BlueCross BlueShield of North Carolina

An independent licensee of the Blue Cross and Blue Shield Association

Corporate Medical Policy

Vectra DA Blood Test for Rheumatoid Arthritis AHS – G2127

File Name:	vectra_da_blood_test_for_rheumatoid_arthritis
Origination:	01/01/2019
Last CAP Review:	2/2020
Next CAP Review:	02/2021
Last Review:	04/2020

Description of Procedure or Service

Definition

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder which results from a complex interaction between genes and environment, leading to a breakdown of immune tolerance and synovial inflammation in a characteristic symmetric pattern. RA usually leads to destruction of joints due to erosion of cartilage and bone, causing joint deformities (Firestein, 2017).

Vectra DA is an multi-biomarker disease activity (MBDA) blood test which employs an algorithm to combine the levels of 12 serum biomarkers into a single score from 1 to 100 to provide an objective measure of RA disease activity intended for use in conjunction with existing symptom-based disease activity measures with the objective of improving long-term outcomes for RA patients(van der Helm-van Mil, Knevel, Cavet, Huizinga, & Haney, 2013).

This policy does not pertain to general inflammation; for guidance on general inflammation testing, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), see policies General Inflammation Testing and ANA/ENA Testing.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

The use of a multi-biomarker disease activity score for rheumatoid arthritis (e.g., Vectra DA score) is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When a multi-biomarker disease activity score for rheumatoid arthritis (Vectra DA) is covered

Not applicable.

When a multi-biomarker disease activity score for rheumatoid arthritis (Vectra DA) is not covered

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

Policy Guidelines

Background

RA affects over 1.3 million people in the US and over 4 million worldwide. Despite the availability of potent biologic treatments, substantial disease activity persists in many patients, with accompanying progressive bone and soft tissue damage, extra-articular consequences, disability, and increased mortality (Centola et al., 2013). The condition usually involves stiffness and swelling joints all around the body, pain, and eventually the destruction of the affected joints. This typically leads to significant motor disability in patients who do not respond to treatment (Venables, 2017).

Measuring disease activity has become important for the management of patients with RA (Curtis et al., 2012). As RA is a chronic illness, earlier and more aggressive treatment may provide significant benefit, especially for patients with more severe forms of the illness (Taylor & Maini, 2017). Tighter control, such as more frequent monitoring and actively striving to meet a disease activity level, has been shown to be helpful in several studies (Bakker, Jacobs, Verstappen, & Bijlsma, 2007; Mease, 2010). However, there is no gold standard for disease activity assessment in RA. Multiple measures are used, and no single best measure of disease activity was recommended in U.S. or international RA guidelines (Centola et al., 2013). Disease activity indices are based on clinical, laboratory, and physical measures. Most of these indices, such as the Disease Activity Score (DAS) and the Routine Assessment of Patient Index Data-3 (RAPID-3) rely on either clinical evaluation of joints, patient-reported outcomes (PROs), or both in assessing disease activity. However, high intra- and inter-observer variability occurs. Furthermore, prior damage to joints or other conditions may influence these measurements (Curtis et al., 2012). Other commonly used tools for diagnosing RA have significant weaknesses; for example, blood tests may be used but are completely normal for many RA patients. MRI may be used due to its ability to identify early signs, but it is expensive and time consuming (Li, Sasso, van der Helm-van Mil, & Huizinga, 2016).

