Clinical Policy Bulletin:
Rheumatic Diseases: Selected Tests

Revised April 2014

Number: 0866

Policy

Aetna considers measurement of anti-cyclic citrullinated peptide (anti-CCP) antibodies medically necessary for diagnosis of rheumatoid arthritis (RA). Aetna considers measurement of anti-CCP antibodies experimental and investigational for all other indications.

Aetna considers the myositis antibody panel medically necessary for diagnosing persons with inflammatory myopathy. Aetna considers the myositis antibody panel experimental and investigational for all other indications.

Aetna considers measurement of anti-mutated citrullinated vimentin (MCV) antibodies (e.g., the Avise MCV test) experimental and investigational in diagnosing RA and for all other indications because there is insufficient clinical evidence to support the use of this test in the diagnosis of RA.

Aetna considers the Avsie PG, Avise SLE, and Avise SLE+ tests experimental and investigational.

Aetna considers the Vectra DA test experimental and investigational for rheumatoid arthritis and other indications.

Aetna considers measurement of isoforms of 14-3-3 protein (beta, gamma, epsilon, eta, sigma, theta, and zeta) experimental and investigational as biomarkers of osteoarthritis and RA.

Background

Rheumatoid arthritis (RA) is a chronic syndrome characterized by nonspecific, usually symmetric inflammation of the peripheral joints, potentially resulting in progressive destruction of articular and periarticular structures, with or without generalized manifestations.

Avise MCV measures antibodies to mutated citrullinated vimentin (MCV), a protein found in the inflamed synovium of patients with RA. Elevated levels of anti-MCV indicate an increased likelihood of having rheumatoid arthritis, and also identify those who may develop more severe forms of RA.

http://qawww.aetna.com/cpb/medical/data/800_899/0866_draft.html 12/08/2014
The Avise MCV test is a proprietary personalized medicine test of Cypress Biosciences. No information on the Avise MCV test was found on the U.S. Food and Drug Administration website.

In patients with undiagnosed early inflammatory arthritis or established RA, the diagnostic and prognostic value of adding anti-MCV antibody testing to anti-CCP and rheumatoid factor (RF) testing, or substituting anti-MCV for other tests, remains uncertain. Further study is required to more clearly define its role in routine clinical practice.

The idiopathic inflammatory myopathies are a group of systemic rheumatological diseases of unknown etiology, characterized by a chronic inflammatory myositis resulting in muscular weakness with or without organ system dysfunction. The three disorders that comprise this group of muscle disorders are polymyositis, dermatomyositis, and a more recently defined disorder called inclusion body myositis.

The Myositis Antibody Panel Plus is a test for autoantibodies commonly present in the sera of patients with idiopathic inflammatory myopathies, a type of autoimmune disorder. The autoantibodies measured in the test include Jo-1, PL-7, PL-12, EJ, OJ, SRP, KU and Mi2. The detection of specific autoantibodies can differentiate polymyositis and dermatomyositis from other autoimmune disorders.

Use of the Myositis Antibody Panel Plus aids in the detection of specific autoantibodies that differentiate the idiopathic inflammatory myopathies; therefore, it is a recommended test for the diagnosing of an idiopathic inflammatory myopathy.

The AviseE SLE test is a blood test for the diagnosis of systemic lupus erythematosus (SLE); it involves a group of proteins called complement (including C4d). The Avise SLE test has a 78% sensitivity and 87% specificity. The Avise SLE+ Connective Tissue™ is a diagnostic test that is offered in addition to the Avise SLE test. It is made up of 14 common connective tissue diagnostic markers. It includes markers for extractable nuclear autoantibodies (ENAs), rheumatoid arthritis and anti-phospholipid syndrome autoantibodies -- cardiolipin IgG, cardiolipin IgM, beta2-glycoprotein 1 IgG, and beta2-glycoprotein 1 IgM -- that supposedly help to differentiate lupus from other connective tissue diseases. The Avise PG test is a blood test used for measuring methotrexate polyglutamates for rheumatoid arthritis (metabolite marker testing). However, there is a lack of evidence regarding the effectiveness of these tests.

