% of subjects with RA. Vectra DA scores were higher in subjects undergoing a relapse than in those remaining in stable remission. On multivariate analysis, the Vectra DA score was reported to be a significant predictor of relapse (odds ratio [OR] 8.54; 95% CI, 2.0 to 36.4), along with treatment arm (OR 5.94; 95% CI, 1.3 to 26.7).

The ability of the Vectra DA score to track the clinical response of RA to different tumor necrosis factor (TNF) inhibitors was evaluated by Hirata and colleagues in 2015. The study consisted of 147 subjects who had received adalimumab, etanercept, or infliximab for at least 1 year. The relationship between baseline scores and response to treatment was measured for the Vectra DA test and for a number of other scores (DAS28, SDAI, CDAI). A good response, as defined by the European League Against Rheumatism clinical criteria, was achieved by 56% of subjects. The mean Vectra DA score decreased from 64 to 34 during the study, and 37% of subjects met the threshold for low activity (Vectra DA score < 30). The Vectra DA score decreased more in good clinical responders (–29 points) than in those with a moderate response (–21 points), and decreased more in subjects with a moderate response compared with nonresponders (+2 points). There was a positive correlation between the Vectra DA score and the DAS28 CRP ($r=0.46$) and the DAS28 ESR ($r=0.48$), and across the three TNF inhibitor groups, but not with the SDAI or the CDAI.

Hambardzumyan and colleagues (2015) performed a post hoc analysis from the Swedish Farmacotherapy (SWEFOT) trial, an RCT of 487 individuals with early RA, who, after the removal of methotrexate (MTX) responders, were randomized to two treatment regimens: a non-biologic and a biologic regimen. A total of 235 (48%) subjects had serum samples available and complete clinical and

radiographic data. The Vectra DA score was reported as a univariate predictor of radiographic progression (OR 1.05; 95% CI, 1.02 to 1.08; p<0.001), and an independent predictor of progression in a variety of multivariate models. For those with a low or moderate Vectra DA score (< 44), radiographic progression was uncommon, occurring in 1 in 40 subjects (2.5%).

Additionally, Hambardzumyan and colleagues (2016) reported repeat scores at multiple time points during the SWEFOT trial. Of 487 enrolled participants, 220 (45.2%) had baseline Vectra DA scores, 205 (42.1%) had scores at 3 months, and 133 (27.3%) had scores at 1 year. Subjects with low initial scores, or with a decrease in scores over time into the low range, had the lowest rate of radiographic progression at 1 year. In addition to small sample size, the authors noted that the MTX responder group was not included in the analysis of MBDA, non-validated cut-offs for CRP and ESR were used to define RA severity, and other changes in treatments between study groups could have affected radiologic findings.

Fleischmann and colleagues (2016) evaluated the ability of Vectra DA to measure disease activity in participants of the Abatacept Versus Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate (AMPLE) trial. In the AMPLE trial (Schiff, 2014), a total of 646 subjects naïve to biological agents were randomized to receive abatacept (n=318) or adalimumab (n=328). MBDA results were available for 259 and 265 subjects, respectively. No association was found between the MBDA score and disease activity as defined by American College of Rheumatology (ACR) recommended disease activity measures (CDAI, SDAI, DAS28-C-reactive protein, or Routine Assessment of Patient Index Data with 3 measures [RAPID-3]) in either treatment group. The authors concluded:

> These findings indicated that the MBDA score should not be used to guide RA management decisions, particularly in patients treated with abatacept or adalimumab as a first biologic agent. Treatment decisions in RA should be based on clinical judgment, utilizing the disease activity measures recommended by the ACR for point-of-care clinical use.

Bouman and colleagues (2017) evaluated the predictive value of the baseline Vectra DA score for tapering or discontinuing TNF inhibitors in individuals with long-standing, low disease RA. Using data (n=171) from the 18-month Dose Reduction Strategy of Subcutaneous TNF inhibitors (DRESS) study, an open RCT that investigated non-inferiority of a dose reduction strategy of adalimumab or etanercept compared with usual care, the researchers looked at the predictive values for successful dose tapering or discontinuation, occurrence of flares and major flares, and occurrence of radiographic progression. In a baseline cross-classification, the Vectra DA showed moderate to high scores for 65% of participants; however, the DAS28-CRP showed low disease activity in 81%. The area under the receiver operating characteristic (AUROC) curve for predicting successful tapering versus no tapering by Vectra DA was 0.53 (95% CI, 0.41 to 0.66), and the discontinuation prediction was 0.51 (95% CI, 0.36 to 0.66). The AUROC for predicting a flare was 0.50 (95% CI, 0.41 to 0.59) and for major flares was 0.46 (95% CI, 0.32 to 0.65). When looking at sub-groups, the researchers noticed the Vectra DA was possibly able to predict a major flare in the usual care group (AUROC 0.72; 95% CI, 0.56 to 0.88). The AUROC for predicting radiographic progression of > 0.5 SvdH points was 0.53 (95% CI, 0.43 to 0.63). Overall, the authors concluded that the Vectra DA baseline score was not predictive of successful tapering or discontinuation of TNF inhibitors, occurrence of flares, or radiographic progression within the context of the DRESS trial. The authors stated that further studies are needed to confirm the findings.