Biologic markers or "biomarkers" can provide objective measurements that reflect underlying pathophysiological processes, pathogenic processes, or responses to treatment. Most measures of monitoring disease and treatment progress rely on subjective measurements, such as joint evaluation, so biomarkers may be a useful complement in patient management (Taylor & Maini, 2017). Joint damage at the molecular level may be occurring before any clinical signs appear, so identifying any indications of disease activity could allow clinical interventions to be taken earlier (Mc Ardle, Flatley, Pennington, & FitzGerald, 2015). Markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are part of clinical measures such as the DAS. However, these two biomarkers are nonspecific; abnormal amounts of these markers may be due to other reasons apart from RA and may even be completely normal in patients with RA (Centola et al., 2013; Curtis et al., 2012). This nonspecificity is not limited to these two biomarkers as well. For example, antibodies (usually called rheumatoid factors and abbreviated RF) produced against immunoglobulin G (IgG) are often tested to diagnose RA, but these antibodies may be produced in response to another rheumatic condition or a separate chronic infection (Shmerling, 2018). RA is a heterogenous condition, and no single biomarker is a reliable predictor of RA disease activity (Mc Ardle et al., 2015). However, the combined assessment of multiple biomarkers, such as through MBDA, may be useful for predicting disease activity and progression (Taylor & Maini, 2017).

Validity and Utility

The MBDA algorithm (Vectra DA) was developed by screening 396 candidate biomarkers and creating an algorithm to general a composite score based on the 12 most correlated to RA clinical disease activity which are as follows:

- 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]
- MMP-3
- CRP
- serum amyloid A [SAA]
- leptin
- resistin.

These biomarkers represent several processes related to RA, such as cartilage remodeling and cytokine signaling pathways. A score of ≤29 is considered "low" activity, between 29 and 44 is "moderate" activity, and >44 is "high" activity. The MBDA is intended to provide separate information from a clinical evaluation of joints and should be used as a complement, not as a replacement (Curtis et al., 2012).

This MBDA has been shown to correlate significantly ($r=0.72$; $p<0.001$) with a disease activity score based on the DAS-28-CRP and has been validated for clinical use as a disease activity marker in RA (Curtis et al., 2012). Both Hirata et al. and Bakker et al. found the MBDA score to correlate well with disease activity and could complement other existing measures of RA assessment (Bakker et al., 2012; Hirata et al., 2013). Remission based on the MBDA score was a significant predictor of radiographic non-progression, whereas remission defined by traditional DAS28-CRP or ACR/EULAR criteria was not. The MBDA test was also useful in assessing the risk of radiographic progression among patients who met clinical remission criteria. MBDA results may provide an important addition to clinical assessment, however, further studies are needed to confirm its clinical utility in the management of RA (van der Helm-van Mil et al., 2013).

Li and colleagues evaluated the impact of an MBDA blood test for rheumatoid arthritis (RA) on treatment decisions made by six health care providers (HCPs) in 101 patients. HCPs completed surveys before and after viewing the MBDA test result, recording dosage and frequency for all RA medications and assessment of disease activity. Frequency and changes in treatment plan that resulted from viewing the MBDA test result were determined. The MBDA test results were found to have changed 38% of patients' treatment plans. Furthermore, treatment plans were changed 63% of the time the MBDA test results were found to be "not consistent" or "somewhat consistent" with the clinical assessment of disease activity. However, any improvement in clinical outcomes caused was not reported, and the overall amount of drug use was not affected (Li, Sasso, Emerling, Cavet, & Ford, 2013).

Another study assessed the correlation between MBDA score and disease progression in 163 RA patients. The study found that low radiographic progression was associated with low MBDA scores and higher scores were associated with more frequent and severe progression. Notably, MBDA scores correlated with progression even when a conventional measure such as the DAS28 indicated otherwise. For example, low risk of progression was associated with a low MBDA score, even when a concurrent DAS28 score was high. The authors concluded that MBDA may be a good complement for conventional measures, as well as provide information on changing treatment plans (Li et al., 2016).

