INTRODUCTION

Rheumatoid arthritis (RA) has high prevalence (1.5 million adult cases in the US\(^1\)) and high median annual healthcare costs ($4,677 for RA patients vs. $1,229 for non-RA patients\(^2\)). RA can be treated with two types of disease modifying anti-rheumatic drugs (DMARDs): traditional non-biologic DMARDs (appropriate with low RA disease activity) and biologic DMARDs (appropriate with high RA disease activity).\(^3\) Biologic DMARDs lead to decreased mean disease activity, hospitalization, sick leave, and work-related disability in RA patients, but cause significant increase in treatment costs.\(^4-6\) Although significant clinical advances have been made in RA over the last two decades, challenges remain in optimizing treatment decisions, which add unnecessary healthcare costs and increase burden on payers. For the most part, clinicians do not use formal measures of disease activity and when they do, the measures used are made up of subjective components, such as the DAS28, CDAI, SDAI, and RAPID3*, and measure on-going efficacy of different therapy selections.\(^7\) There is a need for objective measures of disease activity that provide a comprehensive understanding of disease progression at the patient level, taking into account RA disease heterogeneity, while minimizing the impact on the physician’s time. Vectra® DA fulfills this unmet need by combining multiple serum biomarkers into a single score that can help physicians characterize disease activity in patients, assess response to treatment, identify risk of joint damage, and potentially guide second line treatment after methotrexate and inform tapering decisions for patients in stable remission.\(^+\) Use of Vectra DA may help avoid unnecessary drug exposure and expenditure, potentially creating overall savings for physicians, patients, and payers.

THE VECTRA DA TEST

Vectra DA is an advanced blood test that provides a comprehensive and objective measure of RA disease activity by measuring 12 biomarkers and combining them into a single score ranging from 1 to 100, which is further categorized as low (<30), moderate (30-44), or high (>44).\(^8-10\)

INTENDED USE POPULATION

The Vectra DA test is intended for adult patients diagnosed with RA. The test may be used throughout the course of a patient’s disease and provides clinicians with insight on disease severity, risk of radiographic progression, and response to treatment using a single score. Test results are intended to aid in the assessment of disease activity in RA patients when used in conjunction with standard clinical assessment.\(^+\)

ANALYTICAL VALIDITY

Development of the Vectra DA test included screening approximately 400 candidate biomarkers based on potential biological relevance. Successive studies refined the biomarkers to a set of 12 with the greatest ability to evaluate RA disease activity based on their association with clinical measures, including the 28-Joint Disease Activity Score using C-reactive protein (DAS28-CRP). This development process involved over 1,900 serum samples from more than 1,700 patients in successive cohorts.\(^8,9,11\) The biomarkers included in Vectra DA reflect the complexity of the RA disease process and include markers related to inflammation, cellular trafficking, tissue expansion, cartilage degradation and joint damage, and stromal activity and regulation: adhesion molecules (VCAM-1), growth factors (EGF and VEGF-A), cytokine-related proteins and receptors (IL-6 and TNF-RI), matrix metalloproteinases (MMP-1 and MMP-3), skeletal-related proteins (YKL-40), hormones (leptin and resistin), and acute-phase proteins (SAA and CRP).

* DAS28: 28-Joint Disease Activity Score, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, RAPID3: Routine Assessment of Patient Index Data
+ This test is not intended or validated to diagnose RA, to predict response to specific therapies or classes of therapies, or to guide therapy taper or withdrawal.
CLINICAL VALIDITY

Clinical validation of Vectra DA concluded that a serum-based test score provides both objective and quantitative information about disease activity that had not been previously available to clinicians. A key study found:

- Vectra DA was shown to be associated with the DAS28-CRP in both seropositive and seronegative patients (P<0.001 in both validation analyses). Performance using the AUROC for classifying patients into low vs. moderate to high disease activity was 0.77 and 0.70, and correlation to the DAS28-CRP was 0.56 and 0.43 in seropositive and seronegative patients, respectively.

- Changes in the Vectra DA score from baseline to final visit were significantly correlated with changes in DAS28-CRP (Spearman’s rank correlation coefficient [\( \rho \) = 0.51, p<0.001]).