Kilani et al (2007) (i) examined if 14-3-3 proteins were detectable in synovial fluid (SF) of patients with inflamed joints, and if so, what isoform(s); and (ii) examine if there was a correlation between the levels of these proteins and those of matrix metalloproteinase 1 (MMP-1) and matrix metalloproteinase 3 (MMP-3) in the same samples. In general, 2 sets of synovial and serum samples were analyzed. The
first set of 17 SF -samples from patients with inflamed joints were analyzed for 14-3-3 eta isoform by Western blot. The second set of 12 matching serum and SF samples were analyzed for 14-3-3 eta, gamma, MMP-1, and MMP-3 by the same procedure. The MMP-1 stimulatory effect of various concentrations of 14-3-3 eta in cultured fibroblasts was then evaluated. These researchers found that of the 7 14-3-3 isoforms tested (beta, gamma, epsilon, eta, sigma, Theta, and zeta), the levels of only 2 isoforms, eta and gamma, were easily detectable in SF samples from patients with inflammatory joint diseases. The levels of these proteins were significantly higher in inflammatory SF and serum samples relative to controls. The values of these proteins correlated strongly with the levels of MMP-1 and MMP-3, 2 biomarkers for RA, detected in sera. Furthermore, the level of 14-3-3 eta was significantly higher in a pool of 12 serum samples from patients with inflammatory joint disease than those from healthy individuals. The authors concluded that detection of only 2 (14-3-3 eta and gamma) out of 7 different isoforms in SF suggested they are specific to the site of inflammation, and that distinguishes them from barely detectable levels of these isoforms found in normal serum. The MMP-1 stimulatory effect of the eta isoform explained its correlation with MMP-1 levels seen in these samples. These preliminary findings from a small study (n = 17) need to be validated by well-designed studies.

UpToDate reviews on “Diagnosis and differential diagnosis of rheumatoid arthritis” (Venables and Maini, 2014a) and “Clinical manifestations of rheumatoid arthritis” (Venables and Maini, 2014b) do not mention isoform of 14-3-3 protein (eta and gamma) as biomarkers for RA.

Priam et al (2013) stated that mechanical stress plays an important role in cartilage degradation and subchondral bone remodeling in osteoarthritis (OA). The remodeling of the subchondral bone could initiate cartilage loss in OA through the interplay of bone and cartilage. These researchers identified soluble mediators released by loaded osteoblasts/osteocytes that could induce the release of catabolic factors by chondrocytes. Murine osteoblasts/osteocytes were subjected to cyclic compression, and then conditioned medium from either compressed (CCM) or uncompressed (UCM) cells was used to stimulate mouse chondrocytes. Chondrocyte expression of MMP-3, matrix metalloproteinase 13 (MMP-13), type II collagen, and aggrecan was assessed by reverse transcription-polymerase chain reaction, Western blotting, and enzyme-linked immunosorbent assay. Soluble mediators released by compressed osteoblasts/osteocytes were identified using iTRAQ (isobaric tags for relative and absolute quantification), a differential secretome analysis. Subchondral bone and cartilage samples were isolated from OA patients, and culture medium conditioned with OA subchondral bone or cartilage was used to stimulate human chondrocytes. Stimulation of mouse chondrocytes with CCM strongly induced the messenger RNA (mRNA) expression and protein release of MMP-3 and MMP-13 and inhibited the mRNA expression of type II collagen and aggrecan. Differential secretome analysis revealed that 10 proteins were up-regulated in compressed osteoblasts/osteocytes. Among them, soluble 14-3-3 epsilon (s14-3-3-ε) dose-dependently induced the release of catabolic factors by chondrocytes, mimicking the effects of cell compression. Addition of a 14-3-3ε blocking antibody greatly attenuated the CCM-mediated induction of MMP-3 and MMP-13 expression. Furthermore, in human OA subchondral bone, s14-3-3ε was strongly released, and in cultures of human OA chondrocytes, s14-3-3ε stimulated MMP-3
expression. The authors concluded that the results of this study identified s14-3-3e as a novel soluble mediator critical in the communication between subchondral bone and cartilage in OA. Thus, s14-3-3e may be a potential target for future therapeutic or prognostic applications in OA.