Curtis, Greenberg, Harrold, Kremer, and Palmer (2018) initially studied the influence of age, obesity and other comorbidities on the MBDA test. A cross-sectional analysis of RA patients who have participated in an MBDA test was used (n=357). "Of 357 eligible patients, 76% (n = 273) had normal CRP (<10mg/L) with high (33%), moderate (45%), and low (22%) disease activity by MBDA. The MBDA score was significantly associated with BMI, age, CDAI [clinical disease activity index], and SJC [swollen joint count] (Curtis et al., 2018)." Almost one third of participants had normal CRP scores but high MBDA scores. "In this real-world analysis, the MBDA score was associated with RA disease activity, obesity, and age, and was negligibly affected by common comorbidities (Curtis et al., 2018)."The authors conclude by suggesting that an adjusted MBDA score may require development to account for BMI and age. Such a study was then published the following year. Curtis et al. (2019) developed an MBDA test that will include additional factors such as sex, age and obesity in RA patients. Obesity, or adiposity, was measured using either BMI or serum leptin concentration. Two cohorts were studied, totaling 1736 patients. Overall, the authors have developed "a leptin-adjusted MBDA score that has significantly improved [the] ability to predict clinical disease activity and radiographic progression (Curtis et al., 2019)." It was suggested that this leptin-adjusted MBDA score "significantly adds information to DAS28-CRP and the original MBDA score in predicting radiographic progression. It may offer improved clinical utility for personalized management of RA (Curtis et al., 2019)."

A recent study analyzed the measurement of serum biomarkers at early RA disease onset in hopes to better predict disease progression (Brahe et al., 2019). MBDA score and changes in this score were evaluated to predict DAS28-CRP remission. A total of 180 patients participated in this study and were treated with either methotrexate and adalimumab (n = 89) or methotrexate and placebo (n = 91) in addition to a glucocorticoid injection into swollen joints; results showed that "Early changes in MBDA score were associated with clinical remission based on DAS28-CRP at 6 months (Brahe et al., 2019)."

Guidelines and Recommendations

Applicable Federal Regulations
There are no U.S. Food and Drug Administration (FDA)-approved multibiomarker disease activity (MBDA) tests for measuring disease activity in RA, Vectra included. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

American College of Rheumatology (ACR)
The ACR convened a Working Group (WG) to evaluate the validity, feasibility, and acceptability of available RA disease activity measures.
The WG recommended the following measures:

- Clinical Disease Activity Index
- Disease Activity Score with 28-joint counts (erythrocyte sedimentation rate or C-reactive protein
- Patient Activity Scale (PAS) and PAS-II
- Routine Assessment of Patient Index Data (3 measures)
- Simplified Disease Activity Index

According to the WG, these measures were recommended because "they are accurate reflections of disease activity; are sensitive to change; discriminate well between low, moderate, and high disease activity states; have remission criteria; and are feasible to perform in clinical settings." The WG also recognized "there is no ideal measure of disease activity" and acknowledged that some measures excluded in their review may be superior to the six recommended measures.

However, they believed they identified the best measures of disease activity in RA (Anderson et al., 2012).

In 2015, the ACR published guidelines for the treatment of RA. While these guidelines focus mainly on methods of treatment rather than types of testing, "The team also discussed the following topics and recommended that they be targeted for future research: use of biologics and DMARDs during the period of conception, pregnancy, and breastfeeding; treatment of RA with interstitial lung disease; laboratory monitoring for biologics/tofacitinib; and biomarker testing (Singh et al., 2015)."

European League Against Rheumatism (EULAR), Managing Early Arthritis (2016)
EULAR recommends clinical examination as the method of detecting arthritis, but if a definite diagnosis cannot be reached, other risk factors such as rheumatoid factor or swollen joints should be considered.

EULAR states that the main goal of disease-modifying antirheumatic drugs (DMARDs) is clinical remission and regular monitoring of adverse events, disease activity and comorbidities should occur. Monitoring should include joint counts, patient and physician global assessment, and ESR and CRP measurements. Other measures such as radiographics can complement the main measures.

EULAR notes that several combinations of biomarkers have been evaluated, but not validated. Additionally, EULAR states that current data is not convincing and further study is required (Combe et al., 2017).

National Institute for Care and Excellence, Quality Standard, Rheumatoid arthritis in over 16s (NICE, 2018)
NICE recommends monthly monitoring of CRP and disease activity until remission or low disease activity. Remission is defined as a DAS28 score of under 2.6, and low is defined as a DAS28 score of under 3.2. NICE does not mention biomarkers in its recommendations for research (NICE, 2018).

