

Vectra DA Blood Test for Rheumatoid Arthritis

Policy Number: AHS – G2127 – Vectra DA Blood Test for Rheumatoid Arthritis	Prior Policy Name and Number, as applicable:
Initial Presentation Date: 06/01/2021	
Revision Date: N/A	

I. Policy Description

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder which results from a complex interaction between genes and the environment, leading to a breakdown of immune tolerance and synovial inflammation in a characteristic symmetric pattern. RA usually leads to the destruction of joints due to erosion of cartilage and bone, causing joint deformities (Firestein, 2020).

Vectra DA is a multi-biomarker disease activity (MBDA) blood test which combines the levels of 12 serum biomarkers into a single score from 1 to 100 to provide an objective measure of RA disease activity. It is intended for use with existing symptom-based disease activity measures to improve 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), please see policy AHS-G2155 General Inflammation Testing and policy AHS-G2022 ANA/ENA Testing.

II. Related Policies

Policy Number	Policy Title
AHS-G2022	ANA/ENA Testing
AHS-G2155	General Inflammation Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies

and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

1. The use of a multi-biomarker disease activity score for rheumatoid arthritis (e.g., Vectra DA score) **DOES NOT MEET COVERAGE CRITERIA.**

IV. Scientific Background

Rheumatoid arthritis (RA) affects over 1.3 million people in the U.S. 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 stiff and swollen joints throughout 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, 2019).

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 benefits, especially for patients with more severe forms of the illness (Taylor & Maini, 2020). Tighter control, such as more frequent monitoring and actively striving to meet a disease activity level, has been advantageous 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 measure of disease activity has been 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 disease activity assessment. 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, 2020). 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 be completely normal in patients with RA (Centola et al., 2013; Curtis et al., 2012). This non-specificity is not limited to ESR and CRP. For example, antibodies (usually called rheumatoid factors or 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, 2020). 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 multi-biomarker disease activity (MBDA), may be useful for predicting disease activity and progression (Taylor & Maini, 2020).

Validity and Utility

According to Curtis et al. (2012), the MBDA algorithm (Vectra DA) was developed by screening 396 candidate biomarkers. An algorithm was then created to generate a composite score based on the 12 biomarkers 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 28-joint Disease Activity Score based on CRP (DAS28-CRP) and has been validated for clinical use as a disease activity marker in RA (Curtis et al., 2012). Both Hirata et al. (2013) and Bakker et al. (2012) found the MBDA score to correlate well with disease activity and could complement other existing measures of RA assessment. Remission based on the MBDA score was a significant predictor of radiographic non-progression, whereas both remission-defined DAS28-CRP and American College of Rheumatology/European League Against Rheumatism (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, Sasso, Emerling, Cavet, and Ford (2013) 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 et al., 2013).

Another study by Li et al. (2016) 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).”

In a study by Ma et al. (2020), the MBDA test was used to explore the role of biomarkers in predicting remission of RA. Serum samples for 148 patients were assessed for MBDA score at three months, six months, and at one year. RA patients on greater than six months stable therapy in stable low disease activity were assessed every three months for one year. Patients not fulfilling any remission criteria at baseline were classified as ‘low disease activity state’ (LDAS). Patients not fulfilling any remission criteria over 1 year were classified as ‘persistent disease activity’ (PDA). Of the 148 patients, 27% were in the LDAS group and over 1 year, 9% of patients were classified as PDA. Baseline MBDA score and concentrations of IL-6, leptin, SAA and CRP were significantly lower in all baseline remission criteria

groups in comparison to LDAS groups. The individual MBDA biomarkers (IL-6, leptin, SAA, CRP) and initial MBDA score was able to differentiate between remission at baseline and LDAS. The authors state that these findings highlight the potential value of repeated measurements of MBDA score to evaluate the stability of clinical disease activity over time (Ma et al., 2020).

V. Guidelines and Recommendations

American College of Rheumatology (ACR) (Anderson et al., 2012; Singh et al., 2015)

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 (Anderson et al., 2012).”

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) (Combe et al., 2017; England et al., 2019; Smolen et al., 2020)

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 radiographic 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).

A 2019 EULAR update focused on management of RA with DMARDs stated that “The major weakness of our current treatment approaches is the lack of biomarkers for immediate stratification of an individual patient to the most appropriate drug. Importantly, these considerations emphasise the need to search for predictive markers; however, since a considerable number of patients (about 20%–30%) are refractory to all current treatment options, new therapies also need to be developed” (Smolen et al., 2020).

Another 2019 EULAR update focused on use of disease activity measures for RA. In it, the guideline identified 11 measures of RA disease activity that met the authors’ “minimum standards for regular use”, which was defined to include the following four characteristics:

- “1) providing a numerical value,
- 2) categorizing to ≥ 3 disease states which separate low, moderate, and high disease activity,
- 3) being feasible for regular measurement in clinic and
- 4) possessing adequate psychometric properties”.

The guideline identified Vectra DA as one of the 11 disease activity measures fulfilling these four minimum standards. However, the guideline recommended five other measures of disease activity, while giving Vectra an “Inconclusive” rating (England et al., 2019).