The Vectra DA is a multi-biomarker disease activity (MBDA) test to measure disease activity in adults diagnosed with rheumatoid arthritis. According to the manufacturer, test results are intended to aid in the assessment of disease activity in rheumatoid arthritis patients and help inform patient management decisions when used in conjunction with standard clinical assessment. The manufacturer states that the test is not intended or validated to diagnose rheumatoid arthritis or to guide therapy selection. The Vectra DA is a laboratory developed test that is not subject to U.S. Food and Drug Administration review. Studies of the Vectra DA test have focused on its ability to predict disease progression, its impact on clinical decisions in simulated cases, and the frequency of changes in management with MBDA results in a clinical practice. Current guidelines on rheumatoid arthritis from the American College of Rheumatology or the European League Against Rheumatism have no recommendation for the MBDA test.

Centola, et al. (2013) described the development of the Vectra DA multi-biomarker disease activity (MBDA) test for rheumatoid arthritis. Candidate serum protein biomarkers were selected from extensive literature screens, bioinformatics databases, mRNA expression and protein microarray data. Quantitative assays were identified and optimized for measuring candidate biomarkers in rheumatoid arthritis patient sera. Biomarkers with qualifying assays were prioritized in a series of studies based on their correlations to rheumatoid arthritis clinical disease activity (e.g. the Disease Activity Score 28-C-Reactive Protein [DAS28-CRP], a validated metric commonly used in clinical trials) and their contributions to multivariate models. Prioritized biomarkers were used to train an algorithm to measure disease activity, assessed by correlation to DAS and area under the receiver operating characteristic curve for classification of low vs. moderate/high disease activity. The effect of comorbidities on the MBDA score was evaluated using linear models with adjustment for multiple hypothesis testing. The authors reported that 130 candidate biomarkers were tested in feasibility studies and 25 were selected for algorithm training. Multi-biomarker statistical models outperformed individual biomarkers at estimating disease activity. Biomarker-based scores were significantly correlated with DAS28-CRP and could discriminate patients with low vs. moderate/high clinical disease activity. Such scores were also able to track changes in DAS28-CRP and were significantly associated with both joint inflammation measured by ultrasound and damage progression measured by radiography. The final MBDA algorithm uses 12 biomarkers to generate an MBDA score between 1 and 100. The authors reported that no significant effects on the MBDA score were found for common comorbidities.

Eastman, et al. (2012) stated that accurate and frequent assessment of rheumatoid arthritis disease activity is critical to optimal treatment planning. The authors explained that a novel algorithm has been developed to determine a multi-biomarker disease activity (MBDA) score based upon measurement of the concentrations of 12 serum biomarkers in multiplex format. Biomarker assays from several different platforms were used in feasibility studies to identify biomarkers of
potential significance. These assays were adapted to a multiplex platform for training and validation of the algorithm. In this study, the analytical performance of the underlying biomarker assays and the MBDA score was evaluated. Quantification of 12 biomarkers was performed with multiplexed sandwich immunoassays in three panels. Biomarker-specific capture antibodies were bound to specific locations in each well; detection antibodies were labeled with electrochemiluminescent tags. Data were acquired with a Sector Imager 6000, and analyte concentrations were determined. Parallelism, dynamic range, cross-reactivity, and precision were established for each biomarker as well as for the MBDA score. Interference by serum proteins, heterophilic antibodies, and common rheumatoid arthritis therapies was also assessed. The individual biomarker assays had 3-4 orders of magnitude dynamic ranges, with good reproducibility across time, operators, and reagent lots; the MBDA score had a median coefficient of variation of <2% across the score range. Cross-reactivity as well as interference by serum rheumatoid factor (RF), human anti-mouse antibodies (HAMA), or common RA therapies, including disease-modifying antirheumatic drugs and biologics, was minimal. The same MBDA score was observed in different subjects despite having different biomarker profiles, supporting prior literature reports that multiple pathways contribute to rheumatoid arthritis.