The NICE recently published recommendations regarding laboratory testing for rheumatoid arthritis. These guidelines state that "Enzyme-linked immunosorbent assay (ELISA) tests for therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors (drug serum levels and antidrug antibodies) show promise but there is currently insufficient evidence to recommend their routine adoption in rheumatoid arthritis. The ELISA tests covered by this guidance are Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and tests used by Sanquin Diagnostic Services (NICE, 2019)."

Treat to Target Task Force (2014 Update to 2010 Guidelines)
he task force states that remission or low disease activity is the goal of treatment. Remission is defined as absence of clinical signs and symptoms of disease activity.
The task force was reconvened to update their previously issued guidelines from 2010. The task force recommended regular monitoring and documentation of disease activity. The frequency may depend on activity; for higher disease activity, the frequency may be as high as monthly whereas a lower activity patient may only need be re-evaluated every six months (Smolen et al., 2016).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81490

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Aletaha, D., Nell, V. P., Stamm, T., Uffmann, M., Pflugbeil, S., Machold, K., & Smolen, J. S. (2005). Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther, 7*(4), R796-806. doi:10.1186/ar1740

Anderson, J., Caplan, L., Yazdany, J., Robbins, M. L., Neogi, T., Michaud, K., Kazi, S. (2012). Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res (Hoboken), 64*(5), 640-647. doi:10.1002/acr.21649

Bakker, M. F., Cavet, G., Jacobs, J. W., Bijlsma, J. W., Haney, D. J., Shen, Y., Welsing, P. M. (2012). Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. *Ann Rheum Dis, 71*(10), 1692-1697. doi:10.1136/annrheumdis-2011-200963

Brahe, C. H., Ostergaard, M., Johansen, J. S., Defranoux, N., Wang, X., Bolce, R., . . . Hetland, M. L. (2019). 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, 48*(1), 9-16. doi:10.1080/03009742.2018.1464206

Brown, A. K., Quinn, M. A., Karim, Z., Conaghan, P. G., Peterfy, C. G., Hensor, E., Emery, P. (2006). Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum, 54*(12), 3761-3773. doi:10.1002/art.22190

Centola, M., Cavet, G., Shen, Y., Ramanujan, S., Knowlton, N., Swan, K. A., Curtis, J. R. (2013). Development of a Multi-Biomarker Disease Activity Test for Rheumatoid Arthritis. *PLoS One, 8*(4). doi:10.1371/journal.pone.0060635

Chambers, R. E., MacFarlane, D. G., Whicher, J. T., & Dieppe, P. A. (1983). Serum amyloid-A protein concentration in rheumatoid arthritis and its role in monitoring disease activity. *Ann Rheum Dis, 42*(6), 665-667.

Combe, B., Landewe, R., Lukas, C., Bolosiu, H. D., Breedveld, F., Dougados, M., Yazici, H. (2007). EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis, 66*(1), 34-45. doi:10.1136/ard.2005.044354

Curtis, J. R., van der Helm-van Mil, A. H., Knevel, R., Huizinga, T. W., Haney, D. J., Shen, Y., Weinblatt, M. E. (2012). Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken), 64*(12), 1794-1803. doi:10.1002/acr.21767

Firestein, G. (2017). Pathogenesis of rheumatoid arthritis - UpToDate. In P. L. Romain (Ed.), UpToDate. Waltham. MA. Retrieved from https://www.uptodate.com/contents/pathogenesis-of-rheumatoid-arthritis?source=search_result&search=ra&selectedTitle=6~150.