Johnson and colleagues (2018) conducted a systematic review and meta-analysis on the correlation of the MBDA score with RA disease activity measures. They included 22 studies in the systematic review, including 8 studies (n=3242) that reported the correlation of MBDA with RA disease activity measures. After pooling data in the 8 studies, they found a moderate correlation between MBDA and DAS28-CRP (r=0.41; 95% CI, 0.36 to 0.46) and MBDA and DAS28-ESR (r=0.48; 95% CI, 0.38 to 0.58). Weaker correlations were found with SDAI, CDAI, and RAPID3. They concluded the following:

> While the MBDA score represents another tool to measure RA disease activity, further assessment of its ability to improve RA management (such as the ability to predict treatment response or comparisons of patient outcomes for individuals treated to target with the MBDA score vs. other RA disease activity measures), validation of its performance characteristics, evaluation of a recently proposed scoring modification, as well as appraisal through independently funded efforts is necessary.

In an industry sponsored study, Curtis and colleagues (2019) performed a pooled analysis investigating the MBDA score as a predictor of radiographic progression in comparison to DAS28-CRP and CRP in individuals with RA. The systematic literature review yielded four studies with five cohorts (Leiden, OPERA, SWEFOT, AMPLE-Abatacept, AMPLE-Adalimumab) and a total of 929 participants for qualitative synthesis; however, due to a lack of data in one of the studies, which had two cohorts (AMPLE-Abatacept, AMPLE-Adalimumab), there were only three studies (n=562) included in the pooled analysis. Through the qualitative synthesis, investigators found a statistically significant trend in radiographic progression in relation to increasing MBDA scores when participants were grouped by MBDA category. There was either no statistical significance or less significance in the rates of radiographic progression across categories of DAS28-CRP and CRP for the three cohorts (Leiden, OPERA, SWEFOT) with available data than across MBDA categories. As for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and relative risk (RR) for radiographic progression in the three cohorts with available data (Leiden, OPERA, SWEFOT), the high and not-high disease activity MBDA categories had higher sensitivity for radiographic progression, CRP categories had the greatest specificity, PPVs were similar across all categories, and NPVs and RRs were greater for MBDA score when compared to DAS28-CRP and CRP. The RRs were only statistically significant in the MBDA categories of the OPERA and SWEFOT cohorts; however, the RR in the Leiden cohort was not statistically significant. Even though the results of the pooled analysis of participant-level data from the three included cohorts (Leiden, OPERA, SWEFOT) showed the combined RR for MBDA score (4.6, p<0.0001) was greater than DAS28-CRP (1.7, p=0.02) and CRP (1.7, p=0.002), combined RRs for each of the three disease activity measures were statistically significant. Further analysis of participants cross-classified into subgroups based on high and not-high categories of MBDA score and DAS28-CRP resulted in a significant prediction of radiographic progression for high versus not-high MBDA score independently of DAS28-CRP. Limitations to these results include excluding studies with less than 100 participants, and varying definitions of radiographic progression in the included studies. Furthermore, this study did not demonstrate the clinical utility of the MBDA score in monitoring the treatment of RA.

Leudders and colleagues (2020) assessed the predictive value, validity, and responsiveness of the MBDA score in 130 individuals initiating therapy with methotrexate to manage RA. This post-hoc analysis used data from a 16-week, open-label study that collected serum at baseline and week 16 (n=95 at study end). Multivariable logistic regression models assessed whether MBDA scores predicted treatment response. Baseline MBDA scores did not predict treatment response or lowered disease activity. Higher baseline DAS28-ESR scores were significantly associated with 20% disease severity response (OR 1.89 per unit, 95% CI, 1.20-2.96) but not 50% or 70% improvement, nor lower disease activity. MBDA scores did not predict treatment response to methotrexate. Study authors concluded, “The MBDA score weak-to-moderately correlated with baseline and post-treatment disease activity measures and was less responsive to methotrexate-related improvement than the DAS28-ESR.”