Bakker, et al. (2012) reported that the Vectra DA MBDA test performed well in the assessment of disease activity in rheumatoid arthritis patients in the Computer Assisted Management in Early Rheumatoid Arthritis CAMERA study. However, neither the MBDA score nor clinical variables were predictive of radiographic progression. Investigators measured 20 biomarkers in the CAMERA cohort, in which patients were treated with either intensive or conventional methotrexate-based treatment strategies. The MBDA score was calculated using the concentrations of 12 biomarkers (SAA, IL-6, TNF-RI, VEGF-A, MMP-1, YKL-40, MMP-3, EGF, VCAM-1, leptin, resistin and CRP) according to a previously trained algorithm. The performance of the scores was evaluated relative to clinical disease activity assessments. Change in MBDA score over time was assessed by paired Wilcoxon rank sum test. Logistic regression was used to evaluate the ability of disease activity measures to predict radiographic progression. The investigators stated that the MBDA score had a significant correlation with the disease activity score based on 28 joints-C reactive protein (DAS28-CRP) (r=0.72; p<0.001) and an area under the receiver operating characteristic curve for distinguishing remission/low from moderate/high disease activity of 0.86 (p<0.001) using a DAS28-CRP cut-off of 2.7. In multivariate analysis the MBDA score, but not CRP, was an independent predictor of disease activity measures. Additionally, mean (SD) MBDA score decreased from 53 (18) at baseline to 39 (16) at 6 months in response to study therapy (p<0.0001). The authors found that neither MBDA score nor clinical variables were predictive of radiographic progression.

Curtis, et al. (2012) validated the Vectra DA MBDA test relative to clinical disease activity in rheumatoid arthritis. Serum samples were obtained from the Index for Rheumatoid Arthritis Measurement, Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study, and Leiden Early Arthritis Clinic cohorts. Levels of 12 biomarkers were measured and combined according to a prespecified algorithm to generate the composite MBDA score. The relationship of the MBDA score to clinical disease activity was characterized separately in seropositive and seronegative patients using Pearson's correlations and the area under the receiver
operating characteristic curve (AUROC) to discriminate between patients with low and moderate/high disease activity. Associations between changes in MBDA score and clinical responses 6-12 weeks after initiation of anti-tumor necrosis factor or methotrexate treatment were evaluated by the AUROC. The investigators found that the MBDA score was significantly associated with the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) in both seropositive (AUROC 0.77, P < 0.001) and seronegative (AUROC 0.70, P < 0.001) patients. In subgroups based on age, sex, body mass index, and treatment, the MBDA score was associated with the DAS28-CRP (P < 0.05) in all seropositive and most seronegative subgroups. The investigators reported that changes in the MBDA score at 6-12 weeks could discriminate both American College of Rheumatology criteria for 50% improvement responses (P = 0.03) and DAS28-CRP improvement (P = 0.002). Changes in the MBDA score at 2 weeks were also associated with subsequent DAS28-CRP response (p = 0.02).

Hirata, et al. (2013) reported that Vectra DA MBDA score reflects current clinical disease activity and can track changes in rheumatoid arthritis disease activity over one year. The investigators studied 125 patients with rheumatoid arthritis from the Behandel Strategieën study. Clinical data and serum samples were available from 179 visits, 91 at baseline and 88 at year 1. In each serum sample, 12 biomarkers were measured by quantitative multiplex immunoassays and the concentrations were used as input to a pre-specified algorithm to calculate MBDA scores. The investigators found that MBDA scores had significant correlation with DAS28-ESR (Spearman's ρ = 0.66, P < 0.0001) and also correlated with simplified disease activity index, clinical disease activity index and HAQ Disability Index (all P < 0.0001). Changes in MBDA between baseline and year 1 were also correlated with changes in DAS28-ESR (ρ = 0.55, P < 0.0001). Groups stratified by European League Against Rheumatism disease activity (DAS28-ESR ≤ 3.2, 3.2-5.1 and > 5.1) had significantly different MBDA scores (P < 0.0001) and MBDA score could discriminate ACR/EULAR Boolean remission with an area under the receiver operating characteristic curve of 0.83 (P < 0.0001).