Fleischmann, R., Connolly, S. E., Maldonado, M. A., & Schiff, M. (2016). Brief Report: Estimating Disease Activity Using Multi-Biomarker Disease Activity Scores in Rheumatoid Arthritis Patients Treated With Abatacept or Adalimumab. *Arthritis Rheumatol, 68*(9), 2083-2089. doi:10.1002/art.39714

Goekoop-Ruiterman, Y. P., de Vries-Bouwstra, J. K., Allaart, C. F., van Zeben, D., Kerstens, P. J., Hazes, J. M., Dijkmans, B. A. (2005). Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum, 52*(11), 3381-3390. doi:10.1002/art.21405

Grigor, C., Capell, H., Stirling, A., McMahon, A. D., Lock, P., Vallance, R., Porter, D. (2004). Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet, 364*(9430), 263-269. doi:10.1016/s0140-6736(04)16676-2

Hambardzumyan, K., Bolce, R., Saevarsdottir, S., Cruickshank, S. E., Sasso, E. H., Chernoff, D., van Vollenhoven, R. F. (2015). Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. *Ann Rheum Dis, 74*(6), 1102-1109. doi:10.1136/annrheumdis-2013-204986

Hammer, H. B., Odegard, S., Fagerhol, M. K., Landewe, R., van der Heijde, D., Uhlig, T., Kvien, T. K. (2007). Calprotectin (a major leucocyte protein) is strongly and independently correlated with joint inflammation and damage in rheumatoid arthritis. *Ann Rheum Dis, 66*(8), 1093-1097. doi:10.1136/ard.2006.064741

Hirata, S., Dirven, L., Shen, Y., Centola, M., Cavet, G., Lems, W. F., Allaart, C. F. (2013). A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study. *Rheumatology (Oxford), 52*(7), 1202-1207. doi:10.1093/rheumatology/kes362

Keenan, R. T., Swearingen, C. J., & Yazici, Y. (2008). Erythrocyte sedimentation rate and C-reactive protein levels are poorly correlated with clinical measures of disease activity in rheumatoid arthritis, systemic lupus erythematosus and osteoarthritis patients. *Clin Exp Rheumatol, 26*(5), 814-819.

Klarenbeek, N. B., Koevoets, R., van der Heijde, D. M., Gerards, A. H., Ten Wolde, S., Kerstens, P. J., Allaart, C. F. (2011). Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis. *Ann Rheum Dis, 70*(10), 1815-1821. doi:10.1136/ard.2010.149260

Klimiuk, P. A., Sierakowski, S., Latosiewicz, R., Cylwik, J. P., Cylwik, B., Skowronski, J., & Chwiecko, J. (2002). Soluble adhesion molecules (ICAM-1, VCAM-1, and E-selectin) and vascular endothelial growth factor (VEGF) in patients with distinct variants of rheumatoid synovitis. *Ann Rheum Dis, 61*(9), 804-809.

Li, W., Sasso, E. H., Emerling, D., Cavet, G., & Ford, K. (2013). Impact of a multi-biomarker disease activity test on rheumatoid arthritis treatment decisions and therapy use. *Curr Med Res Opin, 29*(1), 85-92. doi:10.1185/03007995.2012.753042

Lillegraven, S., Prince, F. H., Shadick, N. A., Bykerk, V. P., Lu, B., Frits, M. L., Solomon, D. H. (2012). Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. *Ann Rheum Dis, 71*(5), 681-686. doi:10.1136/ard.2011.154625

Mease, P. J. (2011). The potential roles for novel biomarkers in rheumatoid arthritis assessment. *Clin Exp Rheumatol, 29*(3), 567-574.

NICE. (2018). Rheumatoid arthritis in over 16s. Retrieved from https://www.nice.org.uk/guidance/qs33

NICE. (2019). Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis. Retrieved from https://www.nice.org.uk/guidance/dg36/chapter/1-Recommendations

Pincus, T., Swearingen, C. J., Bergman, M., & Yazici, Y. (2008). RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. *J Rheumatol, 35*(11), 2136-2147.

Pincus, T., Yazici, Y., Bergman, M., Maclean, R., & Harrington, T. (2007). A proposed continuous quality improvement approach to assessment and management of patients with rheumatoid arthritis without formal joint counts, based on quantitative routine assessment of patient index data (RAPID) scores on a multidimensional health assessment questionnaire (MDHAQ). *Best Pract Res Clin Rheumatol, 21*(4), 789-804. doi:10.1016/j.berh.2007.02.009

Prevoo, M. L., van 't Hof, M. A., Kuper, H. H., van Leeuwen, M. A., van de Putte, L. B., & van Riel, P. L. (1995). Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum, 38*(1), 44-48.