Vectra DA can inform treatment decisions, potentially optimize clinical care, and improve the long-term management of patients with RA by providing data that tracks response to therapy and predicts rapid radiographic progression, among other criteria.\(^{11-16}\)

CLINICAL UTILITY AND IMPACT OF VECTRA DA ON PATIENT CARE

The Vectra DA test may be an effective tool for predicting radiographic progression, both in patients with early RA as well as in patients with established RA, and in many cases may be a better predictor of radiographic progression than currently used clinical measures.\(^{17-19}\) A recent study reported that among 235 patients with early RA, 21% of those with a high baseline Vectra DA score experienced rapid radiographic progression (\( \Delta \text{SHS}>5 \)) over one year while only 3% of moderate-scoring patients and 0% of low-scoring patients progressed.\(^{19}\) In contrast, rapid radiographic progression over one year was frequent whether baseline DAS28-ESR was moderate (15%) or high (20%) or whether baseline CRP was low (14%), moderate (15%), or high (25%). A separate analysis at one year was consistent with the baseline results.\(^{20}\)

Recently, the Cochrane Institute reported meta-analysis findings suggesting that, at a group level, non-biologic DMARD combination therapy and biologic DMARD therapy may have similar efficacy.\(^{21}\) However, challenges regarding identification of those patients most likely to benefit from non-biologic vs. biologic therapy remain. Vectra DA may be used as a personalized tool that helps patients identify the most cost-effective treatment after methotrexate.

Another analysis reported that among 157 patients with inadequate response to methotrexate (MTX) at month 3, 12% had a low Vectra DA score, 88% of whom responded well to non-biologic DMARD combination therapy at month 12.\(^{22}\) Conversely, patients with a high Vectra DA score responded more favorably to a biologic therapy at month 12. In a separate analysis, the authors showed that patients with a low Vectra DA score at month 3 who received non-biologic DMARD combination therapy experienced no radiographic progression over 2 years (\( \Delta \text{SHS}>5 \)).\(^{20}\)

\( * \) SHS: van der Heijde modified Sharp score, a measure of joint damage in RA.
An additional study suggests Vectra DA may be used to guide tapering decisions for RA patients in stable remission. Among 94 patients in stable remission undergoing tapering, the Vectra DA score was an independent predictor of sustained remission. Baseline Vectra DA scores were significantly lower in patients who sustained remission than in those who relapsed. Among patients who remained in remission, 79% had a low Vectra DA score while 21% had a moderate or high score.

Vectra DA scores, in combination with ACPA status, enhanced predictive value of sustained remission. Sustained remission was high (87%) for patients with a low Vectra DA score and negative ACPA, moderate in patients with a moderate-to-high Vectra DA score and negative ACPA (66.7%) or a low Vectra DA score and positive ACPA (68.2%), and low in patients with both a moderate-to-high Vectra DA score and positive ACPA (23.6%) over the course of 12 months. Vectra DA may help identify those patients who benefit from treatment tapering, thereby potentially reducing both the adverse events associated with therapy as well as any unnecessary financial burden.

**MEDICARE COVERAGE**

Medicare contractor Palmetto GBA currently has a positive Local Coverage Determination for Vectra DA, which was effective June 30, 2012. This policy determination pertains to Medicare patients nationwide for Vectra DA testing performed at the CLIA-certified Crescendo Bioscience reference laboratory in South San Francisco, CA. Vectra DA coverage is under the Medicare Part B program, which also drives coverage policies for Medicare Advantage plans. Medicare beneficiaries have access to at least two Vectra DA tests annually at no out-of-pocket cost, although Medicare Advantage plans may require a co-pay.

**MEDICAL COVERAGE POLICY RECOMMENDATION**

Crescendo Bioscience recommends the following usage of Vectra DA for medical policy:

1. Physician is establishing a baseline disease activity level to inform future and ongoing treatment decisions
2. Physician is considering whether to perform joint imaging, such as MRI or ultrasound, to assess risk for future joint damage
3. Physician is uncertain regarding patient management because the physician assessment of disease activity is discordant with patient-reported outcomes or with results of conventional laboratory tests (CRP/ESR), or the patient has pain that may not be related to joint inflammation from RA
4. Physician is considering a change in treatment from MTX because the patient is inadequately responding to it and physician is uncertain whether to intensify non-biologic DMARD therapy or whether to move to biologic therapy
5. Physician and patient are considering reducing current treatment because the patient is in stable remission and would like to assess the likelihood the patient will remain in remission

Vectra DA may also be considered as part of a prior authorization requirement along with other clinical assessments to make informed decisions on the usage scenarios described above.
REFERENCES


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