Markusse, et al. (2014) reported that the Vectra DA MBDA score predicts radiographic damage progression over one year in patients with early rheumatoid arthritis. For this study, the investigators used 180 serum samples from the BeSt study: 91 at baseline (84 with radiographs available) and 89 at 1-year followup (81 with radiographs available). Radiographs were assessed using the Sharp/van der Heijde Score (SvdH). Twelve serum biomarkers were measured to determine MBDA scores using a validated algorithm. Receiver-operating curves and Poisson regression analyses were performed, with Disease Activity Score (DAS) and MBDA score as independent variables, and radiographic progression as dependent variable. The investigators reported that, at baseline, MBDA scores discriminated more between patients who developed radiographic progression (increase in SvdH ≥ 5 points) and patients who did not [area under the curve (AUC) 0.767, 95% CI 0.639-0.896] than did DAS (AUC 0.521, 95% CI 0.358-0.684). At 1 year, MBDA score had an AUC of 0.691 (95% CI 0.453-0.929) and DAS had an AUC of 0.649 (95% CI 0.417-0.880). Adjusted for anticitrullinated protein antibody status and DAS, higher MBDA scores were associated with an increased risk for SvdH progression [relative risk (RR) 1.039, 95% CI 1.018-1.059 for baseline MBDA score; 1.037, 95% CI 1.009-1.065 for Year 1 MBDA score]. Categorized high MBDA scores were also correlated with SvdH progression (RR
for high MBDA score at baseline 3.7; low or moderate MBDA score as reference). At 1 year, high MBDA score gave a RR of 4.6 compared to low MBDA score.

van der Helm-van Mil, et al. (2013) reported that the Vectra DA MBDA score predicts limited radiographic progression over 1 year, so that it can potentially be a useful adjunct to clinical assessment to identify progression-free remission and to assess subclinical disease. The study examined 271 visits for 163 rheumatoid arthritis patients in the Leiden Early Arthritis Cohort. The MBDA score and other variables from each visit were evaluated for prediction of progression [change in Sharp-van der Heijde Score (ASHS) >3] over the ensuing 12 months. Positive likelihood ratios (PLRs) for non-progression were calculated for remission based upon DAS based on 28-joint counts and CRP (DAS28-CRP <2.32), EULAR/ACR Boolean criteria and MBDA score (≥25). The investigators reported that 93% of patients in MBDA-defined remission did not experience progression, compared with 70% of patients not in MBDA remission (p = 0.001). The investigators reported that there were no significant differences in the fraction of non-progressors between patients in remission and those not in remission using either DAS28-CRP or EULAR/ACR criteria. The PLR for non-progression over 12 months for MBDA remission was 4.73 (95% CI 1.67, 15.0). Among patients in DAS28-CRP remission, those with a high MBDA score were 2.3 times as likely (95% CI 1.1, 3.7) to have joint damage progression during the next year.

Hambardzumyan, et al. (2014) evaluated the Vectra DA multi-biomarker disease activity (MBDA) score as a baseline predictor for 1-year radiographic progression in early rheumatoid arthritis. Baseline disease activity score based on erythrocyte sedimentation rate (DAS28-ESR), disease activity score based on C-reactive protein (DAS28-CRP), CRP, MBDA scores and DAS28-ESR at 3α...months were analyzed for 235 patients with early rheumatoid arthritis from the Swedish Farmacotherapy (SWEFOT) clinical trial. Radiographic progression was defined as an increase in the Van der Heijde-modified Sharp score by more than five points over 1α...year. Associations between baseline disease activity measures, the MBDA score, and 1-year radiographic progression were evaluated using univariate and multivariate logistic regression, adjusted for potential confounders. Among 235 patients with early rheumatoid arthritis, 5 had low and 29 moderate MBDA scores at baseline. None of the former and only one of the latter group (3.4%) had radiographic progression during 1α...year, while the proportion of patients with radiographic progression among those with high MBDA score was 20.9% (p=0.021). Among patients with low/moderate CRP, moderate DAS28-CRP or moderate DAS28-ESR at baseline, progression occurred in 14%, 15%, 14% and 15%, respectively. MBDA score was an independent predictor of RP as a continuous (OR=1.05, 95% CI 1.02 to 1.08) and dichotomized variable (high versus low/moderate, OR=3.86, 95% CI 1.04 to 14.26). The authors concluded that, in patients with early rheumatoid arthritis, the MBDA score at baseline was a strong independent predictor of 1-year radiographic progression.