Ma and colleagues (2020) conducted a 1-year study in which 148 individuals with RA on > 6 months stable therapy and in stable low disease activity (DAS28-ESR ≤ 3.2) were assessed every 3 months for 1 year. By all remission criteria, baseline MBDA scores sucessfully discriminated baseline remission (AUROCs 0.68–0.75) from intermittent/sustain remission (AUROCs 0.65–0.74). The 6-month MBDA score also discriminated intermittent/sustain remission (AUROCs 0.65-0.79). Baseline MBDA score and concentrations

of IL-6, leptin, SAA and CRP were significantly lower in all baseline remission criteria groups relative to those with low-disease activity. Both baseline and 6-month values were lower among those who achieved intermittent/sustain remission compared to progressive disease activity during the 1 year study follow-up period. This study demonstrated that the MBDA score and its biomarkers IL-6, leptin, SAA and CRP differentiated between small differences in disease activity (i.e. between low disease activity and remission states) and had sustained ability to predict remission over 1 year; the value of the MBDA score's clinical utility compared to established standards of care, was not studied.

Curtis and colleagues (2021) conducted another study in which four cohorts were analyzed (n=953 in total) with an updated version of the MBDA score, which accounts for age, sex, and adiposity. Study participants received conventional treatment with DMARDs and anti-TNFs. The association of annual radiographic progression was compared to the adjusted MBDA score, seropositivity, and clinical measures. The adjusted MBDA score was validated in the previously described Leiden and SWEFOT cohorts, it was compared with other measures across all four cohorts in the current study and then used to predict risk of radiographic progression. Study investigators found the MBDA score to be the strongest, independent predicator of radiographic progression, moreso than seropositivity (rheumatoid factor and/or anti-CCP) and other baseline clinical measures (TSS, DAS28-CRP, CRP SJC, or CDAI). Upon multivariate analysis, no other clinical measures added significant information to the adjusted MBDA score as a predictor, and the frequency of radiographic progression agreed with the adjusted MBDA score when it was discordant with these measures. Authors concluded, "The adjusted MBDA score was a stronger predictor of radiographic progression than conventional risk factors…". The clinical utility of the MBDA score and it's impact on net health outcomes remains to be established.

Other Considerations

In 2019, the ACR selected 11 RA disease activity measures that were most useful and feasible for point-of-care clinical care. MBDA blood tests, such as the Vectra DA, were considered by committee consensus to be of inconclusive value in the clinical setting (England, 2019).

Conclusion

The published data is conflicting as to whether or not MBDA blood tests, such as the Vectra DA, perform as well as other RA disease markers. There is insufficient published evidence indicating that treatment decisions can be influenced by MBDA test scores, and insufficient evidence demonstrating the effect of the MBDA testing on net health outcomes.

Background/Overview

RA is a chronic inflammatory and progressive disease characterized by symmetrical joint involvement, which causes pain, swelling, stiffness, and loss of function in the joints. If left untreated, it may lead to joint destruction and progressive disability. The disease affects over two million Americans, usually affecting people between the ages of 20 and 60, with a peak incidence in mid to late fifties. RA is three times more common in women than in men.

Vectra DA is an MBDA blood test developed in the U.S. for the assessment of RA disease activity. The test is done by taking serum prepared from peripheral blood and sending it to a central laboratory for automated, multiplexed measurement of 12 protein biomarkers that have a known role in the underlying pathophysiology of RA. The MBDA test is based on an algorithm using the concentrations of the 12 biomarkers to generate a score representing the level of RA disease activity on a scale of 1 (lowest disease activity) to 100 (highest disease activity). The MBDA test was designed to correlate with the DAS28 score.

The 12 individual RA biomarkers that make up the Vectra DA test are (Curtis, 2012):

- Interleukin-6 (IL-6)
- Tumor necrosis factor receptor type I (TNFRI)
- Vascular cell adhesion molecule 1 (VCAM-1)
- Epidermal growth factor (EGF)
- Vascular endothelial growth factor A (VEGF-A)
- YKL-40
- Matrix metalloproteinase 1 (MMP-1)
- Matrix metalloproteinase 3 (MMP-3)
- CRP
- Serum amyloid A (SAA)
- Leptin
- Resistin

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service, and such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). There are no U.S. Food and Drug Administration (FDA)-approved MBDA tests for measuring disease activity in RA. Vectra DA is a laboratory-developed test (LDT), and the FDA has generally not enforced approval of LDTs.

Definitions

Disease activity score 28 (DAS28): A measure of disease activity used to monitor the treatment of RA. The score uses a formula that includes the number of tender joints and swollen joints (28 joints maximum).

Disease-modifying antirheumatic drugs (DMARDS): A variety of drugs that work by altering the immune system function to halt the underlying processes causing certain forms of inflammatory arthritis including rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.