Rezaei, H., Saevarsdottir, S., Forslind, K., Albertsson, K., Wallin, H., Bratt, J., van Vollenhoven, R. F. (2012). In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial. *Ann Rheum Dis, 71*(2), 186-191. doi:10.1136/annrheumdis-2011-200038

Rhodes, B., Merriman, M. E., Harrison, A., Nissen, M. J., Smith, M., Stamp, L., Vyse, T. J. (2010). A genetic association study of serum acute-phase C-reactive protein levels in rheumatoid arthritis: implications for clinical interpretation. *PLoS Med, 7*(9), e1000341. doi:10.1371/journal.pmed.1000341

Saleem, B., Brown, A. K., Keen, H., Nizam, S., Freeston, J., Karim, Z., Emery, P. (2009). Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. *Arthritis Rheum, 60*(7), 1915-1922. doi:10.1002/art.24596

Shmerling, R. (2018). Origin and utility of measurement of rheumatoid factors. Retrieved from https://www.uptodate.com/contents/origin-and-utility-of-measurement-of-rheumatoid-factors?topicRef=7503&source=see_link

Singh, J. A., Furst, D. E., Bharat, A., Curtis, J. R., Kavanaugh, A. F., Kremer, J. M., Saag, K. G. (2012). 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken), 64*(5), 625-639. doi:10.1002/acr.21641

Singh, J. A., Saag, K. G., Bridges, S. L., Jr., Akl, E. A., Bannuru, R. R., Sullivan, M. C., McAlindon, T. (2016). 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken), 68*(1), 1-25. doi:10.1002/acr.22783

Smolen, J. S., Aletaha, D., Bijlsma, J. W., Breedveld, F. C., Boumpas, D., Burmester, G., van der Heijde, D. (2010). Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis, 69*(4), 631-637. doi:10.1136/ard.2009.123919

Smolen, J. S., Breedveld, F. C., Schiff, M. H., Kalden, J. R., Emery, P., Eberl, G., Tugwell, P. (2003). A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford), 42*(2), 244-257.

Sokka, T., & Pincus, T. (2009). Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. *J Rheumatol, 36*(7), 1387-1390. doi:10.3899/jrheum.080770

Taylor, P., & Maini, R. (2017). Investigational biologic markers in the diagnosis and assessment of rheumatoid arthritis. In J. O'Dell (Ed.), UpToDate. Waltham. MA. Retrieved from https://www.uptodate.com/contents/investigational-biologic-markers-in-the-diagnosis-and-assessment-of-rheumatoid-arthritis.

van der Heijde, D. M., van 't Hof, M. A., van Riel, P. L., Theunisse, L. A., Lubberts, E. W., van Leeuwen, M. A., van de Putte, L. B. (1990). Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis, 49*(11), 916-920.

van der Helm-van Mil, A. H. M., Knevel, R., Cavet, G., Huizinga, T. W. J., & Haney, D. J. (2013). An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. In *Rheumatology (Oxford)* (Vol. 52, pp. 839-846).

Venables, P., Maini, Ravinder. (2017). Clinical manifestations of rheumatoid arthritis.

Specialty Matched Consultant Advisory Panel review 2/2020

Policy Implementation/Update Information

1/1/19	New policy developed. The use of a multi-biomarker disease activity score for rheumatoid arthritis (e.g., Vectra DA score) is considered investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)
5/14/19	Reviewed by Avalon for 1st Quarter 2019 CAB. Updated Description section. Revised Policy Guidelines section. Added reference. No change to investigational statement. Medical Director review 4/2019. (an)
03/10/20	Specialty Matched Consultant Advisory Panel review 2/19/2020. No change to policy statement. (eel)
5/12/20	Reviewed by Avalon for 1st Quarter 2020 CAB. Updated Description and Policy Guidelines section. Added references. No change to policy statement. Medical Director review 4/2020. (eel)