Li, et al. (2013) assessed how use of Vectra CA affects treatment decisions made by health care providers (HCPs) in clinical practice. At routine office visits, 101 patients with rheumatoid arthritis were assessed by their HCPs (N = 6), and they provided blood samples for MBDA testing. HCPs completed surveys before and after viewing the MBDA test result, recording dosage and frequency for all planned rheumatoid arthritis medications and physician global assessment of disease
activity. Frequency and types of change in treatment plan that resulted from viewing the MBDA test result were determined. The primary outcome measure was the percentage of cases in which the HCP changed the planned treatment after viewing the MBDA test result. Prior to HCP review of the MBDA test, disease modifying anti-rheumatic drug (DMARD) use by the 101 patients included methotrexate in 62% of patients; hydroxychloroquine 29%; TNF inhibitor 42%; non -TNF inhibitor biologic agent 19%; and other drugs at lower frequencies. Review of MBDA test results changed HCP treatment decisions in 38 cases (38%), of which 18 involved starting, discontinuing or switching a biologic or non-biologic DMARD. Other changes involved drug dosage, frequency or route of administration. The total frequency of use of the major classes of drug therapy changed by <5%. Treatment plans changed 63% of the time when the MBDA test result was perceived as being not consistent or somewhat consistent with the HCP assessment of disease activity. The authors stated that study limitations include limited sample size, lack of control group, and no longitudinal follow-up. This study did not report on whether the changes in clinical management with the MBDA test resulted in improved clinical outcomes.

Peabody, et al. (2013) reported on the use of the Vectra DA MBDA test in assessment and treatment decisions for simulated cases of rheumatoid arthritis. Board-certified rheumatologists without prior experience with the MBDA test (N=65; mean age 34 years) were randomized into an intervention or control group as part of a longitudinal randomized-control study. All physicians were asked to care for three simulated rheumatoid arthritis patients, using Clinical Performance and Value (CPV) vignettes, in a before and after design. CPV vignettes have been validated to assess the quality of clinical practice and identify variation in care. The vignettes covered all domains of a regular patient visit; scores were determined as a percentage of explicit predefined criteria completed. Three vignettes, representing typical rheumatoid arthritis cases, were administered each round. In the first round, no physician received information about the MBDA test. In the second round, only physicians in the intervention group were given educational materials about the test and hypothetical test results for each of the simulated patients. The outcome measures were the overall quality of care, disease assessment and treatment. The investigators reported that the overall quality scores in the intervention group improved by 3 percent (p<0.01) post-intervention compared with baseline, versus no change in the control group. The greatest benefit in the intervention group was to the quality of disease activity assessment and treatment decisions, which improved by 12 percent (p<0.01) compared with no significant change in the control group. The intervention was associated with more appropriate use of biologic and/or combination DMARDs in the co-morbidity case type (p<0.01).

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered for indications listed in the CPB:

83516
86200
CPT codes not covered for indications listed in the CPB:
83520

ICD-9 codes covered if selection criteria are met:
359.79 Other inflammatory and immune myopathies, NEC
714.0 - 714.9 Rheumatoid arthritis and other inflammatory polyarthopathies

The above policy is based on the following references:

6. Venables PJW, Maini RN. Diagnosis and differential diagnosis of rheumatoid arthritis. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2014a.
7. Venables PJW, Maini RN. Clinical manifestations of rheumatoid arthritis. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2014b.