Tumor necrosis factor (TNF or TNF-α): A protein manufactured by white blood cells to stimulate and activate the immune system in response to infection or cancer; also referred to as tumor necrosis factor alpha. Overproduction of this protein can lead to diseases, such as arthritis or psoriasis, where the immune system acts against healthy tissues.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. 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.

When services are Investigational and Not Medically Necessary:

For the following procedure code; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score Vectra® DA, Crescendo Bioscience, Inc.
ICD-10 Diagnosis	
	All diagnoses

References

Peer Reviewed Publications:

1. Abdelhafiz D, Baker T, Glascow DA, Abdelhafiz A. Biomarkers for the diagnosis and treatment of rheumatoid arthritis - a systematic review. Postgrad Med. 2023; 135(3):214-223.
2. 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. 2012; 71(10):1692-1697.
3. 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). 2017; 56(6):973-980.
4. Curtis JR, Brahe CH, Østergaard 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. 2019; 35(9):1483-1493.
5. Curtis JR, van der Helm-van Mil AH, Knevel R, et al. Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken). 2012; 64(12):1794-1803.
6. 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. 2021. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7784276/. Accessed on March 30, 2023.
7. Eastman PS, Manning WC, Qureshi F, et al. Characterization of a multiplex, 12-biomarker test for rheumatoid arthritis. J Pharm Biomed Anal. 2012; 70:415-424.
8. Fleischmann R, Connolly SE, Maldonado MA, Schiff M. Brief report: Estimating disease activity using multi-biomarker disease activity scores in rheumatoid arthritis patients treated with abatacept or adalimumab. Arthritis Rheumatol. 2016; 68(9):2083-2089.
9. 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. 2016; 2(1):e000197.
10. 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. 2015; 74(6):1102-1109.
11. Hirata S, Dirven L, Shen Y, et al. A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study. Rheumatology (Oxford). 2013; 52(7):1202-1207.
12. Hirata S, Li W, Defranoux N, et al. A multi-biomarker disease activity score tracks clinical response consistently in patients with rheumatoid arthritis treated with different anti-tumor necrosis factor therapies: A retrospective observational study. Mod Rheumatol. 2015; 25(3):344-349.
13. 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). 2019; 71(11):1459-1472.
14. Luedders BA, Johnson TM, Sayles H, et al. Predictive ability, validity, and responsiveness of the multi-biomarker disease activity score in patients with rheumatoid arthritis initiating methotrexate. Semin Arthritis Rheum. 2020; 50(5):1058-1063.
15. Ma MHY, Defranoux N, Li W, et al. A multi-biomarker disease activity score can predict sustained remission in rheumatoid arthritis. Arthritis Res Ther. 2020. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7313155/. Accessed on March 30, 2023.
16. 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. 2014; 41(11):2114-2119.
17. Rech J, Hueber AJ, Finzel S, et al. Prediction of disease relapses by multibiomarker disease activity and autoantibody status in patients with rheumatoid arthritis on tapering DMARD treatment. Ann Rheum Dis. 2016; 75(9):1637-1644.
18. Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2014; 73(1):86-94.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis.
   - LCD L39424. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39424&ver=3&keyword=Rheumatoid&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Accessed on November 4, 2023.
   - LCD L39427. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39427&ver=3&keyword=Rheumatoid&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Accessed on November 4, 2023.
   - LCD L39436. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39469&ver=3&keyword=Rheumatoid&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Accessed on November 4, 2023.
   - LCD L39467. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39467&ver=3&keyword=Rheumatoid&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Accessed on November 4, 2023.
2. 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). 2019; 71(12):1540-1555.

Websites for Additional Information

1. U.S. National Library of Medicine. National Institutes of Health (NIH). MedlinePlus. Health Topics. Rheumatoid Arthritis. Reviewed May 2, 2018. Available at: https://medlineplus.gov/rheumatoidarthritis.html. Accessed on March 30, 2023.

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	12/06/2023	Revised References section.
Reviewed	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References and Websites sections.
Reviewed	05/12/2022	MPTAC review. Rationale, References, and Websites sections updated.
Reviewed	05/13/2021	MPTAC review. Rationale, References, and Websites sections updated.
Reviewed	05/14/2020	MPTAC review. References, and Websites sections updated.
Reviewed	06/06/2019	MPTAC review. Rationale, References, and Websites sections updated.
Reviewed	07/26/2018	MPTAC review. The document header wording updated from “Current Effective Date” to “Publish Date.” Rationale, References, and Websites sections updated.
New	08/03/2017	MPTAC review. Initial document development.

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