National Institute for Care and Excellence (NICE), Quality Standard, Rheumatoid arthritis in over 16s (NICE, 2019, 2020)

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, 2020).

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) (Smolen et al., 2016)

The 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).

VI. State and Federal Regulations, as applicable

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.

VII. Applicable CPT/HCPCS Procedure Codes

CPT Code Number	Code Description
81490	Autoimmune (rheumatoid arthritis) analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score

Current Procedural Terminology© American Medical Association. All Rights Reserved

Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

- 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
- Bakker, M. F., Jacobs, J. W., Verstappen, S. M., & Bijlsma, J. W. (2007). Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. *Ann Rheum Dis*, *66 Suppl 3*, iii56-60. doi:10.1136/ard.2007.078360
- 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
- 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

- Combe, B., Landewe, R., Daien, C. I., Hua, C., Aletaha, D., Alvaro-Gracia, J. M., . . . van Vollenhoven, R. (2017). 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis*, *76*(6), 948-959. doi:10.1136/annrheumdis-2016-210602
- Curtis, J. R., Flake, D. D., Weinblatt, M. E., Shadick, N. A., Ostergaard, M., Hetland, M. L., . . . Lanchbury, J. S. (2019). Adjustment of the multi-biomarker disease activity score to account for age, sex and adiposity in patients with rheumatoid arthritis. *Rheumatology (Oxford)*, *58*(5), 874-883. doi:10.1093/rheumatology/key367
- Curtis, J. R., Greenberg, J. D., Harrold, L. R., Kremer, J. M., & Palmer, J. L. (2018). Influence of obesity, age, and comorbidities on the multi-biomarker disease activity test in rheumatoid arthritis. *Semin Arthritis Rheum*, *47*(4), 472-477. doi:10.1016/j.semarthrit.2017.07.010
- 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
- England, B. R., Tiong, B. K., Bergman, M. J., Curtis, J. R., Kazi, S., Mikuls, T. R., . . . Michaud, K. (2019). 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. *Arthritis Care Res (Hoboken)*, *71*(12), 1540-1555. doi:10.1002/acr.24042
- Firestein, G. (2020). Pathogenesis of rheumatoid arthritis - UpToDate. In P. L. Romain (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/pathogenesis-of-rheumatoid-arthritis?source=search_result&search=ra&selectedTitle=6~150
- 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
- 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
- Li, W., Sasso, E. H., van der Helm-van Mil, A. H., & Huizinga, T. W. (2016). 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)*, *55*(2), 357-366. doi:10.1093/rheumatology/kev341
- Ma, M. H. Y., Defranoux, N., Li, W., Sasso, E. H., Ibrahim, F., Scott, D. L., & Cope, A. P. (2020). A multi-biomarker disease activity score can predict sustained remission in rheumatoid arthritis. *Arthritis Res Ther*, *22*(1), 158. doi:10.1186/s13075-020-02240-w
- Mc Ardle, A., Flatley, B., Pennington, S. R., & FitzGerald, O. (2015). Early biomarkers of joint damage in rheumatoid and psoriatic arthritis. *Arthritis Res Ther*, *17*(1), 141. doi:10.1186/s13075-015-0652-z
- Mease, P. J. (2010). Improving the routine management of rheumatoid arthritis: the value of tight control. *J Rheumatol*, *37*(8), 1570-1578. doi:10.3899/jrheum.091064
- NICE. (2019). Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis. Retrieved from <https://www.nice.org.uk/guidance/dg36/chapter/1-Recommendations>
- NICE. (2020). Rheumatoid arthritis in over 16s. Retrieved from <https://www.nice.org.uk/guidance/qs33>
- Shmerling, R. (2020). 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., Saag, K. G., Bridges, S. L., Jr., Akl, E. A., Bannuru, R. R., Sullivan, M. C., . . . McAlindon, T. (2015). 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., Breedveld, F. C., Burmester, G. R., Bykerk, V., Dougados, M., Emery, P., . . . van der Heijde, D. (2016). Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*, 75(1), 3-15. doi:10.1136/annrheumdis-2015-207524

Smolen, J. S., Landewé, R. B. M., Bijlsma, J. W. J., Burmester, G. R., Dougados, M., Kerschbaumer, A., . . . van der Heijde, D. (2020). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*, 79(6), 685-699. doi:10.1136/annrheumdis-2019-216655

Taylor, P., & Maini, R. (2020). Investigational biologic markers in the diagnosis and assessment of rheumatoid arthritis. In J. O'Dell (Ed.), *UpToDate*. Retrieved from <https://www.uptodate.com/contents/investigational-biologic-markers-in-the-diagnosis-and-assessment-of-rheumatoid-arthritis>

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. (2019). Clinical manifestations of rheumatoid arthritis. Retrieved from https://www.uptodate.com/contents/clinical-manifestations-of-rheumatoid-arthritis?search=Clinical%20manifestations%20of%20rheumatoid%20arthritis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

IX. Revision History

Revision Date	Summary of Changes
06-01-2021	Initial presentation